A NOVEL SIMPLIFIED APPROACH TO RADIOFREQUENCY CATHETER ABLATION OF IDIOPATHIC VENTRICULAR OUTFLOW TRACT PREMATURE VENTRICULAR CONTRACTIONS

FROM SUBSTRATE ANALYSIS TO RESULTS

ANA LEONOR COSTA PARREIRA

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Because life is not like my favourite movie that I can watch over and over again, I try to live each minute at the fullest, for it is unique and cannot be repeated

Leonor

Prefácio

Ao longo da sua carreira como Médica e como Electrofisiologista a autora tem sido essencialmente uma clínica, dedicada ao tratamento dos doentes e à actividade assistencial.

Todavia, manteve sempre aceso o interesse pela investigação, desenvolvendo paralelamente uma actividade científica em várias áreas da Cardiologia em geral e da Electrofisiologia em particular.

A busca do conhecimento relativamente ao mecanismo das arritmias, com especial destaque no que respeita às arritmias ventriculares idiopáticas, tem sido a sua área de interesse nos últimos anos.

A suspeita de que as extrassístoles ventriculares (ESV) idiopáticas com origem nas camaras de saída ventriculares podem ter um substrato subjacente e que esse substrato pode ser um alvo apropriado para ablação por cateter, motivou o interesse em desenvolver este Doutoramento em Medicina.

Assim, esta dissertação foi a consequência natural da necessidade de dar um passo qualitativo e quantitativo na investigação, através do desenvolvimento de um projecto mais sólido com uma integração entre as ciências básicas, análise estatística, e os resultados clínicos.

Umas palavras sobre a organização desta dissertação;

Ela resulta do trabalho dos últimos 10 anos, no âmbito das extrassístoles ventriculares idiopáticas. Desde o seu significado clínico, ao estudo do mecanismo subjacente, sobretudo baseado no desenvolvimento da metodologia do mapeamento eletrocardiográfico não invasivo (ECGI) do qual a autora foi pioneira em Portugal. Da identificação de um substrato das ESVs, até à sua abordagem eletrofisiológica.

Assim, esta tese está organizada em cinco capítulos fundamentais, em que revemos as evidências do tema do Capítulo, incluindo, obviamente, a nossa participação, em termos de publicações, sobre o tema. Cada capítulo tem a sua bibliografia, e, nesta, destacamos em negrito os artigos de que somos autores ou coautores.

Destacamos o Capítulo V, semelhante ao título da Tese e com o formato convencional deste tipo de trabalho.

Como corolário dos 5 Capítulos, elaborámos um 6º Capítulo de Discussão e Conclusões.

No final da Tese, em anexo, estão apresentados os artigos originais na íntegra, pela ordem em que foram citados no texto, nos vários capítulos.

Todas as fotografias são originais e pertença da autora.

Apesar de não se tratar apenas de uma Tese por junção de trabalhos publicados, apresentamos na primeira página dos anexos, a tabela com o score da soma dos fatores de impacto dos artigos

publicados, de acordo com o Regulamento do Ciclo de estudos conducente ao grau de Doutor em Medicina Faculdade de Ciências Médicas, Regulamento n.º 519/2015 (Publicação: Diário da República, 2.ª série — N.º 153 — 7 de agosto de 2015).

Optámos por escrever a Tese em língua inglesa, por um lado, porque a maioria dos trabalhos está publicada nessa língua. Por outro, porque esta decisão permite uma leitura mais alargada e internacional da Tese.

Agradecimentos

Uma tese de doutoramento implica um trabalho árduo, em que as horas se tornam dias e os dias, meses e anos. Tempo que tem que ser tirado ao tempo que existia na época pré-doutoramento.

Diz-se que tempo é dinheiro, por isso passamos a ter que prescindir de certos luxos e até mesmo de alguns bens essenciais que julgamos adquiridos. O trabalho, esse, tem que manter-se ao mesmo ritmo, por isso os *hobbys,* um luxo, são abolidos, e até alguns bens essenciais, como o tempo para a família, igualmente.

Este trabalho só foi possível com o apoio da família, da instituição e da equipa.

Por isso em primeiro lugar quero agradecer ao meu marido, Zé, aos meus filhos Kiko e Bárbara, e aos meus pais Francisco e Lourdes pela sua compreensão e apoio. O ombro amigo para desabafar, são aqueles que nos vêm sem filtros, e ainda assim nos amam. Agradeço os seus sábios conselhos tão uteis e modeladores das minhas acções. Sem eles teria sido impossível concluir a tarefa. Quero desculpar-me pelo tempo que lhes foi tirado por causa desta dissertação e espero poder compensá-los mais tarde.

Nos dois hospitais em que foi realizado, o Centro Hospitalar de Setúbal e o Hospital da Luz Lisboa contei sempre com o apoio tanto das Direções Hospitalares, como dos Directores do Serviço de Cardiologia, respectivamente o Dr. Rui Caria e o Dr. Francisco Pereira Machado que me concederam a possibilidade de realizar o trabalho de campo.

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Ao Professor Doutor Pedro Adragão, meu coorientador. Com ele iniciei a minha carreira como electrofisiologista e investigadora. Um visionário, com uma capacidade de ver muito à frente do seu tempo. Nunca o ouvi dizer não a um desafio, tendo sido uma inspiração ao longo da minha vida profissional. Numa altura em que a Electrofisiologia era considerada ainda uma

especialidade pouco valorizada, foi capaz de prever o impacto que essa área da Cardiologia iria ter, contribuindo de forma ímpar para o seu desenvolvimento e implementação das novas tecnologias em Portugal. Ajudou-me a dar os primeiros passos, meu amigo e companheiro de muitas aventuras.

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Ao Professor Doutor Rui Providência que embora ainda jovem, já demonstrou o seu enorme valor e o seu reconhecimento nacional e internacional. Considero-o uma inspiração para todos aqueles que se propõem a iniciar a sua actividade de investigação. Um grande obrigado por ter considerado fazer parte da minha comissão de tese.

Ninguém pode realizar alguma coisa sozinho; a nossa equipa é o nosso apoio, tantas vezes, passamos mais tempo com eles do que com a nossa própria família.

Por isso é importante termos uma boa equipa, e no que me diz respeito posso dizer que tenho a melhor. Gosto de pensar neles como a minha segunda família. Quero agradecer-lhes pela sua amizade, por estarem lá para mim, apoiando-me e estando disponíveis quando necessário. Cada um carismático à sua maneira, mais ou menos crítica, mais ou menos condescendente, mas todos igualmente importantes para alcançar o objectivo.

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Idiopathic premature ventricular contractions epidemiological importance, risk factors clinical presentation and prognosis

Premature ventricular contractions (PVCs) are frequent and probably the leading cause of the quite unspecific symptom of palpitations. Almost everyone has experienced palpitations at least once in their lives, but in the majority of cases this symptom is harmless and, in some cases, even occurs in the absence of any sort of arrhythmia. However, it may as well represent a significant arrhythmia and the diagnose may go undetermined for many years.

The PVCs per se do not carry additional risk as long as they are not frequent and not associated with structural heart disease, the so-called idiopathic PVCs.

Definition

PVCs are beats that have their origin anywhere in the ventricles, leading to an arrhythmic pulse. There is an early beat, usually followed by a pause, due to the retrograde conduction over the AV node and this pause is traditionally called compensatory. On the 12 Lead ECG, a PVC appears as an early QRS not preceded by a P wave and displaying an anomalous morphology which depends on its origin within the ventricles.

The morphology of the QRS of the PVC can be utilized to determine its origin. When they present multiple morphologies, they are called multifocal or polymorphic and are more frequently associated with structural heart disease, whilst idiopathic PVCs are more frequently monomorphic, as we have previously reported.[1]

We studied a retrospective cohort of 312 patients, with frequent PVCs during a 24-hour Holter registry, defined as more than 1% of total beats. Structural heart disease was present in 135 and absent in 177. Patients with structural heart disease had more frequently polymorphic PVCs.[1]

PVCs can appear isolated or in groups of two, three or more than three, respectively called pairs, triplets, or runs of non-sustained ventricular tachycardia (NSVT). In our abovementioned cohort, the repetitive forms were associated with the presence of structural heart disease, although they could also be present in its absence. [1]

The assessment of the PVC burden, meaning the percentage of the total daily beats that are PVCs, is very important due to its prognostic implication. In our study the PVC burden was associated with the prognosis in idiopathic patients.[1]

The definition of frequent PVCs is variable in the different studies. Classically, in the Framingham Heart Study,[2] more than 30 PVC/h were considered frequent and associated with an increase of all-cause death. Niwano et al,[3] used the cutoff of 1000 PVCs/ 24 hours to prospectively evaluate

the prognostic significance of frequent PVCs in an apparently healthy population. In our study [1] we used a PVC burden higher than 1% of total beats/24 hours.

According to the current guidelines,[4] periodic assessment is advised in patients with a high PVC count defined as a PVC count above 10.000/ 24 hours, in line with the work of Baman et al.[5]

Prevalence

The prevalence of PVCs in the general population is variable, depending on the age,[6,7] and the duration of the screening. In a single ECG [8], its prevalence is approximately 1%, increasing to 6% if the duration of the ECG is prolonged for 2 min.[6] When using a 24-h Holter recorder the prevalence of asymptomatic PVCs may increase to approximately 69% in a population aged between 25 and 41 years old,[9] or up to 82% in patients over 65 years of age.[10]

This percentage may approximate the 100% if a 14-days wearable device is used for evaluation, as occurred in a group of 804 patients with a mean age of 75 years, who displayed PVCs in 99.5%. [11] Although PVCs can occur in healthy persons, they are more frequent in the presence of structural heart disease, [6,8,10] sleep apnea,**[12]** chronic obstructive pulmonary disease,[13,] or endurance sports. [14,15]

Clinical presentation

Patients with PVCs may be asymptomatic, but when symptomatic the most common symptom is the feeling of palpitations, usually not related to the PVC itself, but to the stronger beat that follows, due to the post PVC pause and enhanced stroke volume. Some patients refer a skipped heartbeat sensation, and rarely patients complain of chest pain or lightheadedness.

Syncope is rare and is usually not related to the PVCs. A reduction in cardiac output during ectopic beats can produce concealed mechanical bradycardia with a symptom similar to severe sinus node dysfunction.

Frequent ventricular ectopy also can negatively affect objective quality-of-life assessments. [16]

As discussed in the next section, other symptoms may be related to the repercussion of the high PVC burden in the heart.

The reason why some patients are asymptomatic despite a high PVC burden and others are very symptomatic with few PVCs is an unexplained issue.

Prognosis

The prognosis associated with frequent PVCs depends greatly on the presence of structural heart disease. Historically idiopathic PVCs have been considered benign.[17,18]

Abdalla et al prospectively studied a cohort of 15,637 apparently healthy white men, aged 35 to 57 years, [19] and reported that the presence of PVCs on a 2 min strip ECG was associated with sudden death. During the follow-up 381 (2.4%) deaths occurred, and 131 were due to coronary artery disease (CAD). Forty-one patients out of the 131 that died of CAD, died suddenly. The risk of dying suddenly was higher in patients with PVCs. Also, the complexity of the PVCs, including the presence of polymorphic forms, couplets, triplets or runs of NSVT further increased the risk.

Although usually idiopathic PVCs have a benign course, evidence has emerged that a small percentage of those patients may present with polymorphic ventricular tachycardia or ventricular fibrillation, [20,21] or evolve to left ventricular dysfunction. [22]

The threshold PVC burden to develop tachycardiomyopathy has been evaluated by many authors. Yarlagadda et al. [23] reported the results of 27 patients that underwent PVC ablation, of whom 8 patients had left ventricular dysfunction that reverted after successful ablation. The authors found no significant difference in the PVC burden of those with and without left ventricular dysfunction, which could develop with as little as 5000 PVCs /24 hours.

Takemoto et al.[24] used the cutoff value of PVC counts of 20% of total heartbeats over 24 h; Baman et al.[5] a cutoff value 24% PVC daily burden; Hasdemir et al.[25] a PVC burden of 16%. Niwano et al.[3] studied 2309 patients with more than 1000 PVCs/24h during a follow-up period of 5.6 years, 13 patients developed left ventricular dysfunction (5%), and the authors found a cutoff value of 31,268 PVCs per 24-h period.

Thus, patients need to have at least over 10,000 PVCs per day over several years to develop left ventricular dysfunction, and the incidence is still low. [26]

A recent study however, showed that a PVC burden of 8%, lower than previously described can be associated with impaired left ventricular function. [27]

In our retrospective cohort of 312 patients[1] with a PVC burden higher than 1% of total beats/24h, patients were followed for a median of 8.3 (5.1–9.9) years. In the idiopathic group, a higher PVC burden was independently associated with higher mortality, but not the complexity of the PVCs defined as polymorphic, triplets or runs of NSVT. In patients with structural heart disease the PVC burden was not associated with lower survival, but the presence of NSVT was associated with a lower survival free from the arrhythmic combined outcome of sudden death or hospitalizations due to ventricular arrhythmias.[1]

The worse prognosis of PVCs in patients with structural heart disease, especially if frequent or presenting with complex forms,[28] was the basis for the treatment of PVCs with antiarrhythmic drugs which proved harmful. [29] However, those studies are outdated, and antiarrhythmic drugs are no longer the only option. Catheter ablation is a successful treatment, although the impact on the prognosis is unproven. [5,23,24,30-32]

Also, a few population-based studies have suggested that PVCs are associated with an adverse outcome with a much lower PVC burden, even in the absence of known structural heart disease.[33-37] The PVC burden in the aforementioned studies is much lower than the one in our cohort, median PVC% of 2.7 (1.6–6.7) %. versus the 0.011% (0.002%–0.123%) in the study by Dukes et al [35] or the mean number of 176 ± 423 PVCs/24 h reported by Lin et al. [37]

Those authors reported that the presence of frequent or complex forms of PVCs, NSVT, or polymorphic PVCs, have been associated with heart failure, atrial fibrillation, and stroke, even in the absence of known structural heart disease, [33-36] but the reason for those findings is unclear.

Patients often have frequent premature atrial contractions (PACs), in addition to frequent PVCs as is the case of older populations, especially in the presence of cardiovascular risk factors. PACs have been considered a benign finding for many years. Recent studies, however, have demonstrated an association between PACs and atrial fibrillation and stroke. [38, 39,40, **41,42**]

In all those previous studies that reported increased risk of HF, stroke, and AF due to a high PVC burden, the authors did not address the presence of frequent PACs in association with frequent or complex PVCs. To the best of our knowledge, we presented for the first time a study[**43**] that demonstrated the role of PAC burden as a marker of prognosis in patients with frequent PVCs. We demonstrated that in patients with frequent PVCs, a high PAC count was independently associated with increased mortality, higher rate of AF, stroke, and HF adverse events. The presence of NSVT was independently associated with increased arrhythmic adverse events, but not with overall mortality, AF, stroke, or HF events (Figure 1)

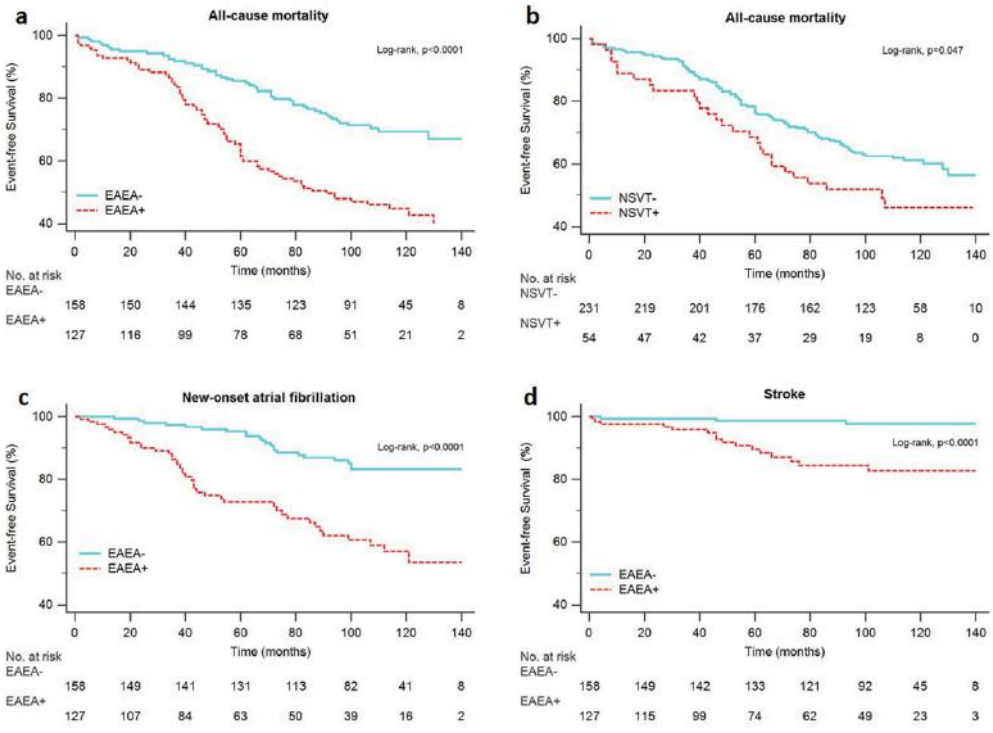

Figure 1. *Kaplan-Meier estimates for overall survival in patients with and without EAEA (a), and with and without NSVT (b), AF free survival in patients with and EAEA (c), stroke free survival in patients with and without EAEA (d). EAEA: excessive atrial ectopic activity; NSVT: non-sustained ventricular tachycardia.*

These results, if replicated in future studies with a higher number of patients, may have potential clinical implications, and shed some light into the mechanisms of the increased risk of HF, stroke, and AF in patients with frequent PVCs.

While those studies seem to demonstrate increased mortality from ventricular ectopy even with such low PVC counts, there is little evidence to support prophylactic intervention to suppress PVCs in patients without underlying SHD with such low PVC burden.

We believe that the presence of PVCs should lead to prompt closer evaluation for possible undiagnosed cardiac disease or reversible underlying etiology, and higher PVC burdens above 10.000 PVCs / 24h should be treated even in idiopathic patients.

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State of the art of catheter ablation of idiopathic premature ventricular contractions

Indications

A 24-hour monitoring is of outmost importance to evaluate the number of PVCs per 24 hours, since the PVC burden is one of the criteria for referral to catheter ablation. It also ensures the focal nature of the PVCs, by showing a monomorphic versus polymorphic pattern, and the number of different morphologies.

Frequent PVCs can be associated with the development of cardiomyopathy, but there are no predictors of left ventricular dysfunction (previous chapter). Thus, in patients with a PVC burden of 10% or higher, a periodic evaluation of left ventricular function is advised to identify the need for catheter ablation, before symptoms of heart failure develop. [1-4]

In the presence of symptoms refractory to antiarrhythmic drugs, or when the medication is not tolerated, or not the patient's preference, catheter ablation is indicated. [1]

In asymptomatic patients with cardiomyopathy suspected to be caused by frequent PVCs and for whom antiarrhythmic drugs, are ineffective, not tolerated, or not preferred for long-term therapy, catheter ablation is also recommended. [1]

However, the usual Holter monitoring only records three ECG leads and a 12 lead ECG, recording the PVC simultaneously in all 12 leads, is important because it allows for a rough estimate of the origin of the arrhythmia.

In case of PVCs from the RVOT due to the low risk and high success rate, an ablation strategy may be favored as opposed to a location near the conduction system for example, where the risk of conduction block may outweigh the benefits of ablation.

The class of recommendation for catheter ablation by the current consensus statement on catheter ablation of ventricular arrhythmias[1] is different according to the location, respectively, class I indication for RVOT PVCs and class IIa for LVOT PVCs. The latter accounting for 12%–45% of all idiopathic VAs. [5,6]

Anatomy

The outflow tracts constitute a complex structure in close continuity with each other (Figure 2).

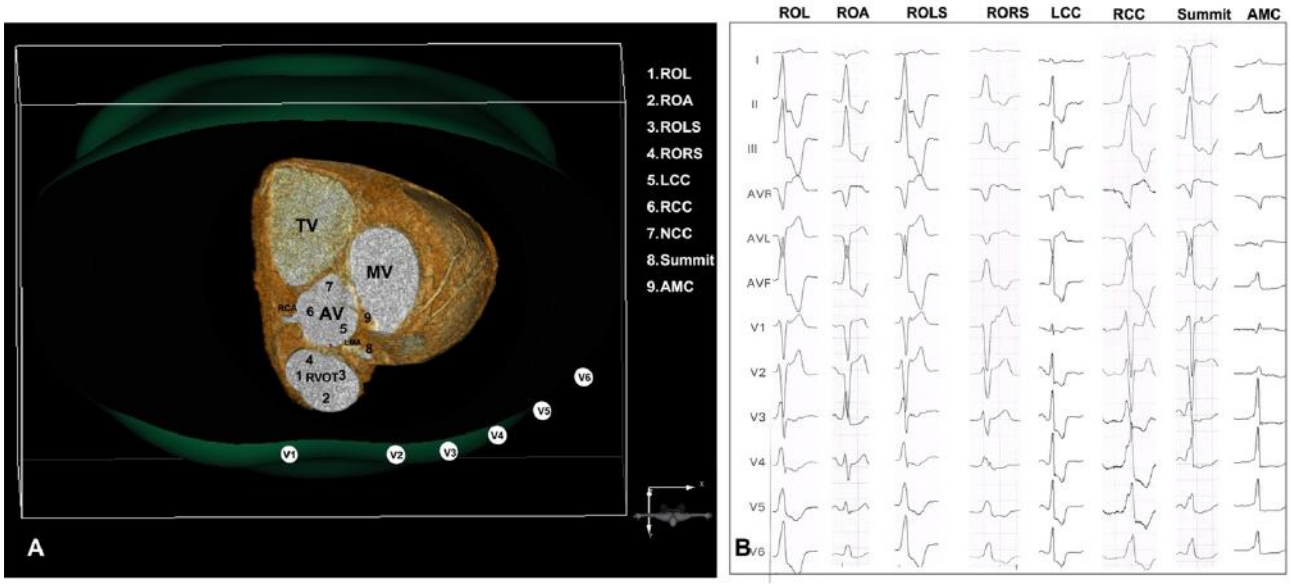

Figure 2. *Anatomy of the outflow tracts (Panel A) and QRS morphology of the PVCs according to the SOO (Panel B). RVOT: right ventricular outflow tract; SOO: site of origin; AV: aortic valve; MV: mitral valve; TV: tricuspid valve; ROL: RVOT: lateral; ROA: RVOT anterior; ROLS: RVOT left septum; RORS: RVOT right septum; LCC: left coronary cusp; RCC; right coronary cusp; NCC: non coronary cusp; AMC: aortomitral continuity*

The RVOT stands anteriorly and superiorly to the LVOT. The level of the pulmonary valve is higher than the aortic valve so that the posterior aspect of the RVOT is actually adjacent to the aortic wall rather than a true interventricular septum and the left side is adjacent to the LCC whereas the right side is in contiguity with the RCC. In that area, both the left and the right coronary arteries run close to both outflow tracts. The aortic valve is part of the fibrous trigone of the heart that also includes the mitral valve and so, roughly speaking the LVOT area between the aortic and the mitral valve is known as the aortomitral continuity. In the area immediately below the aortic valve towards the septum lies the left side of the His bundle, and towards the anterior wall the left main artery (LMA) branches with the epicardial fat pad, usually very thick in that area. The uppermost anterior area of the LV below the LCC where the LMA divides into its two branches, lies the left ventricular summit, a relatively common SOO of idiopathic OT VAs (14.1%) in a series by Letsas et al. [5] Arrhythmias from this region may arise from the epicardium and be accessible by the coronary sinus branches, being the commonest source of idiopathic epicardial arrhythmias. They can also originate intramurally in about 6.7% of cases.[5]

The PVCs at the anterior portion of the LVOT may originate endocardial or epicardial and in the latter the access is difficult due to the fat pad along the coronary arteries, and to the risk of coronary artery injury. In that area the myocardial is very thick, rendering it very difficult to reach an intramyocardial focus from the endocardium, and frequently the ablation needs to be

performed in conjunction, from the RVOT, the LVOT endocardially and inside the great cardiac vein and the anterior intraventricular vein. (Figure 3).

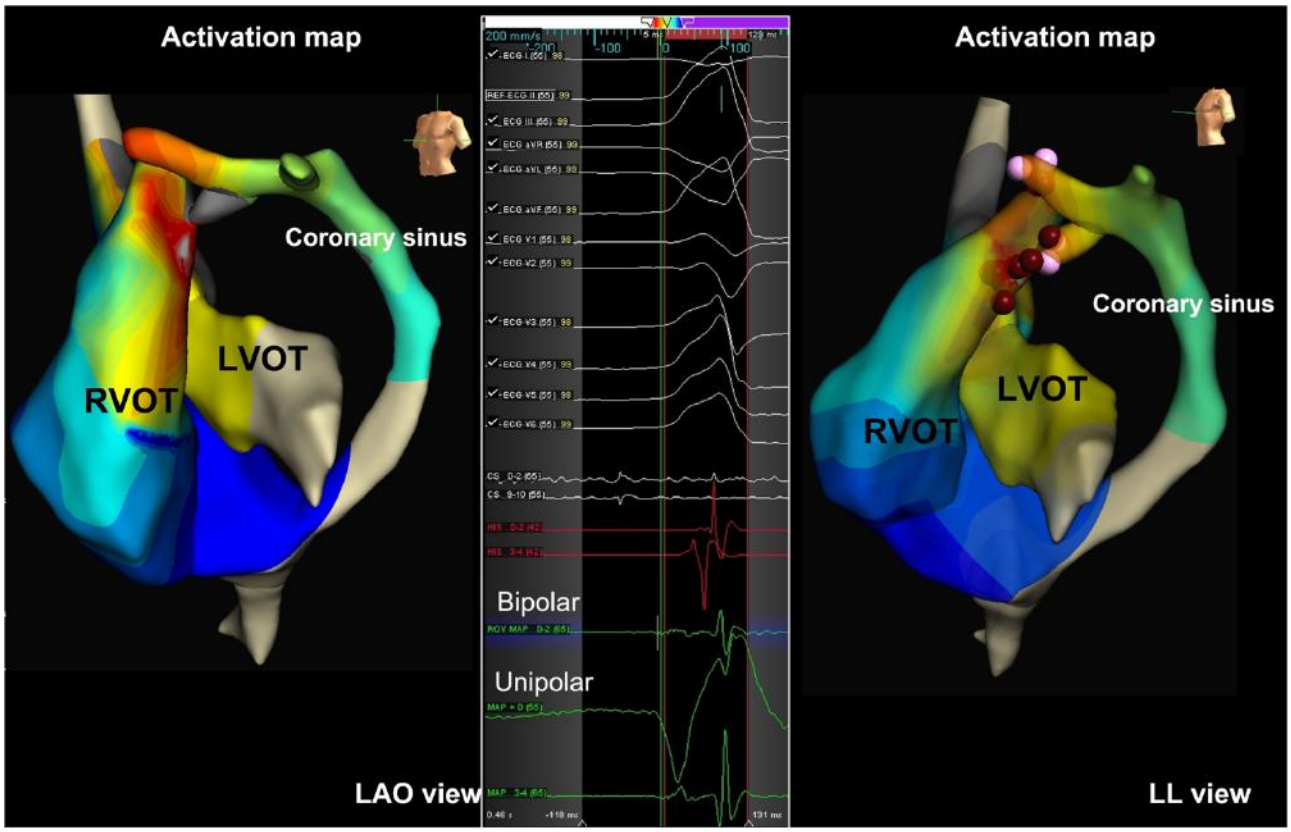

Figure 3. *Activation map of the RVOT, LVOT and the coronary sinus, in a LAO view (left) and LL view with RF applications (pink and red dots) on the right. Intracardiac electrogram at the SOO of the PVC (middle). LAO: left anterior view; LL: left lateral view; RF: radiofrequency: SOO: site of origin*

Electrocardiographic pattern

There are multiple available electrocardiographic algorithms to predict the site of origin of the arrhythmias (SOO), but the accuracy of those algorithms is low, [7,8] and small differences in the position of the precordial leads can be misleading regarding the origin of the outflow tract PVCs.[9] A recent study comparing the accuracy of artificial intelligence–enabled algorithms, with that of the electrophysiologist analysis, and of ECG algorithms, for prediction of the PVC origin, has shown an accuracy respectively, of 0.80, 0.73 and 0.86. [10]

In a study comparing ECG algorithms with the electrocardiographic imaging (ECGI), Jamil-Copley, [11] analyzed the accuracy of three 12-lead electrocardiographic algorithms previously published, (Algorithm A) by Zhang et al, [12] (Algorithm B) by Betensky et al, [13] and (Algorithm C) by Ito et al, [14] in 24 patients with PVCs from the outflow tracts. The diagnostic accuracy of ECGs algorithms analyzed retrospectively by 3 independent electrophysiologists, for predicting the LVOT versus RVOT origin, varied from 79% to 88% using algorithm A, from 67% to 71% using algorithm B, and from 50% to 63% using algorithm C.

In a randomized study comparing the 12 -lead ECG analysis with the ECGI, Erkapic et al found an accuracy for the 12-lead ECG of 38%. [15]

Typically, if the origin of the PVC is in the right ventricle the ECG will display a left bundle branch block pattern (LBBB) and a right bundle branch block (RBBB) if the origin is in the left ventricle. However, in the outflow tracts there is a significant overlapping of the structures, the anterior aspect of the LVOT is closely located to the posterior aspect of the RVOT and so the morphologies of the PVCs are similar to each other, see Figure 2.

In a simplified methodology, we can keep in mind the basics as follows, PVCs from the outflow tracts always display an inferior axis in the frontal plane and a negative QRS in lead aVL and aVR, consistent with a vector that points inferiorly. If the precordial transition of the PVC, defined as the lead in which the QRS changes from predominantly negative to positive, is beyond V4 it is probably coming from the right side and if the transition is before V3, from the left side. However, when the transition is at V3 they can arise both from the LVOT or RVOT.

Each patient has its anatomy and heart/torso's relative position within the chest wall. So, the inability to correct for cardiac rotation, which is unique for each patient, makes all algorithms imperfect.

The value of the ECGI for the diagnosis of the SOO of the PVCs will be discussed in the next chapter.

Methodology

In most cases the better attitude towards infrequent PVCs in the absence of structural heart disease, is patient's reassurance and surveillance. However, this dissertation is about frequent symptomatic PVCs, refractory to medical therapy, so therapy withhold is not an option.

Most patients prefer to initiate an antiarrhythmic drug as first-line therapy. A betablocker or a nondihydropyridine calcium antagonist (diltiazem or verapamil) or in case of left sided PVCs where the threshold for catheter ablation might be higher, even a class I antiarrhythmic (flecainide or propafenone).

Catheter ablation is indicated in case of failure of medical therapy or as first line option taken by an informed patient, to improve the quality of live, or finally when signs of left ventricular disfunction begin to show.[1]

Catheter ablation, as we know it today using radiofrequency, has been initiated in the late eighties. [16] But catheter ablation of PVCs has started later, the first case reports date back to 1994,[17] and were a matter of great controversy at the time, due to the benign nature of the disease. The first series was reported by Zhu et al[18] in 1995, and the cases were performed mainly in the RVOT.

Since the first reports, the numbers have increased, and ablation has been performed in the LVOT, but also in other frequent idiopathic PVC locations, like the tricuspid and mitral annulus, the right ventricular septum near the His bundle, the moderator band, and the papillary muscles or within the great cardiac vein, anterior interventricular vein, or the left ventricular summit.[1]

The methodology has been based mostly on activation mapping, which consists of recording local electrograms from multiple sites during the PVC, looking for the earliest site. The length of the mapping acquisition time depends on the frequency of the PVCs, longer in cases with low intraprocedural PVC frequency.

With the use of the three-dimensional (3D) electroanatomical mapping (EAM) systems, activation map can be displayed in a more intuitive color-coded way, facilitating the identification of the SOO of the arrhythmia. But 3D EAM systems continue to be based on the analysis of the intracardiac electrograms regarding their precocity in relation to a fiducial point. This information is used to generate a 3D EAM activation map, with the electrophysiologic information, color-coded and superimposed on the geometry. The areas latest activated are displayed in purple and the earliest activated in red or white depending on the manufacturer.

Currently, three systems are commercially available, the CARTO (Biosense-Webster, Inc., Diamond Bar, CA, USA), the EnSite Precision (Abbott, St Paul MN, USA) and the Rhythmia (Boston Scientific, Natick, MA.

For focal arrhythmias as happens with PVCs, the earliest activated site identifies the SOO of the arrhythmia and is the target of ablation.[19] At the SOO the local bipolar electrogram precedes the QRS onset, and the unipolar signal (with high-pass filter setting <1 Hz) demonstrates a QS configuration, consistent with a centrifugal spread of activation away from the SOO (Figure 4).

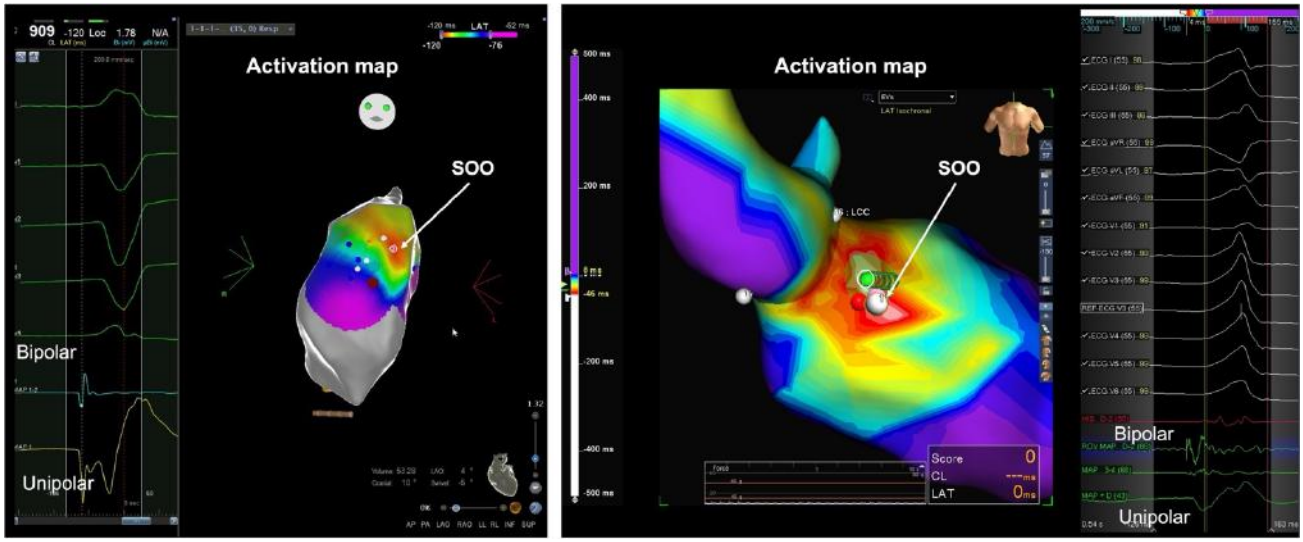

Figure 4 . *3D EAM activation map with respective intracardiac electrograms showing an early activation on the bipolar electrogram and a QS pattern on the unipolar electrogram. The earliest activation site displayed in red with the Carto system (white arrow) (left panel) and white with Ensite system. (right panel). EAM: electroanatomical mapping; SOO: site of origin*

Although this unipolar electrogram configuration is very sensitive for successful ablation sites, it is not specific (70% of unsuccessful ablation sites also manifest a QS complex).[20] The size of the area with a QS complex can be larger than the ventricular arrhythmia SOO, exceeding 1 cm or more in diameter. Concordance of the timing of the onset of the bipolar electrogram with that of the unipolar electrogram, with the rapid downslope of the S wave of the unipolar QS complex coinciding with the initial peak of the bipolar signal, helps ensure that the electrode tip is at the SOO. [21,22]

Standard ablation techniques rely on frequent, spontaneous PVCs. However, despite a high daily PVC burden, intraprocedural PVC burden may be very low, precluding an approach based exclusively on activation map.

Low PVC burden occurs in up to 30% of the procedures[23] and may result from spontaneous variations, [24] autonomic influence, anaesthesia, or sedation. In the presence of low intraprocedural PVC burden, the success may be reduced from 85% to 56%. [23]

In a recent study by Jauregui et al,[25] this number was higher, 43% of the 185 patients referred for catheter ablation, either had the procedure cancelled due to lack of PVCs (11%) or had the procedure done based on pace mapping 32%. In our historical group (see chapter V), 26% of patients did not undergo ablation due to the intraprocedural low PVC burden.[26]

Pace mapping is a mapping technique that consists of pacing by the distal bipole of the ablation catheter to evaluate the morphology of the QRS complex elicited at that specific site, and then, compare it to the morphology of the PVC and assess the matching on the 12-lead ECG. Usually, bipolar pacing is chosen because it results in less artefact interference, but at the expense of capturing a larger area of myocardium, when compared to unipolar pacing and so reducing the accuracy.

It is also used to confirm the results of activation mapping by eliciting a QRS with a perfect match in all 12 leads at the SOO of the arrhythmia (Figure 5).

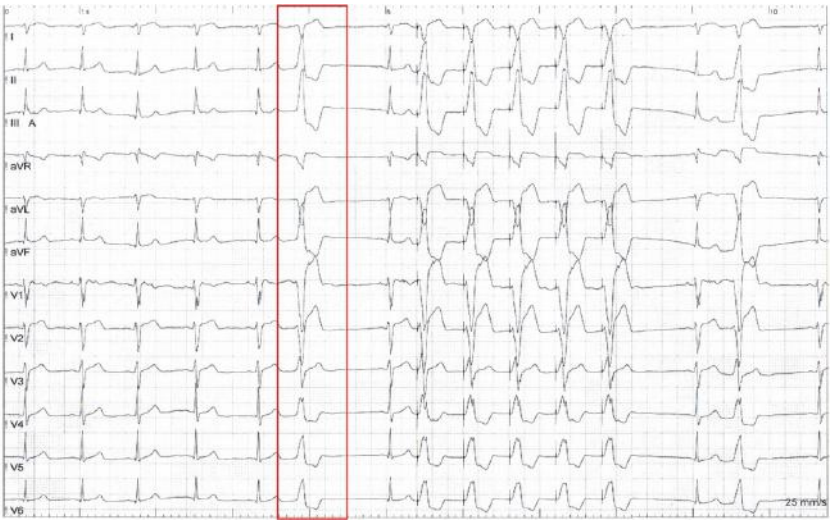

Figure 5. *Pace mapping. PVC morphology inside the red box followed by pacing complexes at the ablation site showing a 12/12 match*

The analysis of the pace matching can be subjective and manually quantified by the electrophysiologist or performed automatically with the use of algorithms available by the current 3D EAM systems (PASO for CARTO (Biosense-Webster, Inc., Diamond Bar, CA, USA) and Score map for EnSite Precision (Abbott, St Paul MN, USA). The software automatically acquires the 12-lead paced QRS morphology and compares it to the reference morphology in order to find the signal set with the highest correlation (100% maximum). A color-coded correlation map is automatically created, which allows viewing the acquired points according to the correlation values of the pace mapping signals associated to the points.

Several studies have used the pace mapping to choose the ablation target site in case of infrequent PVCs .[25,**26**,27-30] However, this technique has many limitations, first of all, it is hampered by the impossibility of capturing the ventricles regardless the stimulus output. When using higher current outputs to achieve capture, a simultaneous capture of remote sites is obtained, potentially decreasing the precision of the pace-map, additionally the morphology of single paced QRS complexes can vary depending on the coupling interval. Secondly, sites with earliest activation time can be spatially distant from sites with the best pace-map due to the presence of abnormal insulated strands of myocardium, which lead to the occurrence of a breakthrough site away from the SOO. [31,32] Another drawback of pace mapping is the presence of an intramural focus with multiple exit points with different QRS morphologies but a common origin. [31, **33**]

The spatial resolution is also worse than that of activation mapping. Azegami et al, [28] reported that multiple best pace-map sites were obtained up to 18 ± 5 mm apart, and Bogun et al [27] (utilizing a 12-point scoring system), reported the spatial resolution of a good pace-map in the RVOT to be 1.8 ± 0.6 cm^2, which is worse than the 1.2 ± 0.7 cm^2 area of the first 10 ms of activation obtained by activation mapping. [27] Using the automatic algorithm PASO for CARTO (Biosense-Webster, Inc., Diamond Bar, CA, USA), or Score map for EnSite Precision (Abbott Medical) Bennet et al [30] found an area with best pace map >90%, of 1.9 ± 1.2 cm^2. [30] Finally, to perform pace map it is essential that at least one clinical PVC is recorded. It is not unusual the total absence of PVC intraprocedural **[34]** and in that case pace mapping is hampered.

When the SOO of the arrhythmia is identified, ablation is accomplished by heating or freezing the tissue in order to destroy the cells. Radiofrequency is the energy of choice, preferably with an irrigated tip catheter with contact-force technology inserted through a long sheath to give stability to the catheter. The power delivery can be used in a power-controlled mode or temperature- controlled mode, with a temperature limit of 43°C, and a flow rate of 20 ml/min. Power delivery should be titrated to a maximum of 50 W for a maximum of 120 s, depending on the ablation site. The contact force should be maintained above 10 g but always under 30 g to avoid perforations and steam pops. [35]

For remote magnetic navigation (RMN), which will be the subject of a section of the current chapter, the contact force technology is not available. **[36,37]** However, since May 2017 the Stereotaxis

Inc. (St. Louis, MO, USA) launched the e-Contact® module which allows a semi-quantitative assessment of the catheter tip-to-tissue contact[38] and should be used to improve ablation results.[37] Early suppression of the PVCs during energy delivery has been suggested as a possible indicator of successful ablation.[39]

The cryoenergy can be the first choice in case of risky locations as for instance para-Hisian PVCs[40,41] with high risk of inadvertent atrioventricular conduction disturbance. This is due to the reversible effects with this energy, in the initial seconds of energy delivery. It is however possible to ablate PVCs from those risky locations using RF, with careful mapping and energy titration, as we have clearly demonstrated in a case of para-LBBB left sided PVCs,[33] and in a case of parahisian PVCs.[42] Cryoenergy may also be helpful in cases where the high impedance precludes RF energy delivery as is the case of ablation within the coronary sinus branches.[43] Other forms of energy are not accepted for PVC ablation yet.

The endpoint of catheter ablation is suppression of PVCs. Successful ablation is defined as the lack of spontaneous or inducible PVCs with and without isoproterenol administration at least 30 minutes after ablation.

Results

The reports on the procedural outcomes of outflow tract PVC ablation in terms of acute success and long-term results have been heterogenous, usually small series, ranging from a 100% success rate[45] to a lower 78% success rate.[46] The results are difficult to compare due to the different definitions of success but also to the difference in the distribution of the SOO of the PVCs.

Wang et al[47] in a retrospective study, of 1231 patients who underwent PVC ablation from January 2010 to December 2016 at a single center, reported an acute success rate of 94%. Those authors referred that the main predictor of acute procedural success was a RVOT origin, while an epicardial origin was a predictor of procedural failure.

The largest scale multicentric study,[48] retrospectively included 1185 patients who underwent catheter ablation for idiopathic PVCs at 8 centers between 2004 and 2013 and reported an acute procedural success in 84% of patients. The highest success rate was achieved in PVCs from the RVOT (93%), and the lowest success rate was in epicardial PVCs (67%).

Our first results of catheter ablation published in 2013 reporting on 32 patients with right and left outflow tract PVCs showed a success rate of 81 % at the first procedure and 88% at the second procedure.[36] In a more recent series of 81 patients that underwent ablation after 2017, using contact-force and catheter-tissue contact technologies, we reported an initial success rate of 88%. [37]

The complication rate is low, around 1%[45] higher in the study by Wang et al,[47] reporting a complication rate of 2.7% including two deaths related to the procedure, one due to coronary artery lesion, and the other due to endocarditis.

However, in the majority of series complications are minor, and usually related to vascular access. In the series by Latchamsetty et al[48], the complication rate was 5.2% (2.4% major complications and 2.8% minor complications), but there were no procedure related deaths or stroke. In our first study we reported 0% complication rate and in the second one 1% corresponding to a patient that developed pericarditis that responded to medical therapy.

Three comparison trials have shown the superiority of catheter ablation versus no therapy or medical therapy. The first one by Bogun et al[49] in 60 consecutive patients with frequent idiopathic PVCs and reduced LV ejection fraction that underwent catheter ablation with a success rate of 80%. In patients that underwent a successful ablation the left ventricular disfunction improved in comparison to 11 patients that did not undergo ablation and the one that that had an unsuccessful procedure.

A retrospective non-randomized study performed by Zhong et al[50] in 510 patients, 215 (40%) underwent catheter ablation and 295 (60%) received antiarrhythmic drugs. The reduction in PVC frequency was greater after catheter ablation than with antiarrhythmic drugs and the left ventricular ejection fraction increased significantly after catheter ablation, but not after antiarrhythmic drugs.

The first randomized trial was performed by the group of Ling et al[51] that prospectively studied 330 patients with idiopathic PVCs from the RVOT and randomized the patients to catheter ablation or antiarrhythmic drugs. The endpoint of the study was the 1-year recurrence of PVCs. Of 165 patients assigned to antiarrhythmic drugs, 50 patients received metoprolol, and 115 patients received propafenone. The primary end point was reached in 32 patients assigned to catheter ablation and in 146 patients assigned to antiarrhythmic drugs. Catheter ablation demonstrated a significant reduction of the PVC recurrence in comparison to antiarrhythmic drugs, $p<0.0001$.

The development of contact-force technologies in recent years by continuously monitoring the contact force between the catheter tip and the tissues, would be expected to improve the efficacy of catheter ablation by an increase of the lesion size, which is proportional to the force applied[52,53] and at the same time decreasing complications resultant from excessive force applied to the heart. Nonetheless, studies comparing manual ablation with and without CF have shown contradictory results.[54-55]

Results in patients with low intraprocedural PVC burden

The results of catheter ablation in patients with intraprocedural low PVC burden are worse than the general reported ones. Baser et al,[23] studied a series of 194 patients with frequent idiopathic PVCs referred for catheter ablation. Patients were divided in two groups according to the intraprocedural burden. The success of ablation decreased from 85% in patients with high intraprocedural PVC burden to 56% in patients with low intraprocedural burden, p=0.0001. Low PVC burden was defined as less than 32 PVCs within the first 30 minutes of the procedure and occurred in 30% of the procedures.

That percentage was higher in a recent study by Jauregui et al[25] that found an intraprocedural low PVC burden in 43% of the patients referred for catheter ablation of frequent PVCs. The approach in patients with low intraprocedural burden ranges from cancelation of the procedure as occurred in 11% of the patients of the above-mentioned study, to ablation based in pace mapping, [25, 29,30] or substrate mapping associated with pace mapping.[**26**, 57,58]

Jauregui et al,[25] reported a success rate of 87%, Shirai et al,[29] of 79%, and Bennet et al, [30] 77%, using just the pace mapping methodology in patients with PVCs from the RVOT and the LVOT.

With a substrate plus pace mapping approach, Letsas et al, [57] reported a 78% success rate, Wang et al,[58] 93% in patients with only RVOT PVCs, and Parreira et al,[**26**] 90% for RVOT and LVOT PVCs (see chapter V).

Improved QOL after ablation

Studies evaluating the improvement in the quality of life (QOL) after PVC ablation are scarce. [59,60] The first one by Huang et al [59] evaluated 58 patients with symptomatic PVCs that were refractory to medication and underwent ablation. The QOL was assessed at 3 months and at one year after ablation. Ablation was successful in 56 patients, and this resulted in a significant improvement in the QoL at 3 and 12 months after the procedure. The second study included patients with PVCs and ventricular tachycardia and the authors observed comparable improvement of QOL in patients with PVCs and ventricular tachycardia, implying that this fact is an additional argument for performing ablation in symptomatic patients with PVCs.[60]

Remote magnetic navigation

Robotization in Medicine is being developed with the aim of improving the precision of the procedures, allowing to achieve goals inaccessible with the human hand and/or contributing to greater comfort on the part of the operator. Robotization has been demonstrating enormous success in several areas, namely in the surgical field, allowing to carry out more complicated and

precise surgeries than those performed manually and contributing to the development of the so-called mini-invasive surgical techniques.

The development of remote magnetic navigation, by using remote control allows the procedure to be carried out from a control room out of reach of fluoroscopy, makes the more complicated and prolonged procedures less physically demanding for the operator. Specifically, RMN, has the additional advantage of a better precision, and greater safety for the patient (Figure 6).

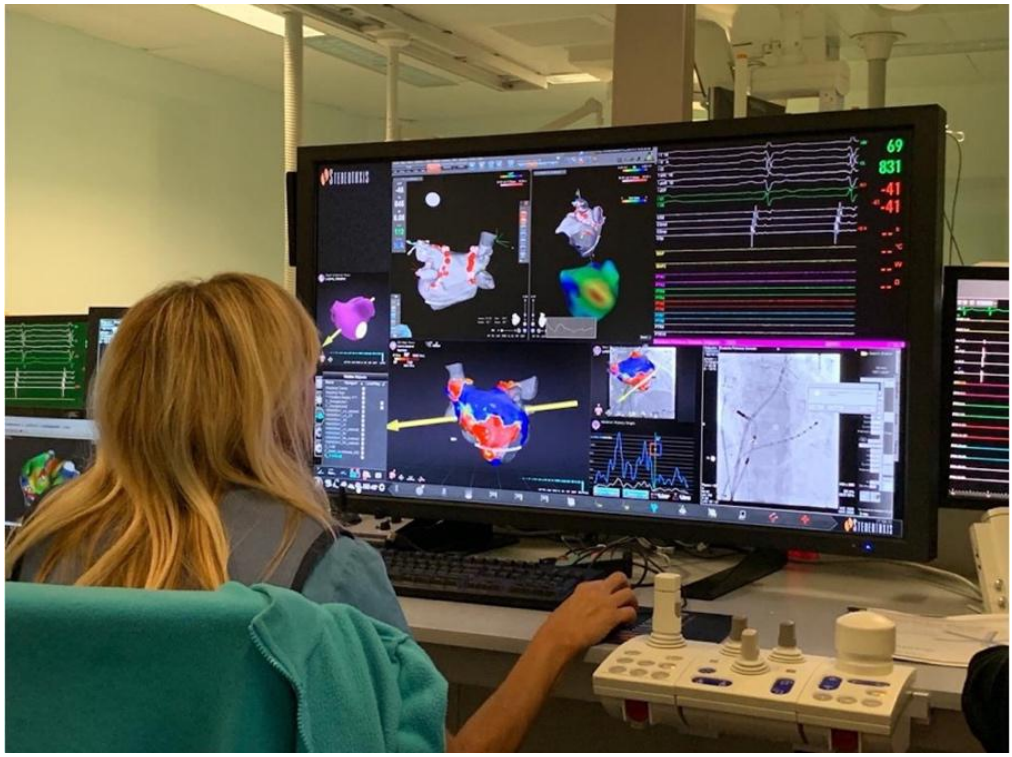

Figure 6. *Control room outside the operating room where remotely the ablation catheter can be manipulated with the computer mouse.*

This system consists of 2 large magnets, positioned on both sides of the fluoroscopy table. The magnets generate a magnetic field (0.1T), very weak compared to that used in diagnostic CMR, allowing its use in patients with implantable devices.[61]

The direction of the magnetic field varies with the relative position of both magnets on the patient's table, which in turn is controlled remotely in the control room (Figure 6).

The ablation catheters used with this system, unlike conventional rigid catheters, are extremely floppy, they have 3 small magnets at the tip, that will align themselves in parallel with the magnetic field created. The catheter is handled in from the control room away from the

fluoroscopy, Changes in the orientation of the magnetic field leads to the deflection of the catheter tip, which is advanced or withdrawn with the aid of a motor connected to the proximal end of the catheter, also remotely performed from the control room.

All the information including intracavitary electrograms, electrocardiographic monitoring, fluoroscopy, electroanatomical mapping, ECGI, CT scan, intracardiac ultrasound and the Stereotaxis screen is displayed on a single giant screen, that allows integration of all the information on a single monitor. (Figure 7)

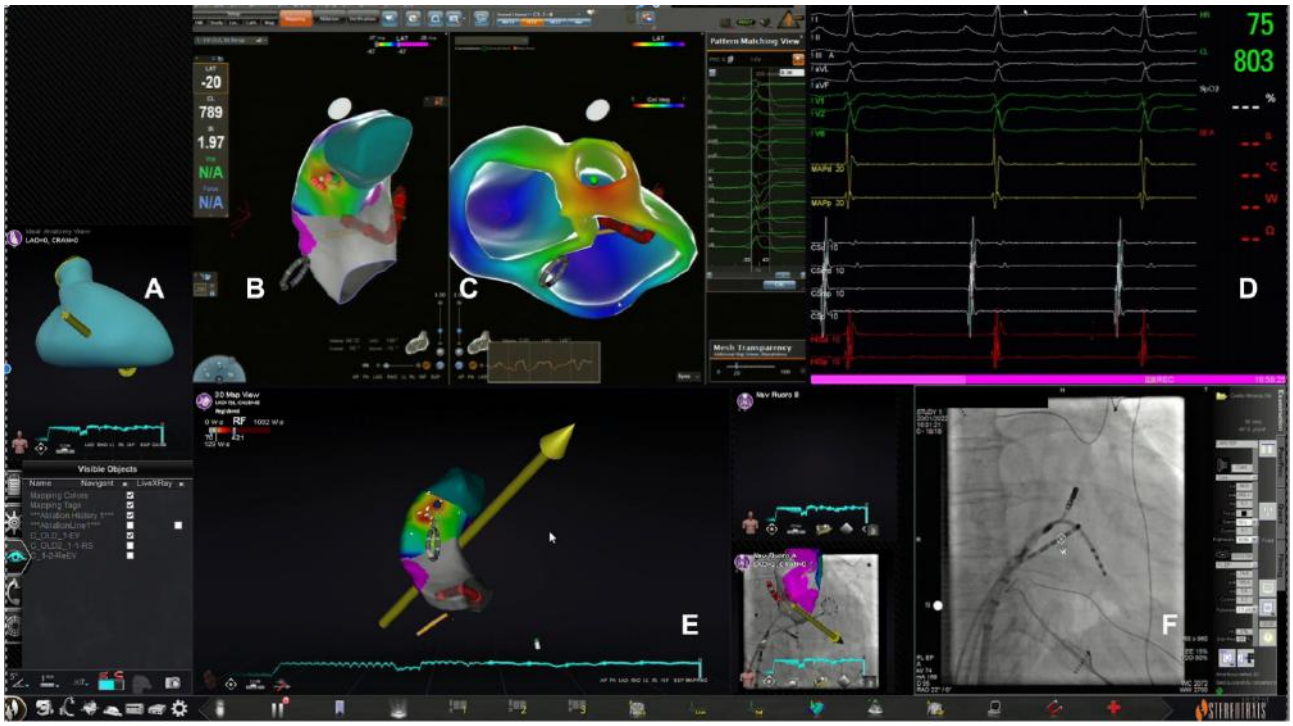

Figure 7. *RMN workstation screen (Odissey) displaying simultaneously the different screens during the procedure.* ***Panel A****: mapped cardiac chamber (RVOT);* ***Panel B****: Carto EAM map;* ***Panel C****: ECGI with the VIVO system;* ***Panel D****: intracardiac electrograms during ablation;* ***Panel E****: RMN screen, showing the yellow arrow that commands the direction of the ablation catheter and the ablation catheter displaying an optimal contact starburst:* ***Panel F****: Fluoroscopy screen with overlaid EAM. EAM: Electroanatomical map; RMN: remote magnetic navigation; RVOT: right ventricular outflow tract.*

Because the catheter navigation is performed remotely, one of the main advantages of the RMN is the reduction of the radiation dose for the operator as we have demonstrated for PVC ablation,[37] AV node reentrant tachycardias,[62] typical atrial flutter,[63] and atrial fibrillation,[64] making the system ideal for prolonged procedures.

In addition, due to the enormous flexibility of the catheter and safety profile, there is a tendency to use less control fluoroscopy, which results in a lower radiation dose to the patient as well.[37,61-64]

This system is characterized by the high stability of the catheter tip, leading to a similar lesion size when compared to conventional ablation, although with less force applied to the tissue.[65] Many studies have demonstrated the efficacy of RMN in the ablation of all types of arrhythmias with a better safety profile than conventional ablation. [37,62,63,64,66,67]

Conventional manual catheter manipulation during mapping in the outflow tracts is not devoid of risks. On one hand the risk of mechanical trauma and even perforation at the level of the thin-walled RVOT, which is reported in 1-5% of cases,[68,69] coronary artery injury in the LVOT,[47] or episodically in the RVOT.[70] On the other hand, the manipulation of catheter can abolish the arrythmia by mechanical trauma or induce PVCs with a very similar morphology. The intracardiac electrogram at that site during those catheter-induced PVCs, will display optimal precocity and a QS pattern on the unipolar recording which can lead to inappropriate assessment of the SOO. RMN presents as an excellent option when catheter manipulation should be smooth to prevent PVCs induced by the catheter, an event so frequent at the level of the outflow tracts. [36,71]

One of the concerns regarding RNM was the unavailability of contact force catheters, but since May 2017 the Stereotaxis Inc. (St. Louis, MO, USA) launched the e-Contact® module which allows a semi-quantitative assessment of the catheter tip-to-tissue contact. [44]

The use of catheter tip-to-tissue contact has allowed an improvement in the results of catheter ablation of idiopathic PVCs as demonstrated in our study[37] in 81 patients comparing 45 that underwent ablation with RMN, 18 patients with manual catheters without contact force technology and 18 patients with contact force catheters. Global success rate was 88% not significantly different between groups. The success rate with RMN was 89% with a significantly lower fluoroscopy time than manual ablation. The success rate using the catheter tip-to-tissue contact technology led to an increase in the acute success rate in the first procedure from 81% to 89%. [36,37]

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Electrocardiographic Imaging (ECGI) for the localization of premature ventricular contractions

Electrocardiographic imaging (ECGI) is a non-invasive electrophysiology imaging tool that displays the reconstruction of epicardial and endocardial potentials, obtained from electrocardiographic body-surface potentials and projects them onto a patient's specific geometry derived form a CT scan or a CMR.

Mathematically, ECGI solves the inverse problem of electrocardiography, meaning it determines the cardiac electrical source for a given body-surface potential distribution. [1-5] This is an ill- posed problem due the fact that a multitude of morphologies of cardiac electrical activity can produce identical body-surface potentials.

Three cardiac sources have been used for the ECGI: transmembrane voltage-based model, extracellular potential-based model, and the activation/recovery-based models. [2,6-8]

There are currently three commercially available ECGI systems, the AMYCARD (EP Solutions SA, Switzerland), the "View into Ventricular Onset" VIVO (Catheter Precision, NJ USA) and the ECVUE (CardioInsight, Cleveland, OH, United States). The cardiac source is different according to the system.

The Amycard and the ECVUE use the extracellular potential-based model and they provide directly the cardiac unipolar electrograms and the isopotential map. These two systems by means of post processing are able to further deliver data regarding the activation and recovery processes. [2,6]

The activation/recovery-time based models provide local times of activation or recovery directly, without reconstruction of extracellular potentials as precursors. The VIVO system uses the equivalent double layer (EDL) model which is and activation time source. [6,8]

The accuracy of the ECGI is highly influenced by the preprocessing e.g., techniques that filter or average the recorded body-surface potentials (Figure 8) or improve the geometrical accuracy, and methods to deal with poor quality signals, [9] and postprocessing algorithms that are used to extract features that are not directly available from inverse solutions, like the calculation of activation time or the recovery time from a reconstructed electrogram, or the use of phase mapping for rotor detection.[6]

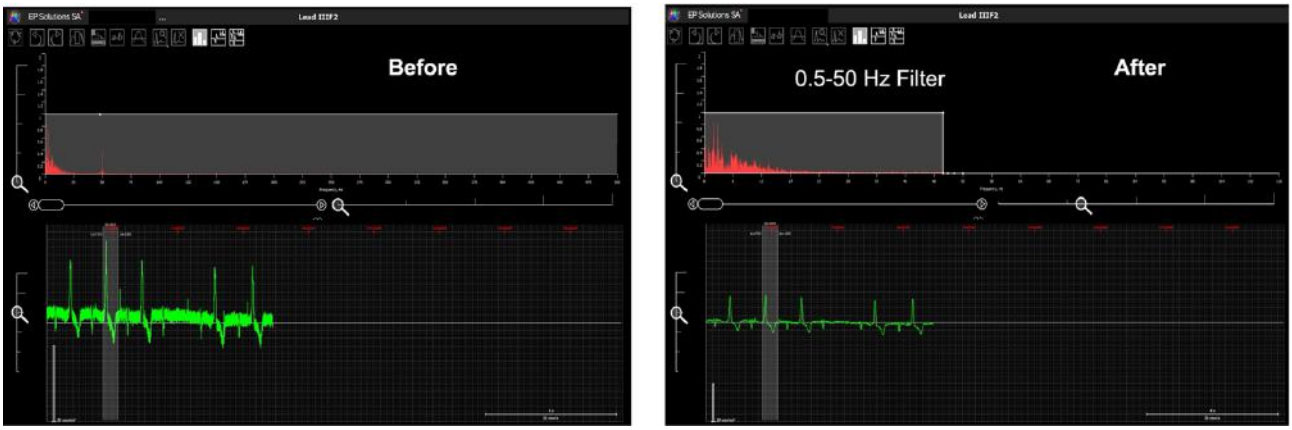

Figure 8. *Body-surface electrograms without additional filtering (left panel) and after a 0.5-50 Hz filter (right panel)*

The unipolar reconstructed electrograms directly obtained by the analysis of the body surface mapping using the inverse problem solution are displayed in the isopotential map, the unipolar electrogram can then be transformed in bipolar electrogram by post processing and an isochronal map can be obtained.

Finally, some advanced options like the assessment of the activation time (AT), calculated as the time of the steepest downslope of the unipolar electrogram, or the recovery time (RT) as the time instant of maximal dV/dt of the T wave on cardiac unipolar electrograms, the latter closely corresponding to the instant of local ventricular recovery independently of T wave morphology. Or the time interval between the RT and the AT known as activation recovery interval (ARI) a surrogate of action potential duration (Figure 9).

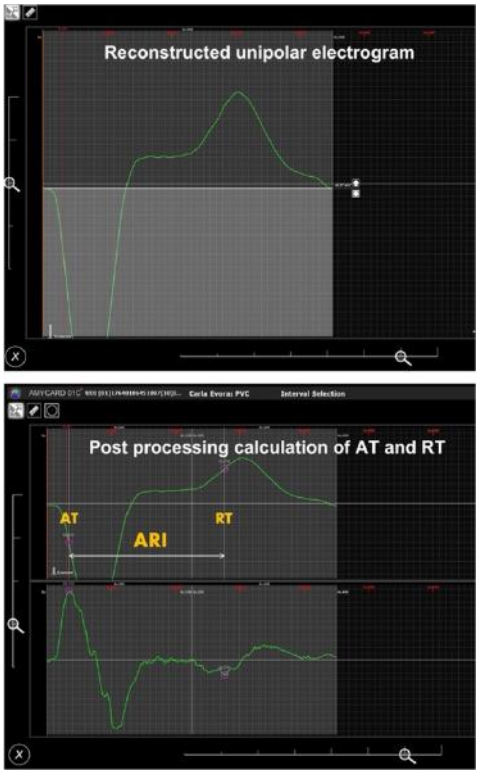

Figure 9. *Reconstructed unipolar electrogram obtained directly with the FND mode displaying a good QS pattern (upper panel). Advanced mode to automatically evaluate the AT, RT, and AR (bottom panel) FND: first negative deflection; AT: activation time; RT: recovery time; ARI: activation recovery interval*

It is important to choose the correct method for a specific problem (Figure 10).

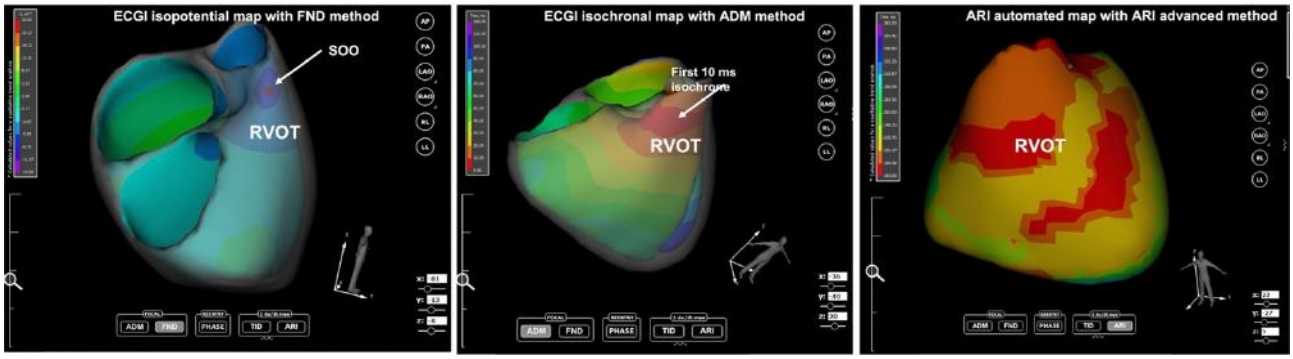

Figure 10. *Different maps available with the Amycard system, from left to right: isopotential map, isochronal map, and ARI map.*

For instance, the analysis of the first negative deflection (FND) in the unipolar electrogram is more accurate to identify the SOO of the PVCs with the Amycard System.[10] But to assess the propagation speed across the RVOT by means of the isochronal map, the activation direction method (ADM) by analyzing the bipolar local electrogram is more accurate.[11] Finally, to assess abnormal gradients of repolarization, the advanced modes should be chosen. This mode automatically measures the AT or the RT and automatically displays the color-coded ARI map.[12]

Importantly, many potential-based implementations of ECGI only provide epicardial reconstructions, like the ECVUE system as opposed to others like the Amycard system, that provide both epicardial and endocardial reconstructions.

There have been some concerns regarding the accuracy of the electrograms obtained with the ECGI, at least with the epicardial ECGI system.[13] Recently, Bear et al.[14] performed a validation study in five anesthetized, closed chest pigs, comparing the reconstructed epicardial unipolar electrograms obtained from the ECGI with the electrograms directly recorded from the epicardium. The authors concluded that the ECGI provides qualitative information on the origin and spread of epicardial activation, but resolution was poorer than previously thought.

Cluitmans et al,[15] also performed a validation study in four anesthetized closed-chest dogs assessing both the depolarization and the repolarization. The authors found a better accuracy of reconstructed activation times than of recovery times and pointed out the improvement obtained by incorporating the local spatiotemporal characteristics of the reconstructed electrograms.

Still, several studies in humans have validated the ECGI system for depolarization and repolarization in different diseases.[16-19]

One of the criticisms of the methods based on the extracellular potential source like the Amycard and ECVUE systems, is the large number of torso electrodes needed to obtain the noninvasive reconstruction [20] (Figure 11).

According to those authors, that requirement is responsible for an increase in ablation costs and work burden, precluding its widespread utilization. Another limitation of the method that is also pointed out, is its interference with the placement of the electroanatomical mapping system's patches and external defibrillator patches.[6]

The concept of ECGI is built upon mathematical equations aimed at solving the inverse problem of the electrocardiogram.[1,3] The inverse problem is ill-posed as previously mentioned, as a result, small errors in the ECGI acquisition and processing, like noise, geometry errors, inaccurate conductivity values can produce infinite errors in the solution.[2] This fact is one of the reasons for the requirement of such a high number of torso leads, a drawback of the ECGI for requiring a high number of chest electrodes or even a vest to achieve the results.

In an attempt to prove that the number of torso leads needed to obtain a good accuracy, may not be so high, we performed a study to evaluate the minimal number of torso leads needed to accurately identify the location of atrial and ventricular arrhythmias using the Amycard System.[21] We studied 20 patients that underwent ablation of PVCs and PACs with the 3D EAM system and had an ECGI performed with AMYCARD system before ablation. We evaluated the agreement regarding the SOO of the arrhythmia between the ECGI and the 3D EAM system, first with the normal number of torso leads and progressively reducing the number to half, and finally one third of the initial number. The first map was obtained with 23 (22-23) electrode bands, corresponding to 143 (130-170) leads per patient and agreement rate was 85%. With half the number of electrode bands including 73 (60-79) leads, agreement rate was still 80%, however, with further reduction to one third the accuracy was substantially reduced to 55%. According to the ROC curve, the minimal number of leads was 74 (AUC 0.981; 95% CI: 0.949–1.00, $p < .0001$). So, we concluded that the number of leads needed to achieve a good spatial resolution was less than the maximal 224 leads available.

The activation time-based VIVO system, overcomes this limitation by using a simple 12-lead ECG to obtain the non-invasive activation map.[8,20,22,]

We have experience with two of these ECGI systems, the Amycard (EP Solutions SA, Switzerland), and the VIVO (Catheter Precision, NJ USA).

The methodology of both systems is different and described elsewhere[8,20,22,23] but briefly, Amycard consists of a multichannel ECG amplifier recorder that analyses up to 224 leads from up to 28 electrode bands, with 8 leads each, placed on the patient's torso (Figure 11).

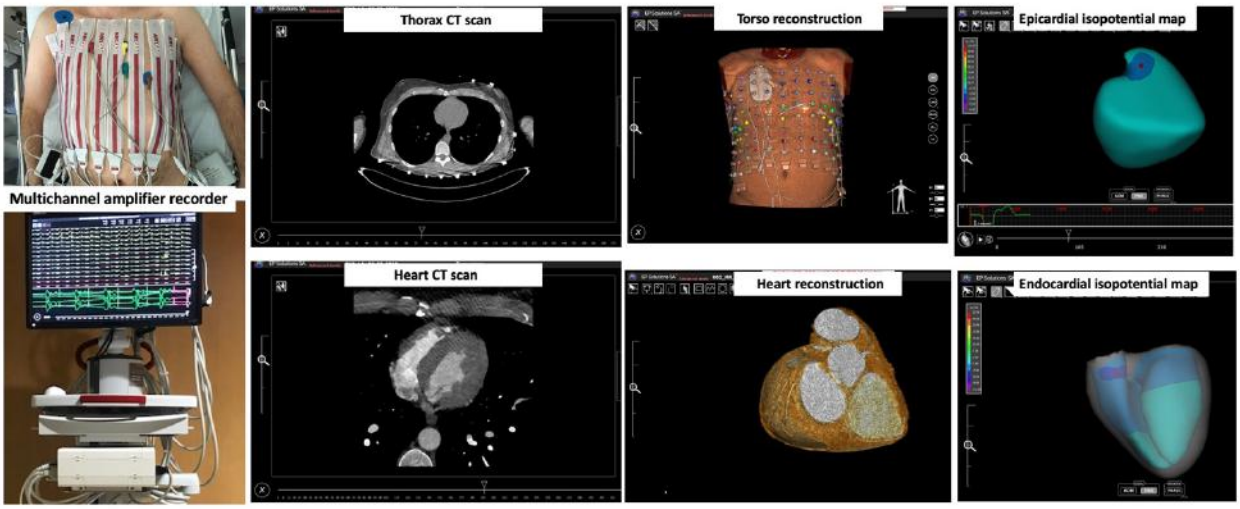

Figure 11. *Amycard system methodology from left to right. Torso leads connected to a multichannel amplifier recorder. Thorax and heart CT scan. Reconstruction of the patient's torso and heart geometry and epicardial and endocardial activation map displaying the earliest activated point (red dot)*

They are recorded with a 0.05- to 500-Hz bandpass filter, digitized with the sampling rate of 1000 samples/s and exported to the Amycard 01C software. Additionally, a 50 Hz frequency noise filter is used. Afterwards, with the electrode bands in place, an ECG-gated CT scanning of the heart and thorax with intravenous contrast, is performed with a third generation 192-slice dual-source SOMATOM Force (Siemens Healthcare). The CT data is imported in the DICOM format into the Amycard 01C software, and a 3D torso and heart model obtained from the CT scan. Body surface ECG data is processed by Amycard system, using its inverse problem solution software[24] in combination with the heart and torso anatomy, allowing for reconstruction of unipolar electrograms at approximately 2500 points on epicardium and endocardium.

The VIVO is an ECGI system that uses a patient specific myocardial model from MRI or CT, a 3D photo to define ECG electrode position, and the 12-lead ECG to localize the origin of the ventricular arrhythmias. VIVO uses semi-automated morphing of a reference model to generate the patient's specific model of the heart and torso. This 3D heart model is used to determine the simulated activation sequences originating from discrete nodes in the heart.[20] Traditionally, ECGI systems match the measured ECG on the thorax with the simulated myocardial potentials. VIVO, in turn, by means of an its inverse solution matches the measured real vectorcardiogram with the simulated vectorcardiogram, so that the origin of the arrhythmia is the ventricular node for which the angle between both initial vectors (anatomic vectorcardiogram and measured vectorcardiogram) is minimal.

The strength of the VIVO system is its simplicity, in comparison with the Amycard system which uses a high number of torso leads (Figure 12).

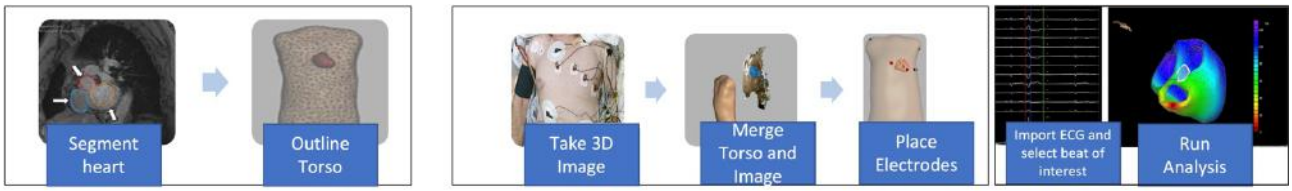

Figure 12. *VIVO system methodology from left to right. Segmentation of the heart and torso. 12-lead ECG and 3D picture of the patient's torso. Merge of the patient's torso with the model. Importation of the ECG and selection of the beat of interest. After analysis, a direct display of the activation map showing the earliest activation in red (red dot)*

Our experience with the VIVO system is less extensive than with Amycard system. On the other hand, since the cardiac model is cut at the valvular level, the acquisition of atrial activation data currently is not possible with this system in comparison with the Amycard. But regarding the accuracy of the system for assessment of PVC origin the results are good.[20]

We presented the first results with the system this year at the EHRA Congress.[25] We studied 11 consecutive patients referred for PVC ablation that had an ECGI performed using both the AMYCARD and the VIVO system. The localization of the PVCs based on the ECGI was done using a segmental model with 22 segments on the left ventricle, and 12 segments on the right ventricle. A near match was defined as a predicted location within the same segment or a contiguous one. Seven patients underwent ablation and in 4 ablation was pending. In patients that underwent ablation the systems localized the site of origin of the PVCs within the same segment or the contiguous segment in all patients with VIVO and in six out of seven (85%) with AMYCARD. We found a near match between both systems in 91% of cases.

We are now including patients in the VIVO European registry.

ECGI and premature ventricular contractions

Several studies have evaluated the ability of the ECGI to accurately identify the origin of PVCs and of ventricular arrhythmias in general.

The first report was made by Intini et al in 2005,[26] of an athlete with focal ventricular tachycardia originating from a left ventricular diverticulum. A reconstructed map of the epicardial activation sequence during a single PVC with an identical QRS morphology to the clinical VT, obtained with the ECGI, localized the PVC to the site of the diverticulum and was coherent with the invasive 3D EAM.

Later, Wang et al,[27] studied 26 ventricular arrhythmias in 25 patients, including sustained ventricular tachycardia, NSVT, or isolated PVCs. The ECGI correctly identified the right or left ventricular location of the arrhythmia in 100 % of studies. When the specific locations within each ventricle were compared, non-invasive ECGI was in agreement with the invasive 3D EAM in 10 out of 11 right ventricular sites (91 %) and in 11 out of 12 left ventricular sites (92 %).

Jamil-Copley et al,[28] studied with ECGI 24 patients with PVCs from the outflow tracts and reported that ECGI could predict the chamber of origin in 96% of the participants (23 of 24) and was 100% accurate at predicting localization regions within the specified chamber.

Using the Amycard system (EP Solutions SA, Yverdon-les-Bains, Switzerland), Wissner et al,[29] studied 20 patients with 21 PVCs or ventricular tachycardia, and the chamber of interest was correctly diagnosed with the ECGI in 20 of 21 patients (95%). In 18 of the 21 (86%) cases, the correct ventricular segment was also diagnosed.

Until now, only one randomized controlled trial has evaluated the accuracy of ECGI to identify the SOO of the PVCs in comparison with standard ECG. Erkapic et al,[30] enrolled 42 patients, randomized in a 1:1 rate to preablation ECGI or 12-lead ECG. The authors reported a 95.2% accuracy in identifying both the chamber and origin of the ventricular arrhythmia for the ECGI in comparison with 38% for the 12-lead ECG.[30]

More recently using the VIVO system (Catheter Precision, NJ USA), Misra et al,[20] in 20 patients with 22 morphologies of PVC or ventricular tachycardia were able to accurately predict the location of the ventricular arrhythmia in 11/13 (85%) of the PVC cases and 8/9 (90%) of the ventricular tachycardia cases.

Reproducibility and comparison between methods

Regarding the ventricular activation, both systems present very coherent results in identifying SOO of the ventricular arrhythmias. To the best of our knowledge, we were the first group reporting the agreement between VIVO and AMYCARD systems**[25]**.

More recently, we studied a series of 61 ECGI procedures performed in 48 patients referred for ablation of frequent idiopathic PVCs at our center. The Amycard system was used in 26 patients, the VIVO in 9, and both systems in 13 patients. 42 patients underwent ablation, successful in 76%. The Amycard identified the SOO in the same or contiguous segment of the invasive 3D EAM in 97% of cases and the VIVO in 100%., and the agreement between both systems was 100% in terms of the same segment or the contiguous segment as well. These results were submitted to the AHA Sessions 2022. **[31]**

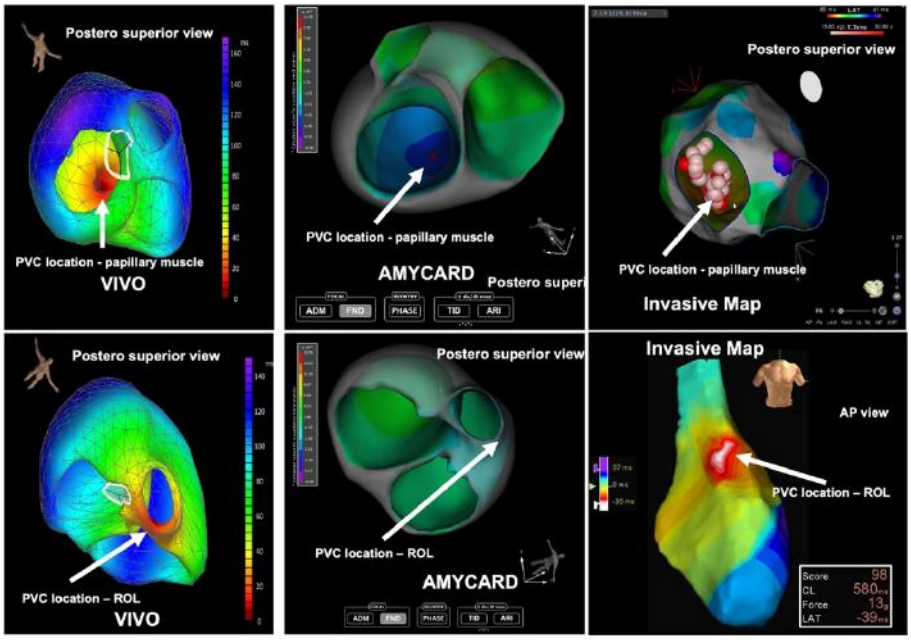

***Figure 13**. A patient with PVCs from the papillary muscle (upper panels), from left to right VIVO, Amycard and invasive map. Patient with PVCs from ROL (bottom panels), from left to right VIVO, Amycard and invasive map. ROL: RVOT lateral; RVOT: right ventricular outflow tract*

ECGI for predicting cardiac resynchronization results

The ECGI has also been used to improve the response to cardiac resynchronization therapy (CRT).[33-34] We participated in a multicentric study the MAP-CRT, to evaluate if the distance between the latest activated area of the left ventricle and the pacing site of the coronary sinus lead could be a predictor of response to CRT. The results are now being submitted but the preliminary results send for the European Congress of Cardiology 2022 as Late Breaking Trial[35] have shown that the distance between the latest electrical activated site and pacing site at left ventricle identified with ECGI correlated strongly with CRT outcome.

Understanding of disease mechanisms

ECGI is a valuable tool to help define the underlying electrophysiological mechanisms of certain cardiac arrhythmias. Understanding normal cardiac excitation provides a necessary baseline for understanding abnormal cardiac electrical activity and rhythm disorders of the heart.

ECGI has been used to study the arrhythmic substrate of innumerous hereditary arrhythmic syndromes as well as the electrophysiological characteristics of the arrhythmic substrate in structural heart disease.[36,37]

Cuculich et al,[36] studied 24 subjects with infarct-related myocardial scar and concluded that ECGI accurately identifies areas of anatomic scar, that are characterized by low voltage, fragmented and late potentials.

Zhang et al,[37] later confirmed these previous findings by studying the substrate of ventricular scar after myocardial infarction and its relation to ventricular tachycardia, and observed that abnormal electrogram amplitude, scar burden and presence of fractionated electrograms within the scar, were able to predict the occurrence of ventricular tachycardia and the authors proposed the ECGI, as a tool for sudden death stratification.

ECGI has also been used to assess the depolarization and repolarization.

In Brugada syndrome the ECGI was able to demonstrate the presence of depolarization and repolarization abnormalities, such as the presence of slow discontinuous conduction and steep dispersion of repolarization in the RVOT.[38,39]

Early repolarization is a common electrocardiographic finding and considered a benign entity, until the reports of its association with sudden death.[40] Reports of invasive catheter mapping in patients with early repolarization provide limited information about the abnormal electrophysiological substrate.[40] However, using ECGI Zhang et al,[41] characterized the epicardial electrophysiological substrate in patients with early repolarization, identifying steep repolarization gradients caused by localized shortening of action potential duration, but no conduction abnormalities.

Presence of repolarization abnormalities were also described in patients with ARVC by Andrews et al.[42] ARVC patients had longer ventricular activation duration and prolonged mean epicardial ARI, and regions of nonuniform conduction and fractionated electrograms that were present in the early concealed phase of ARVC.

The long QT syndrome (LQTS) is an inherited channelopathy associated with the occurrence of a special form of polymorphic ventricular tachycardia, the Torsade de Pointes and sudden death. Using the ECGI Vijayakumarit et al,[43] demonstrated that LQTS patients display regions with steep repolarization dispersion caused by localized action potential duration prolongation. According to the authors, this defines a substrate for reentrant arrhythmias, not detectable by surface ECG and the presence of steeper dispersion in symptomatic patients suggests a possible role for ECGI in risk stratification.

We also used the ECGI to study the electrophysiological substrate in patients with idiopathic PVCs from the outflow tracts which will be the subject of the next chapter.[11,12]

Clinical (and socioeconomic) validation

By non-invasively localizing the arrhythmogenic site or at least providing a hint to the region of interest prior to the ablation procedure, ECGI can provide a useful guide to improve the planning of the procedure and thus reduce procedure times as reported by Erkapic et al.[30]

ECGI is capable of recording and displaying global electrical activation of any single beat and, unlike invasive contact 3D EAM systems, does not require accumulating data from many beats. This feature is particularly useful in patients with infrequent, non-sustained, not tolerated, or multiple ventricular arrhythmias (Figure 14).

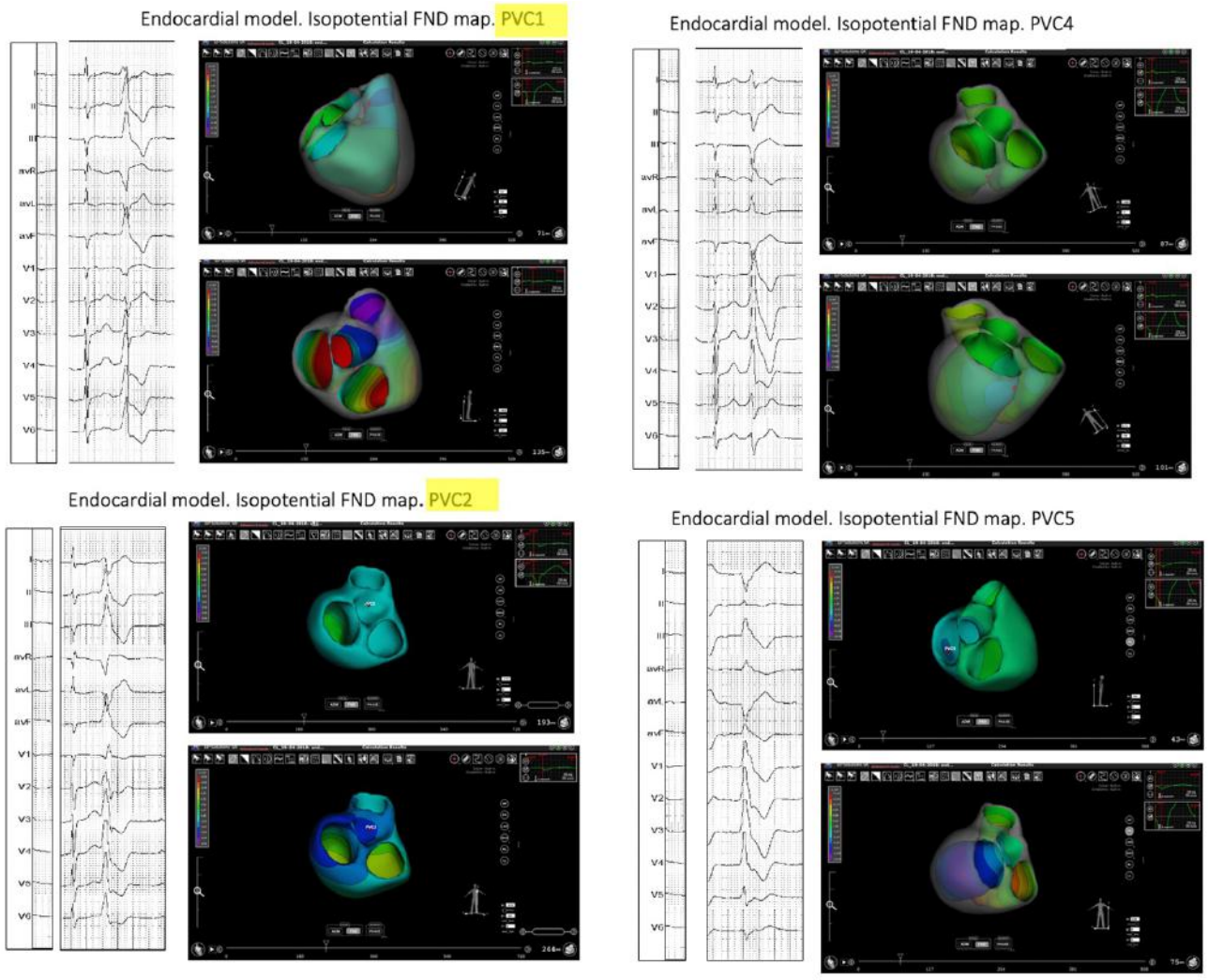

Figure 14. *Patient with multifocal PVCs. More frequent morphologies PVC 1 and 2 (yellow), (left panels). ECGI isopotential maps with the FND method of the multiple morphologies displaying the SOO of the PVC (red dot). FND: first negative deflection; PVC: premature ventricular contraction; SOO: site of origin*

We published a case of a highly symptomatic patient with a high daily PVC burden and runs of NSVT on Holter monitoring, that during the ablation procedure had total absence of PVCs. Luckily, the patient had performed an ECGI with the Amycard system in the week before ablation,

that showed the origin of the arrhythmia at the RVOT posterior wall. So, ablation was successfully performed completely based on the results of the ECGI.[44] (Figure 15).

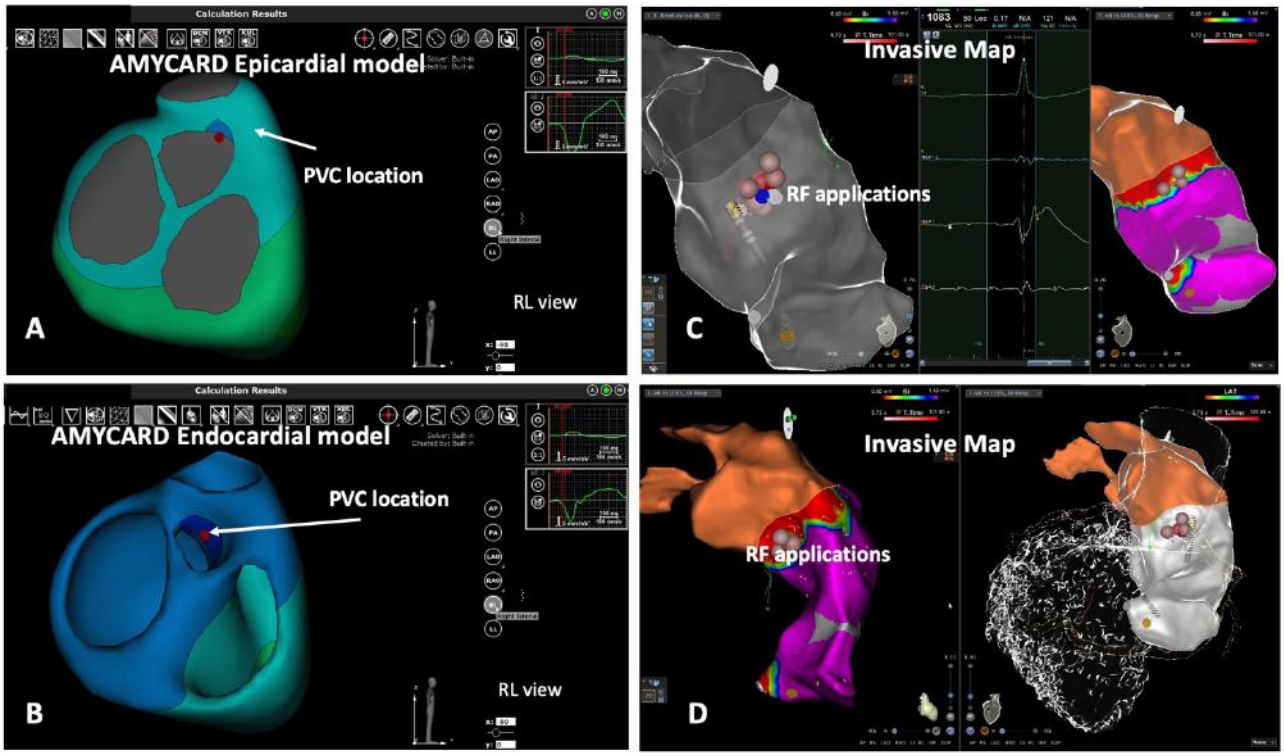

Figure 15. Patient with frequent PVCs from RVOT. Ablation performed based on the ECGI (panel A and B). Invasive map with RF applications (panel C) (pink dots). In transparency overlaid left ventricle and aorta (panel D)

The full adoption of ECGI as a clinical tool, instead of an investigational method, must be based on studies that clearly demonstrate its benefit on the outcomes. The benefit may be evaluated in terms of better success rate, procedure related parameters like reduction of procedure time or fluoroscopy time. This kind of studies are scarce, so far, the only randomized study that demonstrated a reduction of procedural time, and radiofrequency time with the use of ECGI was performed by Erkapic e al.[30] Thus, head-to-head studies comparing efficacy with and without ECGI, along with cost effectiveness studies must be performed.

However, there is a still a long way to definitely establish the ECGI as a clinical tool for catheter ablation, and the simplification of the method is certainly a useful path. There are very few studies evaluating the clinical benefit of the ECGI and even less evaluating the cost benefit ratio.

We are now participating in the European VIVO registry that aims at evaluating the added value of the ECGI for the PVC ablation planning and results.

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Substrate Analysis

Mechanism

We should keep in mind that most of the investigational work regarding the mechanisms of arrhythmias have been performed in small mammals like murine, or bigger ones like dogs, sheep, or pigs. As much resemblance the animal may have with the human heart, the differences still exist, and they are even bigger when small animals are considered.

Two major mechanisms have been implicated in the genesis of cardiac arrhythmias, abnormal impulse formation (*Focal activity*), and abnormal impulse conduction (*Reentry*).

In the absence of structural heart disease ventricular arrhythmias are believed to be due either to abnormal automaticity or triggered activity although, some idiopathic left ventricular idiopathic fascicular VT are due to macroreentry within the His-Purkinje system.[1]

Abnormal impulse formation might be due to enhanced automaticity or triggered activity. The normal myocardial cells both atrial and ventricular, under normal conditions, do not have the capacity to spontaneously, initiate a cardiac impulse. However, under some conditions this may occur, like in cases of elevated extracellular potassium, low intracellular pH, and catecholamine excess. These factors increase the diastolic potential of the myocyte, which becomes closer to the diastolic threshold of depolarization, examples of this mechanism may be ectopic beats.[2]

The triggered mechanism occurs due to oscillations on the membrane voltage after a previous action potential called after depolarizations. They can occur during the phase 2 or 3 of the myocyte action potential and are called early after depolarizations (EADs) or during the phase 4, the delayed after depolarizations (DADs). These oscillations are caused by a variety of conditions that raise the diastolic intracellular Ca2+ concentration, which cause Ca2+ mediated oscillations that can trigger a new action potential if they reach the stimulation threshold.[3] It is generally accepted that the outflow tract ventricular tachycardia is caused by cAMP-mediated DADs and triggered activity.[4-6] The termination of the RVOT tachycardia in response to adenosine and to non-dihydropyridine calcium-channel blockers,[7] along with its inducibility by rapid atrial/ventricular pacing or isoprenaline infusion, have been the clinical milestones for this theory.

Other ventricular tachycardias that are thought to be due to triggered activity are the catecholaminergic polymorphic ventricular tachycardia and the ventricular tachycardia due to digitalis toxicity. The former is due to a mutation in the calcium ryanodine receptor gene (RyR2) or in the cardiac calsequestrin isoform 2 encoding gene (CASQ2) that leads to a cytosolic Ca2+ overload and DADs. [3] An inhibition of the Na+/K+-ATPase mediates the triggered activity due to digitalis toxicity.[8]

Unlike these last two entities, in which the mechanism of the DADs is well known, in the RVOT tachycardia the precise mechanism for the occurrence of the DADs is not completely understood.[9]

The burden of PVCs might be exacerbated by exercise or stress due to an increase in the catecholamines in circulation. [2,10] Also, external factors like caffeine that result in DADs through the release of Ca2+ from the sarcoplasmic reticulum[11] can facilitate the occurrence of PVCs.

Rapid burst pacing, isoproterenol infusion, calcium infusion, or atropine may facilitate arrhythmia induction.[5] These interventions increase the intracellular cAMP, which, via activation of the protein kinase A, increases the slow inward Ca2+ current and the calcium release from the sarcoplasmic reticulum through phosphorylation of the ryanodine receptor. Calcium released from the sarcoplasmic reticulum can activate the electrogenic Na+/Ca2+ exchanger, resulting in a transient inward current and DADs.[6]

Adenosine, via action on the adenosine A1 receptor, which inhibits production of adenylyl cyclase, and consequently cAMP, can terminate triggered ventricular tachycardia. Because catecholamines also activate cAMP, β-blockers may reduce PVCs arising from triggered activity. Finally, nondihydropyridine calcium channel blockers (diltiazem and verapamil) may prevent triggered PVCs by reducing cytosolic calcium accumulation through blockage of L-type calcium channels.[9]

The assumption that RVOT PVCs share the same mechanism of the RVOT ventricular tachycardia remains unproven. Kim et al,[12] studied a group of 127 patients with outflow tract ventricular arrhythmias, presenting with three distinct clinical manifestations, sustained VT, repetitive NSVT, and frequent PVCs. Sustained outflow tract VT was induced at electrophysiology study in 78% of the sustained VT patients, 48% of the NSVT patients, and 4% of patients with PVCs. Adenosine was similarly effective in terminating ventricular tachycardia, in all 3 groups. So, they suggested that outflow tract arrhythmias may represent a continuum with increasing severity and a common mechanism. However, in our opinion this study does not provide enough evidence to assume that all outflow tract arrhythmias, other than the adenosine sensitive ventricular tachycardia share the same mechanism, especially in the case of PVCs. In that study the authors, reported that from 45 patients with frequent PVCs only two (4%) patients had adenosine sensitive VT, so it is difficult in our viewpoint, to extrapolate for all patients with PVCs. As the authors themselves disclosed in the study limitations, where they admit that due to the fact that many patients with either repetitive PVCs or NSVT were not inducible for sustained VT, the conclusions regarding the mechanism of the observed arrhythmia were not definitive. Cheung et al,[13] from the same group described a form or RVOT ventricular tachycardia insensitive to adenosine, but the authors still believe that the mechanism is the same.

Regarding automaticity, the mechanistic cause may be multifactorial, including an exaggerated version of normal automaticity inherent to all cardiomyocytes (such as attributable to intrinsic catecholamines, or extrinsic inotropes),[14] and relative electric isolation attributable to some poorly conducting barrier such as fibrosis, as well.[15]

The clear and consistent predilection for PVCs to arise from certain anatomic regions, such as the outflow tract, has led to recent speculation that the critical origins of the ectopic focus may relate to shared embryological development with cell or tissue types physiologically destined for automaticity, such as specialized conduction tissue.[16]

Anatomical preference sites for the occurrence of clinical arrhythmias are certainly in relation to cardiac conduction system development. Chamber differentiation occurs during rightward looping of the heart tube, which results in positioning of the ventricles and the outflow tract of the heart in an anterior/ventral position, and of the atria in a dorsal/posterior position. Several genes and transcription factors that control chamber differentiation have been identified.[17] The origin of the cells of the cardiac conduction system has been the topic of interest of many studies but currently is accepted that they are derived from cardiomyocytes. However, the mechanisms that determine how the cardiomyocytes differentiate into a myocardial contraction cell, or a cardiac conduction cell are still unclear.[17]

During development and after looping of the primitive heart tube, several so-called "transitional zones" can be recognized, that are related to elements of the putative cardiac conduction system. One of these transitional zones is found at the level of the myocardial outflow tracts,[18] but also at the crista terminalis, ostia of the cava veins, and coronary sinus in the right atrium, in the pulmonary veins in the left atrium and at the myocardium of the AV junction.[17] So, it is possible that PVCs from the outflow tracts can result from either a re-expression of an embryonic phenotype, or embryonic remnants.[18]

Anatomical substrate

Voltage mapping

The 3D EAM systems using either an electromagnetic or an impedance-based catheter location method, or currently both methods, enable the acquisition of a 3D anatomic geometry of the cardiac chamber of interest. The electrograms obtained with the mapping catheter can be analysed in regard of their amplitude and the peak-to-peak signal amplitude of the bipolar electrogram can be measured automatically. and the information used to generate a 3D electroanatomical voltage map of the RVOT, with the electrophysiologic information, color-coded and superimposed on the geometry. The colour display for voltage mapping ranges from purple, representing electroanatomical normal tissue (amplitude> 1.5 mV), to red, representing electroanatomical scar tissue (amplitude <0.5 mV), and the intermediate colours, corresponding

to a bipolar voltage between 0.5 mV a 1.5 mV. Low voltage areas (LVAs) are defined as areas with bipolar electrograms with an amplitude <1.5 mV.

It is usually accepted that in the absence of structural heart disease the intracardiac electrograms display normal duration and normal voltage. [19, 20]

On the contrary, the specific marker of ARVC is the transmural loss of right ventricular myocardium which in turn results in the appearance of areas of low voltage and electrical scar on the 3D voltage mapping. [21,22] The diagnosis of ARVC is based on a series of major and minor criteria regarding clinical, structural, electrocardiographic, and electrophysiological abnormalities, as defined by the 2010 modified Task Force criteria.[23] In the early stage of the disease, structural changes may be absent or subtle, but progressively the disease affects localized areas of the right ventricle, typically the inflow tract, outflow tract, or apex of the right ventricle, the so-called "triangle of dysplasia". [24]

Corrado et al,[22] studied 27 patients with RVOT ventricular tachycardia and apparently normal hearts and performed both 3D voltage map and endomyocardial biopsy. They found LVAs in seven patients (26%), that correlated with fibrofatty myocardial replacement at endomyocardial biopsy. It is however noteworthy, that only two out of those seven patients had performed CMR.

However, the results of 3D EAM voltage map in patients with idiopathic RVOT PVCs are contradictory. Boulos et al,[21] compared the voltage map of patients with idiopathic RVOT tachycardia to that of patients with ARVC and normal controls and concluded that patients with idiopathic ventricular tachycardia, and normal controls had similar 3D voltage maps without LVAs, unlike the ARVC patients, who presented with LVAs.

The bipolar voltage above the pulmonary valve is typically less than 0.5 mV or even less than 0.1 mV due to the absence or scarcity of myocardium at that level. The voltage progressively increases as the catheter is withdrawn to the RVOT[25]. The area immediately below the pulmonary valve displays a voltage between 0.5 and 1.5 mV and is described as the transitional-voltage zone.[26].

Unlike Boulos et al[21], other authors demonstrated the presence of LVAs in the RVOT of patients undergoing catheter ablation of frequent idiopathic PVCs.[25,26,27,**28,29,30**]. Furushima et al,[25] studied 28 patients with frequent PVCs and apparently normal hearts and found LVAs immediately below the pulmonary valve in all patients, the width of the LVA being variable. Two patients had polymorphic ventricular tachycardia/ ventricular fibrillation, and those were the ones with wider LVAs, although the patients did not undergo further investigation to rule out ARVC. The authors concluded that in patients with wider LVAs, a potential arrhythmogenic impact must be addressed.

We also have reported the presence of LVAs in the RVOT of patients with idiopathic PVCs. On our first study,[**28**] we studied 18 consecutive patients with apparently normal hearts that underwent

ablation of idiopathic outflow tract PVCs and had 3D EAM voltage map of the RVOT performed and found LVAs in 39% of patients.

More recently in a larger study[28] including 56 patients, 45 patients with PVCs and 11 control subjects without PVCs, we identified the presence of LVAs in 62 % of patients with PVCs and in none of the subjects in the control group.

This incidence is higher than previously reported and it may seem too high. However, Letsas et al,[27] studied 44 patients with idiopathic PVCs using a multipolar catheter with 2 mm electrodes for high density mapping (mean number of sampled points 1096.6 ± 322.3) and identified at least two low bipolar voltage areas less than 1 mV in 39 out of 44 patients (88%), a higher percentage than ours. These results prove that our high prevalence of LVAs is surely not the result of the lack of multipolar catheters or high-density mapping.

The LVAs described by our group and by other abovementioned authors could not be detected by late Gadolinium enhancement (LGE) CMR in any patient.

Dello Russo et al,[31] studied 13 competitive athletes that had ventricular arrhythmias and apparently absent structural heart disease including normal CMR and still, displayed LVAs at the 3D EAM. The endomyocardial biopsy was performed at the LVAs and diagnosed myocarditis in seven and ARVC in five.

The reason for the incorrectly normal diagnosed CMR, may be due to the small size of the LVAs, below the threshold capacity of detection with the currently available CMR techniques.[32,33] In fact, in a previous study we demonstrated that the use of three-dimensional LGE, increased the diagnostic yield of CMR to detect LVAs when compared to conventional two-dimensional analysis, detecting fibrosis in three out of nine patients with LVAs (33%) while two-dimensional analysis failed to demonstrate fibrosis in all.[34]

Also, using speckle tracking echocardiography in 21 patients with PVCs from the RVOT and normal CMR and in 13 control patients we were able to demonstrate the presence of worse right ventricular longitudinal strain values, and therefore sub-clinical myocardial dysfunction, in the PVC group when compared to healthy controls.[35]

Detection of myocardial fibrosis can be assessed noninvasively with CMR using LGE,[33] but its detection depends on the type of fibrosis, whether replacement or interstitial fibrosis.

Tandri et al, [36] studied 12 patients with a diagnosis of ARVC according to the taskforce criteria[23] and 8 patients (67%) displayed positive LGE. The authors found an excellent correlation between LGE at the CMR and the histopathological findings of fibro-fatty replacement in patients with ARVC. However, in one third of the patients, LGE failed do demonstrate abnormalities in patients with ARVC.

CMR imaging is of fundamental value in the diagnosis of ARVC however, a suspicion of ARVC cannot be confirmed or excluded based on CMR imaging alone.

In the initial phases of non-ischemic cardiomyopathy for instance, although a certain degree of diffuse fibrosis may be present, it goes undetected by LGE techniques and may be detected by T1 mapping.[32] These findings may suggest the presence of an underlying substrate too subtle to be identified by CMR techniques.[37]

The idiopathic nature of the VAs refers to the absence of abnormalities on the currently available diagnostic tests. CMR imaging studies in patients with idiopathic outflow tract PVCs, have shown conflicting data regarding the existence of structural abnormalities in the RVOT of those patients. Initial studies documented the presence of localized wall bulging, focal wall thinning or fatty replacement in a high percentage of patients.[38] O'Donnell et al,[39] studied 50 consecutive patients with 33 with idiopathic and 17 with ARVC ventricular tachycardia and found abnormalities in CMR in 54% of the idiopathic patients.

However, most recent studies using ECG gating and imaging with LGE have shown absence of pathological findings in patients with idiopathic RVOT PVCs.[40]

But on the other hand, the presence of LVAs does not necessarily mean presence of fibrosis. The thickness of the RVOT wall is variable, and in areas where the wall may be thinner the voltage could be lower. Also, the bipolar voltage may be influenced by a series of factors other than the presence of healthy, fibrotic tissue or myocardial fat. The influence of conduction velocity, fibre orientation and curvature, catheter–tissue relationship (angle of incidence, contact force, orientation in relation to wavefront propagation) and tissue oedema, different filter settings and catheter characteristics.[41]

For instance, presence of LVAs can be overestimated due to poor catheter tissue contact, as reported by Sciarra et al.[42] Those authors studied 20 consecutive patients that underwent PVC ablation and had a voltage mapping with a mean of 345 ± 85 points. Applying conventional bipolar voltage settings, they found LVAs in 18 subjects (90%). After excluding points with less than 5 g of contact force the mean number of points in map was reduced to 149 ± 60 points and no more LVAs were present.

In our most recent work, all patients performed CMR before ablation and we only used catheters with contact-force technology for manual ablation and with catheter–tissue contact feedback technology for cases performed with RMN.[43] Only points with optimal contact were considered for the voltage map and yet we found presence of LVAs in the RVOT of idiopathic patients with normal CMR in 62% of the patients. Thus, it is clearly not a question of lack of contact. Although not all patients present LVAs, they were absent in 38% of patients with RVOT ventricular arrhythmias.

The local electrograms in the septum area of the right ventricle have the highest voltage, as opposed to the ones from the RVOT, which display the lowest values.[22] So, it is possible that the LVAs may correspond to zones with a thinner RVOT myocardium. Nevertheless, the prevalence of these LVAs is extremely high in patients with arrhythmias from the RVOT in comparison with the general population, suggesting an association between the two. Additionally, these LVAs do not seem to display normal physiology as will be discussed in the next section. They are associated with slower conduction velocity and presence of deceleration zones as demonstrated by the slower velocity of wavefront propagation across the RVOT in patients with LVAs in comparison with patients with normal voltage.[44] Also, the repolarization of RVOT patients with PVCs from the RVOT is abnormal, as we demonstrated with the use of ECGI, as will be described later in the chapter.[45]

Non-invasive electrocardiographic marker of low voltage

3D EAM voltage mapping is able to unmask subtle anomalies in patients with ventricular arrhythmias and apparently normal hearts, in spite of a normal CMR as we have discussed in the previous section. LVAS are present in a high percentage of cases of idiopathic ventricular arrythmias. However, 3D electroanatomical mapping is not an acceptable screening tool due to its invasive nature. So far, there is no reliable noninvasive method for the diagnosis of these minimal abnormalities identified as LVAs, thus, the identification of a noninvasive marker of LVAs is important.

The Brugada syndrome, caused by an inherited sodium channelopathy, is diagnosed in patients with a Type 1 ST-segment elevation in V1-V3, spontaneously or after drug provocation, at the standard or high position, and in patients with baseline Type 2 pattern that converts to Type 1 with drug provocation.[46-48]

The RVOT lays anteriorly and superiorly to the LVOT and its proximity to the 2nd intercostal space (ICS) increases the sensitivity of the 12-lead ECG to detect abnormalities when the right precordial leads are recorded at this level (Figure 16).[47]

In a pilot study we demonstrated for the first time, that the upward displacement of the ECG, unmasked the presence of ST-segment elevation in V1-V2 at the 2nd ICS absent in the standard ECG, in 18 consecutive patients with PVCs from the RVOT that underwent ablation.[28]

This ECG marker was associated with the presence of LVAs across the RVOT. However, one of the criticisms of this first study was the absence of a control group and the fact that CMR was not performed in all patients.

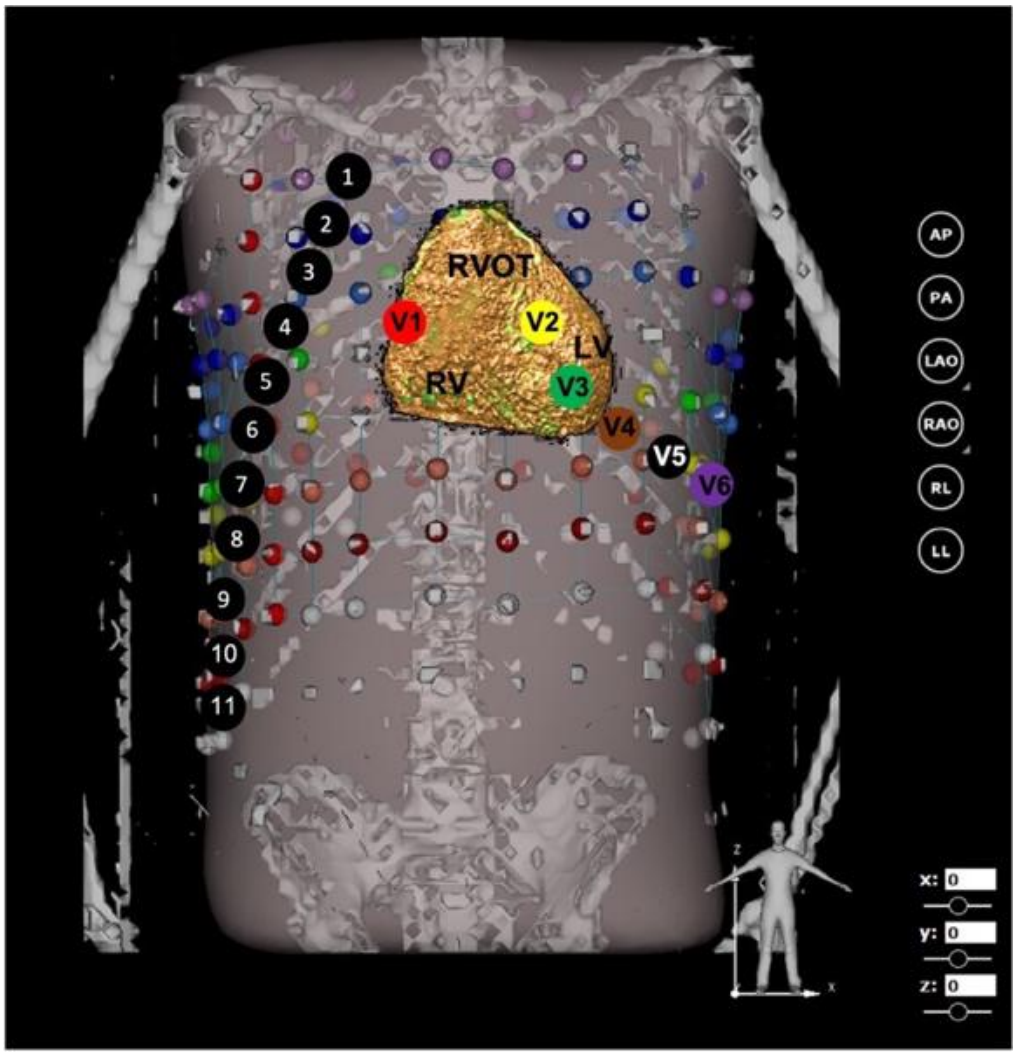

Figure 16. *Relation between the RVOT and the standard 12 precordial leads. Higher proximity of the RVOT with the 2nd ICS than with the 4th ICS. ICS: intercostal space*

So, we performed a second larger study designed to include a control group (11 patients), and all patients in the PVC group had normal CMR.[30] We studied 56 consecutive patients, 45 with frequent PVCs (>10000/24 h) from the outflow tracts and 11 subjects without PVCs. ARVC was ruled out in all patients. An ECG was performed with V1–V2 at the level of the 2nd ICS and the presence of ST-segment elevation with a Type 2 or 3 Brugada pattern (grouped as type 2 BrP) was assessed.

Bipolar voltage map of the RVOT was performed as previously described.[28] Presence of LVAs outside the transitional-voltage zone were estimated.

ST-segment elevation was present in 64% of PVC patients and was absent in all patients from the control group. None of the patients with ST-segment elevation had type 1 Brugada pattern. LVAs were significantly more frequent in patients with ST-segment elevation, 93% versus 4%, $p < 0.0001$ (Figure 17).

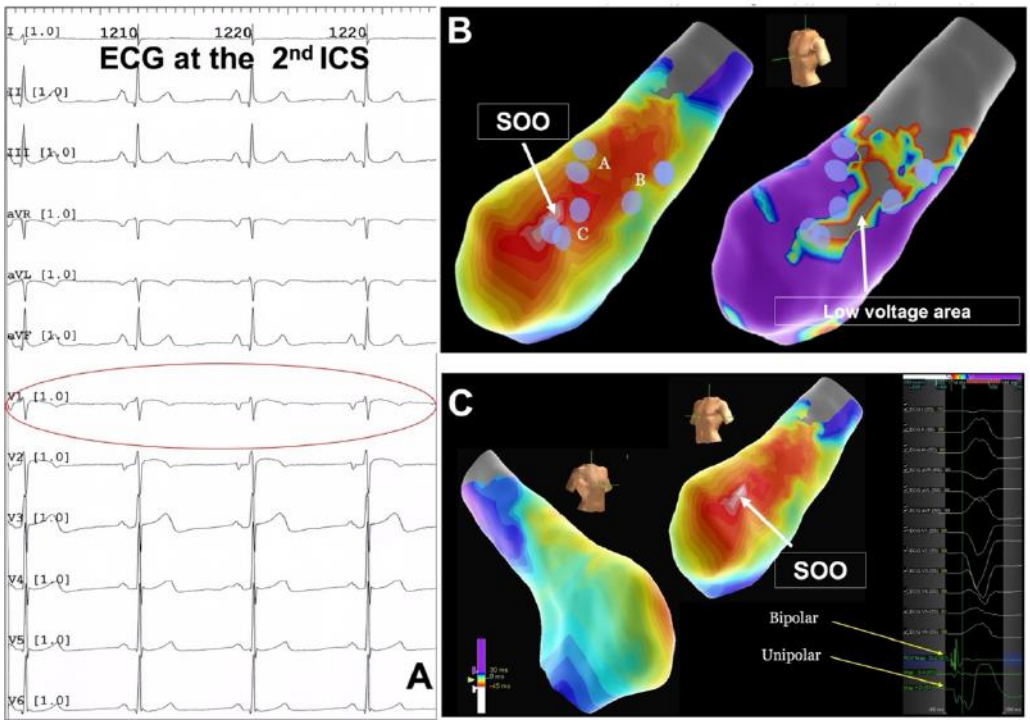

Figure 17. *Patient with PVCs from the anterior RVOT displaying ST-segment elevation in V1-V2 at the 2nd ICS (panel A). Activation with SOO and DPS (blue dots) and voltage map displaying low voltage at the SOO (panel B). Activation map and intracardiac electrograms (panel C)*

ST-segment elevation was absent in 36% of patients with PVCs, 2 patients with LVOT PVCs (40%) and 14 patients with PVCs from the RVOT (31%) those patients also had absence of LVAs (Figure 18).

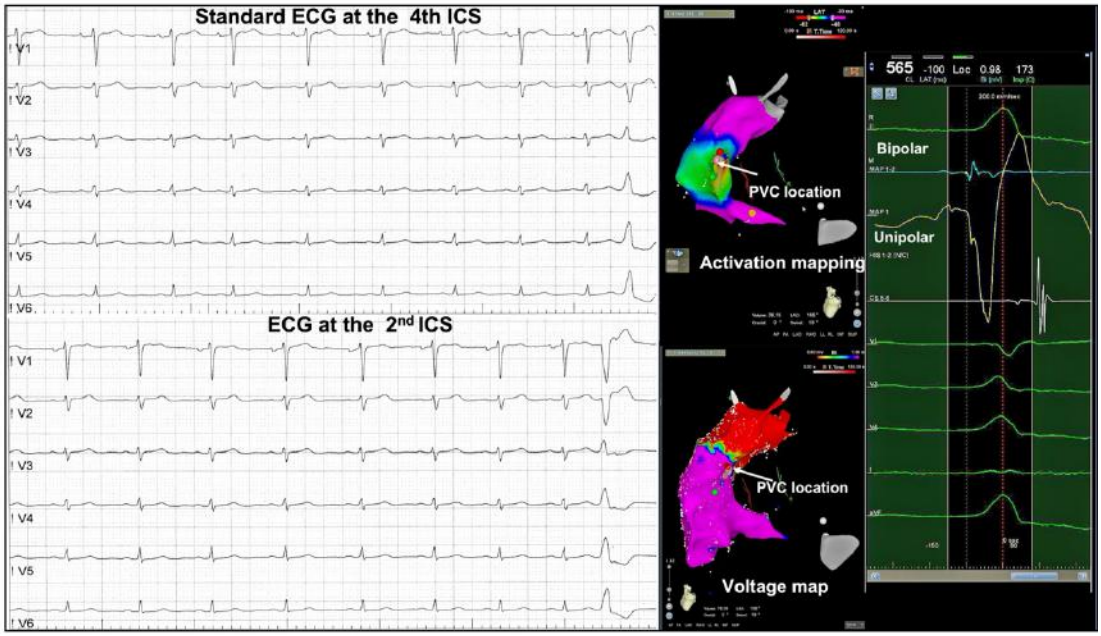

Figure 18. *Patient with PVCs from the RVOT displaying no ST-segment elevation in V1-V2 at the standard or the 2nd ICS (left panel). Activation with SOO (upper right panel) and voltage map displaying absence of low voltage at the SOO (lower right panel). Intracardiac electrogram showing early activation and QS pattern in the unipolar electrogram*

On the other hand, three out of five (60%) patients with PVCs originating in the LVOT had ST-segment elevation. This finding was surprising assuming that this was supposed to be a marker of low voltage across the RVOT, thus unexpected in patients with arrhythmias with an origin outside the RVOT. However, in this second study we did not use catheters with contact-force technology in all patients, and as mentioned above, this can lead to an overestimation of LVAS.

So, we performed a third study to validate the ST-segment elevation at the 2nd ICS as an electrocardiographic marker of LVAs in the RVOT in patients with idiopathic outflow tract ventricular arrhythmias. We include a larger population, with a higher number of patients with PVCs from the LVOT, and a larger control group, and used catheter-tissue contact technology in all patients.[43].

We included 120 patients with idiopathic outflow tract ventricular arrhythmias, frequent PVCs (114 patients) or sustained ventricular tachycardia (6 patients). Three groups were compared, 66 patients with RVOT ventricular arrhythmias, 18 patients with LVOT ventricular arrhythmias and 36 control patients.

ST-segment elevation was present in 46 patients, 41 (62%) in the RVOT group, 3 (17%) in the LVOT and 2 (6%) in the control group both with a saddleback pattern previously described as Type 3 Brugada pattern,[46] this difference was statistically significant between the RVOT and the control groups (62% vs 6%), p<0.0001, but not between the LVOT and the control group.

All patients with ST-segment elevation presented with either coved-type or saddleback pattern defined as type 2 or 3 Brugada ECG pattern, but none presented with ECG diagnostic pattern for Brugada Syndrome, meaning a coved-type pattern with >2 mm in > 1 right precordial lead (V1 to V3).[46]

The presence of T-wave inversion beyond V1 at the level of the 2nd ICS was also significantly more frequent in the RVOT group comparing to the control group as well as in the LVOT group in comparison to the control group, respectively 33% vs 0% and 29% vs 0%, p=0.001.

When evaluating the electrocardiographic findings we found an association between ST-segment elevation and the presence of negative T-wave beyond V1 at the 2nd ICS, and the presence of LVAs, respective unadjusted OR (95% CI) of 32.31 (11.33-92.13), p<0.0001, and 4.137 (1.615-10.60), p=0.003. Also, the RVOT site of the VAs showed an association with LVAs, OR (95% CI) 8.200 (3.309-20.32), p<0.0001. However, after adjustment with multivariate analysis the only independent predictor of LVAs was the ST-segment elevation with an adjusted OR (95% CI) of 20.94 (6.787-64.61), p<0.0001.

The ST-elevation as a noninvasive marker of LVAs has a sensitivity of 80%, specificity of 89%, positive predictor value of 85% and negative predictor value of 85%.[43]

The findings in this study confirm the value of ST- segment elevation at the level of the 2nd ICS to detect the presence of LVAs.

The percentage of ST-segment elevation in patients with LVOT VAs in this last study[43] was lower than in the former one, 17% versus 60%. The higher percentage formerly observed may had to do with the smaller sample size. The observation that the increase in the number of patients with LVOT ventricular arrhythmias led to a significant reduction in the percentage of ST-segment elevation in the LVOT group can support this statement. We can speculate that a further increase in the sample size would lead to additional reduction in this percentage rendering it similar to that of the general population.

However, we cannot rule out the possibility that RVOT and LVOT ventricular arrhythmias may be a global disease of the outflow tracts, thus presenting similar pathological findings despite different clinical manifestations.

In opposition, the increase in the sample size of the group with ventricular arrhythmias originating in the RVOT from 40 to 66 patients did not result in a decrease in the percentage of ST-segment elevation, 67% in the previous study compared to the 62% in the current one, proving that these findings are consistent.

The prevalence of ST-elevation in our control group, with a morphology of type 3 Brugada ECG pattern[46] was 6%, which is similar to the previous reported prevalence in the general population. Holst et al,[49] studied 340 healthy subjects and reported an incidence of type 1, 2, and 3 Type 2 Brugada ECG pattern on the 2nd ICS, respectively of 0%, 3.3%, and 7.1%. Another work by Hunuk et al,[50] registered similar results in 504 healthy male volunteer subjects. The authors found an incidence of type 1, 2, and 3 Brugada ECG pattern of 0.8%, 2%, and 7.5%, respectively. A flecainide test was not performed in any of the patients with ST-segment elevation, because a clinical suspicion of Brugada Syndrome was absent in all.[46]

It remains to be explained why some patients with arrhythmias from the RVOT do not display ST-segment elevation nor LVAs or why patients without ventricular arrhythmias show LVAs within the RVOT.

Regarding the former we can speculate that the mechanism for the arrhythmia may be different from patient to patient, or likewise the repercussion of the arrhythmia on the heart may differ among patients.

Regarding the presence of ST-segment elevation and LVAs in normal subjects, we may speculate that the occurrence of ventricular arrhythmias depends on the presence of both the substrate and the triggers and so arrhythmias may never occur in the absence of the appropriate triggers, despite the presence of the substrate.[51]

Another interesting finding in this study[43] was the high percentage of patients with T-wave inversion beyond V1 when the ECG was obtained at the level of the 2nd ICS (40%), in comparison with 7% at the standard position, similar to previously reported.[39] The diagnosis of ARVC is sometimes difficult, and T wave inversion in V1–V2 is considered a minor criterion.[23] If we accept that the T wave inversion at a higher ICS could have a similar value, then the number of ARVC "possible" cases would increase. However, despite its association with LVAs in univariate analysis, unlike the ST-segment elevation the presence of T-wave inversion was not independently associated with the presence of LVAs.

With this study we obtained consistent evidence of an association between ST-elevation and LVAs. In fact, it was the only independent predictor of LVAs. Their presence was not associated with a worse outcome, and the success rate was similar in patients with and without LVAs. They may, however, be considered a possible substrate for RVOT arrhythmias and thus a target for ablation.

Electrophysiological substrate

Significant alterations in conduction and repolarization appear to precede detectable morphological changes using conventional cardiac imaging in patients with desmoplakin allele deletion.[52] Abnormalities like for instance a longer total endocardial activation time, may serve as markers for structural heart disease including ARVC.[52]

Fibrosis is associated with late local activation and areas of slow conduction and slower wavefront propagation speed, known as deceleration zones. [53,54]

Abnormal wavefront propagation speed and presence of deceleration zones in sinus rhythm

We studied 29 patients[44] with idiopathic PVCs from the outflow tract, and a control group of 15 patients without PVCs. The aim of the study was to assess the pattern of propagation of the endocardial activation in RVOT looking for the presence of deceleration zones (DZ) and evaluate the association with the presence of LVAs. We demonstrated that patients with PVCs had a longer duration of the endocardial activation across the endocardium of the RVOT in comparison with the control subjects. RVOT endocardial activation duration and number of 10 ms isochrones were higher in the PVC group; 56 (41–66) ms vs. 39 (35–41) ms, $p = 0.001$ and 5 (4–8) vs 4 (4–5), $p = 0.001$. Presence of DZs defined as zones where there is a confluence of isochrones and a deceleration of the wavefront propagation speed, and LVAs were more frequent in the PVC group than in the control subjects; 20 (69%) vs. 0 (0%), $p < 0.0001$ and 21 (72%) vs. 0 (0%), $p < 0.0001$. The wavefront propagation speed was significantly lower in patients with PVCs than in the control group, 0.35 (0.27–0.40) vs. 0.63 (0.56–0.66) m/s, $p < 0.0001$ (Figure 19).

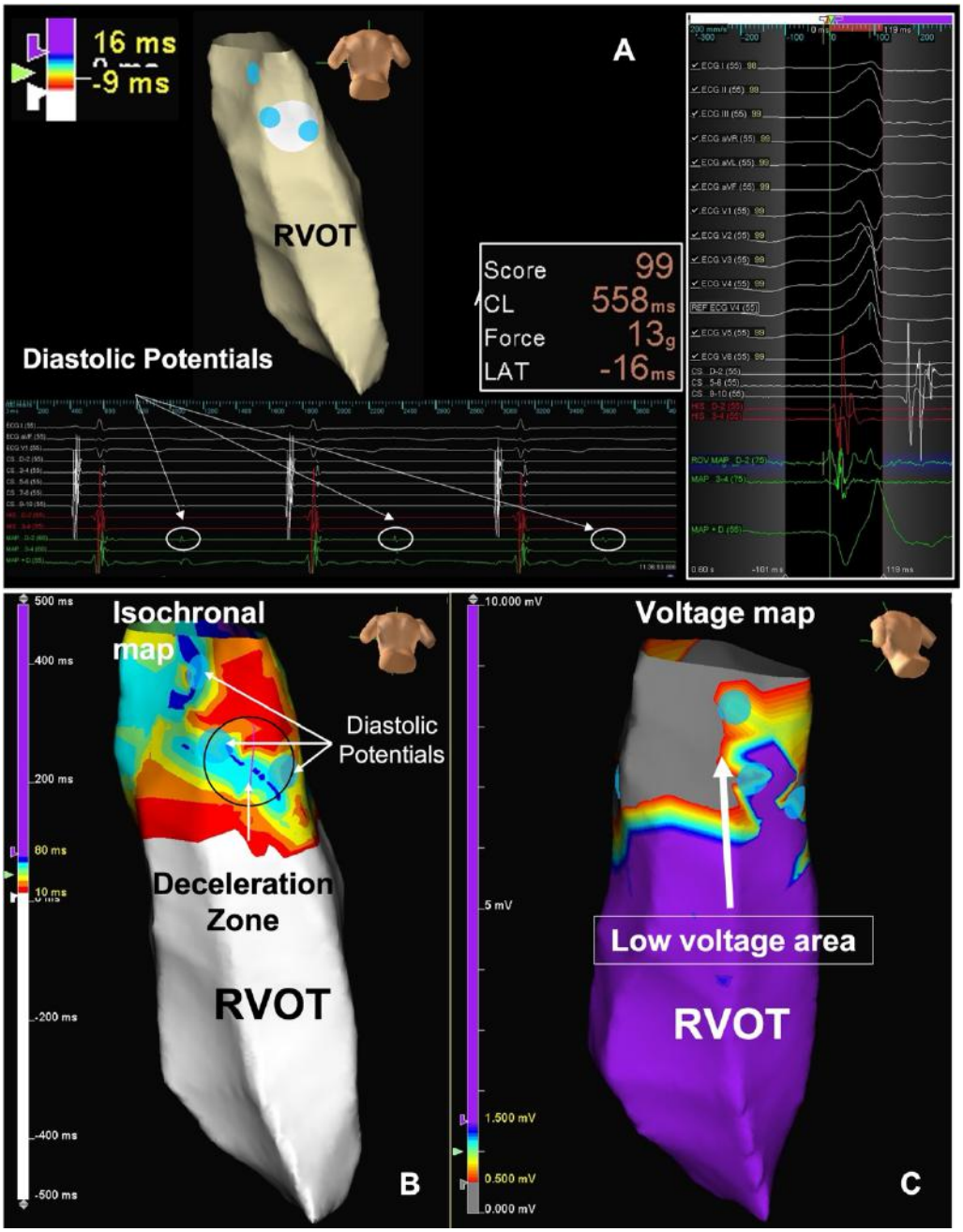

Figure 19. *Patient from the PVC group with DZ in the LVAs. Anatomical mapping with tagged DPS (blue dots) Intracardiac electrograms corresponding to the points with blue dots. Earliest activation electrogram on the right displaying QS pattern on the unipolar electrogram. (panel A) RVOT isochronal map sinus rhythm) with DZ in the RVOT free wall with confluence of isochrones (panel B). Voltage map in sinus rhythm with large low voltage area (panel C). DP: diastolic potentials; DZ: deceleration zone; RVOT: right ventricular outflow tract.*

Patients with LVAs had longer activation duration 60 (52–67) vs. 36 (32–40) ms, $p < 0.0001$, more frequently DZs, 20 (95%) vs. 0 (0%), $p < 0.0001$, and lower wavefront propagation speed, 0.30 (0.26–0.36) vs. 0.54 (0.36–0.66) m/s, $p = 0.002$, than patients without LVAs.

However, although activation duration was longer in the PVC group than in controls, it was nevertheless still within the normal range previously described by other authors. 52.[55]

Tandri et al,[52] studied a group of 25 patients with frequent LBBB morphology PVCs, 14 with ARVC and 11 patients with idiopathic PVCs. The authors evaluated the total right ventricular endocardial activation duration and observed that an activation duration higher than 65 ms was highly suggestive of ARVD and was never present in patients with idiopathic PVCs. The authors concluded that total right ventricular activation duration was a more sensible and earlier marker of disease than low voltage.

Letsas et al,[55] performed a high-density map of the RVOT in 8 patients with Brugada Syndrome and 20 patients with idiopathic PVCs. The mean RVOT endocardial activation time was significantly prolonged in patients with Brugada Syndrome in comparison with patients with idiopathic arrhythmias, 86.4 ± 16.5 vs. 63.4 ± 9.7 ms, $p < 0.001$. None of the abovementioned authors studied a population of normal subjects without PVCs, therefore, the value of 65 ms for the RV activation duration in the study by Tandri et al, or 63.4 ms for the RVOT reported by Letsas et al and referred as normal might as well be augmented in relation to normal subjects without PVCs as we have proven.[44]

In our study, [44] in normal subjects the earliest activated region of the RVOT is the area of the anterior septum and then activation spreads up in the direction of the pulmonary artery. In normal subjects the activation time is short, and the activation speed is high with RVOT being activated in a median of 39 (35–41) ms and an activation speed of 0.63 (0.56–0.66) m/s. [44]

Additionally, the median activation speed at the areas with a higher confluence of isochrones, was significantly slower in the PVC group than in controls. The presence of DZs was associated with the presence of LVAs and were absent in patients without LVAs. Furthermore, the observed lower speed of the wavefront propagation, was worse in patients with PVCs that presented with LVAs than in those without LVAs. However, in 10% of cases the DZs occurred outside the LVAs, and this was also described by Tandri et al,[52] that observed that the presence of delayed activated areas was not always associated with decreased endocardial voltage and/or fractionated potentials.

Voltage mapping is dependent on contact force, electrode area and orientation of the catheter tip in relation to the direction of the wavefront activation and so may be less accurate to evaluate substrate than activation mapping when the contact is suboptimal because the latter is less dependent on these parameters.[54] But even activation mapping is dependent on the methodology of LAT annotation and may be influenced by the presence of low amplitude pre-potentials, presence of multiple components or fractionated electrograms.[56] Nevertheless, the absence of these abnormal findings in the control group speaks against the hypothesis that the slower velocity and the presence of DZs might be due to inaccurate measurements.

Abnormal wavefront propagation speed and presence of deceleration zones in premature ventricular contraction

Masuda et al,[57] studied the velocity of propagation of the PVC in a group of 23 patients with idiopathic arrhythmias from the outflow tracts. Those authors assessed the propagation speed indirectly by measuring the areas encompassing the first 5, 10, 15, and 20 ms isochrones. Mapping of the RVOT during the PVC was performed using an ultra-high resolution electroanatomic mapping system. The wavefront propagation speed of the PVC over the RVOT was slower for PVCs originating from the RVOT than for PVCs originating from adjacent sites. The authors used this information to differentiate arrhythmias originating from the RVOT from the non-RVOT arrhythmias as previously described by Herczku et al,[58] using a conventional mapping catheter in a point-by-point manner.

Both groups explained their findings based on the myocardial fiber arrangement in the RVOT that leads to a different propagation speed according to the SOO of the arrhythmia. Therefore, when the PVC originates in the LVOT it reaches the RVOT through multiple connections and the activation becomes faster in this case.

So, to address the question of whether the slower conduction during the PVC might be due to the presence of LVAs we performed another study to evaluate the RVOT endocardial activation duration and wavefront propagation speed of the PVC, both invasively and with the ECGI.**[59]** To the best of our knowledge this was the first paper evaluating the duration and speed of the RVOT wavefront activation during PVC invasively and with the ECGI.

We studied 18 consecutive patients, 8 males, median age 55 (35–63) years that underwent ablation of PVCs with inferior axis and had an ECGI performed before ablation. Isochronal activation maps of the RVOT in PVC were obtained with the ECGI and invasively. Total RVOT activation duration was measured as the time between the earliest and latest activated region, and propagation speed by measuring the area of the first 10 ms of RVOT activation.

Cut-off values for activation duration, activation speed and number of 10 ms isochrones to predict the origin of the PVCs, were obtained with the ROC curve analysis. Agreement between methods was done with Pearson correlation test and Bland-Altman plot. The PVCs originated from the RVOT in 11 (61%) patients. The stronger predictor of PVC origin was the activation duration. The median activation duration in PVCs from RVOT was significantly longer than in PVCs from outside the RVOT, both with ECGI and invasively, respectively 62 (58–73) vs 37 (33–40) ms, $p < 0.0001$ and 68 (60–75) vs 35 (29–41) ms, $p < 0.0001$. Patients with LVAs had longer PVC endocardial activation duration than patients without LVAs (Figure 20).

Agreement between the two methods was good ($r = 0.864$, $p < 0.0001$). The cut-off value of 43 ms for AD measured with ECGI predicted the origin of the PVCs with a sensitivity and specificity of 100%.

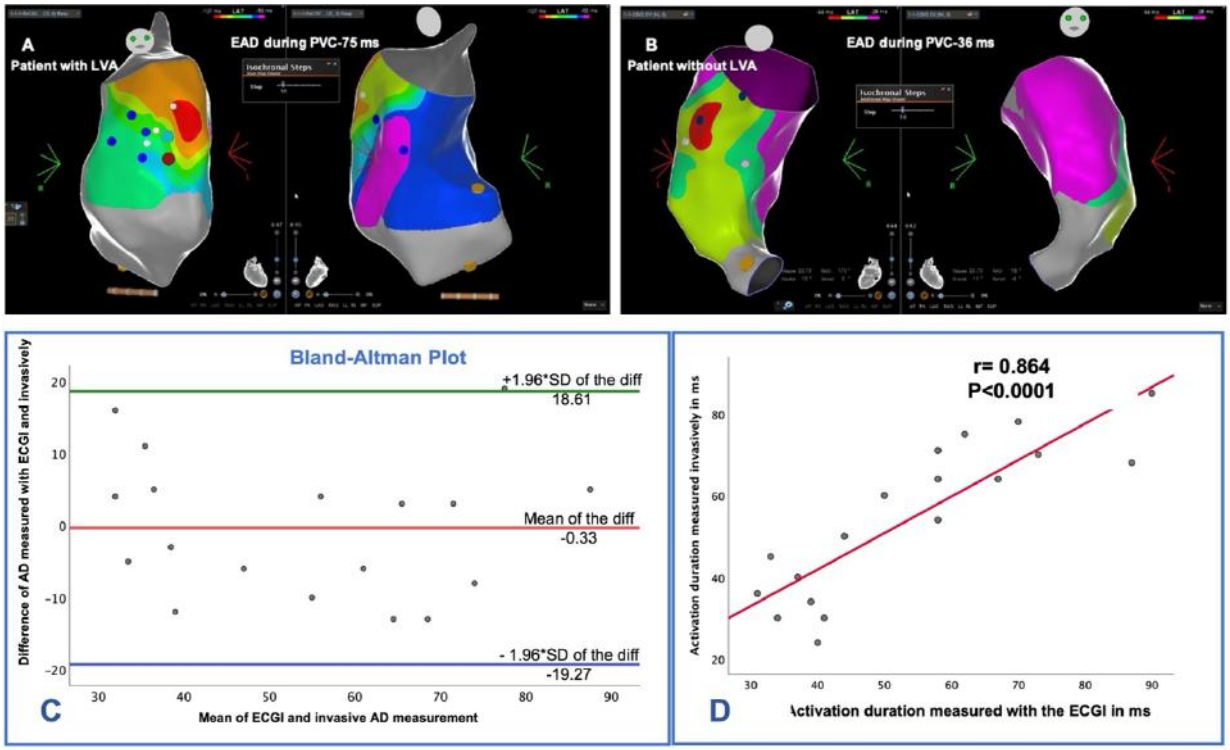

Figure 20. *Patient with PVCs from the ROA with LVAs displaying a long EAD during PVC (panel A). Patient with PVCs from the ROLS without LVAs displaying a short EAD during PVC (panel B). Bland and Altman diagram showing the plot of the difference between the activation duration measured with ECGI and invasively in ms, against the mean of the pair measurements. Green and blue lines show limits of agreement, and the red line shows the mean value of the differences between measurements. (panel C). Scatter plot showing the Pearson correlation coefficient (r) and p-value (p) between activation duration measured with ECGI and invasively. (panel D).*

The results were similar to the ones presented by the abovementioned authors, but additionally provided evidence that it was possible to achieve the same results noninvasively. The ability to obtain noninvasively an isochronal map of the PVC before the ablation procedure and assess the activation duration and the activation speed may be helpful in identifying the SOO of the PVCs from the RVOT or LVOT and plan the procedure in advance.

The mechanism implicated in the shorter activation duration and higher activation speed when PVCs originate outside the RVOT is in our viewpoint different from the mechanism implicated by both Herczku et al,[58] and Masuda et al.[57] Those authors as previously specified above, explained their findings based on the myocardial fiber arrangement in the RVOT. We have demonstrated that patients with PVCs from the RVOT had lower velocity of propagation of the wavefront of activation over the endocardium of the RVOT also in sinus rhythm, in comparison with the control subjects.[44] The presence of a pathological substrate in the RVOT may be the cause of this slower conduction velocity which is supported by the presence of LVAs in the RVOT that were absent in the control group.

Understanding normal cardiac excitation provides a necessary baseline ground for understanding abnormal cardiac electrical activity and arrhythmias. Most of the studies

evaluating cardiac depolarization and repolarization were performed in animals and then extrapolated to humans, not taking into account the interspecies differences in anatomy and electrophysiology. Human studies have been performed intraoperatively with anesthetized patients and most of them in subjects with pathological hearts.

ECGI as discussed in the previous chapter, is a noninvasive cardiac electrical imaging modality that can image cardiac endocardial and epicardial potentials, activation, and recovery sequences in vivo and under physiological conditions.

Abnormal activation recovery interval

Body surface electrocardiographic mapping was firstly used almost thirty years ago. That system consisted of eighty-seven unipolar electrodes recording simultaneously from the surface of the thorax.[60] Those authors studied with that system the patterns of depolarization and repolarization in a number of pathological situations. Subsequently, experimental work done in isolated pig hearts, has demonstrated that the ARI, estimated from unipolar electrograms recorded at the surface of the heart, is independent of the activation time, and can be used as an appropriate surrogate of action potential duration and repolarization.[61,62]

The activation recovery interval (ARI) is defined as the time difference between recovery time measured at the steepest ascending slope of the T wave in the unipolar electrogram, and the activation time measured at the steepest downslope of the QRS in the unipolar electrogram (Figure 9).

Depolarization and repolarization have been extensively studied in Brugada syndrome, to explain the occurrence of the ST-segment elevation, giving rise to two different theories, the depolarization[63] and the repolarization theory.[64] Zhang et al,[65] obtained panoramic maps of activation and repolarization of patients with Brugada syndrome using ECGI and the authors concluded that both abnormal repolarization and abnormal conduction are present in the substrate, leading to steep repolarization gradients and delayed activation. The same group also studied the repolarization pattern in patients with early repolarization[66] and observed the presence of steep repolarization gradients caused by localized shortening of the action potential duration. The ECGI used in these two studies only evaluated epicardial electrograms.

Rudic et al,[67] with a system identical to ours (Amycard system), studied the epicardial and endocardial repolarization in patients with Brugada syndrome. They reported the presence of ST-segment elevation in the unipolar electrograms recorded both in the epicardial and endocardial surface of the RVOT. The authors also reported delayed activation time in the endocardium and significantly prolonged ARI in the epicardium in comparison to controls.

As mentioned in the previous section, we demonstrated for the first time, that the presence of ST-segment elevation in lead V1 at the 2nd ICS was associated with the presence of LVAs in the RVOT, assessed with 3D EAM systems, in patients with idiopathic PVCs.[28,30,43,59]

With the aid of the ECCI we were able to evaluate the presence of ST-segment elevation and study the activation and recovery across the RVOT, in order to understand the underlying mechanisms responsible for the ST-segment elevation. This was the first study in man, reporting on simultaneous epicardial and endocardial electrocardiographic mapping, to evaluate the electrophysiological substrate of idiopathic PVCs from the RVOT.[45]

We studied with the Amycard (EP Solutions SA, Switzerland) ECGI system, 24 consecutive patients with frequent PVCs from the RVOT, and a control group of 17 patients without PVCs or with PVCs from another location.

The first important finding in our study was the observation of ST elevation on the endocardial and epicardial unipolar electrograms throughout the RVOT, in a significantly higher percentage of patients with PVCs from the RVOT that in controls.

The most striking finding was the presence of an ARI dispersion in the epicardium of patients with PVCs from the RVOT (Figure 21). This ARI dispersion was associated with a shorter recovery time both in the endocardium and the epicardium.

Figure 21. *Automatic ARI map in a control patient showing absence of epicardial ARI dispersion in the RVOT (left panel) and in a patient with PVCs from the RVOT showing epicardial ARI dispersion in the RVOT. ARI: activation recovery interval; RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions*

The association of ST-segment elevation with an ARI dispersion was previously described in both the Brugada, and the early repolarization syndromes using ECGI [65,66] The ARI dispersion was accompanied by a prolongation of the recovery time in the Brugada syndrome[65], and by a shortening of the recovery time in the early repolarization syndrome.[66]

The reason for this shorter recovery time in our patients with PVCs is unknown. We hypothesize that just as it is possible that the refractory period may decrease in result of rapid pacing,[68] it is also conceivable that the constant ectopic activation by the PVCs may induce a reduction of the

refractory period of the RVOT with time, as a form of electrical remodelling. Recently Sakamoto et al,[69] described the presence of abnormal repolarization properties in patients with frequent PVCs from the RVOT assessed by the presence of T-wave changes and QRST time integral. This phenomenon involves changes in repolarization properties resulting from the abnormal activation sequence.[70]

Those T-wave abnormalities were more pronounced in patients with a PVC burden higher than 10.000 PVCs per day, as is the case of our study group, and progressively returned to normal a few weeks after successful ablation.[70] The authors attributed these T-wave changes to cardiac memory. They reported a statistically significant difference in the amplitude of the T-wave in lead V2 when compared to normal subjects and this difference attenuates after successful ablation. Patients with PVCs from the RVOT had also much lower QRST time integral values in V2 than normal subjects,[70] although the authors did not comment on those findings.

So, it is possible that our findings obtained from the reconstructed electrograms might be associated with the T-wave changes described by these authors and be a consequence of the PVCs. But it could be the other way round, and the repolarization abnormalities being the cause and not the consequence of the PVCs. In fact, in the study group from Zhang et al,[66] with early repolarization syndrome the authors reported the presence of PVCs in two of those patients, and in both, the origin of the PVCs was in the area with ST-segment elevation and repolarization abnormalities.

Idiopathic PVCs from the RVOT are thought to be due to DADs,[2] but this theory has never been proved. DADs result from an increase in intracellular Ca2+, so a critical factor should be the action potential duration. Longer action potentials are associated with more Ca2+ overload and facilitated DADs.[70] Considering the fact that ARI correlates with the action potential duration, one would have expected that in patients with PVCs from the RVOT the ARI would be higher than in controls, but that was not the case.

Hamon et al,[71] studied in a porcine model, the effect of PVCs from the RVOT on electrical stability and on dispersion of repolarization and found a significant increase in the dispersion of the repolarization on the sinus beats immediately after the PVCs, that progressively returned to normal in the subsequent sinus beats. Those authors also studied the effect of PVCs on the cardiac neurons that respond to both afferent and efferent cardiovascular stimuli and demonstrated that almost half of those neurons (46%) responded to PVCs. This fact indicates that PVCs pose a strong and unique stress to intrinsic cardiac nervous system neurons. The recovery time and the ARI dispersion that we observed in our patients may result from the stress to intrinsic cardiac nervous system neurons, imposed by the presence of PVCs from the RVOT.[71]

There has been some concern regarding the accuracy of the electrograms obtained with the ECGI at least with the epicardial ECGI.

Still, several studies in humans have validated the ECGI system for depolarization and repolarization in different diseases[65,66]. With our epicardial and endocardial system, the number of studies is inferior, and invasive validation of this system for repolarization has not been performed, except for some limited data presented in the work by Rudic et al.[67]

In a recent study Yang et al,[72] assessed the ARI with an endocardial and epicardial ECGI system, during the PVC in 10 patients, compared the values obtained noninvasively with the intracardiac measurements and found a good correlation between them.

We also performed a validation study[73] of ECGI's ARI measurements, during sinus rhythm in 8 patients that underwent ablation of PVCs from the RVOT and performed an ECGI exam before the procedure. The RVOT was divided into 8 segments and the ARI across the RVOT was measured with ECGI that automatically calculates the difference between the recovery time and the activation time (Figure 9). The invasive ARI measurements were manually calculated from the extracted invasive unipolar electrograms at the exact same site, using the MATLAB. We assessed the correlation between the measurements obtained with both methods in 64 segments across the RVOT. The median absolute value of ARI measured with the ECGI was significantly higher than the ARI assessed from the intracardiac unipolar electrogram, respectively, 332 (320-364) ms and 312 (292-333) ms, p<0.001. However, we found a good correlation between both forms of measurement (R=0.614, p<0.001) (Figure 22).

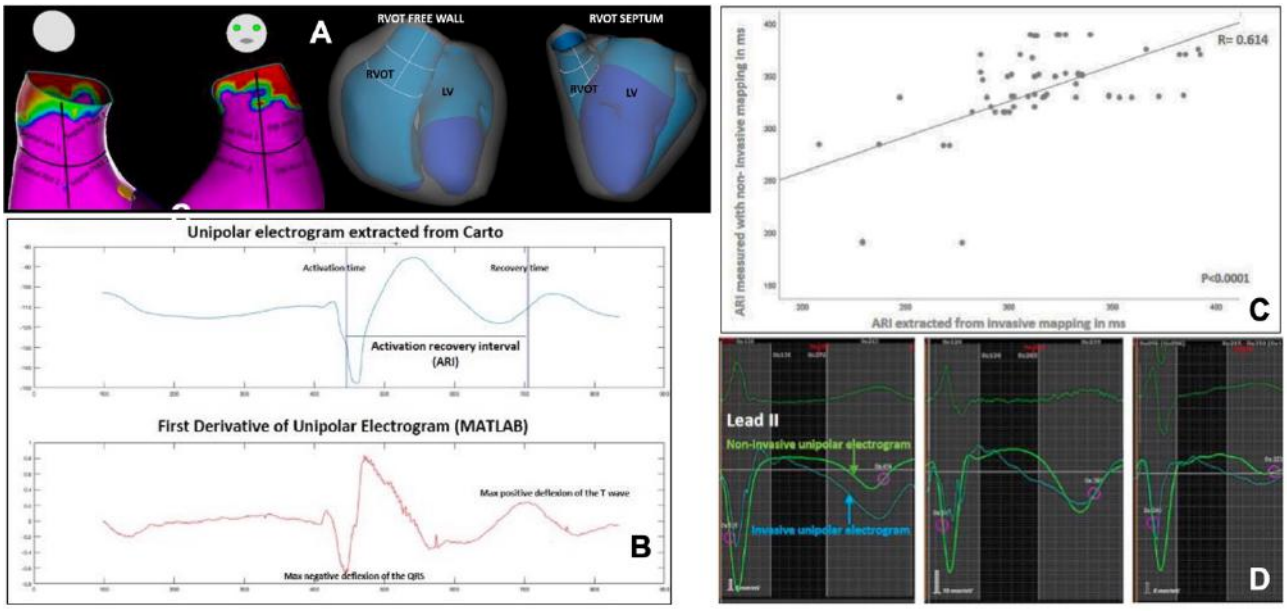

Figure 22. *Panel A: Segmentation of the RVOT into 8 segments Carto in the left and Amycard in the right. Panel B: Calculation of the AT and RT of the imported Carto unipolar electrogram using MATLAB. Panel C: correlation between ARI automatic measurements by ECGI and ARI calculated from intracardiac extracted electrograms in MATLAB. Panel D. Three examples of ECGI and the Carto unipolar electrograms overlayed.*

The results of our study should be interpreted with caution as more validation studies are needed prior to the widespread use of ECGI to assess repolarization.

Fibrosis leads to conduction abnormalities. However, whether the presence of LVAs, ST-segment elevation and deceleration zones and ARI dispersion may denote the presence of a subtle substrate for the PVCs or are the result of the electric remodelling triggered by the frequent PVCs is unknown.

Much in the same way, the Brugada syndrome was also initially believed to be just an electrical disease because the endocardial voltage map was normal. However, more recent studies published by Nademanee et al,[74] and Pappone and Brugada et al,[75] provided evidence of a disease of the RVOT, with epicardial abnormal electrophysiological findings, but also presence of LVAS, pointing to an anatomical substrate.

One way or the other, those patients should continue to be closely followed after ablation to evaluate the evolution of the disease.

Diastolic potentials

The presence of discrete diastolic potentials (DPs) on the bipolar intracardiac electrograms at the successful ablation site have been described previously by Liu et al.[76] The authors studied 25 consecutive patients with idiopathic PVCs from the RVOT and 10 control subjects. DPs were recorded in all patients in the vicinity of successful ablation sites during sinus rhythm before ablation and could still be recorded after ablation except in one patient. They were recorded in one patient in the control group, so, the incidence of DPs was significantly higher in patients with PVCs from the RVOT than in the control group (100% vs. 10%, $P < 0.001$).[76]

We also observed similar potentials at the successful ablation site in patients with idiopathic PVCs from the RVOT.[29] These are low amplitude potentials, occurring after the T wave of the ECG in sinus rhythm, that become pre-systolic, preceding the local bipolar ventricular electrogram during the PVCs (Figure 23).

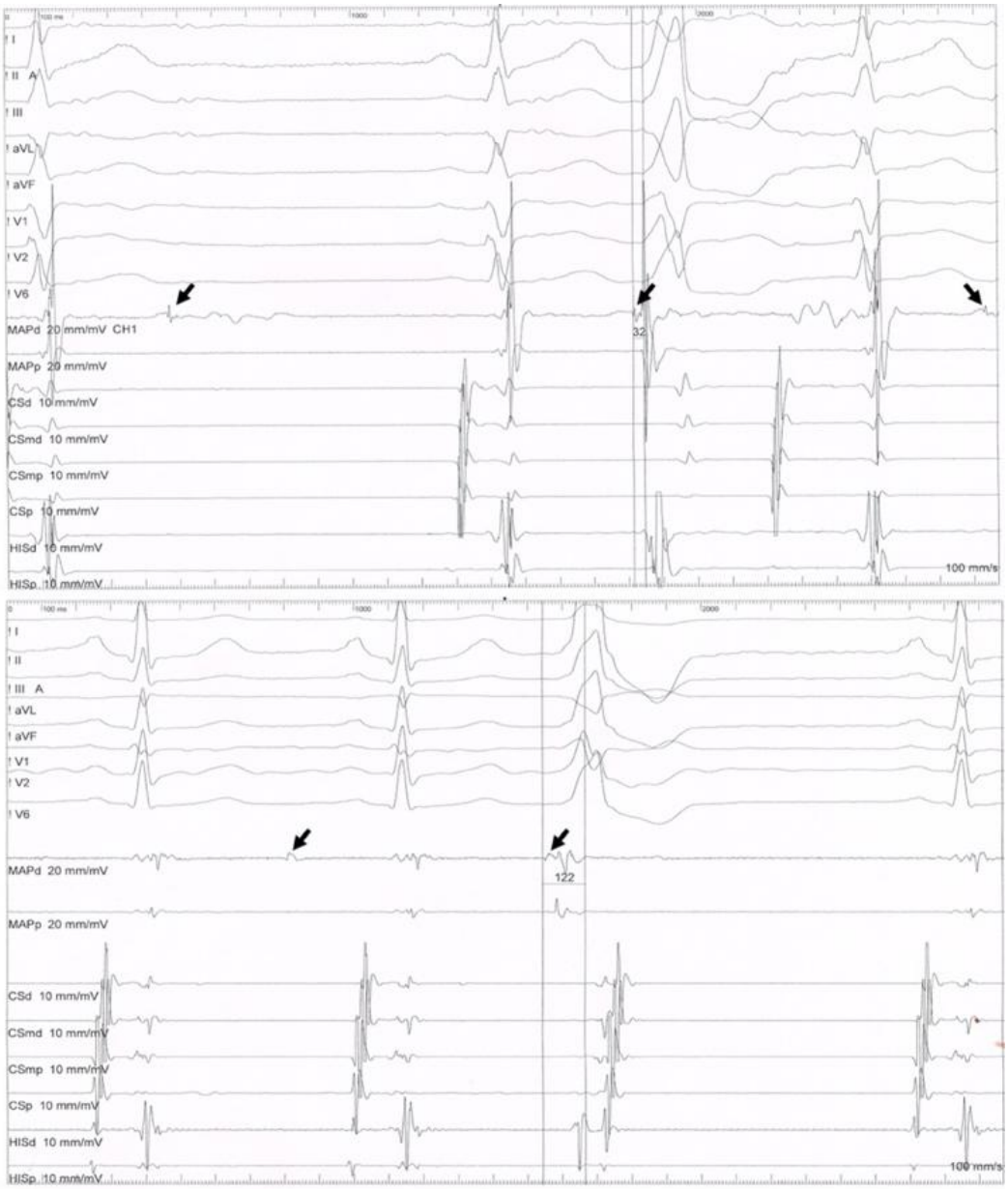

Figure 23. *Diastolic potentials. Intracardiac electrograms of two patient with PVCs from the RVOT. The distal dipole of the ablation catheter (MAPd) exhibits DPs (black arrows) after the T wave in sinus rhythm and presystolic during the PVC. The DPs have a sharp morphology (upper panel) and a blunt morphology (bottom panel). The gain in the ablation catheter is 20mm/1mV and sweep speed is 100mm/s. DP: diastolic potentials; PVCs: premature ventricular contractions; RVOT: right ventricular outflow tract*

These potentials were more frequently recorded at areas of low voltage and fractionated electrograms. Their meaning is unknown, but we speculate that they may represent a form of triggered activity that results in a potential with a very low amplitude, only recorded when the catheter is in close proximity to their origin.[29] In both the abovementioned studies the DPs were recorded in the RVOT. There is one previous report of similar DPs at the ablation site on left-sided PVCs, reported by Itoh et al[77] in a patient with PVCs from the aortomitral continuity.

However, in a recent study[78] we demonstrated the presence of DPs at the ablation site in all patients in the study group, regardless the right or left side of origin of the PVCs. These DPs were recorded below the pulmonary valve and both below and above the aortic valve and are

characterized by occurring late in diastole and separated from local ventricular electrogram by an isoelectric segment. These features differentiate them from the formerly described sharp local potential after the end of the local electrogram, first by Timmermans et al,[79] in PVCs originating above the pulmonary valve, and later by Thomsen et al,[80] in 24 patients with RVOT arrhythmias originating below the pulmonary valve.

Unlike the potentials described by those authors,[79,80] our DPs occur late in diastole, after the end of the T wave, corresponding to the phase 4 of the cardiac action potential,[81] suggesting that they may result from DADs. Therefore, representing a form of triggered activity that originates a potential with a very low amplitude, only recorded when the catheter is in close proximity to their origin. If we accept that they may be the source of the PVCs, it would be expected that their location would be at the site of successful RF application. When this potential is capable of propagating to a critical number of adjacent myocytes it elicits the occurrence of the PVC.

That may depend on the intensity of the DADs or on the degree of exit block. This finding is in agreement with the generally accepted theory that the outflow tract ventricular tachycardia is caused by cAMP-mediated DADs and triggered activity.[6] The DPs were also found in 3 patients (8%) in the validation group, this value is similar to the 10% in the control group reported by Liu et al.[76]

There are several publications reporting the association of idiopathic ventricular arrhythmias and AVNRT.[82,83] Hasdemir et al,[82] reported an incidence of spontaneous AVNRT among patients with idiopathic ventricular arrhythmias in 9%, and idiopathic ventricular arrhythmias in 11% of patients with clinical AVNRT. This association might be explained by the persistence of tissue with nodal properties at the area around the atrioventricular ring, in the fibrous septum, and in the outflow tracts, like a third branch of the conduction system present during embryologic development, known as the septal dead-end-tract connecting these regions.[84,85] This fact might be the reason for the presence of DPs in 8% of our validation group.

Romero et al,[86] described similar DPs, but those authors concluded that they were artifacts that were present when mapping the aortic cusps, in eleven out of 28 patients (39%) subjected to ablation of LVOT PVCs.

They found the alleged artifacts in the left coronary cusp in eleven patients, in the right coronary cusp in two and never in the non-coronary cusp. The authors refer that the artifacts are related to the reversal of arterial flow in the ascending aorta after closure of the aortic valve that gives rise to a recoil force in the aortic cusps, corresponding to the dicrotic notch in the aortic pressure curve. This mechanism does not explain the observed potentials because, firstly the dicrotic notch registered in the ascending aorta occurs immediately after the end of the T wave, and the artifacts they observed occur at variable intervals from the end of the T wave. Secondly, the timing and contour of the ascending aorta pulse varies with age,[87] the dicrotic notch becomes earlier with

age and in the series of Romero et al, doesn't seem to be a relation between age of the patients and the interval between the end of T wave and the artifact. Finally, the authors did not show objective evidence for the appearance of the artifacts in just 30 % of cases, and for their absence in the non-coronary cusp.

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Novel simplified approach to radiofrequency catheter ablation of idiopathic ventricular outflow tract premature ventricular contractions

State of the art

PVCs are a common finding in the normal population. The most common sites of PVCs, in patients without structural heart disease, are the RVOT and the LVOT.[1]

The prognosis associated with frequent PVCs depends on the presence of structural heart disease, so that idiopathic PVCs have been considered benign.[2,3] The definition of an idiopathic situation results from the lack of knowledge of the cause, but it does not imply absence of pathological abnormalities.

In the recently published guidelines, catheter ablation for frequent symptomatic PVCs refractory to medical therapy, is a class I indication.[4]

Ablation based on activation mapping and pace-mapping is considered the standard technique for eliminating idiopathic PVCs.[4] Radiofrequency delivery should be performed at the site of the earliest ventricular activation with a QS pattern in the unipolar electrogram. The ideal pace-match at ablation site is an identical QRS pattern in all 12 surface ECG leads (12/12 match).

The two main reasons for unsuccessful ablation, are the failure to reach the site of origin (SOO) of the PVCs, for instance when it is located in the epicardium, and the failure to find the SOO, due to absence of PVCS during the procedure.

Intraprocedural low PVC burden was reported in 30% of the procedures by Baser et al,[5] or in up to 43% of the cases, in a more recent study by Jauregui et.[6]

This may result from spontaneous variations, autonomic influence, anesthesia, or sedation. The approach in patients with low intraprocedural burden ranges from cancelation of the procedure as occurred in 11% of the patients in the study by Jaregui or ablation performed alternatively based only on pace-mapping.

However, the latter is hampered by the impossibility of capturing the ventricles and is less precise than activation mapping. The spatial resolution is around 1. 8 ± 0.6 cm2 when compared with the spatial resolution of activation mapping (1.2 ± 0.7 cm2)[7].

In the study by Bogun et al,[7] the sites with a 12/12 pace mapping match, were located at a median distance of 7.3 ± 5.0 mm away from the successful ablation site.

In the presence of low intraprocedural PVC burden the success may be reduced from 85% to 56%.[5]

It has been accepted for many years that idiopathic PVCs from the outflow tracts display normal anatomic and electrophysiological findings.[8]

However, in the previous chapter of this dissertation, we have provided evidence for the presence of an anatomical and electrophysiological substrate associated with frequent PVCs from the outflow tracts. These substrate consists of LVAs, with abnormal conduction, displaying dispersion of ARI and presence of DPs which we believe to be also associated with the occurrence of PVCs.

Furthermore, we identified a noninvasive electrocardiographic marker of LVAs, the ST-segment elevation at the level of the 2nd ICS, that can be used in the procedure planning.

There is an increasingly trend to go for substrate ablation in the majority of arrhythmias. This is the case of cavotricuspid isthmus for typical atrial flutter, scar homogenization for ischemic ventricular tachycardia, pulmonary vein isolation for atrial fibrillation or epicardial RVOT ablation for Brugada Syndrome.

Some authors have previously published their approach in patients with low intraprocedural PVC burden, ranging from cancelation of the procedure, as occurred in 11% of the patients in the study by Jauregui et al,[6] to ablation based in pace mapping only, with success rates between 77% and 87%,[6,9,10] or substrate mapping associated with pace mapping, with success between 78% and 93%.[11,12]

The presence of LVAs and DPs may be considered a new target for ablation. Substrate mapping to identify LVAs and searching for DPs may be a possible ablation strategy for ablation of outflow tracts PVCs in patients in whom despite the daily high number of PVCs in Holter recording, display a low PVC burden during the ablation procedure.

Recently, non-invasive mapping systems based on the electrocardiogram analysis have been developed (ECGI). They are capable of mapping an arrhythmia with just one beat instead of the usual point by point acquisition. It is certainly an option to perform in case of rare arrhythmias. However, the accuracy and reproducibility of this method has not been proven yet.

In conclusion, currently when a patient displays a very low intraprocedural PVC burden, the physician either sends the patient back home or risks continuing the procedure and come out with a bad result.

Objectives

Main Objective

Develop a new methodology that allows the possibility of treating a higher number of patients with frequent PVCs, regardless the presence of a low intraprocedural PVC burden.

Specific Objectives

- Demonstrate that this new methodology for mapping the PVCs is superior to current mapping technology in patients with a low intraprocedural PVC burden, in terms of immediate success and recurrence rate, while allowing for a reduction of the procedure, fluoroscopy, and radiofrequency times.
- Validate ST-segment elevation at the 2nd ICS as a non-invasive marker of LVAs in patients with outflow tract PVCs
- Evaluate the accuracy of the ECGI for identification the SOO of the PVCs.

Study design

This was a prospective single-arm clinical trial with comparison with a historical group carried out in two hospitals, Setubal Hospital Center, and Luz Hospital Lisbon. The feasibility and efficacy of the new proposed substrate-based ablation was assessed by comparing the procedure, fluoroscopy and radiofrequency time, and the success and recurrence rate in the study and historical groups.

A validation group without PVCs was studied to evaluate the prevalence of the abnormal substrate and the ECG marker in the general population and validate those findings as a PVC substrate.

In patients that had and ECGI performed before ablation the results of the ECGI were compared to those of the invasive mapping.

Patient selection

Inclusion criteria

Consecutive patients referred for catheter ablation of frequent (more than 10.000 PVCs/24 hours during Holter monitoring), idiopathic PVCs with an inferior axis, at the two hospitals. The inclusion criteria was the presence of an intraprocedural low PVC burden, defined as less than 2 PVCs/min in the first 5 minutes of the ablation procedure (**study group**).

The historical group consisted of consecutive patients that underwent PVC ablation by the same operator using the standard technique between 2016 and 2018. They were selected based on the review of all patient's files and selecting the ones that either had the ablation canceled due to low PVC burden or had an ablation report mentioning a low PVC burden during the procedure. The ablation procedure was reviewed to assess the PVC burden in the first 5 minutes of the procedure (**historical group**).

A validation group, of consecutive patients that underwent catheter ablation of supraventricular tachycardias and agreed to have an electroanatomical map of the RVOT performed in sinus rhythm were also studied. Patients were not included if there was any evidence of arrhythmias from the RVOT, either in the patient's files or during ablation of the supraventricular arrhythmia (**validation group**).

Exclusion criteria

Patients with known structural heart disease, history of sustained ventricular arrhythmias, inability to perform cardiac magnetic resonance (CMR), previous ablation and standard 12-Lead ECG with evidence of conduction or electrical disease or abnormal QRS morphology were excluded

Preprocedural evaluation

All patients underwent transthoracic echocardiography with evaluation of left ventricular ejection fraction and left atrium diameter, and standard 12-lead ECG.

A CMR with LGE was performed to rule out structural heart disease in all patients in the study group by protocol, and at the discretion of the attending physician in the historical group. ARVC was ruled out according to the Task Force Criteria.[13]

A 24-hour Holter recording was performed before ablation in patients with PVCs and the number of PVCs per 24 hours and the presence of NSVT, defined as >3 PVCs s in a run were assessed.

Estimation of Sample Size

For estimation of sample size for the study and historical groups, we used the formula:

$$N = \frac{P1x(100-P1) + P2 \times (100-P2) \times f(\alpha, \beta)}{(P2-P1) \times (P2-P1)}$$

P1- Current success rate in patients with low PVC burden (56%)

P2- Expected success rate using the new approach in patients with low PVC burden (85%)

α - Type I error (probability of rejecting a true null hypothesis)

β - Type II error (failure to reject a false null hypothesis)

f (α, β) is given by table: f (α=0.05, β=0.05) =7.9

For a desired power of 0.8

The estimated sample size was 38 patients in each group

For estimation of sample size for the study and validation groups, we used the formula:

$$N = \frac{P1x(100-P1) + P2 \times (100-P2) \times f(\alpha, \beta)}{(P2-P1) \times (P2-P1)}$$

P1- Prevalence of DPs in patients with PVCs[14] (62%)

P2- Expected prevalence of DPs in the validation group (30%)

α - Type I error (probability of rejecting a true null hypothesis)

β - Type II error (failure to reject a false null hypothesis)

f (α, β) is given by table: f (α=0.05, β=0.05) =7.9

For a desired power of 0.8

The estimated sample size was 37 patients in each group

Estimation was performed using the site https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

Methodology

Standard 12-Lead ECG and High Right Precordial Lead ECG

The ECG was performed immediately before the ablation with standard paper speed and calibration. After a standard 12-lead ECG recording, the ECG was repeated with V1 and V2 leads placed at the level of the 2nd ICS and maintaining the other lead's position. The presence of ST-segment elevation >1 mm in V1 and V2, and T wave inversion beyond V1 was assessed both on the standard ECG and on the high right precordial lead ECG. ST-segment elevation was measured at the take-off point of the QRS-ST.[15,16]

All ECG recordings were evaluated by two independent reviewers blinded to the patient group or the result of the voltage map or activation map.

Electroanatomic Mapping and Ablation

Patients were studied in a fasting non sedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. During endocardial mapping of the LVOT heparin was administrated to achieve an ACT of 250-300 sec. All procedures at Luz Hospital Lisbon were performed with remote magnetic navigation (RMN)

using the Niobe II Magnetic Navigation System (Stereotaxis, Inc., Saint Louis, MO, USA) with the CARTO 3 RMT (Biosense-Webster, Inc., Diamond Bar, CA, USA) system. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster Inc., Diamond Bar, CA, USA) was used with a 3.5-mm distal tip electrode and a 2–5–2 interelectrode distance as previously described.[17]

At Setubal Hospital Centre, all procedures were performed manually using the EnSite Precision (Abbott, St Paul MN, USA) system, with an irrigated tip TactiCath catheter (Abbott, St Paul MN, USA) with a 3.5-mm distal tip electrode and a 2–2–2 interelectrode distance. The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT with the RMN system or manually under fluoroscopic guidance, and then placed at multiple sites on the endocardial surface of the RVOT.

Mapping of the LVOT endocardium and the aortic coronary cusps was performed using a transaortic approach in all patients. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed.

Two maps were created, a voltage bipolar map of the RVOT in sinus rhythm and an activation map during the PVC.

Sinus rhythm map

The RVOT voltage map was performed in sinus rhythm without isoprenaline, both in patients from the study and the validation groups.

Only points with optimal contact were considered for the voltage mapping. For procedures done manually, 10 g was the minimal contact force accepted, and for RMN procedures the catheter–tissue contact qualitative indicator, displaying a good contact.[18]

The electrograms were analyzed in regard of their amplitude and the information was used to generate a 3-dimensional electroanatomical voltage map of the RVOT, with the electrophysiologic information, color-coded and superimposed on the geometry. The fill threshold used for mapping was 5-7.

The color display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude $\geq$ 1.5 mV), to red, representing electroanatomical scar tissue (amplitude <0.5 mV).

The level of RVOT/pulmonary valve junction was thoroughly determined based on electroanatomical voltage mapping by passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT until bipolar electrograms were absent in the distal pair of electrodes but present in the proximal pair. Voltage above the pulmonary valve is usually less than 0.5 mV. The area immediately below the level of the pulmonary valve displays intermediate colors,

corresponding to a bipolar voltage between 0.5 mV a 1.5 mV, defined as the transitional-voltage zone.[19] LVAs were defined as zones with local bipolar voltage<1.5 mV. Presence of LVAs outside the transitional-voltage zone were assessed.

DPs defined as persistent low amplitude discrete potentials occurring at late diastole, after the end of the T wave of the surface ECG in sinus rhythm that became presystolic during the PVCs[14] (Figure 23) were searched for and tagged in the map. The number of points acquired in sinus rhythm, the mapping time, the presence of LVAs outside the transitional-voltage zone, the presence of DPs and the area of the RVOT that displayed DPs were recorded.

Activation map of PVC and ablation

In the study group the activation map was directly aimed at the area with LVAs and DPs. The map was obtained by mapping points during the PVC while using a surface ECG lead as reference. In the absence of LVAs and DPs in the RVOT, the aortic cusps and the LVOT, the coronary sinus, the great cardiac vein and anterior interventricular vein were mapped. The number of points in PVC and the mapping time were recorded. At the earliest activation site, pace mapping was performed, and the pace mapping match was assessed.

In the historical group the activation map was performed conventionally by mapping several points during the PVC while using a surface ECG lead as reference.

The ablation site both in the study and historical group, was selected as the site with the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided a pace match of at least 11 /12 leads between paced and spontaneous PVC.

Energy was delivered between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 seconds, to a maximum temperature of 43 °C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed.

The site of ablation and its relation to the LVAs and the DPs were recorded in the study group.

Duration of the procedure defined as the time interval between the beginning of the procedure and the removal of the sheaths, the success of the procedure, defined as abolition of PVCs until 30 min after ablation, was also registered. Fluoroscopy time and duration of radiofrequency application were recorded.

Major complications defined as those that resulted in prolongation of hospital stay or another hospitalization, those that required additional intervention for treatment, and/or those that resulted in significant injury or death[4] were assessed.

All the intracardiac electrograms were reviewed by two senior electrophysiologists.

Non-invasive electrocardiographic imaging (ECGI)

The ECGI when available was performed before ablation using the Amycard system (EP Solutions SA, Switzerland) since 2018 and additionally the VIVO (Catheter Precision, NJ USA) since 2019.

The Amycard system uses a special body-surface electrode arrays with a total of 224 contacts that are placed on the patient's torso followed by same day ECG-gated contrast CT of the heart and torso Imaging data is imported in DICOM format and semi-automatically processed by the system to reconstruct realistic 3-dimensional models of the torso and heart. In the electrophysiology laboratory, the body-surface electrode arrays are connected to the ECG amplifier and ECG recordings taken during sinus rhythm and PVCs. Data from the body-surface ECG is processed by the system using its inverse-problem solution software in combination with anatomical data from the heart and torso. This allows the reconstruction of local electrogram of more than 2500 nodes at the epicardium and endocardium and the creation of epicardial and endocardial activation maps of the PVCs.

The VIVO system uses a patient specific myocardial model from MRI or CT, a 12-lead ECG of the PVC, and a 3D photo of the patient's torso to define ECG's electrodes position. VIVO uses semi-automated morphing of a reference model to generate a patient specific model of the heart and torso. This 3D heart model is used to determine the simulated activation sequences originating from discrete nodes in the heart.[20]

The localization of the PVCs based on ECGI was done using a segmental model with 22 segments on the left ventricle, to include the classical 17[21] segment model plus the aortic cusps and the papillary muscles, and 12 segments on the right ventricle including 4 on the RVOT (anterior, lateral, right septum and left septum). A perfect match was defined as a predicted location within the same anatomic segment where ablation was performed, whereas a near match, as a predicted location within the same segment or a contiguous one.

The accuracy of the ECGI and coherence between the Amycard and the VIVO systems were assessed.

Follow-up

Follow-up was performed on outpatient clinical visits with evaluation of symptom and standard ECG, at 1 month 6 months, 1 year and regularly once a year thereafter. Patients underwent a 24-hours Holter recording at 1 month, 1 year after the procedure and once a year thereafter. For patients that were followed at another institution data were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients'

files. Patients who failed to have recent clinical records were contacted by phone. Recurrence was defined as reappearance of symptoms or a 24-hour Holter with a PVC number higher than 1000 PVCs per 24 hours

Statistical analysis

All analyses were performed using SPSS statistical software, version 26.0 (SPSS, Inc, Chicago, Illinois).

Data is presented as median and lower and upper quartile (Q1-Q3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann Whitney test for two independent samples or Kruskal-Wallis test for multiple independent samples. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples.

The Kaplan-Meier survival function was used to compare the recurrence-free survival after successful ablation, and the PVC-free survival in the study and historical groups, and the Log-rank test was used for comparison between groups

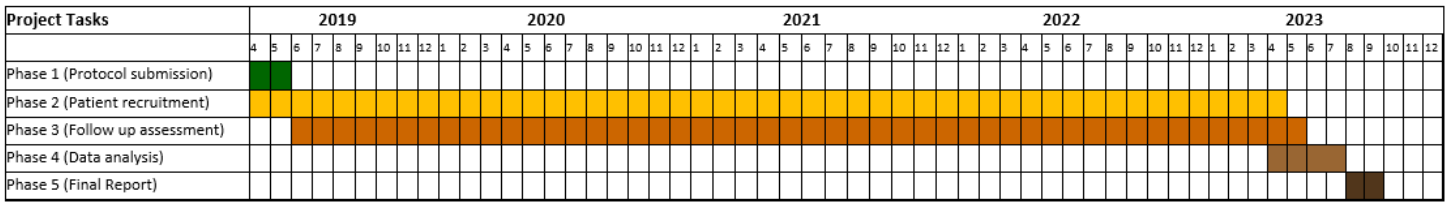
Univariable binary logistic regression analysis and calculation of the respective odds ratios (OR) and 95% confidence intervals (CI) was used to evaluate the discriminative power of the ST-segment elevation to predict the presence of LVAs adjusted to the other variables. We included in the multivariate analysis those variables with a p-value < 0.05 in the univariate analysis. The performance of ST-segment elevation as a diagnostic test including the positive and negative predictive value as well as specificity and sensitivity was based on 2x2 contingency table and chi square test.

For all tests a p value <0.05 was considered as statistically significant.

Ethics

All patients signed the informed consent form, and the study was approved by the Ethical Committee of Setubal Hospital Center, Luz Hospital Lisbon, and Nova Medical School. The study is in compliance with the Helsinki Declaration.

Timeline



Protocol Summary

MAIN OBJECTIVE	Develop a new methodology that allows the possibility of treating a higher number of patients with frequent PVCs, regardless the presence of a low PVC burden in the day of the procedure
SPECIFIC OBJECTIVES	- Demonstrate that this new methodology is superior to current mapping technology in patients with a low intraprocedural PVC burden. - Validate ST-segment elevation at the 2nd ICS as a non-invasive marker of LVAs in patients with outflow tract PVCs - Evaluate the accuracy of non-invasive mapping for identification of the SOO of PVCs
STUDY DESIGN	Prospective single-arm two-center clinical trial with comparison with a historical group and a validation group in the same institutions.
PATIENT SELECTION	**Eligibility** Age >18 years **Study group** Inclusion criteria • Consecutive patients undergoing mapping and ablation of frequent PVCs defined as more than 10.000 /24 hours with inferior axis • Less than 2 PVCs /min in the first 5 minutes of the procedure Exclusion criteria • Known structural heart disease • History of sustained ventricular arrhythmias • Inability to perform CMR • Previous ablation • Standard 12-Lead ECG evidence of conduction or electrical disease or abnormal QRS morphology **Historical group** Inclusion criteria • Consecutive patients undergoing mapping and ablation of frequent PVCs defined as more than 10.000 /24 hours with inferior axis between 2016-2018 • Either had the ablation canceled due to low PVC burden, or had an ablation report mentioning a low intraprocedural PVC burden Exclusion criteria • Known structural heart disease • History of sustained ventricular arrhythmias **Validation group** Inclusion criteria • Consecutive patients undergoing ablation of supraventricular arrhythmias Exclusion criteria • Known structural disease • History of PVC or ventricular arrhythmias • Standard 12-Lead ECG evidence of conduction or electrical disease or abnormal QRS morphology

SAMPLE SIZE	38 patients in the study group 38 patients in the historical group 38 patients in the validation group

WORKPLAN	**Initial evaluation**
	<u>Study group</u>
	• 12 lead ECG
	  o Standard
	  o Upward displacement of V1 and V2 leads
	• 2D and M Mode and Doppler echocardiogram
	• CMR with Late Gadolinium Enhancement (LGE)
	• Non-invasive mapping when available
	• Invasive mapping and Ablation Procedure
	  o Electroanatomical voltage mapping of the RVOT in sinus rhythm
	  o Mapping and tagging of the DPs in sinus rhythm
	  o Activation mapping in the area of interest
	  o Pace-mapping in the area of interest
	  o Ablation
	<u>Historical group</u>
	• Review of patient's files
	• Review of the ablation procedure
	<u>Validation group with no PVCs</u>
	• 12 Lead ECG
	  o Standard
	  o Upward displacement of V1 and V2 leads
	• Invasive mapping
	  o Electroanatomical voltage mapping of the RVOT in sinus rhythm
	  o Mapping and tagging of the DPs in sinus rhythm
	Follow-up evaluation at 1 month, 6 months, 1 year and once a year
	• Evaluation of symptoms every visit
	• Standard ECG at every visit
	• Holter monitoring at 1 month, 1 year and once a year

ASSESSMENT SCHEDULE	**Initial evaluation**
	• Outpatient clinics
	  o 12-Lead ECG
	  o 2D, M Mode and Doppler echocardiogram
	  o CMRI with LGE
	  o ECGI
	Hospital admission
	  o Catheter ablation
	Follow-up
	• Outpatient clinics

OUTCOMES PARAMETERS	• Identification of a substrate for PVC ablation • Identification of a non-invasive marker of substrate • Improved results with the new substrate-based approach • Accuracy of ECGI to detect the origin of the PVCs

ETHICS	All patients signed the informed consent form, and the study was approved by Setubal Hospital Center, Luz Hospital Lisbon and Nova Medical School, Ethical Committees. The study was in compliance with the Helsinki Declaration.
STATISTICAL ANALYSIS	The main aims of the proposed study were - Test the null hypothesis that LVAs and DPs are not a substrate for PVC ablation. - Test the null hypothesis that ST-segment elevation is not a non-invasive marker of that substrate. - Test the null hypothesis that the proposed substrate-based ablation is not superior to the conventional strategy All analyses were performed using SPSS statistical software, version 26.0 (SPSS, Inc, Chicago, Illinois). Data is presented as median and lower and upper quartile (Q1-Q3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann Whitney test for two independent samples or Kruskal-Wallis test for multiple independent samples. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples. The Kaplan-Meier survival function was used to compare the recurrence-free survival after successful ablation, and the PVC-free survival in the study and historical groups, and the Log- rank test was used for comparison between groups Univariable binary logistic regression analysis and calculation of the respective odds ratios (OR) and 95% confidence intervals (CI) was used to evaluate the discriminative power of the ST-segment elevation to predict the presence of LVAs adjusted to the other variables. We included in the multivariate analysis those variables with a p-value < 0.05 in the univariate analysis. The performance of ST-segment elevation as a diagnostic test including the positive and negative predictive value as well as specificity and sensitivity was based on 2x2 contingency table and chi square test. For all tests a p value <0.05 was considered as statistically significant.
DURATION OF STUDY PERIOD	Enrolment started July 2019 and ended April 2022. First patient enrolled in Setubal Hospital Center in July 2019 Minimum follow-up time of 1 month
TIMELINE (Final)	**Phase 1.** Protocol accepted July 2019 (**Setubal Hospital Center**) October 2019 (**Luz Hospital Lisbon**) **Phase 2.** Patient enrollment started July 2019- April 2022 **Phase 3.** Follow-up started August 2019 **Phase 4**. Data analysis started June 2022 **Phase 5.** Final report finished by July 2022
GRANT	Grant from the Luz Hospital Lisbon as project NoSA-APVC (Reference LH.INV.F2019005) under the initiative “Luz Investigação.”

Results

Population

Since July 2019 and April 2022, thirty-eight patients were enrolled in the study group. Between 2016 and 2018, retrospectively, thirty-eight patients were included in the historical group. Since July 2019 and April 2022, thirty-eight patients were enrolled in the validation group, of whom thirty underwent ablation of atrioventricular nodal reentrant tachycardia (AVNRT), four of typical atrial flutter, two of occult accessory pathways and two of right atrial tachycardia (Table 1).

Table 1. *Evaluated parameters and comparison between groups*

	Overall sample (n=114)	Study Group (n=38)	Historical Group (n=38)	Validation Group (n=38)	P value
Demographic data					
Age in years, median (Q1-Q3)	50 (38-61)	53 (41-65)	50 (41-61)	50 (35-58)	0.555
Male Gender, n (%)	48 (42)	16 (42)	17 (44)	15 (40)	0.898
Weight in Kg, median (Q1-Q3)	70 (60-80)	70 (60-81)	70 (62-76)	64 (59-77)	0.670
Height in cm, median (Q1-Q3)	167 (164-172)	165 (161-170)	165 (161-173)	167 (165-171)	0.341
BMI in Kg/m2, median (Q1-Q3)	24 (22-27)	24 (22-28)	24 (22-26)	23 (22-27)	0.736
Risk factors, history, and medications					
Hypertension, n (%)	26 (23)	7 (18)	8 (21)	11 (29)	0.523
Diabetes, n (%)	7 &)	2 (5)	3 (8)	2 (5)	0.867
Syncope, n (%)	6 (5)	4 (11)	2 (5)	0 (0)	0.121
Family history of sudden death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-
Betablockers, n (%)	58 (51)	26 (68)	23 (61)	9 (24)	**<0.0001**
Antiarrhythmic drugs, n (%)	12 (11)	7 (18)	2 (5)	3 (8)	0.141
Transthoracic echocardiogram					
LVEF in %, median (Q1-Q3)	59 (57-60)	58 (56-60)	60 (58-60)	59 (58-60)	0.330
LAD in mm, median (Q1-Q3)	35 (33-37)	35 (30-40)	34 (33-35)	35 (33-38)	0.283
24-hour Holter recording*					
N° of PVCs, in n x104, median (Q1-Q3)	1.8 (1.3-2.6)	1.9 (1.3-2.6)	1.8 (1.3-2.6)	-	0.988
NSVT, n (%)	22 (29)	13 (34)	9 (24)	-	0.312

* in the study group and historical group; BMI: body mass index; LAD: left atrium diameter; LVEF: left ventricular ejection fraction; NSVT: non-sustained ventricular tachycardia

The three groups did not differ in relation to age or gender. Patients in the study and historical group were more frequently on betablocker therapy than in the validation group, 68% and 61% versus 24%, p<0.0001.

Patients with PVCs were all symptomatic. Seventy complained of palpitations, six patients had typical vagal syncope, and no patient had family history of sudden death. Physical examination, and transthoracic echocardiography, including 2-dimensional, M-mode, were normal and demonstrated normal right ventricle size and function. None of the CMRs performed (all patients in the study group and 22 patients in the historical group) showed evidence of RVOT abnormalities.

The 24-hour Holter recording displayed a high PVC burden with a median of 18000 (13000-26000)/24 hours not significantly different in the study and historical group. Twenty-two patients (29%) had episodes of NSVT, also not significantly different between the two groups.

Standard 12-Lead ECG and High Right Precordial Lead ECG

The results of the standard 12-lead ECG and the ECG performed at the level of the 2nd ICS are displayed in Table 2.

Table 2. *Standard 12-Lead ECG and High Right Precordial Lead ECG*

	Overall sample (n=114)	Study Group (n=38)	Historical Group (n=38)	Validation Group (n=38)	P value
Standard 12 lead ECG					
ST-segment elevation at V1 or V2, n (%)	12 (11)	6 (16)	6 (16)	0 (0)	**0.035**
T wave inversion beyond V1, n (%)	4 (4)	2 (5)	2 5)	0(0)	0.335
High right precordial leads ECG‡					
ST-segment elevation at V1 or V2, n (%)	29 (38)	27 (71)	-	2 (5)	**<0.0001**
T wave inversion beyond V1, n (%)	16 (21)	16 (42)	-	0 (0)	**< 0.0001**

‡ in the study group and validation group.

The standard 12-lead ECG revealed ST-segment elevation in V1 or V2 in 6 (16%) patients in both the study and the validation groups, significantly higher than in the validation group (0%), p=0. 035.. That percentage increased to 71 % in the study group when performed at the 2nd ICS, significantly higher than in the validation group (5%), p<0.0001.

Regarding the prevalence of T-wave inversion beyond V1 in the standard ECG, it was not significantly different between groups. However, at the 2nd ICS, we found presence of T-wave inversion beyond V1 in 16 patients of the study group (42%) and in none of the patients from the validation group, p<0.0001.

All patients with ST-segment elevation presented with either coved-type or saddleback pattern (Figure 24) defined as type 2 or 3 Brugada ECG pattern, but none presented with ECG diagnostic

pattern for Brugada Syndrome, meaning a coved-type pattern with >2 mm in > 1 right precordial lead (V1 to V3).[22]

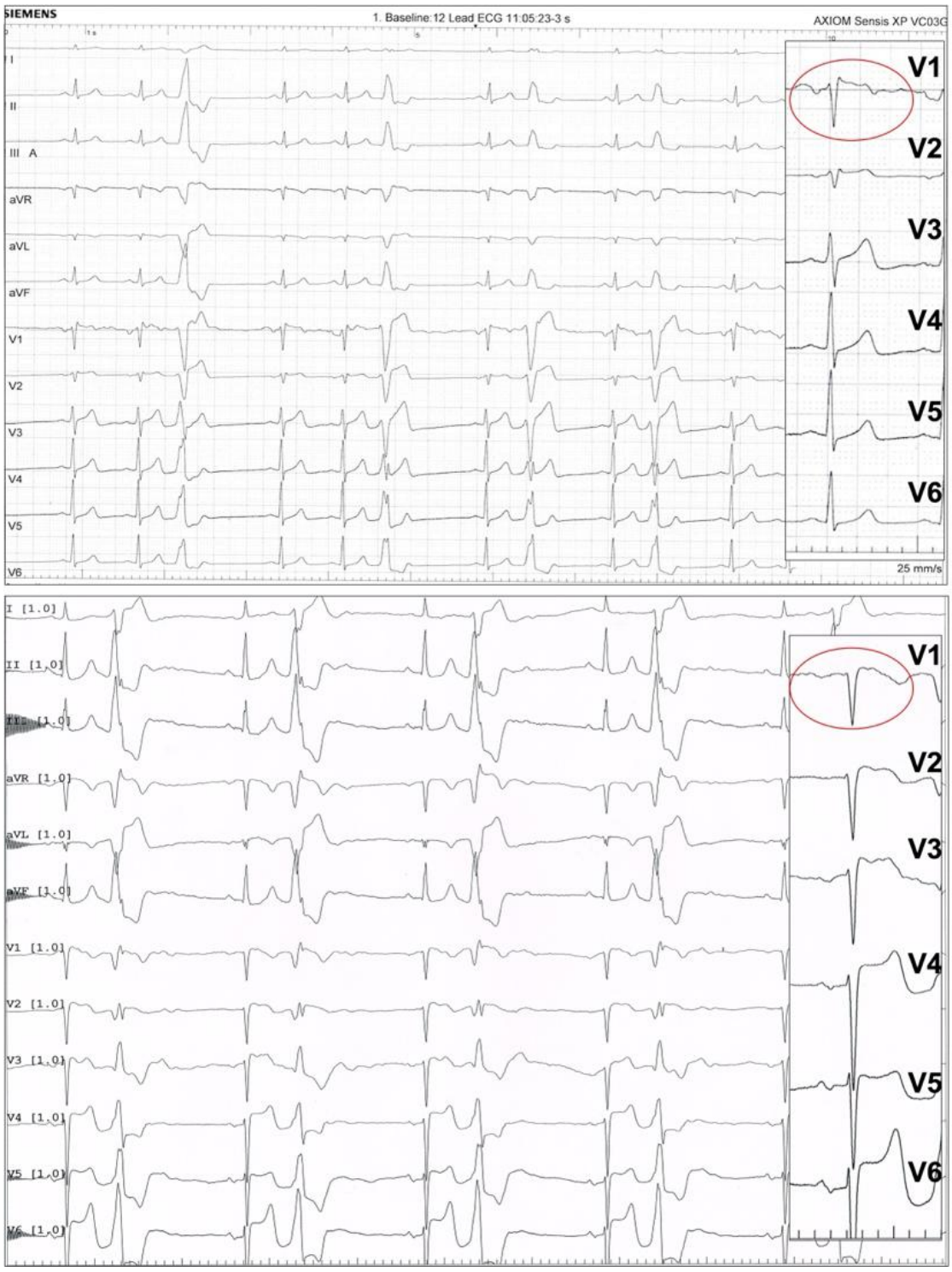


Figure 24. *Two patients with the ECG performed at the 2nd ICS displaying a saddleback ST-segment elevation (upper panel), and a coved-type pattern (bottom panel). Amplified on the right side of the figure*

Regarding the site of origin of the PVCs (Table 3), we found no significant difference in the prevalence of ST-segment elevation and T wave inversion beyond V1 in the standard or high position. However, ST-segment elevation at the 2nd ICS was significantly more frequent in patients with PVCs from the RVOT than from the LVOT, 86% versus 22%, p=0.001.

Table 3. *Standard 12-Lead ECG and High Right Precordial Lead ECG in the study group according to the site of the PVCs*

	Overall sample (n=38)	RVOT PVCs (n=29)	LVOT PVCs (n=9)	P value
Standard 12 lead ECG				
ST-segment elevation at V1 or V2, n (%)	6 (16)	5(17)	1(11)	1.000
T wave inversion beyond V1, n (%)	2 (5)	2 (7)	0 (0)	1.000
High right precordial leads ECG‡				
ST-segment elevation at V1 or V2, n (%)	27 (71)	25 (86)	2 (22)	**0.001**
T wave inversion beyond V1, n (%)	16 (42)	14 (48)	2 (22)	0.254

PVC: premature ventricular contractions; LVOT: left ventricular outflow tract: RVOT: right ventricular outflow tract.

Electroanatomic Mapping and Ablation

Sinus rhythm map

Seventy-six patients, 38 in the study group and 38 in the validation group underwent successful mapping of the RVOT in sinus rhythm (Table 4).

Table 4*. Invasive mapping comparison between the study group and the validation group*

	Overall sample (n=76)	**Study group (n=38)**	**Validation group (n=38)**	**P value**
Invasive voltage map of the RVOT in SR				
RMN/manual ablation, n/n (%)	51/25 (67)	16/22 (42)	35/3 (92%)	**<0.0001**
Mapping time in min, median (Q_1-Q_3)	20 (15-23)	20 (13-29)	18 (15-21)	0.439
Number of points, median (Q_1-Q_3)	382 (329-450)	395 (330-435)	352 (327-476)	0.526
Fluoroscopy time, in sec median (Q_1-Q_3)	71 (5-350)	339 (203-600)	5 (0-10)	**<0.0001**
Presence of LVAs in the RVOT, n (%)	31 (41)	27 (71)	4 (11)	**<0.0001**
Presence of DPs in the RVOT, n (%)	36 (47)	33 (87)	3 (8)	**<0.0001**

DPs: diastolic potentials; LVAs: low voltage areas; RMN: remote magnetic navigation; RVOT: right ventricular outflow tract; SR: sinus rhythm

The mapping was performed with RMN in 51 patients (67%). In the validation group the percentage of cases performed with RMN was significantly higher than in the study group respectively, 92% vs 42%, p<0.0001.

The median number of points was not significantly different between the study and the validation groups, 395 (330-435) and 352 (327-476) p=0.526, taking a median of 20 (15-23) min to acquire, not significantly different in the two groups. The fluoroscopy time for mapping of the RVOT in the validation group was remarkably low, 5 (0-10) sec, significantly shorter than in the study group.

The presence of LVAs was found in a significantly higher percentage of patients in the study group, in comparison with the validation group., respectively 27 patients (71%) and four patients (11%), p<0.0001. The prevalence was significantly higher in patients with PVCs from the RVOT than from the LVOT (Table 5), 83% versus 33%, p=0.009. Five patients with PVCs from the RVOT did not display LVAs (Figure 18).

Table 5. *Procedure data in the study group according to the site of the PVCs*

	Overall sample (n=38)	RVOT PVCs (n=29)	LVOT PVCs (n=9)	P value
Procedure Data				
RMN/manual ablation, n/n	34/32	14/15	2/7	0.254
Presence of LVAs in the RVOT, n (%)	27 (71)	24 (83)	3 (33)	**0.009**
Presence of DPs in the RVOT, n (%)	33 (87)	29 (100)	4 (44)	**<0.0001**
LAT in ms, median (Q1-Q3)	36 (30-47)	38 (30-49)	30 (22-42)	0.155
Procedure time in min, median (Q1-Q3)	130 (100-167)	130 (108-167)	130 (100-178)	0.946
RF time in seconds, median (Q1-Q3)	400 (200-618)	410 (240-627)	60 (120-612)	0.566
Fluoroscopy time in min, median (Q1-Q3)	6 (3.5-10)	5.7 (3-9.8)	6 (4.5-10.1)	0.417
Acute success, n (%)	34 (90%)	25 (86)	9 (100)	0.554
Complications, n (%)	1 (3)	0 (0)	1 (11)	0.237

DPs: diastolic potentials; LVAs: low voltage areas; RMN: remote magnetic navigation; LAT: local activation time measured in ms before the beginning of the QRS; LVOT: left ventricular outflow tract; RF: radiofrequency RVOT: right ventricular outflow tract

The presence of DPs in the RVOT was found in three patients (8%) from the validation group, respectively with an area of 1, 1.2 and 1.5 cm^2, and in 33 patients (87%) in the study group, p<0.0001, with and area of 1.5 (1-2.3) cm^2 (Figure 17). Their presence was significantly higher in patients with PVCs from the RVOT than from the LVOT 100% versus 44%, (4 patients), p<0.0001. DPs were located in LVAs in 82 % of cases in the study group and in one out of three (33%) patients from the validation group, p=0.116.

Activation map of premature ventricular contraction and ablation

The PVCs originated from the RVOT in 29 patients and the LVOT in nine. (Figure 25)

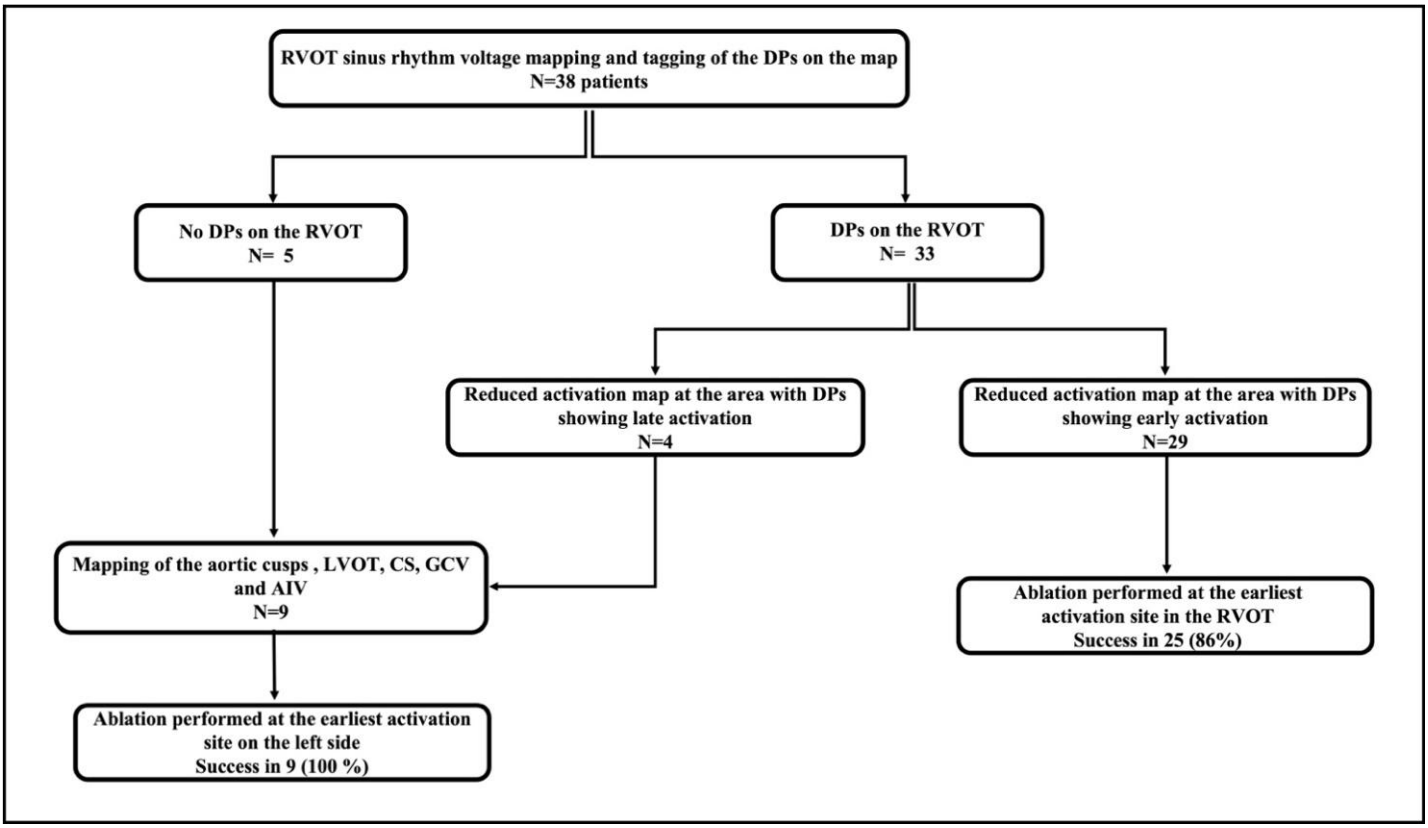


Figure 25. *Flowchart of the ablation procedure*

In the thirty-three patients from the study group with DPs in the RVOT in sinus rhythm, the area was directly mapped during PVC. In four out of 33 patients, the local activation time (LAT) in the RVOT was late in relation to the beginning of the QRS, so we went directly to the left side, as with the remaining five patients that did not present DPs in the RVOT in sinus rhythm.

In the 29 patients with DPS in the RVOT, and an early activation in the area with DPs, the PVC was successfully mapped with a low number of points, median of 34 (20-43), minimum 2 points, and a mapping time in PVC of 30 (19-50) min, minimum 2 min (Figure 26).

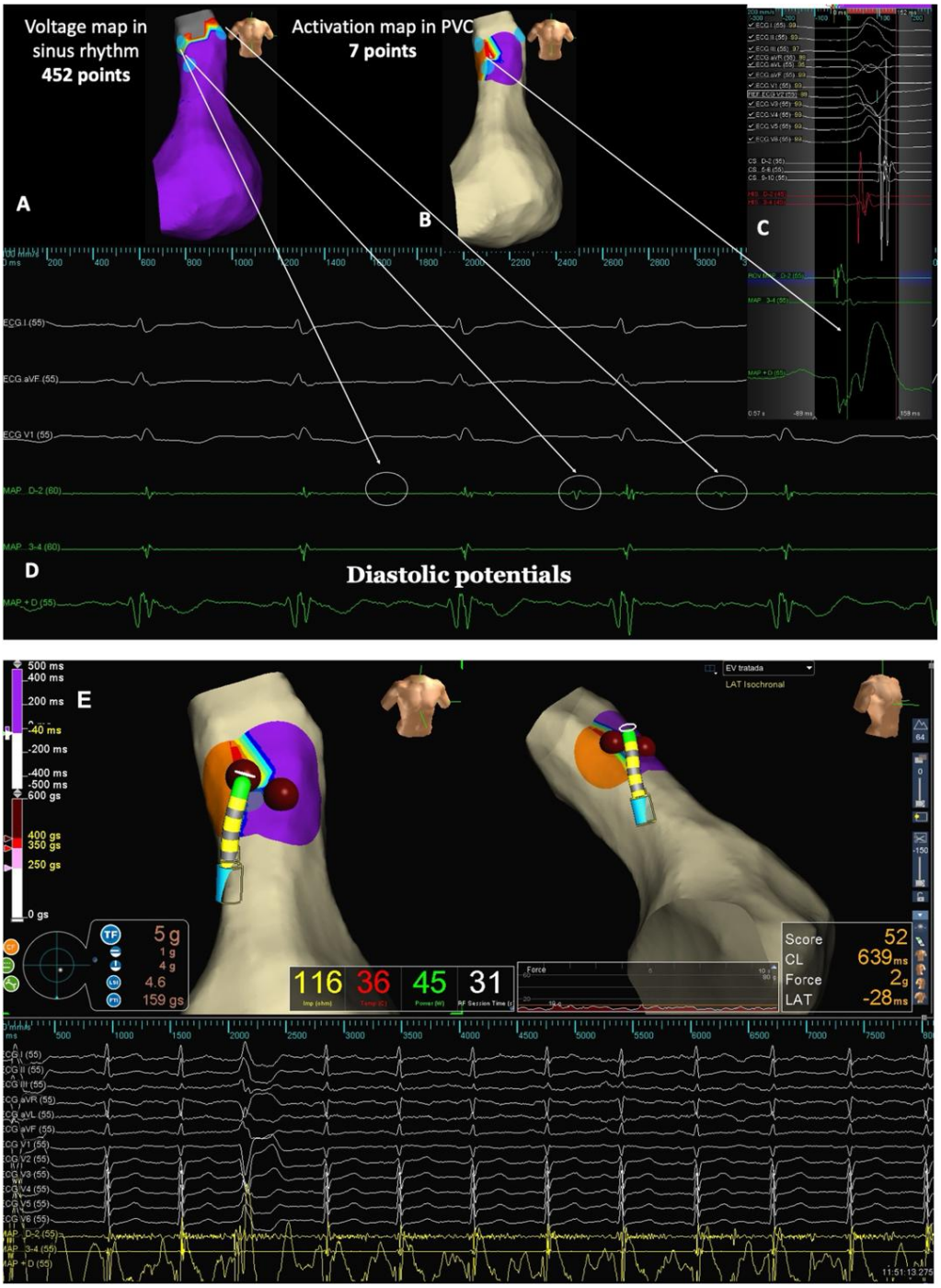


Figure 26. *Voltage map in sinus rhythm looking for DPs with 452 points (panel A). Activation map in PVC in the area with DPs with 7 points (panel B). Intracavitary electrogram at the earliest activation point displaying a QS pattern in the unipolar electrogram (panel C). DPs in sinus rhythm corresponding to the blue dots (panel D). Radiofrequency application with disappearance of the PVCs within the first seconds. DP: diastolic potentials. PVC: premature ventricular contractions*

On the right side, the PVCs originated in the free wall in 13 patients and in the septal wall in 16 patients. On the left side, the PVCs originated from the LVOT under the LCC in three patients, from the LCC in two, the aortomitral continuity in two, the RCC-LCC commissure in one, and in the LV summit in another.

The LAT at the ablation site was 38 (30-49) ms before the beginning of the QRS in the RVOT and 30 (22-42) ms in the LVOT, p=0.155.

At the ablation site the pace mapping match was at least 11/12 leads in all patients. For right-sided PVCs, the ablation site was in an area of low voltage in 24 patients (63%), either in the transitional zone in 13 or in a LVA outside the transitional zone in 11 patients.

All patients in the study group displayed DPs at the ablation site, that became pre-systolic during PVC and did not disappear after successful ablation.

The procedure time, RF time and fluoroscopy time were not significantly different for PVCs from the RVOT and LVOT, respectively, 130 (108-167) vs 130 (100-178) min, p=0.946, 410 (240-627) vs 360 (120-612) min, p=0.566, and 5.7 (3-9.8) vs 6 (4.5-10.1) min, p=0.417. The overall success rate of ablation was 90%, 100% for left-sided PVCs and 86% for right-sided, p=0.554, respectively (Figure 25). Unsuccessful cases were all from the RVOT, in three patients the SOO was in the left septum the thickest portion of the RVOT, and one in the anterior free wall.

The complication rate was low, (2.6%), one patient that developed a femoral pseudoaneurysm that resolved with injection of fibrin glue.

Comparison between the study group and the historical group

The comparison between the study and historical group is displayed in (Table 6).

The median number of PVCs /min in the first 5 minutes of the procedure was not significantly different between the two groups, respectively, 1 (0.9-2) in the study group, and 1 (0.4-1.3) in the historical group p=0.107.

However, in the historical group only 34 patients (90%) underwent electrophysiological mapping, the other 4 patients (11%) had the procedure canceled due to the low PVC burden.

Ablation was attempted in 28 patients out of the 34 patients that underwent electrophysiological study, corresponding to 74% of the patients from historical group, which was significantly lower than in the study group (100%), p=0.001.

The proportion of patients that underwent ablation with RMN versus manual was not significantly different between the study and the historical group, respectively 42% and 64%, p=0.075

The two groups did not differ in the right versus left origin of the PVCs, fluoroscopy, and radiofrequency time.

The procedure time however, in patients that underwent ablation, was significantly shorter in the study group when comparing to the historical group, 130 (100-164) vs 183 (160-203) min, p<0.0001. The success rate was significantly higher in the study group 36/38 (90%) vs 18/28 (64%), p=0.013, with a similar complication rate.

Table 6. *Procedure and follow-up data between the study group and the historical group*

	Overall sample (n=76)	Study group (n=38)	Historical group (n=38)	P value
Procedure Data				
Procedure performed, n (%)	72 (95)	38 (100)	34 (90)	0.115
Ablation performed, n (%)	66 (87)	38 (100)	28 (74)	**0.001**
RMN/manual ablation, n/n *	34/32	16/22	18/10	0.075
Number of PVC/min, median (Q1-Q3)	1 (0.5-2)	1 (0.9-2)	1 (0.4-1.3)	0.107
RVOT/LVOT, n/n (%) *	49/17	29/9	29/8	0.654
Procedure time in min, median (Q1-Q3) *	155 (120-190)	130 (100-164)	183 (160-203)	**<0.0001**
Fluoroscopy time in min, median (Q1-Q3) *	5 (3-8)	5.6 (3.4-10)	4 (3-6)	0.111
RF time in seconds, median (Q1-Q3) *	380 (206-600)	390 (191-609)	340 (240-600)	0.833
Acute success, n (%) *	52 (79%)	34 (90)	18 (64)	**0.013**
Complications, n (%) *	1 (2)	1 (3)	0 (0)	1.000
Follow-up				
Follow-up time in days, median (Q1-Q3)	1060 (574-1807)	581 (411-935)	1769 (1299-2199)	**<0.0001**
Recurrence, n (%) †	4 (8)	4 (12)	0 (0)	0.285
Post ablation last 24-h Holter recording#				
Number of PVCs, in $nx10^4$, median (Q1-Q3)	10 (1-87)	12 (1-146)	5 (0-53)	0.422
NSVT, n (%)	0 (0)	0 (0)	0 (0)	-

*In patients that underwent ablation
† In patients that underwent successful ablation
#In patients that underwent successful ablation and did not have recurrence
LVOT: left ventricular outflow tract; NSVT: non-sustained ventricular tachycardia; PVCs: premature ventricular contractions; RF: radiofrequency; RMN: remote magnetic navigation; RVOT: right ventricular outflow tract

ST-segment elevation as a non-invasive marker of LVAs

When evaluating the electrocardiographic findings we found an association between ST-segment elevation, and the presence of negative T-wave beyond V1 at the 2nd ICS and the presence of LVAs, respective unadjusted OR (95% CI) of 145.1 (24.86-847.2), p<0.0001, and 17.71 (3.363-86.34), p<0.0001.

Also, the RVOT site of the VAs showed an association with LVAs, OR (95% CI) 27.43 (7.825-96.14), p<0.0001 (Table 7).

However, after adjustment with multivariate analysis the only independent predictor of LVAs was the ST-segment elevation at the 2nd ICS with an adjusted OR (95% CI) of 167.5 (9.006-3116), p=0.001.

The ST-segment elevation at the 2nd ICs as a noninvasive marker of LVAs had a sensitivity of 87%, specificity of 96%, positive predictor value of 93% and negative predictor value of 91%.

Table 7. *Binary logist regression analysis with crude and adjusted odds ratios OR (95%CI) showing the discriminative power of the evaluated parameters to predict the presence of LVAs**

	Unadjusted		Adjusted	
Variables	OR (95% CI)	P value	OR (95% CI)	P value
ST elevation in V1 or V2 at the 2nd ICS	145.1 (24.86-847.2)	<0.0001	167.5 (9.006-3116)	**0.001**
Negative T-wave beyond V1 at the 2nd ICS	17.71 (3.3631-86.34)	<0.0001	12.29 (0.750-201.2)	0.079
RVOT site of PVCs	27.43 (7.825-96.14)	<0.0001	0.592 (0.033-10.71	0.723

OR: odds ratio; RVOT: right ventricular outflow tract; PVC: premature ventricular contractions

*In the group of patients that underwent RVOT voltage map in SR (study group and validation group)

Follow-up

The median follow-up time in the overall population with PVCs was 1060 (574-1807) days, minimum 30 days, and maximum 2313 days. No patients were lost to follow-up. The follow-up was significantly shorter for the study group (Table 6).

In the beginning of the follow-up, 34 patients (90%) from the study group had their PVCs abolished, in comparison to 18 patients (47%) in the historical group, p<0.0001, the survival curves free from PVCs in the study group was better than in the historical group, Log-Rank= 0.002 (Figure 27).

During this time, four patients (8%) out of 52 patients that underwent successful ablation, had recurrence of the PVCs, all in the study group. Two patients had an early recurrence within the first 24 hours, during hospital stay. One patient had recurrence two weeks after ablation and one patient 300 days after ablation. One patient repeated ablation with RF applications at the same site and is well without PVCs, and the other three patients declined a second ablation procedure. The recurrence rate in the two groups was not significantly different (Log-rank=0.125).

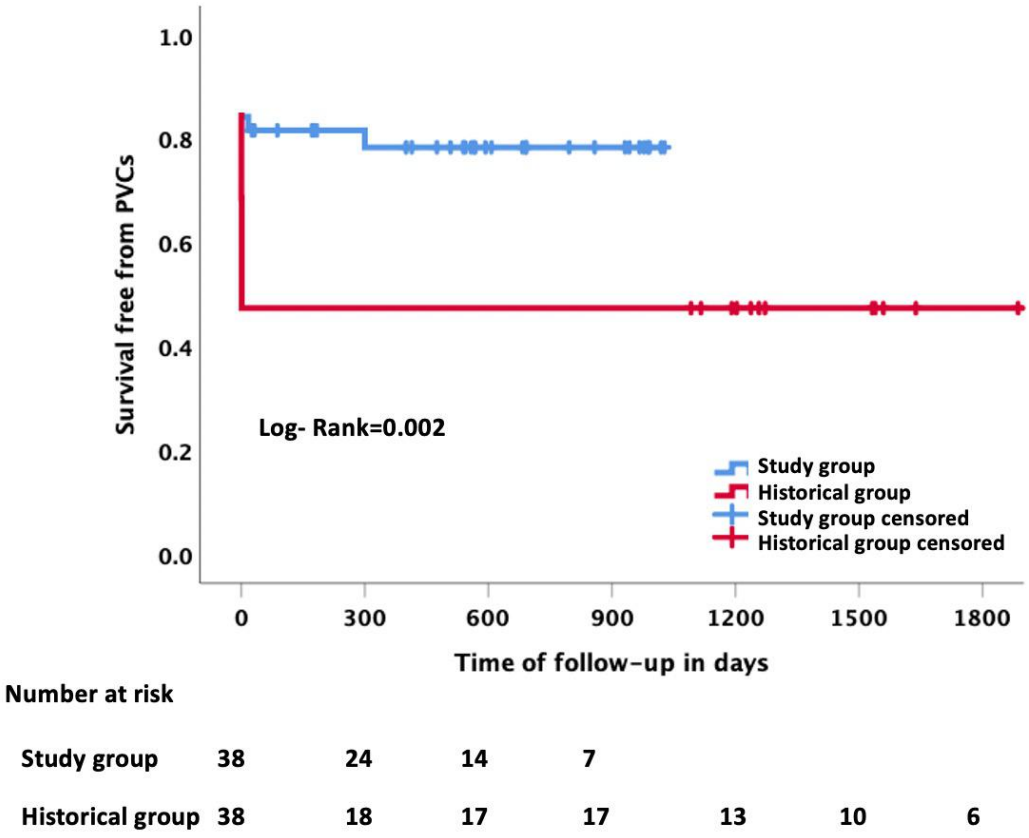


Figure 27. *Kaplan-Meier survival curves comparing the survival free from PVCs in the study and historical groups*

The Holter performed at the last follow-up both in the study and historical groups in patients that underwent a successful procedure and did not have recurrence of the arrhythmia, showed a median of 10 (1-87) PVCs /24 hours, not significantly different in the two groups, respectively 12 (1-146) and 5 (0-53), p=0.442 (Table 6).

Non-invasive electrocardiographic imaging (ECGI)

ECGI before ablation was performed in 17 patients in the study group. In six patients the ECGI was performed with the Amycard system only, in two with the VIVO system only and in 9 patients both systems were used.

The agreement between the predicted site and the invasive mapping is displayed in the Table 8. The Amycard system was able to correctly identify the SOO of the PVC in the same or contiguous segment in 14/15 patients (93%) and the VIVO system in 100% of patients. When both systems were used simultaneously, the agreement between them was 8/9 (90%) (Figure 28).

Table 8. *Results of the non-invasive electrocardiographic imaging (ECGI)*

Patient	ECGI system	Ablation segment	Amycard segment	VIVO segment	Amycard accuracy	VIVO accuracy	Amycard/VIVO agreement
1	Amycard	ROLS	ROLS	-	PM	-	-
2	Both	RCC	ROLS	RCC	No match	PM	No match
3	VIVO	ROL	-	ROL	-	PM	-
4	Both	ROLS	ROLS	ROLS	PM	PM	PM
5	Both	ROLS	ROLS	ROLS	PM	PM	PM
6	Amycard	ROL	ROL	-	PM	-	-
7	Amycard	ROL	ROL	-	PM	-	-
8	Amycard	RORS	ROLS	-	NM	-	-
9	Amycard	SUMMIT	SUMMIT	-	PM	-	-
10	Both	LAB	LAB	LAB	PM	PM	PM
11	VIVO	AMC	AMC	AMC	PM-	PM	PM
12	Both	ROLS	ROLS	ROLS	PM	PM	PM
13	Both	ROLS	ROLS	ROLS	PM	PM	PM
14	Both	ROLS	RORS	ROLS	NM	PM	NM
15	Both	ROL	RORS	RORS	NM	NM	PM
16	Both	ROLS	RORS	ROLS	NM	PM	NM
17	Amycard	ROLS	ROLS	-	PM	-	-

ROL: RVOT: lateral; ROLS: RVOT left septum; RORS: RVOT right septum; RCC; right coronary cusp; AMC: aortomitral continuity; LAB: LVOT anterior; PM: perfect match; NM: near match

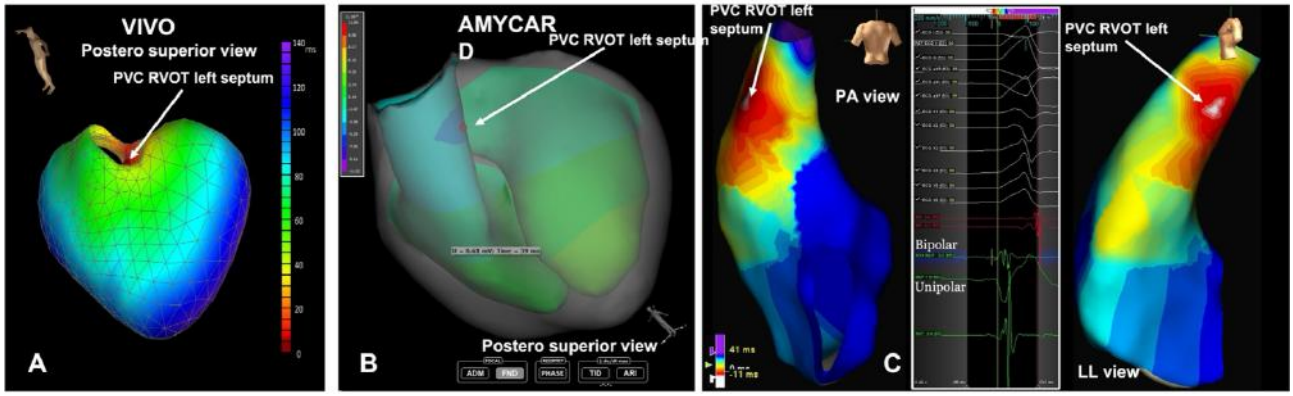


Figure 28. *Example of a patient with PVCs from the RVOT left septum (white arrow). Exhibiting a perfect match between the VIVO (panel A) and Amycard systems (panel B) and the invasive mapping (panel C).*

Limitations

This study has some limitations. Firstly, two different mapping systems were used to obtain the voltage map, and patients in the control group were mostly mapped with CARTO 3 RMT (Biosense-Webster, Inc., Diamond Bar, CA, USA) and RMN with Niobe II Magnetic Navigation System (Stereotaxis, Inc., Saint Louis, MO, USA).

RMN was the technique of choice to study the control group because due to the softer catheter tip and its higher safety profile we were able to obtain the voltage map of the RVOT with near zero fluoroscopy, which would be impossible to achieve with manual catheters. So, the percentage of RMN versus manual is significantly higher in the validation group in comparison with the study group. However, in patients with PVCs there were no significant differences regarding the use of manual vs RMN techniques between the study and the historical group.

Secondly, patients in the validation group did not perform an Holter registry to exclude asymptomatic frequent PVCs.

Thirdly, the level of the pulmonary valve was assessed just with the fluoroscopy and electroanatomical mapping, so we cannot be sure if some of the LVAs especially in the control group are not just the normal low voltage in the transitional zone.

Intracardiac echocardiography would be a useful tool to assess the level of the pulmonary valve if available.

There is some criticism regarding the nature of the DPs, some arguing that they may be just artifacts. The use of intracardiac echocardiography once again, would have been useful to rule out inadvertent contact with intracavitary structures or valves that would result in such signals. However, that seems not to be the case, due to the absence DPs in the majority of subjects in the control group.

Fourthly, we did not perform a pharmacological test in patients with ST-segment elevation, which would be the only way to definitely rule out Brugada electrocardiographic pattern. However, none of the patients presented with any of the additional criteria required in the current

Guidelines to perform the test, so, from a clinical point of view and due to the non-negligible risk, we opted to not perform the test.

Finally, some authors believe that high-density endocardial bipolar voltage mapping may increase the detection of LVAs, We did not use such catheters but still got a similar 83% prevalence of LVAs across the RVOT in patients with PVCs from the RVOT in comparison with the 88% obtained with high-density mapping.

Conclusions

We demonstrated that this new methodology of PVC ablation is superior to current mapping technology in patients with a low intraprocedural PVC burden.

ST-segment elevation at the 2nd ICS was validated as a non-invasive marker of LVAs in patients with outflow tract PVCs

ECGI is an accurate diagnostic tool with reproducible results regardless the cardiac source used for analysis.

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General discussion and conclusions

Importance of catheter ablation

We have shown that PVCs are a common finding, most times disabling, and if frequent, being implicated in a worse prognosis, even in the absence of structural heart disease. They can be the trigger of more severe arrhythmias, and although the cut-off value is not yet perfectly established, a PVC burden above 10.000 PVCs/24 h can induce left ventricular dysfunction.

The good results of catheter ablation, with high success and low complication rates, in comparison with antiarrhythmic drugs, favor this approach.

Results with intraprocedural low PVC burden

However, in case of intraprocedural low PVC burden, which may occur in up to 48% of the procedures, the results are much worse, ranging from cancelation of the procedure to lower success rates as low as 56%. Many alternative approaches have been attempted with more or less success.

Underlying substrate

It is clear that idiopathic PVCs display an underlying substrate, regardless of their mechanism.

The accepted theory that they share the same mechanism with the idiopathic RVOT adenosine sensitive ventricular tachycardia is still to be proven.

There is a great amount of scientific evidence to date, regarding the presence of LVAs across the RVOT in patients with PVCs and apparently normal hearts, that go undiagnosed with current imaging techniques.

Despite the criticism that this theory may rise, especially of those who claim that these findings might be due to inadequate point acquisition or overestimation of normal findings, we still believe the LVAs represent an abnormal finding, that is absent in the great majority of normal subjects.

These LVAs also display abnormal electrophysiological features. We demonstrated that the wavefront propagation speed across the RVOT was lower in patients with LVAs and deceleration zones with confluence of isochrones were present in that area, when compared with normal subjects. This slower wavefront propagation speed was detected during sinus rhythm beats but also during PVCs. Some authors also found a slower propagation speed during PVCs which the authors attributed to the fiber arrangement across the RVOT. However, we studied the activation speed in sinus rhythm in patients with and without PVCs and despite the assuredly same fiber arrangement across the RVOT, patients with PVCs and LVAs had slower wavefront propagation than normal subjects.

Also, using ECGI we demonstrated a dispersion of the ARI which is a surrogate of action potential dispersion in the epicardium of patients with PVCs from the RVOT and presence of LVAs.
Finally, the DPs characterized by occurring late in diastole and separated from local ventricular electrogram by an isoelectric segment, are always present at the SOO of the PVCs.
Due to their timing in the cardiac cycle, during the phase 4 of the action potential we may speculate that they represent evidence of triggered activity but might as well represent some form of automaticity protected by entrance block. One way or the other, we demonstrated that they can be a valuable target when ablating idiopathic PVCs.

ST-segment elevation as a non-invasive marker

As extensive as the LVAs may appear on the 3D EAM voltage mapping they still are not detected with methods as sophisticated as the CMR with LGE. Using 3D LGE seems to slightly improve the sensitivity of the method but nevertheless a lot of LVAs still go undetected.
In this dissertation we have provided scientific evidence to accept the ST-segment elevation in V1-V2 at the level of the 2nd ICS as a non-invasive marker of LVAs across the RVOT.
Its prevalence is extremely high in the presence of LVAs and is almost absent in normal subjects. The ST-segment elevation as a noninvasive marker of LVAs had a sensitivity of 87%, specificity of 96%, positive predictor value of 93% and negative predictor value of 91%.
The meaning of the ST-segment elevation in patients with idiopathic PVCs remains to be elucidated, but we can speculate that it might be related to the abnormal findings regarding the repolarization which is emphasized by the high percentage of T-wave inversion beyond V1 at the 2nd ICS also more frequent in patients with PVCs than in normal subjects.

Non-invasive electrocardiographic imaging (ECGI)

As a new electrophysiological tool, ECGI has demonstrated a good accuracy in the diagnosis of the arrhythmia's site of origin. It is valuable in providing evidence on the normal electrophysiology of the heart as well as of pathological substrates. We believe that the trend in Medicine will be to perform less and less invasive treatments. Ablating complex ventricular arrhythmias without intracardiac catheters, using stereotactic radiotherapy has been successfully done previously and has opened the doors to a huge range of future developments in Electrophysiology. Most of the procedures performed with stereotactic radiotherapy were based on the ECGI, to non-invasively identify the epicardial breakthrough of the ventricular tachycardia and thus, delineate the area to treat.

Simplified approach

In patients with intraprocedural low PVC burden, the substrate-based approach developed and evaluated in this dissertation proved to be feasible and more effective than the historical approach. In this study we were able to record DPs during sinus rhythm at the ablation site, in all patients in the study group regardless the right or left side of origin of the PVCs.

The percentage of patients form the historical group that had the procedure cancelled due to the low PVC burden was high (11%). Furthermore, from the 34 patients that underwent electrophysiological study, ablation was attempted in only 28 patients, and aborted in another six. Whereas, in the study group ablation was performed in all patients.

In comparison with the historical approach, the new methodology was significantly faster and more successful, with similar recurrence rate during follow-up.

The acute success rate in our study group was 90% significantly higher than the 64% in the historical group. As we already discussed above, other authors have used substrate-based approaches to deal with the low intraprocedural PVC burden. The results have not been as good as ours when considering a population with PVCs originating from both the left and right outflow tracts.

Conclusions

LVAs within the RVOT were frequently present in patients with idiopathic PVCs, and ST-segment elevation at the level of the 2nd ICS was the only independent predictor of their presence and performed well as a non-invasive marker of these LVAs showing a good positive predictive value and a good specificity.

Also, DPs were significantly more prevalent in patients with PVCs than in normal subjects.

The proposed approach partially based on substrate mapping including searching for LVAs and DPs, proved to be feasible, faster, and more efficient than the previous approach based exclusively on activation mapping.

ECGI has proved to be a valuable tool in the treatment of PVCs, showing good accuracy when compared to invasive mapping.

Although the presence of LVAs as well as the presence of ST-segment elevation were significantly more frequent in patients with PVCs than in general population, and DPs were always present at the ablation site, we think that further studies are needed to confirm these results, before assuming they represent a substrate for PVCs.

A randomized multicentric trial comparing the results of conventional versus substrate-based ablation for idiopathic outflow tract PVCs would be an important endeavor to pursue.

As extrassístoles ventriculares (ESV) são um achado comum na população geral. Os locais de origem mais comuns das ESV em doentes sem cardiopatia estrutural são as camaras de saída do ventrículo direito (CSVD) e do ventrículo esquerdo (CSVE).

O prognóstico associado às ESV frequentes depende da presença de cardiopatia estrutural, de forma que as ESV idiopáticos têm sido consideradas benignas. Recentemente, porém, surgiram evidências de que uma pequena percentagem desses doentes pode apresentar arritmias mais graves, como taquicardia ventricular polimórfica ou fibrilhação ventricular, ou desenvolver disfunção ventricular esquerda. A ablação por cateter é indicada no caso de ESV sintomáticas frequentes e refratárias à terapêutica médica ou em caso de preferência do paciente.

Actualmente, a ablação por cateter é baseada no mapeamento de activação, confirmado por pacemapping que demonstre uma correspondência de pelo menos 11/12 derivações entre a ESV e o complexo provocado pela estimulação. A taxa de sucesso agudo varia entre 78% e 100% de acordo com as séries e com a localização das ESV. A navegação magnética por controle remoto, apresenta-se como uma boa opção para ablação de ESV, mostrando uma elevada eficácia com um melhor perfil de segurança.

Numa percentagem de casos que varia entre 30% a 48%, a carga de ESV é muito baixa durante o procedimento, resultando em cancelamento da ablação em até 11% dos doentes ou redução da taxa de sucesso de 85% para 56% quando se insiste em efectuar o procedimento.

Recentemente, têm sido desenvolvidos sistemas de mapeamento tridimensional não invasivo, baseados na análise do eletrocardiograma (ECGI). Esses sistemas são capazes de mapear uma arritmia com apenas um batimento, em vez da habitual aquisição ponto a ponto, sendo especialmente úteis no caso de arritmias raras.

O EGGI também constitui uma ferramenta não invasiva valiosa para estudar os mecanismos das arritmias. Com este sistema demonstrámos a presença de um substrato electrofisiológico na CSVD de doentes com ESV e corações aparentemente normais.

Tem sido aceite desde há muitos anos que nos doentes com ESV idiopáticas da CSVD, esta apresenta características normais no mapeamento electroanatómico e propriedades eletrofisiológicas normais. No entanto, ao longo desta dissertação demonstrámos que existe um substrato para as ESV da CSVD, o qual se manifesta pela presença de zonas de baixa voltagem (ZBV), não detectadas pelos métodos de imagem usuais, incluindo a ressonância magnética cardíaca (RMC). Identificámos, pela primeira vez, a presença de uma associação entre o supradesnivelamento do segmento ST em V1-V2 no 2º espaço intercostal (EIC) e a presença de ZBV na CSVD, pelo que, fomos avaliar qual o seu valor como marcador não invasivo dessas ZBV.

Também identificámos a presença de potenciais anormais no electrograma intracardíaco no local de ablação, que ocorrem durante a diástole após a onda T do ECG de superfície em ritmo

sinusal, e se tornam pré-sistólicos durante a ESV, os quais denominamos potenciais diastólicos (PD).

No Capítulo V descrevemos em detalhe o estudo que validou esses achados e avaliou a exequibilidade e eficácia da metodologia proposta para ablação de doentes com baixa carga arrítmica definida como menos de 2 ESV/min nos primeiros 5 minutos do procedimento. Esta metodologia consiste no mapeamento rápido da CSVD em ritmo sinusal procurando ZBV e PD e, após identificação da zona, efectuar um mapa de activação limitado a essa área.

Resumidamente, foi um ensaio clínico prospectivo com um único braço, realizado em dois centros hospitalares, tendo sido estudados três grupos: a) doentes com baixa carga de ESV intraprocedimento que foram submetidos à ablação de ESV com o novo método (grupo de estudo); b) doentes com baixa carga de ESV intraprocedimento que foram submetidos à ablação pelo método padrão de mapeamento de ativação entre 2016 e 2018 (grupo histórico); e c) doentes sem ESV, submetidos a ablação por cateter de taquicardias supraventriculares que concordaram em realizar um mapa de voltagem da CSVD em ritmo sinusal (grupo validação).

Os doentes dos grupos de estudo e validação efectuaram um ECG no 2º EIC para avaliar a presença de supradesnivelamento do segmento ST e um mapa de voltagem da CSVD em ritmo sinusal para identificar a presença de ZBV e PD, respectivamente. Os resultados foram comparados entre os dois grupos.

O grupo de estudo e o grupo histórico foram comparados quanto à eficácia do novo método de ablação, em termos de abolição das ESV e melhoria da velocidade do procedimento e suas taxas de sucesso.

Quando disponível, o ECGI foi efectuado no grupo de estudo para avaliar a precisão do método na identificação do local de origem das ESV. O ECGI foi realizado com dois sistemas, o Amycard (EP Solutions SA, Suíça) e o VIVO (Catheter Precision, NJ USA).

A prevalência de ZBV e PD foi significativamente maior no grupo de estudo em comparação com o grupo de validação, respectivamente, 71% vs 11%, p<0,0001 e 87% vs 8%, p<0,0001. O supradesnivelamento do segmento ST constituiu um bom predictor de ZBV com uma sensibilidade de 87%, especificidade de 96%, valor predictor positivo de 93% e valor predictor negativo de 91%.

A nova abordagem simplificada aboliu as ESV em 90% dos doentes em oposição a 47% no grupo histórico, p<0,0001. Apenas 74% dos doentes foram submetidos à ablação no grupo histórico contra 100% no grupo de estudo.

Nos doentes submetidos à ablação, o tempo de procedimento foi significativamente menor no grupo de estudo quando comparado com o grupo histórico, 130 (100-164) e 183 (160-203) min, p<0,0001 e a taxa de sucesso foi significativamente maior, 90 % e 64%, p=0,013. A taxa de

recorrência após um tempo mediano de seguimento de 1060 (574-1807) dias, em doentes submetidos a ablação bem sucedida não foi significativamente diferente entre os dois grupos, Log-Rank=0,125.

Foi efectuado ECGI antes da ablação em 17 doentes no grupo de estudo. Em 6 doentes o ECGI foi efectuado apenas com o sistema Amycard, em dois apenas com o sistema VIVO, e em 9 doentes com ambos. Verificámos uma boa concordância entre o ECGI e o mapeamento invasivo, quanto ao local de origem das ESV em 14/15 doentes (93%) com o sistema Amycard e em 100% dos doentes com o sistema VIVO. Quando ambos os sistemas foram utilizados simultaneamente, a concordância entre eles foi de 8/9 (90%).

Assim, em conclusão, a abordagem proposta parcialmente baseada no mapeamento de substrato, incluindo a busca de ZBV e PD, mostrou-se exequível, mais rápida e mais eficiente do que a abordagem baseada exclusivamente no mapa de ativação. O supradesnivelamento do segmento ST no 2º ICS mostrou-se um bom preditor de ZBV. O ECGI mostrou-se uma ferramenta valiosa para prever de forma não invasiva o local de origem da arritmia.

Premature ventricular contractions (PVCs) are a common finding in the general population. The most common site of PVCs, in patients without structural heart disease, is the right ventricular outflow tract (RVOT) and the left ventricular outflow tract (LVOT).

The prognosis associated with frequent PVCs depends on the presence of structural heart disease, so that idiopathic PVCs have been considered benign. Recently however, evidence has emerged that a small percentage of those patients may present with polymorphic ventricular tachycardia or ventricular fibrillation or evolve to left ventricular dysfunction. Catheter ablation is indicated for frequent symptomatic PVCs refractory to medical therapy or in case of patient's preference.

Currently, catheter ablation is based on activation mapping, confirmed by pace mapping match of at least 11/12 ECG leads between the paced beat and the PVC morphology. The acute success rate ranges from 78% to 100% according to the series, and to the location of the PVCs. Remote magnetic navigation presents as a good option for PVC ablation offering a high success rate with better safety profile.

Intraprocedural low PVC burden occurs in up to 30% to 48% of cases, resulting in either, cancelation of the ablation procedure in up to 11% of patients, or reduction of the success rate from 85% to 56% when ablation is attempted with pace mapping only.

Recently non-invasive mapping systems based on the electrocardiogram analysis (ECGI) have been developed. These systems are capable of mapping an arrhythmia with just one beat, instead of the usual point by point acquisition, being especially useful in the case of rare arrhythmias.

EGGI also constitutes a valuable noninvasive tool for studying the mechanisms of arrhythmias. With this system we were able to demonstrate the presence of an electrophysiological substrate in the RVOT of patients with PVCs and apparently normal hearts.

It has been accepted for many years that in patients with idiopathic PVCs from the outflow tracts, the RVOT displays normal electroanatomical mapping features and electrophysiological properties. However, we have demonstrated that there is a substrate for idiopathic PVCs in the form of low voltage areas (LVAs) that are not detected by usual image methods including cardiac magnetic resonance (CMR). We described for the first time, the association between the presence of ST-segment elevation in V1-V2 at the 2nd intercostal space (ICS) with LVAs across the RVOT and have proposed it as a non-invasive electrocardiographic marker of LVAs.

We also identified the presence of abnormal potentials in intracardiac electrograms at the ablation site during diastole, after the T wave of the surface ECG that became presystolic during the PVC and were called diastolic potentials (DPs).

In Chapter V we describe in detail the study that validated those findings and evaluated the feasibility and efficacy of a proposed simplified substrate approach, for catheter ablation in

patients with low intraprocedural PVC burden, defined as less than 2 PVCs/min in the first 5 minutes of the procedure.

It consists of fast mapping of the RVOT in sinus rhythm looking for LVAs and DPs, identifying the area, and finally performing a restricted activation map of the PVCs at that area. Briefly, it was a prospective single-arm clinical trial at two centers and three groups were studied: a) patients with low intraprocedural PVC burden that underwent ablation with the novel simplified approach method (study group); b) patients with low intraprocedural PVC burden that underwent ablation using the standard activation mapping method between 2016 and 2018 (historical group); and c) patients without PVCs, subjected to catheter ablation of supraventricular tachycardias that agreed to have a voltage map of the RVOT in sinus rhythm performed (validation group).

The calculated sample size was 38 patients in each group. The exclusion criteria were as follows: known structural heart disease, history of sustained ventricular arrhythmias, inability to perform CMR, previous ablation and standard 12-Lead ECG with evidence of conduction or electrical disease or abnormal QRS morphology were excluded.

Patients in the study and validation groups, had an ECG performed at the 2nd ICS and the RVOT mapped in sinus rhythm to assess the presence of ST-segment elevation, and LVAS and DPs, respectively. The results were compared between both groups.

The study group and the historical group were compared regarding the efficacy of the new simplified ablation method in terms of abolishment of the PVCs and improvement of procedure speed and success rate.

When available, ECGI was performed in the study group to evaluate the accuracy of the method to identify the site of origin of the PVCs. The ECGI was performed with two systems, the Amycard (EP Solutions SA, Switzerland) and the VIVO (Catheter Precision, NJ USA).

The prevalence of LVAs and DPs was significantly higher in the study group in comparison with the validation group, respectively, 71% vs 11%, $p<0.0001$ and 87% vs 8%, $p<0.0001$. The ST-segment elevation was a good predictor of LVAS with a sensitivity of 87%, specificity of 96%, positive predictor value of 93% and negative predictor value of 91%.

The novel simplified approach abolished the PVCs in 90% of the patients as opposed to 47% of patients in the historical group, $p<0.0001$. Only 74% patients underwent ablation in the historical group versus 100% in the study group. In patients that underwent ablation, the procedure time was significantly lower in the study group when comparing to the historical group, 130 (100-164) vs 183 (160-203) min, $p<0.0001$ and the success rate was significantly higher, 90% vs 64%, $p=0.013$. The recurrence rate in patients with a successful ablation after a median follow-up time of 1060 (574-1807) days, was not significantly different between both groups, Log-Rank=0.125.

ECGI before ablation was performed in 17 patients in the study group. In 6 patients the ECGI was performed just with the Amycard system, in two just with the VIVO system and in 9 patients both systems were used. We found a good agreement between the ECGI and the invasive mapping, with the predicted site of origin being in the same or contiguous segment of the ablation site in 14/15 patients (93%) with the Amycard system and in 100% of patients with the VIVO system. When both systems were used simultaneously, the agreement between them was 8/9 (90%).

So, in conclusion, the proposed approach partially based on substrate mapping including searching for LVAs and DPs, proved to be feasible, faster, and more efficient than the previous approach based exclusively on activation mapping. ST-segment elevation at the 2nd ICS proved to be a good predictor of LVAs. ECGI was a valuable tool to noninvasively predict the site of origin the arrhythmia.

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Attachments

Original publication research included in this dissertation by order of reference

Sum of the impact factors of the various publications included in this dissertation

Paper Title	Authors	Journal	Impact factor	Weighting factor	Value
1. Remote magnetic navigation for mapping and ablation of right and left ventricular outflow tract arrhythmias	**Parreira L,** Cavaco D, Reis-Santos K, et al	Revista Portuguesa Cardiologia	1,651	2	3,302
2. Remote magnetic navigation for ablation of typical atrial flutter: Long-term results	**Parreira L,** Cavaco, Carmo P, et al	Revista Portuguesa Cardiologia	1,651	2	3,302
3. Safety and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using Magnetic Navigation versus Manual Conventional Ablation: A Propensity-Score Analysis	Adragao P,...**Parreira** L, et al	J Cardiovascular Electrophysiology	2,942	0,5	1,471
4. Excessive atrial ectopic activity as an independent risk factor for ischemic stroke	Marinheiro R, **Parreira L,** Pedro Amador, et al	International Journal of Cardiology	4,039	1	4,039
6. Ventricular Arrhythmias in Patients with Obstructive Sleep Apnea.	Marinheiro R, **Parreira L,** Pedro Amador, et al	Current Cardiology Reviews	1,61	1	1,61
7. Isolated diastolic potentials as predictors of success in ablation of right ventricular outflow tract idiopathic premature ventricular contractions	**Parreira L,** Marinheiro R, Carmo P, et al	PLoS ONE	3,24	2	6,48
8. Premature ventricular contractions of the right ventricular outflow tract: Upward displacement of the ECG unmasks ST elevation in V1 associated with the presence of low voltage areas	**Parreira L,** Marinheiro R, Carmo P, et al	Revista Portuguesa Cardiologia	1,651	2	3,302
9. Atrioventricular node reentrant tachycardia: Remote magnetic navigation ablation versus manual ablation - impact on operator fluoroscopy time	**Parreira L,** Marinheiro R, Carmo P, et al	Revista Portuguesa Cardiologia	1,651	2	3,302
10. Excessive Atrial Ectopic Activity Worsens Prognosis and Predicts the Type of Major Adverse Cardiac Events in Patients with Frequent Premature Ventricular Contractions	**Parreira L,** Marinheiro R, Mesquita D, et al	Cardiology Research	0,68	2	1,36
11. Non-invasive electrocardiographic imaging in patients with idiopathic premature ventricular contractions from the right ventricular outflow tract: New insights into arrhythmia substrate	**Parreira L,** Carmo P, Adragão P, et al	Journal of Electrocardiology	1,31	2	2,62
14. Slow pathway region as the exit site of parahisian premature ventricular contractions: Why choose safety over the earliest activation?	Marinheiro R, **Parreira L,** Amador P, et al	J Cardiovascular Electrophysiology	2,942	1	2,942
15. Electrocardiographic imaging (ECGI): What is the minimal number of leads needed to obtain a good spatial resolution?	**Parreira L,** Carmo P, Adragao P, et al.	Journal of Electrocardiology	1,31	2	2,62
16. Successful ablation of premature ventricular contractions exclusively guided by epicardial and endocardial noninvasive mapping (ECGI) and confirmed by substrate mapping.	**Parreira L,** Carmo P, Adragao P, et al.	Journal of Electrocardiology	1,31	2	2,62
17. Idiopathic premature ventricular contractions from the outflow tract display an underlying substrate that can be unmasked by a type 2 Brugada electrocardiographic pattern at high right precordial leads.	**Parreira L,** Marinheiro R, Carmo P, et al	Frontiers in Physiology	4,134	2	8,268
19. Frequent premature ventricular contractions. Association of burden and complexity with prognosis according to the presence of structural heart disease	**Parreira L,** Marinheiro R, Amador P, et al	Annals of Noninvasive Electrocardiololgy	1,485	2	2,97
20. Successful radiofrequency ablation of para-left bundle branch premature ventricular contractions: Aiming at the breakout point to spare the conduction system.	**Parreira L,** Mesquita D, Marinheiro R, et al	Interventional Cardiology	1,34	2	2,68
22. Premature ventricular contractions of the right ventricular outflow tract: is there an incipient underlying disease? New insights from a speckle tracking echocardiography study.	Fonseca M, Parreira L, Farinha J, et al	Indian Pacing Electrophysiol Journal	1,25	1	1,25
23. Prolonged Right Ventricular Outflow Tract Endocardial Activation Duration and Presence of Deceleration Zones in Patients With Idiopathic Premature Ventricular Contractions. Association With Low Voltage Areas	**Parreira L,** Carmo P, Marinheiro R, et al	Frontiers in Physiology	4,134	2	8,268
26. Assessment of wave front activation duration and speed across the right ventricular outflow tract using electrocardiographic imaging as predictors of the origin of the premature ventricular contractions: A validation study.	**Parreira L,** Carmo P, Marinheiro R, et al	Journal of Electrocardiology	1,31	2	2,62
27. Acute and Long-Term Results of Catheter Ablation of Outflow Tract Arrhythmias using Remote Magnetic Navigation with Catheter–Tissue Contact Feedback Technology: Comparison with Manual Ablation.	**Parreira L,** Carmo P, Marinheiro R, et al	J. Atrial Fibrillation and Electrophysiology*	1,034	2	2,068
30. Validation of an electrocardiographic marker of low voltage areas in the right ventricular outflow tract in patients with idiopathic ventricular arrhythmias	**Parreira L,** Marinheiro R, Carmo P, et al	J Cardiovascular Electrophysiology	2,942	2	5,884
31. A simplified approach to radiofrequency catheter ablation of idiopathic ventricular outflow tract premature ventricular contractions.	**Parreira L,** Carmo P, Marinheiro R, et al	J Cardiovascular Electrophysiology	2,942	2	5,884

*Journal of Atrial fibrillation (JAFIB) changed its name to Journal of Atrial fibrillation and Electrophysiology (JAFIB-EP) in 2022. Since the journal has not an Impact Factor calculated yet we used the previous JAFIB impact factor

All papers total - **78,862;** Papers as first author- **68,8**

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Letter to editor

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ORIGINAL ARTICLE

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Frequent premature ventricular contractions. Association of burden and complexity with prognosis according to the presence of structural heart disease

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Abstract

Introduction: Premature ventricular contractions (PVC) have been associated with mortality and heart failure (HF) regardless the presence of structural heart disease (SHD). The aim of this study was assessing the impact of burden and complexity of PVCs on prognosis, according to presence of SHD.

Methods: 312 patients were retrospectively evaluated out of 1967 consecutive patients referred for 24-hr Holter at a single hospital, with a PVC count >1% of total beats. Two groups with and without SHD. PVC burden (PVC%), presence of complex forms, incidence of all-cause death, combined outcomes of all-cause death and cardiovascular hospitalizations, HF death and HF hospitalizations and, sudden death (SD) or hospitalizations due to ventricular arrhythmias (VA)were assessed.

Results: Premature ventricular contraction burden was 2.7 (IQR: 1.6–6.7). SHD patients had more polymorphic PVCs, 77% versus 65%, $p = .022$, triplets and episodes of non-sustained ventricular tachycardia (NSVT): 44% versus 27%, $p = .002$; 30% versus 12%, $p < .0001$. In idiopathic patients, a PVC% in the third quartile was independently associated with all-cause mortality hazard ratio (HR) 2.288 (1.042–5.026) $p = .039$, but not in SHD. The complexity of the PVCs was not independently associated with outcomes in both groups. In SHD group, NSVT was associated with lower survival free from SD and VA hospitalizations, $p = .028$; after multivariable, there was a trend for a higher arrhythmic outcome with NSVT, HR 3.896 (0.903–16.81) $p = .068$.

Conclusion: Premature ventricular contractions in SHD showed more complex patterns. In idiopathic patients, a higher PVC count was associated with higher mortality but not is SHD patients. Complexity was not independently associated with worse prognosis.

KEYWORDS
idiopathic, premature ventricular contractions, prognosis, PVC burden, PVC complexity, structural heart disease

1 | INTRODUCTION

Premature ventricular contractions (PVCs) are a common finding during long-term monitoring (Arnar et al., 2019). Although PVCs can occur in healthy persons, they are more frequent in the presence of structural heart disease (SHD), sleep apnea (Marinheiro et al., 2019), chronic obstructive pulmonary disease, and hyperthyroidism or stimulants (Einvik et al., 2017). They have been associated with a worse prognosis in patients with SHD, especially if frequent or presenting with complex forms (Kostis et al., 1987). Those findings were the basis for the treatment of PVCs with antiarrhythmics which proved harmful in patients with SHD (Echt et al., 1991). However, those studies are outdated and antiarrhythmics are no longer the only option. Catheter ablation is a successful treatment and has shown an improvement in left ventricular systolic function after successful ablation, but the impact on the prognosis is unproven (Baman et al., 2010; Bogun et al., 2007; Latchamsetty et al., 2015; Ling et al., 2014). Historically idiopathic PVCs have been considered benign (Gaita et al., 2001). Recently, a few population-based studies have suggested that PVCs are associated with an adverse outcome, even in the absence of known SHD (Agarwal et al., 2012, 2017; Dukes et al., 2015; Lin et al., 2015, 2016).

The aim of this study was to evaluate the characteristics of the PVCs on the 24-hr Holter recording in terms of frequency and complexity, and secondly assess their impact on prognosis in patients with and without SHD.

2 | METHODS

2.1 | Study population

We evaluated 1,967 consecutive patients older than 18 years who underwent 24-hr Holter monitoring in our center, between June 2006 and December 2010. We selected patients with frequent PVC, defined as PVCs representing more than 1% of total number of heart beats (n = 530 patients). We select this value based on the work of Dukes et al (Dukes et al., 2015) that demonstrated that this cutoff value provides the best sensitivity/specificity relation for prediction of adverse outcomes. Patients with AF, atrial flutter, or any rhythm other than sinus during recording (n = 168) were excluded. Patients who were lost to follow-up (n = 50) were also excluded. The final study population included 312 patients. For the purpose of assessing the combined endpoint of sudden death (SD) or hospitalizations due to VA, patients with unknown cause of death were excluded from the analysis (n = 35).

2.2 | Study design

We retrospectively collected data from the medical records including demographic data, presence of SHD and its type, diabetes, hypertension, antiarrhythmic, and beta-blocker use. Transthoracic echocardiographic data were retrospectively obtained. Echocardiographic evaluation included M-mode measurements of the left atrium diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and left ventricular fractional shortening (LVFS) obtained in the left parasternal view. Holter recording was performed with the use of three-channel tape recorders (GE SEER LIGHT®). Recordings had to exceed 20 hr and be of good quality to be analyzed and all of them were reviewed. SHD was ruled out based on echocardiogram, treadmill exercise test, coronariography, and cardiac magnetic resonance. Cardiac investigation was conducted at the discretion of the patient's physician.

On Holter evaluation, number of PVCs/24 hr, the percentage of PVCs (determined by dividing the total number of PVCs by the total number of beats recorded during Holter monitoring), the morphology of the PVCs, presence of couplets, triplets and runs of non-sustained ventricular tachycardia (NSVT) defined as more than 3 PVCs in a run were evaluated. The presence of episodes of AF, defined as runs of irregular supraventricular rhythm lasting more than 30 s (Calkins et al., 2017) and runs of supraventricular ectopic beats, defined as more than 3 consecutive supraventricular beats with an accelerated cycle length lasting <30 s, was also assessed. The 24-hr Holter reports were supervised by the same senior physician.

Follow-up was performed in the second half of 2018, thus including up to 12 years of follow-up in some patients. Data were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone. We assessed the occurrence of all-cause death, combined rate of total death and cardiovascular (CV) hospitalizations, combined rate of heart failure (HF) death or hospitalizations due to HF, and combined rate of SD or hospitalizations due to sustained ventricular arrhythmias (VA). Death was ascertained by reviewing medical records or from national patient registry. HF death was defined as worsening HF, manifested as cardiogenic shock, pulmonary edema or increase in HF symptoms and drug therapy, or hospitalization due to decompensated HF prior to death. SD was defined as unexpected fatal event occurring within 1 hr of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hr before the event (Priori et al., 2015). When the cause of death could not be established, the death was classified as of unknown cause. Hospitalization was defined as an overnight stay in a hospital ward. The cause of hospitalization was

obtained from medical records, and CV hospitalization included the ones due to de novo or aggravated HF, ventricular arrhythmia, bradyarrhythmia, or acute coronary syndromes. Time-to-event for those without the event was censored either at death, or at the last follow-up, whichever occurred earlier Patients were divided according to the presence or absence of SHD, and the characteristics of the PVCs as well as the outcomes during the follow-up were compared in both groups. We assessed the association between PVC burden, PVC morphology, presence of triplets and NSVT and the occurrence of major cardiac events during follow-up adjusting for the other covariables.

2.3 | Statistical analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc). Data are presented as median and lower and upper quartile (Q_1–Q_3) for continuous variables due to lack of normal distribution assessed with the Kolmogorov–Smirnov test. Categorical variables are presented as absolute numbers and percentages. Continuous variables were compared with the use of Mann–Whitney test. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples. Patients were divided into quartiles according to the PVC percentage, and the PVC burden analyzed as percentage and as quartiles, taking the first quartile as reference.

Survival curves free from the analyzed outcomes were calculated by the Kaplan–Meier method and stratified by the burden and complexity of the PVCs, using the log-rank test for comparison. The influence of Holter variables, on adverse events occurrence during follow-up, was evaluated by univariate and multivariate Cox proportional-hazards regression analysis. Unadjusted hazard ratios (HR) and their 95% confidence intervals (CI) for all-cause mortality, all-cause mortality or CV hospitalizations, HF death or HF hospitalizations, and SD or hospitalizations due to VA were calculated. The proportional hazard assumption was tested for each of the Cox models based on Schoenfeld residuals for continuous variables and on "log-minus-log" plot for categorical variables. The HRs were adjusted to potential confounders covariables that displayed $p < .05$ on univariable analysis. For all tests, a two-tailed p-value of $< .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

The study population included 312 patients. The PVCs were idiopathic in 177, and SHD was present in 135 patients. The etiology of SHD was ischemic in 93 patients, non-ischemic cardiomyopathy in 22, hypertrophic cardiomyopathy in 7, aortic stenosis in 9 and mitral stenosis in 3, left ventricular non-compaction in 1 patient, and myocarditis in another. The baseline characteristics and comparison between patients with idiopathic PVCs and PVCs in the context of SHD are presented in Table 1. Patients with SHD were more frequently male, had a higher incidence of diabetes and hypertension, and were more frequently on beta-blockers. The echocardiographic evaluation showed higher values of LAD, LVEDD, LVESD, and lower LVFS. (Table 1).

3.2 | 24-hr Holter recording

The comparison of the characteristics of the PVCs on the 24-hr Holter recording in the two groups is displayed in Table 1. The PVC burden was not significantly different in patients with idiopathic PVCs and in those with SHD respectively, 2,833 (1,619–7,192) versus 3,050 (1,504–6,894), $p = .634$ and PVC percentage 2.7% (1.7%–6.8%) versus 2.8% (1.6%–6.6%), $p = .997$. Quartiles 1 through 4 represented PVC burdens of 1%–1.63%, 1.63%–2.74%, 2.74%–6.77%, and more than 6.67%, respectively. The median percentage in each quartile was as follows, quartile 1:1.25 (1.1–1.43); quartile 2:2.0 (1.8–2.4); quartile 3:4.3 (3.6–5.4) and quartile 4:11.4 (8.0–18.1). The complexity of the PVCs in terms of polymorphic morphologies and presence of couplets, triplets, and runs of NSVT was significantly higher in the group with SHD, respectively 77% versus 65%, $p = .022$; 87% versus 67%, $p < .0001$; 44% versus 27%, $p = .002$; 30% versus 12%, $p < .0001$. The presence of supraventricular runs was more frequent in idiopathic patients, 40% versus 28%, $p = .041$. Three patients had episodes of AF during Holter monitoring corresponding to 0.96%, two in the idiopathic group (1.1%) and one in the group with SHD (0.7%), $p = 1.000$.

3.3 | Follow-up

During a median follow-up of 8.3 (5.1–9.9) years, 133 patients (43%) died, 157 (49%) had the combined outcome of all-cause death or CV hospitalizations, 18 (5.8%) the combined outcome of HF death or HF hospitalizations, and 13 (4.2%) the combined outcome of SD or hospitalizations due to VA. The events per 1,000 person-years observed in up to 12 years of follow-up in the two studied groups are shown in Table 2. Patients with SHD had significantly higher rates of all-cause mortality, combined outcome of all-cause mortality, or CV hospitalizations and combined outcome of HF death or HF hospitalizations. The rate of SD or hospitalizations due to VA was also higher but did not reach statistical significance, 10.1 versus 3.7 per 1,000 person-years, $p = .089$. The cause of death was non-cardiac in 75 patients (24%), due to HF in 13 patients (4%), due to SD or documented VA in 8 patients (2.6%), and due to acute coronary syndrome in 2 patients (0.6%). In 35 patients (11%), the cause of death was unknown. The rate of different causes of death per 1,000 person-years in patients with idiopathic PVCs and patients with SHD is shown in Table S1. Patients with SHD had significantly higher rates of death due to HF, 13.3 versus 0.7 per 1,000 person-years, $p < .0001$. The comparison of baseline characteristics of patients that experienced

TABLE 1 Baseline characteristics. Comparison between the two groups with idiopathic PVCs and with structural heart disease

	Overall sample ($n = 312$)	Idiopathic PVCs ($n = 177$)	Structural heart disease ($n = 135$)	p-value
Demographic data				
Age in years, median (Q_1–Q_3)	69 (61–77)	68 (60–77)	70 (62–76)	.226
Male gender, n (%)	186 (60)	85 (48)	101 (75)	<.0001
Risk factors				
Diabetes, n (%)	64 (26)	28 (20)	36 (36)	.003
Hypertension, n (%)	212 (86)	121 (82)	91 (91)	.045
Medications				
Beta-blockers, n (%)	104 (37)	41 (25)	63 (55)	<.0001
Echocardiogram				
LAD in mm, median (Q_1–Q_3)	40 (35–45)	36 (34–42)	42 (37–47)	<.0001
LVEDD in mm, median (Q_1–Q_3)	53 (49–59)	50 (48–54)	58 (53–64)	<.0001
LVESD, in mm, median (Q_1–Q_3)	35 (30–40)	31 (29–35)	42 (35–50)	<.0001
LVFS (%), median (Q_1–Q_3)	36 (28–40)	39 (35–41)	27 (20–36)	<.0001
24-hr Holter recording				
Nº of PVCs/24 hr, median (Q_1–Q_3)	2,894 (1,594–7,025)	2,833 (1,619–7,192)	3,050 (1,504–6,894)	.634
PVC percentage, median (Q_1–Q_3)	2.7 (1.6–6.7)	2.7 (1.7–6.8)	2.8 (1.6–6.6)	.997
Polymorphic morphology, n (%)	211 (70%)	112 (65)	99 (77)	.022
Couplets, n (%)	236 (75)	118 (67)	118 (87)	<.0001
Triplets, n (%)	106 (34)	47 (27)	59 (44)	.002
NSVT, n (%)	62 (20)	22 (12)	40 (30)	<.0001
SV runs, n (%)	108 (35)	70 (40)	38 (28)	.041
Episodes of AF, n (%)	3 (1)	2 (1.1)	1 (0.7)	1.000

Abbreviations: AF, atrial fibrillation; LA, left atrium; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVFS, left ventricular fractional shortening; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular contractions; SV, supraventricular.

the cardiac adverse outcomes versus patients that did not is presented in Table S2.

3.4 | PVC burden and prognosis

The PVC burden as a continuous variable was not associated with a worse prognosis. In idiopathic patients, the analysis per quartile of the PVC% showed a lower overall survival in patients with a PVC% in the third quartile when compared with the lower quartile (Figure 1; Table 3), with an unadjusted HR (95% CI) of 2.331 (1.090–4.984), $p = .029$. After adjustment to significant covariables (Table S3), it was still associated with a higher all-cause mortality, adjusted HR (95% CI) 2.288 (1.042–5.026), $p = .039$. The PVC burden was not significantly associated with the other adverse outcomes (Table 3; Figure 1; Figures S1 and S2).

In patients with SHD, the PVC burden was associated with a better overall survival and survival free from CV hospitalizations (Figure 1), the increase in PVC percentage was associated with a reduction of all-cause mortality and combined all-cause mortality or CV hospitalizations (Table 3). The per quartile analysis has shown that having a PVC percentage above the upper quartile versus below the lower quartile was associated with a better overall survival and survival free from CV hospitalizations (Figure 1). The unadjusted and adjusted HR (95% CI) for a PVC percentage above the fourth quartile was respectively 0.384 (0.191–0.772), $p = .007$ and 0.417 (0.203–0.858), $p = .017$ for all-cause mortality, and 0.462 (0.250–0.856), $p = .014$ and 0.484 (0.257–0.911), $p = .025$, for all-cause

TABLE 2 Events per 1,000 person-years in patients with idiopathic PVCs and PVCs with SHD

	Overall sample ($n = 312$)	Idiopathic PVCs ($n = 177$)	PVCs in SHD ($n = 135$)	p value[a]
All-cause death	57.2	42.8	80	<.0001
All-cause death or CV hospitalizations	71.4	51.2	106	<.0001
HF death or HF hospitalizations	7.8	0.7	19.3	<.0001
SD or VA hospitalizations[b]	6.1	3.7	10.1	.089

Note: Values are presented in number of events per 1,000 person-years.

Abbreviations: CV, cardiovascular; HF, heart failure; PVCs, premature ventricular contractions; SD, sudden death; SHD, structural heart disease; VA, ventricular arrhythmia.

[a]p values were calculated using the Log-rank test.

[b]For this outcome deaths of unknown cause were excluded ($n = 35$).

mortality or CV hospitalizations. In the SHD group, the PVC burden was not associated with the other combined outcomes either (Table 3; Figures S1 and S2).

3.5 | Prognostic implications of PVC complexity on survival

In the idiopathic group, patients with triplets had lower overall survival or survival free from CV hospitalizations (Figure 2). Patients with NSVT or polymorphic pattern had a lower survival free from CV hospitalization (Figures 3 and 4). In univariable analysis, the unadjusted HR (95% CI) was respectively, 1.982 (1.173–3.350), $p = .011$ and 1.867 (1.145–3.045), $p = .012$ for triplets, and 2.162 (1.149–4.070), $p = .017$ and 1.785 (1.031–3.093), $p = .039$, respectively for the NSVT and polymorphic morphology (Table 3). After adjustment for the other confounding covariables, the presence of triplets, NSVT, or polymorphic morphology was no longer associated with the outcomes (Table 3).

In patients with SHD, the complexity of the PVCs was not associated with all-cause mortality or the combined outcomes, the only exception was the presence of NSVT. Patients with SHD and runs of NSVT had a lower survival free from the arrhythmic combined outcome of SD or hospitalizations due to VA (Figures 2–4; Figures S1 and S2). The presence of NSVT was associated with that outcome in univariable analysis, HR (95% CI) 4.345 (1.037–18.20), $p = .044$, but after adjustment, the significance was lost, although there was a trend toward a worse outcome, HR (95% CI) 3.896 (0.903–16.81), $p = .068$ (Table 3).

4 | DISCUSSION

In our population of almost 2,000 consecutive patients that underwent 24-hr Holter monitoring, more than one fourth had a percentage of PVCs above 1% of total beats with a median PVC% of 2.7 (1.6–6.7) %. This value is much higher than the observed in previous studies evaluating the impact of the burden or the complexity of the PVC on prognosis. Dukes et al. (2015) in a population-based study evaluated 1,139 Cardiovascular Health Study participants randomly assigned to 24-hr Holter monitoring that had a normal left ventricular ejection fraction and no history of CHF. The median PVC percentage was 0.011% (0.002%–0.123%). Lin et al. (2016) in a hospital population of 3,767 patients referred for 24-hr Holter monitoring at Taipei Veterans General Hospital reported a mean PVC% of 176 ± 423 beats per day and none of the patients had a PVC burden of more than 5% of the total beats.

In our group of patients, the PVC burden was not significantly different between idiopathic patients and patients with SHD. However, in the former the PVCs had a less complex pattern. Idiopathic patients with a higher PVC burden had a lower overall survival and survival free from CV hospitalizations. The lower survival however was not associated with the upper quartile but rather with the third. These results may be related with the fluctuations in the PVC burden from day to day. Mullis et al, studied the variation in 24-hr PVC burden over up to 14 days in 59 patients (Mullis et al., 2019). The authors found that the median of the absolute 24-hr PVC burden change was 9.9% (IQR: 5.4%–14.5%) and 72.9% patients fell into at least two categories of PVC burden depending on the 24-hr period considered.

The survival free from adverse outcomes was also significantly lower in idiopathic patients with complex PVCs. The prognostic value of PVC morphology (monomorphic vs. polymorphic) or presence of triplets or NSVT has been investigated previously. Lin et al followed 3,351 patients with apparently normal hearts for 10 ± 1 years and found that patients with polymorphic PVCs had an increased risk of mortality, CV hospitalization, ischemic stroke, and new-onset HF (Lin et al., 2015). Later, the same authors reported that NSVT was also independently associated with a higher incidence of the same outcomes (Lin et al., 2016).

In patients with SHD, neither the burden nor the complexity of the PVCs was associated with a worse prognosis. Remarkably, in this group the higher PVC burden acted as a protective factor, in fact a PVC% in the upper quartile was independently associated with a better prognosis. The reason for these unexpected results is unknown. However, we may speculate that the presence of SHD

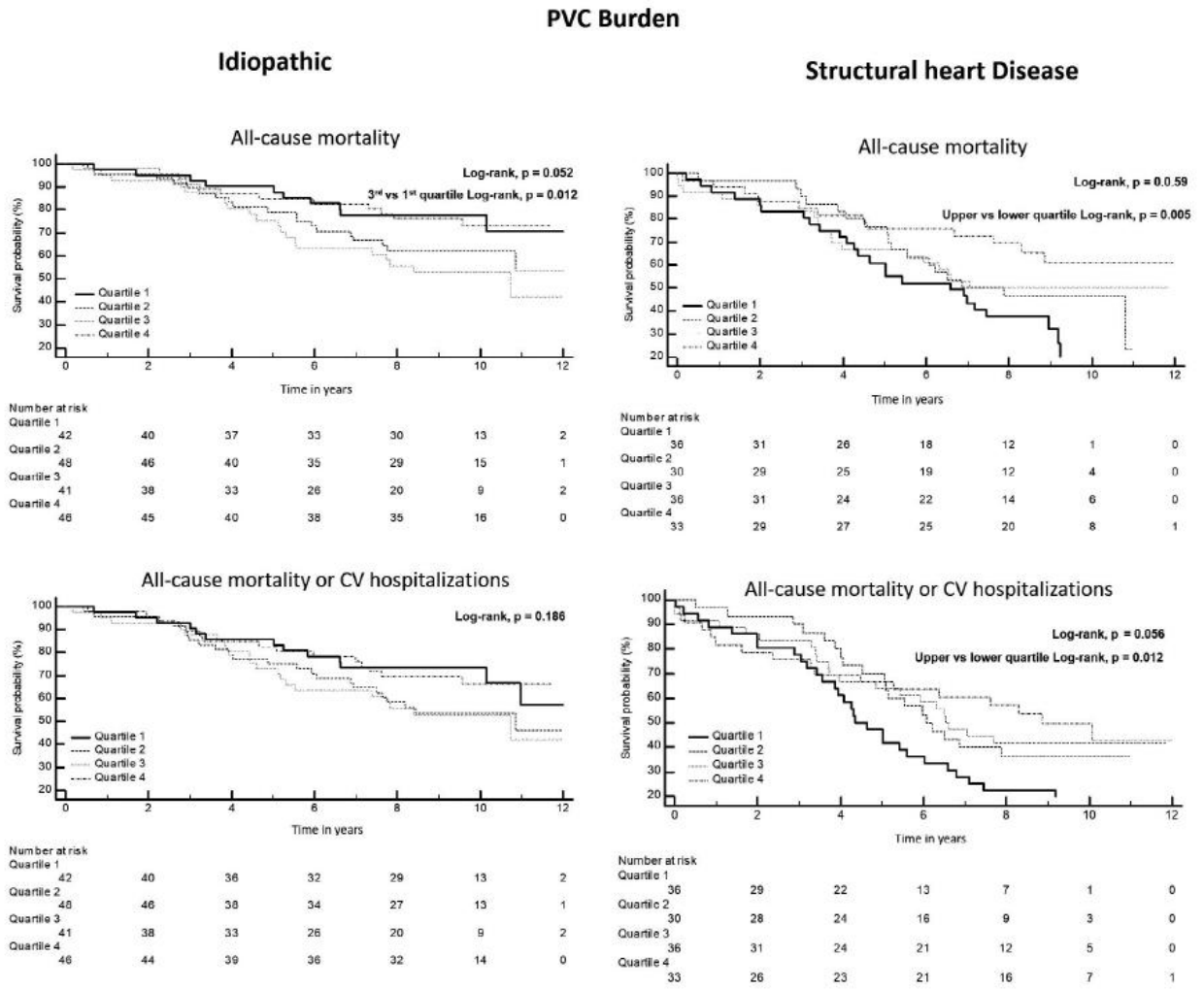

FIGURE 1 Kaplan–Meier survival estimate of overall survival and CV hospitalizations-free survival stratified by the quartile of PVC percentage in both groups with and without structural heart disease. Quartiles 1 through 4 represented PVC burdens of 1%–1.63%, 1.63%–2.74%, 2.74%–6.77%, and more than 6.67%, respectively. CV, cardiovascular; PVC, premature ventricular contractions

may dilute the effect of the PVC burden. Furthermore, the studies assessing the impact of PVC burden on adverse events have shown that the existence of PVCs per se is responsible for the adverse outcomes, whereas the further increase in the burden or complexity does not bring about significant additional risk. In a population-based study, Agarwal et al. have shown that the risk associated with having just one PVC on a 2 min ECG recording was the same as having a higher burden or complexity (Agarwal et al., 2012). Likewise, in the study by Dukes, the authors showed that patients in the upper quartile of PVC% had a 48% increased risk of incident HF. The chart displaying the PVC% plotted against incident HF shows a plateau in the incidence of HF for additional increases in PVC% above 1.5% (Dukes et al., 2015). Noteworthy, in our study the lower quartile corresponded to a median PVC% of 1.25% which corresponds to the fourth quartile of the work by Dukes. This fact may explain why a PVC burden in the upper quartile is not more deleterious than one in the lower in patients with a high competing risk of death or adverse outcome. Besides, the absence of prognostic impact of the PVC burden and complexity in patients with SHD it is not totally unexpected and has been observed previously. Agarwal et al in a retrospective population-based study concluded that the impact of the PVC burden on the incidence of HF was higher in young idiopathic patients without competing risks for adverse outcomes than in patients with SHD (Agarwal et al., 2017).

Another important finding was the absence of an association between PVC burden and complexity and prognosis after multivariable analysis. This probably results from the fact that patients who experienced the adverse outcomes were also older, had more frequently comorbidities, had a lower LVFS and a larger LAD. These last two covariables reflect the severity of both systolic and diastolic left ventricular disfunction. The dimension of the

TABLE 3 Cox regression analysis of the association between PVC burden and complexity and outcomes in two groups

	Idiopathic				Structural heart disease			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause death								
PVC%	0.960 (0.912–1.011)	.119	–		0.944 (0.899–0.992)	.023	0.951 (0.905–1.000)	.048
PVC% per quartile								
Quartile 1	Reference		Reference		Reference		Reference	
Quartile 2	1.733 (0.806–3.728)	.159	–		0.629 (80.335–1.181)	.149	–	
Quartile 3	2.331 (1.090–4.984)	.029	2.288 (1.042–5.026)	.039	0.645 (0.351–1.187)	.159	–	
Quartile 4	1.247 (0.426–2.553)	.611	–		0.384 (0.191–0.772)	.007	0.417 (0.203–0.858)	.017
Polymorphic	1.713 (0.952–3.085)	.073	–		1.275 (0.707–2.296)	.419	–	
Triplets	1.982 (1.173–3.350)	.011	1.289 (0.740–2.245)	.370	1.117 (0.702–1.779)	.641	–	
NSVT	2.162 (1.149–4.070)	.017	1.898 (0.984–3.662)	.056	1.033 (0.621–1.717)	.902	–	
All-cause death or CV hospitalizations								
PVC%	0.973 (0.931–1.016)	.210	–		0.960 (0.921–1.001)	.055	–	
PVC% per quartile								
Quartile 1	Reference				Reference		Reference	
Quartile 2	1.659(0.840–3.276)	.145	–		0.594 (0.333–1.062)	.079	–	
Quartile 3	1.796 (0.891–3.618)	.101	–		0.572 (0.325–1.007)	.053	–	
Quartile 4	1.035 (0.493–2.176)	.927	–		0.462 (0.250–0.856)	.014	0.484 (0.257–0.911)	.025
Polymorphic	1.785 (1.031–3.093)	.039	1.222 (0.679–2.201)	.504	1.075 (0.637–1.816)	.786	–	
Triplets	1.867 (1.145–3.045)	.012	1.004 (0.970–1.040)	.498	0.999 (0.651–1.5349	.997	–	
NSVT	1.724 (0.926–3.211)	.086	–		1.006 (0.632–1.603)	.980	–	
HF death or HF hospitalizations[a]								
PVC%	–				0.989 (0.913–1.072)	.796	–	
PVC% per quartile								
Quartile 1	Reference				Reference			
Quartile 2	–				1.345 (0.301–6.014)	.698	–	
Quartile 3	–				1.217 (0.272–5.449)	.798	–	
Quartile 4	–				1.265 (0.282–5.666)	.759	–	
Polymorphic	–				4.086 (0.531–31.47)	.176	–	
Triplets	–				2.757 (0.942–8.069)	.064	–	
NSVT	–				1.620 (0.576–4.551)	0.360	–	
Sudden death or hospitalization due to VA								
PVC%	0.817 (0.546–1.220)	.323	–		0.980 (0.872–1.102)	.736	–	
PVC% per quartile								
Quartile 1	Reference		Reference		Reference		Reference	
Quartile 2	0.469 (0.043–5.174)	.536	–		0.246 (0.028–2.204)	.210	–	
Quartile 3	1.144 (80.161–8.137)	.893	–		0.223 (0.025–2.004)	.181	–	
Quartile 4	0.013 (000–1,209)	.459	–		0.430 (0.078–2.357)	.331	–	
Polymorphic	44 (0.025–7,766)	.319	–		1.046 (0.211–5.187)	.956	–	
Triplets	2.315 (0.387–13.86)	.358	–		0.188 (0.023–1.524)	.117	–	
NSVT	2.498 (0.279–22.41)	.413	–		4.345 (1.037–18.20)	.044	3.896 (0.903–16.81)	.068

Abbreviations: AF, atrial fibrillation; CV, cardiovascular; LAD, left atrium diameter; LVFS, left ventricular fractional shortening; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular contractions; SV, supraventricular; VA, ventricular arrhythmias.

[a]The analysis of the combined outcome of HF death or HF hospitalizations the analysis was only done in the SHD group because there was only 1 event in the idiopathic group. In multivariable analysis, only covariables with a $p < .05$ in univariable analysis were included (Table S3), respectively: for *all-cause mortality*, the covariables included were age, presence of supraventricular runs, presence of episodes of AF, LAD, and LVFS; for the combined outcome of *all-cause mortality and CV hospitalizations*, the covariables included were age, gender, presence of episodes AF, LAD, and LVFS; for the combined outcome of *sudden death or VA hospitalization*, the only significant covariable included was LAD.

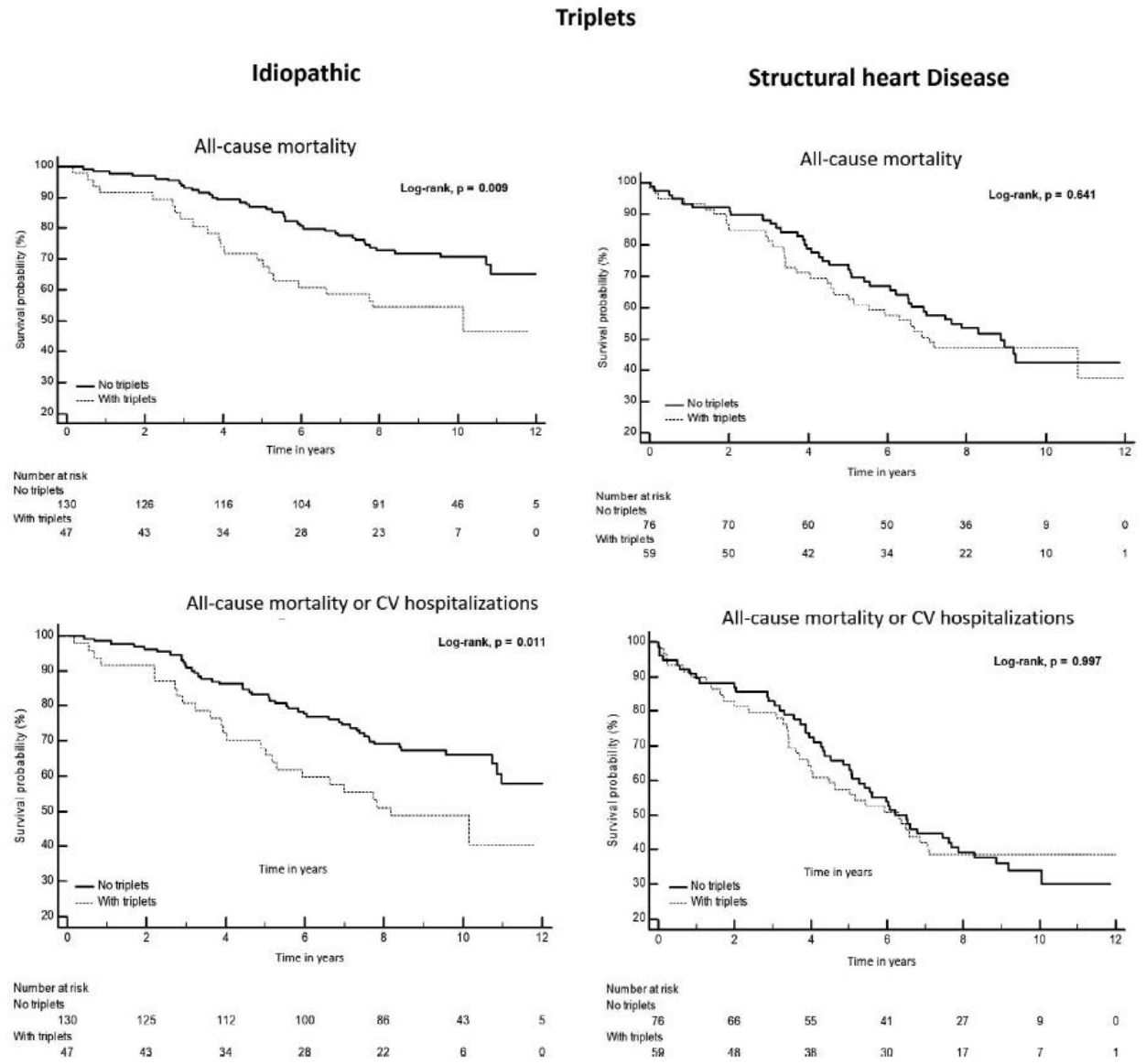

FIGURE 2 Kaplan–Meier survival estimate of overall survival and CV hospitalizations-free survival stratified by the presence of triplets in both groups with and without structural heart disease. CV, cardiovascular

LA reflects the diastolic function (Yoshida et al., 2009), meaning that the diastolic function might be impaired in patients with LA dilation. Furthermore, LAD has been independently associated with a worse prognosis if the patients are in sinus rhythm (Tsang et al., 2006).

In the previous abovementioned studies, the PVC burden and complexity remained significantly associated with a worse prognosis after multivariable analysis. However, in those studies the authors did not include in their analysis the LA dimension.

Regarding the incidence of the combined outcome of HF death or HF hospitalizations, no association was detected between the PVC burden or complexity and the outcomes. During up to 12 years of follow-up, this outcome occurred in 18 patients (5.8%), much more uncommon than previously reported, respectively 27% by Dukes (Dukes et al., 2015) and 19.4% by Argawal (Agarwal et al., 2012). These results are conflicting since not only our PVC burden was much higher than in those studies, but also because HF hospitalizations only occurred in patients with SHD. Frequent PVCs are usually defined as the presence of at least one PVC on a 12-lead ECG or >30 PVCs per hr (Al-Khatib et al., 2018). But although this is a widely accepted guideline, in most of the studies assessing the impact of the PVC burden on the left ventricular dysfunction, the reported PVC burden is above 10% and usually higher than 20% of total beats (Arnar et al., 2019).Thus, higher than the PVC burden of our population and much higher than the PVC burden reported by Dukes and Argawal. It is possible that some subjects in those population-based cohorts simply present PVCs as the

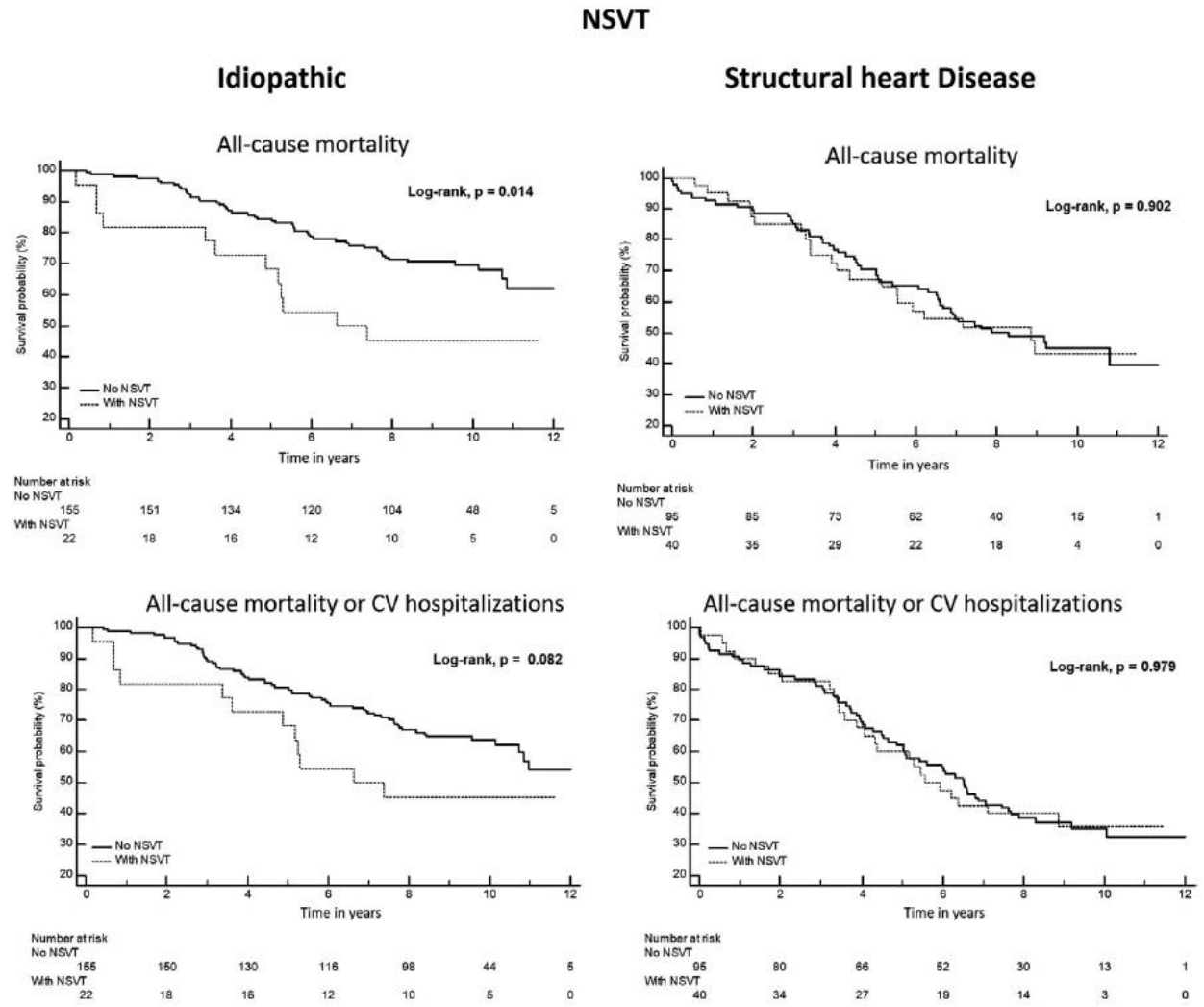

FIGURE 3 Kaplan–Meier survival estimate of overall survival and CV hospitalizations-free survival stratified by the presence of NSVT in both groups with and without structural heart disease. CV, cardiovascular; NSVT, non-sustained ventricular tachycardia

first evidence of a subclinical cardiomyopathy that would have been the cause of the incident HF during the follow-up.

Finally, regarding the incidence of the combined outcome of SD or VA hospitalizations, it would be expected that at least in the presence of SHD, the presence of frequent PVCs or complex forms would have an impact on prognosis. In fact, the presence of NSVT was associated with a lower survival free from SD or hospitalizations for VA. However, once again after adjustment to covariables the association was lost although a trend was maintained.

While previous studies seem to demonstrate increased mortality from ventricular ectopy even with very low PVC counts, there is little evidence to support prophylactic intervention to suppress PVCs in patients without underlying SHD with such low PVC burden. Higher PVC burdens should be treated in idiopathic patients and the presence of PVCs should lead to prompt closer evaluation for possible undiagnosed cardiac disease or reversible underlying etiology.

5 | CONCLUSIONS

In this group of patients, the PVCs had a more complex pattern if SHD was present. The complexity of PVCs was not independently associated with worse prognosis; however, in patients with SHD, the presence of NSVT showed a trend toward a higher incidence of the combined outcome of SD or hospitalizations due to VA. In idiopathic patients, a higher PVC count was independently associated with higher mortality, but in patients with SHD, it was not.

5.1 | Limitations

This was a retrospective study so we cannot rule out selection bias due to the fact that patients were referred for a 24-hr Holter recording because of symptoms, for risk stratification or due to the presence of SHD, so these results cannot be extrapolated to other

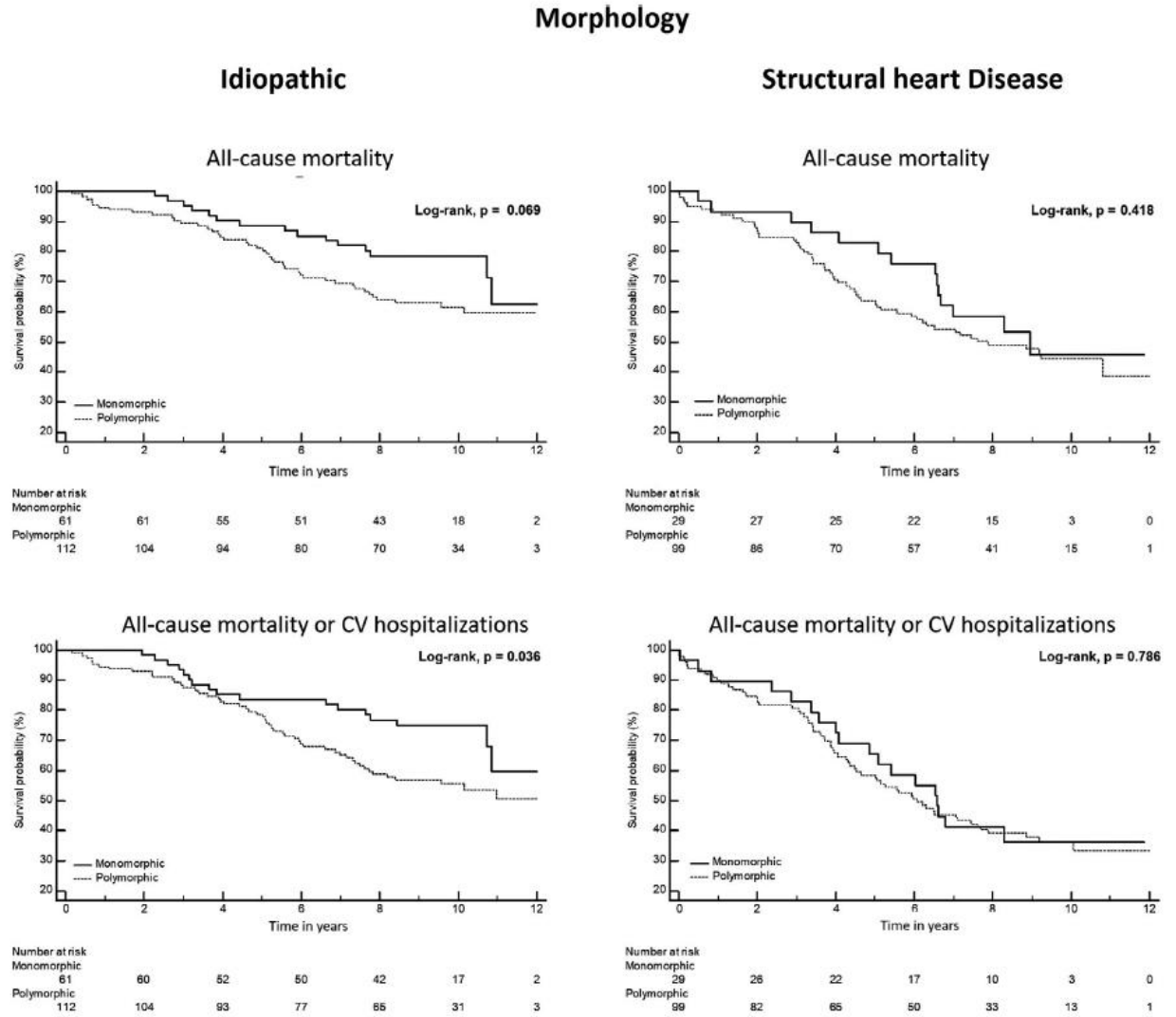

FIGURE 4 Kaplan–Meier survival estimate of overall survival and CV hospitalizations-free survival stratified by the morphology of the PVCs in both groups with and without structural heart disease. CV, cardiovascular; PVC, premature ventricular contractions

populations. The sample size was small and the population with SHD was very heterogeneous. The cause of death was unknown in 26% of cases, and we cannot exclude the possibility that some of those deaths might have been sudden and due to CV causes.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

The Ethical Committee of the Centro Hospitalar de Setubal approved the study. The study is in compliance with the Helsinki Declaration. The informed consent was waived via the Ethical Committee.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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REVIEW ARTICLE

Ventricular Arrhythmias in Patients with Obstructive Sleep Apnea

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Abstract: Obstructive Sleep Apnea (OSA) is a prevalent condition thought to increase in the future. Being mostly undiagnosed, the most serious complications are cardiovascular diseases, among which are arrhythmias. Controversy remains as to whether OSA is a primary etiologic factor for ventricular arrhythmias, because of the high incidence of cardiovascular comorbidities in OSA patients. However, there is mostly a strong evidence of a relation between OSA and ventricular arrhythmias. A few mechanisms have been proposed to be responsible for this association and some electrocardiographic changes have also been demonstrated to be more frequent in OSA patients. Treatment of OSA with Continuous Positive Airway Pressure (CPAP) has the potential to reduce arrhythmias and confer a mortality benefit.

Keywords: Obstructive sleep apnea, ventricular arrhythmias, premature ventricular contractions, ventricular tachycardia, sudden cardiac death, continuous positive airway pressure.

1. INTRODUCTION

Searching for Obstructive Sleep Apnea (OSA) in patients presenting with Atrial Fibrillation (AF) is a common and recommended practice [1] due to the strong evidence of an association between these two entities [2-6]. While most studies have focused on the links between OSA and AF, associations with Ventricular Arrhythmias (VA) have also been characterized, although pooling and meta-analysis of studies have not been possible due to the heterogeneity of data [7]. A few mechanisms have been proposed to be responsible for this association and some electrocardiographic changes have also been demonstrated to be more frequent in OSA patients.

2. OBSTRUCTIVE SLEEP APNEA

OSA is a highly prevalent disease, affecting 4% of men and 2% of women [8]. Due to its association with obesity, the prevalence of which is rising, OSA will represent an escalating public health burden.

OSA is characterized by repetitive upper airway collapses during sleep resulting in intermittent hypoxia and hypercapnia, sleep fragmentation and repetitive intrathoracic pressure changes due to increased respiratory efforts against occluded upper airway. The mechanism by which the upper airway collapses is not fully understood but is multifactorial and includes obesity, craniofacial changes, alteration in upper airway muscle function, pharyngeal neuropathy and fluid shift towards the neck [9].

A detailed medical history (including the patient's partner as he or she can provide important information about what occurs during the night) and clinical examination are important in the evaluation of patients suspected of having OSA. Some predictive information can be obtained from self-reported questionnaires intended to measure daytime sleepiness [Epworth Sleepiness Scale (ESS) [10], the Berlin Questionnaire [11] or Stop-Bang Questionnaire [12]].

Polysomnography (PSG) is the preferred method to diagnose OSA. Apnea is defined as a cessation of airflow for >10 seconds, while hypopnea is a reduction in but not complete cessation of airflow to <50% of normal, usually in association with a reduction in oxyhemoglobin saturation. The most commonly used index to diagnose OSA and define its severity is the Apnea/Hypopnea Index (AHI), calculated as the number of obstructive events per hour of sleep. A diagnosis is made if there are more than five predominantly obstructive respiratory AHI in a symptomatic patient [13]. Symptoms and clinical signals include excessive daytime sleepiness, non-restorative sleep, fatigue or insomnia; waking up with choking, breath holding or gasping; headaches in the morning, witnessed habitual snoring and/or breathing interruptions; and hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive Heart Failure (HF), AF or type 2 diabetes mellitus [13]. Importantly, sleep apnea discovered in a sleep recording without any symptoms is usually not considered to be OSA, except if the AHI is >15 [14]. In this review, otherwise indicated, we use the following cutoffs for graduating OSA: mild ($5 < AHI < 15$), moderate ($15 < AHI < 30$) and severe ($AHI \geq 30$) OSA.

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Continuous Positive Airway Pressure (CPAP) is the primary treatment modality in patients with moderate to severe OSA. It is a treatment that uses mild air pressure to keep the airways open. The beneficial effect of CPAP on symptoms and quality of life is obtained after only a few days of treatment [15, 16] but it depends on adherence [17, 18]. Which is not easy to achieve.

3. CARDIAC ARRHYTHMIAS IN OSA PATIENTS

Cardiac arrhythmias are reportedly in 30%-60% of patients with OSA and include sinus arrest and second-degree atrioventricular conduction block, AF and flutter, atrial and ventricular extrasystoles, nonsustained and sustained Ventricular Tachycardia (VT) and even Sudden Cardiac Death (SCD) [19-27]. The higher the number of AHI and severity of the associated hypoxemia, the higher the prevalence of such arrhythmias [28-33].

VA, primarily premature ventricular contractions (PVCs), have been reported in up to two-thirds of patients with OSA, which is significantly higher than the rates reported in persons without OSA (0% to 12%) [20, 21]. In most OSA patients, VA appear most often during sleep, with the greatest frequency occurring during apneic periods [29, 34, 35]. This is opposed to the pattern of VA distribution in individuals without OSA. Furthermore, VA (particularly PVCs) occur more frequently during the apneic phases than during hyperpnea in OSA patients, which is in contrast to those patients with Central Sleep Apnea (CSA), in whom ventricular ectopy was noted to occur more frequently during hyperpneas than apneas [36].

4. MECHANISMS OF OSA-INDUCTED VENTRICULAR ARRHYTHMIAS

OSA itself causes a complex impairment of myocardium through multifactorial mechanisms. Key findings implicate OSA-related autonomic nervous system fluctuations typified by enhanced parasympathetic activation during and sympathetic surges subsequent to respiratory events, which contribute to augmented arrhythmic propensity. Other more immediate pathophysiologic influences of OSA enhancing arrhythmogenesis include intermittent hypoxia and hypercapnia/acidemia, sleep fragmentation and intrathoracic pressure swings leading to myocardial stretch. Intermediate pathways by which OSA may trigger arrhythmia include increased systemic inflammation, oxidative stress, enhanced prothrombotic state and vascular dysfunction [37]. These mechanisms lead to ventricular hypertrophy and dysfunction at the organ level, presented at the tissue and cellular levels as multifocal infarcts, myocyte hypertrophy and apoptosis and inflammatory infiltrations [38]. Long-term OSA sequelae such as hypertension, ventricular hypertrophy, fibrosis and coronary artery disease also predispose to cardiac arrhythmia [37].

4.1. Sympathovagal Imbalance

In OSA patients, there are sequential autonomic alterations which lead to enhanced arrhythmia susceptibility. First, enhanced vagal efferent outflow to the heart leads to the bradycardia observed during the apneic event (*i.e.* the diving reflex due to increased respiratory efforts of progressive magnitude to achieve restoration of airway patency). After upper airway patency restoration, strong sympathetic nervous system responses are elicited secondary to the interacting effects of central respiratory sympathetic coupling, hypoxia, hypercapnia and absence of sympatho-inhibition from normal lung initiation reflexes [37, 39]. Local cardiac stretch reflexes and baroreflexes might also play a role [39].

4.2. Hypoxia and Hypoxemia

Apneas and hypopneas impair gas exchange resulting in hypoxia and hypoxemia. Hypoxemia directly stimulates chemoreceptors in the carotid body, precipitating increased ventilation and sympathetic discharges [40-42]. In addition, hypoxia leads to peripheral vasoconstriction which increases both preload and afterload, alters ventricular repolarization and increases expression of Left Ventricle (LV) endocardial calcium channels [43].

Furthermore, re-oxygenation after termination of upper airway obstruction may lead to the formation of hazardous Reactive Oxygen Species (ROS). ROS generation has been linked with arrhythmogenesis, as a result of changes in calcium channel activity and by the promotion of microvascular ischemia [44, 45].

4.3. Intrathoracic Pressure Alterations

In healthy individuals, intrathoracic pressure during inspiration is normally about -8 cmH_2O. In patients with OSA, upper airway occlusion generates negative intrathoracic pressures of less than -30 cmH_2O. These large pressure shifts during obstructive apneas increase venous return to the right heart and LV afterload, decrease LV compliance and increase cardiac wall stress [46, 47], which appear to be sufficient to cause ventricular remodeling [37]. Supporting this hypothesis, healthy subjects who performed the Müller maneuver (inspiration against an occluded mouthpiece) simulating increased intrathoracic pressures were found to have an acute increase in LV afterload [48]. In animal experiments, intrathoracic pressure swings during obstructive apneas contribute to changes in ventricular repolarization, which are not observed with central apneas and are mainly driven by sympathetic activation [49].

4.4. Myocardial Ischemia

The combination of hypoxemia, increased Heart Rate (HR) and Blood Pressure (BP) and increased LV afterload - due to augmented sympathetic nerve activity and increased intra-thoracic pressure - leads to an imbalance between increased myocardial oxygen consumption and decreased oxygen supply. All could lead to myocardial ischemia, which could predispose to VA and SCD.

4.5. Changes in Cardiac Structure

The repetitive fluctuations in HR, BP and intrathoracic pressure during sleep and increased sympathetic nerve activity during sleep and wakefulness, lead to remodeling of the ventricles over time, which then could lead to right and left ventricular hypertrophy and subsequently to systolic and

diastolic dysfunction. Also, the repetitive ischemic insults may promote ventricular fibrosis [50]. Indeed, mechanical effects of OSA promote cardiac stretching and can elucidate a mechano-electrical mechanism responsible to predispose to arrhythmias [51].

Due to the pathological abnormalities occurring in OSA, several mechanisms of arrhythmogenesis can be implicated:

- Abnormal automaticity involves spontaneous cardiac impulse formation and may arise due to hypoxemia and respiratory acidosis accompanying apneic events [52].
- Reentry mechanisms may occur through the vagal stimulation that results from respiration against a partially occluded airway.
- Triggered automaticity may occur due to enhanced sympathetic nervous system activity associated with a respiratory event–related hypoxemia and arousal [53].
- Triggered activity precipitants via early after-depolarizations include hypoxia, acidosis and ventricular hypertrophy.
- Delayed after-depolarizations often occur in response to increased catecholamine levels [37].

Indeed, acute and chronic hemodynamic, autonomic, electrical and structural myocardial changes can all contribute to cardiac arrhythmias in OSA patients (Fig. 1).

5. ECG PREDICTORS OF VENTRICULAR ARRHYTHMIAS IN OSA PATIENTS

Parameters that can be used to evaluate ventricular repolarization are QT interval (QT), corrected QT interval (QTc), QT dispersion (QTd) and transmural dispersion of repolarization, which can be assessed using the time interval from the peak to the end of the T wave (TpTe interval). TpTe/QT and TpTe/QTc ratios are among the other electrocardiographic indices representing ventricular arrhythmogenic potential. It has been extensively reported these parameters are associated with VA and SCD [23-26, 54-62]. Since increased heterogeneity in ventricular recovery time and repolarization time are correlated with VA, these studies provide a mechanistic basis for OSA as a predisposing factor for VA and SCD [37].

5.1. QT Interval Prolongation

The QT interval represents the electrocardiographic correlate of ventricular de- and repolarization, including the vulnerable period for reentry tachycardia and it is considered a marker of ventricular electrical instability and a risk factor for the occurrence of malignant cardiac arrhythmias and SCD [63].

Previous explained pathophysiologic mechanisms suggest that apneic episodes in OSA are associated with both significant QT prolongation due to increased vagal activity and abrupt QT shortening during post-apnea due to increased sympathetic tone and/or vagal withdrawal [64].

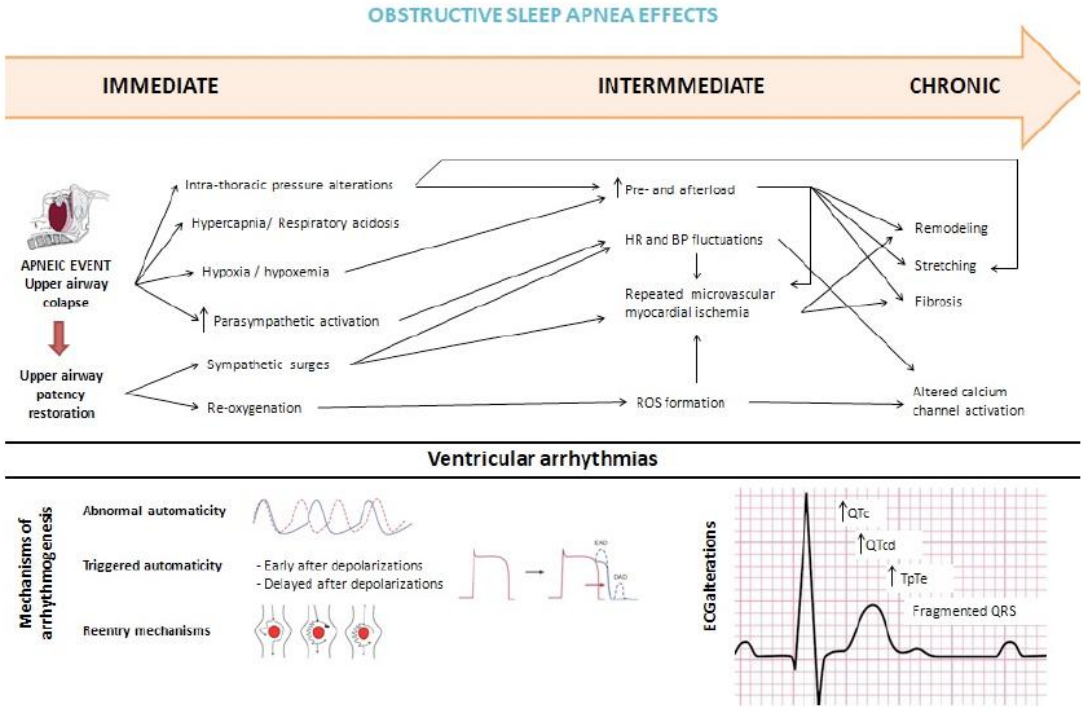

Fig. (1). Proposed mechanisms responsible for enhanced arrhythmogenesis in Obstructive Sleep Apnea (OSA) patients. BP: Blood Pressure. DAD: Delayed After-Depolarizations. EAD: Early After-Depolarizations. HR: Heart Rate. ROS: Reactive Oxygen Species.

In fact, QTc interval was revealed to show a significant prolongation during the apnea period in patients with mild to severe OSA [64-66]. Several mechanisms responsible for prolongation in action potential duration (thus QTc prolongation) have been proposed. According to Schalatzer *et al*., the QTc interval increased more at the end and even further after the release of the Mueller maneuver, suggesting enhanced sympathetic tone and also intrathoracic pressure swings and associated acute cardiac volume changes are responsible for QTc prolongation [67]. Hypoxia, hypercapnia and acidemia also play a role in QTc prolongation. Hypoxia has been shown to impact the activity of all of the channels involved in cardiac action potential generation (I_{Na}, I_{CaL}, slow component of I_{Ks}) [68]. Low pH depolarizes the voltage dependence of INa channel activation and inactivation [69].

In what concerns QTc interval behavior during post-apnea hyperventilation period, conflicting results were published: some authors found an abruptly decrease [64], others demonstrated no differences [70] and others found QTc interval persisted to be prolonged in the post-apnea hyperventilation period [65]. The latter authors proposed increased sympathetic activation and rapid alterations in the intrathoracic pressure during this period as mechanisms by which persistent prolongation of the QTc occurred even in the post-apnea hyperventilation period [65]. Also in daytime ECG, Shamazzuman found a significant increase in QTc [66].

5.2. QT Dispersion

QTd is the difference between the maximum and minimum QT intervals on ECG and reflects inhomogeneity in ventricular repolarization and myocardial electrical instability [71]. An increased corrected QT dispersion (QTcd) > 60 ms is a strong and independent risk factor for cardiac mortality [62].

QTcd was found to be increased in severe OSA patients without hypertension [72] and contrasting with no-OSA patients, it increased during sleep (65.0 ± 14.6 ms) compared with before sleep (57.0 ± 13.5 ms, $p < 0.0001$) [73]. However, on the contrary, Barta el al found that QTd and QTcd did not increase during the nighttime period [74]. The high value of AHI in the former studies (42.4±17.6/ h [72] and 51.9 ± 18.5/h [73], respectively) can justify this different result (25.8 ±18.5/ h in Barta study [74]). Probably the AHI and the severity of apnea-hypopnea-related hypoxemia had a significant effect on the QTcd during sleep in OSA patients [75, 76]. A correlation between QTcd during sleep and AHI (r=0.38, P=0.009) and the percentage of time that SaO2 was inferior to 90% (r=0.34, p=0.018) was demonstrated by Nakamura *et al.* Other factors may contribute to QTcd increasing during sleep: CO_2 retention/academia [75], change in parasympathetic nerve activity [77, 78] and fluctuating intrathoracic pressure, which induces myocardial wall stress, cardiac distortion and changes in venous return.

5.3. TpTe interval

The interval between the electrocardiographic T-wave peak and end (TpTe) has been studied as a measure of cardiac dispersion and repolarization. The TpTe interval is a measure of cardiac transmural dispersion of repolarization, which is explained by a gradient of action potential duration from endo- (longest) to epicardial cells (shortest) [79, 80]. A prolongation of the TpTe interval leads to increased vulnerability for the occurrence of early afterdepolarizations and has been associated with ventricular tachycardia and an increased risk for SCD [25, 81-83]. Specifically, recent findings from Panikkath *et al.* suggest that patients with an uncorrected TpTe interval >100 ms in the resting ECG are at increased risk of SCD [25]. Comparisons of OSA patients versus controls identified increased TpTe in those with OSA [43, 70, 84, 85]. Camen *et al*. investigating the effect of simulated obstructive apnea and hypopnea on arrhythmic potential on a healthy group of individuals, reported a prolongation in QTc and TpTe intervals, suggesting negative intrathoracic pressure changes as a contributory mechanism. Schalatzer *et al*. found the increase in TpTec was only significant after release of the Mueller manoeuvre, but not during the manoeuvre, suggesting a key contribution of enhanced sympathetic tone and intrathoracic pressure swings [67]. The impact of hypoxia and hypercapnia/acidemia on the transmural refractory behavior needs to be investigated.

In addition to the prolonged QTc and TpTe intervals, an increased TpTe/QT and TpTe/QTc ratios, a measure of disproportional prolongation of global dispersion relative to the QT interval, may have an important role in arrhythmogenesis [86]. These ratios have the advantage of more reliably eliminating the confounding effects of the heart rate variability in the ECG and the inter-individual variation in the length of the QT interval [83]. They are prolonged in patients with moderate and severe OSA patients and correlated with AHI index [70]. They were found to be increased during the apnea period compared to pre-apnea period, and decreased significantly in the post-apnea hyperventilation period [65]. Rossi *et al*. demonstrated an increase in the TpTe/QT ratio after CPAP withdrawal, further substantiating a potential risk for arrhythmias in this situation [87].

5.4. Fragmented QRS

Not only repolarization was found to be impaired in OSA patients. Fragmented QRS (fQRS) complexes are markers of depolarization abnormality and reflect disordered electrical activation of ventricles through the inhomogeneous substrate and/or localized intramyocardial/ intraventricular conduction blocks [88, 89]. Abnormal impulse conduction creates a milieu for VA through reentry mechanisms and fQRS complexes are a predictor of cardiovascular death in patients with structural heart disease [88, 90]. Recent studies found fQRS in patients with OSA (independently of obesity), suggestive of electrical myocardial remodeling [87, 91, 92]. One of the mechanisms thought to be responsible for fQRS is cellular apoptosis and interstitial fibrosis in cardiac structure, which may be secondary to chronic hypoxia, metabolic abnormalities and oxidative stress [87, 91, 92]. Adar *et al.* found fQRS is an independent predictor of subclinical LV dysfunction in patients with OSA, suggesting it could identify OSA patients who could be at risk for developing overt cardiac dysfunction. Also, a higher C-reactive Protein (CRP) level in OSA patients with fragmented QRS may suggest that inflammation could also play a role in the alterations of the QRS morphology [92].

6. EVIDENCE-BASED VENRICULAR ARRHYTHMIAS IN OSA PATIENTS

6.1. Premature Ventricular Contractions

The frequency of PVCs normally falls during nonrapid eye movement (NREM) sleep, which comprises approximately 85% of total sleep time. This decline parallels the decrease in sympathetic outflow and the increase in vagal outflow to the heart that accompanies the transition from wakefulness to NREM sleep [93]. Conversely, the frequency of PVCs tends to rise just before and after waking, a time when cardiac sympathetic tone increases [94]. Indeed, it is expectable that PVCs frequency is higher in patients with OSA due to sympathovagal imbalance.

PVCs were demonstrated to occur in a characteristic cyclic fashion that is synchronous with respiratory oscillations [29] and there was a significantly greater frequency of PVCs during apnea than during hyperpnea in OSA patients [36, 95] (contrary to patients with CSA) [95]. This is probably related to the generation of negative intrathoracic pressure and hypoxia, hypercapnia and recurrent arousals, which induce repetitive surges in sympathetic neural outflow, HR and BP. Study of Camen *et al*. support these mechanisms, since the authors found simulated obstructive apnea and hypopnea in healthy individuals are associated with an increase of PVCs [96].

Abe *et al*. (2010) found PVCs (Lown IVa, IVb or V) were more frequent when increasing severity of OSA patients: 0 in non-OSA; 0.5% in mild OSA; 3.0% in moderate OSA and 4.2% in severe OSA (p= 0.004) [30]. In sleeping breathing disorders (SBD) patients (including OSA and CSA) similar results were found [21, 28]. Mehra *et al*. found a significant relationship between SDB and PVCs/h during sleep period (p=0.0003), but only in patients with severe SBD (AHI>30/h) [97]. In another study, AHI was independently associated with an increased prevalence of PVCs not only at night [Odds Ratio (OR) per 1-U increase of log-transformed AHI 1.5, 95% confidence interval (CI) 1.1 to 2.0, p=0.008] but also during the day (OR 1.37, 95% CI 1.0 to 1.8, p=0.035) after adjusting for relevant confounders and even in middle-aged patients with mainly mild or moderate OSA [98]. Although the authors did not provide possible mechanisms responsible for the higher number of PVCs during the day [98], the long-term effects in cardiac structure in OSA patients could be involved in arrhythmogenesis in daytime.

The prevalence of frequent PVCs in OSA patients depends on the cutoff value used to define it. More than 35 years ago, Guilleminault *et al*. found 19% of patients with SBD had frequent PVCs (>2/min) [20]. More recently, other studies addressed this question. When considering the cutoff ≥5 PVCs/h, PVCs were almost two times more prevalent in subjects with OSA comparing with those with no-OSA during night [98, 99] and also during day [98]. When a cutoff of >30PVCs/h was used, a non-significant higher proportion of patients with OSA had frequent PVCs comparing with non-OSA patients [100]. There are other studies which do not confirm the high frequency of PVCs in OSA patients [21, 85, 99, 101, 102]. Of note, in the majority of these studies [21, 85, 99, 102], the non-OSA/SBD patients had a relatively high prevalence of arrhythmias, which can be explained by a "particular" control group (patients referred for PSG in whom OSA was not confirmed).

6.2. Complex Ventricular Ectopy

Almenneessier *et al*. found non-isolated PVCs (bi-,tri- and quadrigeminism) in 10.8% of patients with OSA comparing to 2.3% in patients with no-OSA (p=0.04) [99]. Mehra *et al*. achieved similar results but they studied patients with SDB: almost twice the odds of complex ventricular ectopy [OR 1.74; 95% CI, 1.11–2.74 after adjusting for age, sex, body mass index, and prevalent coronary heart disease] [103]. Tilkian *et al*. found complex PVCs occurred in 10 of 15 patients with OSA [22].

6.3. Non-sustained Ventricular Tachycardia

Non-sustained VT (NSVT) was defined as three or more consecutive PVCs with duration less than 30 seconds. Only two studies addressed NSVT in OSA patients. According to Abe *et al*., NSVT were not more frequent in OSA patients: 0 in non-OSA; 1.0% in mild OSA; 1.5% in moderate OSA and 1.3% in severe OSA (p= 0.417) [30]. Aydin *et al*. found no NSVT in OSA (and non-OSA) patients [100]. In SBD patients, a few studies found a high prevalence of NSVT [28, 104]. Mehra *et al*. demonstrated that, compared with those without SDB and adjusting for age, sex, body mass index, and prevalent coronary heart disease, individuals with SDB had three times the odds of NSVT (OR 3.40; 95% CI, 1.03–11.20) [97].

All NSVT studied by Guilleminault *et al*. happened during an apneic event in SBD patients[20]. Monahan *et al*. studied SBD patients and cardiac arrhythmias, including NSVT and AF in the same analysis, and they found a direct temporal association between arrhythmia and a preceding respiratory event, enhancing a very probably causal inference. Although the absolute arrhythmia rate is low, the relative risk of NSVT and AF during sleep is markedly increased shortly after a respiratory disturbance (within a 90-second hazard period): the odds of an arrhythmia following a respiratory disturbance were nearly 18-times (OR 17.5; 95% CI 5.3–58.4) the odds of an arrhythmia occurring following normal breathing. The absolute rate of arrhythmia associated with respiratory disturbances was low (1 excess arrhythmia/40000 respiratory disturbances). Only 57 patients with OSA (AHI 5-30/h) and arrhythmias (62 arrhythmias) contributed to these results [104], but it is the first study supporting a direct temporal link between OSA events and the development of arrhythmias.

6.4. Sustained Ventricular Tachycardia

Most studies did not detect sustained VT in patients with OSA [30, 85, 98, 99]. Javaheri *et al*. found no correlation between sustained VT and OSA (percentage of patients with sustained VT was similar in the control and the OSA groups) [35].

6.5. Appropriate ICD Therapy

No published studies exclusively on OSA patients were found, but studies on SDB patients (including a significant

proportion of OSA patients) demonstrated an association between Implantable Cardioverter-defibrillator (ICD) shocks and SBD [31, 32, 105, 106]. In patients with ICD, VA were significantly more often associated with apneas/hypopneas than with normal breathing [95, 105]. The risk for VA [32], anti-tachycardia pacing therapy (ATP) [106] and ICD shocks [106, 107] was higher in SBD patients due to an increase in events occurring between midnight and 6 a.m., with no discernible effect on appropriate ICD therapy during nonsleeping hours. The presence of SBD was an independent predictor for appropriate ICD therapy (hazard ratio 4.05, 95% CI 1.20 to 13.65, p=0.015 [102]) and the severity of OSA correlates with the risk of nocturnal arrhythmias [32]. ICD appropriate shocks in patients with HF are independently associated with AHI as a continuous variable and inversely and independently associated with minimum oxygen saturation during the night [31].

Recently, the relationship between OSA and VA burden has been evaluated by means of a device allowing simultaneous nasal pressure recordings, as a surrogate for PSG, and ECG, in 214 patients with an ICD or Cardiac Resynchronization Therapy (CRT). This study confirmed that the number of VA was significantly higher in patients with moderate or severe OSA than in those with mild or non-OSA [105].

6.6. Sudden Cardiac Death

In the general population, the circadian distribution of cardiovascular events follows the circadian pattern of the autonomic nervous system: they are suppressed during sleep in parallel with the nocturnal nadir of sympathetic activity and vagal predominance [108] and increase in the morning hours [109].

The first study suggesting an association between OSA and SCD was carried out by Gami *et al.* in 2005. They reviewed the death certificates of 112 patients who suddenly died from cardiovascular causes and had previously undergone a PSG. They demonstrated that from midnight to 6 a.m., SCD occurred in 46% of people with OSA, as compared with 21% of people without OSA (p=0.01) and 16% of the general population (p<0.001). The authors concluded that people with OSA have a peak in SCD from cardiac causes during sleeping hours (from midnight to 6 a.m.) [110], which contrasts with the nadir of SCD from cardiac causes in patients without OSA and in general population. Later on, a longitudinal study of more than 10.000 patients conducted by the same author found that OSA predicted SCD (including ICD shocks as a surrogate of SCD in some patients) and the magnitude of the risk was predicted by parameters that characterize OSA severity: AHI (>20), lowest and mean nocturnal oxygen desaturation (<78% and <93%, respectively). However, in this study SCD was not inevitably due to VT/VF since it included deaths due to acute myocardial infarction (13%) or acute pulmonary embolism (1%) [33].

7. OSA IN "IDIOPHATIC" VENRICULAR ARRHYTMIAS PATIENTS

Koshino *et al.* found that approximately 51% of patients with idiopathic VA (VT or ≥300 PVCs/h) had OSA (≥5 AHI), which suggests a strong association between OSA and VA in patients without heart failure. Of interest, in this study, there were no differences in ESS score, showing that patients with OSA had no symptoms of daytime sleepiness [111].

In HF patients with VA, the prevalence of OSA is particularly high [112], but an impaired LV function itself may be a substrate for VA.

8. TREATMENT OF VENTRICULAR ARRHYTHMIAS IN OSA PATIENTS

Continuous positive airway pressure (CPAP) is the primary treatment modality in patients with severe OSA, whereas oral appliances are also widely used in mild to moderate forms. Other treatment options include weight loss, avoidance of alcohol and sedatives and surgery [19]. Whether these treatment modalities have a role in VA of OSA patients is still controversial.

8.1. Continuous Positive Airway Pressure

CPAP is a treatment that delivers positive pressure through a mask to maintain the opening of the upper airways during sleep, usually indicated in patients with moderate or severe OSA. Adherence and compliance to the treatment are the main problems faced by clinicians, mainly due to mask application and difficulty dealing with the equipment [113].

CPAP alleviates apnea-related hypoxia and arousals from sleep and abolishes exaggerated negative intrathoracic pressure swings [114]. The possible mechanisms of action of CPAP in VA may include improved myocardial oxygen delivery, decreased sympathetic activity, LV transmural pressure and afterload [115]. By reducing oxygen demand and increasing oxygen supply, CPAP could attenuate PVCs either by preventing ischaemia in patients with ischaemic heart disease or by improving ventricular repolarization [116]. A second potential mechanism is through a reduction in cardiac sympathetic nerve traffic [117]. This is supported by the finding of reduced overnight urinary norepinephrine in the CPAP treated group [118, 119]. Another mechanism may involve unloading of the ventricles with the elimination of their transient mechanical distension and a consequent alleviation of electrical-mechanical dissociation [120].

Relevant studies that addressed CPAP effects on VA in OSA patients are presented in Table **1**. A few studies were not included due to the reduced number of patients with OSA (<10 patients) [34, 35, 121, 122]. Of note, the majority of studies support a protective effect of CPAP against the occurrence of VA, but definitive evidence is still lacking. In studies that did not confirm a reduction in arrhythmia frequency after CPAP, the low number of events (patients with arrhythmia) is likely the reason for the absence of significantly favorable results.

Overall, the duration of CPAP application, compliance with treatment, baseline severity of OSA and cardiac pathology are important confounding factors that influence the effect of CPAP treatment. The small sample sizes that limit extrapolation, as well as the inconsistencies in methodologies for the measurement of outcomes and variables of interest, indicate that larger controlled randomized studies will provide the homogeneity warranted to promote a more useful synthesis of the current evidence.

Table 1. Principal characteristics of studies regarding CPAP effects on ventricular arrhythmias (VA) in obstructive sleep apnea (OSA) patients.

Author, Year	Study Design	Patients	AHI Before Treatment; Mean (SD)	Findings
Abe [30] 2010	Observational, prospective	632 pts, suspected of having OSA. 316 had moderate to severe OSA (>20AHI) and were treated with CPAP during average 3.9 weeks	50.3 (22.3)	After CPAP treatment, PVCs were less frequent (p=0.016) but no significant reduction in ventricular arrhythmias (PVCs or NSVT) were found
Craig [129] 2009	Interventional, randomized controlled trial	83 pts with moderate to severe OSA (AHI ND). 43 with therapeutic CPAP and 40 with non-therapeutic CPAP* during 1 month	41.2 (24.3)	CPAP therapy reduces mean 24-h heart rate possibly due to reduced sympathetic activation, but did not result in a significant decrease in dysrhythmia frequency. A trend toward a fewer daytime VT events
Dediu [130] 2015	Interventional, non-controlled	15 pts with OSA (AHI>5) and PVCs. 8 with CPAP and pharmacological therapy and 7 with no-CPAP during 6 months.	N.D.	More patients with class II Lown ventricular extrasystoles passed in class I Lown in those with CPAP (non-significant).
Dursunoglu [131] 2007	Observational,prospective	30 pts with moderate to severe OSA (AHI≥15). 18 compliant** with nasal CPAP and 11 non-compliant, during 6 months	50.1 (11.6)	The QTcd at baseline [54.5 (8.7) ms] significantly decreased after CPAP therapy [35.5 (4.2) ms, p<0.001] and it did not significantly change in 11 non-compliant patients.
Nakamura [70] 2004	Observational, prospective	48 pts with moderate to severe OSA (AHI≥20) after one night and 1 month of nasal CPAP	51.9 (18.5)	After 1 night and after one month of nCPAP therapy, the QTcd during sleep [50.6 (11.4) ms] decreased from that before treatment (p < 0.0001)
Peled [132] 1999	Observational, prospective	15 pts with OSA (AHI>5) treated with CPAP during 1 night, of whom 9 had nocturnal ischemia	35.1(6.2)	Treatment with CPAP significantly ameliorated the nocturnal ST depression time from 78 min to 33 min (p < 0.001)
Roche [133] 2005	Observational-prospective	38 pts with moderate to severe OSA (≥15) before and after CPAP (and 38 pts with no OSA - control group)	56.9 (28.4)	QT length related to heart rate significantly improved with the treatment of the OSAS [−0.151(0.051); p<0.01 vs pretreatment status]. There was no significant impact of CPAP therapy on PVCs.
Rossi [87] 2012	Interventional, randomized controlled trial	41 pts with OSA (severity N.D) and previously CPAP. 20 continued CPAP and 21 received placebo-CPAP during 2 weeks	36.0 (17.3) (CPAP group) *vs.* 45.3 (22.3) (control) NS	CPAP withdrawal is associated with the prolongation of the QTc and TpTec intervals and TpTe/QT ratio
Ryan [116] 2005	Interventional, randomized	18 HF pts with moderate to severe OSA (AHI>20) and >10PVCs/h. 10 treated with CPAP during 1 month	29.3 (4.8) (CPAP group) *vs.* 57.9 (5.50) (control) (p=0.017)	A 58% significant reduction in the frequency of PVCs during total sleep [from 170 (65) to 70 (28) per hour, p=0.011] after 1 month of CPAP treatment.
Seyis [134] 2018	Observational, prospective	80 HF pts with newly diagnosed moderate to severe OSAS and >30PVCs/h. 40 pts accepted CPAP and 40 did not.	35.85 (8.61) (CPAP group) *vs.* 32.45 (8.88) (control) NS	CPAP treatment significantly reduced the frequency of PVCs, T-peak to T-end, QTc, QTcd, and T-peak to T-end/corrected QT ratio

*Subtherapeutic CPAP was physically identical to therapeutic CPAP except the pressure was less than 1 cmH_2O, and inadequate to splint open the pharynx as previously described.
**Patients were considered to be compliant if they used CPAP an average 3.5 hours per night at the six-month follow-up.
N.D. no data. CPAP: continuous positive airway pressure. nCPAP: nasal CPAP. NS: non-significant. QTcd: QT corrected dispersion. Pts: patients. VT: ventricular tachycardia.

8.2. Anti-arrhythmics

No studies addressed the efficacy of drug therapy in VA and if a particular class of Antiarrhythmic Drug (AAD) is more effective than the others in OSA patients. In what concerns AF, patients with severe OSA are less likely to respond to AAD therapy than those with milder forms of OSA [123] and possibly the same is true in VA.

8.3. Catheter Ablation

Koshino *et al.* demonstrated that VA in patients with OSA (defined as AHI ≥10) have a higher rate of recurrence of VT/PVCs after catheter ablation compared with non-OSA patients (45% versus 6%, p=0.02) during a mean follow-up period of 13.5 (7.3) months [111]. However, this study had some important limitations: the sample size was small (n=44), patients with AHI 0-9 were considered as having no OSA and the authors did not explain if OSA patients were treated with CPAP after OSA diagnosis.

8.4. Other Therapies

The role of oxygen treatment in preventing VA in OSA patients had been proposed but there are insufficient studies with a low number of patients [120, 124].

Weight loss is likely to be an effective measure, not only due to beneficial effects on OSA itself but also on cardiovascular comorbidities, very frequent in these patients. Alcohol consumption is also not advised since it is associated *per si* to cardiac arrhythmias [125, 126].

9. GAPS IN EVIDENCE / LIMITATIONS

Due to the nature of the outcome and the presence of comorbidities in OSA patients, the observational studies demonstrating an association between OSA and VA are not enough to prove a causal relationship.

The definition for OSA and its severity (regarding AHI cutoffs) were not uniform across all studies, which may be responsible for some conflicting results.

Given the small number of studies available, studies including not only obstructive but also CSA (SDB) were analysed. Although we only used OSA sub-analysis, in some cases, it was difficult to definitely separate the outcomes. OSA is characterized by repetitive collapse of the upper airway, whereas the hallmark of CSA is recurrent complete or partial withdrawal of central respiratory drive. Only a few of the possible mechanisms responsible for arrhythmogenesis are shared by these two entities. In CSA, the increased respiratory effort is absent, and only the presence of peripheral mechanisms such as intermittent hypoxia, increased catecholamines, and frequent arousals are responsible for the increased sympathetic activation [127, 128].

CONCLUSION

OSA is a prevalent condition thought to increase in the future. Being mostly undiagnosed, the most serious complications are cardiovascular diseases, among which are arrhythmias. Treatment of OSA has the potential to reduce arrhythmias and confer a mortality benefit.

The controversies regarding the relationships between OSA and VA can be explained by selection bias and inhomogeneity in OSA definition and disease severity. Also, OSA is a complex syndrome that involves hypoxemia, endothelial dysfunction, inflammation and sympathetic stimulation and is commonly present in patients with other cardiovascular risk factors. In general, the evidence suggests OSA is associated with VA. From our point of view, the main questions are "Is this association significant enough to establish OSA as a risk factor for SCD due to VA?" and "Is the available evidence strong enough to come up with new treatment strategies in patients with VA and OSA?"

We propose that patients with VA should be screened for OSA due to the lack of symptoms in this population and the possible high prevalence of OSA in patients with "idiopathic" VA. However, not all patients with arrhythmias need to undergo PSG to establish OSA diagnosis. The authors suggest considering for evaluation for possible OSA patients with (1) Nocturnal arrhythmias (2) Arrhythmias refractory to standard therapy or (3) Other clinical indicators of OSA such as obesity, disruptive snoring, witnessed apnea or gasping and hypersomnolence.

In some particular conditions, the authors advocate CPAP therapy may be considered to prevent VA. For example, CPAP may be indicated with respect to an increased QTc or QTcd or when VA is detected at night, because the evidence suggests they are independent risks factors for cardiac mortality and CPAP may reduce them.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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Excessive atrial ectopic activity as an independent risk factor for ischemic stroke

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ABSTRACT

Background: Excessive atrial ectopic activity (EAEA) has been related with an increased risk of atrial fibrillation (AF) and stroke but different cutoff values have been used. We aimed to determine the association between EAEA and stroke, AF and overall death.

Methods: Consecutive 24-hour Holter monitoring performed between 2005 and 2010 in a single center was evaluated. Patients with a previous diagnosis of stroke or AF were excluded. The number of premature atrial contractions (PACs) during 24 h was analyzed in 2480 subjects and according to that 3 sub-groups were defined: >97 PACs/h (above the top 5th percentile of the population) (EAEA+); intermediate value of PACs/h (below the top 5th percentile but above 30 PACs/h) (EAEA+/−) and <30 PACs/h (EAEA−).

Results: After adjusting for risk factors, laboratory findings and medication, EAEA+ was associated with ischemic stroke (hazard ratio [HR] 2.83; 95% confidence interval [CI], 1.65–4.84, $p < 0.001$). Both EAEA+ and EAEA+/− were independently associated with AF (HR 2.05; 95% CI 1.31–3.23, $p = 0.010$ for EAEA+ and HR 1.90; 95% CI 1.10–2.78, $p = 0.020$ for EAEA+/−) and overall death (HR 2.17; 95% CI 1.48–3.28, $p = 0.031$ for EAEA+; HR 2.01; 95% CI 1.06–2.52, $p = 0.029$ for EAEA+/−).

Conclusion: In this population, having >30 PACs/h was independently associated with a higher risk of AF and overall death but only subjects with >97 PACs/h had a higher risk of ischemic stroke. In the majority of subjects with stroke and EAEA+, AF has not been detected before stroke event.

1. Introduction

The role of atrial ectopic activity in the initiation of atrial fibrillation (AF) is well established. In 1998, Haissaguerre et al. demonstrated that the pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of atrial fibrillation [1]. Premature atrial contractions (PACs) may be a marker for foci that are or will be capable of firing rapidly to initiate AF [2] through a reentry-maintaining substrate. Rapid and repetitive stimulation of the atrial muscle is known to alter its electrophysiological properties by shortening atrial refractoriness, leading to the development and maintenance of AF. Alternatively, PACs may be a marker of developing atrial electrophysiological changes that promote AF, such as interstitial fibrosis and abnormal intracellular calcium handling [3]. Recent studies suggested that excessive atrial ectopic activity (EAEA) not only increases risk of AF but it is also associated with an increased risk of stroke, adverse cardiovascular events and death [4–8]. The lack of precise definition for "excessive" atrial ectopy leads investigators to use arbitrary cut-off values according to top percentiles for frequency of PACs [6–8]. However, considering the number of PACs as a continuous variable, the risk of adverse events is related to the number of PACs. The aim of this study was to use a higher *cutoff* value in order to identify high risk patients that would benefit from therapeutic intervention.

2. Methods

2.1. Patients

Between January 2005 and December 2010, 3589 consecutive patients were referred to our non-invasive cardiology laboratory for elective 24-hour (h) Holter monitoring. Patients were excluded if they had previously documented AF (n = 396), AF diagnosed during the exam (n = 206), history of stroke or transient ischemic attack (n = 409) or if they were under medication with anticoagulants (n = 98). The final analysis thus involved 2480 subjects.

2.2. Study design

Demographic data, cardiovascular risk factors, indications for 24 h Holter monitoring, transthoracic echocardiograms and medications were recorded. Hypertension was defined as resting systolic or diastolic blood pressure ≥ 140/90 mm Hg on two occasions or prescription of anti-hypertensive drugs. Diabetes mellitus was defined as a serum fasting glucose ≥7.0 mmol/L or prescription of anti-diabetic medication. Smoking status was recorded as

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; EAEA, excessive atrial ectopic activity; ECG, electrocardiogram; h, hour; HR, hazard ratio; LDL, low-density lipoprotein; PACs, premature atrial contractions.

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current smoker or non-smoker. The CHA_2DS_2VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) score was calculated [9]. All transthoracic echocardiograms were retrospectively collected and reviewed by study personnel. Holter recording was performed with the use of 3-channel tape recorders (*GE SEER LIGHT®*). Recordings had to exceed 20 h and be of good quality to be analyzed and all of them were reviewed and edited manually. Subjects were asked about PACs-related symptoms, namely palpitations during the exam. Premature atrial complexes were quantified using the number of PACs/h (PACs/h). Patients with PACs/h at the top 5th percentile in the present cohort were considered to have EAEA (n = 124) (EAEA +). Subjects with less than the commonly accepted *cutoff* value for frequent PACs (30 PACs/h) were assumed to have no EAEA (EAEA −). Patients with >30 PACs/h but <97 PACs/h were considered as an intermediate group with frequent but not excessive PACs/h (EAEA +/−). According to gender and age, propensity score matching method was used to obtain pairs of matched subjects: 124 for EAEA− group and 114 for EAEA +/− group, in order to exclude bias in recruitment. The selection of patients for analysis is shown in the study flow diagram (Fig. 1).

Events of stroke, AF and overall death were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone. Ischemic stroke was defined as a neurological deficit of sudden onset that persisted for >24 h, corresponded to a vascular territory in the absence of primary hemorrhage and that could not be explained by other causes (trauma, infection, vasculitis). It was confirmed by computerized axial tomography or magnetic resonance imaging of the brain. New occurrence of AF was defined as AF documented by a standard 12 lead electrocardiogram (ECG) or a new 24-h Holter monitoring.

2.3. Ethics

All participants provided written informed consent. The Ethical Committee of Centro Hospitalar de Setubal approved the study. The study is in compliance with the Helsinki Declaration.

2.4. Statistics analysis

SPSS version 23 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data is expressed as means ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Baseline characteristics and outcomes were compared using the chi-square test for categorical variables and the ANOVA test for continuous variables. Univariate and multivariate Cox-proportional-hazards regression analysis was used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of ischemic stroke, new-onset AF and overall death between patients in the studied groups. Kaplan–Meier survival function and the log-rank test were used to compare the survival distributions. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

Clinical characteristics are shown in Table 1. Median follow-up was 7.1 years and it was similar between the groups. No patients were lost to follow-up.

3.2. Follow-up

Events per 1.000 person-years observed in up to 11 years of follow-up in the three studied groups are shown in Table 2. Supplementary Fig. 1 represents the percentage of events that occurred during the follow-up in the three groups.

3.2.1. Stroke

Stroke occurred in 54 of all patients. Subjects who experienced a stroke were older (74 ± 6 years versus 70 ± 9 years; $p < 0.001$), had more hypertension (76% versus 89%, $p = 0.02$) and had a higher CHA_2DS_2VASc score ($CHA_2DS_2VASc \geq 3$ in 78% versus 61%; $p = 0.03$). Other baseline variables and risk factors were not significantly different between the groups (Supplementary Table 2).

Subjects with EAEA + had 34.9 strokes/1.000 person-years; those with EAEA +/− had 15.1 strokes/1.000 person-years and those with EAEA − 11.5 strokes/1.000 person-years ($p < 0.001$ for EAEA +). In univariate analysis, EAEA + was associated with ischemic stroke (HR 2.71; 95% CI 1.60–4.61, $p = 0.002$ for EAEA + group). This remained significant after adjustment for conventional risk factors (sex, age, body mass index, current smoking, hypertension, diabetes mellitus) (HR 2.87; 95% CI 1.68–4.91, $p < 0.001$). Further adjustment for blood glucose, creatinine, low-density lipoprotein (LDL) cholesterol, coronary or peripheral arterial disease and heart failure did not affect the results (HR 2.83; 95% CI 1.65–4.84, $p < 0.001$). If use of medication is considered, including aspirin, the results will remain almost unchanged. Of note, EAEA +/− were not included in the model, regardless of adjustments. Fig. 2A shows Kaplan-Meier curve for stroke-free survival in patients with and without EAEA.

In patients with stroke, AF was detected in 18 (60%) of patients with EAEA + and in 8 (62%) of patients with EAEA +/− comparing to 4

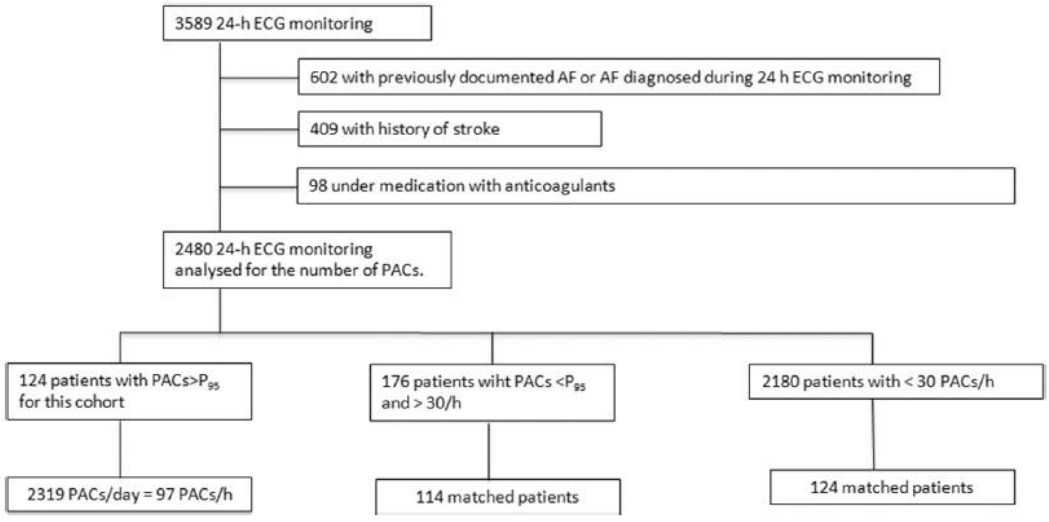

Fig. 1. Flow diagram of the study selection process. Flow diagram of patients included in analysis: 124 patients with EAEA, 114 age- and gender-matched subjects with intermediate EAEA and 124 age- and gender-matched subjects with no EAEA. EAEA: excessive atrial ectopic activity. ECG: electrocardiogram. h: hour. PACs: premature atrial contractions.

Table 1
Baseline characteristics of the studied groups.

	EAEA+ (n = 124)	EAEA+/− (n = 114)	EAEA− (n = 124)	p-Value
Demographic data				
Male gender, n (%)	63 (51)	66 (58)	75 (60)	0.25
Age (years), mean ± SD	70.6 ± 5.6	71.9 ± 9.3	71.4 ± 8.6	0.58
Body mass index, kg/m^2, mean ± SD	28.1 ± 10.1	27.1 ± 6.1	26.8 ± 5.6	0.28
Risk factors and history				
Hypertension, n (%)	97 (78)	87 (76)	97 (78)	0.51
Diabetes mellitus, n (%)	32 (26)	31 (27)	28 (23)	0.70
Current smoking, n (%)	30 (24)	17 (15)	22 (18)	0.17
Alcohol consumption > 101 g/wk, n (%)	5 (4)	4 (3)	3 (2)	0.77
Coronary or peripheral arterial disease, n (%)	25 (20)	23 (20)	26 (21)	0.98
Heart failure, n (%)	9 (7)	12 (10)	16 (13)	0.14
Obstructive sleep apnea, n (%)	11 (9)	7 (6)	11 (9)	034
Chronic obstructive pulmonary disease or asthma, n (%)	16 (13)	8 (7)	18 (15)	0.17
Thyroid dysfunction, n (%)	4 (3)	5 (4)	1 (1)	0.22
Laboratory				
Glucose (mg/dL), mean ± SD	111 ± 23	118 ± 25	114 ± 33	0.28
Creatinine (mg/dL), mean ± SD	1.17 ± 0.72	1.15 ± 0.51	1.09 ± 0.50	0.41
LDL cholesterol (mg/dL), mean ± SD	129 ± 57	124 ± 45	128 ± 40	0.76
Echocardiographic parameters				
Left atrial volume/BSA, mL/m^2, mean ± SD	37 ± 11	36 ± 12	35 ± 10	0.31
Symptoms				
Palpitations, n (%)	25 (20)	14 (12)	11(9)	0.03
CHA_2DS_2VASc score[a]				0.70
0–1, n (%)	20 (16)	18 (16)	18 (14)	
2, n (%)	32 (26)	21 (18)	27 (22)	
≥3, n (%)	72 (58)	75 (60)	79 (64)	
Medication				
Beta-blocker, n (%)	25 (20)	18 (16)	25 (20)	0.59
Ivabradine, n (%)	2 (2)	1 (1)	0 (0)	0.37
Diuretic, n (%)	19 (15)	21 (18)	17 (14)	0.96
ACEI/ARB, n (%)	79 (64)	69 (60)	79 (64)	0.89
Aspirin/clopidogrel, n (%)	54 (43)	46 (40)	44 (35)	0.25
Beta2-agonist, n (%)	10 (8)	6 (5)	6 (5)	0.48
24-h ECG monitoring				
PACs/h, mean ± SD	344 ± 276	56 ± 19	5 ± 5	<0.001
Runs of ≥ 5 PACs	66 (53)	59 (52)	43 (35)	0.005
Follow-up (years)	6.8 ± 2.3	7.0 ± 2.4	7.3 ± 2.6	0.08

Values are presented as mean ± standard deviation (SD) and number (%).
BSA: body surface área. EAEA: excessive atrial ectopic activity. PACs: premature atrial contractions. wk: week.
EAEA+: >97 PACs/h; EAEA+/−: PACs/h = 30–97; EAEA−: PACS/h < 30.
[a] The CHA_2DS_2VASc score was calculated according to the presence of congestive heart failure/left ventricular dysfunction (1 point); hypertension (1 point); age ≥ 75 years (2 points); diabetes mellitus (1 point); history of stroke, TIA or thromboembolism (2 points); vascular disease (history of MI, PVD or aortic atherosclerosis) (1 point); age 65–74 years (1 point) and female gender (1 point).

(36%) of patients with EAEA−. However, AF was detected before the stroke event in 9 patients and only 3 of this patients initiated oral anticoagulation (for reasons unrelated with investigators) (Supplementary Table 1).

3.2.2. Atrial fibrillation

Table 2 shows AF/1.000 person-years in participants. Subjects who developed AF during the follow-up period were older (74 ± 6 years versus 70 ± 7 years, p = 0.009) and had more frequently hypertension (91% versus 69%, p < 0.001) and diabetes mellitus (35% versus 23%, p = 0.004). In Cox regression models, EAEA+ and EAEA+/− were both associated with an increased risk of AF in both univariate (HR 2.05; 95% CI 1.31–3.20, p = 0.002 and HR 1.68; 95% CI 1.05–2.69, p = 0.03, respectively) and adjusted models for conventional risk factors (HR 2.00; 95% CI 1.27–3.15, p = 0.003; HR 1.66; 95% CI 1.04–2.67, p = 0.035; respectively). Adjusted model for blood glucose, creatinine, low-density lipoprotein (LDL) cholesterol, coronary or peripheral arterial disease, heart failure and medication use showed similar results (HR 2.05; 95% CI 1.31–3.23, p = 0.01 for EAEA+ and HR 1.90; 95% CI 1.10–2.78, p = 0.02 for EAEA+/−). Fig. 2B shows AF-free survival in patients with EAEA+, EAEA+/− and EAEA−.

In addition to EAEA+ and EAEA+/−, hypertension (HR 2.78; 95% CI 1.31–3.82, p = 0.006) was associated with an increased risk of AF during follow-up.

Table 2
Events per 1.000 person-years in subjects with EAEA+, EAEA+/− and no EAEA−.

	EAEA+ (n = 124)	EAEA+/− (n = 114)	EAEA− (n = 124)	p-Value
Stroke	34.9	15.1	11.5	<0.001*
AF	67.2	55.8	33.3	0.014**
Overall death	77.8	56.8	33.3	<0.001**

AF: Atrial fibrillation. EAEA: excessive atrial ectopic activity.
EAEA+: >97 PACs/h; EAEA+/−: PACs/h = 30–97; EAEA−: PACS/h < 30.
* For EAEA+.
** For EAEA+ and EAEA+/−.

3.2.3. Overall death

Fifty-eight patients with EAEA+ (47%), 42 (37%) with EAEA+/− and 29 patients (23%) with EAEA− died during the follow-up (Supplementary Fig. 1) (HR 2.40; 95% CI 1.54–3.73, p < 0.001 for EAEA+; HR 1.69; 95% CI 1.06–2.72, p = 0.029 for EAEA+/−, in univariate analysis). This

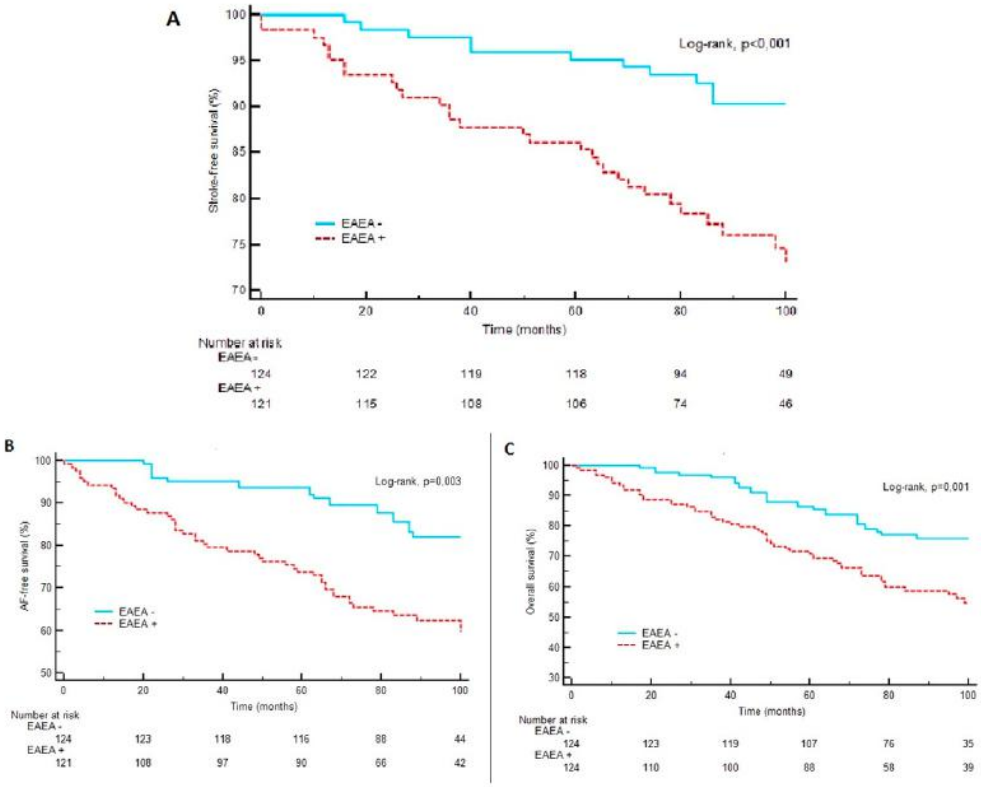

Fig. 2. Kaplan-Meier survival estimate of stroke-free survival (A), AF-free survival (B) and overall survival (C) in subjects with EAEA+, EAEA+/− and EAEA−.

remained significant after adjustment for conventional risk factors (HR 2.02; 95% CI 1.35–3.24, p = 0.028 for EAEA+; HR 1.78; 95% CI 1.02–2.46, p = 0.034 for EAEA +/−) and for blood glucose, creatinine, LDL cholesterol, coronary or peripheral arterial disease, heart failure and medication (HR 2.17; 95% CI 1.48–3.28, p = 0.031 for EAEA+; HR 2.01; 95% CI 1.06–2.52, p = 0.029 for EAEA +/−). Fig. 2C shows overall survival in the three groups.

Besides EAEA, age (in years) was associated with an increased risk of death (HR = 1.1 per year; 95% CI 1.07–1.13, p < 0.001). Other risk factors were not significantly associated to death.

4. Discussion

There is no clear and accepted cutoff value for the frequency of PACs to be considered pathological. Assuming that PACs had to be excessive to increase the adverse events substantially, we set the cutoff at the top 5th percentile of the present cohort: patients with >97 PACs/h were considered to have EAEA. An intermediate group defined as having more than the general accepted cut-off value (30 PACs/h) but less than 97 PACs/h was also studied in order to better define if having "excessive" PACs/h is distinct from having "frequent" PACs/h. Previous studies considered lower cutoff values [4–8]. Bicini et al. [7] and Larsen et al. [5] used the higher cutoff value and even thought it was 30 PACs/h, which corresponded to top 10th percentile in Bicini's study.

In our study, having more than 97 PACs/h was independently associated with almost a 3-fold increased in the rate of ischemic stroke, after adjustment for other risk factors. Interesting, subjects who had 30–97 PACs/h do not have an increased risk of ischemic stroke, demonstrating that a higher burden of EAEA is necessary. Two possible pathophysiological mechanisms could be involved: EAEA precedes undiagnosed incident AF or EAEA may lead to the dilatation of left atrium and stasis in the left atrial appendage, fibrosis and endothelial dysfunction resulting in a hypercoagulable state similar to that seen in AF [10–11]. Some authors proposed that EAEA could be a marker of a higher prevalence of cardiovascular (CV) risk factors such as hypertension, diabetes, dyslipidemia and smoking status [5–6]. Although underpowered for such findings, our results did not corroborate such hypothesis since there were no significant differences regarding CV risk factors between patients in the EAEA + group comparing to EAEA +/− or EAEA − group. Although still arbitrary, a fairly stringent cutoff value suggests that defining a higher cutoff (e.g. >100 PACs/h) can identify more accurately patients at a higher risk of stroke.

As in others studies [5–8], EAEA was associated with new-onset AF, demonstrating that a close follow-up of these patients is needed. Both EAEA + and EAEA +/− patients had an increased risk of developing AF, although EAEA + group had a higher risk. These results are in accordance with Alhede et al. [12], who demonstrated that lower PACs burden after catheter ablation or medical therapy in patients with known AF were associated with lower long-term AF burden. These findings may raise the question of treating EAEA in order to decrease this risk.

Other main question is the importance of an early detection of AF in order to prevent embolic events since it is a well-known risk factor for ischemic stroke. In recent years, more efforts have been done to detect possible AF in patients with cryptogenic stroke [13–17]. Identifying patient populations at high risk for occult AF may provide a more targeted and higher yield AF screening approach [18], since it is time consuming and expensive. Using EAEA as a method to predict AF [19] is very useful since EAEA is more frequent than AF episodes.

Patients with EAEA also had an increased risk of overall death, which was in accordance with other studies. While it is conceivable that the

EAEA predicts the development of new AF, the mechanism by which EAEA results in an increased risk of death is not as clear. The increased risk of death may be attributable to AF and/or stroke but also to underlying cardiac conditions in which EAEA is more frequent (e.g. coronary heart disease, left ventricular dysfunction) or more severe/uncontrolled CV risk factors. However our study did not analyzed specific causes of death, namely cardiovascular deaths to draw this conclusion. According to Conen et al. [19], PACs frequency is independently associated with age, height, history of cardiovascular disease, natriuretic peptide levels, physical activity and high-density lipoprotein cholesterol. Although in our study there were no differences in these risk factors between the three groups and death was more frequent in EAEA+ and EAEA+/− groups, the study may be underpowered to find such differences.

Of note, PACs-related symptoms were uncommon in our study; only 20% of subjects with >97 PACs/h and 12% of those with more than 30 PACs/h complained of palpitations. While no differences were found in the number of patients with beta-blockers at the time of the Holter recording, beta-blockers dosage or titration during follow-up were not analyzed. No differences in endpoints were found between symptomatic and asymptomatic subjects.

Conventionally, only AF and atrial flutter are considered to cause ischemic stroke. Our study suggests that other atrial electric instabilities as EAEA can contribute to some cryptogenic strokes. However, it remains to clarify if EAEA is associated with an increased risk of ischemic stroke by itself or through the appearance of paroxysmal AF (detected or not). Larsen et al. (2015) found a correlation between EAEA and ischemic stroke beyond AF when censoring analysis and modeling AF as a time-varying exposure. However in a competing risk analysis with death and AF as competing events, the association between EAEA and ischemic stroke attenuated to insignificantly [5]. In our study, 40% of patients with EAEA and stroke had no AF detected suggesting that EAEA could have been the responsible for the stroke event. Even in those with AF detected after acute stroke (37%), there is no certainty about the mechanism for stroke: EAEA that increased the risk for AF after acute stroke or occult AF not detected before acute stroke. Given these results, it is possible that patients with EAEA (in particular those with more than 100 PACs/h) can benefit from therapeutic intervention (oral anticoagulation) if CHA_2DS_2VASc score was high, even in the absence of AF diagnosis. Further studies are needed to answer these questions. Until then, the best manner to treat patients with EAEA in order to reduce the risk of AF, stroke and death is appropriate risk factor modification.

4.1. Study limitations

It was an observational and retrospective study. The diagnosis of atrial fibrillation in our study is probably underestimated because it was based on admission for AF or occasional ECG or 24 h Holter monitoring during follow-up. Indeed the number of cases of asymptomatic AF is not known.

5. Conclusions

EAEA is associated with an increased risk of stroke, AF and death. Subjects with >100 PACs per hour are at higher risk and need strict close follow-up, risk factor modification and may benefit from therapeutic intervention. More investigation in this field is needed.

Grant support

None.

Conflicts of interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.08.054.

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Letter to the Editor

"Excessive" atrial ectopy is worse than "frequent" atrial ectopy

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Dear Dr. Liu and colleges,

Thank you for your comments. We are entirely in agreement with you, there is not a precise definition for "excessive" atrial ectopy, as we referred in our article [1]. However, we intended to study a higher cut-off value than other previous studies, which in fact used the top 10th percentile [2,3]. Following their idea and with the aim of understanding if "excessive" atrial ectopy is worse than "frequent" atrial ectopy, we used the top 5th percentile in our population. A cut-off value determined by the receiver operating characteristic curve using stroke occurrence would probably give similar results but would not be able to distinguish if excessive is worse than frequent atrial ectopy.

In what concerns CHA_2DS_2VASc score [4] it has been compared between the three groups and it was not different between them ($p = 0.70$) (Table 1) [1]. In patients with ischemic stroke, CHA_2DS_2VASc score remained not different between the three groups and in multivariate analysis it was not independently associated with a higher risk of stroke.

The stroke-free survival, AF-free survival and overall survival in subjects with EAEA +/− were lacking in the Kaplan-Meier survival curves for reasons unrelated to the authors. We have already contact the editor in order to correct it.

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Original Article

Cardiol Res. 2019;10(5):268-277

Excessive Atrial Ectopic Activity Worsens Prognosis and Predicts the Type of Major Adverse Cardiac Events in Patients With Frequent Premature Ventricular Contractions

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Abstract

Background: The aim of the study was to evaluate the impact of premature atrial contractions (PACs) burden, and the presence of non-sustained ventricular tachycardia (NSVT) on prognosis and type of major adverse cardiovascular events in patients with frequent premature ventricular contractions (PVCs).

Methods: We retrospectively studied 285 consecutive patients with frequent PVCs defined as PVC count equal or higher than 1% of total beats assessed with 24-h Holter recording. Patients with atrial fibrillation (AF) were excluded. We evaluated the impact of PAC burden and the presence of NSVT on the primary end points of all-cause mortality, stroke and new-onset AF, and secondary end points; arrhythmic end point (arrhythmic death or hospitalizations for ventricular arrhythmias) or heart failure (HF)-related end point (death or hospitalizations due to HF).

Results: The PAC number showed an adjusted hazard ratio (HR) (95% confidence interval (CI), P value) of 1.077 (1.014 - 1.145, P = 0.017) for all-cause mortality, 1.250 (1.080 - 1.447, P = 0.003) for stroke, 1.090 (1.006 - 1.181, P = 0.036) for new-onset AF and 1.376 (1.128 - 1.679, P = 0.002) for the HF end point. The presence of NSVT showed an adjusted HR (95% CI) of 3.644 (1.147 - 11.57, P = 0.028) for the arrhythmic end point.

Conclusions: In patients with frequent PVCs a high PAC count was independently associated with increased mortality, higher rate of AF, stroke and HF adverse events, but not with arrhythmic adverse events. The presence of NSVT was independently associated with increased arrhythmic adverse events, but not with overall mortality, AF, stroke or HF events.

Keywords: Atrial fibrillation; Excessive atrial ectopic activity; Heart failure; Premature atrial contractions; Premature ventricular contractions; Stroke

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Introduction

Premature ventricular contractions (PVCs) are a common finding during long-term monitoring [1]. Although PVCs can occur in healthy persons, they are more frequent in the presence of structural heart disease (SHD), sleep apnea [2], chronic obstructive pulmonary disease, and hyperthyroidism or stimulants [3]. Frequent PVCs in the presence of SHD are associated with a worse prognosis, especially in ischemic heart disease and in the presence of complex forms. Lown's grading of PVCs into six categories [4] was initially proposed as a prognostic classification in the acute myocardial infarction (MI) scenario. Currently this classification is no longer used as an indication for therapy, however some of the definitions are still used, like the severity based on the morphology or in the presence of runs of non-sustained ventricular tachycardia (NSVT). Recently the presence of frequent or severe forms of PVCs have been associated with increased mortality, heart failure (HF), atrial fibrillation and stroke, even in the absence of known SHD [5-8].

However, patients often have frequent premature atrial contractions (PAC), in addition to frequent PVCs as in the case of older populations, especially in the presence of cardiovascular risk factors [9]. PACs have been considered a benign incident for many years. Recent studies have demonstrated an association between PACs and atrial fibrillation (AF) and stroke [10-13]. In fact, frequent PACS have been considered an independent marker of stroke, adverse cardiovascular events and death, suggesting that the risk associated with frequent PACs is beyond the association with AF [10, 12].

In previous studies that evaluated the role of frequent PVCs as predictors of outcomes like HF, new-onset AF and stroke [7, 8, 14], none has assessed the role of concomitant frequent PACs. The aim of this study was to evaluate the impact of the number of PACs and the presence of NSVT on all-cause mortality and on major adverse cardiovascular events (MACEs) in patients with frequent PVCs.

Materials and Methods

Patients

We evaluated 1,967 consecutive patients older than 18 years

who underwent 24-h Holter monitoring in our center, between June 2006 and December 2010. We selected patients with frequent PVC, defined as PVCs representing more than 1% of total number of heart beats, because according to Dukes et al [5] this is the cut-off point that provides the best sensitivity/specificity relation for prediction of adverse outcomes (n = 530). Patients with AF, atrial flutter or any rhythm other than sinus during recording were excluded (n = 168). Patients who were lost to follow-up (n = 50) and patients with previous history of documented atrial AF or atrial flutter (n = 27) were further excluded. The final study population included 285 patients.

Study design

We retrospectively recorded the demographic data. From the medical records we collected the presence of diabetes, hypertension, hypercholesterolemia, antiarrhythmic and beta-blocker use, presence of SHD and its type. The CHA_2DS_2VASc risk was calculated according to the presence of congestive HF/left ventricular dysfunction (1 point); hypertension (1 point); age ≥ 75 years (2 points); diabetes mellitus (1 point); history of stroke, transient ischemic attack (TIA) or thromboembolism (2 points); vascular disease (history of MI, vascular disease or aortic atherosclerosis) (1 point); age 65 - 74 years (1 point) and female gender (1 point). We considered the presence of a high stroke risk if the CHA_2DS_2VASc score was higher than 2 in men or 3 in women.

All transthoracic echocardiograms were retrospectively collected. Echocardiographic evaluation included M-mode measurements of the left atrium diameter (LAD), left ventricular end diastolic diameter (LVDD), left ventricular end systolic diameter (LVSD) and left ventricular fractional shortening (LVFS) obtained in the left parasternal view. Holter recording was performed with the use of three-channel tape recorders (GE SEER LIGHT®). Recordings had to exceed 20 h and be of good quality to be analyzed and all of them were reviewed.

On Holter evaluation, maximal, minimal and mean heart rate, number of PACs/24 h (PACs/day), presence of supraventricular runs of more than five PACs, number of PVCs/24 h (PVCs/day), morphology of the PVCs, polymorphic versus monomorphic, this variable was not available in 10 patients corresponding to 3.5% of the study population, presence of runs of more than five PVCs (NSVT) and presence of atrioventricular (AV) node disease were assessed.

Follow-up data were retrieved from the national patient registry and from medical records or discharge letters, and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone.

Death was ascertained by reviewing medical records, or from national patient registry.

HF death was defined as worsening HF, manifested as cardiogenic shock, pulmonary edema or increase in HF symptoms and drug therapy, or hospitalization due to decompensated HF prior to death. Arrhythmic death was defined as instantaneous death or death in patients who were resuscitated from a sudden cardiac arrest or occurred within 24 h of acute symptoms in the absence of pre-existing circulatory failure, and if unobserved, assumed to be acute and instantaneous.

Ischemic stroke was defined as a neurological deficit of sudden onset that persisted for more than 24 h. It was confirmed by computerized axial tomography or magnetic resonance imaging of the brain. New-onset AF was defined as AF documented by a standard 12-lead electrocardiogram (ECG) or a new 24-h Holter monitoring. Hospitalization was defined as an overnight stay in a hospital ward. The cause of hospitalization was obtained from medical records, and cardiovascular hospitalization included the ones due to aggravated HF, ventricular arrhythmia, bradyarrhythmia or acute coronary syndromes. The primary end points determined were all-cause mortality, stroke and new-onset AF. Secondary end point was the type of MACE during follow-up: arrhythmic MACE; arrhythmic death or hospitalizations due to ventricular arrhythmias (VA), or HF-related MACE; death or hospitalizations due to HF.

Ethics

The Ethical Committee of the Centro Hospitalar de Setubal approved the study. The study is in compliance with the Helsinki Declaration. The informed consent was waived via the Ethical Committee.

Statistical analysis

All analyses were performed using SPSS statistical software, version 24.0 (SPSS, Inc, Chicago, Illinois). Data are expressed as median and interquartile range (IQR) for continuous variables due to lack of normal distribution, and as frequencies and percentages for categorical variables.

The relative risk for a given end point associated with the different variables studied was estimated by calculating the hazard ratio (HR) using a Cox regression hazards model. To adjust for potential confounders like age, gender, cardiovascular risk factors, CHA_2DS_2VASc, presence of SHD, incident AF, LVFS, and LAD, multivariable Cox proportional-hazards model was used. The assumption of linearity for continuous covariates was tested and confirmed. We used a log (base 2) transformation of the PVC count and PAC count to meet model linearity assumptions. The proportional hazard assumption was tested for each of the Cox models based on Schoenfeld residuals for continuous variables and on "log-minus-log" plot for categorical variables.

Receiver operator characteristic curves (ROC) and areas under the curve (AUC) were obtained to determine the discriminative power of PAC burden as predictor of all-cause death (AUC = 0.669, $P < 0.0001$; 95% confidence interval (CI) (0.606 - 0.733). Optimal cut-point value for the number of PACs/day was obtained (Youden index) and patients were divided according to this value (Fig. 1). The optimum cut-point value for predicting mortality was 70 PACs on 24-h ECG monitoring (70 PACs/day), with sensitivity 61% and specificity of 65%, $P < 0.0001$, which was considered excessive atrial ectopic activity (EAEA). Baseline characteristics in patients with and without EAEA and in patients with and without NSVT were compared using the Chi-square test for categorical vari-

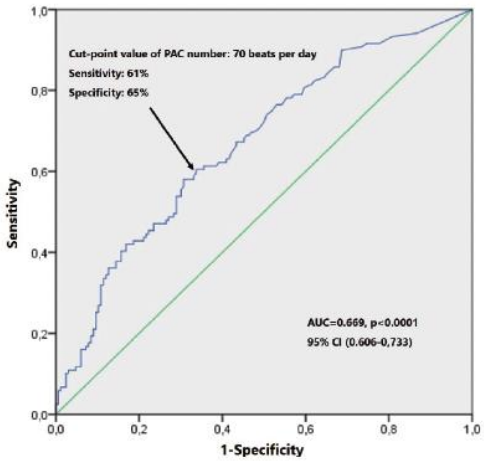

Figure 1. ROC curve survival analysis by PAC number. PAC: premature atrial contraction; ROC: receiver operator characteristic.

ables and the Mann-Whitney U test for continuous variables. Kaplan-Meier survival function was used to compare the event-free survival in the groups with and without EAEA and with and without NSVT. The Log- rank test (Mantel-Cox test) was used for comparison between groups.

Results

Baseline characteristics

The baseline characteristics of patients with and without EAEA are presented in Table 1. Patients with EAEA were generally older, with a higher incidence of hypertension, higher CHA_2DS_2VASc score and were less frequently on beta-blockers. On the Holter recording patients with EAEA had lower maximal and mean heart rate, lower number of PVCs/day. The PVCs were more frequently polymorphic and finally, had more frequently runs of PACs. The echocardiographic evaluation showed larger LAD and larger LVDD. Patients with NSVT were more frequently male, had more SHD; the morphology of the PVCs was more frequently polymorphic and had larger left atrium and left ventricle (Table 2).

Follow-up

The median follow-up time was 8.4 (5.1 - 10) years, corresponding to 2,158 person-years. It was significantly shorter in the EAEA group, respectively, 7.6 (3.9 - 9.6) versus 8.7 (7.6 - 10.3) years, $P < 0.0001$, and in patients with NSVT, 7.8 (3.8 - 9.5) versus 8.6 (5.5 - 10) years, $P = 0.026$.

During the follow-up period, there were 119 (42%) deaths, 10 (4%) due to HF and eight (3%) arrhythmic deaths, 19 (7%) strokes. Sixty-four patients (25%) developed AF. There were 48 (17%) cardiovascular (CV) hospitalizations, 14 (5%) due to HF and five (2%) due to ventricular arrhythmias. The numbers of events per 1,000 person-years according to the presence of EAEA or NSVT are displayed in Table 3.

End points

Number of PACs and primary end points

The number of PACs was associated with higher all-cause mortality, with an unadjusted estimated HR (95% CI) of 1.131 (1.080 - 1.084), $P < 0.0001$ (Table 4). After adjustment to age, CHA_2DS_2VASc score, presence of SHD, beta-blocker therapy, new-onset AF, LAD and LVFS, the number of PACs was still associated with an increase in all-cause mortality with an estimated HR (95% CI) of 1.077 (1.014 - 1.145), $P = 0.017$. The number of PACs was also associated with higher rates of stroke and new-onset AF unadjusted HR (95% CI) of 1.321 (1.163 - 1.501), $P < 0.0001$ and 1.193 (1.117 - 1.275), $P < 0.0001$ respectively. After multivariable adjustment for confounding variables the number of PACS was still associated with a higher risk of stroke and new-onset AF, with an adjusted HR (95% CI) of 1.250 (1.080 - 1.447), $P = 0.003$ for stroke and 1.090 (1.006 - 1.181), $P = 0.036$ for new-onset AF.

NSVT and primary end points

The presence of NSVT episodes was associated with an increase in the risk of all-cause mortality with unadjusted HR (95% CI) of 1.530 (1.001 - 2.337), $P = 0.049$ (Table 4). After adjustment to age, CHA_2DS_2VASc score, beta-blocker therapy, presence of SHD, new-onset AF, LAD and LVFS, the presence of episodes of NSVT was not associated with an increase in all-cause mortality.

Number of PACs and secondary end points

The number of PACs/day was associated with an increase in the risk of HF MACE with unadjusted HR (95% CI) of 1.287 (1.119 - 1.482), $P < 0.0001$ (Table 4), and after adjustment to age, presence of SHD, beta-blocker therapy, new-onset AF and LVFS, the rate remained higher, with an adjusted HR (95% CI) of 1.376 (1.128 - 1.679), $P = 0.002$. The number of PACs was not associated with the risk of arrhythmic MACE.

NSVT and secondary end points

The presence of NSVT was associated with the risk of HF and arrhythmic MACE with unadjusted HR (95% CI) of 4.255 (1.542 - 11.74), $P = 0.049$ and 4.424 (1.484 - 13.19), $P = 0.008$ (Table 4). After adjustment for confounding variables, NSVT was associated with the rate of arrhythmic MACE with an adjusted HR (95% CI) of 3.644 (1.147 - 11.57), $P = 0.028$ but not with HF MACE.

Table 1. Baseline Characteristics in the Two Groups With and Without EAEA

	Overall sample (n = 285)	EAEA (-) (n = 158)	EAEA (+) (n = 127)	P value[c]
Demographic data				
Age (years)	68 (60 - 76)	62 (53 - 73)	74 (66 - 79)	< 0.0001
Male gender, n (%)	171 (60)	92 (58)	79 (62)	0.544
Risk factors				
Diabetes, n (%)	66 (26)	35 (26)	31 (27)	0.887
Hypertension, n (%)	216 (86)	108 (80)	108 (93)	0.003
Dyslipidemia, n (%)	143 (57)	78 (58)	65 (56)	0.799
High CHA_2DS_2VASc[a]	191(76)	87 (64)	104 (90)	< 0.0001
Previous stroke, n (%)	39 (14)	19 (12)	20 (15)	0.390
Etiology				
Structural heart disease, n (%)	118 (41)	67 (42)	51 (40)	0.718
Ischemic heart disease n (%)	86 (30)	49 (73)	37 (73)	0.999
Medications				
Beta-blockers, n (%)	106 (37)	67 (42)	39 (31)	0.049
Antiarrhythmics[b], n (%)	16 (6)	8 (5)	8 (6)	0.797
24 - h Holter recording				
Maximal heart rate (bpm)	113 (100 - 126)	115 (102 - 126)	109 (98 - 128)	0.048
Minimal heart rate (bpm)	49 (43 - 54)	49 (44 - 55)	48 (42 - 53)	0.153
Mean heart rate (bpm)	71 (64 - 79)	73 (65 - 81)	69 (63 - 78)	0.035
Number of PVCs/day	2,776 (1,594 - 7,025)	3,475 (1,623 - 8,402)	2,461 (1,526 - 4,790)	0.038
Polymorphic morphology, n (%)	192 (69%)	94 (61)	98 (81)	< 0.0001
NSVT, n (%)	54 (19)	25 (16)	29 (23)	0.171
Number of PACs/day	48 (7 - 445)	11 (1 - 29)	636 (167 - 2,900)	< 0.0001
Supraventricular runs, n (%)	92 (32)	22 (14)	70 (55)	< 0.0001
AV node conduction disease, n (%)	49 (17)	24 (15)	25 (20)	0.346
Echocardiogram				
LAD (mm)	37 (35 - 42)	40 (35 - 45)	38 (35 - 43)	0.004
LVDD (mm)	53 (49 - 58)	51 (48 - 56)	55 (50 - 59)	0.029
LVSD (mm)	34 (30 - 40)	33 (30 - 40)	35 (30 - 40)	0.325
LVFS (%)	36 (30 - 40)	36 (28 - 40)	36 (30 - 40)	0.975
Follow-up in years	8.4 (5.1 - 10)	8.7 (7.6 - 10.3)	7.6 (3.9 - 9.6)	< 0.0001

Values are presented as median (interquartile range) or n (%). [a]The CHA_2DS_2VASc score was calculated according to the presence of congestive heart failure/left ventricular dysfunction (1 point); hypertension (1 point); age ≥ 75 years (2 points); diabetes mellitus (1 point); history of stroke, transitory ischemic attack or thromboembolism (2 points); vascular disease (history of MI, vascular disease or aortic atherosclerosis) (1 point); age 65 - 74 years (1 point) and female gender (1 point). [b]Class I or class III antiarrhythmics. [c]P values were calculated using Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. EAEA: excessive atrial ectopic activity; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contraction; PAC: premature atrial contraction; AV: atrioventricular; LAD: left atrium diameter; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVFS: left ventricular fractional shortening.

Predictors of risk

Presence of EAEA

The numbers of events per 1,000 person-years in the groups with and without EAEA are shown in Table 3. Patients with EAEA had a worse prognosis, higher all-cause mortality (83.2 versus 36.8 per 1,000 person-years), higher rate of stroke (18.8 versus 2.3 per 1,000 person-years), higher rate of new-onset AF (49.2 versus 16.9 per 1,000 person-years) and, higher rate of the HF MACE (16.4 versus 0.8 per 1,000 person-years). The EAEA was not associated with the rate of arrhythmic MACE.

They had a shorter overall survival (Fig. 2a), survival free from new-onset AF (Fig. 2c), survival free from stroke (Fig.

Table 2. Baseline Characteristics in the Patients With and Without NSVT

	Overall sample (n = 285)	NSVT (+) (n = 54)	NSVT (-) (n = 231)	P value[c]
Demographic				
Age (years)	68 (60 - 76)	68 (61 - 76)	68 (60 - 76)	0.986
Male gender, n (%)	171 (60)	43 (80)	128 (55)	0.001
Risk factors				
Diabetes, n (%)	66 (26)	11 (23)	55 (27)	0.715
Hypertension, n (%)	216 (86)	41 (87)	175 (86)	0.9999
Dyslipidemia, n (%)	143 (57)	27 (57)	116 (57)	0.9999
High CHA_2DS_2VASc[a]	191(76)	40 (87)	151 (74)	0.082
Previous stroke, n (%)	39 (14)	7 (13)	32 (14)	0.999
Etiology				
SHD, n (%)	118 (41)	19 (35)	148 (64%)	< 0.0001
IHD n (%)	86 (30)	23 (34)	63 (76)	0.266
Medications				
Beta-blockers, n (%)	106 (37)	21 (39)	85 (37)	0.876
Antiarrhythmics[b], n (%)	16 (6)	1 (2)	15 (7)	0.322
24 - h Holter recording				
Maximal heart rate (bpm)	113 (100 - 126)	113 (102 - 126)	113 (100 - 125)	0.573
Minimal heart rate (bpm)	49 (43 - 54)	51 (44 - 56)	48 (43 - 53)	0.097
Mean heart rate (bpm)	71 (64 - 79)	76 (65 - 82)	70 (64 - 78)	0.088
Number of PVC/day	2,776 (1,594 - 7,025)	3,573 (1,758 - 11,600)	2,589 (1,564 - 6,172)	0.068
Polymorphic, n (%)	192 (69%)	46 (89)	146 (66)	0.001
PAC > 70/day n (%)	127 (44)	29 (54)	98 (43)	0.171
Number of PACs/day	48 (7 - 445)	86 (6 - 1,092)	46 (7 - 382)	0.587
Supraventricular runs, n (%)	92 (32)	16 (30)	76 (33)	0.447
AV node disease, n (%)	49 (17)	12 (22)	37 (16)	0.316
Echocardiogram				
LAD (mm)	37 (35 - 42)	41 (36 - 45)	38 (35 - 44)	0.007
LVDD (mm)	53 (49 - 58)	55 (52 - 63)	51 (48 - 57)	< 0.0001
LVSD (mm)	34 (30 - 40)	35 (30 - 48)	33 (30 - 39	0.004
LVFS (%)	36 (30 - 40)	34 (24 - 40)	36 (30 - 40)	0.081
Follow-up in years	8.4 (5.1 - 10)	7.8 (3.8 - 9.5)	8.6 (5.5 - 10)	0.026

Values are presented as median (interquartile range) or n (%). [a]The CHA_2DS_2VASc score was calculated according to the presence of congestive heart failure/left ventricular dysfunction (1 point); hypertension (1 point); age ≥ 75 years (2 points); diabetes mellitus (1 point); history of stroke, transitory ischemic attack or thromboembolism(2 points); vascular disease (history of MI, vascular disease or aortic atherosclerosis) (1 point); age 65 - 74 years (1 point) and female gender (1 point). [b]Class I or class III antiarrhythmics. [c]P values were calculated using Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. EAEA: excessive atrial ectopic activity (> 70 PACs/day); SHD: structural heart disease; IHD: ischemic heart disease; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contraction; PAC: premature atrial contraction; AV: atrioventricular; LAD: left atrium diameter; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVFS: left ventricular fractional shortening.

2d), and survival free from HF death or HF hospitalizations (Fig. 3a).

Presence of NSVT

The numbers of events per 1,000 person-years in the groups with and without NSVT are shown in Table 3. Patients with NSVT had higher all-cause mortality (78 versus 50.5 per 1,000 person-years), higher rate of the HF MACE (19.5 versus 4.4 per 1,000 person-years) and higher rate of the arrhythmic MACE of arrhythmic death or VA hospitalizations (16.8 versus 5.5 per 1,000 person-years). The presence of NSVT was not significantly associated with a higher rate of stroke or new-onset AF.

Table 3. Events per 1,000 Person-Years According to the Presence of EAEA or NSVT

	Overall sample	EAEA (-)	EAEA (+)	P value[a]
	2,158 person-years	1,305 person-years	853 person-years	
All-cause death	55	36.8	83.2	< 0.0001
Stroke	8.8	2.3	18.8	< 0.0001
New-onset AF	29.7	16.9	49.2	< 0.0001
HF death or HF hospitalizations	7	0.8	16.4	< 0.0001
Arrhythmic death or VA hospitalizations	6	5.4	7	0.661

	Overall sample	NSVT (-)	NSVT (+)	P value[a]
	2,158 person-years	1,800 person-years	358 person-years	
All-cause death	55	50.5	78	0.047
Stroke	8.8	7.2	16.6	0.670
New-onset AF	29.7	27.2	42	0.052
HF death or HF hospitalizations	7	4.4	19.5	0.002
Arrhythmic death or VA hospitalizations	6	5.5	16.8	0.003

Values are presented in number of events per 1,000 person-years. AF; atrial fibrillation; HF: heart failure; VA: ventricular arrhythmia; EAEA: excessive atrial ectopic activity; EAEA excessive atrial ectopic activity; NSVT: non-sustained VT episodes; NSVT: non-sustained VT episodes. [a]P values were calculated using the Log-rank test.

Patients with NSVT had a shorter overall survival (Fig. 2b), shorter survival free from HF death or HF hospitalizations (Fig. 3b) and shorter survival free from arrhythmic death or VA hospitalizations (Fig. 3d).

Discussion

Our study population was old and almost half of them had structural heart disease which may explain the high mortality and cardiovascular event rates. One of the inclusion criteria to enter the study was having a minimum of 1% of ventricular beats that were ectopic. So according to previous studies, this is a population with a higher mortality and higher risk of cardiovascular adverse events [5, 6, 15]. We observed that the presence of NSVT was independently associated with increased all-cause mortality, and with arrhythmic death or VA hospitalizations. Patients with NSVT were older and sicker, yet after

Table 4. Cox Regression Models Showing the Hazard Ratio of Number of PACs, and Presence of NSVT in Relation to the Primary and Secondary End Points

End points	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value[f]
Log_2 number of PACs/day				
All - cause death	1.131 (1.080 - 1.084)	< 0.0001	1.077 (1.014 - 1.145)[a]	0.017
Stroke	1.321 (1.163 - 1.501)	< 0.0001	1.250 (1.080 - 1.447)[b]	0.003
New-onset AF	1.193 (1.117 - 1.275)	< 0.0001	1.090 (1.006 - 1.181)[c]	0.036
HF death or HF hospitalizations	1.287 (1.119 - 1.482)	< 0.0001	1.376 (1.128 - 1.679)[d]	0.002
Arrhythmic death or VA hospitalizations	1.080 (0.941 - 1.240)	0.273	-	
NSVT				
All - cause death	1.530 (1.001 - 2.337)	0.049	1.584 (0.990 - 2.534)[a]	0.055
HF death or HF hospitalizations	4.255 (1.542 - 11.74)	0.005	1.519 (0.497 - 4.643)[c]	0.464
Arrhythmic death or VA hospitalizations	4.424 (1.484 - 13.19)	0.008	3.644 (1.147 - 11.57)[e]	0.028

[a]HR adjusted to age, CHA_2DS_2VASc score, presence of SHD, beta-blocker therapy,new-onset AF, LAD and LVFS. [b]HR adjusted to age, CHA_2DS_2VASc score, previous stroke, LAD and new-onset AF. [c]HR adjusted to age, hypertension, diabetes, beta-blocker therapy, presence of SHD and LAD. [d]HR adjusted to the presence of age, SHD, beta-blocker therapy, new-onset AF and LVFS. [e]HR adjusted to the presence of age, beta-blocker therapy, structural heart disease and LVFS. [f]P values were calculated using the Cox proportional-hazards model. PAC: premature atrial contraction; AF: atrial fibrillation; HF: heart failure; VA: ventricular arrhythmia; NSVT: non-sustained ventricular tachycardia; LAD: left atrium diameter; LVFS: left ventricular fractional shortening; SHD: structural heart disease.

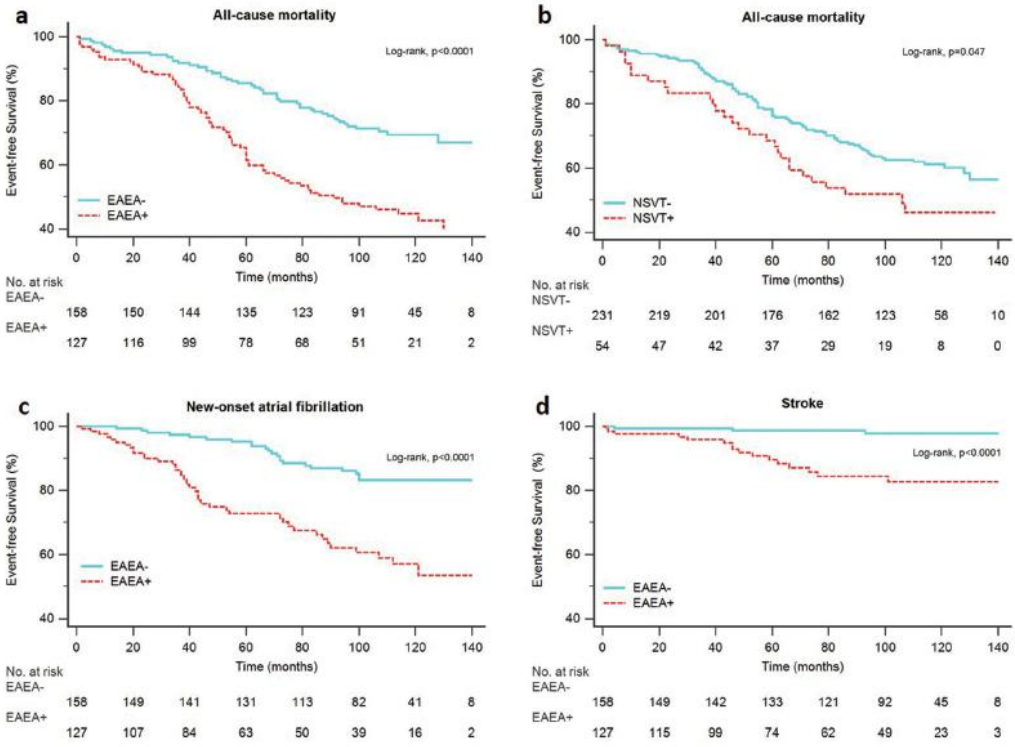

Figure 2. Kaplan-Meier estimates for the primary end points. Overall survival in patients with and without EAEA (a), overall survival in patients with and without NSVT (b), AF free survival in patients with and EAEA (c), stroke free survival in patients with and without EAEA (d). EAEA: excessive atrial ectopic activity; NSVT: non-sustained ventricular tachycardia.

adjustment to other covariables the presence of NSVT was still associated with arrhythmic death or VA hospitalizations.

In a recent work, Lin et al [8] followed 3,767 patients with apparently normal hearts for 10 ± 1 year and found that patients with NSVT had an increased risk of mortality, cardiovascular hospitalization, ischemic stroke, and new-onset HF.

In our group of patients, we also found a higher rate of HF death or HF hospitalizations in patients with NSVT. However, this effect is lost when adjusted to other risk variables.

Dukes et al [5] found an increase in mortality in patients with frequent PVCs that according to the authors appeared to be partly explained by incident HF. Left ventricular dysfunction induced by frequent PVCs has been described previously [16] although the underlying mechanism is still a matter of debate. Studies with catheter ablation have demonstrated left ventricular dysfunction in patients with a high PVC burden which is reversible after successful catheter ablation [17].

However, in most of these studies left ventricular dysfunction has been associated with a greater PVC burden, higher than 10% and usually higher than 20% of total beats [16, 17].

Therefore, in the presence of a lower PVC burden as is the case of our study, with PVCs representing a median of 2.7% of all heart beats (IQR: 1.65-6.8 %) or that of Dukes et al with PVCs representing a median of 0.011% of all heart beats (IQR: 0.002-0.123%) [5], or in the study by Lin et al [8] with a mean PVC burden of 176 ± 423 beats per day, the possibility that the increase in HF rate might be due to PVCs is questionable. Also intriguing is the association between frequent PVCs and stroke described by Lin et al [7, 8] and previously reported by Agarwal et al [14]. In the latter, the authors found a stronger association between frequent PVCs and embolic stroke than thrombotic stroke. Therefore, the authors hypothesized that the reason for that might have been an increased risk of AF in those patients, and even suggested that patients with high PVC burden could be monitored for AF.

In our study the presence of NSVT was not associated with stroke or new-onset AF. On the other hand, the number of PACs was associated with an increased risk of stroke and new-onset AF, both before and after multivariable adjustment.

In all those previous studies that reported increased risk of HF, stroke and AF due to high PVC burden, the authors did not address the presence of frequent PACs in association with frequent or complex PVCs. To the best of our knowledge we present for the first time a study that demonstrates the role of PAC burden as a marker of prognosis in patients with frequent PVCs and is capable of explaining the high rate of HF events,

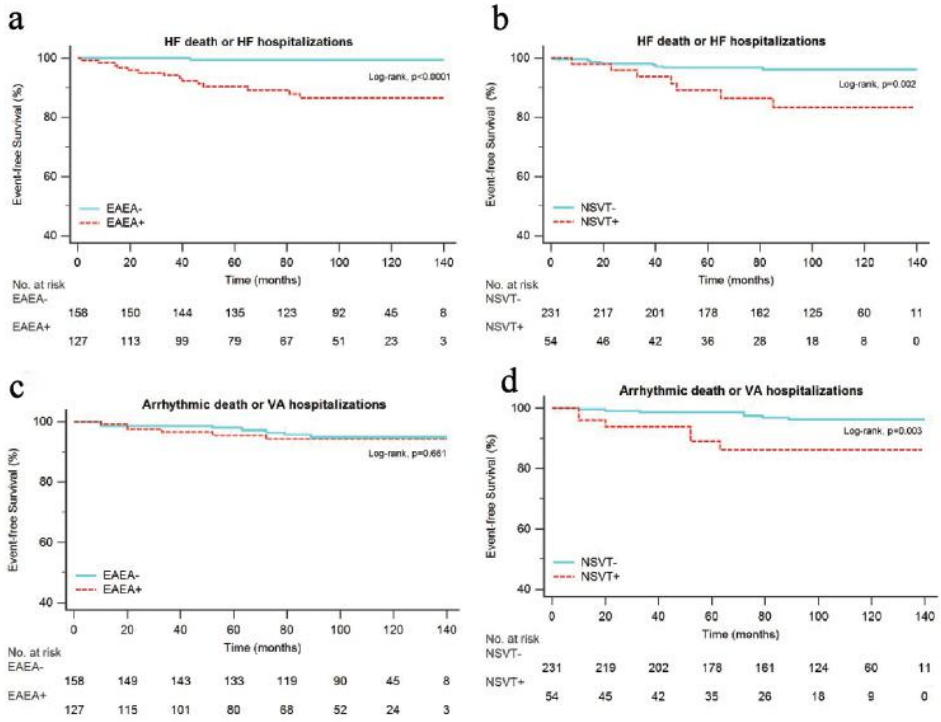

Figure 3. Kaplan-Meier estimates for the secondary end points. Survival free from HF death or HF hospitalizations in patients with and without EAEA (a), survival free from HF death or HF hospitalizations in patients with and without NSVT (b), survival free from arrhythmic death or VA hospitalizations in patients with and without EAEA (c), survival free from arrhythmic death or VA hospitalizations in patients with and without NSVT (d). EAEA: excessive atrial ectopic activity; HF: heart failure; NSVT: non-sustained ventricular tachycardia; VA: ventricular arrhythmia.

stroke or AF occurrence in patients with PVCs.

Patients with EAEA were older, had more hypertension and larger left atrium dimension. Old age is a recognized risk factor for development of AF and for PACs [9]. Several studies have shown that PACs and subclinical atrial arrhythmias are independent predictors of AF and stroke [10, 11, 13]. Some authors proposed that frequent PACs could be a marker of a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, dyslipidemia and that could explain the higher incidence of stroke, independently of the development of AF [11, 12]. In our study population, patients with frequent PACs were older, had more frequently hypertension, and had a higher CHA2DS2VASc score. However, the number of PACs was independently associated with the risk of stroke. One explanation for this fact might be that EAEA may lead to the dilatation of left atrium and stasis in the left atrial appendage, fibrosis and endothelial dysfunction resulting in a hypercoagulable state similar to that seen in AF [18]. Likewise, subclinical atrial arrhythmias like device-detected atrial high rate episodes have been related to an increased risk of AF and stroke [19, 20].

The presence of frequent PACs on the other hand is not associated with arrhythmic events as opposed to the presence of NSVT that was associated with an adjusted 3.6-fold higher rate of arrhythmic death or VA hospitalizations.

These results, if replicated in other future studies with a higher number of patients may have potential clinical implications and shed some light into the mechanisms of high rates of HF, stroke and AF in patients with frequent PVCs.

Limitations

There were some limitations to our study. First of all, it was an observational and retrospective study and the high cardiovascular adverse event rate may result from a type of reference bias. The cut-point value of PVCs equal or higher than 1% of total beats may have selected a very high-risk population, although by using multivariable regression, we aimed at overcoming this limitation. We cannot exclude the presence of other risk factors that were not assessed like smoking habits, sleep apnea or chronic obstructive pulmonary disease. Further prospective studies with a higher number of patients are needed.

Conclusions

In conclusion, in this group of patients with frequent PVCs, the presence of EAEA was independently associated with increased mortality, higher rate of incident AF, stroke, HF death or HF hospitalization but not with arrhythmic death or VA hospitalizations. Patients with NSVT had also a worse prognosis, and were more likely to have arrhythmic events. However, the presence of NSVT was not independently associated with increased all-cause mortality, a higher risk of HF events, stroke or new-onset AF.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Informed Consent

The informed consent was waived via the Ethical Committee.

Conflict of Interest

None to declare.

Author Contributions

Leonor Parreira contributed to conception and design of the study, analysis and interpretation of data drafting and revising the article. Rita Marinheiro was involved in acquisition of data and revising the article. Dinis Mesquita was involved in acquisition of data and revising the article. Jose Farinha was involved in acquisition of data. Marta Fonseca was involved in acquisition of data. Pedro Amador was involved in acquisition of data. Duarte Chambel was involved in acquisition of data. Artur Lopes was involved in acquisition of data. Rui Caria, MD was involved in revising the article.

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ORIGINAL ARTICLE

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A simplified approach to radiofrequency catheter ablation of idiopathic ventricular outflow tract premature ventricular contractions

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Abstract

Introduction: Frequently, low voltage areas (LVAs) and diastolic potentials (DPs) are present at ablation sites in sinus rhythm in patients with idiopathic premature ventricular contractions (PVCs).

Objective: Validate these findings as substrates for PVCs and evaluate the feasibility of a simplified substrate approach based on LVAs and DPs for ablation of idiopathic outflow tract PVCs, in patients with a low PVC burden during the procedure.

Methods: Prospective single-arm clinical trial at two centers with comparison with a historical group, matched to age and gender. The study group consisted of consecutive patients referred for ablation of frequent idiopathic PVCs with inferior axis, that presented with less than two PVCs/min in first 5 min of the procedure. The ablation was based on fast mapping of the right ventricular outflow tract in sinus rhythm looking for LVAs and DPs, defined as isolated small amplitude potentials occurring after the T wave of the surface echocardiogram. The area with LVAs and DPs was tagged, and a simplified activation mapping of the PVCs was done in that area. The procedure time, success rate, and recurrence rate were compared with the historical group in whom ablation was performed based on activation and pace mapping only. A validation group without PVCs was also studied to assess the prevalence of LVAs and DPs in the general population.

Results: The study ($n = 38$), historical ($n = 38$), and validation ($n = 38$) groups did not differ in relation to age or gender. Prevalence of LVAs and DPs was significantly higher in the study group in comparison with the validation group, respectively, 71% versus 11%, $p < 0.0001$ and 87% versus 8%, $p < 0.0001$. Procedure time was significantly lower in the study group when comparing to the historical group, 130 (100–164) versus 183 (160–203) min, $p < 0.0001$ and the success rate was significantly higher, 90% versus 64%, $p = 0.013$. The recurrence rate in patients with a successful ablation was not significantly different between both groups, Log-rank = 0.125.

Conclusion: The prevalence of LVAs and DPs was significantly higher in the study group than in the validation group. The proposed approach proved to be feasible, faster, and more efficient than the historical approach.

KEYWORDS
catheter ablation, diastolic potentials, idiopathic outflow tract arrhythmias, low voltage areas, substrate ablation

1 | INTRODUCTION

Premature ventricular contractions (PVCs) are a common finding in the normal population. The most common sites of PVCs in patients without structural heart disease are the right ventricular outflow tract (RVOT) and the left ventricular outflow tract (LVOT).[1]

In the latest published guidelines, catheter ablation for frequent symptomatic PVCs refractory to medical therapy is a class I indication.[2] Ablation based on activation mapping and pace-mapping is considered the standard technique for eliminating idiopathic PVCs.[3] Radiofrequency (RF) delivery should be performed at the site of the earliest ventricular activation. The ideal pace-match at ablation site has an identical QRS pattern in all 12 surface echocardiogram (ECG) leads (12/12 match).

The main reasons for unsuccessful ablation are the failure to reach the site of origin, for instance, in case of deep intramyocardial focus, and the failure to find the site of origin, due to absence of PVCS during the procedure.

A low PVC burden occurs in up to 30% of the procedures[4] and may result from spontaneous variations, autonomic influence, anesthesia, or sedation. In the presence of low PVC burden in the day of the procedure, the success may be reduced from 85% to 56%.[4] In those cases, an alternative approach could be the pace-mapping technique. However, the latter is hampered by the impossibility of capturing the ventricles and is less precise than activation mapping. The spatial resolution is around $1.8 \pm 0.6\,cm^2$ when compared with the spatial resolution of activation mapping ($1.2 \pm 0.7\,cm^2$). In the study by Bogun et al.,[5] the sites with a 12/12 pace-matching were located at a median distance of 7.3 ± 5.0 mm away from the successful ablation site.

It has been accepted for many years that in the case of idiopathic PVCs from the ventricular outflow tract, the electroanatomical mapping shows no significant abnormalities.[6] However, previous studies have shown the presence of low voltage areas (LVAs) in the RVOT of patients undergoing catheter ablation of frequent idiopathic PVCs.[7–11] As previously, reported by our group, LVAs were predicted by the presence of ST-elevation in V1 or V2 at the level of the second intercostal space (2nd ICS).[9,10] Furthermore, the presence of discrete diastolic potentials (DPs) on the bipolar intracardiac electrograms at the successful ablation site have also been described previously.[12–14] These are low amplitude potentials, occurring after the T wave of the ECG in sinus rhythm, that become presystolic, preceding the local bipolar ventricular electrogram during the PVCs. These potentials were more frequently recorded at areas of low voltage and fractionated electrograms. Their meaning is unknown, but we speculate that they may represent a form of triggered activity that results in a potential with a very low amplitude, only recorded when the catheter is in close proximity to their origin.[13]

The aim of this study was to validate LVAs and DPs as markers of a substrate for PVCs and evaluate the feasibility and efficacy of a new strategy based on this substrate mapping for ablation of idiopathic PVCs from the outflow tracts that present with a low PVC burden during ablation.

2 | MATERIAL AND METHODS

2.1 | Patient population

Since July 2019, we prospectively studied consecutive patients referred for catheter ablation of frequent (more than 10.000 PVCs/24 h during Holter monitoring), idiopathic PVCs with an inferior axis, at two centers that presented with intraprocedural low PVC burden defined as less than two PVCs/min in the first 5 min of the ablation procedure (study group). Patients with known structural heart disease, history of sustained ventricular arrhythmias, inability to perform cardiac magnetic resonance (CMR), previous ablation, and standard 12-Lead ECG with evidence of conduction or electrical disease or abnormal QRS morphology were excluded.

A historical group of consecutive patients that underwent PVC ablation by the same operator using the standard technique between 2016 and 2018 was also studied They were selected based on the review of patient's files and either had the ablation canceled due to low PVC burden, or had an ablation report mentioning a low PVC burden during the procedure. The ablation procedure was reviewed to assess the PVC burden in the first 5 min of the procedure (historical group). A validation group of consecutive patients that underwent catheter ablation of supraventricular tachycardias in 2019 and agreed to have an electroanatomical map of the RVOT performed in sinus rhythm were also studied. Patients were excluded if there was any evidence of arrhythmias from the RVOT either in the patient's files or during ablation of the supraventricular arrhythmia (validation group).

All patients underwent transthoracic echocardiography with evaluation of the left ventricular ejection fraction and left atrium

diameter, and standard 12-lead ECG. A CMR with late Gadolinium enhancement was performed to rule out structural heart disease in all patients in the study group by protocol, and at the discretion of the attending physician in the historical group. Arrhythmogenic right ventricular cardiomyopathy (ARVC) was ruled out according to the Task Force Criteria.[15] A 24-h Holter recording was performed before ablation in patients with PVCs and the number of PVCs per 24 h and the presence of episodes of nonsustained ventricular tachycardia (NSVT), defined as >3 PVCs s in a run were assessed.

2.2 | Study design

This was a prospective single-arm clinical trial with comparison with a matched historical group carried out in two centers. The feasibility and efficacy of the proposed substrate-based ablation was assessed by comparing the procedure, fluoroscopy and RF time, and the success and recurrence rate in the study and historical groups.

A validation group without PVCs was studied with voltage map in sinus rhythm to assess the prevalence of LVAs and DPs in the RVOT in the general population and validate these findings as markers of a PVC substrate.

2.3 | Electroanatomic mapping and ablation

Patients were studied in a fasting, non sedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. During endocardial mapping of the LVOT, heparin was administrated to achieve an ACT of 250–300 s. All procedures at Luz Hospital Lisbon were performed with remote magnetic navigation (RMN) using the Niobe II Magnetic Navigation System (Stereotaxis Inc.) with the CARTO 3 RMT (Biosense-Webster Inc.) system. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster Inc.) was used with a 3.5-mm distal tip electrode and a 2–5–2 interelectrode distance as previously described.[16] At Setubal Hospital Center, all procedures were performed manually using the EnSite Precision (Abbott) system, with an irrigated tip TactiCath catheter (Abbott) with a 3.5-mm distal tip electrode and a 2–2–2 interelectrode distance. The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT with the RMN system or manually under fluoroscopic guidance, and then placed at multiple sites on the endocardial surface of the RVOT. Mapping of the LVOT endocardium and the aortic coronary cusps was performed using a transaortic approach in all patients. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed. Two maps were created, a voltage bipolar map of the RVOT in sinus rhythm and an activation map during the PVC.

2.3.1 | Sinus rhythm map

The RVOT voltage map was performed in sinus rhythm without isoprenaline, both in patients from the study and the validation groups. Only points with optimal contact were considered for the voltage mapping. For procedures done manually, 10 g was the minimal contact force accepted, and for RMN procedures the catheter–tissue contact qualitative indicator, displaying a good contact.[17] The electrograms were analyzed in regard of their amplitude and the information was used to generate a three-dimensional electroanatomical voltage map of the RVOT, with the electrophysiologic information, color-coded, and superimposed on the geometry. The fill threshold used for mapping was 5–7. The color display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude > 1.5 mV), to red, representing electroanatomical scar tissue (amplitude < 0.5 mV). LVAs were defined as areas with bipolar electrograms with an amplitude <1.5 mV. The level of RVOT/pulmonary valve junction was thoroughly determined based on electroanatomical voltage mapping by passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT until bipolar electrograms were absent in the distal pair of electrodes but present in the proximal pair. Voltage above the pulmonary valve is usually less than 0.5 mV. The area immediately below the level of the pulmonary valve displays intermediate colors, corresponding to a bipolar voltage between 0.5 and 1.5 mV, defined as the transitional-voltage zone.[7] Presence of LVAs outside the transitional-voltage zone were assessed. DPs defined as persistent low amplitude discrete potentials occurring at late diastole after the end of the T wave of the surface ECG in sinus rhythm that became presystolic during the PVCs[13] (Figure 1) were searched for and tagged in the map. The number of points acquired in sinus rhythms, the mapping time, the presence of LVAs outside the transitional-voltage zone, the presence of DPs, and the area of the RVOT that displayed DPs were recorded.

2.3.2 | Activation map of PVC and ablation

In the study group, the activation map was directly aimed at the area with LVAs and DPs. The map was obtained by mapping points during the PVC while using a surface ECG lead as reference. In the absence of LVAs and DPs in the RVOT, the aortic cusps and the LVOT, the coronary sinus, the great cardiac vein, and anterior interventricular vein were mapped (Figure 2). The number of points in PVC and the mapping time were recorded. At the earliest activation site, pace mapping was performed and the pace mapping match was assessed.

In the historical group, the activation map was performed conventionally by mapping several points during the PVC while using a surface ECG lead as reference. The ablation site was selected both in the study and historical group, based on the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous

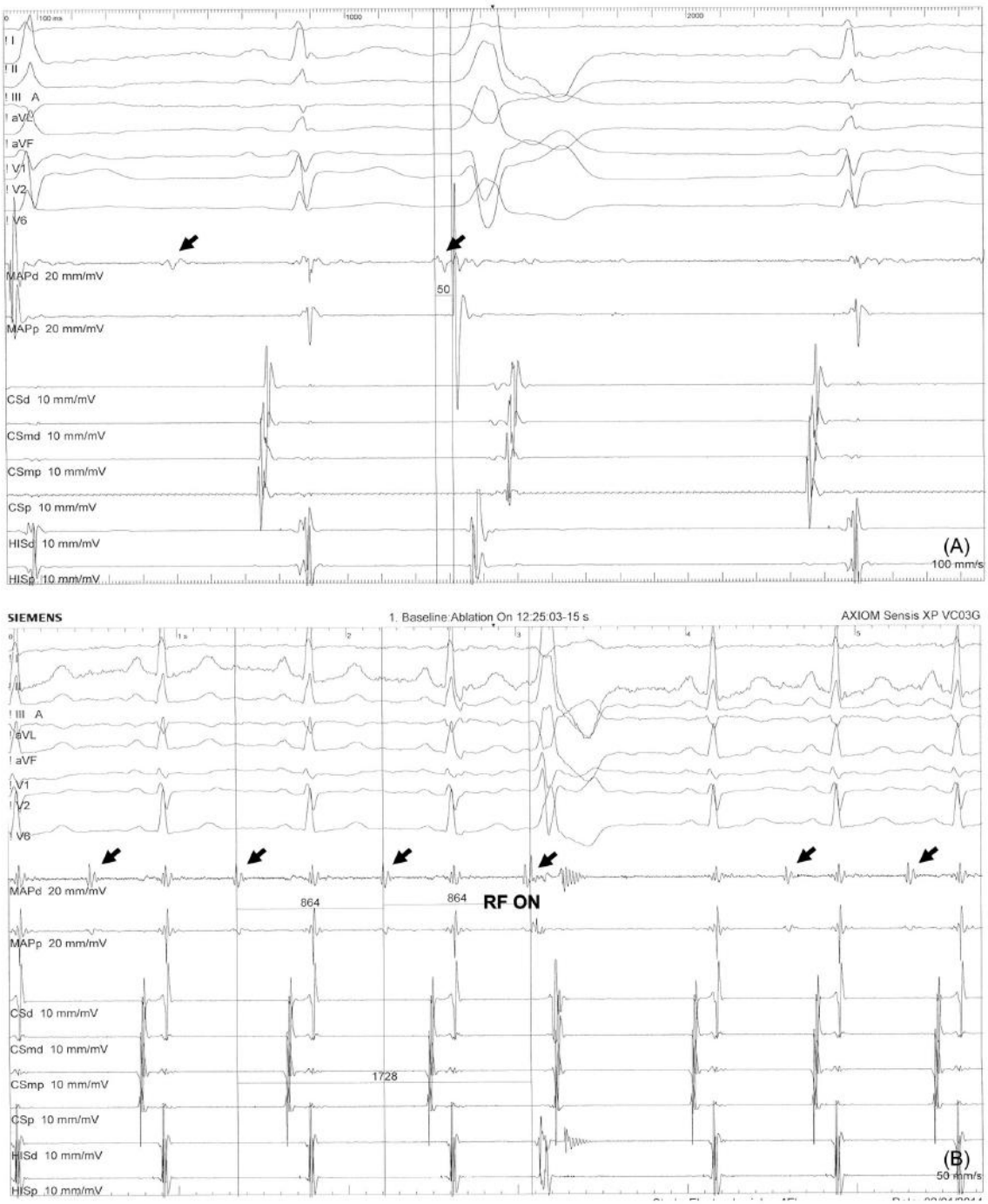

FIGURE 1 Diastolic potentials. Intracardiac electrograms of a patient with PVCs from the RVOT (black arrows) after the T wave in sinus rhythm and presystolic during the PVC (A). Another patient to show that the DPs persist during and after RF application (B). The gain in the ablation catheter is 20mm/1mV and sweep speed is 100 mm/s in panel A and 50 mm/s in panel B. The distal dipole of the ablation catheter (MAPd) exhibits DPs (arrow). DP, diastolic potential; PVC, premature ventricular contraction; RF, radiofrequency; RVOT, right ventricular outflow tract.

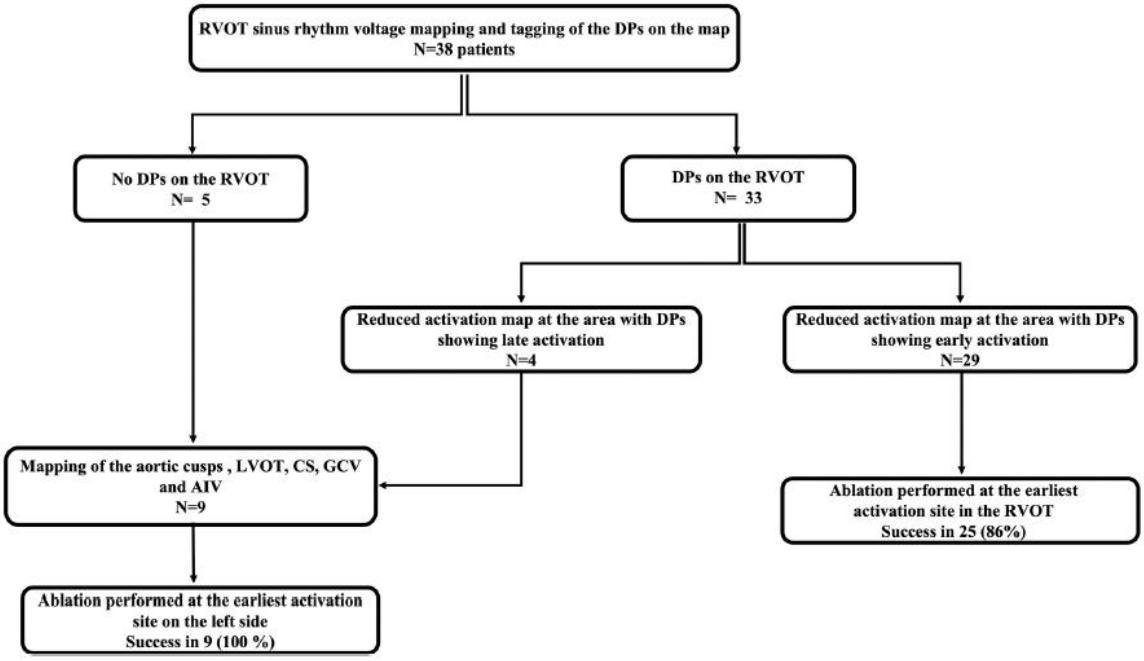

FIGURE 2 Flow diagram of the substrate approach for mapping and ablation of idiopathic outflow tract PVCs. AIV, anterior interventricular vein; CS, coronary sinus; DP, diastolic potential; GCV, great cardiac vein; LVOT, left ventricular outflow tract; PVC, premature ventricular contraction; RF, radiofrequency; RVOT, right ventricular outflow tract.

PVC. Energy was delivered between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 s, to a maximum temperature of 43°C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. The site of ablation and its relation to the LVAs and the DPs was recorded in the study group. Duration of the procedure defined as the time interval between the beginning of the procedure and the removal of the sheaths, and the success of the procedure, defined as abolition of PVCs until 30 min after ablation was registered. Fluoroscopy and duration of RF application were recorded. Major complications are defined as those that result in prolongation of hospital stay or another hospitalization, those that require additional intervention for treatment, and/or those that result in significant injury or death[18] were assessed. All the intracardiac electrograms were reviewed by two senior electrophysiologists.

2.4 | Follow-up

Follow-up was performed on outpatient clinical visits at 1 month and regularly every 6 months thereafter. Patients underwent a 24-h Holter recording at 1 month, 1 year after the procedure, and once a year thereafter. For patients that were followed at another institution, data were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone. Recurrence was defined as reappearance of symptoms or a 24-h Holter with a PVC number higher than 1000 PVCs per 24 h.

2.5 | Statistical analysis

All analyses were performed using SPSS statistical software, version 26.0 (SPSS Inc.).

Assuming a current success rate in patients with a low PVC burden of 56%,[4] and a success rate of 85% with the new approach, for a desired power of 0.8, at a two-sided α level of 0.05, a sample size of 38 patients for the study group and 38 patients for the historical group was estimated. Assuming a prevalence of 60% of DPs in patients with PVCs[13] and an expected prevalence in the normal validation group under 30%, the calculated sample size for the validation group was 38 patients.

Data are presented as median and lower and upper quartile (Q1–Q3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann–Whitney test for two independent samples or Kruskal–Wallis test for multiple independent samples. Categorical variables were compared with the use of two-side

Fisher's exact-test or the χ^2 test as appropriate for independent samples. The Kaplan–Meier survival function was used to compare the recurrence-free survival in the study and historical groups and the Log-rank test for comparison between groups. For all tests, a p-value <0.05 was considered as statistically significant.

2.6 | Ethics

All patients signed an informed consent form, and the study was approved by the Ethical Committee of Setubal Hospital Center, Luz Hospital Lisbon, and Nova Medical School. The study is in compliance with the Helsinki Declaration.

3 | RESULTS

3.1 | Patient population

Since July 2019 and April 2022, 38 patients were enrolled in the study group. Between 2016 and 2018, 38 patients were included in the historical group. Since July 2019 and April 2022, 38 patients were enrolled in the validation group, of whom 30 underwent ablation of atrioventricular nodal reentrant tachycardia (AVNRT), four of typical atrial flutter, two of accessory pathways and two of right atrial tachycardia. The three groups did not differ in relation to age or gender (Table 1). Patients in the study and historical group were more frequently on betablocker therapy than in the validation group, 68% and 61% versus 24%, $p < 0.0001$.

Patients with PVCs were all symptomatic. Seventy complained of palpitations, six patients had typical vagal syncope, and no patient had a family history of sudden death. Physical examination, and transthoracic echocardiography, including two-dimensional, M-mode, were normal and demonstrated normal right ventricle size and function. None of the CMRs performed showed evidence of RVOT abnormalities.

The 12-lead ECG displayed T wave inversion beyond V1 in four patients, but none had diagnostic criteria for ARVC,[15] and 12 patients had ST-segment elevation in V1 or V2, but none had diagnostic criteria for Brugada Syndrome (Table 1). None of the patients in the validation had ST-segment elevation or T wave inversion beyond V1 (Table 1).

The 24-h Holter recording displayed a high PVC burden with a median of 18 000 (13 000–26 000)/24 h not significantly different in the study and historical group. Twenty-two patients (29%) had episodes of NSVT, also not significantly different between the two groups.

3.2 | Electroanatomic mapping and ablation

3.2.1 | Sinus rhythm map

Seventy-six patients, 38 in the study group and 38 in the validation group underwent successful mapping of the RVOT in sinus rhythm (Table 2). The mapping was performed with RMN in 51 patients (67%). In the validation group, the percentage of cases performed with RMN was significantly higher than in the study group, respectively, 92% versus 42%, $p < 0.0001$. The fluoroscopy time for mapping of the RVOT in the validation group was 5 s (0–10). The median number of points was not significantly different between the study and the validation groups, 395 (330–435) and 352 (327–476) $p = 0.526$, taking a median of 20 (13–29) min to acquire, not significantly different in the two groups. The presence of LVAs was found in four patients (11%) from the validation group (Figure 3) and in 27 patients (71%) in the study group, $p < 0.0001$ (Figure 4). The prevalence was significantly higher in patients with PVCs from the RVOT than from the LVOT (Figure 5), 83% versus 33%, $p = 0.009$. Five patients with PVCs from the RVOT did not display LVAs (Figure 6). The presence of DPs in the RVOT was found in three patients (8%) from the validation group (Figure 3), respectively, with an area of 1, 1.2, and 1.5 cm^2, and in 33 patients (87%) in the study group, $p < 0.0001$, with and area of 1.5 (1–2.3) cm^2 (Figures 4–7). Their presence was significantly higher in patients with PVCs from the RVOT than from the LVOT 100% versus 44% (four patients) (Figure 7), $p < 0.0001$, even in the absence of LVAs as is the case of the patient on Figure 7. DPs were located in LVAs in 82% of cases in the study group and in one out of three (33%) patients from the validation group, $p = 0.116$.

3.2.2 | PVC activation map and ablation in the study group

The PVCs originated from the RVOT in 29 patients and the LVOT in 9 (Figure 2). In 33 patients from the study group with DPs in the RVOT in sinus rhythm, the area was directly mapped during PVC. In 4 out of 33 patients, the local activation time (LAT) in the was late in relation to the beginning of the QRS, so we went directly to the left side, as with the remaining 5 patients that did not present DPs in the RVOT in sinus rhythm. In 29 patients with DPS in the RVOT, and an early activation in the area with DPs, the PVC was successfully mapped with a low number of points, median of 34 (20–43), minimum two points, and a mapping time in PVC of 30 (19–50) min, minimum 2 min (Figure 2). On the right side, the PVCs originated in the free wall in 13 patients and in the septal wall in 16 patients. On the left side, the PVCs originated from the LVOT under the left coronary cusp (LCC) in three patients, from the LCC in two, the aortomitral continuity in two, the right coronary cusp–LCC commissure in one, and in the LV summit in another. The LAT at the ablation site was 38 (30–49) ms before the beginning of the QRS in the RVOT and 30 (22–42) ms in the LVOT, $p = 0.155$. At the ablation site, the pace mapping match was at least 11/12 in all patients (Figure 6). For right-sided PVCs, the ablation site was in an area of low voltage in 24 patients (63%), either in the transitional zone in 13 or in a LVA outside the transitional zone in 11 patients. All patients in the study group displayed DPs at the ablation site, that became presystolic during PVC and did not

TABLE 1 Evaluated parameters and comparison between groups

	Overall sample ($n = 114$)	Study Group ($n = 38$)	Historical Group ($n = 38$)	Validation Group ($n = 38$)	p Value
Demographic data					
Age in years, median (Q_1–Q_3)	50 (38–61)	53 (41–65)	50 (41–61)	50 (35–58)	0.555
Male gender, n (%)	48 (42)	16 (42)	17 (44)	15 (40)	0.898
Weight in Kg, median (Q_1–Q_3)	70 (60–80)	70 (60–81)	70 (62–76)	64 (59–77)	0.670
Height in cm, median (Q_1–Q_3)	167 (164–172)	165 (161–170)	165 (161–173)	167 (165–171)	0.341
BMI in Kg/m^2, median (Q_1–Q_3)	24 (22–27)	24 (22–28)	24 (22–26)	23 (22–27)	0.736
Risk factors, history and medications					
Hypertension, n (%)	26 (23)	7 (18)	8 (21)	11 (29)	0.523
Diabetes, n (%)	7 &)	2 (5)	3 (8)	2 (5)	0.867
Syncope, n (%)	6 (5)	4 (11)	2 (5)	0 (0)	0.121
Family history of sudden death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-
Betablockers, n (%)	58 (51)	26 (68)	23 (61)	9 (24)	<0.0001
Antiarrhythmic drugs, n (%)	12 (11)	7 (18)	2 (5)	3 (8)	0.141
Standard 12 lead ECG					
ST-segment elevation at V1 or V2, n (%)	12 (11)	6 (16)	6 (16)	0 (0)	0.035
T wave inversion beyond V1, n (%)	4 (4)	2 (5)	2 (5)	0 (0)	0.355
Transthoracic echocardiogram					
LVEF in %, median (Q_1–Q_3)	59 (57–60)	58 (56–60)	60 (58–60)	59 (58–60)	0.330
LAD in mm, median (Q_1–Q_3)	35 (33–37)	35 (30–40)	34 (33–35)	35 (33–38)	0.283
24-h Holter recording[a]					
Number of PVCs, in $n \times 10^4$, median (Q_1–Q_3)	1.8 (1.3–2.6)	1.9 (1.3–2.6)	1.8 (1.3–2.6)	-	0.988
NSVT, n (%)	22 (29)	13 (34)	9 (24)	-	0.312

Abbreviations: BMI, body mass index; ECG, echocardiogram; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia.

[a]Only in patients with PVCs ($N = 76$).

TABLE 2 Invasive mapping comparison between the study group and the validation group

	Overall sample ($n = 76$)	Study group ($n = 38$)	Validation group ($n = 38$)	p Value
Invasive voltage map of the RVOT in SR				
RMN/manual ablation, n/n (%)	51/25 (67)	16/22 (42)	35/3 (92%)	<0.0001
Mapping time in min, median (Q_1–Q_3)	20 (13–29)	20 (13–29)	18 (15–21)	0.439
Number of points, median (Q_1–Q_3)	382 (329–450)	395 (330–435)	352 (327–476)	0.526
Presence of LVAs in the RVOT, n (%)	31 (41)	27 (71)	4 (11)	<0.0001
Presence of DPs in the RVOT, n (%)	36 (47)	33 (87)	3 (8)	<0.0001

Abbreviations: DP, diastolic potential; LVA, low voltage area; RMN, remote magnetic navigation; RVOT, right ventricular outflow tract; SR, sinus rhythm.

disappear after successful ablation (Figure 1). The procedure time, RF time, and fluoroscopy time were not significantly different for PVCs from the RVOT and LVOT, respectively, 130 (108–167) versus 130 (100–178) min, $p = 0.946$, 410 (240–627) versus 360 (120–612) min, $p = 0.566$, and 5.7 (3–9.8) versus 6 (4.5–10.1) min, $p = 0.417$. The overall success rate of ablation was 90%, 100% for left-sided PVCs, and 86% for right-sided, $p = 0.554$, respectively (Figure 2). Unsuccessful cases were all from the RVOT, in three

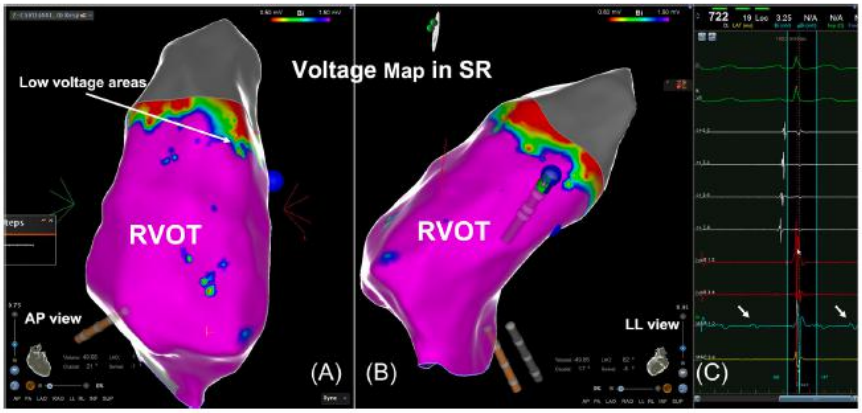

FIGURE 3 Patient from the validation group displaying LVAS and DPs in the RVOT. (A) Voltage map in SR, AP view with LVAs (white arrow). (B) Voltage map in SR, LL view with DPs (blue dots). (C) Intracardiac electrogram with the distal dipole of the ablation catheter (MAP 1–2) displaying DPs (white arrows). AP, anteroposterior; DP, diastolic potential; LL, left lateral; LVA, low voltage area; RVOT, right ventricular outflow tract; SR, sinus rhythm.

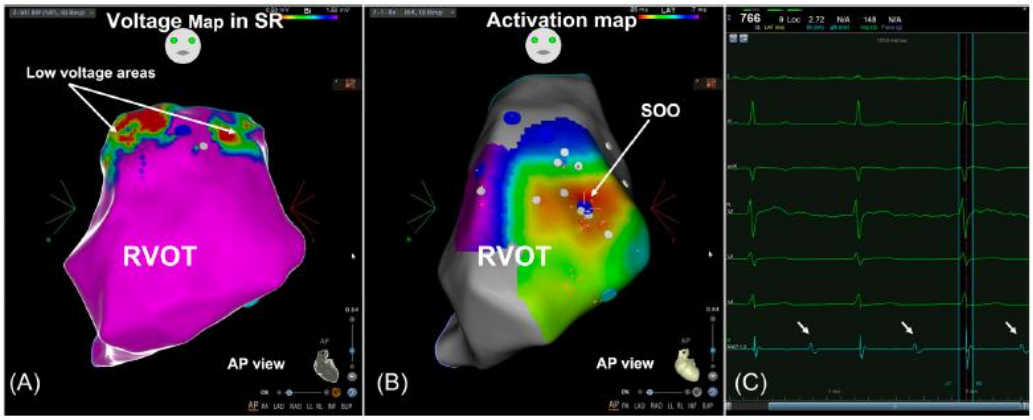

FIGURE 4 Patient with PVCs from the RVOT displaying LVAs and DPs in the RVOT. (A) Voltage map in SR (585 points) with LVAs (white arrows). (B) Activation map in PVC (64 points) with DPs (blue dots). (C) Intracardiac electrogram showing DPs (white arrows) at the distal dipole of the ablation catheter (MAP 1–2) at the RVOT (blue dots). AP, anteroposterior; DP, diastolic potential; LVAs, low voltage areas; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; SOO, site of origin of the arrhythmia; SR, sinus rhythm.

patients the SOO was at the left septum, the thickest portion of the RVOT, and one at the anterior free wall.

One patient developed a femoral pseudoaneurysm that resolved with injection of fibrin glue.

3.2.3 | Comparison between the study group and the historical group

The median number of PVCs/min in the first 5 min of the procedure was not significantly different between the two groups, respectively, 1 (0.9–2) in the study group, and 1 (0.4–1.3) in the historical group $p = 0.107$ (Table 3). However, in the historical group, only 34 patients (90%) underwent electrophysiological mapping, the other 4 patients had the procedure canceled due to the low PVC burden. Ablation was attempted in 28 patients (74%), which was significantly lower than in the study group (100%), $p = 0.001$. The proportion of patients that underwent ablation with RMN or manually was not significantly different between the study and the historical group, respectively, 42% and 64%, $p = 0.075$ (Table 3). The two groups did not differ in the right versus left origin of the PVCs, fluoroscopy, and RF time. The procedure time, however, in patients that underwent ablation, was significantly shorter in the study group when comparing to the historical group, 130 (100–164) versus 183 (160–203) min, $p < 0.0001$. The success rate was significantly higher in the study group 90% versus 64%, $p = 0.013$, with a similar complication rate.

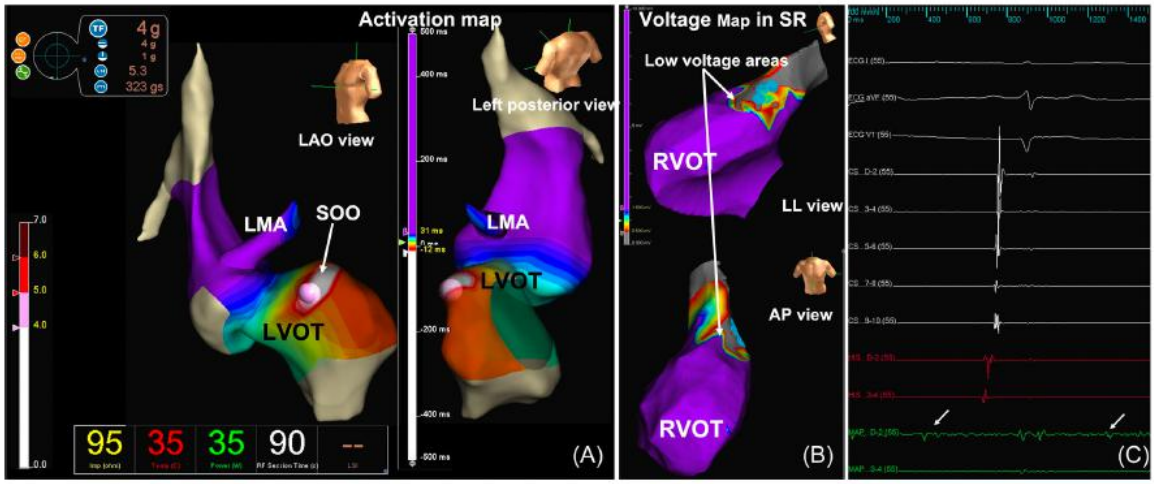

FIGURE 5 Patient with PVCs from the LVOT displaying LVAs and DPs in the RVOT. (A) Activation map in PVC (7 points) with LAT at the SOO of −13 ms. RF applications at the SOO (pink dots). (B) Voltage map in SR (186 points) with LVAs (white arrows) and DPs (blue dots). (C) Intracardiac electrogram showing DPs (white arrows) at the distal dipole of the ablation catheter (MAP D-2) at the RVOT (blue dots). AP: anteroposterior; DP, diastolic potential; LAT, local activation time; LAO, left anterior; LL: left lateral; LMA, left main artery; LVA, low voltage area; LVOT, left ventricular outflow tract; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; SOO, site of origin of the arrhythmia; SR, sinus rhythm.

3.3 | Follow-up

In the beginning of the follow-up, 90% of the patients from the study group had their PVCs abolished, in comparison to 47% in the historical group, $p < 0.0001$. The median follow-up time in the overall population with PVCs was 1060 (574–1807) days, minimum 30 days, and maximum 2313 days. No patients were lost to follow-up. The follow-up was significantly shorter for the study group (Table 3). During this time, 4 patients (8%) out of 52 patients that underwent successful ablation had recurrence of the PVCs, all in the study group. So, the recurrence rate in the study group was 11%. Two patients had an early recurrence within the first 24 h, during hospital stay. One patient had recurrence 2 weeks after ablation and one patient 300 days after ablation. One patient repeated ablation with RF applications at the same site and is well without PVCs, and the other three patients declined a second ablation procedure. The recurrence rate in the study and historical group was not significantly different (Log-rank = 0.125). The Holter performed at the last follow-up both in the study and historical groups in patients that underwent a successful procedure and did not have recurrence of the arrhythmia, showed a median of 10 (1–87) PVCs/24 h, not significantly different in the two groups, respectively, 12 (1–146) and 5 (0–53), $p = 0.442$.

4 | DISCUSSION

The first important finding in this study was the recording of DPs during sinus rhythm on the intracardiac bipolar electrogram at the ablation site, in all patients in the study group regardless of the side of origin of the PVCs. Liu et al.[12] had already reported their occurrence in patients with PVCs from the RVOT which was confirmed by our previous work.[13] However, there is only one report of similar DPs at the ablation site on left-sided PVCs by Itoh et al.[14] in a patient with PVCs from the aortomitral continuity. These DPs were recorded below the pulmonary valve, both below and above the aortic valve and are characterized by occurring late in diastole and separated from local ventricular electrogram by an isoelectric segment. These features differentiate them from the formerly described sharp local potential after the end of the local electrogram, first by Timmermans et al.[19] in PVCs originating above the pulmonary valve, and later by Thomsen et al.[20] in 24 patients with RVOT arrhythmias originating below the pulmonary valve. Unlike the potentials described by those authors,[19,20] our DPs occur late in diastole, after the end of the T wave, corresponding to the phase 4 of the cardiac action potential,[21] suggesting that they may result from delayed after depolarizations (DADs). Therefore, representing a form of triggered activity that originates a potential with a very low amplitude, only recorded when the catheter is in close proximity to their origin. If we accept that they may be the source of the PVCs, it would be expected that their location would be at the site of successful RF application. When this potential is capable of propagating to a critical number of adjacent myocytes, it elicits the occurrence of the PVC. That may depend on the intensity of the DADs or on the degree of exit block. This finding is in agreement with the generally accepted theory that the outflow tract ventricular tachycardia is caused by cyclic adenosine monophosphate -mediated DADs and triggered activity.[22] The DPs were also found in three patients (8%) in the validation group, this value is similar to the 10%

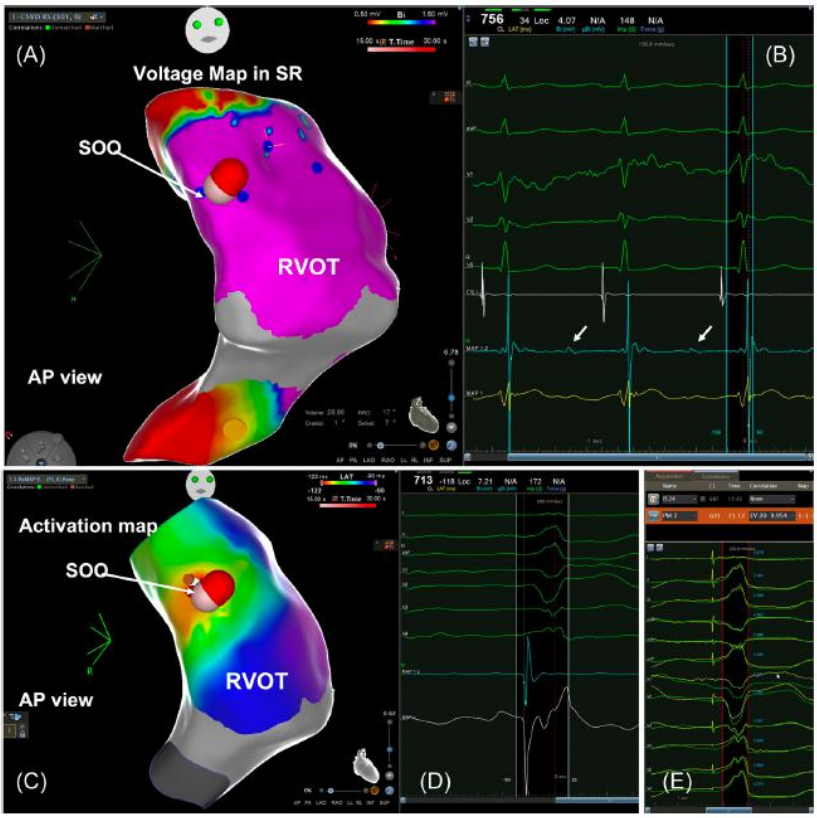

FIGURE 6 Patient with PVCs from the RVOT with DPs in the RVOT but no LVAs. (A) Voltage map in SR (301 points) with DPs (blue dots), without LVAs. (B) Intracardiac electrogram showing DPs (white arrows) at the distal dipole of the ablation catheter (MAP 1–2) at the RVOT. (C) Activation map in PVC (75 points), RF applications at SOO (red dots). (D) Intracardiac electrogram at the distal dipole of the ablation catheter showing a local activation time of −50 ms (Map 1–2) and a QS unipolar pattern (MAP 1). (E) Pace mapping at the SOO with a perfect pace match. AP, anteroposterior; DP, diastolic potential; LVA, low voltage area; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; SOO, site of origin of the arrhythmia; SR, sinus rhythm.

in the control group reported by Liu et al.[12] There are several publications reporting the association of idiopathic ventricular arrhythmias and AVNRT.[23,24] Hasdemir et al.[24] reported an incidence of spontaneous AVNRT among patients with idiopathic ventricular arrhythmias in 9%, and idiopathic ventricular arrhythmias in 11% of patients with clinical AVNRT. This association might be explained by the persistence of tissue with nodal properties at the area around the atrioventricular ring, in the fibrous septum, and in the outflow tracts, like a third branch of the conduction system present during embryologic development, known as the septal dead-end-tract connecting these regions.[25,26] This fact might be the reason for the presence of DPs in 8% of our validation group.

The second most important finding was the presence of LVAs in a high percentage of patients in the study group (71%). It is usually accepted that in the absence of structural heart disease the intracardiac electrograms display normal duration and normal voltage.[27] However, we observed areas of low voltage in the majority of our patients even though the ECG and CMR imaging did not demonstrate any form of structural disease. The voltage in the RVOT is usually lower than in the remaining part of the right ventricle. Boulos et al.,[28] studied the voltage map in patients with ARVC, with idiopathic RVOT ventricular arrhythmias and seven normal subjects. They found a regional difference in the bipolar voltage throughout the right ventricle, and the RVOT displayed the lowest voltage, but they found no LVAs in any of the 7 normal subjects or in any of the 12 patients with RVOT ventricular arrythmias.[28] The area immediately below the pulmonary valve displays a voltage between 0.5 and 1.5 mV and is described as the transitional-voltage zone.[7] The length of this area is variable and according to the authors, longer in patients with malignant arrhythmias than in those with a benign course. In our study, the LVAs were outside the transitional-voltage zone, into the RVOT body. Their presence was significantly higher in patients with an RVOT versus LVOT origin and were also present in four patients in the validation group. These results are conflicting with our previous

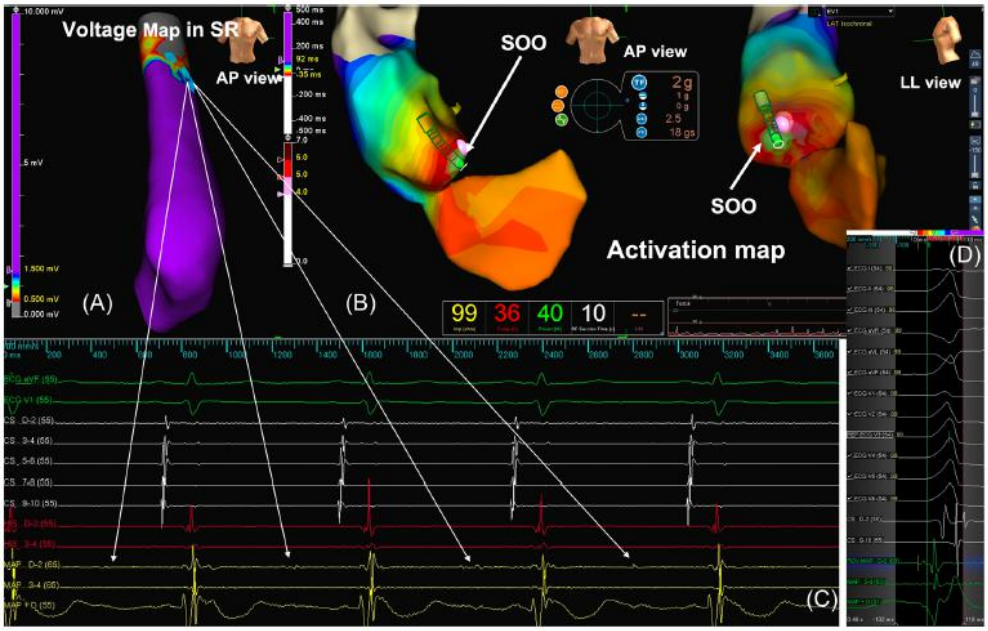

FIGURE 7 Patient with PVCs from the LVOT with DPs in the RVOT but no LVAs. (A) Voltage map in SR (325 points) with DPs (blue dots), without LVAs. (B) Activation map in PVC (23 points) displaying the ablation catheter at the SOO delivering RF (pink dots). (C) Intracardiac electrogram showing DPs (white arrows) at the distal dipole of the ablation catheter (MAP D-2) at the RVOT (blue dots). (D) Intracardiac electrogram at the distal dipole of the ablation catheter showing as early activation of −30 ms (Map D-2) and QS unipolar pattern (MAP D). AP, anteroposterior; DP, diastolic potentials; LL, left lateral; LVA, low voltage area; LVOT, left ventricular outflow tract; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; SOO, site of origin of the arrhythmia; SR, sinus rhythm.

data[10] in 56 patients, 45 with PVCs, and 11 control subjects, we found no LVAs in the control group and a similar prevalence in patients with PVCs from the RVOT and LVOT. We believe that the differences between the two studies, might be due to the increase in the sample size of the current study, and probably, it may also be the reason for the absence of LVAs reported by Boulos et al. in their study, in addition to the small number of sampled points used when comparing to ours, mean of 93 ± 12 versus median of 352 (327–476). The presence of LVA in patients with idiopathic PVCs is not a recent finding. In fact, a high number of previous studies have already demonstrated this occurrence, either with conventional ablation catheters,[7–10] or recently, with the use of a multipolar catheter to obtain a high-density endocardial voltage mapping.[11] It is difficult to explain the occurrence of LVAs. However, we have to bear in mind that the low bipolar voltage amplitude is influenced by many variables including the contact force.[29] The majority of patients in the validation group had the voltage map obtained with RMN, we can hypothesize that the lack of contact-force technology may be the cause for the LVAs detected, but the availability of a catheter–tissue contact feedback technology may overcome this limitation,[17] as well as the absence of LVAs in the remaining 34 patients. We can hypothesize that the presence of LVAs and DPs in the validation group may simply indicate that there is a substrate to develop PVCs, either not diagnosed yet, or in the dependence of other factors that can lead to the occurrence of PVCs, like stress, sleep apnea,[30] or training.[31] On the other hand, in our group of patients, LVAs were not always present. This may imply failure to identify the area of interest, but it can also mean that PVCs may have different mechanisms or substrates.

The DPs were mostly recorded at LVAs, which also displayed abnormal electrophysiological properties, namely a slower propagation speed both in sinus rhythm[32] and in PVC.[33] Using electrocardiographic imaging, we were able to demonstrate the presence of a dispersion of the activation-recovery interval, a known surrogate of the action potential duration across the RVOT in patients with PVCs.[34]

There is an increasing trend to go for substrate ablation in the majority of arrhythmias. This is the case of cavotricuspid isthmus for typical atrial flutter, scar homogenization for ischemic ventricular tachycardia, pulmonary vein isolation for atrial fibrillation, or epicardial RVOT ablation for Brugada Syndrome. Substrate mapping to identify areas of low voltage and search for DPs may be a possible strategy for ablation of outflow tract arrythmias in patients in whom despite the daily high number of PVCs in Holter recording, have a low PVC burden during the ablation procedure. To the best of our knowledge, this is the first study that compares an approach based on substrate mapping during sinus rhythm with a conventional approach, in patients with low PVC burden during the procedure. We were able

TABLE 3 Procedure and follow-up data between the study group and the historical group

	Overall sample ($n = 76$)	Study group ($n = 38$)	Historical group ($n = 38$)	p Value
Procedure data				
Procedure performed, n (%)	72 (95)	38 (100)	34 (90)	0.115
Ablation performed, n (%)	66 (87)	38 (100)	28 (74)	**0.001**
RMN/manual ablation, n/n[a]	34/32	16/22	18/10	0.075
Number of PVC/min, median (Q1–Q3)	1 (0.5–2)	1 (0.9–2)	1 (0.4–1.3)	0.107
RVOT/LVOT, n/n (%)[a]	49/17	29/9	20/8	0.654
Procedure time in min, median (Q1–Q3)[a]	155 (120–190)	130 (100–164)	183 (160–203)	<0.0001
Fluoroscopy time in min, median (Q1–Q3)[a]	5 (3–8)	5.6 (3.4–10)	4 (3–6)	0.111
RF time in seconds, median (Q1–Q3)[a]	380 (206–600)	390 (191–609)	340 (240–600)	0.833
Acute success, n (%)[a]	52 (79%)	34 (90)	18 (64)	0.013
Complications, n (%)[a]	1 (2)	1 (3)	0 (0)	1.000
Follow-up				
Follow-up time in days, median (Q1–Q3)	1060 (574–1807)	581 (411–935)	1769 (1299–2199)	<0.0001
Recurrence, n (%)[b]	4 (8)	4 (12)	0 (0)	0.285
Post ablation 24-h Holter recording[c]				
Number of PVCs, in $n \times 10^4$, median (Q1–Q3)	10 (1–87)	12 (1–146)	5 (0–53)	0.422
NSVT, n (%)	0 (0)	0 (0)	0 (0)	-

Abbreviations: LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; RF, radiofrequency; RMN, remote magnetic navigation; RVOT, right ventricular outflow tract.

[a]In patients that underwent ablation.

[b]In patients that underwent successful ablation.

[c]In patients that underwent successful ablation and did not have recurrence.

to demonstrate that this approach was faster than the conventional one based on activation and pace mapping, making ablation possible in a higher percentage of patients with a higher success rate and a similar recurrence rate. Previously other groups reported the results of a substrate approach for idiopathic PVCs. Liu et al.,[12] in a series of 25 points with RVOT PVCs, used a strategy based on electro-anatomical mapping in sinus rhythm looking for the DPs in three patients with low PVC burden and in four patients with high PVC burden that failed conventional ablation based on activation map and performed a more detailed activation map at the area with DPs. The authors obtained success in all patients, both with conventional ablation and ablation based on DPs mapping. The DPs remained in 24 patients but became split in 9 as opposed to ours that remained in all patients. In the paper by Liu et al.,[12] the arrhythmias originated in areas with voltage below 1.5 mV in 22 (88%) patients and in the normal voltage areas in 3 (12%), a value similar to ours, 83% for RVOT cases. One of the limitations pointed out by the authors was that acquisition of points for the voltage map was performed after ablation. Three additional limitations in our point of view might also be implicated, the use of catheters without contact-force, the absence of results of the voltage map in the control group, and the fact that the study only included patients with RVOT arrhythmias.

Using an approach based on mapping of endocardial late fractionated potentials during sinus rhythm, defined as >4 fractionated signals of <0.5 mV after the end of the major ventricular deflection, Lee et al.,[35] retrospectively studied 28 patients with idiopathic ventricular arrhythmias from the RVOT. The patients were divided in two groups with and without fractionated electrograms in sinus rhythm. In the group with fractionation ($N = 10$), ablation of those potentials was successfully attempted, and the success rate was superior, also the recurrence rates were lower in those patients than in the ones without fractionation. However, as the authors point out, none of the patients had a CMR performed so it is impossible to assure that the RVOT was normal in that study population.

Letsas et al.,[11] studied 44 patients with RVOT ventricular arrhythmias and negative CMR and found LVAs in a sinus rhythm map in 39 patients (88%). In a subgroup of 11 patients that had low PVC burden, the authors used a substrate-based approach aiming at the LVAs and confirming the origin of the arrythmia with pace mapping. In our experience, pacing from the LVAs is difficult to accomplish, and with our approach we were able to perform the ablation with as little as two PVCs to confirm a good LAT. The follow-up was short in the study by Letsas et al.,[11] only 6 months during

which 22% of the patients had recurrence of the arrhythmia which is higher than our 11% recurrence rate.

In comparison with previous studies using substrate mapping, our study has some unique technicalities, first of all, it was a prospective study, all patients underwent CMR to rule out right ventricular morphologic abnormalities, the voltage map was performed either with contact-force technology for manual ablation or catheter–tissue contact feedback technology for RMN ablation, and finally the results were compared with an historical group. The presence of LVAs and DPs may be considered a new target for ablation, and the results of our study have shown that this approach is superior to conventional activation and pace mapping, in patients with low PVC burden during the procedure.

5 | LIMITATIONS

RMN was the technique of choice to study the control group; due to the softer catheter tip and its higher safety profile,[17] we were able to obtain the voltage map of the RVOT with near zero fluoroscopy, which would be impossible to achieve with manual catheters. So, the percentage of RMN versus manual is significantly higher in the validation group in comparison with the study group. However, in patients with PVCs, there were no significant differences regarding the use of manual versus RMN techniques between the study and the historical group.

Patients in the validation group did not perform an Holter registry to exclude asymptomatic frequent PVCs, which means some of them might have asymptomatic PVCs.

The level of the pulmonary valve was assessed just with the electroanatomical mapping, so we cannot be sure if some of the LVAs especially in the control group could be just the normal low voltage in the transitional zone. The procedures were all done without intracardiac echocardiogram (ICE), which could be a useful tool to assess the level of the pulmonary valve. There is some criticism regarding the nature of the DPs, some arguing that they may be just artifacts. The use of ICE once again would have been useful to rule out inadvertent contact with intracavitary structures or valves that would result in such signals. However, that seems not to be the case due to the absence of DPs in the majority of subjects in the control group.

Some authors[11] believe that high-density endocardial bipolar voltage mapping may increase the detection of minimal electrical abnormalities within the RVOT that possibly represent targets for successful catheter ablation. We did not use such catheters but still got a similar 83% prevalence of LVAs at the RVOT in patients with PVCs from the RVOT in comparison with the 88% obtained by those authors with high-density mapping.

We believe that a randomized multicentric trial comparing the results of conventional versus substrate-based ablation for idiopathic outflow tract PVCs might be an important endeavor to pursue.

6 | CONCLUSIONS

The prevalence of LVAs and DPs was significantly higher in the study group than in patients without PVCs. The proposed approach, partially based on substrate mapping including searching for LVAs and DPs, proved to be feasible, faster, and more efficient than the previous approach based exclusively on activation mapping.

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Case Report

Interventional Cardiology

Successful radiofrequency ablation of para-left bundle branch premature ventricular contractions: Aiming at the breakout point to spare the conduction system

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Abstract:

Background: The origin of the arrhythmia and its breakout point may be located apart. This has been described for arrhythmias originating within the His-Purkinje system. Case presentation: We report a case of a 70-year-old man with right bundle branch block and left anterior fascicular block with idiopathic nonsustained ventricular tachycardia originating in the septal left ventricular outflow close to the proximal left bundle branch. Ablation was successfully and safely performed away from the origin of the arrhythmia near the left anterior fascicle, at the breakout point. Arrhythmias from the conduction system may have different preferential exits and meticulous activation sequence mapping is the preferable strategy to select the ablation site.

Keywords: Left ventricular outflow tract . Premature ventricular contractions . Membranous septum . Radiofrequency ablation . Right bundle branch block

Introduction

Idiopathic Premature Ventricular Contractions (PVCs) arise more frequently from the right ventricular outflow tract (RVOT) followed by the Left Ventricular Outflow Tract (LVOT), mainly from the aortic cusps [1]. Less common sites include the tricuspid annulus and the right ventricular inflow free wall region [2] on the right. The basal septum immediately below the Right Coronary Cusp (RCC) is also an uncommon site of origin of idiopathic PVCs. The distinctive electrocardiographic pattern being an inferior lead discordance, with a negative QRS polarity in lead III and positive polarity in lead II, and a positive polarity in lead aVL [3]. The proximity to the left His bundle and the proximal Left Bundle Branch (LBB) is a drawback for ablation at this location due to the risk of Atrioventricular Block (AVB) or LBB block during ablation [3,4].

Case Report

A 70-year-old man was referred to our institution by his primary care physician due to extremely frequent PVCs and runs of Non-Sustained Ventricular Tachycardia (NSVT) refractory to bisoprolol and sotalol. The patient complained of recurrent palpitations and precordial discomfort at rest, but he denied syncope. The episodes were not worsened by exercise or emotional stress. His past history was unremarkable and there was no family history of sudden death or cardiac diseases. The 12-lead ECG in sinus rhythm showed a Right Bundle Branch Block (RBBB) and a left anterior fascicular block with a QRS duration of 160 ms and frequent PVCs with a QRS duration of 130 ms, RBBB morphology, inferior lead discordance (positive lead II and negative lead III), tall R wave in lead I and aVL and QS in aVR (Figure 1A). Transthoracic echocardiogram was normal and the 24-hour Holter on bisoprolol,

Case Report

revealed 42966 multiform PVCs/24 h (1837 PVCs/hour) but with a clear predominance of one morphology, 1051 couplets, 112 triplets and 15 episodes of Non-Sustained Ventricular Tachycardia (NSVT). A cardiac magnetic resonance imaging study (CMR) was performed after the first evaluation at our center and the 24-hour Holter was repeated. The CMR showed mild left and right ventricular enlargement but it was otherwise normal with no late gadolinium enhancement. The repeated 24-hour Holter on sotalol showed an increase in the PVC burden with 49254 PVCs/24 hours (2141 PVCs /hour) same morphologies, 394 couplets, 72 triplets and 8 runs of NSVT. Arrhythmia-induced biventricular dilatation was assumed, and catheter ablation was proposed.

After written informed consent was obtained, the patient underwent an electrophysiological study and catheter ablation.

The RVOT and LVOT mapping were performed with the electro-anatomical mapping system EnSite Precision (Abbott) using an irrigated tip catheter (Tacticath, Abbott) with a 3.5-mm distal tip electrode and a 1-4-1 interelectrode distance. The RVOT was reached by the right femoral vein and the LVOT was accessed by retrograde approach. The activation map of the PVCs was obtained, showing late activation of the RVOT in relation to the LVOT. The earliest activation was identified in the high left ventricular septum below the RCC (Figure 2A). The local activation time preceded

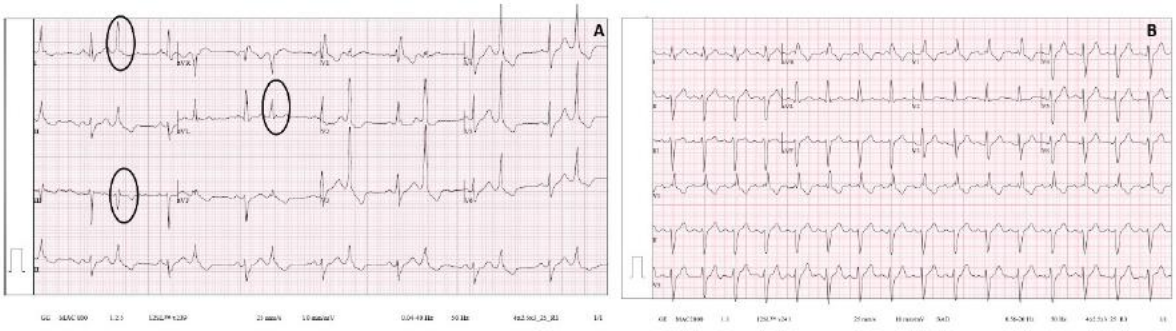

Figure 1: 1A: 12-lead electrocardiogram pre-ablation, inferior discordance, and tall R waves in Lead I and aVL and 1B: post-ablation.

the onset of the QRS by 33 ms and the local electrogram displayed an LBB potential at the distal bipolar electrode pair (Figure 2B). Pacing at this site showed a 12/12 pace-map match. Delivering radiofrequency (RF) to this site would result in complete AV block due to pre-existing RBBB so we kept moving the ablation catheter in the area and found a second point 5 mm away from the first site (Figures 2A and 2C) showing a local electrogram that was equally early preceding the onset of the QRS by 26 ms separated from the first site by points with more delayed local activation times. The local electrogram did not display a LBB potential, but a fascicular potential was present in sinus rhythm (Figure 2D), corresponding to the left anterior fascicle. Unipolar electrograms showed a QS morphology at both sites, although at the first site the descend was sharper. Pacemapping was not possible at the second site due to absence of ventricular capture. Considering that the patient already had a left anterior fascicular block at the beginning of the procedure we decided to apply RF at this site carefully uptitrating energy delivery to a maximal power of 45 watts for 60 seconds. The PVCs disappeared in the first 4 seconds of RF application (Figure 3) and no junctional rhythm or blocked P-waves were observed during ablation, the His-Ventricular interval did not increase significantly (58 ms before and 60 ms after ablation). The QRS developed a more pronounced left anterior fascicular block pattern but the QRS duration did not increase (Figure 1B). At 1 month of follow-up, the patient was asymptomatic, and no PVCs were detected on ECG (Figure 1B). The 24-hour Holter recording without antiarrhythmics detected 2300 multiform PVCs/24 h, all different from the ablated morphology. At 6 months the patient remained asymptomatic and referred an improvement in exercise tolerance and the 24-hour Holter recording detected 2100 multiform PVCs/24 h.

Case Report

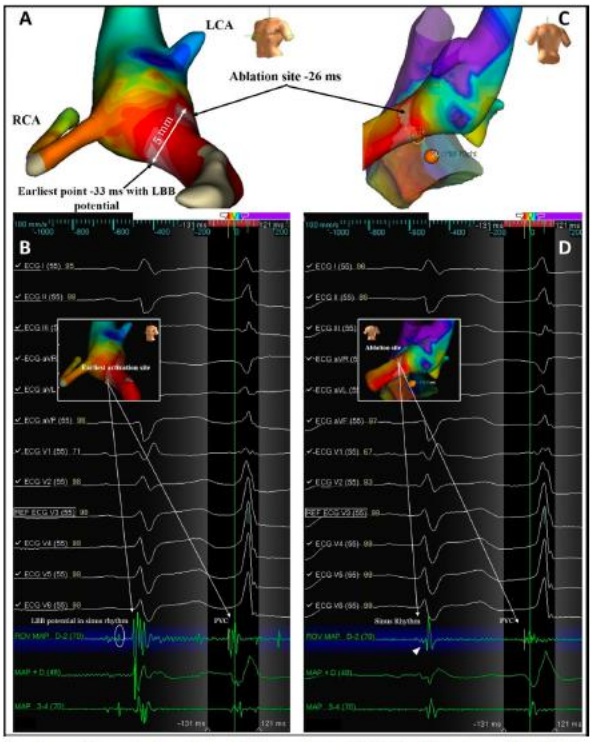

Figure 2: 2A: Electroanatomical mapping showing earliest activation site and ablation site in LAO. 2B: Unipolar and bipolar electrogram at the site with earliest ventricular activation with local PVC activation preceding QRS onset by 33 ms with an LBB potential recorded by the distal bipolar pair of the ablation catheter. 2C: PA projection of the LVOT and RVOT with right and His location tagged by the orange dot. 2D: Unipolar and bipolar electrogram at the ablation site preceding the onset of the QRS by 26 ms with a fascicular potential (white arrowhead). ROV MAP D-2: distal bipolar electrogram of the ablation catheter; MAP+D: unipolar electrogram of the ablation catheter; MAP 3-4: proximal bipolar electrogram of the ablation catheter; LCA: Left Coronary Artery; LBB: Left Bundle Branch; PVC: Premature Ventricular Contraction; RCA: Right Coronary Artery.

Figure 3: Radiofrequency application at ablation site (superior panel). Disappearance of the clinical PVCs after 4 seconds of RF (inferior panel), white arrows indicating occurrence of PVCs with a different morphology.

Results and Discussion

In this report we describe a case of frequent PVCs with a relatively narrow QRS originating from the left ventricular septum underneath the aortic valve, in a patient with RBBB and left anterior fascicular block. Idiopathic PVCs arising from the high left ventricular septum are uncommon [5]. The septum at this level is partially fibrous and is adjacent to the bifurcating atrioventricular bundle and the origin of the LBB [6]. A His-bundle or a LBB potential can be recorded at this site in a high percentage of cases, contraindicating ablation due to the risk of damage to the conduction system. In a series of 8 patients with PVCs from this location, ablation was not attempted in almost 40% of the cases3. The concern about LBB damage was higher in our patient due to the presence of a baseline RBBB. The electrocardiographic pattern of the PVC with a negative polarity in lead III and a tall R in aVL and lead I raised concern about this specific location [3] differentiating it from an RCC origin. This electrocardiographic pattern can also be observed in PVCs originating from the His bundle region in the right septum [4,7] except for the R wave in V1 and V2 which is less frequent for right sided focus, and besides, electrocardiographic algorithms are not reliable due to their low accuracy [8]. The patient was refractory to medical therapy and the ventricles were already dilated, so the benefits were balanced against the risks of atrioventricular conduction block, and ablation was contemplated. An LBB potential was recorded at the earliest activation site which totally contraindicated ablation. The narrow QRS width of the PVCs suggested an origin in the conduction system. Arrhythmias originating within the His-Purkinje system do often show preferential conduction with single or multiple exit points leading to single or multiple morphologies of the PVCs. This has been demonstrated by Itoh et al [9] in a series of 30 consecutive patients that underwent ablation of arrhythmias from the His-Purkinje system. The authors also observed that most patients had disease of the conduction system associated to the PVCs from the His-Purkinje system. For arrhythmias from within the conduction system the risk of damage to the conduction system is a major concern regarding catheter ablation.

Whenever the arrhythmia has its origin in the proximal segment of a bundle branch or atrioventricular node or His bundle, the presence of a complex net connecting the proximal with the distal parts of the system may be perceived as a possibility to map at more distal segments without such a dramatic impact on conduction when compared to ablation at more proximal sites. Successful ablation at a site 5 mm away from the earliest activation site, at a location displaying a fascicular potential in sinus rhythm, and a QS pattern during the PVC, suggests the presence of preferential conduction within the conduction system from the origin of the PVC near the proximal LBB to a more distal exit point near the left anterior fascicle. Marinheiro et al [10] previously described a similar case of PVCs originating from the His bundle in a patient with conduction system disease that underwent successful ablation of the PVCs at a distal site at the level of the slow pathway region. Our patient had a left fascicular block before ablation so we thought that ablating near the left anterior fascicle would not affect overall conduction. Since we were mapping the PVCs with an RF catheter, we didn't change to cryoablation and decided to apply RF energy with careful titration of power delivery and careful monitoring for accelerated junctional rhythm or conduction block. Although cryoablation is usually considered as a safer energy when ablating near the conduction system, it is also associated with a higher recurrence rate [11] and besides, complete atrioventricular block has also been reported in the case of parahisian PVCs [12].

We believe that in this patient we ablated the main breakout point located at a secure distance from the LBB potential that allowed successful ablation without conduction block. This property of preferential conduction may explain the variable electrocardiographic morphologies of the PVCs arising from the His-Purkinje system, according to the breakout sites, that may be multiple [9].

Although we observed a decrease of over 95% in the PVC burden during 24-Holter recording at 1-month and at 6-months follow-up, the persistence of multiform PVCs may indicate either that the principal breakout site was ablated but there were still secondary breakouts accounting for the persistence of multiform PVCs or that the remaining PVCs may be unrelated to the ones previously ablated and were allowed to emerge due to the elimination of the more prevalent ones. Nonetheless, the patient is asymptomatic and the reduction in PVC burden was significant, discouraging any repeated procedures.

Conclusion

Successful RF ablation of a PVCs originating near the LBB in a patient with RBBB and left anterior fascicular block could be successfully ablated at a site with less precocity, distally within the conduction system, sacrificing the left anterior fascicle but without risking occurrence of complete atrioventricular block.

Acknowledgments

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Conflict of Interest

The authors have no conflicts to disclose.

Informed Consent

The patient described in the case report had given informed consent for the case report to be published.

Author Contributions

Each author has individually been involved in and has made

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Successful ablation of premature ventricular contractions exclusively guided by epicardial and endocardial non-invasive mapping (ECGI) and confirmed by substrate mapping☆

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ABSTRACT

Ablation of premature ventricular contractions (PVCs), relies mostly on a detailed activation mapping. This can be impossible to achieve in case of paucity or even absence of PVCs during the procedure. Pacemapping as an alternative has many limitations. We present a case of a patient with very frequent symptomatic PVCs, that on the day of the procedure had total absence of PVCs. We performed successful ablation based exclusively on electrocardiographic imaging confirmed by substrate mapping.

Introduction

Activation mapping is the cornerstone of catheter ablation in case of focal arrhythmias. Regarding ablation of premature ventricular contractions (PVCs) this approach is hampered by the lack of PVCs during the procedure. Pacemapping as an alternative methodology has many pitfalls [1]. Electrocardiographic imaging systems (ECGI) are being developed. However, the accuracy of this methods is lower in the region of the outflow tracts. [2,3]. On the other hand, we have recently observed the presence of isolated diastolic potentials at the successful ablation site in patients with PVCS from the outflow tracts [4]. An additional strategy for ablating patients with a low burden of PVCs in the day of the procedure, might be a kind of substrate mapping looking for the presence of diastolic potentials, which we believe are associated with the PVC mechanism [4].

Case report

A 72 -year-old male patient, was observed for symptoms of palpitations, tachycardia and lightheadedness, that started six months before. The patient had a history of hypertension, diabetes and permanent atrial fibrillation. Medicated with Olmesartan/amlodipine, Glimepiride, Spironolactone, Pravastatin and Rivaroxaban. The 12-lead ECG demonstrated atrial fibrillation with no other relevant findings. A transthoracic echocardiography displayed left and right atrial dilation and no other structural changes. The 24 h Holter recording showed frequent monomorphic PVCs (13,502/24 h) with runs of nonsustained ventricular tachycardia (NSVT). The patient underwent a treadmill exercise test that showed monomorphic PVCs at rest. The PVC had an inferior axis, with a precordial transition at V3 and negative QRS in aVL, suggesting an outflow tract origin (Fig. 1). The PVCs increased in frequency with exercise, including couplets, triplets and runs of polymorphic NSVT, suggestive of a possible ischemic etiology. A cardiac magnetic resonance imaging with gadolinium was performed and was normal, without ischemia, with normal biventricular function and absence of fibrosis/scar. Due to the presence of severe bradycardia at rest, betablockers or calcium antagonists were not attempted. The Holter recording was repeated four months after the first one, with the same PVC burden. The patient performed an ECGI with the Amycard 01C system (EP Solutions SA, Switzerland). This method has been previously described [5]. However, briefly it consists of a multichannel ECG amplifier recorder that analyses up to 224 leads from up to 28 electrode bands, with 8 leads each, placed on the patient's torso. The ECG was recorded with a 0.05- to 500-Hz bandpass filter, digitized with the sampling rate of 1000 samples/s and exported to the Amycard 01C software. Afterwards, with the electrode bands in place, an ECG-gated CT scanning of the heart and thorax with intravenous contrast, was performed with a third-generation 192-slice dual-source SOMATOM Force (Siemens Healthcare). Scanning of the torso and heart was performed simultaneously. The CT data was imported in the DICOM format into the Amycard 01C software, and a 3-dimensional torso and heart model were obtained from the CT. Body surface ECG data was processed by Amycard system, using its

☆ Tweet: Amycard epicardial and endocardial ECGI system proved a useful tool for ablation of infrequent arrhythmias and not just an investigational technique.

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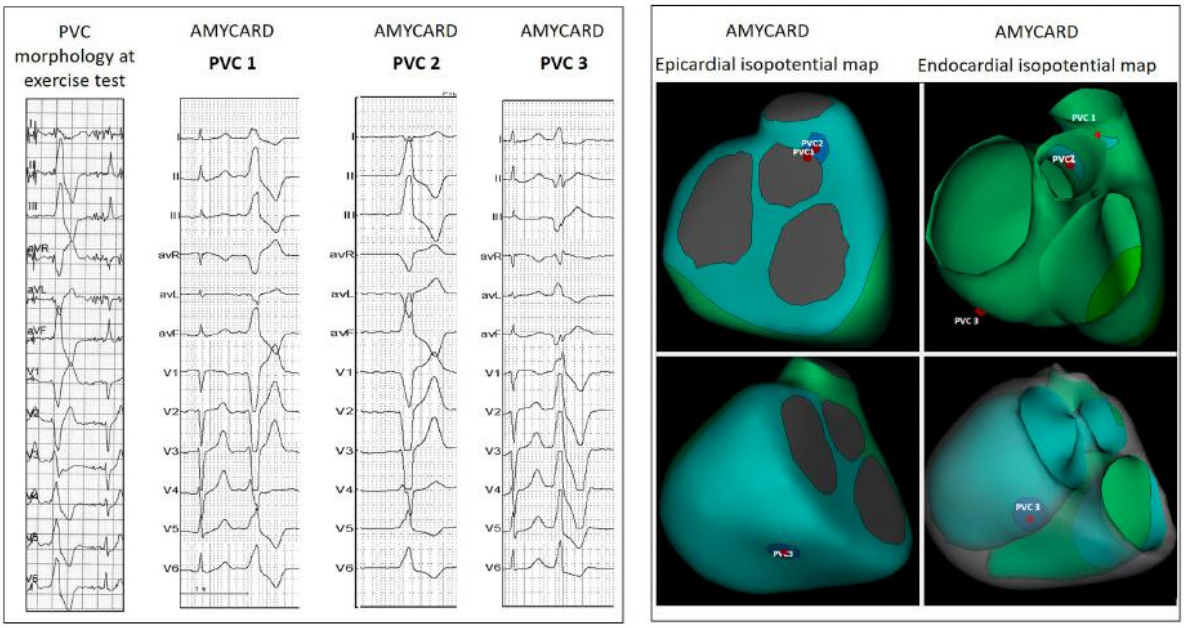

Fig. 1. Results of the ECGI mapping. Left panel; 12-lead ECG of the predominant PVC morphology during the treadmill exercise test. Amycard 12-lead recording of 3 different PVC morphologies. PVC1 was the predominant morphology. Right panel: images of the ECGI isopotential epicardial and endocardial map showing the site of origin of the 3 different PVCs. PVC: premature ventricular contraction.

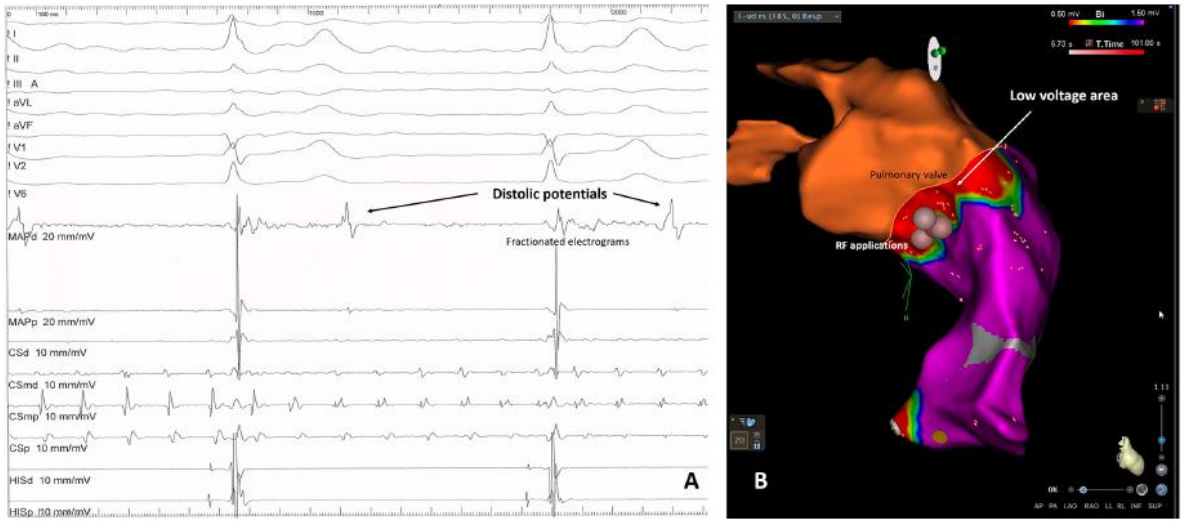

Fig. 2. Intracardiac electroanatomical mapping. Panel A: intracardiac recordings showing the presence of diastolic potentials on the bipolar electrogram at the distal bipole of the ablation catheter (black arrows). Panel B: Carto bipolar voltage map displaying a transitional low voltage area (white arrow) below the pulmonary valve and the RF applications (pink and red dots). CS: coronary sinus; MAP: ablation catheter; RF: radiofrequency. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

inverse problem solution software in combination with heart and torso anatomy, allowing for reconstruction of unipolar electrograms at approximately 2500 points on epicardium and endocardium. The earliest activation site was visually estimated using isopotential map by an experienced user. In this patient we used 23 electrode bands corresponding to 180 torso leads, four leads were excluded due to high noise. During Amycard ECG recording 3 morphologies of the PVCs were identified but PVC 1 was the predominant form and according to the ECGI map the site of origin was the RVOT septum The other two morphologies were rare and originated respectively from the right aortic cusp (PVC 2) and from the infero-basal left ventricle wall (PVC3) (Fig. 1). Catheter ablation of the PVC 1 was scheduled for two days later.

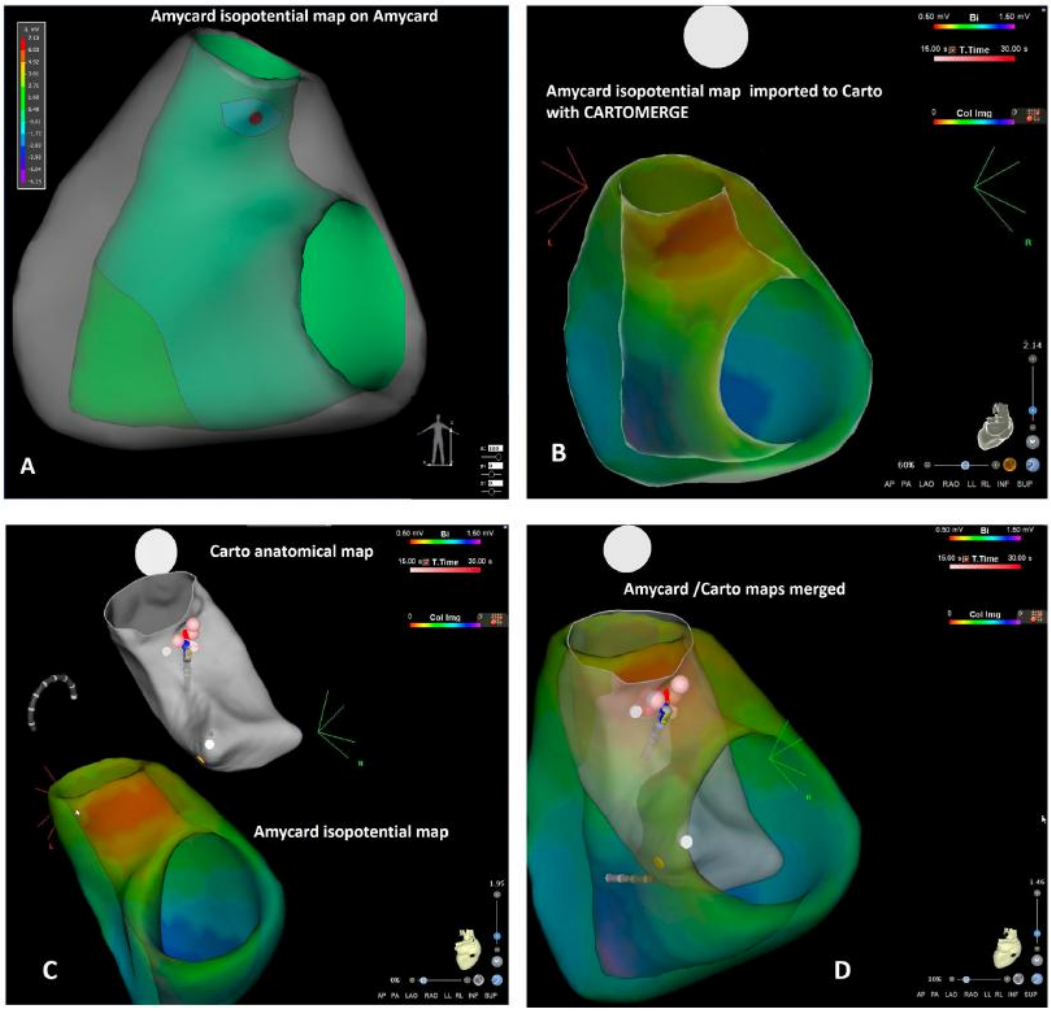

Fig. 3. Images of Amycard and Carto merge. Panel A: The endocardial ECGI isopotential mapping showing only the right ventricle and displaying the site of origin of the PVC (red dot) as appears in the Amycard screen. Panel B: Same map after integration in the Carto system using the CARTOMERGE, displaying the site of origin of the PVC with the usual Carto colour scale. Panel C: the two maps side by side, above in gray the carto anatomical map of the right ventricular outflow tract and below the ECGI map of the right ventricle. Panel D both maps merged showing the ablation catheter and the area with diastolic potentials (blue dot) and the RF applications (pink and red dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The electrophysiological study was performed after informed consent in a fasting non-sedate state without antiarrhythmic drugs. Isoprenaline was administered intravenously, but throughout the procedure the patient had no PVCs, and the programmed ventricular stimulation did not induce any ventricular arrhythmias. After discussing with the patient, the indication for ablation including the benefits and the risks, we decided to move on to ablation of the more prevalent PVC. We performed an anatomical and a voltage map of the RVOT using 185 sampled points (Fig. 2). The invasive mapping was performed with CARTO 3 version 6 (Biosense Webster), using the Niobe magnetic navigation system (Stereotaxis) and an irrigated tip Navistar RMT Thermocool™ catheter (Biosense-Webster) with a 3.5-mm distal tip electrode and a 2–5-2 interelectrode distance [6]. Sites showing isolated diastolic potentials on the bipolar electrograms, defined as, persistent low amplitude discrete potentials occurring at late diastole, after the end of the T wave of the surface ECG, were tagged (Fig. 2). The ECGI map was merged with the Carto electroanatomical map. The merge was performed with the use of the CARTOMERGE Plus Module Enhancements on the Carto workstation. First, the isopotential map was imported to Carto in a VTK format with the exact same file name as the Carto map file. After that step, the Amycard map was displayed in a format similar to the carto activation maps, with the earliest site in red and the latest in purple (Fig. 3 B). Finally, CARTOMERGE module displays both maps (Fig. 3 C) and automatically merges them (Fig. 3 D). After the merging, we confirmed that the site of origin of the PVC 1 obtained with the ECGI was overlapping with the area of diastolic potentials recorded by the ablation catheter on the electroanatomical map. We applied radiofrequency in that area for a total 6 min, to a maximum temperature of 43 °C and a power output limit of 50 W. (Fig. 3).

Two months after the procedure the patient was asymptomatic, the 24-h Holter recording showed disappearance of the PVCs. At a six- months follow-up the efficacy of the procedure was confirmed.

Discussion

In the presence of low PVC burden on the day of the procedure, the success of catheter ablation may be reduced from 85% to 56% [7]. One alternative strategy is the use of pacemapping, but its spatial resolution is lower than that of activation mapping [1]. Additionally, it has also been described that the pace match can be poor at the successful RVOT ablation site in 18% of patients [1]. And finally, pacemapping is sometimes impossible due to the absence of capture. In the case presented here, that couldn't even be possible because the patient had no clinical PVCs in the day of the procedure.

The ECGI is capable of identifying the site of origin of infrequent or unstable arrythmias because it allows a completion of an activation map with just a single beat [2,4,5]. However, this method is less accurate when the arrhythmia has its origin in the septum of the ventricular outflow tracts [2,3].

Although the 12-lead ECG of this patient pointed out to a RVOT origin, the precordial transition in V3 would always leave the possibility of a left origin. In the present case the patient had no PVCs on the day of the procedure so there was not a chance to validate the result of the ECGI with a single measure of invasive local activation time or pace mapping.

Combining the results of the ECGI with the mapping of diastolic potentials allowed for a more consistent selection of the ablation site. Liu at al [8] have also described similar potentials however, according to those authors they were not related to the PVCs. Differently, we believe that diastolic potentials are in the origin of the PVCs and may constitute a target for substrate mapping.

Limitations

Idiopathic PVCs from the RVOT was not the most plausible hypothesis in this patient due to the advanced age and response to exercise. An ischemic etiology would have been more typical. However, the ischemic etiology was ruled out. Both the ECGI and the substrate mapping used to guide ablation in this patient are not validated yet. Thus, confirmation of the presence of diastolic potentials at the site indicated by the ECGI was reassuring, and important to back up the ablation strategy. The short- and long-term response to ablation proved that the diagnosis was right.

Conclusion

We present a case of a patient with very frequent symptomatic PVCs, that in the day of the procedure had total absence of PVCs. Successful ablation was performed based only on the ECGI confirmed by substrate mapping.

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None.

Declaration of Competing Interest

Margarita Budanova is consultant of EP Solutions.

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ORIGINAL ARTICLE

Remote magnetic navigation for mapping and ablation of right and left ventricular outflow tract arrhythmias☆

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KEYWORDS
Ventricular tachycardia;
Premature ventricular contractions;
Radiofrequency ablation;
Remote magnetic navigation;
Stereotaxis

Abstract
Objective: The aim of this study was to assess the efficacy and potential complications of a remote-controlled magnetic navigation system (Niobe II, Stereotaxis) for mapping and ablation of right or left ventricular outflow tract ventricular tachycardia or premature ventricular contractions.
Methods: We studied 32 consecutive patients, mean age 43±11 years, 24 female. Mapping of the arrhythmia was performed using the CARTO RMT mapping system, remotely guided by the Niobe II. Radiofrequency ablation was performed at the site of earliest ventricular activation with pacemapping of at least 11/12 leads.

Acute success was defined as suppression and non-inducibility of the arrhythmia after stimulation with isoprenaline. After a minimum 3-month follow-up, we assessed clinical success (absence of symptoms and suppression of the arrhythmia on Holter recording), defined as less than 50 premature ventricular contractions/24 hours.
Results: The origin of the arrhythmia was in the right ventricular outflow tract in 28 patients (88%), in the left in three, and in the epicardium in one. Acute success was achieved in 26 patients (81%). Two patients underwent a second successful procedure, in one of which an epicardial approach was necessary. The overall clinical success rate, after two repeat procedures, was 88%. No complications occurred.

There were two recurrences during a mean follow-up of 307±204 days.
Conclusion: The Niobe II remote control system for mapping and ablation of ventricular outflow tract arrhythmias is effective and safe, and provides precise mapping and a high success rate, with no complications.

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PALAVRAS-CHAVE
Taquicardia ventricular;
Extrassístoles ventriculares;
Ablação por radiofrequência;
Navegação magnética;
Estereotaxia

Ablação de arritmias da câmara de saída do ventrículo direito e esquerdo com sistema de navegação magnética por controlo remoto

Resumo
Objetivos: Avaliar a eficácia e segurança do sistema de navegação magnética por controlo remoto Niobe ii (Stereotaxis) na ablação de taquicardia ventricular ou extrassístoles ventriculares da câmara de saída do ventrículo direito e esquerdo.
Métodos: Estudaram-se 32 doentes consecutivos, idade média 43±11 anos, 24 mulheres referenciados para ablação. O mapeamento da arritmia foi efetuado com o sistema CARTO RMT, orientado por controlo remoto. A ablação foi realizada com radiofrequência no local de ativação mais precoce com *pacemapping* de pelo menos 11/12. O sucesso foi definido como a supressão da arritmia e a sua não inducibilidade sob isoprenalina.
Após um seguimento mínimo de 3 meses avaliámos o sucesso clínico, definido como a ausência de sintomas e a supressão de arritmias no Holter, definido como < 50 extrassístoles ventriculares/24 h.
Resultados: Em 28 doentes, a arritmia originava-se na câmara de saída do ventrículo direito (88%), em 3 no esquerdo, e noutro no epicárdio. O sucesso agudo foi obtido em 26 doentes (81%). Dois doentes efetuaram um segundo procedimento com sucesso, um deles por abordagem epicárdica. O sucesso final, após 2 procedimentos em 2 doentes, foi de 88%. Não ocorreram complicações. Durante um período de seguimento de 307±204 d, ocorreram 2 recorrências.
Conclusões: O sistema de navegação magnética por controlo remoto mostrou-se eficaz e seguro para mapeamento e ablação de arritmias das câmaras de saída ventricular, permitindo um mapeamento preciso com uma elevada taxa de sucesso e sem complicações.

Abbreviations

EAS	earliest activation site
LVOT	left ventricular outflow tract
MNS	magnetic navigation system
PVCs	premature ventricular contractions
RF	radiofrequency
RVOT	right ventricular outflow tract
VT	ventricular tachycardia

Introduction

Ventricular tachycardia (VT) and idiopathic premature ventricular contractions (PVCs) of the right (RVOT) or left ventricular outflow tract (LVOT) are common, accounting for 10% of all ventricular arrhythmias.[1]

The focal nature of these arrhythmias makes ablation an effective treatment, with success rates between 81% and 100%.[2,3]

The standard technique to locate the origin of an arrhythmia is activation mapping during VT or PVCs, together with pacemapping of the earliest activation site (EAS).[3] However, manipulation of conventional catheters in the ventricular outflow tract is a lengthy and difficult process due to catheter stiffness, and is not without risk of perforation, which is reported in 1–5% of cases.[4,5]

Two remote navigation systems have recently been developed aimed at improving catheter manipulation and reducing radiation exposure – the Niobe II magnetic navigation system (MNS) (Stereotaxis)[6] and the Hansen robotic remote navigation system (Sensei).[7] Clinical experience with the latter for VT ablation is limited,[8] and while initial studies on the Niobe II MNS for VT/PVCs have been promising, they were mainly on small series, only 13 and eight patients respectively,[9,10] or case reports.[11] Other studies have included a larger number of patients but presented no follow-up data.[12,13]

The aim of this study was to assess the efficacy and potential complications of the MNS for ablation of VT/PVCs originating in the RVOT or LVOT, with a larger number of patients and longer follow-up.

Methods

Patient selection

Between July 2008 and June 2011, 32 consecutive patients underwent electrophysiological study in our institution, followed by ablation of symptomatic VT or PVCs of probable origin in the RVOT or LVOT.

No patient was contraindicated for magnetic navigation, and all gave their informed consent.

Electrophysiological study

Patients were assessed after six hours' fasting and without sedation. All antiarrhythmic medication was suspended at least five half-lives before the electrophysiological study; no patient was taking amiodarone.

Surface electrocardiograms and intracavitary electrograms were recorded on an AXIOM Sensis system (Siemens Systems). Programmed stimulation was performed using a UHS 3000 heart stimulator (Biotronik). The catheters were inserted via the femoral vein and positioned under fluoroscopic guidance in the His bundle and in the great cardiac vein via the coronary sinus. Isoprenaline infusion was titrated until induction of VT/PVCs. The protocol included ventricular stimulation in the apex and RVOT with a basic cycle of 600/500/400 ms and S4 until the refractory period was reached and continuous ventricular and atrial stimulation.

Magnetic navigation

All procedures were performed using an AXIOM Artis (Siemens) fluoroscopic imaging system.

The MNS has been previously described[6]; it basically consists of two computer-controlled magnets positioned on either side of the fluoroscopy table, which create a magnetic field (0.1 T). The position of the magnets is controlled from a console, the Navigant workstation, which orientates the magnetic field according to vectors selected by the operator. The ablation catheter has three magnets at its distal end, which orientate it parallel to the magnetic field. Changes in the orientation of the magnetic field deflect the catheter, which is advanced remotely by a motor at the proximal end of the catheter (Cardiodrive, Stereotaxis). Magnetic field vectors can be stored, enabling subsequent automatic navigation to previous sites.

Mapping and ablation

The MNS is integrated with a CARTO XP RMT (Biosense Webster) electroanatomical mapping system and receives real-time information on the position and orientation of the mapping catheter tip.

This information is overlaid on the fluoroscopic images on the Navigant workstation, providing real-time monitoring of the catheter position without the need for further fluoroscopy (Figure 1).

Mapping was performed during VT or in sinus rhythm for those with PVCs. A 4-mm Navistar RMT (Biosense Webster) catheter with three magnets at its tip was used until the Navistar RMT Thermocool (Biosense Webster) magnetic irrigated catheter became available, which was then used in all subsequent procedures. The ablation catheter was introduced via the femoral vein and advanced manually to the right atrium, and then remotely to the His bundle and the RVOT. The locations of the His bundle and the pulmonary valve were marked.

Detailed mapping of ventricular activation was performed in patients in sinus rhythm with PVCs and in those in VT.

Bipolar activation times were reviewed manually and activation maps were generated in automatic mode, the earliest isochrone being considered the EAS. Following isochronal reconstructions of the RVOT and LVOT, pacemapping was performed in multiple endocardial sites close to the EAS. Ventricular stimulation for pacemapping was performed with the same cycle as that of VT or with the coupling interval of the PVCs. Radiofrequency energy (RF) was applied at the EAS showing a QS pattern on the unipolar signal and pacemapping with 11/12 or 12/12 lead match. When mapping of the RVOT did not identify a site meeting these criteria, the LVOT was mapped by introducing the ablation catheter into the left ventricle using a retrograde approach via the femoral artery, with administration of intravenous heparin after arterial puncture.

Using an EP Shuttle RF generator (Stockert), RF was applied between the distal electrode of the ablation catheter and a cutaneous patch electrode for up to 120 s, with a power limit of 55 W and maximum temperature of 55 °C in the case of the 4-mm catheter, and power limit of 35 W and maximum temperature of 43 °C with the irrigated catheter. When this was ineffective, additional RF applications were performed at sites adjacent to the EAS with good pacemapping. Light sedation with midazolam (bolus) or remifentanil (perfusion) was administered during RF application when necessary.

Procedure and fluoroscopy times were recorded, as well as the number and duration of RF applications. Procedure time was defined as the interval between venous puncture and removal of the introducer.

Success was defined as suppression of PVCs or non-inducibility of VT following stimulation with isoprenaline up to 30 min after ablation.

All patients remained under surveillance in hospital for 24 hours after the procedure.

Follow-up

Follow-up consultations included clinical assessment and 24-h Holter monitoring in the first month, at three months and every six months thereafter.

Clinical success was defined as absence of symptoms and suppression of arrhythmias on Holter monitoring (<50 PVCs/24 h).

Statistical analysis

Data are presented as means ± standard deviation for continuous variables and as frequencies for discrete variables.

Results

Population

Thirty-two patients, mean age 43±11 years, 24 female, underwent ablation of VT or frequent PVCs.

Six had documented VT, while 26 presented frequent PVCs on 24-h Holter monitoring (minimum of 10 000/24 h) that were symptomatic and refractory to therapy. All patients underwent echocardiographic study, on which none presented left or right ventricular morphological changes. Four patients had hypertension. Sustained VT could not be induced in four of the six patients with documented VT, while well-tolerated VT, with cycles of 388 ms and 400 ms, was induced in two with isoprenaline perfusion.

Figure 1 Reference fluoroscopic images on the Navigant workstation in right and left anterior oblique views showing the position of the ablation catheter (blue star) in real time without need for further fluoroscopy; MNS automatic vector indicating the right ventricular outflow tract (yellow vector) and the His bundle (yellow dots).

Mapping and ablation

The RVOT was identified as the origin of the arrhythmia in 28 patients, septal in 20 and in the free wall in eight. The arrhythmia originated in the left ventricle in three patients, one in the right coronary cusp and two in the LVOT. Mapping of the right and left ventricles in one patient failed to identify a sufficiently early activation site, and an epicardial origin was assumed.

Mapping was performed during VT in two patients, and in sinus rhythm in those with PVCs. At the ablation site, the ventricular electrogram preceded the start of the QRS complex by at least 30 ms, with pacemapping of 11/12 or 12/12 leads.

In the three patients with left ventricular arrhythmias, coronary angiography was performed prior to ablation. Remote magnetic navigation was used to map the RVOT and LVOT in all procedures; a 4-mm catheter was used in the first three procedures and an irrigated catheter in the other 31.

During the first seconds of RF application at sites of successful ablation, VT runs of similar morphology to the clinical arrhythmia occurred, and when ablation during VT was performed, the arrhythmia was suppressed during application. Ablation was successful in 26 patients (81%), and was unsuccessful in six; in one patient the EAS was less than 5 mm from the right coronary ostium (Figure 2), and the origin of the arrhythmia was assumed to be epicardial in another.

Two patients underwent repeat procedures. A transpericardial approach was used in the patient with an epicardial focus; an irrigated ablation catheter was introduced into the pericardial space through a long sheath and epicardial mapping was performed using the MNS. The EAS was identified in the anterior side of the LVOT next to the anterior interventricular vein. The epicardial electrogram at the ablation site preceded the QRS complex by 42 ms with pacemapping of 12/12 leads; following coronary angiography, RF ablation at this site suppressed the EAS (Figure 3). The other patient, with the EAS in the RVOT, underwent successful repeat ablation 11 months after the first procedure. The overall success rate, after repeat procedures in two patients, was 88%. Mean procedure time was 208±79 min and mean fluoroscopy time was 10±7.8 min. An average of 9±7 applications per patient were performed, with a mean RF application time of 460±290 s.

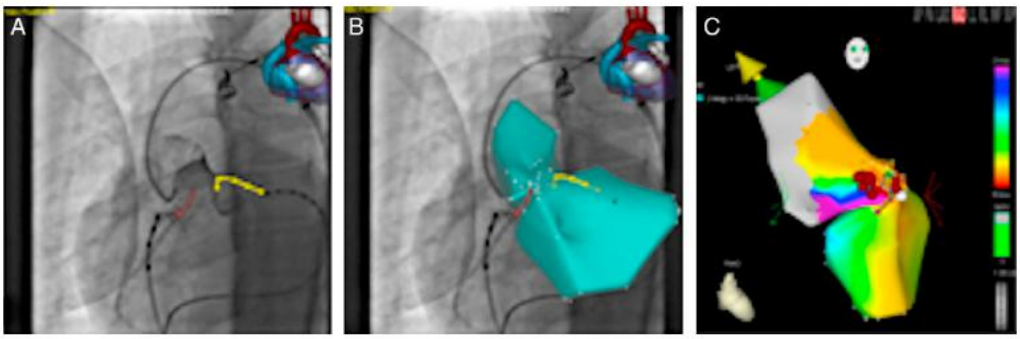

Figure 2 Reference fluoroscopic images on the Navigant workstation showing the coronary arteries (A) and left ventricular anatomy superimposed (B). Activation map showing earliest activation site (white dot) next to the right coronary artery ostium (C).

Follow-up

No complications related to remote mapping or ablation were observed. During a mean follow-up of 307±204 days, two patients presented recurrent PVCs on Holter monitoring, one of whom was asymptomatic and PVCs decreased from 24 000/24 h before ablation to 5000/24 h after ablation; the other reported symptoms but refused a repeat procedure.

Discussion

Conventional ablation catheters have to negotiate two curves to reach the RVOT, the first between the right atrium and the RVOT and the second between the inflow tract and the outflow tract, which makes manipulation difficult and hinders rapid and accurate mapping.

The Niobe II MNS enables the ablation catheter to negotiate various curves within the cardiac chambers, and the

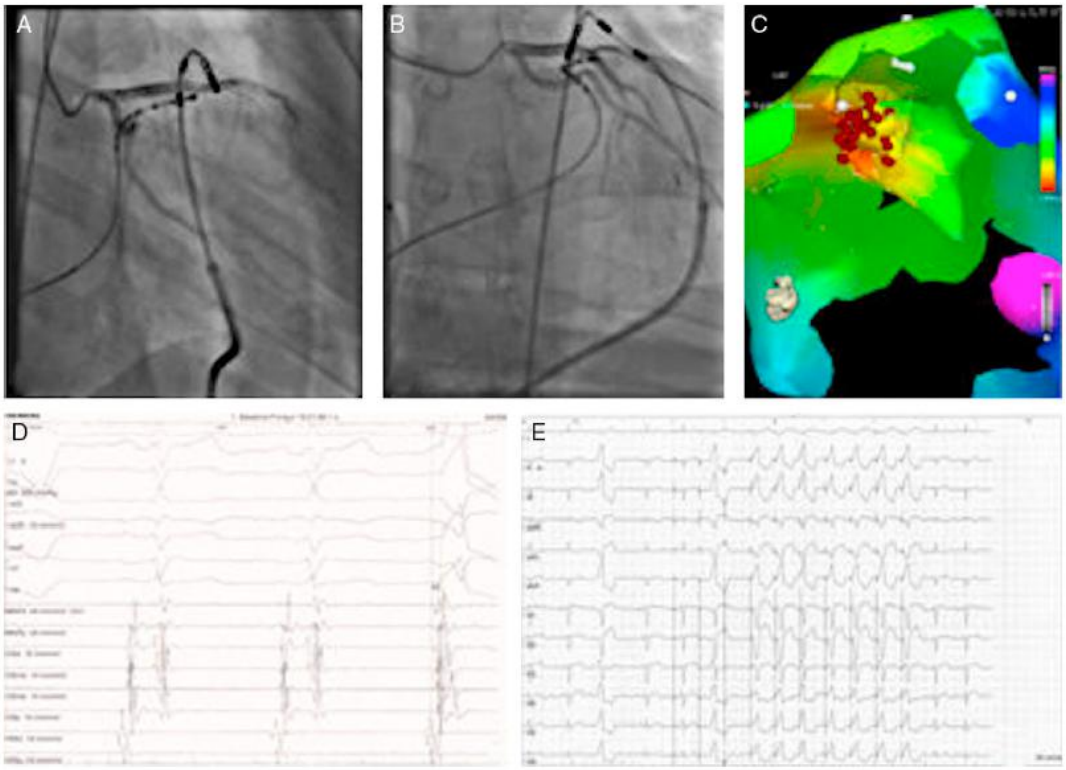

Figure 3 Epicardial ablation: catheter at the ablation site in right (A) and left (B) anterior oblique views. Activation map (C) showing earliest activation site in the anterior side of the left ventricular outflow tract next to the anterior interventricular vein (red dots). Electrogram and pacemapping with 12/12 lead match at the site of successful ablation (D and E).

tip can be steered in any direction, thus providing ease and precision of mapping unobtainable with conventional catheters.[14] With the MNS, the ablation catheter can easily be positioned at any site in the RVOT or LVOT without the need for long sheaths, enhancing catheter stability, as previously demonstrated.[15]

The options for automatic mapping (AutoMap) on the Navigant workstation, together with the possibility of returning to previously mapped sites using stored magnetic field vectors without fluoroscopic guidance, reduce overall fluoroscopy times. The mean fluoroscopy time with this method of 10±7.8 min is much shorter than in other studies with conventional ablation using three-dimensional mapping systems (45.9±17.9 min)[16] or multielectrode mapping catheters (49.7±26.3 min).[17] A study comparing conventional techniques and the MNS in ablation of various type of arrhythmia, including VT, showed significantly less fluoroscopy time with the MNS (30±20 vs. 35±25 min, $p<0.01$).[13] A previous study of VT ablation with the MNS reported shorter fluoroscopy time than in our series (7.5±4.3 min), but it did not include LVOT or epicardial ablation[9].

Manipulation of catheters in structures like the LVOT and RVOT carries a risk of perforation.[4,5] The flexibility of the MNS catheter, together with its soft tip, reduces the force applied to the endocardium compared to conventional catheters,[18] which may explain the absence of complications in this and other studies.[9–13]

Limitations

The present study was not randomized and included a small number of patients, and no comparison was made with conventional ablation in terms of procedure or fluoroscopy times or efficacy.

Conclusion

The remote control Niobe II system for mapping and ablation of arrhythmias originating in the ventricular outflow tracts was effective and safe in our patient group, with reduced fluoroscopy times and no complications.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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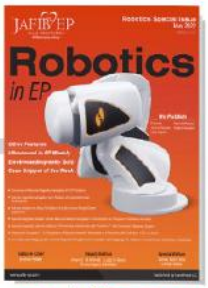

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Acute and Long-Term Results of Catheter Ablation of Outflow Tract Arrhythmias using Remote Magnetic Navigation with Catheter–Tissue Contact Feedback Technology: Comparison with Manual Ablation

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Abstract

Background and aim: Studies evaluating the results of remote magnetic navigation (RMN) using catheter–tissue contact feedback technology are scarce. The aim of this study was to compare the results of ablation of ventricular outflow tract arrhythmias with RMN using the catheter–tissue contact feedback technology with manual ablation with and without contact-force (CF) technology.

Methods: Retrospective study of patients that underwent ablation of ventricular outflow tract arrhythmias between May 2017 and December 2021 by the same operator in two hospitals. Patients were excluded in the presence of structural heart disease or previous ablation. Procedural data, success and complication rates and recurrence were compared.

Results: Total of 81 patients, 45 underwent ablation with RMN (RMN group), 18 with manual catheters without CF technology (Manual group) and 18 with CF catheters (CF group). The three groups did not differ in relation to baseline characteristics. Patients in the CF group had a higher frequency of arrhythmias originating from the LVOT. The procedure and radiofrequency times were not significantly different, the fluoroscopy time was significantly lower in the RMN group when comparing with Manual and CF groups, 3 (2-5.5) min vs 12 (5.7-17) vs 9.5 (4.9-14.4) min, p<0.0001. There was a direct correlation between fluoroscopy time and procedure time for manual ablation (R=0.480, p=0.003), but not for RMN (R=0.200, p=0.188). p<0.0001). Global success rate was 88% and complication rate was 1% which were not significantly different between groups. Median follow-up was 910 (485-1440) days, recurrence rate was not significantly different (Log-Rank=0.455)

Conclusions: RMN ablation of ventricular outflow tract arrhythmias using the catheter–tissue contact feedback technology demonstrated high success and low recurrence rates, with a significantly lower fluoroscopy time than manual or CF guided ablation. When ablation was performed with RMN there was no correlation between the length of the procedure and the fluoroscopy time.

Introduction

Ablation of premature ventricular contractions (PVCs) is an effective procedure and a class I indication in symptomatic patients with a high PVC burden[1]. The ventricular outflow tracts are the most frequent sites of origin of idiopathic arrhythmias. Not only the right ventricular outflow tract (RVOT) but as shown in a recent contemporary study, also the left ventricular outflow tract (LVOT) and especially the aortic cusps[2].

Remote magnetic navigation (RMN) presents as an excellent option when catheter manipulation should be smooth to prevent PVCs induced by the catheter, an event frequent at the level of the outflow tracts [3,4]. It is known for a long time that the tissue-catheter contact is important for lesion formation[5]. In recent years, the development of contact force (CF)-sensing catheters has promised an improvement in outcomes of manual catheter ablation of ventricular arrhythmias. One of the concerns regarding RNM is the unavailability of contact force

Key Words
Remote Magnetic Navigation; Premature Ventricular Contractions; Ventricular Outflow Tracts; Catheter Ablation; Catheter-Tissue Contact Feedback

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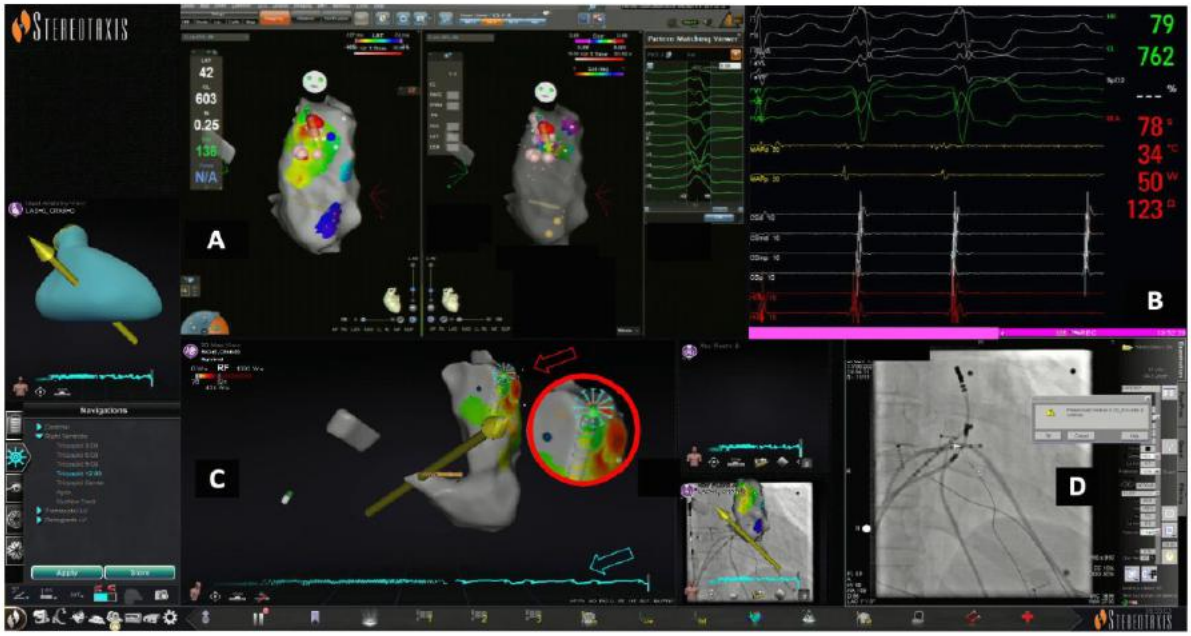

Figure 1: RMN workstation screen displaying simultaneously the different screens during the procedure.

Panel A: EAMshowing RF applications at the earliest activation site (red and pink dots), His tagged (yellow dots); Panel B intracardiac electrograms during ablation displaying the RF application parameters; Panel C: RMN screen showing the yellow arrow that remotely commands the direction of the ablation catheter. Good contact of the catheter tip showing an optimal starburst (red arrow) and a contact tracing displaying a solid line (blue arrow); Panel D Fluoroscopy screen with overlaid EAM. EAM: Electroanatomical map; RF: radiofrequency; RMN: remote magnetic navigation.

catheters, but this would go against the concept of RMN. This system is characterized by the high stability of the catheter tip, leading to a similar lesion size when compared to conventional ablation, although with less force applied to the tissue[6]. Contact feedback technology became available for RMN with the development of the e-Contact Module (ECM), which allows a semi-quantitative assessment of the catheter tip-to-tissue contact[7]. Studies comparing manual vs. RMN guided ablation after the advent of this technology are lacking. The aim of this study was to compare the results of RMN ablation of outflow tract arrhythmias using the catheter–tissue contact feedback technology against manual with and without CF catheters.

2. Material and methods

2.1. Patient population

This was a retrospective series of consecutive patients who underwent catheter ablation of idiopathic PVCs or ventricular tachycardia (VT) from the outflow tracts by the same operator, from May 2017 to December 2021. This study was performed in two hospitals, the procedures using RMN took place at the Luz Hospital Lisbon and the manual procedures at Setubal Hospital Center.

All patients underwent 12-lead ECG, transthoracic echocardiography and cardiac magnetic resonance with late gadolinium enhancement to exclude the presence of structural heart disease. Arrhythmogenic right ventricular cardiomyopathy (ARVC) was ruled out according to the Task Force Criteria[8]. Patients with evidence of structural heart disease and those that had undergone a previous ablation were excluded. A 24-hour Holter recording was performed before ablation and the number of PVCs per 24 hours and the presence of episodes of non-sustained ventricular tachycardia (NSVT), defined as >3 PVCs in a run were assessed.

2.2. Study design

Patients were divided in three groups whether ablation was performed with RMN (RMN group), manually with catheter without CF sensor (Manual group) or manually with a CF catheter (CF group). Baseline characteristics and procedural data were evaluated and compared between groups. Correlation between the procedure time and fluoroscopy time was assessed. Patients were followed and recurrence was registered, the recurrence-free survival curves were obtained and compared in the three groups. The influence of predictive variables related to the procedure on recurrence during follow-up was evaluated.

2.3. Electroanatomic Mapping and Ablation

Patients were studied in a fasting non sedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. In patients with VT, programmed ventricular stimulation was performed to induce VT and isoprenaline was administered when needed. During endocardial mapping of the LVOT heparin was administrated to achieve an ACT of 250-300 sec. In the RMN group the procedures were performed with the Niobe ES Magnetic Navigation System (Stereotaxis, Inc., Saint Louis, MO,

USA) and the CARTO 3 RMT (Biosense-Webster, Inc., Diamond Bar, CA, USA) system. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster Inc., Diamond Bar, CA, USA) was used with a 3.5-mm distal tip electrode and a 2–5–2 interelectrode distance (Figure 1).

Manual procedures were all performed with the EnSite Precision (Abbott, St Paul, MN, USA) system, using an irrigated tip FlexAbility (Abbott, St Paul, MN, USA) catheter with a 4-mm distal tip electrode and 1-4-1 interelectrode spacing in the first 18 patients (Figure 2) and a TactiCath catheter (Abbott, St Paul, MN, USA) with a 3.5-mm distal tip electrode and a 2–2–2 interelectrode distance in the last 18 patients (Figure 3). Mapping of the LVOT endocardium and the aortic coronary cusps was performed using a transaortic approach in all patients. When ablation was unsuccessful at the coronary cusps or the LVOT, the coronary sinus, the great cardiac vein and anterior interventricular vein were mapped. With the CARTO 3 RMT (Biosense-Webster, Inc.) system, local activation time (LAT) was defined as the time of the maximum downslope of the unipolar distal electrogram displayed on the corresponding bipolar signal. With the EnSite Precision system LAT was defined as the time of the first peak of the bipolar electrogram[9]. The ablation site was selected based on the earliest endocardial activation time in relation to the onset of the surface QRS, with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous PVCs. LAT at the ablation site was measured in relation to the beginning of the QRS on the surface ECG. In patients in whom the site of the origin of the PVCs was the LVOT or aortic coronary cusps, a coronary angiography was performed before ablation. Energy was delivered from an RF generator between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 sec, to a maximum temperature of 43° C and titrated according to the location of the PVCs, to a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. In the CF group a contact force above 30 g was avoided for all ablations. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. There were no differences between ablation strategies in the Manual, CF, or RMN ablation groups. Success was defined as non-induction of VT or abolition of PVCs until 30 min after ablation. The evaluated parameters were procedure time assessed as the interval between patient's entrance and exit of the room, fluoroscopy time, total radiofrequency time, site of origin of the arrhythmia, LAT at ablation site, acute success rate, and complications related to catheter manipulation or ablation, like steam pops, thrombus formation and stroke, perforation, tamponade, pericarditis, or lesions to adjacent structures. All intracardiac electrograms were reviewed by two senior electrophysiologists.

2.4. e-Contact Module

All RMN procedures were done with the ECM that provides a semi-quantitative evaluation of the catheter tip-to-tissue contact,and optimal contact was the goal throughout the procedure (Figure 1), This technology has already been well described by Noten et al[7] but basically, the ECM software algorithm analyses 3 categories of data to determine whether the catheter is in contact with cardiac tissue. These categories are electrical impedance measurements, cardiac-induced motion of the catheter tip, and the torque being applied by the magnetic field. The contact assessment is visualized to the user on the RMN screen as a starburst at the catheter tip (Figure 1 red arrow) and as a blue line on the contact tracing (Figure 1 blue arrow). When there is no contact the starburst is absent, with minimal contact the starburst is faint and has only few lines, and with optimal contact the starburst is bold and has multiple lines. Regarding the contact tracing, it shows a dotted line when the contact is suboptimal and a solid line when the contact is optimal.

2.5. Follow-up

The follow-up was performed at the office on the first month, at six months, at one year and yearly after that. Clinical assessment was carried out and at least one 24-hour Holter recording was performed between one month and six months after ablation and once a year

Table 1: Baseline characteristics and comparison between groups

	Overall sample (n=81)	RMN group (n=45)	Manual group (n=18)	Manual CF group (n=18)	P value
Demographic data					
Age in years, median (Q_1-Q_3)	50 (40-63)	50 (40-60)	48 (39-65)	60 (43-66)	0.199
Male Gender, n (%)	36 (44)	16 (36)	11 (61)	9 (50)	0.158
Risk factors, history, and medications					
Hypertension, n (%)	17 (21)	6 (13)	7 (39)	4 (22)	0.079
Diabetes, n (%)	5 (6)	1 (2)	1 (6)	3 (17)	0.098
Syncope or pre-syncope, n (%)	8 (10)	4 (9)	2 (11)	2 (11)	0.946
Duration of symptoms in months, median (Q_1-Q_3)	24 (12-30)	24 (12-25)	24 (12-36)	24 (12-42)	0.636
Family history of sudden death, n (%)	3 (4)	1 (2)	1 (6)	1 (6)	0.732
Betablockers, n (%)	56 (69)	31 (69)	15 (83)	10 (56)	0.196
Class I or III AA*	13 (16)	5 (11)	3 (17)	5 (28)	0.265
Standard 12 lead ECG					
PVC/VT	77/4	45/2	18/0	16/2	0.298
T wave inversion beyond V1, n (%)	5 (6)	3 (7)	1 (6)	1 (6)	0.979
PVC precordial transition					
V1 or V2, n (%)	11 (14)	5 (11)	1 (6)	5 (27)	0.116
V3, (n%)	18 (22)	11 (24)	4 (22)	3 (17)	0.799
Beyond V3, n (%)	52 (64)	29 (64)	13 (72)	10 (56)	0.580
24-Hour Holter Monitoring					
Number of PVCs, in nx100, median (Q_1-Q_3)	200 (140-272)	200 (140-247)	214 (156-305)	228 (133-334)	0.667
NSVT, n (%)	26 (32)	13 (29)	7 (39)	6 (33)	0.857
Echocardiogram					
LVEF in %, median (Q_1-Q_3)	58 (55-60)	58 (57-60)	57 (54-60)	57 (55-60)	0.497
LAD in mm, median (Q_1-Q_3)	35 (33-40)	35 (33-37)	37 (33-42)	36 (35-40)	0.222

*Except amiodarone; LAD: left atrium diameter; LVEF: left ventricular ejection fraction; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contractions; VT: ventricular tachycardia

Table 2: Procedural data and follow-up data

	Overall sample (n=81)	RMN Group (n=45)	Manual group (n=18)	Manual CF group (n=18)	P value
Procedure time in min, median (Q1-Q3)	138 (120-180)	140 (118-180)	159 (114-205)	120 (118-165)	0.680
Fluoroscopy time in min, median (Q1-Q3)	5 (2.5-10)	3 (2-5.5)	12 (5.7-17)	9.5 (4.9-14.4)	<0.0001
RF duration in sec, median (Q1-Q3)	300 (120-540)	300 (120-530)	400 (120-625)	330 (120-650)	0.796
Site of origin					
RVOT, n (%)	61 (75)	36 (80)	15 (83)	10 (56)	0.085
LVOT, n (%)	15 (19)	6 (13)	2 (11)	7 (39)	0.041
LV summit, n (%)	5 (6)	3 (7)	1 (6)	1 (6)	0.979
LAT at ablation site, median (Q1-Q3)	37 (30-45)	34 (24-43)	40 (35-45)	37 (27-47)	0.148
Overall acute success rate, n (%)	71 (88)	40 (89)	15 (83)	16 (89)	0.819
Acute success in the RVOT, n (%)	53 (87)	32 (89)	12 (80)	9 (90)	0.658
Acute success in the LVOT, n (%)	15 (100)	6 (100)	2 (100)	7 (100)	-
Acute success in the LV summit, n (%)	3 (60)	2 (67)	1 (100)	0 (0)	0.329
Complications, n (%)	1 (1)	0 (0)	0 (0)	1 (6)	0.170
Follow-up time in days, median (Q1-Q3)	910 (485-1440)	1095 (571-1569)	1229 (896-1669)	330 (82-650)	<0.0001
Recurrence*, n (%)	11 (16)	5 (13)	4 (27)	2 (13)	0.404

* After a successful procedure. CF: contact-force; LAT: local activation time; LVOT: left ventricular outflow tract; LV: left ventricle; RF: radiofrequency; RMN: remote magnetic navigation; RVOT: right ventricular outflow tract.

thereafter. For patients that were followed at another institution data were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone. Recurrence was defined as reappearance of symptoms or a 24-hour Holter with a PVC number higher than 1000 PVCs per 24 hours.

2.6. Statistical analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc, Chicago, Illinois). Data is presented as median and lower and upper quartile (Q1-Q3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Kruskal Wallis test for multiple samples. Categorical variables were compared with the use of the chi-squared test for independent samples. The correlation between the procedure time and the fluoroscopy time was performed with a Pearson correlation coefficient, R. Kaplan-Meier survival function was used to compare the recurrence-free survival in the three groups and the Log- rank test for comparison between groups. The influence of predictive variables on recurrence during follow-up was evaluated by Cox regression analysis. Univariate analysis was performed to select the variables to be included in the multivariate analysis. We included in the multivariate analysis those variables with a p-value ≤ 0.05 in the univariate analysis. Hazard ratios and their 95% confidence intervals were calculated. For all tests a p value <0.05 was considered as statistically significant.

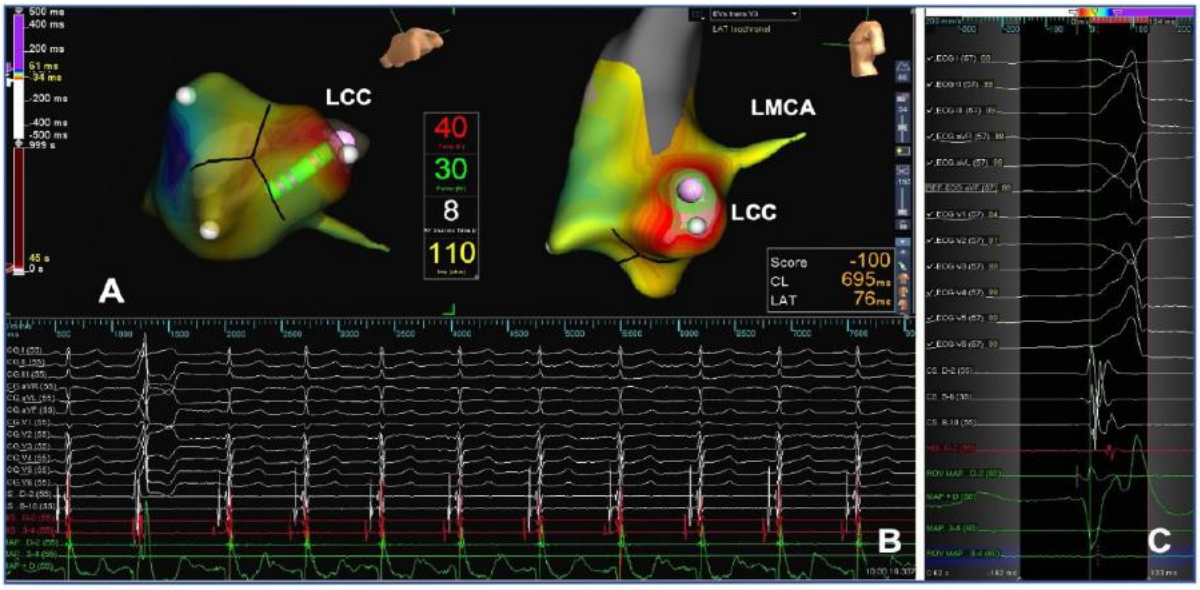

Figure 2: Example of a case of PVCs from the LCC performed manually with a catheter without CF technology.

Panel A: EAM showing the tip of the ablation catheter at the SOO; Panel B: PVCs disappear in the first seconds of RF application; Panel C: PVC morphology and intracardiac signals at ablation site. CF: contact force; EAM: electroanatomical map; LCC: left coronary cusp; LMCA: left main coronary artery; PVC: premature ventricular contractions; RF: radiofrequency; SOO: site of origin

Figure 3: Example of a case of PVCs from the LVOT performed manually with a CF-catheter.

Panel A: EAM showing the tip of the ablation catheter at the SOO; Panel B: PVCs disappear during RF application; Panel C: PVC morphology and intracardiac signals at ablation site. CF: contact force; DA: descending thoracic aorta; EAM: electroanatomical map; LCC: left coronary cusp; LMCA: left main coronary artery; PVC: premature ventricular contractions; RF: radiofrequency; SOO: site of origin

2.7. Ethics

All patients signed the informed consent form, and the study was approved by the Ethical Committee of both hospitals. The study is in compliance with the Helsinki Declaration.

3. Results

3.1. Patient population

We included 81 patients, median age 50 (40-63) years, 44% males. Baseline characteristics of the study patients as well as comparison between the groups are displayed in Table 1. All patients were symptomatic mostly with palpitations, the median duration of symptoms was 24 (12-30) months and 10% had a history of syncope or pre-syncope. Only four patients presented with sustained VT, the other seventy-seven had frequent PVCs with a median of 20,000 (14,000-27,200) of PVCs/24 hours prior to ablation. Five patients had T wave inversion beyond V1 but none with diagnostic criteria for ARVC, the transition of the PVC was at V3 or after V3 in 86% of patients. The median LVEF was 58% (55-60) and only four patients had LVEF below 45% that recovered after successful ablation. Patients in the three groups did not differ in relation to the analyzed parameters (Table 1).

3.2. Electroanatomical Mapping and ablation

3.2.1. Procedure Data

Procedure data is displayed in Table 2. The procedure time, RF duration, or precocity of the electrogram at the ablation site were not significantly different between groups. Regarding the site of origin of the PVCs, the LVOT was more frequently the site of origin of the arrhythmia in the CF group (39% vs 13% vs 11%, p=0.041), than in the RMN and Manual groups respectively, the RVOT and the LV summit were equally represented in the three groups. All patients with sustained VT had the origin of the arrhythmia in the RVOT. Fluoroscopy time was significantly lower in the RMN vs Manual and CF groups, respectively 3 (2-5.5) min, 12 (5.7-17) min and 9.5 (4.9-14.4) min, p<0.0001. The overall acute success rate of 88% was not significantly different among groups. The site of origin of the PVCs was not associated with differences in the success of the procedure. One patient in the CF group developed a pericardial effusion that prolonged the hospital stay for another 48 hours and responded to pharmacological management.

Table 3: Cox regression analysis with crude and adjusted hazard ratios (HR) of recurrence for the evaluated procedure variables

Variables	Unadjusted		Adjusted†	
	HR (95% CI)	P value	HR (95% CI)	P value
Procedure with RMN	0.552 (0.168-1.804)	0.327		
Procedure with CF	0.972 (0.208-4.54)	0.971		
Procedure time	1.015 (1.004-1.026)	0.007	1.013 (1.00-1.025)	0.049
Radiofrequency time	1.001 (0.999-1.003)	0.251	-	
Fluoroscopy time	1.057 (0.985-1.135)	0.122	-	
LAT at SOO	1.019 (0.971-1.068)	0.452	-	
RVOT site	0.768 (0.203-2.902)	0.697		
LVOT site	0.414 (0.053-3.236)	0.401		
LV summit site	7.604 (1.599-36.17)	0.011	2.283 (0.356-14.64)	0.384

† HR adjusted to procedure time and summit site . CF: contact-force; LAT: local activation time; LVOT: left ventricular outflow tract; LV: left ventricle; RMN: remote magnetic navigation: SOO: site of origin.

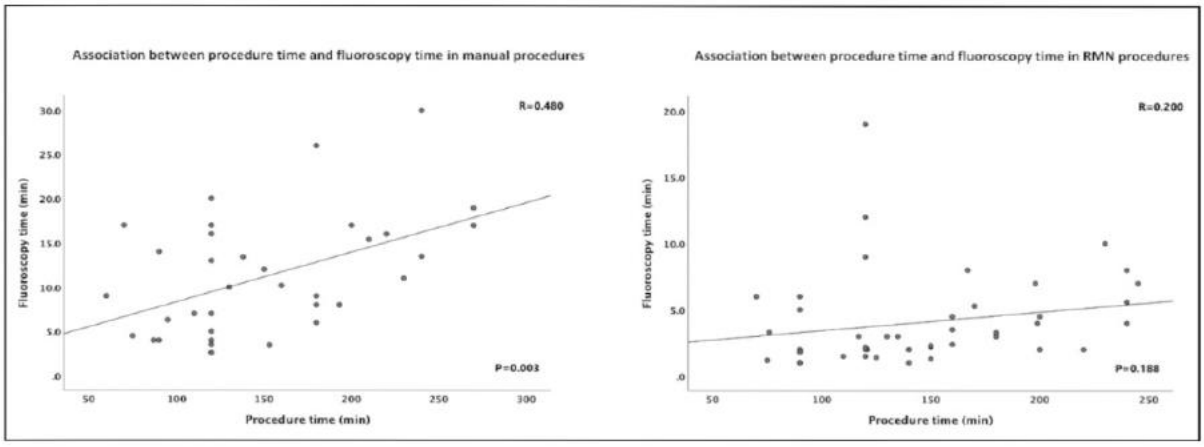

Figure 4: Correlation between procedure time and fluoroscopy time during manual and RMN procedures

3.2.2. Correlation between procedure time and fluoroscopy time

The fluoroscopy time was positively correlated with the procedure time in the overall sample increasing with the latter (R=318; p=0.004). However, although this was also true for the manual group in whom the correlation was stronger (R =0.480; p=0.003) in the RMN group there was no correlation (Figure 4).

3.3. Follow-up

The median follow-up time in the overall study population was 910 (485-1440) days, minimal 31 days, and maximal 1775 days. No patients were lost to follow-up. The follow-up was significantly shorter for the CF group. During this time eleven patients (16%) had recurrence of the PVCs, four within the first 24 hours, two in the RMN group and one patient in the other two groups. The survival free from recurrence Kaplan-Meier curves for the three groups are displayed in Figure 5. The recurrence rate was not significantly different (log-rank =0.455). The first Holter performed after ablation in patients that underwent a successful procedure and did not present recurrence of symptoms, showed a median of 10 (0-100) PVCs /24 hours.

3.4. Predictors of recurrence

The influence of the analyzed variables on recurrence during follow-up were tested with Cox regression analysis. The HR (95% CI) are displayed in Table 3. The use of RMN or the use of CF was not associated with recurrence when compared to manual non-contact catheters. Both the length of the procedure and the location at the LV summit were associated with a higher recurrence rate, but only the former was independently associated, with an adjusted HR (95% CI) of 1.013 (1.000-1.025), p=0.049.

4. Discussion

The stability of the magnetic catheters used in RMN enables lesion formation with less dependency on CF than with conventional catheters[6]. However, there were some concerns regarding the lack of a contact indicator for RMN, especially after the development of CF technology for manual ablation.

Theoretically CF technology by continuously monitoring the contact force between the catheter tip and the tissues, aims at improving efficacy by an increase of the lesion size which is proportional to the force applied[10,11], and at the same time decreasing complications resultant from excessive force applied to the heart. Nonetheless, studies comparing manual ablation with and without CF have shown contradictory results[12-14].

Many previous studies have demonstrated the efficacy of RMN in the ablation of all types of arrhythmias with a better safety profile than conventional ablation[15-19]. Since ECM is now available for RMN it is important to assess its efficacy. This new feature has proved to increase the performance of RMN for ablation of atrial fibrillation leading to a significant reduction in the duration of the RF application that resulted in a shorter duration of the procedure[20]. Also, in the ablation of ischemic ventricular tachycardia has demonstrated higher long-term efficacy and lower fluoroscopy use[18]. However, to the best of our knowledge this is the first study comparing the acute and long-term results of manual versus RMN ablation of PVCs from the outflow tracts, using the novel catheter–tissue contact feedback technology.

Previous studies comparing RMN with manual ablation with and without CF catheters, have already reported no differences in the success rate or the procedure time[21,22]. Our results are similar although with longer procedure times than the ones reported by Shauer et al[22] respectively, 140 (118-180) min for RMN group, 159 (114-205) min for Manual group and 120 (118-165) min for CF group versus 113+ 53 min for RMN and 115 + 69 min for manual ablation which is probably due to the different definitions of procedure duration in that study. As previously reported our study also showed a significant shorter fluoroscopy duration in the RMN group. What is remarkable is the magnitude of the difference in our study in comparison with the studies

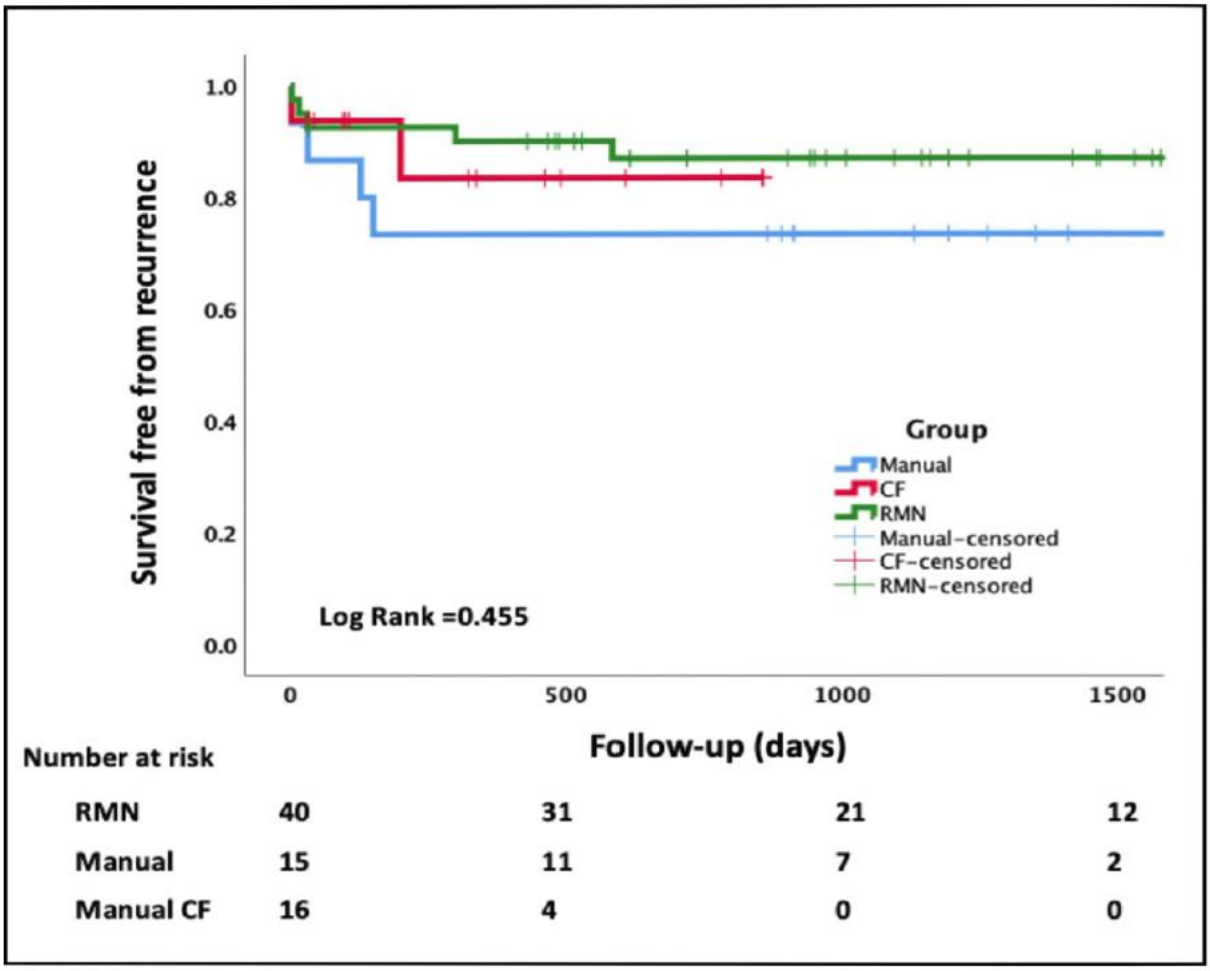

Figure 5: Kaplan-Meier survival estimate of recurrence after a successful ablation in the three groups

CF: contact-force; RMN: remote magnetic navigation

by Vries et al[21], Shauer et al[22], and with our own previous data[4], which is probably due to the use of ECM technology. A major finding not reported previously, is the absence of correlation between the duration of the procedure and the fluoroscopy time in the RMN group as opposed to the manual procedures where we found a direct correlation. The fact that the dose of radiation remains low independently of the length of the procedure, is particularly important for very long procedures where the use of RMN may lead to an even lower amount of radiation exposure to the patient.

The success rate was not significantly different between groups as previously reported[21,22]. Nevertheless, the success rate with RMN reported in this study was higher than previously reported by our group (89% versus 81%) [4], or the 80% success rate reported by Shauer et al[22], using a previous version of the system without ECM. RMN is associated with a better safety profile than conventional ablation[23] and the development of CF technology has not been able to revert this trend[19].

The recurrence rate with RMN using ECM technology is low, half the recurrence rate of manual ablation although not reaching statistical significance and lower than previously reported with a similar follow-up time[21], which may be due to more durable lesions obtained with this technology. The only independent predictor of recurrence was the procedure time. Long procedures usually mean difficult cases, mostly related to one of the following, difficulty on finding the site of origin of the arrhythmia due to infrequent PVCs, inaccessible sites, inability to achieve durable lesions due to intramural focus or a combination of all. So, it is not surprising that the longer the procedure the higher the possibility of recurrence.

5. Limitations

There are some potential limitations of the present study. Firstly, there was no randomization, resulting in unbalanced numbers of PVCs from the LVOT in the different groups, however the success of the procedure for PVCs from this location was not different between groups, nor was it associated to recurrence. The follow-up time was significantly shorter for the CF group, but looking at survival curves, had the follow-up time been the same the results would have been at most similar but never better. Secondly, it was a retrospective study with a relatively small number of patients making it insufficient to interpret similar results as non-significant. However, taking into consideration that the success rates for RMN and CF were the same, it is difficult to accept that a bigger sample would show different results. As for the recurrence rate, we may speculate that with a bigger sample and a longer follow-up the recurrence rate might have been lower for the RMN group.

6. Conclusions

In this group of patients RMN ablation of outflow tract ventricular arrhythmias using the ECM technology demonstrated a high success and low recurrence rate with significantly lower fluoroscopy times than manual or CF guided ablation. The fluoroscopy time was not correlated with the length of the procedure when performed with RMN, which is particularly important for prolonged procedures.

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ARRHYTHMIA ROUNDS

Slow pathway region as the exit site of parahisian premature ventricular contractions: Why choose safety over the earliest activation?

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1 | INTRODUCTION

Approximately 10% of idiopathic right ventricle (RV) arrhythmias arise at sites other than the RV outflow tract (OT).[1] Ventricular arrhythmias (VAs) arising from the RV septum near the His bundle (parahisian) can be successfully ablated in approximately 70% to 90% of patients,[2] but radiofrequency (RF) application at the His-bundle region has the potential risk for atrioventricular (AV) conduction disturbance. Moreover, in the presence of a baseline left bundle branch block (LBBB) in sinus rhythm, the potential injury to the conduction system must be balanced against the benefit of successful ablation. Recently, the electrocardiographic (ECG), anatomical, and electrophysiological characteristics of VAs successfully ablated from the slow pathway region (SPR) were described, suggesting this region could be the origin of 20% of parahisian VAs.[3]

2 | CASE REPORT

A 69-year-old woman was referred to our institution due to recurrent palpitations at rest. She described the sensation as the heart skipping a beat. The episodes were not worsened with exercise or emotional stress and other symptoms were denied. Her past history was unremarkable, except for hypertension and dyslipidemia, controlled with ramipril 1.25 mg and simvastatin 20 mg, respectively. She has no family history of cardiac disease or sudden cardiac death. She had occasional extrasystoles on cardiac auscultation, but her examination was otherwise normal. Her 12-lead ECG showed an LBBB in sinus rhythm and PVCs with a QRS duration of 130 ms, LBBB morphology (transition in V3), inferior lead discordance (positive lead II and negative lead III), R wave in lead I and aVL and QS in aVR (Figure 1A). Transthoracic echocardiogram (TEE) and myocardial perfusion single-photon emission computed tomography (SPECT) were normal and 24-hour Holter revealed 22511 PVCs/24 h (1023 PVCs/h).

At this time, treatment options were discussed with the patient and beta-blockers and propafenone were tried but they were not effective. After 1 year, the patient repeated TEE and it was noted a mild enlarged LV with mildly depressed ejection fraction (48%). A cardiovascular magnetic resonance (CMR) imaging confirmed these abnormalities but it was otherwise normal with no late gadolinium enhancement. Arrhythmia-induced cardiomyopathy was assumed. After written informed consent was obtained, the patient underwent an electrophysiological study and catheter ablation.

During the study and when the catheter was in the right ventricle (RV) the patient had a transitory complete heart block (CHB), immediately treated with ventricular pacing. During mapping, atrial fibrillation (AF) was induced. Activation mapping was performed in AF with the electroanatomical mapping (EnSite Precision system; Abbott). The earliest activation was identified in the tricuspid annulus adjacent to the His bundle (Figure 2A). The local electrogram preceded the onset of the QRS by 42 ms (Figure 2B) and displayed small-amplitude His potentials (Figure 2C). Due to the high risk of permanent CHB, other sites were explored. By moving down the catheter to the septal portion of the tricuspid valvular RV region (right midseptum), corresponding to the SPR (Figure 3A), PVC activation preceded QRS onset by 30 ms (Figure 3B) and no His potential was found (Figure 3C).

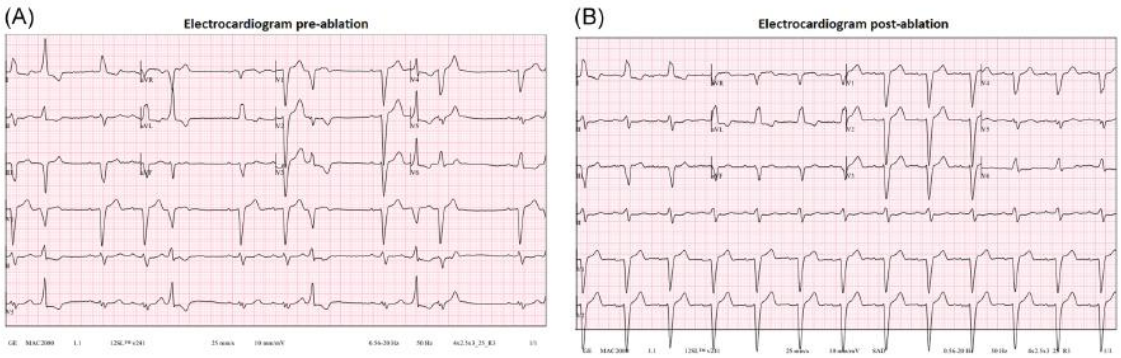

FIGURE 1 Electrocardiogram (A) preablation and (B) postablation

Radiofrequency catheter ablation (RFCA) was carefully performed with an irrigated-tip catheter (35 W) in this local during 60 seconds (Figure 3D), scrutinizing for the occurrence of junctional rhythm. The PVCs were abolished 2 seconds after the RF delivery. After 1 month of follow-up, the patient remains asymptomatic and no PVCs were detected on ECG (Figure 1B). Twenty-four-hour Holter recording detected 134 multiform PVCs/24 h.

3 | DISCUSSION

In patients presenting with frequent PVCs 12-lead ECG is essential to visualize PVC's morphology, but also to look carefully for the QRS/ST-segment in sinus rhythm since it can raise the suspicion of cardiomyopathy. This patient had an LBBB in sinus rhythm, which may be a sign of structural heart disease. However, TEE and myocardial perfusion SPECT were normal at presentation and CMR (performed during the follow-up) was normal apart from LV dilatation and mild systolic dysfunction (related to arrhythmia-induced cardiomyopathy).

PVCs had an LBBB morphology, R wave in DI and aVL and inferior discordance, which meets the proposed criteria for parahisian RV VAs[4,5] but also corresponds to the described ECG characteristics for SPR VAs.[3] According to Enrique et al,[6] the presence of a positive QRS in lead II with negative QRS in III is associated with particular RV anatomical locations, namely, the parahisian region in the majority of patients. Lian-Pin et al[7] proposed

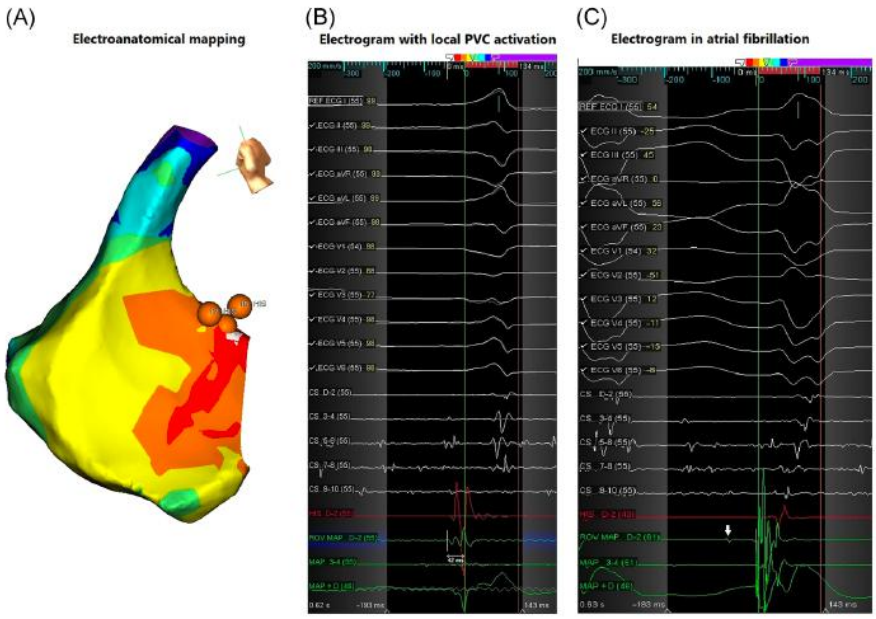

FIGURE 2 Electroanatomical mapping (A) and recording electrogram at the site with earliest ventricular activation with local PVC activation preceding QRS onset by 42 ms (B) and during atrial fibrillation demonstrating a His potential (arrow) (C)

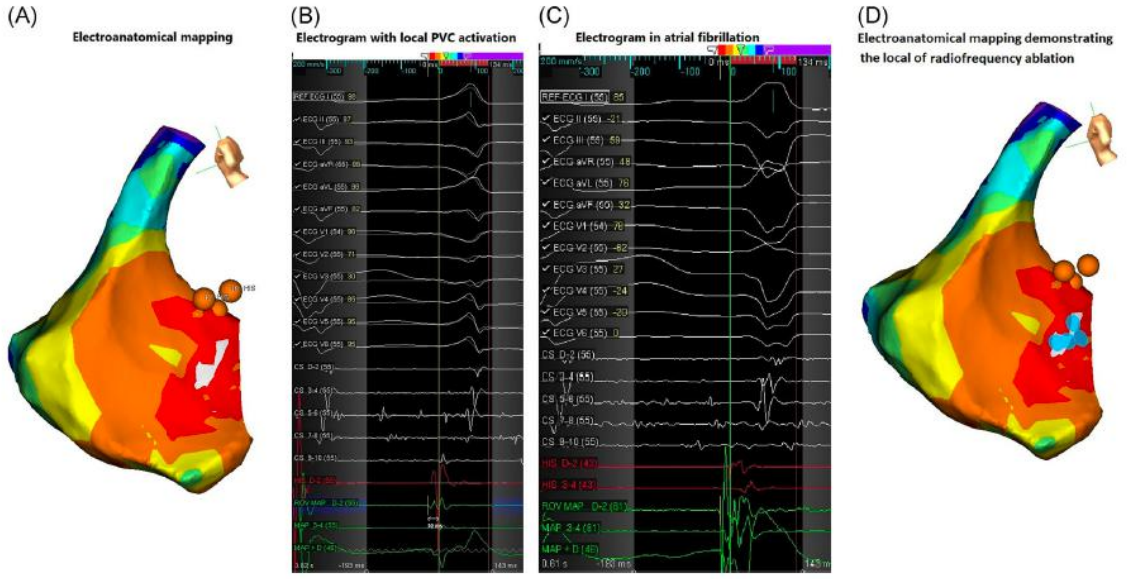

FIGURE 3 Electroanatomical mapping (A) and recording electrogram at the site where local PVC activation precedes QRS onset by 30 ms (B) but no His potential is detected during atrial fibrillation rhythm (C). Electroanatomical mapping demonstrating the local where radiofrequency ablation was delivered (D)

that the earlier precordial R-wave transition (<V4) is more common in PVCs arising from the tricuspid valvular septum than the basal RV septum because the origin of VAs in the former was located in the more posterior portion of the RV. Finally, Briceño et al[3] described exactly the same electrocardiographic characteristics we found in SPR VAs. However, VAs originating near the His bundle, including those arising from the aortic sinuses,[8] have similar ECG characteristics and the exact origin is not easily determined only by analyzing QRS morphology in the ECG.

Several series reported a higher likelihood of abandoning attempts at ablation of parahisian PVCs due to the possibility of inducing AV block.[4,6,7] In this particular patient, LBBB in sinus rhythm increases this concern. In a recent published study, among patients with LBBB pattern who performed left septal mapping, complete conduction block within the proximal left conduction system was observed in 64%.[9] Since right bundle branch lesion can occur during RF application, persistent CHB can be caused by His Bundle or by right bundle damage. In fact, the permanent right bundle branch block (RBBB) has been previously described during RF application in the distal His bundle for the ablation of parahisian PVCs.[10,11] Due to the anticipated challenges in RFCA, the first attempt with drugs was proposed to the patient. However, beta-blockers and propafenone were ineffective, which had been also frequent in SPR VAs.[3] Mild LV enlargement and dysfunction occurred, imposing the need to proceed with RFCA.[2] The occurrence of a transitory CHB during mapping was probably caused by a transitory RBBB while manipulating the catheters in the RV.[12] Although it was reversible and immediately treated with ventricular pacing, it raised further concerns about the possibility of permanent damage to the conduction system.

Electroanatomical mapping showed the earliest activation in the tricuspid annulus near the His bundle (local activation −42 ms before the onset of the QRS) with small-amplitude His potentials at this side. All the spots with a His recording were tagged on the electroanatomic map, creating a His cloud to avoid it. Due to the potential of CHB when applying RF energy in this zone, other sites were explored. Mapping in detail all the neighboring structures before any attempt of delivering ablation is of paramount importance. Even if activation is worse than that recorded in the His catheter, ablation may be safer and still capable of eliminating the arrhythmia.[4] Targets for RF delivery include earliest local bipolar activation preceding the QRS and the presence of a QS pattern in the unipolar electrogram of the ablation catheter. The "second" earliest activation was localized in the septal portion of the tricuspid annulus RV region (right midseptum), in a region recently described as corresponding to the SPR[3]: here, the local PVC activation preceded QRS onset by 30 ms but with no His potentials recorded and a QS pattern was present in the unipolar electrogram. A distance of at least 5 mm away from the site recording the largest His potential is desired.[10] Since this "second" site was more than 10 mm away from the His cloud, RF application was considered to be safe. Catheter stability was considered appropriate so RF energy application was initiated in this local, resulting in the abolishment of PVCs in the first seconds. RF delivering was continued for an additional 60 seconds, without causing CHB or accelerated junctional rhythm. Some authors proposed a stepwise incremental of RF energy when RF is delivered in the right parahisian region, starting with a low initial power (20 W), and if VT/PVC suppression is noted without evidence of CHB, the energy is gradually increased to a maximum power of 50 W.[3,4,10,13]

However, since this "second" earliest activation site is considered to be far enough of the His cloud, stepwise incremental power changes were not felt to be necessary. If the optimal ablation site contains a visible His electrogram and no other alternative site was found, the careful use of cryoablation could also have been an option to prevent damage to the conduction system, but with a lower success rate.[14]

PVCs described in our case had the same electrocardiographic, anatomical, and electrophysiological characteristics of VAs that were successfully ablated from the SPR.[3] In fact, VAs targeted from the SPR had been described previously,[1] but only one in 29 patients with idiopathic RV arrhythmias not arising from the OT had a similar anatomical side of origin (a septal portion of the tricuspid valve annulus superiorly). Recently, it has been demonstrated SPR can be the origin of 20% of parahisian VAs,[3] suggesting that it can occur in approximately 1% to 3% of all RV VAs. In the present case, we demonstrated that the earliest activation was present near the His bundle, suggesting the SPR could be the exit site of the VA. Indeed, in only 25% of patients with the earliest activation in SPR a perfect pace map matched the clinical PVC, probably due to the proximity to the conduction system and possible intramural component.[3] In our case, probably PVCs originated intramurally nearer the His bundle and SPR was the exit site. Unfortunately, no diastolic potentials before and/or after the ablation were identified to clarify the arrhythmogenic mechanism of these frequent PVCs.

4 | CONCLUSION

Successful RF ablation of parahisian PVCs can be safely achieved if adequate caution is taken, including in patients with baseline impairment of the conduction system. Even if the precocity of the local activation is worse than the one recorded in the His bundle region, ablation may be still capable of eliminating the arrhythmia and is definitely safer. SPR as the origin or the exit side of VAs are being increasingly recognized.

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Navegação Magnética por Controle Remoto na Ablação de Arritmias Cardíacas

Leonor Parreira, Pedro Adragão

Introdução

A robotização em Medicina surge com o objetivo de melhorar a precisão de uma determinada técnica permitindo efetuar procedimentos inacessíveis com a mão humana e por outro lado contribuir para uma maior comodidade por parte do operador. A robotização tem vindo a demonstrar um enorme sucesso em várias áreas, nomeadamente no campo cirúrgico, permitindo levar a cabo cirurgias mais complicadas e precisas do que as efectuadas manualmente e contribuindo para o desenvolvimento de técnicas cirúrgicas ditas mini-invasivas.

Os procedimentos de intervenção em Cardiologia sobretudo na área da Electrofisiologia são por vezes muito prolongados, efetuados sob fluoroscopia exigindo por parte dos operadores um esforço marcado e obrigando-os a exposição a largas doses de radiação. O desenvolvimento de sistemas de navegação robótica por controlo remoto permitem a realização do procedimento a partir de uma sala de comandos fora do alcance da radiação, tornando fisicamente menos exigentes os procedimentos mais complicados e prolongados, visando uma maior precisão, maior segurança e conforto para o operador e maior segurança para o paciente. Vários sistemas de navegação remota tem sido desenvolvidos na última década. Basicamente estes sistemas dividem-se em dois grupos, os sistemas que permitem manipular à distância os cateteres convencionais por meio de um braço robótico e os sistemas que utilizam cateteres magnéticos dedicados, manipulados através da aplicação de um campo magnético. No primeiro grupo incluem-se o sistema Sensei Robotic Navigation System (Hansen Medical Inc., Mountain View, CA,USA) e o sistema AMIGO Remote Catheter System (Catheter Robotics Inc., Mount Olive, NJ, USA), ambos os sistemas têm em comum o facto de poderem utilizar qualquer tipo de cateter de ablação ou mapeamento e serem compatíveis com todos os sistemas de mapeamento. O controle dos movimentos dos cateteres é efetuado a partir de um braço robótico instalado na mesa do doente ligado a uma bainha deflectível no caso do Sistema Sensei ou ligado diretamente ao cateter no caso do sistema AMIGO. Ao contrário do sistema de navegação magnética estes dois sistemas utilizam cateteres rígidos em que a manipulação embora efectuada remotamente é baseada na manipulação convencional e por este motivo apenas podem responder pelos dois primeiros requisitos, melhoria da performance do cateter, maior comodidade e segurança para o operador, mas pelo facto de funcionarem com cateteres rígidos estão associados a um maior risco de complicações. Com efeito o número de doentes tratados com esta técnica é muito inferior ao número tratado com o sistema de navegação magnética e a incidência de tamponamentos e de fistula esofágica tem sido superior com este sistema.

No segundo grupo incluem-se o sistema Niobe Magnetic Navigation System (Stereotaxis Inc., St Louis, MO, USA) e o Catheter Guidance Control and Imaging (Magnetecs Corp., Inglewood, CA, USA). Os sistemas de navegação magnética dada a flexibilidade e suavidade dos cateteres utilizados estão associados a um menor risco de complicações. O sistema da Magnetecs foi apenas recentemente disponibilizado para o uso clínico e os estudos utilizando este sistema têm ainda um número reduzido de doentes. Pelo contrário o sistema Niobe da Stereotaxis foi o primeiro a ser desenvolvido e disponibilizado para uso clínico com uma experiência de mais de dez anos [1,2] e será o tema deste capítulo.

Sistema de Navegação Magnética por controle remoto

O sistema Niobe® Magnetic Navigation System (SNM) encontra-se perfeitamente estabelecido, a funcionar em cerca de 180 centros de electrofisiologia em todo o mundo. Lançado em 2003 e com os primeiros casos publicados em 2004, conta atualmente com mais de 80.000 procedimentos efetuados. O sistema tem sofrido

várias alterações a nível de hardware e software ao longo do tempo encontrando-se agora disponível a quarta geração do sistema, a versão Niobe EPOCH.
Tem sido usado em todos os tipos de procedimentos incluindo a ablação de taquicardias supraventriculares, fibrilhação auricular, taquicardia ventricular e mais recentemente tem demonstrado também a sua eficácia na ablação epicárdica.

Conceito e Descrição

O sistema consiste em 2 grandes magnetos, posicionados em ambos os lados da mesa de fluoroscopia e controlados por computador (Figura 1). Estes magnetos originam um campo magnético (0.1T), este campo magnético é muito fraco comparativamente ao utilizado na RMN diagnostica permitindo a sua utilização em doentes portadores de dispositivos implantáveis nomeadamente pacemakers e cardioversores-desfibrihadores implantáveis. A direcção do campo magnético varia com a posição relativa de ambos os magnetos na mesa de doente que por sua vez é controlada por uma consola, a estação de trabalho (Navigant; Stereotaxis Inc.), que origina as variações na orientação do campo magnético de acordo com os vetores escolhidos pelo operador (Figura 2).
Os cateteres de ablação utilizados com este sistema, ao contrário dos cateteres rígidos convencionais são extremamente flexíveis (Figura 3), possuem na ponta 3 pequenos magnetos que se vão alinhar paralelamente com o campo magnético criado. As alterações na orientação do campo magnético levam à deflexão da ponta do cateter que por sua vez é avançado ou recuado remotamente com o auxílio de um motor ligado à extremidade proximal do cateter, o Cardiodrive (Stereotaxis Inc) (Figura 1). O avanço ou retracção do cateter pode ser efectuado por intermédio de um joystick ou com as teclas (↓↑) da estação de trabalho Navigant permitindo a escolha da amplitude do movimento entre 1 e 9 mm.
A navegação do cateter pode ser feita de forma manual através da variação da direção dos vectores por intermédio do rato da estação de trabalho ou a navegação pode ser efectuada sem necessidade de controle manual, em modo totalmente automática para zonas pré-definidas como o His ou a camara de saída do ventrículo direito ou pode mapear uma camara em modo automático como por exemplo a aurícula esquerda e veias pulmonares e efectuar ablação linear automaticamente sobre linhas previamente determinadas como por exemplo linhas de ablação para isolamento das veias pulmonares. O vetor relativo a cada campo magnético pode ser guardado permitindo posteriormente navegar o cateter para locais prévios de forma automática.
A aplicação de um campo magnético constante durante a aplicação de radiofrequência assegura a estabilidade do cateter e o contacto entre a ponta do cateter e o tecido. O sistema funciona associado a um sistema de fluoroscopia Siemens com uma interface com o sistema CARTO 3® utilizando cateteres dedicados para navegação magnética comercializados pela Biosense Webster inicialmente apenas não irrigados (Celsius® RMT 4 mm e 8 mm) e desde 2008 também cateteres irrigados (NaviStar® RMT ThermoCool Catheter).
Os cateteres são manipulados na sala de comandos onde toda a informação incluindo os electrogramas intracavitários a monitorização electrocardiográfica, a fluoroscopia, o mapeamento electroanatómico, a ecografia intracardíaca e o ecrã da Stereotaxis é exibida num só ecrã gigante o Odyssey Vision™ System que permite a integração de toda a informação num só monitor. Com o novo sistema Carto 3 é possível visualizar todos os cateteres em tempo real e é possível sobrepor o mapa electroanatómico no ecrã da fluoroscopia para uma maior segurança (Figura 4)
Em 2015 é aprovado o sistema Vdrive® de manipulação remota de cateteres convencionais nomeadamente o cateter circular LASSO ® evitando que o operador tenha que se re- esterilizar para reposicionar os cateteres podendo fazê-lo remotamente a partir da sala de comandos. (Figura 1 e 5)
Uma das principais críticas feitas ao SNM resultava da demora resultante da manipulação indirecta dos cateteres por intermédio da mudança do campo magnético. Com a nova geração EPOCH a velocidade de alteração dos campos magnéticos reduziu-se substancialmente e o movimento do cateter é praticamente simultâneo com a mudança do vector. Um estudo recente efectuado pelo grupo de Da Costa et al [3] que comparou 92 doentes submetidos a ablação de FA com o sistema Niobe II (terceira geração) com 92 doentes submetidos a ablação com o novo sistema EPOCH (quarta geração) e concluíram que o sistema novo permitiu reduzir significativamente o tempo de procedimento (2.7 vs 1.9 horas $p<0.0001$) e o tempo de fluoroscopia (15 ± 7 vs 12 ± 4 vs $p= 0.001$).
Mais recentemente foi também desenvolvido um novo módulo de iteração (e-Contact™ module), que permite aferir o grau de contacto da ponta do cateter com os tecidos baseado em informação sobre a impedância bipolar embora não o faça de forma quantitativa, mas apenas qualitativa (Figura 6).

Vantagens

Pelo facto de a navegação do cateter ser efectuada de forma remota uma das principais vantagens do SNM é a comodidade e a redução da dose de radiação para o operador tornando o sistema ideal para procedimentos prolongados. Além disso devido à enorme flexibilidade do cateter e à sua estabilidade existe uma tendência para utilizar menos fluoroscopia de controle o que resulta em menor dose de radiação para o paciente também. A grande manobrabilidade do cateter de ablação o qual tem a capacidade de efectuar várias curvas em sentidos opostos, aliada à grande segurança resultante da sua flexibilidade, torna o SNM o sistema de eleição para ablação em doentes com cardiopatias congénitas ou anatomias complexas (Figura 7), ou substratos difíceis como as taquicardias ventriculares[4].
Outra vantagem do SNM é a menor taxa de complicações descrita, que poderá ser devida a uma menor força aplicada aos tecidos pela ponta do cateter. Fadis et al demonstrou que a máxima força aplicada aos tecidos com o sistema da Stereotaxis é de 26.8 g versus 45.4 g com o cateter convencional com consequente menor risco de perfuração[5]. Num registo recente de 3637 doentes submetidos a ablação de FA com SNM não foram registados casos de fistula esofágica[6]. Apesar da menor força aplicada ao tecido, as lesões são semelhantes em dimensão e profundidade o que resulta de um maior contacto e estabilidade do cateter magnético.
A flexibilidade do cateter oferece a vantagem adicional de não inibir a arritmia por contacto durante a manipulação do cateter como no caso das extrassístoles da camara de saída do ventrículo direito.
Numa recente meta-analise de estudos comparando a ablação manual com a ablação com SNM, Shurrab et al mostraram que o SNM apresenta uma tendência para uma maior taxa de sucesso e redução de recorrências com uma menor taxa de complicações[7].
Muitos estudos isolados comparativos têm mostrado um maior tempo de procedimento com o SNM comparativamente à ablação manual, porém uma revisão publicada em 2012 por Bradfield et al [2] que incluiu 88 estudos de ablação de vários tipos de substracto mostrou ausência de diferenças estatisticamente significativas nos tempos de procedimento dos vários tipos de substracto arrítmico.
A quarta geração do SNM permite uma resposta quase imediata do cateter em resposta às mudanças do vector do Navigant o que poderá vir a reduzir no futuro os tempos de procedimento como parece ser evidente no estudo publicado por Da Costa et al [3].
Não esquecer também que os tempos de procedimento têm relação com a curva de aprendizagem e que muitos dos estudos publicados traduzem a experiência inicial dos centros.

Ablação de Flutter Típico

Têm sido levantadas algumas questões em relação à eficácia do SNM na ablação de flutter istmo dependente, com efeito Bradfield et al [2] observaram, numa revisão de 4 estudos uma taxa de sucesso imediato de 77% e de sucesso intermédio (>3 meses, mas menos de 18 meses após o procedimento) de 68%, resultados muito inferiores aos classicamente obtidos com a técnica convencional. No entanto excluindo os procedimentos efectuados com cateter de 4 mm as taxas elevaram-se respectivamente para 86% e 74%, de referir que a maioria das ablações foi efectuada com cateter de 8 mm. A utilização de cateteres irrigados que só estão disponíveis desde 2008 veio melhorar estes resultados.
A nossa experiência na ablação de flutter típico tem sido diferente[8], em 38 doentes a taxa de sucesso imediato foi de 97% e a taxa de sucesso a longo prazo foi 95% claramente superior a estudos de referência com ablação convencional, sem diferenças significativas entre o cateter de 8 mm e o irrigado.

Ablação de Taquicardias Supraventriculares

O primeiro estudo prospectivo randomizado multicêntrico de comparação entre a ablação de taquicardias supraventriculares com SNM e ablação manual foi publicado em 2008 por Wood et al[2]. O estudo incluiu 71 doentes com taquicardia por reentrada intranodal (TRNAV) e com taquicardia por reentrada aurículo ventricular (TRAV). Os resultados foram semelhantes em relação à taxa de sucesso, complicações, e ao tempo de procedimento, mas o tempo de fluoroscopia total e tempo de radiofrequência foram significativamente inferiores no grupo da navegação magnética.
Depois deste primeiro estudo vários trabalhos foram publicados e de uma maneira geral as taxas de sucesso são sobreponíveis à descrita com a ablação convencional em média 97.4% para a TRNAV e 86.4% para a TRAV com taxas de sucesso intermédio de 96.3% e 89.6% respectivamente[2]. Mostrando tempos de procedimento e de radiofrequência e de fluoroscopia sobreponíveis à ablação convencional[2].
Todas estes trabalhos apresentam números pequenos com tempos de seguimento muito curtos. O nosso grupo demonstrou haver vantagem na utilização do SNM na ablação de TRNAV. Comparámos retrospectivamente os resultados da ablação de TRNAV efectuada com SNM em 139 doentes consecutivos, com 101 doentes consecutivos submetidos a ablação convencional pelo mesmo operador. Não foram

encontradas diferenças na taxa de sucesso (100% vs 100%) ou complicações (1% vs 1%), porem verificou-se uma tendência para uma maior taxa de recidiva com a ablação convencional (4% vs 0.7 % p=0.097). O tempo de procedimento e de fluoroscopia total foram semelhantes, mas o tempo de fluoroscopia para o operador foi um terço do tempo de fluoroscopia com a ablação convencional (2.4 ±1.5 min vs 7.2± 4 min; P<0.001).
Nas taquicardias auriculares os dados são muito escassos. No nosso centro o SNM tem mostrado resultados promissores com taxas de sucesso superiores à técnica convencional. Numa serie de 12 doentes submetidos a ablação de taquicardia auricular focal com SNM [9] obtivemos uma taxa de sucesso de 100% com apenas 1 recidiva num seguimento de 13 ± 8 meses.

Ablação de Fibrilhação Auricular

A ablação por cateter está hoje perfeitamente estabelecida como terapêutica para a fibrilhação auricular (FA), tendo demonstrado superioridade na manutenção de ritmo sinusal e da qualidade de vida comparativamente com os fármacos antiarrítmicos. A ablação de FA revelou também uma redução da incidência de acidentes vasculares cerebrais e mortalidade associando-se ainda a uma redução do aparecimento de demência.
A técnica actualmente aceite para ablação de FA paroxística consiste no isolamento eléctrico das veias pulmonares. No entanto com este método a taxa de sucesso na FA persistente é mais baixa e por isso têm sido sugeridos procedimentos adicionais nomeadamente a realização de linhas adicionais de bloqueio eléctrico, a eliminação de potencias fragmentados (CFAES), de rotores ou a eliminação de focos fora das veias pulmonares.
Trata-se, portanto, de procedimentos muito prolongados e nesse sentido o SNM veio trazer benefícios óbvios para o operador no que respeita ao tempo de fluoroscopia e a uma maior comodidade durante o procedimento.
Em 2006 o grupo de Pappone publicou os primeiros resultados de ablação de FA com o SNM demonstrando a sua exequibilidade e segurança, nessa altura ainda utilizando cateteres não irrigados[7]. Os autores evidenciaram, no entanto, a necessidade de ultrapassar a curva de aprendizagem não só do operador, mas de toda a equipe.
Desde 2008 estão disponíveis os cateteres irrigados para o SNM e nos últimos anos têm sido publicados vários estudos não randomizados comparando a ablação de FA com SNM com a ablação convencional e em comum estes estudos demonstraram uma taxa de sucesso agudo e de recorrência sobreponível, com tempos de procedimento e de radiofrequência superiores e com tempos de fluoroscopia inferiores. Num estudo não randomizado mas com homogeneização dos grupos com base num *propensity score matching* efectuado por Adragao et al [10] de comparação entre a ablação com SNM e a ablação convencional foram estudados um número elevado de doentes, 287 doentes em cada grupo e com um tempo de seguimento prolongado (2.6 ± 1.5 anos). Os autores observaram uma taxa de recidiva e de complicações major com o SNM sobreponível à da ablação convencional respectivamente (18.4% ao ano vs 22.3% ao ano; hazard ratio 0.81, 95% CI 0.63–1.05; P = 0.108) e (0.7% vs 2.1%; P = 0.286). O tempo de procedimento foi significativamente superior (213 ± 58 minutos vs 152 ± 52 minutos; P < 0.001) e o tempo de fluoroscopia significativamente inferior (12 ± 9 minutos vs 21 ± 10 minutos; P < 0.001) com o SNM.
Uma meta-analise recente que incluiu 15 estudos num total de 1647 doentes[7] mostrou resultados sobreponíveis, tendo sido possível demonstrar também uma tendência para uma menor taxa de complicações major com o SNM (0.4% vs. 3%, OR 0.33 (95% CI 0.097; 1.14, p = 0.081)), e considerando apenas a incidência de tamponamento o risco foi significativamente inferior com o SNM ((0.3% vs.2.5%, P = 0.005).
Recentemente foi publicado um registo multicêntrico internacional de avaliação da incidência de fistula atrio-esofágica em doentes submetidos a ablação de FA com o SNM que foram comparados com um registo multicêntrico canadiano de avaliação de incidência de fistula atrio-esofágica com a ablação convencional [6]. Foram incluídos 3637 doentes no grupo do SNM e 7016 doentes no grupo de ablação convencional e os autores observaram que apesar da maior energia aplicada na parede posterior no grupo do SNM (33±5 vs. 28.6±4.9 W; p=0.02) não houve registo de ocorrência de fistulo atrio-esofágico em nenhum dos 3637 doentes do grupo do SNM tendo-se observado a ocorrência de fistula atrio-esofágica em 5 dos 7016 (0.07 %) doentes.
Com o desenvolvimento de cateteres com avaliação da força de contacto para a ablação convencional surgiram estudos que demonstraram uma maior eficácia na criação de linhas transmurais e actualmente não está disponível para o SNM uma avaliação quantitativa da força de contacto do cateter. No entanto em 2015 o nosso grupo avaliou o papel da força de contacto versus a estabilidade do cateter de SNM na taxa de recidiva e concluímos que não existem diferenças significativas [11].

Ablação de taquicardia ventricular

A ablação de taquicardia ventricular (TV) está hoje em dia aceite quer como terapêutica curativa de taquicardias ventriculares em doentes sem cardiopatia estrutural quer como adjuvante da terapêutica com cardioversor-desfibrilhador implantável em doentes com cardiopatia estrutural. A técnica baseia-se na obtenção de um mapa de activação ou de pacemapping da TV, método em geral utilizado para a ablação focal como é o caso das arritmias na ausência de cardiopatia estrutural ou na ablação de substracto na qual se identificam em ritmo sinusal as zonas de baixa voltagem e os canais de condução lenta no seio da cicatriz com vista à homogeneização da cicatriz como é o caso das taquicardias ventriculares na presença de cardiopatia estrutural.

A obtenção de um mapa da zona de interesse no caso das arritmias ventriculares é por vezes extremamente difícil com a técnica manual devido a condicionantes anatómicas. Por outro lado, a manipulação de cateteres rígidos nas camaras ventriculares desencadeia muitas vezes a ocorrência de arritmias ventriculares que podem confundir o mapa de activação e que em presença de cardiopatia estrutural são muitas vezes mal toleradas com a necessidade de cardioversão eléctrica. O SNM pelas suas características próprias nomeadamente apresenta-se como um potencial método de eleição.

Na ausência de cardiopatia estrutural a maior parte das arritmias ventriculares têm origem na CSVD e menos frequentemente da CSVE e seios de Valsalva ou acima da válvula pulmonar. A natureza focal desta arritmia é responsável pela elevada taxa de sucesso reportada com a ablação convencional.

O SNM tem mostrado a sua superioridade na ablação de extrassístoles (ESV) das camaras de saída ventricular. O nosso grupo publicou em 2013 uma série de 36 doentes com uma taxa de sucesso global agudo de 88% e subagudo de 94% sem ocorrência de complicações [12].

O único estudo randomizado comparando o SNM com a ablação manual em 30 doentes ESV/TV sem cardiopatia estrutural publicado por Zhang et al [4], mostrou um tempo de procedimento semelhante com um tempo de fluoroscopia para o doente e operador muito inferior. A taxa de sucesso final foi de 100% sem complicações mas cinco dos 15 doentes do grupo do SNM mudaram para ablação manual e 1 doente do grupo manual teve que mudar para SNM

A primeira publicação descrevendo a exequibilidade do SNM na ablação de TV na cardiopatia estrutural foi em 2007 por Aryana et al[4], o procedimento foi efectuado com cateteres não irrigados que poderão ser eficazes na ablação de TV idiopáticas das camaras de saída ventriculares, mas não nas cardiopatias estruturais com necessidade de lesões transmurais, efectivamente os cateteres irrigados só estão disponíveis para o SNM em 2008 na Europa e em 2009 nos EUA. Com um total de 24 doentes, 21 TVs foram submetidos a ablação com SNM uma taxa de sucesso agudo de 81%, que aumentou para 97% após mudança para ablação manual com cateter irrigado.

Mais tarde, em 2012 Dinov et al [13] publicaram os resultados de um estudo retrospectivo incluindo 102 doentes com TV isquémica utilizando o SNM em 49% dos casos e o sistema manual em 51%. Neste estudo foram utilizados cateteres irrigados. A taxa de sucesso agudo foi semelhante, 82% para o SNM e 71% para o manual ($p = 0.246$). O SNM associou-se a um menor tempo de fluoroscopia (13 ± 12 minutos vs 32 ± 17 minutos, $p = 0.0001$) e de RF (1589.95 ± 1047.42 segundos vs 2337.59 ± 1248.22 segundos, $p = 0.049$), o tempo de procedimento foi sobreponível (157 ± 40 minutes vs 148 ± 50 minutes, $P = 0.42$). Verificou-se uma tendência para uma menor taxa de recorrência no grupo do SNM embora sem significado estatístico (63% dos doentes livres de recorrência no grupo SNM vs 53% no grupo manual, p=0.206

O primeiro estudo prospectivo multicêntrico avaliando o papel da ablação com SNM na TV pós enfarte foi publicado recentemente por Skoda et al[14]. Este estudo incluiu 53 doentes e os autores reportam uma taxa de sucesso agudo de 94.2% e aos 12 meses de 62%, sem ocorrência de complicações que correspondem a resultados superiores aos descritos com a tecnologia convencional.

Numa revisão recente de ablação de TV com SNM [4] que inclui 13 estudos com e sem cardiopatia estrutural mantem-se a evidência de uma eficácia sobreponível tanto em agudo como no seguimento, com um menor tempo de fluoroscopia e uma menor taxa de complicações. A taxa de sucesso global com o SNM foi menor na TV isquémica (71% a 80%) e maior na TV idiopática (86% a 100%.) As taxas de sucesso são mais elevadas com os cateteres irrigados os quais permitem entregar de forma mais segura energias mais elevadas (40-50W) e mais prolongadas capazes de criar lesões mais profundas habitualmente necessário no miocárdio do ventrículo esquerdo.

Estes resultados são confirmados por uma meta-analise[13] incluindo 328 doentes com e sem cardiopatia estrutural em 4 estudos não randomizados comparando a ablação manual (n=137) com a ablação com o SNM (n=191). As taxas de sucesso agudo e a taxa de recorrência foram semelhantes nos dois grupos. A taxa de complicações major foi superior no grupo de ablação convencional (12% vs 2.9%; $p = 0.024$). Todos os 4 estudos reportaram tempo de procedimento e de fluoroscopia que foi significativamente inferior no grupo de SNM.

A ablação epicárdica (Figura 8) parece ser um campo de excelência para o SNM dadas as características da técnica, mas os dados são ainda muito reduzidos.

Encontra-se actualmente em curso um estudo randomizado prospectivo que irá comparar os resultados do SNM na ablação de taquicardia ventricular isquémica [15] que seguramente irá permitir comprovar a superioridade da ablação por navegação magnética.

Conclusões

O sistema de navegação magnética da Stereotaxis está em uso há mais de 10 anos, mas tem tido um desenvolvimento notável na última década. A sua eficácia é pelo menos sobreponível à da ablação convencional, embora em determinados substractos tenha demonstrado superioridade. As características inerentes a esta tecnologia são particularmente importantes na ablação de substractos complicados ou em procedimentos prolongados como é o caso da ablação de fibrilhação auricular ou taquicardia ventricular. No entanto a redução do tempo de procedimento e de fluoroscopia bem como a quase ausência de complicações favorecem a sua escolha como técnica de eleição para arritmias mais simples nos laboratórios com disponibilidade da tecnologia como é o caso do nosso em que todos os procedimentos são efectuados com SNM.
A ablação com SNM requer uma curva de aprendizagem como qualquer outra técnica, neste caso não apenas do operador, mas de toda a equipa, exigindo a utilização regular da técnica para permitir a agilizar o procedimento e obter o maior rendimento.
Acreditamos que o futuro passa pela robotização dos procedimentos e o SNM parece ser o mais eficaz e seguro. Aguardamos que os estudos randomizados venham confirmar a superioridade deste sistema na ablação das arritmias cardíacas.

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Figuras

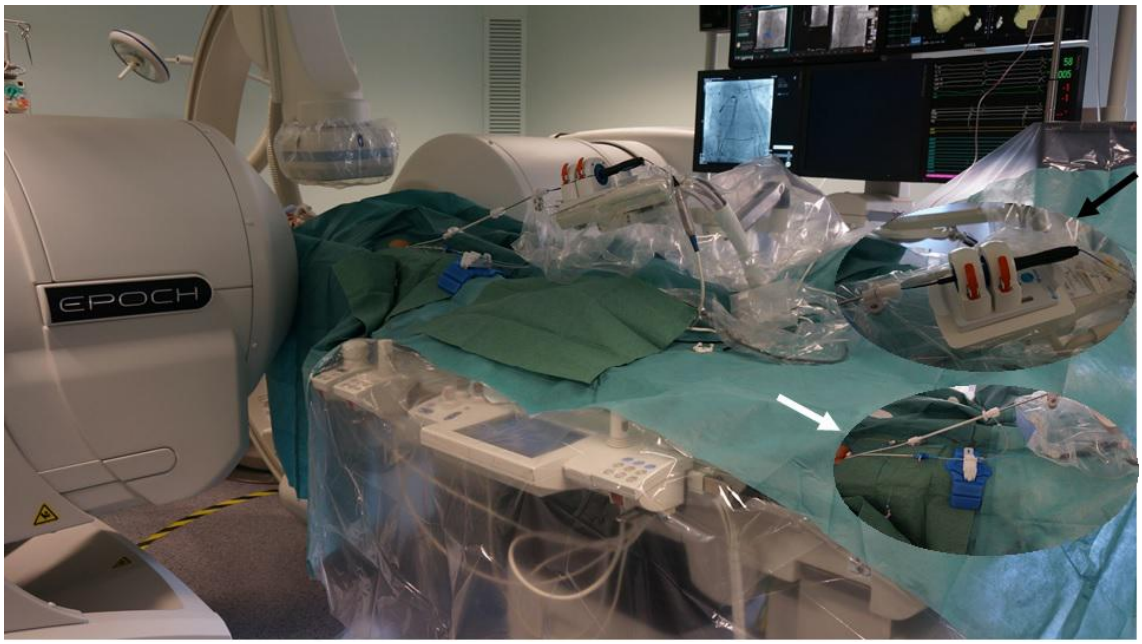

Figura 1. Sala de Electrofisiologia com o Sistema de Navegação Magnética (Stereotaxis). Sistema de braço robótico V-Drive (seta preta) com o cateter Lasso® conectado. Sistema Cardiodrive (seta branca).

Figura 2. Sala de comandos com a estação de trabalho Navigant com a respectiva consola e rato. O painel de controle da fluoroscopia (seta preta). O controle remoto do sistema V-drive (seta branca).

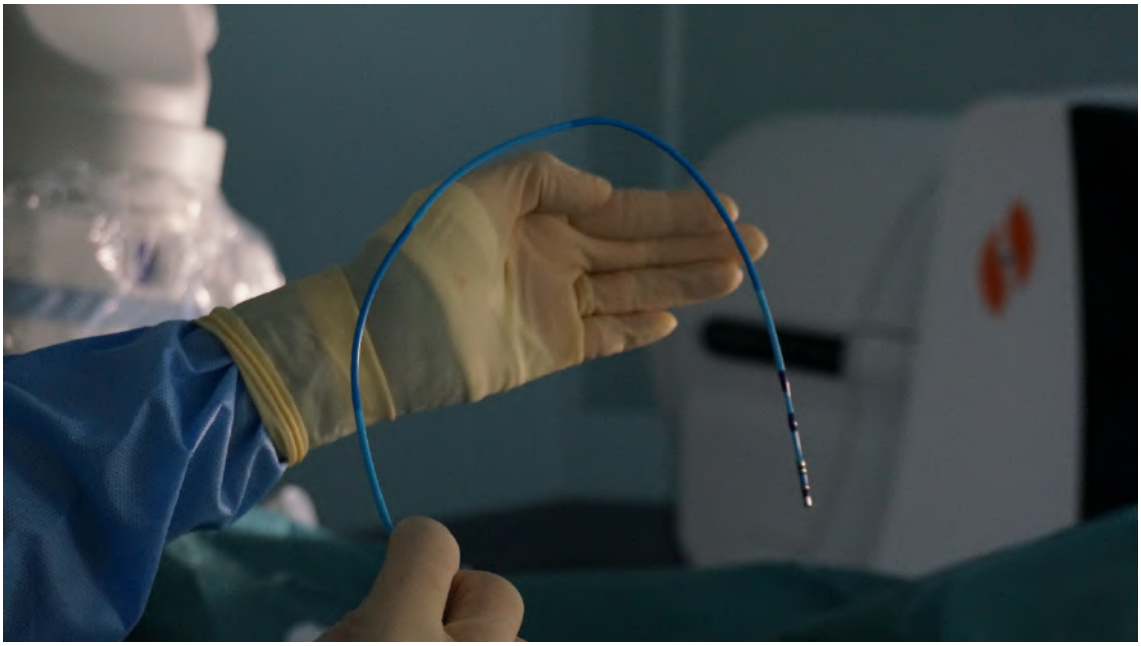

Figura 3. Cateter de navegação magnética Celsius® RMT 4 mm (Biosense®)

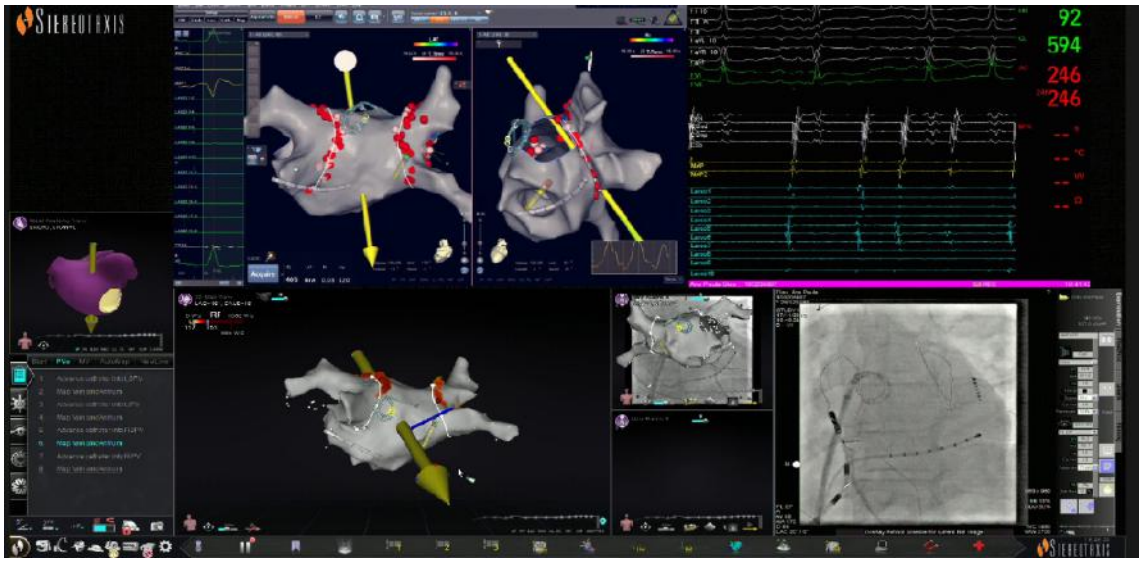

Figura 4. Ecrã gigante Odyssey Vision™ System. Canto superior direito electrogramas intracavitários. Canto inferior direito imagem da fluoroscopia com a projecção do mapa electroanatómico na imagem de RX. Canto superior esquerdo ecrã do Carto 3 em projeção PA e lateral esquerda. Canto inferior direito ecrã da Stereotaxis com os vectores magnéticos e o historial de ablação.

Figura 5. Consola do sistema V-Drive ® para controle remoto do cateter circular Lasso® utilizando o braço robótico na mesa do doente.

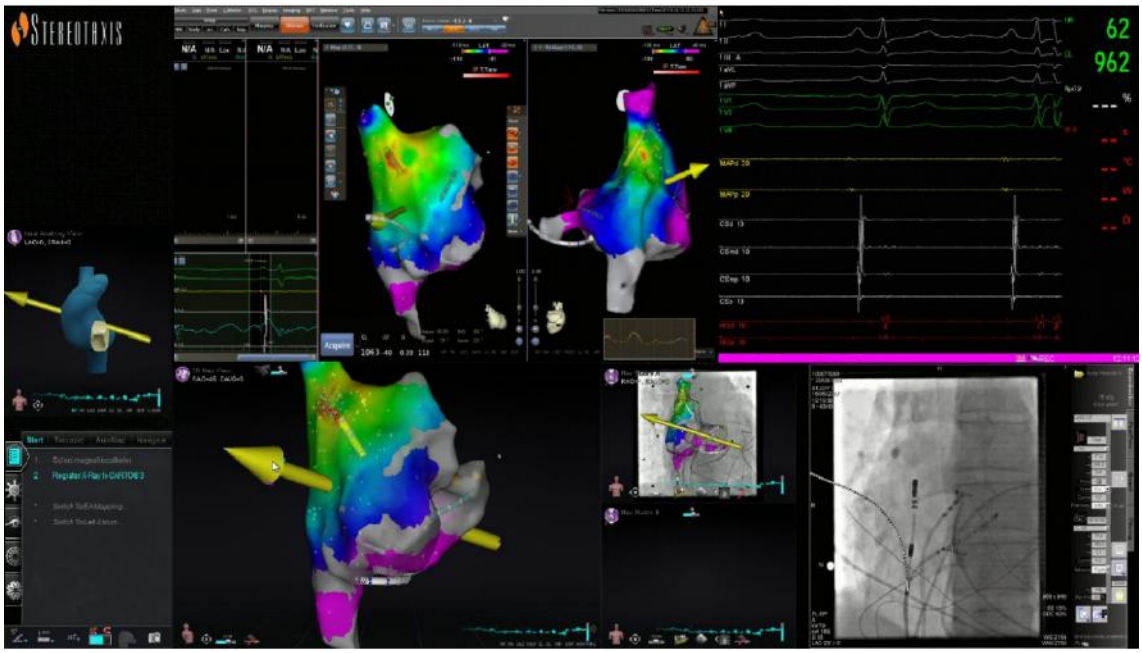

Figura 6. Ecrã gigante Odyssey Vision™ System numa taquicardia auricular esquerda. No canto inferior direito no ecrã da Stereotaxis observando-se a ponta do cateter de ablação apresentando um halo estrelado azul (seta laranja) que comprova de forma qualitativa o bom contacto do cateter com o tecido (e-Contact module).

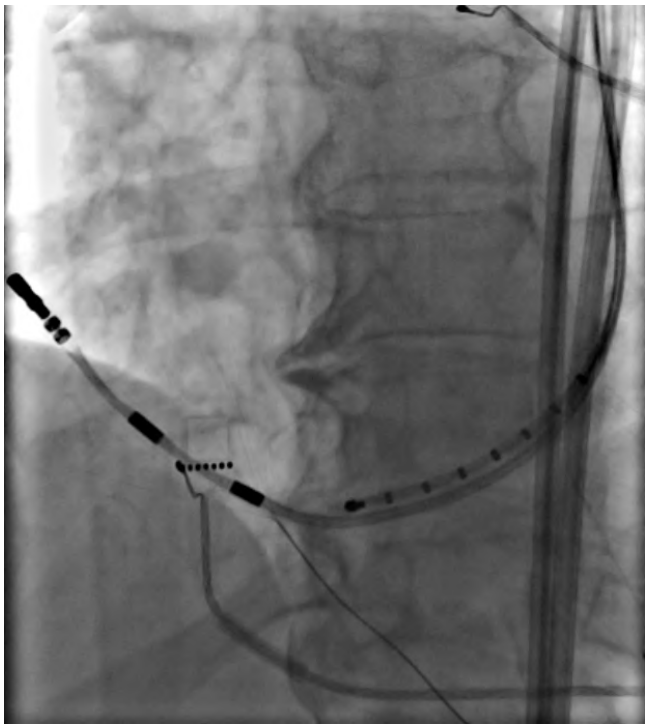

Figura 7. Imagem de RX em incidência OAE de doente com taquicardia auricular direita e presença de veia cava superior esquerda drenando para o seio coronário. Mapeamento da aurícula direita com o cateter de ablação introduzido pela veia cava superior esquerda.

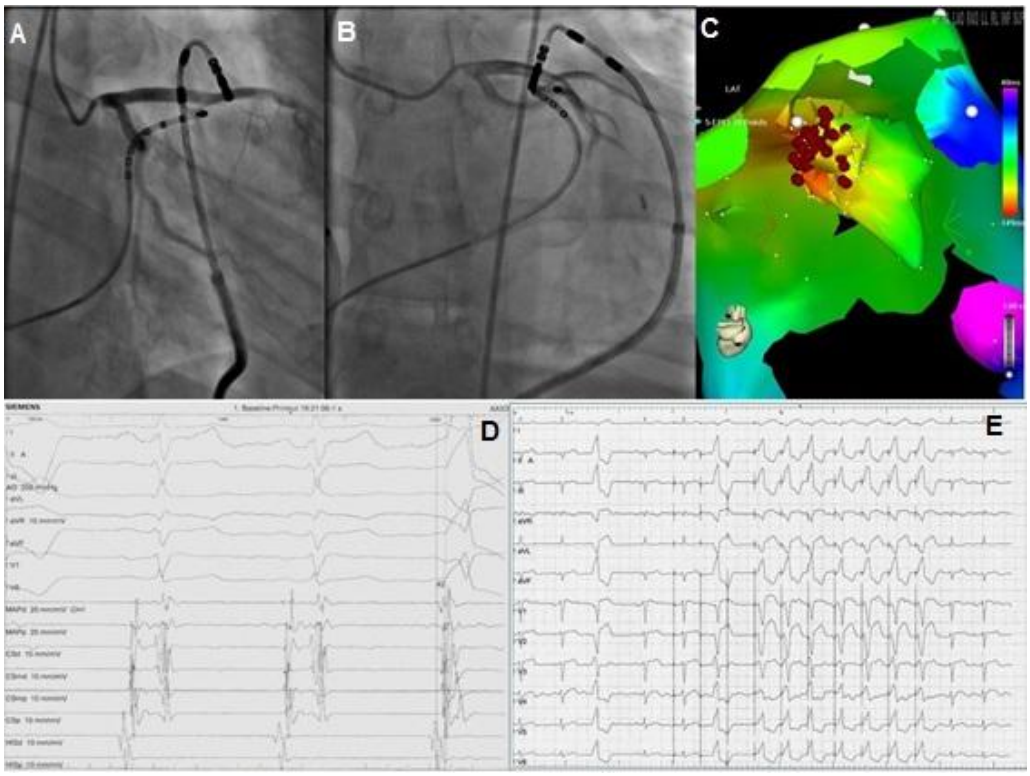

Figura 8. Ablação epicárdica: cateter no local de ablação em incidência obliqua anterior direita (A) e obliqua anterior esquerda (B). Mapa de activação (C) mostrando local de maior precocidade na face anterior da camara de saída do ventrículo esquerdo. Electrograma e pacemapping com concordância 12/12 no local de ablação (D e E).

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ORIGINAL ARTICLE

Atrioventricular node reentrant tachycardia: Remote magnetic navigation ablation versus manual ablation – impact on operator fluoroscopy time

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KEYWORDS
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Atrioventricular nodal reentrant tachycardia;
Catheter ablation;
Magnetic navigation system

Abstract
Introduction and Aims: Remote magnetic navigation systems have demonstrated benefits in the ablation of difficult substrates. Their role in the ablation of atrioventricular nodal reentrant tachycardia (AVNRT), however, has only been studied in small patient series. The aim of this study was to compare the results of AVNRT ablation using magnetic navigation, in a center where every procedure is performed with this system, with manual ablation.
Methods: We selected 139 consecutive patients undergoing AVNRT ablation with magnetic navigation by a single operator between January 2009 and June 2016 and compared them to a group of 101 consecutive patients undergoing manual ablation in the same period by the same operator in another hospital. The methodology was the same in both groups. Success rates, complications, procedure time, radiofrequency time, total and operator fluoroscopy time, and recurrence rates were compared.
Results: There were no differences in success and complication rates. Procedure and total fluoroscopy times were not significantly different, but operator fluoroscopy time was significantly shorter with the magnetic navigation system (2.4±1.5 min vs. 7.2±4 min; $p<0.001$). The recurrence rate was higher in the manual group, although without statistical significance.
Conclusions: The ablation of AVNRT with magnetic navigation is feasible using the same methodology as for manual ablation. Success and complication rates were similar. Operator fluoroscopy time was significantly less with the magnetic navigation system.

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PALAVRAS-CHAVE
Taquicardia supraventricular;
TRNAV;
Ablação por cateter;
Navegação magnética

Taquicardia por reentrada intranodal: ablação por navegação magnética *versus* ablação manual – impacto no tempo de fluoroscopia para o operador

Resumo
Introdução e objetivos: A ablação por navegação magnética tem demonstrado benefícios na ablação de substratos de difícil acesso. O seu papel na ablação de arritmias simples tem sido estudado apenas em séries pequenas. O objetivo deste estudo foi comparar a ablação de taquicardia por reentrada intranodal com sistema de navegação magnética num centro em que todos os casos são efetuados com este sistema, com a ablação manual.
Métodos: Desde janeiro de 2009 selecionaram-se 139 doentes consecutivos submetidos a ablação de taquicardia intranodal com sistema de navegação magnética por um único operador que foram comparados com um grupo de 101 doentes submetidos a ablação manual pelo mesmo operador no mesmo período, noutro hospital. A técnica utilizada foi a mesma nos dois grupos. Comparou-se a taxa de sucesso e complicações, o tempo de procedimento, o tempo de fluoroscopia total e para o operador, o tempo de radiofrequência e a taxa de recidiva.
Resultados: Não se verificaram diferenças significativas em relação à taxa de sucesso ou complicações. O tempo de procedimento e o tempo de fluoroscopia foram semelhantes nos dois grupos, mas no grupo de navegação magnética o tempo de fluoroscopia para o operador foi significativamente inferior. A taxa de recidiva foi superior no grupo de ablação manual embora sem significado estatístico.
Conclusões: A ablação de taquicardia intranodal com sistema de navegação magnética é exequível com uma metodologia sobreponível à técnica convencional. A taxa de sucesso e complicações é semelhante. No grupo com navegação magnética o tempo de fluoroscopia para o operador é significativamente mais baixo.

Introduction

Remote magnetic navigation systems (MNS) have demonstrated benefits in the ablation of difficult arrhythmic substrates.[1] Their role in the ablation of atrioventricular nodal reentrant tachycardia (AVNRT), however, has only been studied in small patient series[2] with short follow-up times.

The stability of the magnetic catheters used in MNS facilitates successful application of a radiofrequency (RF) lesion with less force applied to the endocardium and less power than with conventional catheters,[3,4] which may be important in the ablation of AVNRT to avoid damaging the atrioventricular (AV) node.

Studies on the use of this technology in AVNRT ablation have been small, with short follow-up times. Some involve catheters that are no longer in use with only one magnet in the catheter tip,[5,6] and most use different methodology from that of conventional ablation, with less RF power, resulting in a lower junctional rhythm (JR) rate during RF application.[7,8] Most also report the center's initial experience, and so their results tend to be worse than with conventional ablation.

In our center we perform all ablations with MNS. The aim of this study was to compare the results of AVNRT ablation using MNS in a high-volume center with those of conventional manual ablation by the same operator in another hospital.

Methods

Patient population

We retrospectively selected 139 consecutive patients undergoing AVNRT ablation guided by an MNS by a single operator (MNS group) between January 2009 and June 2016 (procedures before 2009, the learning period, were excluded) and compared them to a group of 101 consecutive patients undergoing manual AVNRT ablation in the same period by the same operator in another hospital (MAN group). The characteristics of both patient groups are displayed in Table 1. Patients who had already undergone ablation were excluded.

Electrophysiological study

Patients were studied in a fasting non-sedated state under local anesthesia. All antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. Patients gave their written informed consent.

We used the standard number of catheters inserted via the right femoral vein under fluoroscopic guidance: a quadripolar catheter in the right ventricle recording the His bundle electrogram in the proximal dipole and a decapolar catheter in the coronary sinus. The presence of dual AV node conduction was assessed, and accessory pathways were excluded. When AVNRT was not inducible in the resting

Table 1 Population and procedure characteristics and follow-up data.

	MNS	MAN	p
Age, years	45±14	52±16	0.01
Female gender, %	78	74	NS
Hypertension	9	17	0.02
Structural heart disease	5	7	NS
Procedure time, min	120±37	98.6±29.6	0.07
Total fluoroscopy time, min	7.28	7.15	NS
Operator fluoroscopy time, min	2.4±1.5	7.2±4	<0.001
RF time, s	229±208	181±31	0.03
Success	100%	100%	NS
Complications	1	1	NS
Follow-up time, months	44.8±24	47.3±25	NS
Recurrence	1 (0.7%)	4 (4%)	0.097

MAN: manual; MNS: magnetic navigation system; RF: radiofrequency.

state, an isoproterenol infusion was administered intravenously, as needed.

Magnetic navigation

All procedures were performed using the Niobe II MNS (Stereotaxis) working with the single-plane AXIOM Artis fluoroscopy system (Siemens).

The MNS, previously described,[5] consists of two computer-controlled permanent magnets positioned on opposite sides of the fluoroscopy table. These magnets create a magnetic field of 0.1 T. The position of the magnets is remotely controlled by a console, the Navigant workstation, which changes the orientation of the magnetic field according to the vectors chosen by the operator (Figure 1). The ablation catheter has three magnets in its distal portion that keeps it parallel to the magnetic field. Changes in the orientation of the magnetic field deflect the catheter, which is remotely advanced or retracted with the aid of a motor drive, Cardiodrive (Stereotaxis). Magnetic field vectors can be stored in order to automatically navigate the ablation catheter to previous sites.

Mapping and ablation

The procedures in the MAN group took place in an electrophysiology laboratory equipped with a Philips BV Pulsera fluoroscopy system. The methodology of mapping and ablation was the same in both groups. Koch's triangle was mapped by bending and pulling the ablation catheter from the His position and rotating to the coronary sinus in order to obtain a slow pathway potential with a small atrial and large ventricular electrogram in the distal bipole. RF energy was applied at this site in order to obtain JR during RF delivery. The catheter was moved to another site whenever JR did not appear within seconds of RF application. A 4-mm tip Navistar RMT magnetic catheter (Biosense Webster) was used in the MNS group and a 4-mm tip catheter (Medtronic Marinr®, Biosense Webster Celsius® or St. Jude Medical Therapy®) was used in the MAN group. RF was applied under fluoroscopic guidance in order to check catheter position, for up to 120 s in the MNS group and 90 s in the MAN group, to a maximum temperature of 55 °C and a power output limit of 55 W. RF was applied for longer in the MNS group due to the lower force applied by the magnetic catheter to the endocardium, in an empiric attempt to improve lesion formation without increasing risk in view of the greater softness and stability of this catheter. During ablation, light sedation with midazolam (bolus) was administered when needed.

Total procedural and fluoroscopy times were recorded. Procedure time was defined as the time between the beginning of venous puncture until removal of the sheaths. Fluoroscopy times were measured for the patient and separately for the operator.

Acute success was defined as failure to induce AVNRT, including after isoproterenol infusion. The presence of a nodal echo beat was not perceived as failure.

All patients were monitored in the hospital for 24 hours after the procedure.

Follow-up

Follow-up was performed at outpatient clinical visits or by telephone. Recurrence was defined as the presence of symptoms (palpitations) and electrocardiographic documentation of AVNRT.

Statistical analysis

Continuous variables were presented as mean and standard deviation and compared with the Student's t test for independent samples. Categorical data were expressed as percentages and compared with the chi-square test. Outcomes were analyzed with time-to-event methods. Kaplan-Meier plots were calculated using the log-rank test for AVNRT recurrence. Statistical analysis was performed using IBM SPSS 23.0 (IBM SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p<0.05$.

Figure 1 Navigant workstation screen: junctional rhythm during radiofrequency delivery (top panel); reference X-ray image in left anterior oblique view displaying the real-time position of the ablation catheter, His bundle catheter and His bundle location (white dots); the magnetic navigation system's automatic vector to slow pathway location (vector).

Results

Study population

The characteristics of the two patient groups are displayed in Table 1. Patients in the MNS group were younger (45±14 vs. 52±16 years, p=0.01) and fewer had hypertension (nine vs. 17 patients, p=0.02), but the prevalence of structural heart disease was not significantly different.

Electrophysiological study and ablation data

Typical slow-fast AVNRT was induced in all patients in both groups. Procedure time and total fluoroscopy time were not significantly different (Table 1) but operator fluoroscopy time was significantly shorter in the MNS group (2.4±1.5 min vs. 7.2±4 min, p<0.001). The mean duration of RF applications was higher for the MNS group (229±208 vs. 181±131, p=0.03). JR appeared during RF application in all patients in both groups. Ablation was successful in all patients in both groups. RF delivery was interrupted in one patient in the MNS group and in one patient in the MAN group due to transient second-degree AV block, which disappeared within seconds of RF interruption. No charring was found on the catheter tip in either group. There were no other procedure-related complications.

Follow-up

The duration of follow-up was similar in the two groups (44.8±24 months in MNS and 47.3±25 in MAN). During this period three patients died in the MAN group, two of cancer and one of heart failure. No patients were lost to follow-up. Five patients had recurrence of AVNRT, four in the MAN group (two in the first month, one after six months and one after eight months) and one in the MNS group (after nine months). Although the recurrence rate was higher in the MAN group, this was not statistically significant (0.7% vs. 4%, p=0.097 by the log-rank test). All these patients underwent a second successful procedure and there were no further recurrences.

Discussion

Although MNS are relatively new, the characteristics of the magnetic catheter, particularly its stability, maneuverability and softness, make this technology the best choice for the ablation of complex arrhythmias or difficult substrates. However, reports on its role in more common and simple arrhythmias such as AVNRT are scarce, based on small patient series, and most papers on this subject analyze the initial cases using this technology.[2]

We report results in a center where every procedure is done with MNS, excluding those performed in the first year (learning period).

Efficacy of the magnetic navigation system

In our study the procedure time was similar in the two groups, unlike in previous studies[8,9] which report a longer procedure time with MNS. The fact that most such studies report an initial experience may be responsible for their longer procedure time.

The RF settings used in previous studies were not uniform, each group using its own settings. In the first reports of MNS for AVNRT, Ernst et al.[5] used a maximum of 40 W, Davis et al.[9] used 30 W and others, including Kerzner et al., [10] up to 50 W. Some state that the use of higher power is associated with clot formation at the catheter tip[8] and accordingly use less power. We use the same settings with MNS as with manual ablation, namely power up to 50 W to a maximum temperature of 55 °C, and have never observed charring or popping. The high temperature (65 °C) programmed by Moreno et al.'s group[8] was probably responsible for the charring they observed at the catheter tip.

Ricard et al.[11] reported a lower incidence of JR during RF application, which according to the authors was due to the greater catheter stability, which minimizes microdislodgement toward the AV node. By contrast, Davis et al.[9] found that JR appeared sooner with lower maximum temperature and explained this as resulting from greater catheter stability.

JR was achieved in all patients in both MNS and MAN groups, either at the initial position or after remapping and re-ablating at another site. We are convinced that the presence of JR is as important in MNS as in MAN ablation and is essential to obtain successful slow pathway ablation. In our series, RF application time was longer in the MNS group, which is not in agreement with previous studies. This is probably related to the longer duration of RF for each lesion that was routine in the MNS group compared to the MAN group.

The acute success rate with the MNS was high and comparable to MAN ablation.

Although not statistically significant, there was a trend towards a lower recurrence rate in the MNS group. This finding was also observed by our group in the ablation of other arrhythmias[12,13] and may be explained by better catheter contact and less edema formation, leading to longer-lasting lesions. However, we cannot exclude the possibility that the longer duration of RF application could affect long-term results.

Safety of the magnetic navigation system

The overall complication rate was similar in both groups, with one transient second-degree AV block in one patient in each group. This is a known complication in 1-2% of AVNRT ablation procedures.[14]

The most important difference in terms of radiation exposure is the reduction of operator fluoroscopy time with MNS to one third that with manual ablation. This finding is consistent in all studies, and is undoubtedly due to the fact that after positioning the catheters the operator can leave the patient's side and perform the ablation remotely in another room. The cumulative radiation dose during a lifetime of exposure is a concern for healthcare professionals involved in fluoroscopically driven procedures, especially electrophysiologists and interventional cardiologists. This significantly decreased operator fluoroscopy time reduces the risk of malignancy and other potentially deleterious effects of radiation.[15,16]

There is less agreement concerning reduction of total fluoroscopy time. In some studies MNS enabled reductions in radiation for both patients and medical staff. Kim et al.[17] found a significant reduction in total fluoroscopy time with MNS, although the authors did not discuss the reason for this finding. Some authors[8,11,18] found no significant reduction in total fluoroscopy time, as was the case in our series, while others, like Ricard et al.,[11] recorded longer total fluoroscopy time. In our opinion there is no reason that total fluoroscopy time would be reduced in AVNRT ablation. The main reason that fluoroscopy time is reduced with the use of MNS is that the catheter can be manipulated more safely without fluoroscopy due to the softness of the catheter tip. This may make a difference in complex cases with a greater need for catheter manipulation such as ablation of atrial fibrillation, atrial flutter or ventricular tachycardia.[12,13,19] In the case of AVNRT the amount of fluoroscopy needed to place the ablation catheter over the slow pathway is low with both manual and magnetic navigation. Most of the radiation exposure occurs during RF application, since we always apply RF energy under fluoroscopic guidance, even with the MNS. In fact, although the MNS catheter itself is very stable, and some authors[2] state that due to the stability of the catheter the RF may be applied without fluoroscopy, we believe that in situations such as deep breathing, intense cough or inadvertent body movements we cannot totally rely on the stability of the catheter, given its proximity to the AV node.

Limitations

The results for MNS ablation of AVNRT presented in our study are not randomized, are retrospective, come from a single center where every procedure is performed with MNS, and exclude results from the first year to avoid the learning period. There are other methods to decrease fluoroscopy time, such as the use of electroanatomical mapping systems, and it would be interesting to compare the cost and efficacy of both strategies.

Therefore, prospective randomized trials will be needed to better assess the role of MNS for catheter ablation of AVNRT.

Conclusions

Ablation of AVNRT with MNS is feasible with the same methodology as manual ablation, and success and complication rates were similar. Operator fluoroscopy time was significantly less with the MNS.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Remote magnetic navigation for ablation of typical atrial flutter: Long-term results☆

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KEYWORDS
Typical atrial flutter;
Radiofrequency ablation;
Remote magnetic navigation;
Stereotaxis

Abstract
Introduction and Aim: Remote magnetic navigation has proved to be effective in the ablation of most supraventricular and ventricular arrhythmias. Initial studies reported worse results with this system compared to conventional ablation for atrial flutter. The aim of this study was to assess the acute and long-term success of atrial flutter ablation with remote magnetic navigation and to retrospectively compare the results obtained with an 8-mm tip catheter versus an irrigated catheter.
Methods: We studied 38 consecutive patients, mean age 61±15 years, 28 male, who underwent ablation of typical atrial flutter with the Niobe II remote magnetic navigation system (Stereotaxis). Ablation was performed with an 8-mm tip catheter in 17 patients and with an irrigated-tip catheter in 21 patients. Acute success was defined as the presence of bidirectional isthmus block, and long-term success as absence of symptoms and atrial flutter during Holter monitoring.
Results: Bidirectional isthmus block was achieved in 37 patients (97%), and the success rate was similar in both groups. Total procedure time was not significantly different between the groups but fluoroscopy time was shorter in the irrigated tip group (13.4±3.7 min vs. 6±4.4 min; $p<0.01$). The number of applications and total radiofrequency time did not differ. There were no complications. During a follow-up of 32±19 months there were two relapses, one in each group.
Conclusions: The Niobe II remote control system for ablation of typical atrial flutter is safe and effective in both the short and long term. The 8-mm and irrigated-tip catheters showed similar safety and efficacy.

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PALAVRAS-CHAVE
Flutter auricular típico;
Ablação por radiofrequência;
Navegação magnética;
Estereotaxia

Ablação do istmo cavo-tricúspide com sistema de navegação magnética por controlo remoto no tratamento do *flutter* auricular típico – resultados a longo prazo

Resumo
Introdução e objetivos: A ablação com sistema de navegação magnética tem demonstrado ser eficaz em vários tipos de procedimentos de ablação. Estudos iniciais apontam para uma menor eficácia deste método na ablação do istmo cavo-tricúspide. O objetivo deste estudo foi avaliar a eficácia imediata e a longo prazo deste método e comparar retrospetivamente os resultados obtidos com o cateter de 8 mm com os obtidos com o cateter irrigado.
Métodos: Estudaram-se 38 doentes consecutivos, idade média 61 ± 15 anos, 28 homens, referenciados para ablação de *flutter* típico com sistema de navegação magnética Niobe II (Stereotaxis) com um período de seguimento superior a seis meses. A ablação foi efetuada com cateter de 8 mm em 17 doentes e com cateter irrigado em 21 doentes. O sucesso imediato foi definido como presença de bloqueio ístmico bidirecional e o sucesso a longo prazo definido com ausência de sintomas e de *flutter* auricular no registo de Holter.
Resultados: O bloqueio ístmico bidirecional foi obtido em 37 doentes (97%). A taxa de sucesso foi semelhante nos dois grupos. O tempo de procedimento não diferiu entre os dois grupos, mas o tempo de fluoroscopia foi significativamente inferior no grupo com cateter irrigado (13,4 ± 3,7 min *versus* 6 ± 4,4 min; p < 0,01). O número de aplicações e o tempo de radiofrequência foram semelhantes nos dois grupos. Não foram registadas complicações. Após um período de seguimento médio de 32 ± 19 meses ocorreram duas recidivas, uma em cada grupo.
Conclusões: O sistema de navegação magnética Niobe II mostrou-se eficaz e seguro na ablação de *flutter* típico permitindo uma taxa de sucesso elevada com uma eficácia mantida a longo prazo. O cateter de 8 mm e o cateter irrigado mostraram-se igualmente eficazes e seguros.

List of abbreviations

AF	atrial fibrillation
AFL	atrial flutter
CS	coronary sinus
CTI	cavotricuspid isthmus
IVC	inferior vena cava
MNS	magnetic navigation system
RF	radiofrequency

Introduction

Atrial flutter (AFL) is an abnormal cardiac rhythm characterized by rapid regular atrial depolarizations with a rate of approximately 300/min and regular ventricular rate. Typical AFL is the most common macroreentrant atrial tachycardia.[1] Catheter ablation of the cavotricuspid isthmus (CTI) is the treatment of choice for this arrhythmia due to its high success rate and low rate of complications compared to drug therapy, which is relatively ineffective.[2]

The Niobe magnetic navigation system (MNS) (Stereotaxis) was developed for remote control of ablation procedures, aimed at improving steering of the catheters and reducing fluoroscopy time. The system has been shown to be effective and safe in ablation of different types of supraventricular and ventricular arrhythmias, and is superior to conventional ablation for ventricular tachycardia.[3,4] In a randomized trial of ablation of supraventricular tachycardias with the Niobe system compared to manual navigation, the MNS was associated with reduced fluoroscopy time and number of radiofrequency (RF) applications.[5] However, initial studies of AFL ablation reported lower success rates than with manual steering,[6–8] which may be due to the limited contact force possible with flexible catheters.

The aim of this study was to assess the feasibility and safety of the MNS for ablation of AFL and its long-term success and to compare the results obtained with an 8-mm tip catheter versus an irrigated catheter.

Methods

Study population

Between January 2008 and October 2012, 38 consecutive patients underwent electrophysiological study and catheter ablation of typical AFL with the Niobe MNS at our institution. AFL was documented by 12-lead ECG and the patients were symptomatic despite medication. No patient was contraindicated for magnetic navigation, and all gave their written informed consent.

Electrophysiological study

Patients were assessed after six hours' fasting and antiarrhythmic medication was suspended for five half-lives; amiodarone was suspended at least one month before the

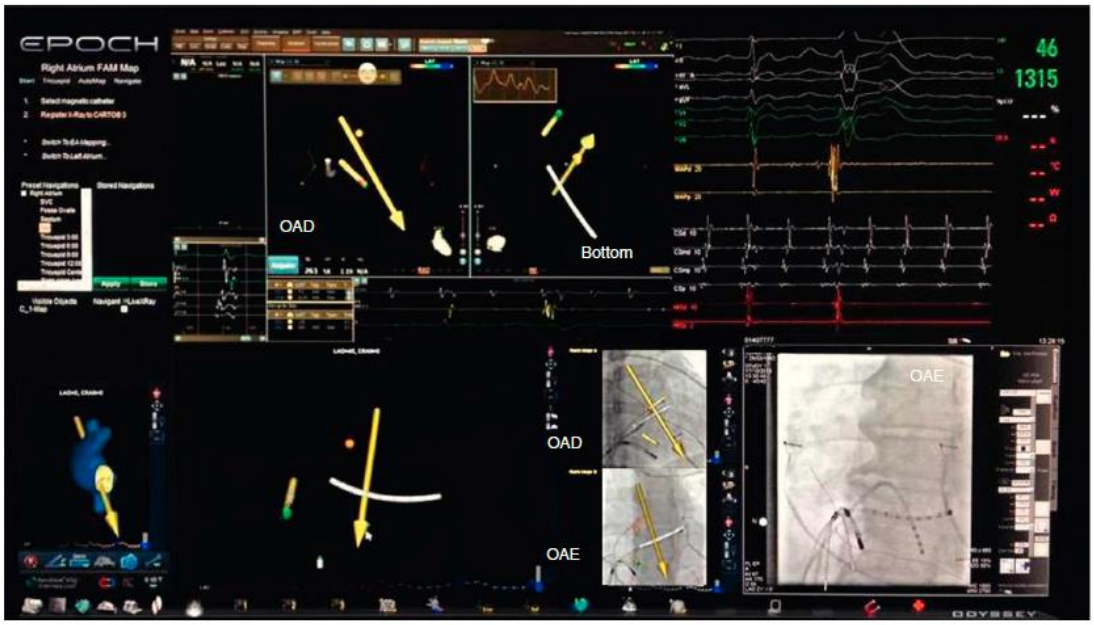

Figure 1 Reference fluoroscopic images on the Navigant workstation in right and left anterior oblique views showing the real-time position of the ablation catheter, without further fluoroscopy, in the cavotricuspid isthmus at the 5 o'clock position, the automatic vector of the magnetic navigation system (yellow arrow) and the His bundle (yellow point). OAD: right anterior oblique; OAE: left anterior oblique.

procedure. Patients with persistent AFL who were not under oral anticoagulation underwent transesophageal echocardiography to exclude the presence of left atrial thrombi.

Surface electrocardiograms and intracavitary electrograms were recorded on an AXIOM Sensis system (Siemens Healthcare). Programmed stimulation was performed using a UHS 3000 heart stimulator (Biotronik). The catheters were inserted via the femoral vein and positioned under fluoroscopic guidance, a quadripolar catheter (Navistar, Biosense Webster) in the His bundle and an octapolar catheter (Dynamic XT, Bard) in the coronary sinus (CS).

When ablation was carried out in AFL rhythm, entrainment pacing was used to demonstrate the presence of isthmus-dependent atrial flutter. Patients in sinus rhythm underwent CS pacing to measure conduction time across the CTI before ablation.

Magnetic navigation

All procedures were carried out using the Niobe II system. The MNS has been previously described[9]; it basically consists of two computer-controlled magnets positioned on either side of the fluoroscopy table, which create a magnetic field (0.1 T). The position of the magnets is controlled from a console, the Navigant workstation, which orientates the magnetic field according to vectors selected by the operator. The ablation catheter has three magnets at its distal end, which orientate it parallel to the magnetic field. Changes in the orientation of the magnetic field deflect the catheter tip, which is advanced or withdrawn remotely by a motor at the proximal end of the catheter (Cardiodrive, Stereotaxis). Magnetic field vectors can be stored, enabling subsequent automatic navigation to previous sites.

Mapping and ablation

The MNS is integrated with a CARTO XP RMT (Biosense Webster) electroanatomical mapping system and provides real-time information on the position and orientation of the mapping catheter tip. This information is overlaid on the fluoroscopic images on the Navigant workstation, providing real-time monitoring of the catheter position without the need for further fluoroscopy (Figure 1). The location of the His bundle is marked on the screen of the CARTO workstation.

A Navistar RMT (Biosense Webster) catheter with an 8-mm tip was used for the first 17 procedures and a Navistar RMT Thermocool (Biosense Webster) irrigated-tip catheter for the subsequent 21 procedures. The ablation catheter was introduced via the femoral vein and advanced manually to the right atrium without the need for long sheaths, then remotely to the tricuspid annulus at the 6 o'clock position in left anterior oblique view and subsequently to the right ventricle, after which it was gradually withdrawn until an atrial potential was detected on the distal bipole of the ablation catheter. RF energy was then applied at this point and the ablation catheter was progressively withdrawn under remote control to the inferior vena cava (IVC).

The MNS vector was directed downward in the initial portion of the CTI and more anteriorly in the final portion,

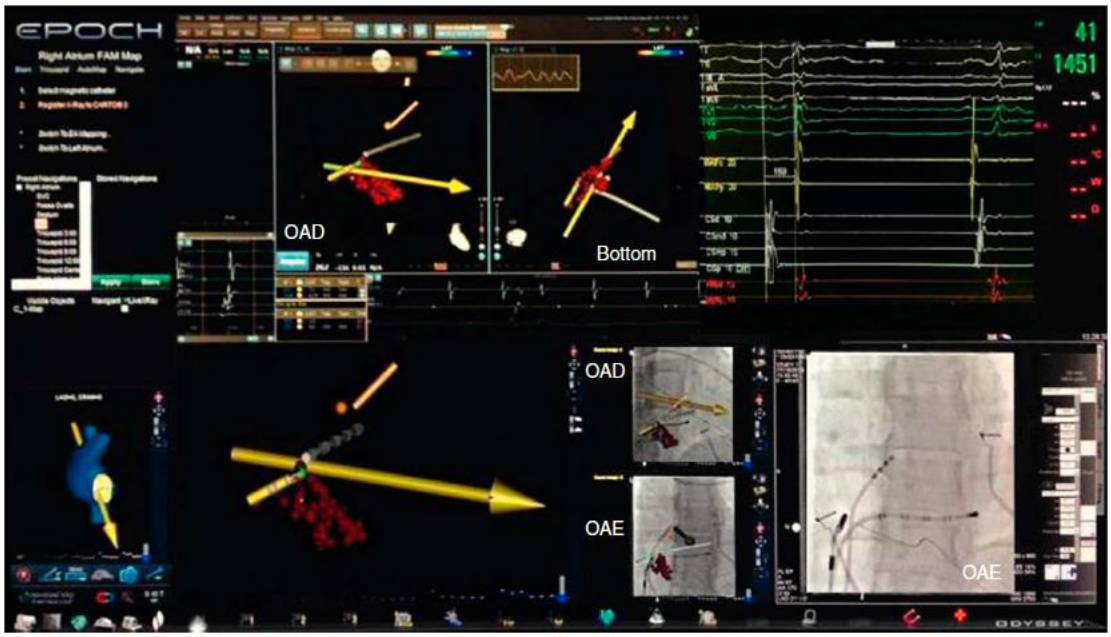

Figure 2 Radiofrequency applications (red circles) on the CARTO mapping system. On the right, fluoroscopic image showing the ablation catheter and the magnetic navigation vector. OAD: right anterior oblique; OAE: left anterior oblique.

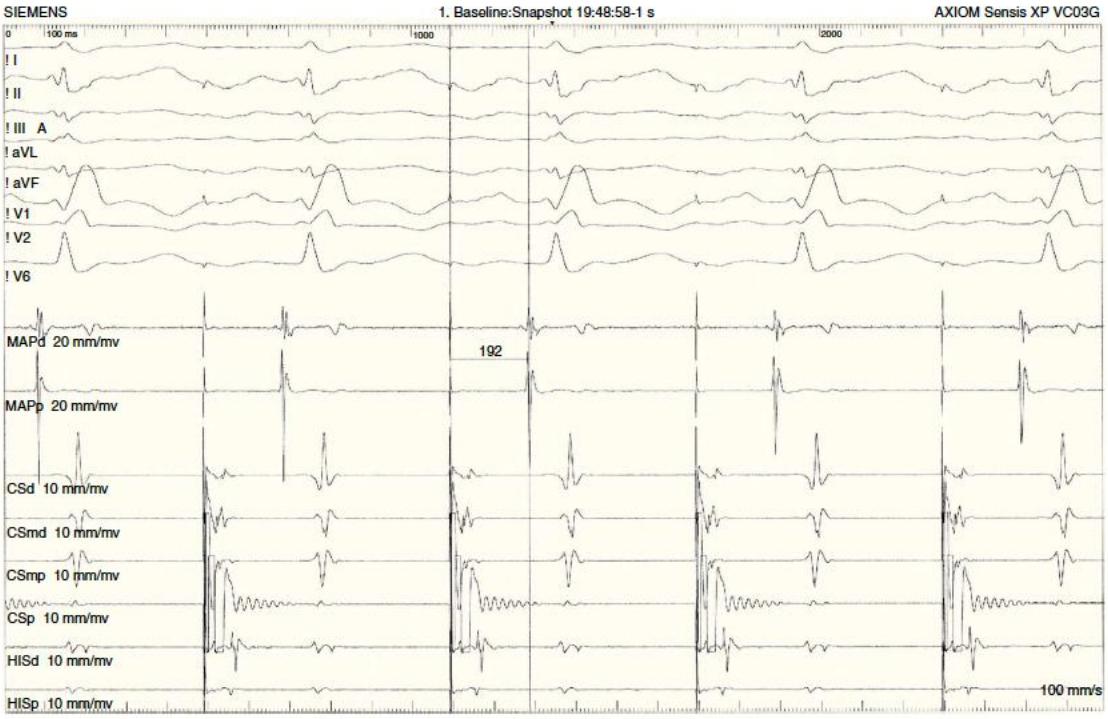

Figure 3 Pacing by the mid-proximal bipole in the coronary sinus with the mapping catheter on the lateral side of the ablation line, showing a conduction delay of 192 ms in the cavotricuspid isthmus.

Table 2 Ablation procedure characteristics.

	8-mm tip catheter	Irrigated catheter	p
AFL during ablation	14	17	NS
Procedure time (min)	189±61	151±71	0.09
Fluoroscopy time (min)	13.4±3.7	6±4.4	0.01
No. of RF applications	22±15	21±14,8	NS
RF application time (min)	25±15	24±13	NS
Success	16/17	21/21	NS

AFL: atrial flutter; RF: radiofrequency energy.

Follow-up

There were no procedure-related complications.

During a follow-up of 32±19 months (6–60) two patients had relapse of AFL, one in each group (Table 3). One patient refused reablation and in the other the procedure was repeated with an irrigated catheter, which was successful. Six patients developed atrial fibrillation (AF) during follow-up that was treated by ablation. After pulmonary vein isolation, conduction across the CTI was assessed and continuing bidirectional block was confirmed in all patients.

There were no deaths during follow-up.

Discussion

The main finding of this study was that the Niobe II MNS is safe and effective for treatment of AFL, with similar success rates to conventional ablation.[11] We also found that 8-mm tip and irrigated catheters are equally effective, which is in agreement with previous studies comparing these two types of catheter for AFL ablation.[12–14]

Linear CTI ablation, first described by Cosio et al.,[15] is the first-line strategy for treatment of typical AFL. The first procedures used a 4-mm tip catheter, but success rates were as low as 67% in some series.[16] Efforts to improve these figures included the development of 8-mm tip catheters and then irrigated-tip catheters designed to increase the size of lesions, improving success rates, which in some cases have reached 99%.[12,14,16,17] The high success rates of AFL ablation, together with the poor results of drug therapy,[2] have led to catheter CTI ablation becoming a common procedure.

Previous studies comparing conventional AFL ablation with remote navigation-controlled systems showed that the latter produced worse results (91% vs. 84%).[7]

In our study, the success rates with the MNS of 94% using an 8-mm tip catheter and 100% with an irrigated catheter are higher than those described with conventional systems.[11] Previous studies have also shown that procedure time and RF time tend to be longer with the MNS but fluoroscopy time is significantly shorter.[7,8] Mean fluoroscopy time in our series (7.8±5.3 min) was also significantly shorter than reported for conventional ablation.[12,14,16,17] The longer fluoroscopy time seen in the 8-mm tip catheter group may be due to the greater difficulty in adjusting the larger tip to the anatomy of the CTI, but may also be the result of the learning curve associated with the MNS, since the first cases using the remote system were treated with an 8-mm tip catheter. Randomized trials comparing the two catheter types have shown similar success and complication rates as well as procedure and fluoroscopy times.[12,15]

Table 3 Follow-up.

	8-mm tip catheter	Irrigated catheter	p
Follow-up (months)	48±11	18.5±12	0.01
Recurrence of AFL	1 (6%)	1 (5%)	NS
Incidence of AFL	4 (24%)	2 (10%)	NS

AFL: atrial flutter.

Our long-term success rate (5% relapse at 32±19 months) was better than that described for conventional ablation, well below the 10.9% at 13.8±0.3 months of Perez et al.[11] and the 20% at 21±11 months reported by Blomstrom-Lundqvist et al.[2] Although we did not assess coagulum formation on the catheter tip in our study, most studies show a tendency for higher prevalence of this complication with 8-mm tip catheters than with irrigated catheters (between 6% and 15%).[8,12] For this reason, notwithstanding the good results obtained with the 8-mm tip catheter, the irrigated catheter has been our choice for AFL ablation since it became available for the MNS.

The occurrence of AF following ablation of AFL, although not strictly speaking a relapse of the initial arrhythmia, is a cause of morbidity and hospitalization. The incidence of AF after AFL ablation depends on whether it had occurred before the procedure and on the duration of follow-up, and ranges between 8 and 52%.[10] In our patient population the incidence of AF was 16% in a mean follow-up of 32±19 months; the figure was higher in the 8-mm tip catheter group, but without statistical significance, and may be due to the longer follow-up in this group.

Limitations

The present study was not randomized and included a small number of patients, and no comparison was made with conventional ablation in terms of procedure or fluoroscopy times or efficacy. The comparison between the two different catheter types was performed retrospectively.

Conclusions

Our study demonstrates that the remote control Niobe II system is safe and effective for AFL ablation, with a high rate of acute success and a low rate of relapse. Irrigated

catheters and 8-mm tip catheters were equally effective and safe for the ablation of typical AFL using the MNS.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Safety and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using Magnetic Navigation versus Manual Conventional Ablation: A Propensity-Score Analysis

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Magnetic versus Manual Ablation of Atrial Fibrillation. ***Introduction:*** **Whether or not the potential advantages of using a magnetic navigation system (MNS) translate into improved outcomes in patients undergoing atrial fibrillation (AF) ablation is a question that remains unanswered.**

Methods and Results: **In this observational registry study, we used propensity-score matching to compare the outcomes of patients with symptomatic drug-refractory AF who underwent catheter ablation using MNS with the outcomes of those who underwent catheter ablation using conventional manual navigation. Among 1,035 eligible patients, 287 patients in each group had similar propensity scores and were included in the analysis. The primary efficacy outcome was the rate of AF relapse after a 3-month blanking period. At a mean follow-up of 2.6 ± 1.5 years, AF ablation with MNS was associated with a similar risk of AF relapse as compared with manual navigation (18.4% per year and 22.3% per year, respectively; hazard ratio 0.81, 95% CI 0.63–1.05; P = 0.108). Major complications occurred in two patients (0.7%) using MNS, and in six patients (2.1%) undergoing manually navigated ablation (P = 0.286). Fluoroscopy times were 21 ± 10 minutes in the manual navigation group, and 12 ± 9 minutes in the MNS group (P < 0.001), whereas total procedure times were 152 ± 52 minutes and 213 ± 58 minutes, respectively (P < 0.001).**

Conclusions: **In this propensity-score matched comparison, magnetic navigation and conventional manual AF ablations seem to have similar relapse rates and a similar risk of complications. AF ablations with magnetic navigation take longer to perform but expose patients to significantly shorter fluoroscopy times.**
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atrial fibrillation, catheter ablation, efficacy, magnetic navigation system, manual ablation, propensity score, safety

Introduction

Catheter ablation has now become a well-established treatment for selected patients with atrial fibrillation (AF).[1-3] Enduring success of pulmonary vein isolation (PVI) depends on the creation of permanent and uninterrupted transmural scar in order to block electrical conduction between the left atrium (LA) and the pulmonary veins. The creation of this scar can be challenging even for experienced electrophysiologists and recurrences are common, usually due to pulmonary vein reconduction.[4,5] Procedures are also associated with a relatively high level of radiation exposure and a non-negligible risk of complications.[6]

Recently, a magnetic navigation system (MNS) was introduced as a way to ensure stable and reproducible catheter positioning, provide adequate tissue contact, and reduce radiation exposure to both patient and physician.[7,8]

Whether or not these potential advantages translate into improved clinical outcomes is an important question that remains essentially unanswered.

The purpose of this study was to assess the safety and long-term efficacy of a single AF ablation procedure using MNS as compared to conventional manual navigation.

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Methods

Patient Characteristics and Study Design

We conducted a registry-based analysis of all consecutive patients with symptomatic drug-refractory AF undergoing percutaneous PVI in 2 centers (Hospital Santa Cruz,

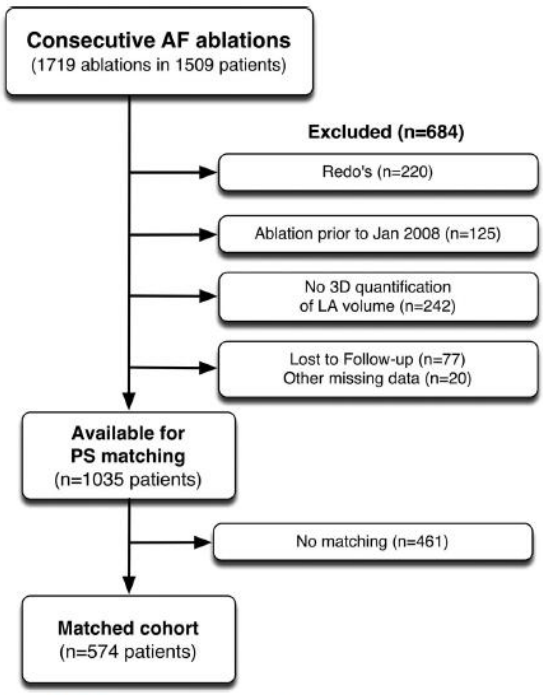

Figure 1. *Patient selection and study design.*

Carnaxide, Portugal; and Hospital da Luz, Lisbon, Portugal). In order to account for the learning curve with new technology, AF ablations performed during the first 6 months after the introduction of magnetic navigation (i.e., July through December 2007) were excluded. The analyzed procedures were performed between January 2008 and April 2014, when both techniques were in use. Exclusion criteria also comprised any previous AF ablation procedure, no 3-dimensional quantification of LA volume, and loss to follow-up (Fig. 1).

Data on patient demographics, symptoms, and previous medical history were obtained from a pre-procedure interview, supplemented with information provided by the referring physician and electronic medical records. AF was categorized as paroxysmal if self-terminated in <7 days, persistent if episodes lasted ≥7 days or required pharmacological or electrical cardioversion, or longstanding persistent if AF was maintained for more than 12 months.[3] The presence of structural heart disease (known cardiomyopathy, moderate or severe valvular heart disease, congenital heart disease, or left ventricular systolic dysfunction from any cause) was assessed by clinical history, physical examination, and transthoracic echocardiography. Sixty-four slice cardiac computed tomography performed less than 48 hours before the ablation procedure was used to assess LA volume, an important predictor of AF recurrence.[9] When cardiac CT could not be performed for logistical reasons (n = 162, 28.2%), electroanatomical mapping at the time of ablation was used to calculate LA volume, as previously described.[10-12]

This study was approved by both of the institutional review boards and all patients gave written informed consent.

Ablation Protocol

Ablation procedures were guided by CARTO™ (Biosense Webster® Inc., Diamond Bar, CA, USA) or NavX™ (St. Jude Medical® Inc., St. Paul, MN, USA) electroanatomical mapping. Three catheters were introduced via right femoral venous access under local anesthesia. A multipolar diagnostic catheter was placed in the coronary sinus. An irrigated-tip ablation catheter and a duodecapolar circular mapping catheter were placed at the pulmonary veins (PV) ostia via transeptal access. In Hospital Santa Cruz all patients underwent conventional manually guided ablation, whereas in Hospital da Luz a Niobe II magnetic navigation system (Stereotaxis® Inc., St. Louis, MO, USA) was used. Irrigated radiofrequency ablation was performed with continuous lesions encircling both pairs of pulmonary veins and deployed more than 5 mm from the PV ostia in order to achieve pulmonary vein isolation. In patients with previously documented typical atrial flutter or when typical sustained atrial flutter occurred during the procedure, a cavotricuspid isthmus ablation line was also performed. Whenever necessary, patients were cardioverted to sinus rhythm at the end of the procedure. Anticoagulation was restarted within 24 hours, maintained for 6 months, and then suspended according to $CHADS_2$ criteria (CHA_2DS_2-VASc from 2013 onward). As a general rule, patients were maintained on class I or III antiarrhythmic drugs for the first 3 months and then withdrawn if there was no AF recurrence. Despite this department guidance, the decision to withhold drug therapy was ultimately left to the treating electrophysiologist. Proton pump inhibition was used by protocol during the first month. Throughout the study period, the ablation procedures were performed by the same team of experienced electrophysiologists, who worked in both institutions.

Study Endpoints and Patient Follow-Up

The efficacy endpoint was AF recurrence, defined as the presence of symptomatic or documented AF after a 3-month blanking period. Symptomatic AF was defined as the presence of symptoms possibly related to AF episodes. Documented AF was defined by the presence of at least one episode of AF lasting more than 30 seconds in any electrocardiogram (ECG), 24-hour Holter monitoring or event-loop recording. AF recurrence was assessed independently of the use of antiarrhythmic drugs at the time of relapse. The follow-up protocol consisted of outpatient visits with 12-lead ECGs and 24-hour Holter monitoring at 1, 3, 6, and 12 months in the first year, and yearly thereafter. Patients were encouraged to contact the department whenever they experienced symptoms of AF recurrence or signs of complications. Additional ECGs, 24-hour Holter monitoring, and event-loop recordings were performed whenever necessary to assess symptoms of possible recurrence. When clinical records were insufficient, a structured telephonic interview was conducted. Seventy-seven patients (5.1%) were lost to follow-up and excluded from this analysis.

The primary safety endpoint was the occurrence of any major complication, defined as a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours.[3] Our secondary safety endpoint was fluoroscopic time.

Statistical Analysis

Given the differences in the baseline characteristics between patients undergoing PVI with MNS versus conventional manual navigation, propensity-score matching was used to identify a cohort of individuals with similar baseline characteristics. The propensity score (PS) is a conditional probability of receiving a particular treatment given a set of baseline-measured covariates.[13] The PS was estimated by a multivariable logistic regression model with 'AF ablation using MNS' as the dependent variable, and the following baseline characteristics as covariates: age, gender, body mass index, type of AF, hypertension, structural heart disease, and indexed left atrial volume. For every MNS ablation, matching patients with the closest propensity score were identified from the pool of manual navigation ablations. The maximal allowable difference in propensity score for matching was 0.2 (caliper width equal to 0.2 of the standard deviation of the logit of the propensity score). When 2 or more manual navigation patients had the same propensity-score match, the match for the analysis was chosen randomly. Matched subjects were removed from the pool and the next MNS ablation and its matched manual navigation patient were selected until no further matches could be identified.

Comparisons between groups were performed using independent samples *t*-test and Fisher's exact test for continuous and categorical variables, respectively. Kaplan–Meier curves were used to describe the occurrence of AF relapse over time, and any differences in AF-free survival were assessed with the log-rank test. Annualized event rates for AF relapse were also calculated by dividing total numbers of first events by total number of person-years of follow-up for each group. Finally, the comparative risk of AF relapse was further adjusted for in the matched cohort with the use of a Cox proportional-hazards model. This model included the treatment modality (MNS vs. conventional manual navigation), the propensity score, and potentially confounding variables whose standardized difference between groups remained above 10% after matching.[14] Statistical analyses were performed with SPSS version 19.0 (SPSS® Inc., Chicago, IL, USA). Two-tailed P values <0.05 were considered statistically significant.

Results

Among the 1,509 registry patients, 1,035 were available for matching, of whom 633 (61.2%) underwent PVI with MNS and 402 (38.8%) with conventional manual navigation. Before propensity-score matching, there were significant differences between the 2 groups in several of the baseline characteristics (Table 1). Using the propensity score, 287 patients who underwent AF ablation using MNS were matched with 287 who underwent ablation with conventional manual navigation. The C-statistic for the model was 0.82. After matching, the 2 cohorts were well balanced with respect to baseline variables except for indexed LA volume, where a trend toward smaller left atriums in the MNS group was still observed (standardized difference of 12%, P = 0.088). PVI was achieved in all patients. Overall, 63 patients (11.0%) remained on antiarrhythmic drugs for longer than 3 months after ablation, despite the absence of AF recurrence. The proportion of antiarrhythmic drug persistence was similar between patients who underwent PVI with manual navigation versus MNS (13.1% vs. 9.9%, respectively, P = 0.284).

At a mean follow-up of 2.6 ± 1.5 years, 251 patients (43.7%) experienced AF relapse (131 in the manual navigation group and 120 in the MNS group). Recurrences occurred a median of 1.2 years after the ablation procedure (interquartile range 0.5–2.5), and were established by symptoms in 69 cases, by electrocardiographic documentation of AF in 27 patients, and by both in the remainder 155 subjects. Kaplan–Meier AF-free survival curves for the matched MNS and manual navigation patients are presented in Figure 2. AF ablation with MNS was associated with a similar risk of AF relapse as compared with conventional manual navigation (18.4% per year and 22.3% per year, respectively; hazard ratio 0.81, 95% CI 0.63–1.05; P = 0.108). Further Cox regression adjustment for propensity-score value and indexed LA volume confirmed that treatment modality (MNS vs. manual navigation) was not an independent predictor of AF relapse in this cohort (Table 2).

Safety Outcomes

Observed complications and procedure characteristics are detailed in Table 3. Major complications occurred in 2 patients (0.7%) using the MNS, and 6 patients (2.1%) undergoing conventional manually navigated ablation (P = 0.286). Fluoroscopy times were significantly shorter with MNS, with an average 9-minute reduction in exposure as compared to manual navigation. On average, procedures using MNS took 61 minutes longer to perform and applied radiofrequency for 23 minutes longer than manual conventional navigation.

Discussion

Ever since its introduction in 2003, magnetic navigation for AF ablation has been proposed as a way to overcome some of the limitations of this demanding procedure. The potential advantages of magnetic navigation include finer control of small catheter movements, greater stability, and the possibility of standardizing catheter positions, which could theoretically produce better electrical isolation of the pulmonary veins.[15] Magnetic guidance, and the need of lower forces to maintain stable tissue contact, might also mean less fluoroscopy time and fewer complications. Notwithstanding these potential benefits, and despite being used for several years, magnetic navigation for PVI has never been compared to conventional manual ablation in a large randomized controlled trial with long-term follow-up. Applying a pseudo-randomization procedure to a large dataset of patients, we sought to compare the safety and long-term efficacy of a single AF ablation procedure performed with each of these techniques. Our results suggest that the 2 methods have similar relapse rates and a similar risk of complications. According to our findings, AF ablations with magnetic navigation take longer to perform, but expose patients to significantly shorter fluoroscopy times.

To the best of our knowledge, this is the largest and longest follow-up comparison between MNS and manually navigated AF ablation. Several studies have addressed this subject, but these have generally been limited by non-randomized design, small sample sizes, and relatively short follow-up periods.[8,16-22] The available evidence gathered in 2 recent systematic reviews and meta-analyses suggests that both techniques have similar relapse rates, a notion that is strengthened by our study.[15,23]

TABLE 1
Baseline Characteristics Before and After Propensity-Score Matching

	Before Matching				After Matching			
Characteristic	**Manual Navigation (n = 402)**	**Magnetic Navigation (n = 633)**	**Standardized Difference**	**P Value**	**Manual Navigation (n = 287)**	**Magnetic Navigation (n = 287)**	**Standardized Difference**	**P Value**
Age (years)	57.7 ± 11.0	59.2 ± 11.1	13.6%	0.036	57.9 ± 11.2	58.3 ± 10.7	3.7%	0.640
Male sex	274 (68.2%)	437 (69.0%)	1.7%	0.783	194 (67.6%)	201 (70.0%)	5.2%	0.589
Body mass index (kg/m^2)	27.7 ± 3.8	27.0 ± 3.8	18.4%	<0.001	27.6 ± 3.8	27.7 ± 4.0	2.6%	0.724
Body surface area (m^2)	1.96 ± 0.22	1.93 ± 0.21	14.0%	<0.001	1.96 ± 0.22	1.96 ± 0.22	0.1%	0.990
Paroxysmal AF	291 (72.4%)	493 (77.9%)	12.3%	0.053	207 (72.1%)	213 (74.2%)	4.7%	0.638
Hypertension	160 (39.8%)	233 (36.8%)	6.2%	0.358	112 (39.0%)	109 (38.0%)	2.1%	0.864
Structural heart disease	36 (9.0%)	35 (5.5%)	15.7%	0.043	21 (7.3%)	22 (7.7%)	1.5%	1.000
Indexed LA volume (mL/m^2)	63 ± 18	46 ± 16	99.8%	<0.001	57 ± 16	55 ± 18	11.7%	0.088

Standardized differences of less than 10.0% indicate a relatively small imbalance between groups.

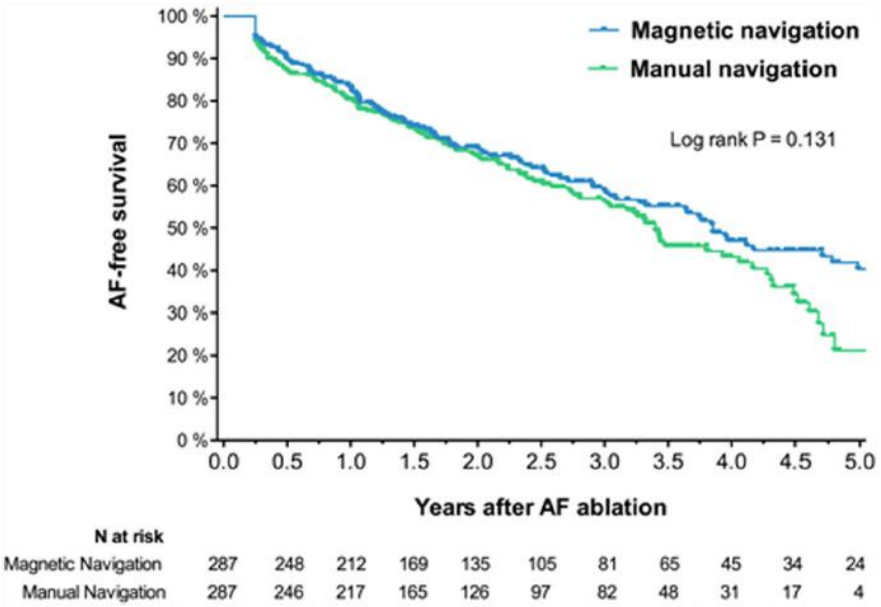

Figure 2. *Kaplan–Meier AF-free survival curves after single ablation procedure.*

TABLE 2
Cox Regression Adjustment for Propensity Score and Indexed Left Atrium Volume in the Matched Cohort

Variable	**Adjusted HR**	**95% CI**	**P Value**
Propensity score	0.78	0.23–2.70	0.694
Indexed LA volume*	1.08	0.94–1.26	0.284
Magnetic navigation	0.81	0.63–1.04	0.104

HR = hazard ratio; CI = confidence interval.
*Hazard ratio for each 10 mL/m^2 increment.

The reasons for the apparent similar results of MNS in terms of long-term efficacy are beyond the scope of this study, but it can be speculated that the potential advantages of MNS including catheter stability are balanced by the higher contact forces of conventional manual ablation.[24,25]

Our results are also in general agreement with the published evidence regarding the safety of AF ablation with each of the 2 navigation methods. One of the systematic reviews and meta-analyses comparing MNS to conventional manual navigation reported less peri-procedural complications, while the other found similar complication rates except for pericardial tamponade or effusion requiring intervention/hospitalization, which were significantly less numerous when MNS was used.[15,23] In our study, major complications were relatively rare and, although numerically more frequent in the manual navigation group, this difference did not reach statistical significance. However, it should be recognized that our analysis is underpowered to detect differences in major

TABLE 3
Observed Complications and Procedure Characteristics in the Matched Cohort of Patients Undergoing Ablation with Manual versus Magnetic Navigation

	Manual Navigation (n = 287)	Magnetic Navigation (n = 287)	P Value
Complications			
Death	0	0	NA
Atrioesophageal fistula	0	0	NA
Stroke or TIA	0	1 (0.35%)	1.000
Cardiac tamponade/perforation	2 (0.70%)	1 (0.35%)	1.000
Pulmonary vein stenosis	0	0	NA
Major bleeding	1 (0.35%)	0	1.000
Vascular access complication	5 (1.74%)	1 (0.35%)	0.216
Any major complication	6 (2.09%)	2 (0.70%)	0.286
Fluoroscopy time	21 ± 10 minutes	12 ± 9 minutes	<0.001
Radiofrequency application duration	31 ± 18 minutes	54 ± 22 minutes	<0.001
Procedure duration	152 ± 52 minutes	213 ± 58 minutes	<0.001

NA = non-applicable.

complications, since these are relatively infrequent events, best assessed in large randomized controlled trials or multicenter registries.

Finally, our findings corroborate other studies showing that MNS ablations take longer to perform but expose patients to less fluoroscopy time.[8,17-22,26] Since the radiofrequency power was similar by protocol in both groups, the lower contact force in the MNS might be responsible for a longer time to achieve pulmonary vein isolation. Regarding fluoroscopy time, given that a significant proportion of patients need repeat procedures in order to remain free of AF, the reduction in fluoroscopy time seems an important goal. This may be particularly relevant for younger patients (especially women) since they are more susceptible to the biological effects of ionizing radiation.[27] On the other hand, longer procedure times may pose additional challenges to already overloaded electrophysiology departments struggling to treat an ever increasing number of patients with AF.

Limitations

Some limitations of this study should be taken into account. First, the observational design of the study: even though propensity scoring can provide excellent matching of baseline characteristics, it does not guarantee the absence of significant differences in covariables that were not systematically collected and entered into the model, such as AF burden, sleep apnea, and LA fibrosis. Some of our patients were lost to follow-up, and AF relapse may be underreported, since recurrences are frequently asymptomatic and the follow-up protocol did not include continuous ECG monitoring. Finally, sample size limitations preclude subgroup analyses based on type of AF or other baseline characteristics.

Conclusion

In this propensity-score matched comparison, magnetic navigation and conventional manual AF ablations seem to have similar relapse rates and a similar risk of complications. AF ablations with magnetic navigation take longer to perform but expose patients to significantly shorter fluoroscopy times. Large truly randomized controlled trials are warranted to confirm these findings.

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9.3.1 - Electrocardiography (ECG)

40521

Accuracy of noninvasive electrocardiographic imaging using isopotential versus isochronal map for identifying the site of origin of ventricular arrhythmias

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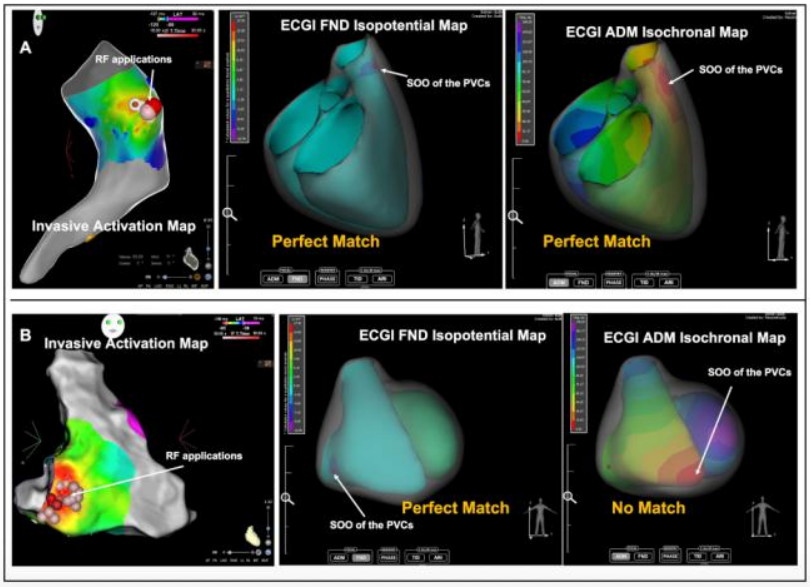
Background and aim: Previous studies reporting the results of noninvasive electrocardiographic imaging (ECGI) used both isopotential map and isochronal map to assess the site of origin (SOO) of premature ventricular contractions (PVCs). The aim of this study was to evaluate the accuracy of both methods globally, and according to the location of the arrhythmia: from the right ventricular outflow tract (RVOT) or other locations (non-RVOT).

Methods: We studied with ECGI 35 consecutive patients with frequent (>10.000/24 h) PVCs. Patients were excluded if the ablation was not performed (7 patients) or was unsuccessful (7 patients). The study group consisted of 21 patients, 11 male, median age of 56 (44-71) years. The ECGI was performed with the epi-endocardial system Amycard. Two noninvasive maps were obtained: isopotential map based on the analysis of the shape and amplitude of the unipolar electrogram (FND method) and an isochronal map obtained using the activation direction method (ADM) (Figure). The invasive activation map was obtained with the Carto or the Ensite system and radiofrequency was applied at the earliest activation site with QS morphology on the unipolar electrogram and a pace match of at least 11/12. The SOO of the PVCs was considered the site where the PVCs were abolished. We assessed the accuracy of the ECGI to identify the SOO of the PVCs using both methods. A perfect match was defined as a predicted location by the ECGI within the same anatomic segment of the actual SOO of the PVCs, whereas a near match as a predicted location within the same segment or a contiguous one. Values are presented as median (Q1-Q3)

Results: PVCs originated in the RVOT in 11 (52%) patients. The percentage of near matches was not significantly different between FND and ADM methods (95% vs 86%, p=0.50), however the percentage of perfect matches was significantly higher with the FND than with the ADM technique (95% vs 67 %, p=0.031). We found no significant differences in accuracy according to the location of the PVCs, in the RVOT or outside (Table).

Conclusions: We found a good agreement between ECGI and invasive maps, however the FND technique showed a better accuracy regardless the site of the PVCs.



Europace 2022 Volume 24 Supplement 1

9.3.1 - Electrocardiography (ECG)

	Overall sample N=21	RVOT PVCs N=11	Non-RVOT PVCs N=10	P value
Age in years	56 (44-71)	56 (42-65)	59 (45-72)	0.705
Male gender, n (%)	11 (52)	5 (50)	6 (60)	0.670
Nº of leads, n (%)	139 (117-159)	129 (117-157)	145 (115-159)	0.809
FND perfect match, n (%)	20 (95)	11 (100)	9 (90)	0.476
ADM perfect match, n (%)	14 (67)	9 (82)	5 (50)	0.183
FND near match, n (%)	20 (95)	11(100)	9 (90)	0.476
ADM near match, n (%)	18 (86)	11 (100)	7 (70)	0.090
ADM/FND match, n (%)	19 (90)	11 (100)	8 (80)	0.214

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Assessment of wave front activation duration and speed across the right ventricular outflow tract using electrocardiographic imaging as predictors of the origin of the premature ventricular contractions: A validation study

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ABSTRACT

Aims: Evaluate right ventricular outflow tract (RVOT) activation duration (AD) and speed, invasively and with the electrocardiographic imaging (ECGI), as predictors of the origin of the PVCs, validating the ECGI.
Methods: 18 consecutive patients, 8 males, median age 55 (35–63) years that underwent ablation of PVCs with inferior axis and had ECGI performed before ablation. Isochronal activation maps of the RVOT in PVC were obtained with the ECGI and invasively. Total RVOT AD was measured as the time between earliest and latest activated region, and propagation speed by measuring the area of the first 10 ms of activation. Cut-off values for AD, activation speed and number of 10 ms isochrones to predict the origin of the PVCs, were obtained with the ROC curve analysis. Agreement between methods was done with Pearson correlation test and Bland-Altman plot.
Results: PVCs originated from the RVOT in 11 (61%) patients. The stronger predictor of PVC origin was the AD. The median AD in PVCs from RVOT was significantly longer than from outside the RVOT, both with ECGI and invasively, respectively 62 (58–73) vs 37 (33–40) ms, $p < 0.0001$ and 68 (60–75) vs 35 (29–41) ms, $p < 0.0001$. Agreement between the two methods was good ($r = 0.864$, $p < 0.0001$). The cut-off value of 43 ms for AD measured with ECGI predicted the origin of the PVCs with a sensitivity and specificity of 100%.
Conclusions: We found good agreement between ECGI and invasive map. The AD measured with ECGI was the best predictor of the origin of the PVCs.

Introduction

Catheter ablation is currently indicated in patients with frequent symptomatic premature ventricular contractions (PVCs) from the outflow tracts [1]. For many years the right ventricular outflow tract (RVOT) has been considered the most frequent site of origin of idiopathic PVCs. However, more recent studies have shown that other sites, mainly the LVOT and the aortic cusps are as frequent as the RVOT [2]. The class of recommendation is different if the PVC originates in the RVOT or LVOT due to the different success rates and possible adverse events of the ablation procedure [1]. Thus, predicting the origin of the PVCs before ablation is important to delineate the therapeutic approach. However, using the standard 12-lead electrocardiogram (ECG) algorithms is complicated and the accuracy is limited [3]. The non-invasive electrocardiographic imaging (ECGI) has proved its benefit in identifying the site of origin of PVCs [4], however the percentage of correctly diagnosed cases varies [5–8]. Previous studies have reported that activation speed across the RVOT can distinguish PVCs with a RVOT origin from PVCs with a LVOT origin based on the propagation speed during the PVC [9,10]. The aim of this study was to evaluate the RVOT endocardial activation duration and wavefront propagation speed, both invasively and with the ECGI, assess their value as predictors of the origin of the PVCs and validate the new technique.

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Material and methods

Patient population

From February 2018 to December 2021, we retrospectively studied consecutive patients presenting to our center for ablation of frequent idiopathic PVCs, defined as more than 10.000 per 24 h, with an inferior axis, that had an ECGI performed before ablation. All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler study and 12-lead ECG, and cardiac magnetic resonance with late gadolinium enhancement to exclude the presence of structural heart disease. Arrhythmogenic right ventricular cardiomyopathy was ruled out according to the Task Force Criteria [11]. A 24-Hour Holter recording was performed before ablation and the number of PVCs per 24 h and the presence of episodes of non-sustained ventricular tachycardia (NSVT), defined as >3 PVCs in a run were assessed. Patients with evidence of structural heart disease, conduction delays, electrical diseases or abnormal QRS morphology in sinus rhythm were excluded. Patients that did not perform electroanatomical map of the RVOT during PVC or those that underwent previous ablation were also excluded.

Study design

We assessed the duration of the endocardial activation and the wavefront propagation speed on the RVOT during PVC using both invasive mapping and ECGI and tested for their ability to predict the origin of the PVCs validating the ECGI for the assessment of those parameters.

Non-invasive electrocardiographic imaging

The ECGI was performed with the non-invasive epicardial and endocardial Amycard system (EP Solutions SA, Switzerland), before the catheter ablation. This method has been previously described [12]. However, briefly it consists of a multichannel ECG amplifier recorder that analyses up to 224 leads from up to 28 electrode bands, with 8 leads each, placed on the patient's torso. They were recorded with a 0.05- to 500-Hz bandpass filter, digitized with the sampling rate of 1000 samples/s and exported to the Amycard 01C software. Additionally, a 50 Hz frequency noise filter was used as needed. Afterwards, with the electrode bands in place, an ECG-gated cardiac tomography (CT) scanning of the heart and thorax with intravenous contrast, was performed with a third-generation 192-slice dual-source SOMATOM Force (Siemens Healthcare). The CT data was imported in the DICOM format into the Amycard software, and a 3-dimensional torso and heart model were obtained from the CT. Body surface ECG data was processed by Amycard system, using its inverse problem solution software [13] in combination with heart and torso anatomy, allowing for reconstruction of unipolar electrograms at approximately 2500 points on epicardium and endocardium. Isochronal activation maps of the PVCs were obtained with the activation direction method (ADM) of the ECGI by an experienced user. Total duration of activation across the RVOT was measured as the time interval between the earliest and the latest activated region. The 10 ms isochronal maps were automatically obtained by using a scale starting from 0 ms for the earliest activation time and above 120 ms for the latest activation. With this scale, the isochronal map automatically displays 12 isochrones with a duration of 10 ms each (Figs. 1 and 2). The number of isochrones across the RVOT was assessed for each patient. The ECGI was done without isoprenaline in all patients.

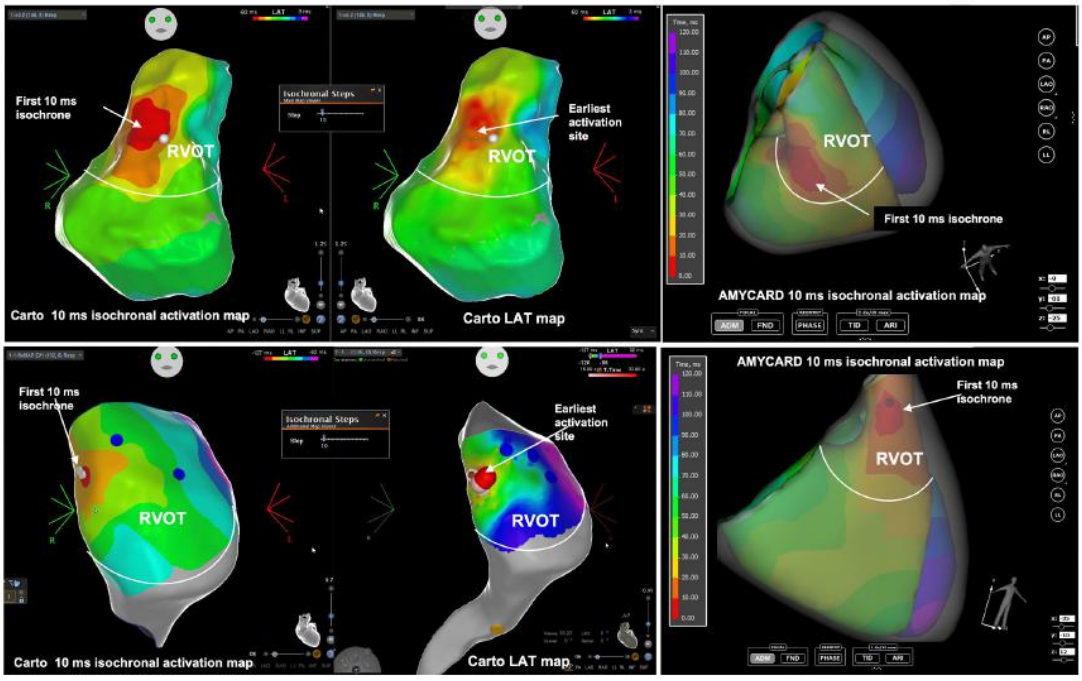

Fig. 1. Representative cases of PVCs from the RVOT.
Top panel: invasive isochronal map of a patient with PVCs from the anterior aspect of the RVOT (left), activation map displaying the earliest activation site (middle) and ECGI isochronal map (right) both showing a narrow area of the first 10 ms of activation and a high number of 10 ms isochrones across the RVOT. Bottom panel: the same as above in a patient with PVCs from lateral aspect of the RVOT. RVOT: right ventricular outflow tract; LAT: local activation time.

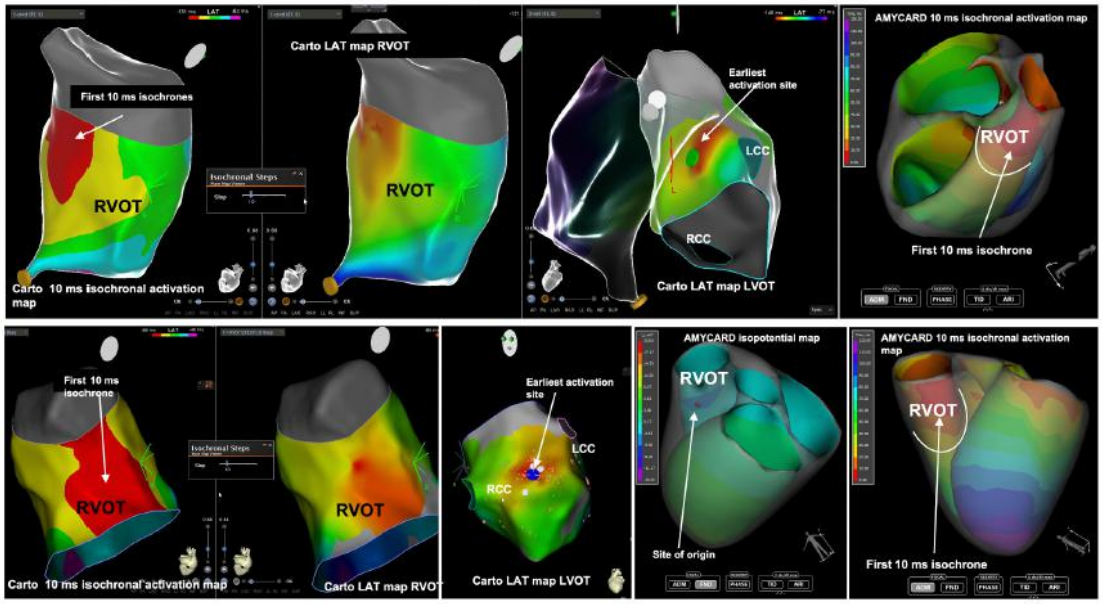

Fig. 2. Representative cases of PVCs from the LVOT.
Top panel: invasive isochronal map of the RVOT during PVC (left) of a patient with PVCs from the LCC. Activation map of the LVOT displaying the earliest activation site (middle) and ECGI isochronal map (right) both showing a wide area of the first 10 ms of activation and only three 10 ms isochrones across the RVOT. Bottom panel: the same as above in a patient with PVCs from the area between the RCC and the LCC. The ECGI identified the site of origin of the PVC in the RVOT left septum. LAT: local activation time; LCC: left coronary cusp; LVOT. left ventricular outflow tract; RCC: right coronary cusp. RVOT: right ventricular outflow tract.

Invasive electroanatomic mapping and ablation

Patients were studied in a fasting non sedate state. All beta-blockers and antiarrhythmic drugs were.

discontinued at least five half-lives before the electrophysiological study. All studies were performed off isoprenaline. During endocardial mapping of the LVOT heparin was administrated to achieve an ACT of 250–300 s. All patients underwent electroanatomical mapping with CARTO 3 (Biosense-Webster) or EnSite Precision (Abbott). With the former, all procedures were performed using the Niobe magnetic navigation system (Stereotaxis) working with the monoplane fluoroscopy system AXIOM Artis (Siemens) as previously described [14]. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster) was used with a 3.5-mm distal tip electrode and a 2–5–2 interelectrode distance. With the EnSite Precision system all procedures were done manually with the monoplane fluoroscopy and using an irrigated tip TactiCath catheter (Abbott) with a 3.5-mm distal tip electrode and a 2–2–2 interelectrode distance. Mapping of the LVOT endocardium and the aortic coronary cusps was performed using a transaortic approach in all patients. When ablation was unsuccessful at the coronary cusps or the LVOT, the coronary sinus, the great cardiac vein and anterior interventricular vein were mapped. The activation map was created by mapping several points during each PVCs while using a surface ECG lead as reference. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed.

With the Carto system, local activation time (LAT) was defined as the time of the maximum downslope of the unipolar distal electrogram displayed on the corresponding bipolar signal. With the Ensite system LAT was defined as the time of the first peak of the bipolar electrogram [15]. Total activation duration across the RVOT was measured as the time interval from the earliest RVOT endocardial activation to the latest RVOT endocardial activation recorded during PVC. The geometry of the RVOT depicting the LAT recorded was constructed in real time with the electrophysiological information colour coded and superimposed on the reconstruction. The level of RVOT/pulmonary valve junction was thoroughly determined based on electroanatomical voltage mapping by passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT. A voltage map of the RVOT in PVC was also obtained and the presence of areas of low voltage with bipolar electrogram amplitude below 1.5 mV, outside the transitional-voltage zone immediately below the pulmonary valve as previously described [16], were assessed. The data derived from the isochronal map analysis were obtained offline, and therefore, the procedure results were not dependent on these data. Activation isochronal maps were displayed as 10 ms isochrones. The total number of 10 ms isochrones across the RVOT was measured. The ablation site was selected based on the earliest endocardial activation time in relation to the onset of the surface QRS, with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous PVCs. Local activation time at the ablation site was measured in relation to the beginning of the QRS on the surface ECG. In patients in whom the site of the origin of the PVCs was the LVOT or aortic coronary cusps, a coronary angiography was performed before ablation. Energy was delivered from an RF generator between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 s, to a maximum temperature of 43 °C and titrated according to the location of the PVCs, to a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. Success was defined as abolition of PVCs until 30 min after ablation. All the intracardiac electrograms were reviewed by two senior electrophysiologists.

Measurement of the wavefront propagation speed

The centrifugal wave front propagation speed was assessed both non-invasively as well as invasively by measuring the area encompassing the first 10 ms of the RVOT activation on the isochronal map. Each propagated area was measured by manually tracing the border of the isochrone and the area automatically calculated. All measurements were performed without isoprenaline.

Statistical analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc., Chicago, Illinois). Data was tested for normality with the Shapiro- Wilk test and presented as median and lower and upper quartile (Q1-Q3) for continuous variables as median (min-max) for discrete variables, and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann Whitney test for independent samples. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples.

Receiver operator characteristic curves (ROC) and areas under the curve (AUC) were obtained to determine the discriminative power of covariables as predictors of the site of origin of the PVCs and obtain the optimal cut-point value based on the Youden index. Sensitivity and specificity were calculated with contingency tables and Chi-Square test. Binary logistic regression was used to evaluate the value of covariables as predictors of the site of the PVCs. The assumption of linearity for continuous variables was tested and confirmed with the Box-Tidwell test. To evaluate the agreement between the ECGI and the invasive mapping measurements in case of continuous variables the Pearson correlation test was used for assessment of precision and the Bland-Altman plot, to evaluate the presence of a systematic difference in the measurements and the limits of agreement, by providing an estimate of a range in which 95% of the differences between test results are expected to fall, assuming those differences are normally distributed. In the case of discrete variables, the Cohen's Kappa test was used to assess the agreement between both methods.

For all tests, a two-tailed p-value <0.05 was considered as statistically significant.

Ethics

All patients signed the informed consent form, and the study was approved by the Ethical Committee of the Hospital da Luz and Hospital Centre of Setubal. The study is in compliance with the Helsinki Declaration.

Results

Patient population

Eighteen consecutive patients were enrolled, 8 males, median age 55 (35–63) years. Physical examination, 12-lead ECG and transthoracic echocardiography were normal. All patients were symptomatic, mostly palpitations and no patient had family history of sudden death. The 24-h Holter recording showed a high PVC burden with a median of 15,000 (12750–21,854) PVCs/24 h and presence of NSVT in two patients (11%). The cardiac magnetic resonance did not show evidence of RVOT abnormalities in any patient.

Eleven patients had PVCs with a RVOT origin and seven patients with an LVOT origin, four in the left coronary cusp (LCC), one in the commissure between the LCC and the right coronary cusp (RCC), one in the LV summit and one in the aortomitral continuity. Baseline characteristics of the study patients as well as comparison between the above groups are displayed in Table 1. Patients with PVCs from the RVOT and LVOT did not differ in relation to the analyzed parameters.

Non-invasive electrocardiographic imaging

The median number of leads used for the ECGI map was 144 (119–17), not significantly different for patients with RVOT PVCs versus LVOT PVCs (Table 2). Total duration of endocardial activation across the RVOT was 54 (39–68) ms and the median number of 10 ms isochrones across the RVOT was 5 (3–7). The area of the first 10 ms isochrone of the RVOT activation during the PVC was 4.7 (2.9–6.1) cm^2. The values of total RVOT activation duration and number of 10 ms isochrones were significantly higher and the area of the first 10 ms isochrone of the RVOT activation was significantly narrower if the PVCs originated from the RVOT (Table 2).

Invasive electroanatomic mapping and ablation

The invasive electroanatomic mapping of the RVOT in PVC was successfully acquired in all patients, the Carto system was used in sixteen patients and the Ensite system in two. The median number of points per patient collected in the RVOT to obtain the map was 109 (48–144), not significantly different for patients with RVOT PVCs versus LVOT PVCs (Table 3). The median duration of endocardial activation

Table 1
Patient characteristics.

	Overall sample (n = 18)	RVOT PVCs (n = 11)	LVOT PVCs (n = 7)	p value
Demographic data				
Age in years, median (Q_1-Q_3)	55 (35–63)	56 (42–62)	53 (25–70)	1.000
Male Gender, n (%)	8 (44)	5 (46)	3 (43)	1.000
Body mass index in Kg/ m^2, median (Q_1-Q_3)	23 (21–27)	22.6 (19.6–27.7)	23.9 (21.3–26.6)	0.596
Risk factors and medications				
Hypertension, n (%)	2 (11)	0 (0)	2 (29)	0.137
Diabetes, n (%)	0 (0)	–	–	–
Betablockers, n (%)	8 (44)	6 (55)	2 (29)	0.367
Antiarrhythmic drugs, n (%)	4 (22)	3 (17)	1 (14)	1.000
12 lead ECG				
QRS duration in ms, median (Q1-Q3)	80 (79–81)	80 (78–85)	80 (79–80)	0.860
T wave inversion beyond V1, n (%)	3 (17)	2 (18)	1(14)	1.000
24-Hour Holter Monitoring				
Number of PVCs, median (Q1-Q3)	15,000 (12750–21,854)	15,000 (14500–23,923)	13,000 (12000–15,000)	0.69
NSVT, n (%)	2 (11)	1 (9)	1 (14)	1.000
Echocardiogram				
LVEF in %, median (Q_1-Q_3)	58 (55–64)	58 (57–66)	55 (55–64)	0.375
LAD in mm, median (Q_1-Q_3)	37 (35–39)	38 (35–40)	35 (30–37)	0.104

LAD: left atrial diameter in parasternal view; LVEF: left ventricular ejection fraction; NSVT: non sustained ventricular tachycardia; PVC: premature ventricular contractions.

Table 2
Non-invasive mapping.

	Overall sample (n = 18)	RVOT PVCs (n = 11)	LVOT PVCs (n = 7))	P value
Number of leads, median (Q_1-Q_3)	144 (119–170)	140 (120–175)	154 (117–165)	0.659
RVOT endocardial activation duration in ms, median (Q1-Q3)	54 (39–68)	62 (58–73)	37 (33–40)	<0.0001
N° of 10 ms isochrones in the RVOT, median (min-max)	5 (3–7)	5 (4–7)	3 (3–4)	<0.0001
Area of the first 10 ms isochrone in cm^2, median (Q1-Q3)	4.7 (2.9–6.1)	4 (2.5–5)	6 (5–10)	0.015

PVC: premature ventricular contractions; RVOT: right ventricular outflow tract.

Table 3
Invasive mapping and ablation.

	Overall sample (n = 18)	RVOT PVCs (n = 11)	LVOT PVCs (n = 7)	P value
Carto/Ensite, n/n	16/2	10/1	6/1	1.000
Number of points, median (Q_1-Q_3)	109 (48–144)	112 (52–148)	70 (40–110)	0.126
RVOT endocardial activation duration in ms, median (Q1-Q3)	60 (38–70)	68 (60–75)	35 (29–41)	<0.0001
N° of 10 ms isochrones in the RVOT, median (min-max)	7 (3–9)	7 (6–9)	4 (3–5)	<0.0001
Area of the first 10 ms isochrones in cm^2, median (Q1-Q3)	1.6 (0.7–0.2.3)	0.8 (0.3–1.7)	2.5 (1.5–4.0)	0.006
LAT at the ablation site in ms, median (Q1-Q3)	−30 (−17-(−41))	−31 (−24-(−43))	−30 (−15-(−30))	0.151
Presence of low voltage areas, n (%)	11 (61%)	11 (100)	1 (14)	<0.0001
Successful ablation, n (%)	15 (83)	10 (91)	5 (71)	0.528

LAT: local activation time; PVC: premature ventricular contractions; RVOT: right ventricular outflow tract.

across the RVOT was 60 (38–70) ms and the median number of 10 ms isochrones across the RVOT was 7 (3–9). The area of the first 10 ms isochrone of the RVOT activation during the PVC was 1.6 (0.7–2.3) cm^2. The values of total RVOT activation duration and number of 10 ms isochrones were significantly higher and the area of the first 10 ms isochrone of the RVOT activation was significantly narrower if the PVCs originated from the RVOT (Table 3). Representative examples of patients with PVCs from the RVOT and LVOT are displayed in Figs. 1 and 2. Low voltage areas outside the transitional zone were present in all patients with PVCs from the RVOT and in just one patient with PVCs from the LVOT. The local activation time at the ablation site was −30 [−17-(−41)] ms and the ablation was successful in 15 (83%) patients, not significantly different in the above-mentioned groups (Table 3).

Activation duration, activation speed and number of 10 ms isochrones across the RVOT as predictors of origin of the PVC

With ROC curve analysis using activation duration as a predictor of the site of the PVCs, a cut-off value of 43 ms (AUC =1.000, $p < 0.0001$) for ECGI and 48 ms (AUC = 1.00, $p < 0.0001$) for the invasive measurement was obtained. An activation duration respectively shorter than 43 ms and 48 ms was a good predictor of a LVOT site, with 100% sensitivity and 100% specificity, $p < 0.0001$.

The ROC curve analysis for the number of 10 ms isochrones as a predictor of a LVOT origin of the PVCs showed a cut-off value of 4 for the ECGI (AUC = 0.987, $p = 0.001$) and 6 for the invasive map (AUC = 1.000, $p < 0.0001$). Thus, the presence of less than 4 isochrones assessed with ECGI predicted the origin of the PVCs from the LVOT with a sensitivity and specificity respectively of 86% and 100%, $p < 0.0001$, and the presence of less than 6 isochrones with the invasive mapping predicted the origin of the PVCs from the LVOT with a sensitivity and specificity respectively of 100% and 100%, $p < 0.0001$.

The area of the first 10 ms of activation, measured with ECGI as a continuous variable showed with binary logist regression a trend towards prediction of the site of the PVC, OR (95% CI) of 2.092 (0.958–4.570), $p = 0.064$. The ROC curve analysis showed a cut-off value of 5 cm^2 (AUC = 0.844, $p = 0.016$), so that an area of the first 10 ms of activation assessed with the ECGI >5 cm^2 predicted the origin of the PVCs from the LVOT with a sensitivity and specificity respectively of 71% and 82%, $p = 0.049$.

The area of the first 10 ms of activation measured with the invasive mapping, as a continuous variable was predictor of the site of the PVC, OR (95% CI) of 5.35 (1.148–24.90), $p = 0.033$, corresponding to a five-fold increase in the probability that the PVC originates from the LVOT for each 1 cm^2 increase in the measured area. The ROC curve analysis showed a cut-off value of 2 cm^2 (AUC = 0.877, $p = 0.009$), so that an area of the first 10 ms of activation assessed with the invasive mapping >2 cm^2 predicted the origin of the PVCs from the LVOT with sensitivity and specificity respectively of 71% and 91%, $p = 0.013$.

Dichotomizing the area of the first 10 ms of activation using these cut-off values performed well on logist regression analyses, with ORs (95% CI) of 11.25 (1.193–106.1), $p = 0.035$ and 25 (1.803–346.6) $p = 0.016$, respectively for the ECGI and invasive measurements.

A representative patient with a PVC origin outside the RVOT, in the commissure between the RCC and the LCC is displayed in Fig. 2 (bottom panel). The ECGI suggested an origin of the PVCs in the RVOT septum, but the short activation duration, the wide area of the first 10 ms, and the small number of isochrones across the RVOT, suggested an origin outside the RVOT. Another case where these predictors showed added value is displayed in Fig. 3. The PVCs originated in the LV summit and the earliest activation was found inside the anterior interventricular vein. The ECGI indicated an origin between the RVOT and the LVOT, but the isochronal activation map was suggestive of a focus outside the RVOT.

Evaluation of agreement between non-invasive and invasive measurements

There was a good agreement between ECGI and the invasive mapping measurements for the RVOT activation duration, the Pearson correlation coefficient was $R = 0.864$, $p < 0.0001$ and the Bland-Altman plot showed a mean of the difference between measurements near zero, an absence of systematic bias and all measurements were within the limits of agreement (Fig. 4). As for the number of 10 ms isochrones across the RVOT, although the Pearson correlation coefficient was reasonable $R = 0.779$, $p < 0.0001$, the Cohen's kappa showed a poor agreement between both methods, $K = 0.49$, $p = 0.544$. Finally, regarding the assessment of the area of the first 10 ms, there was not agreement between the two tests, the Pearson's correlation coefficient was bad, $R = 0.359$, $p = 0.143$ and a systematic error between the two measurements was detected, precluding further assessment of the Bland-Altman plot.

Discussion

To the best of our knowledge this is the first paper evaluating the duration and speed of the RVOT wavefront activation during PVC invasively and with the ECGI. Previous studies have already

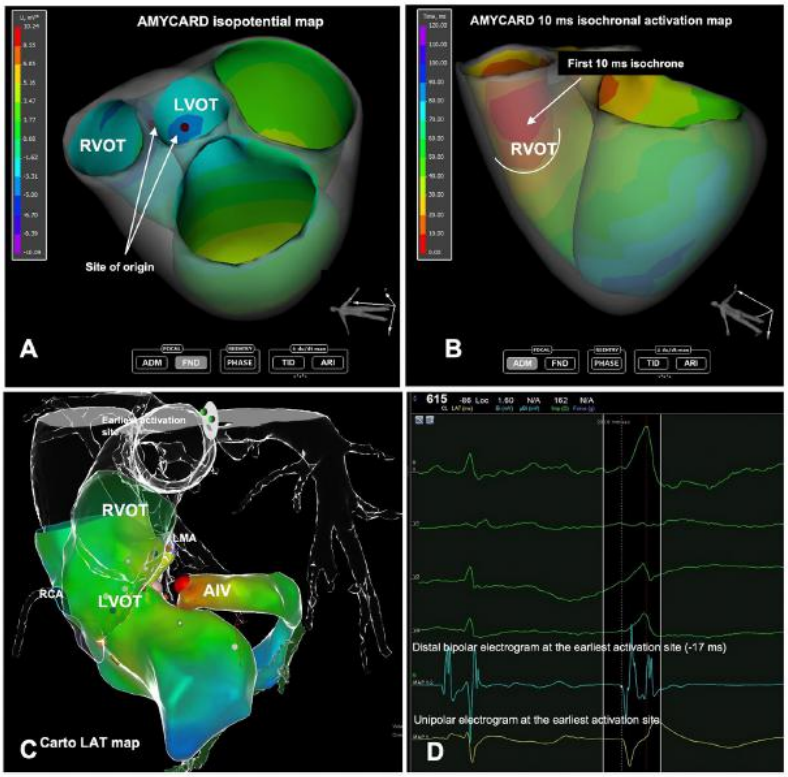

Fig. 3. Representative case of a patient with PVCs from the LV summit.
Panel A. ECGI isopotential map suggesting an activation simultaneous in the RVOT and LCC. Panel B ECGI isochronal map showing a short activation duration in the RVOT, with a wide first 10 ms isochrone and 3 isochrones across the RVOT. Panel C. Carto activation map with the RVOT map displayed in transparent mode and RF applications in the RVOT, LVOT and AIV. Transparent CT scan superimposed on Carto map. Panel D. Intracardiac electrograms at the earliest activation site inside the AIV. AIV: anterior interventricular vein; LAT: local activation time; LMA: left main artery; LVOT. left ventricular outflow tract; RCA: right coronary artery; RVOT: right ventricular outflow tract.

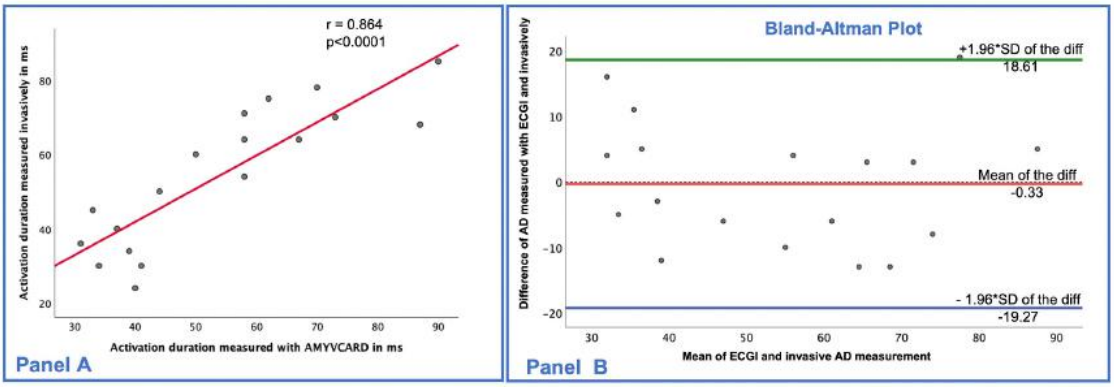

Fig. 4. Panel A. Scatter plot showing the Pearson correlation coefficient (r) and p-value (p) between activation duration measured with ECGI and invasively. Panel B. Bland and Altman diagram showing the plot of the difference between the activation duration measured with ECGI and invasively in ms, against the mean of the pair measurements. Green and blue lines show limits of agreement, and the red line shows the mean value of the differences between measurements. Dotted line shows the zero-line used to assess the discrepancy of the observed mean difference from zero. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

demonstrated that the activation speed could differentiate PVCs originating in the RVOT from PVCs originating in the LVOT. Herczku et al. studied a series of 15 patients that underwent ablation of of PVCs from the outflow tract with a transition at V3, and evaluated the accuracy of the area of the first 10-ms of activation in the RVOT was smaller for PVCs with an origin in the RVOT when compared with PVCs from the LVOT respectively 1.2 (0.4–2.1) versus 3.4 (2.4–3.9) cm^2 and an area > 2.3 cm^2 predicted the origin of the PVCs from the LVOT with a 85.7% sensitivity and 87.5% specificity [9]. In a more recent study Masuda et al., studied 23 patients with outflow tract PVCs using the ultra-high-resolution system to evaluate the wave front propagation speed on the right ventricular map assessed by measuring the area surrounded by a propagated wave front and concluded that the area was significantly smaller at 5 ms, 10 ms, 15 ms and 20 ms when the PVCs originated from the RVOT than from outside the RVOT. According to the authors a propagated area of <5 cm^2 at 15 ms predicted an origin in the RVOT

with 87% sensitivity and 100% specificity [10]. Our study not only corroborates these findings but also provides evidence for achieving the same results non-invasively. The ability to obtain non-invasively an isochronal map of the PVC before the ablation procedure and assess the activation duration and the activation speed may be helpful in identifying the site of origin of the PVCs from the RVOT or LVOT and plan the procedure in advance.

Isochronal mapping as predictor of the site of the PVCs

Isochronal mapping of the RVOT obtained invasively as well as with the Amycard system was successfully performed in all patients. An automatic display of a 10 ms isochronal map of the PVC was easily obtained for assessment of total RVOT activation duration and number of isochrones across the RVOT. In addition, the measurement of the area of the first 10 ms of RVOT activation was also easily assessed. However, in our group of patients, both the activation duration and the number of isochrones were better predictors of the site measured invasively or with the ECGI than the area of the first 10 ms of activation in itself as previously described [9,10]. In fact, the latter was the predictor with the worst sensitivity and specificity measured invasively or non-invasively, respectively 71% and 91% and 71% and 82% when comparing with the 100% sensitivity and specificity for the former variables.

Agreement between invasive and non-invasive isochronal mapping

The agreement between the invasive and the non-invasive measurements was good for the activation duration but not for the other two evaluated parameters. However, both methods showed good results in terms of prediction of the site of the PVCs, and we still think that the evaluation of the number of isochrones and area of the first 10 ms assessed with the ECGI is accurate and may be helpful in addition of the isopotential map to identify non-invasively and in advance the site of origin of the PVCs. Thus, the lack of agreement with the invasive measurements prevents the comparison between both methods in absolute terms but not in relative ones by using the appropriate cut-off values.

Mechanism of shorter activation duration and higher activation speed when PVCs originate outside the RVOT

Both Herczku et al. [9] and Masuda et al. [10] explained their findings based on the myocardial fiber arrangement in the RVOT that leads to a different propagation speed according to the site of origin of the arrhythmia. Therefore, when the PVC originates in the LVOT it reaches the RVOT through multiple connections and the activation becomes faster in this case. We have demonstrated that patients with PVCs from the RVOT had lower velocity of propagation of the wavefront of activation over the endocardium of the RVOT also in sinus rhythm in comparison with the control subjects [17]. The presence of a pathological substrate in the RVOT may be the cause of this slower conduction velocity which is supported by the presence of low voltage areas in the RVOT that were absent in the control group [17,18]. Other authors have also described the presence of low voltage areas in the RVOT in patients with apparently normal hearts. Wang et al. have demonstrated that the PVC originated from a low voltage area defined as bipolar electrogram amplitude <0.5 mV in 3% of patients, and in areas with amplitude between 0.5 and 1.5 mV in 89% of patients [19]. Similarly, Letsas et al. identified low voltage areas mainly located below or at the level of the pulmonary valve in 39 of 44 patients [20]. The findings in the present group of patients regarding the longer activation duration and slower activation speed for PVCs from RVOT might be related to direction of the wavefront activation as endorsed by those authors [9,10], or due to the presence of a subclinical pathological substrate as previously suggested [17–20].

Advantage of using activation duration and activation speed to differentiate PVCs with a RVOT origin from PVCs originating outside the RVOT

Symptomatic frequent monomorphic PVCs are an excellent indication for catheter ablation. The success rate of the procedure relies on an accurate activation map, which may be a lengthy procedure due to the lack of PVCs. It also depends on the location of the PVCs, and some are more prone to failure or complications [1]. The ECGI by non-invasively localizing the site of the arrhythmia with just one beat can offer diagnostic information regarding the location of the arrhythmia when performed prior to the ablation, helping on planning the procedure or withhold it. Although, monomorphic idiopathic PVCs are one of the most well validated indications for ECGI, its accuracy is still not perfect. It may incorrectly identify the ventricular chamber of origin in up to 20% of cases, independently of the commercial system or the cardiac source used [5–8]. Particularly, when the PVCs originate in the RVOT posterior septum or the right coronary cusp, the ECGI is unreliable to correctly discriminate the true location of the PVCs. Adding the analysis of the activation duration and speed of the PVC across the RVOT with the ECGI using specific cut-off values, may provide useful additional information to help differentiate PVCs from the RVOT from PVCs from outside the RVOT. The ECGI displays the isochronal map automatically, offering a panoramic view of the number of 10 ms isochrones and of the area of the first 10 ms of activation that can be used in combination with the usual evaluated parameters.

Limitations

This study has some limitations, first of all, it is a retrospective analysis, and the authors were not blind to the results of the ablation. The procedures are all done by the same operator, and the sample size is small. However, previous studies calculating the sample size have come to a number of patients in both groups smaller than ours [10]. We assumed the site of origin of the PVC based on the invasive map regardless the success of the procedure. A prospective study including a larger number of patients may be warranted to evaluate the value of this approach.

Conclusions

Activation duration and wavefront activation speed can be assessed non-invasively. In these group of patients, they were both predictors of the PVC site. However, activation duration was a better predictor.

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Declaration of Competing Interest

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Non-invasive electrocardiographic imaging in patients with idiopathic premature ventricular contractions from the right ventricular outflow tract: New insights into arrhythmia substrate

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ABSTRACT

Aims: The aim of this study was to use non-invasive electrocardiographic imaging (ECGI) to study the electrophysiological properties of right ventricular outflow tract (RVOT) in patients with frequent premature ventricular contractions (PVCs) from the RVOT and in controls.
Methods: ECGI is a combined application of body surface electrocardiograms and computed tomography or magnetic resonance imaging data. Unipolar electrograms are reconstructed on the epicardial and endocardial surfaces. Activation time (AT) was defined as the time of maximal negative slope of the electrogram (EGM) during QRS, recovery time (RT) as the time of maximal positive slope of the EGM during T wave, Activation recovery interval (ARI) was defined as the difference between RT and AT. ARI dispersion (Δ ARI) and RT dispersion (Δ RT) were calculated as the difference between maximal and minimal ARI and RT respectively. We evaluated those parameters in patients with frequent PVCs from the RVOT, defined as >10.000 per 24 h, and in a control group.
Results: We studied 7 patients with frequent RVOT PVCs and 17 controls. Patients with PVCs from the RVOT had shorter median RT than controls, in the endocardium and in the epicardium, respectively 380 (239–397) vs 414 (372–448) ms, $p = 0.047$ and 275 (236–301) vs 330 (263–418) ms, $p = 0.047$. The dispersion of ARI and of RT in the epicardium was higher than in controls, Δ ARI of 145 (68–216) vs 17 (3–48) ms, $p = 0.001$ and Δ RT of 201 (160–235) vs 115 (65–177), $p = 0.019$.
Conclusion: In this group of patients we found a shorter median RT in the endocardium and in the epicardium of the RVOT and a higher dispersion of the ARI and RT across the epicardium in patients with PVCs from the RVOT when comparing to controls.

Introduction

It has been accepted for years that idiopathic premature ventricular contractions (PVCs) with origin in the right ventricular outflow tract (RVOT) are benign in the absence of structural heart disease [1]. They are thought to result from triggered activity and most studies do not describe abnormal findings on the electroanatomical mapping. However, we have previously reported the presence of low voltage electrograms in patients with PVCs from the RVOT and apparently normal hearts. The presence of low voltage was associated with the presence of coved type ST elevation in V1 obtained in the second intercostal space [2].

Body surface electrocardiographic mapping was firstly used almost thirty years ago. That system consisted of eighty-seven unipolar electrodes recording simultaneously from the surface of the thorax [3]. Those authors studied with that system the patterns of depolarization and repolarization in a number of pathological situations. Subsequently, experimental work done in isolated pig hearts has demonstrated that the activation recovery interval (ARI), estimated from unipolar electrograms recorded at the surface of the heart, is independent of the activation time (AT), and can be used as an appropriate surrogate of action potential duration (APD) and repolarization [4,5].

ARI has been defined as the difference between recovery time (RT) measured at the steepest ascending slope of the T wave in the unipolar electrogram and the AT, measured at the steepest downslope of the QRS in the unipolar electrogram. In a recent study, ARI measurement was assessed with a type of non-invasive electrocardiographic imaging similar to ours. The values obtained non-invasively correlated with the intracardiac measurements [6].

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Depolarization and repolarization have been extensively studied in Brugada syndrome, to explain the occurrence of the ST elevation, giving rise to two different theories, the depolarization [7] and the repolarization theory [8]. Zhang et al. [9], obtained panoramic maps of activation and repolarization of patients with Brugada syndrome using a non-invasive electrocardiographic imaging system (ECGI) different from ours. The ECGI is not the same as body surface electrocardiographic mapping, since the former is capable of reconstructing and displaying the unipolar electrograms on the surface of the heart. Using the ECGI, the authors concluded that both abnormal repolarization and abnormal conduction are present in the substrate, leading to steep repolarization gradients and delayed activation. The same group also studied the repolarization pattern in patients with early repolarization [10], and observed the presence of steep repolarization gradients caused by localized shortening of APD.

Recently, a new ECGI system has emerged, which has the ability of obtaining simultaneous epicardial and endocardial unipolar electrograms [11]. This system has been validated for mapping of PVCs [12] and structural ventricular tachycardia [13]. The evaluation of repolarization using this system was first reported by Rudic et al. [14] in patients with Brugada syndrome and with right bundle branch block.

In the current study, using the same ECGI system as reported in the previous study, we characterized the epicardial and endocardial electrophysiological substrate of RVOT in patients with frequent PVCs originating in that region.

Material and methods

Study patients

From February 2018 to February 2019, we retrospectively studied 24 consecutive patients, 7 patients with frequent PVCs from the RVOT, defined as >10.000 per 24 h, and a control group of 17 patients without PVCs or with PVCs from another location. Patients underwent electrophysiological study and catheter ablation of the arrhythmia and had an ECGI performed before the ablation. All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler echocardiography and 12-lead electrocardiograms (ECG), and whenever there were symptoms that might suggest the presence of coronary heart disease, a treadmill exercise test was done. All patients with PVCs from the RVOT had a cardiac magnetic resonance imaging (cMRI) performed to exclude the presence of RVOT anomalies.

Patients were excluded if the intrinsic rhythm was not sinus rhythm, if the ECG showed conduction abnormalities or the investigation, including cardiac magnetic resonance imaging, suggested presence of disease in the RVOT.

We studied with the ECGI the endocardial and epicardial electrophysiological substrate of the RVOT in both groups.

12 lead ECG

All patients performed a standard ECG, and we assessed the presence of negative T wave beyond V1, the presence of ST elevation in V1 and the presence of a coved-type shaped ST segment.

Non-invasive electrocardiographic imaging

The ECGI was performed with the novel non-invasive epicardial and endocardial electrocardiographic imaging system, Amycard 01C EP (EP Solutions SA, Switzerland), before the invasive electrophysiological study. This method has been previously described [11]. However, briefly it consists of a multichannel ECG amplifier recorder that analyses up to 224 electrodes placed on the patient's torso. For the purpose of this study the ECG recordings were analyzed during sinus rhythm in all patients with PVCs from RVOT and controls. They were recorded with a 0.05- to 500-Hz bandpass filter, were digitized with the sampling rate of 1000 samples/s and exported to the Amycard laboratory software. The map was done with a single beat and, except for patients with bigeminy we used a beat at least three cycles away from the previous PVC.

Afterwards, with the electrodes in place, an ECG-gated computed tomography (CT) scanning of the heart and thorax with intravenous contrast, was performed with a third-generation 192-slice dual-source SOMATOM Force (Siemens Healthcare). Scanning of the torso and heart was performed simultaneously. The CT data was imported in the DICOM format into the Amycard laboratory software, and a 3-dimensional torso and heart model was obtained from the CT segmentation (Supplementary Fig. A1). Body surface ECG data were processed by Amycard system, using its inverse problem solution software [11] in combination with heart and torso anatomy, allowing for reconstruction of unipolar electrograms at approximately 2500 points on epicardium and endocardium.

We obtained the maps in the advanced mode based on the first derivative of the unipolar electrogram (Fig. 1). In that mode, the system performs automatic assessment of the local AT and RT and displays in a color-coded fashion the ARI maps, based on automatic ARI measurements (Fig. 2). The evaluation of AT, RT and ARI with the ECGI system used in our study has been performed previously in patients with right bundle brunch block, Brugada syndrome and normals [14]. Validation of noninvasive reconstruction unipolar electrograms at the

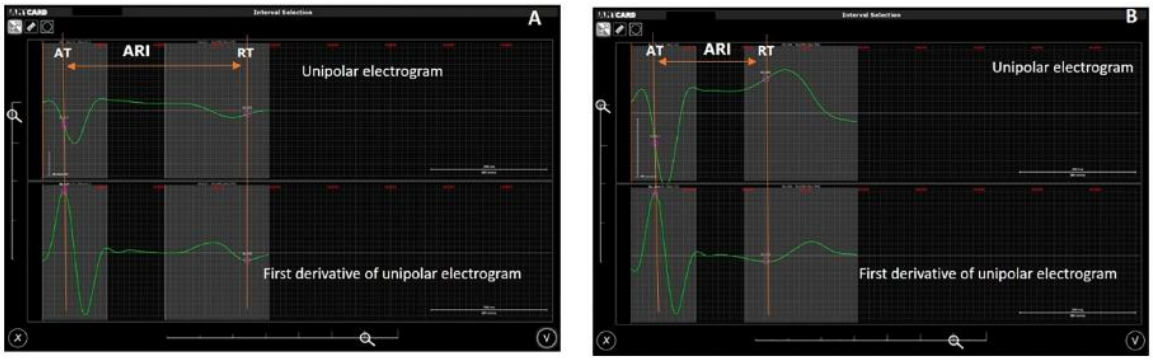

Fig. 1. Advanced mode based on the first derivative of the unipolar electrogram. Panel A advanced mode based on the first derivative of the unipolar electrogram with a negative T wave (above). The RT is measured in the ascending limb of the T wave. Panel B ARI measurement in case of a unipolar electrogram with a positive T wave (above). The RT is measured in the ascending limb of the T wave as well. The ARI is shorter in the positive T wave electrogram. AT: activation time; RT recovery time; ARI: activation recovery interval.

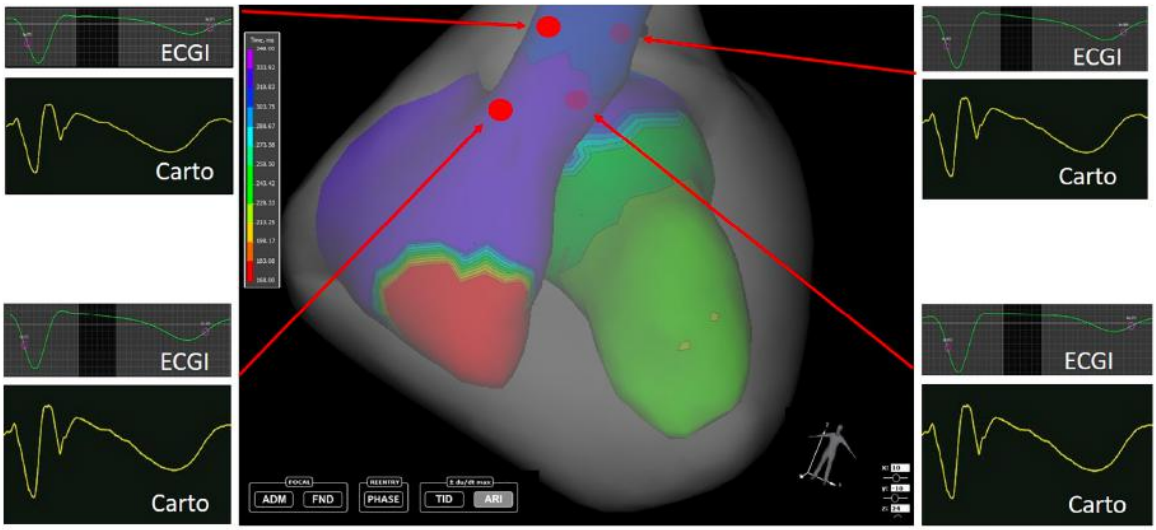

Fig. 2. Automatic ARI map. Automatic ARI map in the endocardium showing absence of ARI dispersion (ARI varies between 330 and 320 ms). Red dots correspond to the endocardial points collected both with the ECGI and Carto invasive mapping (arrows). ARI: activation recovery interval. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

epicardial surface when assessing repolarization, has been performed before [15]. Our system has not been systematically validated for repolarization assessment, but a previous study has shown some limited data on its validation [14].

The accuracy of the automatic measurements depends on the quality of the unipolar electrogram and, additional filtering can help to attenuate noise and improve the reliability of the measures. Usually, when studying the depolarization an additional 50 Hz filter is used [11]. However, when studying the repolarization, a 30 Hz filter is advised [16]. Duijvenboden et al. [16], have demonstrated experimentally that the best accuracy is obtained when using a filter at a cutoff frequency of 10 to 15 Hz. We customized the filter between 30 and 15 Hz in order to obtain the best signal to noise ratio of the unipolar electrograms (Supplementary Figs. A2 and A3).

Spatial properties of the EP substrate were determined by dividing the RVOT in 24 segments, 16 in the endocardium and 8 in the epicardium. The RVOT endocardium was divided into free wall and septum. Each wall was further divided into an anterior and posterior part, and finally from pulmonary valve to the assumed location of the His bundle area, was divided in 4 segments [17]. The RVOT epicardium was divided in anterior and posterior wall and each wall further divided in 4 segments from the pulmonary valve to the assumed location of the His bundle area (Fig. 3).

We evaluated the presence of T wave inversion, ST segment elevation defined as elevation of >1 mV above the baseline and the presence of a coved-type ST segment in the unipolar electrogram in any of the 24 segments.

AT, referenced to the beginning of the QRS in ECG lead II, was determined by the maximal negative slope of the EGM during QRS. RT, referenced to the beginning of the QRS in ECG lead II, was determined by the maximal positive slope of the EGM during T wave, regardless the morphology of the T wave (Fig. 1).

Epicardial and endocardial activation duration (AD) was defined as the interval between the earliest and the latest AT.

For the epicardium and the endocardium separately, we calculated the median, maximal and minimal values of AT, RT and ARI for all segments. ARI dispersion and RT dispersion were calculated as the difference between maximal and minimal ARI and RT respectively, in the endocardium and the epicardium (Δ ARI) and (Δ RT).

Statistical analysis

SPSS version 23 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A Kolmogorov-Smirnov test was performed to test for the normality of continuous variables and in the presence of normality, data is expressed as medium and standard deviation and, in its absence, as median and interquartile range (IQR). Data is present as frequencies and percentages for categorical variables. Categorical variables were compared with the use of Fischer's exact-test or the chi-square test as appropriate. Continuous variables were compared with the use of Student's t-test or Mann Whitney test, as appropriate. The Wilcoxon test for continuous variables and the McNemar test for categorical variables were used to compare values from epicardial and endocardial measurements. Linear regression was used to evaluate the effect of AT and RT on ARI. A value of $p < 0.05$ was considered statistically significant.

Ethics

All patients signed the informed consent form and the study was approved by the Ethics Committee for Health of Hospital da Luz. The study is in compliance with the Helsinki Declaration.

Results

Study population

24 patients were enrolled, 7 patients with PVCs from the RVOT, and 17 patients in the control group (9 with PVCs outside the RVOT and 8 patients with supraventricular arrhythmias). Two subjects had structural heart disease both in the control group, 1 had a mitral prothesis and the second had a previous history of myocarditis without involvement of the right ventricle. The two groups did not differ in relation to age or gender (Table 1).

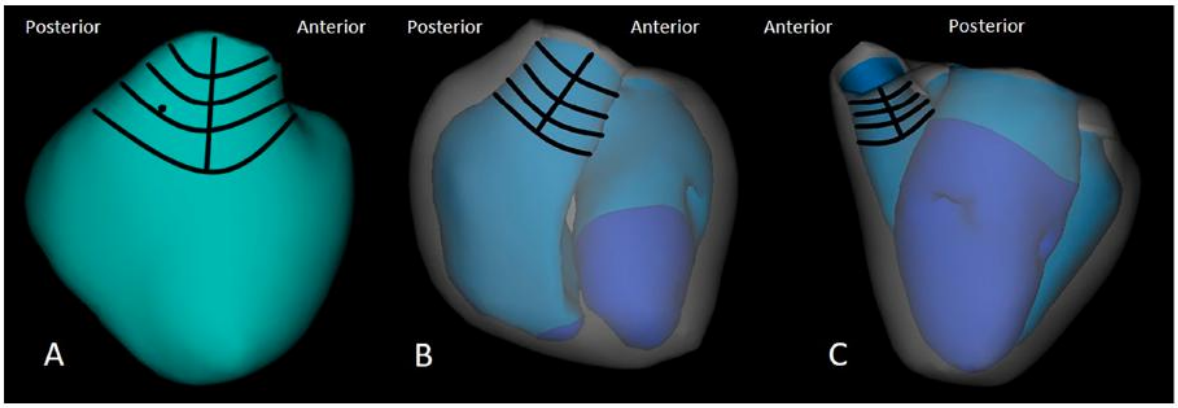

Fig. 3. RVOT segmentation. Schematic display of the 24 segments analyzed. Epicardium of the RVOT (A), free wall of the RVOT (B) and septal wall of the RVOT (C). RVOT: right ventricular outflow tract.

12 lead ECG

Patients with PVCs from the RVOT had more frequently ST elevation in the V1-V3 leads 71% versus 18%, $p = 0.021$. (Table 1).

Non-invasive electrocardiographic imaging

Endocardium

ST segment elevation was observed in at least one segment of the endocardium in all patients with PVCs from the RVOT versus 7 patients (41%) in the control group, $p = 0.019$. This ST elevation was also present in the intracardiac unipolar electrograms obtained with Carto (Fig. 4 and Supplementary Fig. A4). Presence of negative T waves or coved-type ST elevation was not significantly different in both groups (Table 2). The median AT was not significantly different between groups and the activation was almost simultaneous across the RVOT, in both groups, with AD of approximately of 0 ms. Patients with PVCs from the RVOT had a shorter median RT of 380 (239–397) versus 414 (372–448) ms, $p = 0.047$, but the ARI was not significantly different, and we found no ARI or RT dispersion across the endocardium in both groups.

Table 1
Baseline characteristics in the two groups.

	Overall sample ($n = 24$)	RVOT PVCs ($n = 7$)	Controls ($n = 17$)	P value[a]
Demographic data				
Age mean (SD) in years	57 (12)	58 (10)	57 (13)	0.824
Male gender, n (%)	16 (67)	4 (57)	12 (71)	0.647
Structural heart disease, n (%)	2 (8)	0 (0)	2 (12)	0.9999
Medications				0.9999
No medication, n (%)	16 (67)	5 (71)	11 (65)	
Betablockers, n (%)	5 (20)	1 (14)	4 (23)	
Sotalol, n (%)	1 (4)	0 (0)	1 (6)	
Propafenone, n (%)	1 (4)	1 (14)	0 (0)	
Amiodarone, n (%)	1 (4)	0 (0)	1 (6)	
ECG				
(−) T wave beyond V1, n (%)	3 (13)	2 (29)	1 (6)	0.194
Coved-type ST segment, n (%)	6 (25)	3 (57)	3 (43)	0.397
V1-V3 ST elevation, n (%)	8 (33)	5 (71)	3 (18)	**0.021**

Values are presented as mean (standard deviation) and n (%).
RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions.
[a] p values were calculated using the t-test for continuous variables and the Fisher test for categorical variables.

Epicardium

The two groups did not differ in relation to the presence of ST elevation or T wave inversion. The median AT was not significantly different between groups. The median RT was shorter in the epicardium, in patients with PVCs from the RVOT as well as the minimal ARI, respectively, 275 (236–301) versus 330 (263–418) ms, $p = 0.047$ and 170 (154–196) versus 222 (200−320) ms, $p = 0.004$.

We observed the presence of RT and ARI dispersion in the epicardium of the RVOT in patients with PVCs from the RVOT, that was not present in controls, Δ RT of 201 (160–235) vs 115 (65–177), $p = 0.019$ and Δ ARI of 145 (68–216) versus 17 (3–48) ms, $p = 0.001$ (Fig. 4).

Epicardium-endocardium differences

Presence of a negative T wave in the unipolar electrogram of at least one segment of the RVOT, was more frequent in the endocardium that in the epicardium as was the case of ST elevation (Table 3). As would be expected the median AT was significantly shorter in the endocardium 55 (46–66) versus 63 (53–69) ms, $p < 0.0001$. The AD in the endocardium was also shorter leading to an almost simultaneous activation of the RVOT, with an AD of 0 (0–0.75) versus 8 (2.3–17) ms, $p < 0.0001$ (Table 3). The RT and ARI were significantly shorter in the epicardium, respectively 303 (261–386) versus 396 (360–439), $p = 0.001$ and 234 (199–342) versus 335 (319–354) ms, $p = 0.001$. Dispersion of RT and ARI was observed only in the epicardium.

Association between ARI and AT or RT

ARI was linearly associated with RT, $R^2 = 0.864$, $p < 0.0001$ for the endocardium and $R^2 = 0.831$, $p < 0.0001$ for the epicardium), but not with the AT (Fig. 5).

Discussion

This is the first study in man, reporting on simultaneous epicardial and endocardial electrocardiographic mapping, to evaluate the electrophysiological substrate of idiopathic PVCs from the RVOT. Yang et al. [6] have previously studied the distribution of ARI in patients with PVCs from the RVOT, however those authors assessed the ARI during the PVCs instead of during sinus rhythm.

The usefulness of the ECGI to evaluate repolarization, is that it allows a panoramic view of global segmental repolarization. In our study, patients with PVCs from the RVOT as well as controls, displayed negative

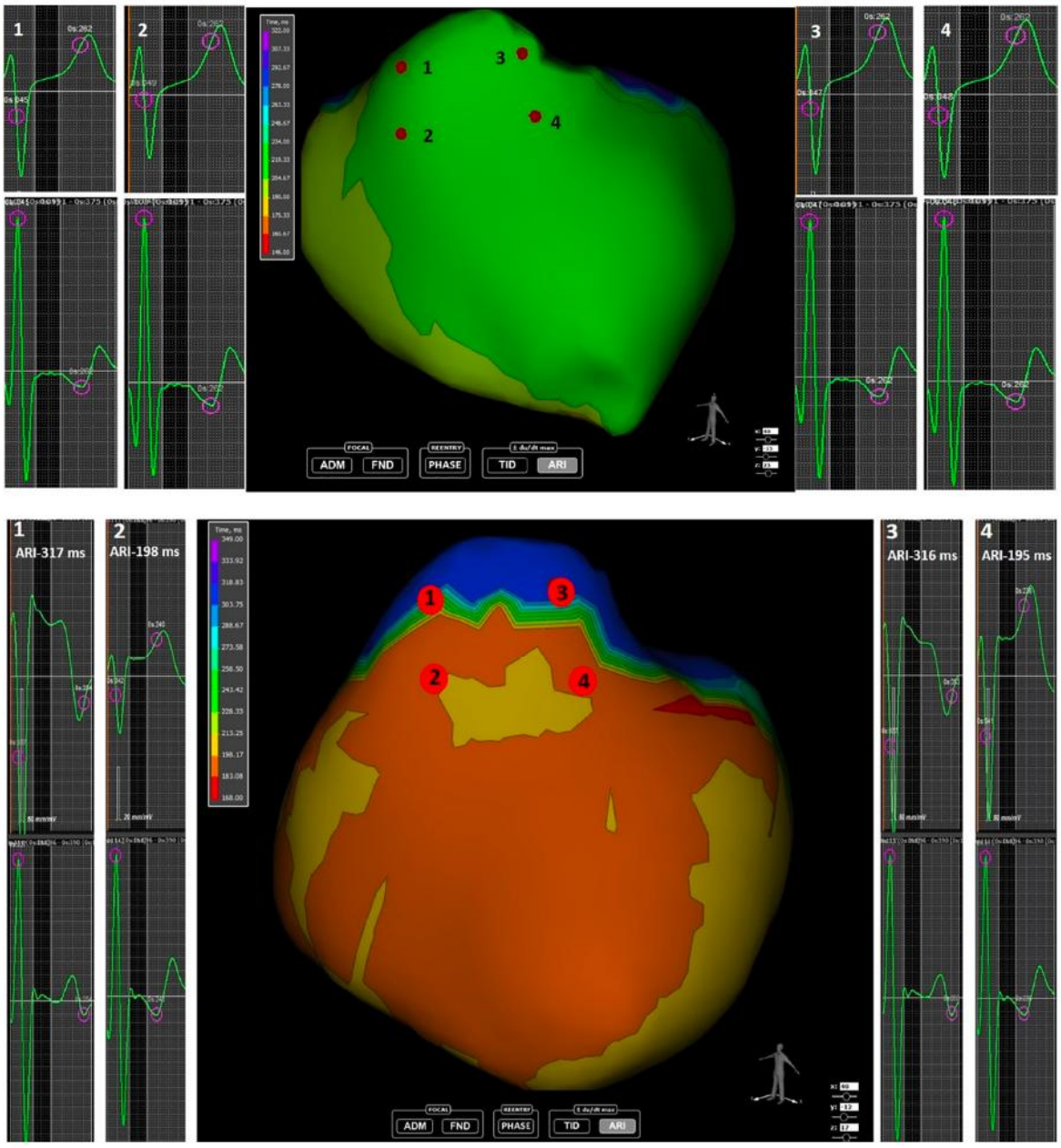

Fig. 4. Automatic ARI map in a control patient and in a patient with PVCs from the RVOT. Epicardial automatic ARI map of a control patient showing absence of ARI dispersion in the RVOT (top panel), dots correspond to the respective ECGI unipolar electrogram and below its first derivative. In the bottom panel a patient with PVCs from the RVOT showing a dispersion of ARI with higher values in the upper RVOT [1 and 3] segments and significantly lower values in the segments below (2and 4). ARI: activation recovery interval; RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions.

T waves in at least one segment in the endocardium or in the epicardium in most cases. It has been suggested that the presence of negative T waves may disqualify the calculation of RT and ARI [18]. According to those authors the methodology of measuring the RT at the ascending limb of the T wave may lead to overestimation of the RT and consequently of ARI. However, several experimental studies indicate the contrary [19,20]. The time instant of maximal dV/dt of the T wave on epicardial unipolar electrograms, closely corresponds to the instant of local ventricular recovery independently of T wave morphology. More recently, Coronel et al. [4], have elegantly demonstrated that repolarization time in the local unipolar electrogram is to be measured at the positive slope of the T wave. Those authors measured ARI as the interval between dV/dt minimum of the QRS complex and the dV/dt maximum of the T wave (irrespective of the polarity of the T wave). In all instances,

Table 2
Non-invasive electrocardiographic imaging data in the two groups.

	Overall sample ($n = 24$)	RVOT PVCs (n = 7)	Control (n = 17)	P value[a]
Endocardium of RVOT				
ST elevation, n (%)	14 (58)	7 (100)	7 (41)	**0.019**
Negative T wave, n (%)	22 (92)	5 (71)	17 (100)	0.076
Coved-type ST segment, n (%)	11 (46)	4 (57)	7 (41)	0.659
Median ST elevation (IQR) in mV	1(0.12–1)	1 (1–2)	0.5 (0–1)	**0.013**
Median AT (IQR) in ms	55 (46–66)	55 (41–61)	56 (49–94)	0.455
AD, median (IQR) in ms	0 (0–0.75)	0 (0–1)	0 (0–0)	0.534
Median RT (IQR) in ms	396 (360–439)	380 (239–397)	414 (372–448)	**0.047**
Median ARI (IQR) in ms	335 (319–354)	322 (253–339)	337 (323–367)	0.130
Maximal ARI, median (IQR) in ms	342 (322–359)	322 (257–33)	344 (327–374)	0.075
Minimal ARI, median (IQR) in ms	334 (316–353)	322 (253–339)	337 (323–367)	0.099
Δ ARI, median (IQR) in ms	0 (0–2.50)	8 (0–1.50)	0 (0–1.0)	0.804
Δ RT, median (IQR) in ms	0.0 (0.0–1.75)	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.757
Epicardium of RVOT				
ST elevation, n (%)	6 (25)	3 (43)	3 (18)	0.307
Negative T wave, n (%)	15 (63)	5 (72)	10 (59)	0.669
Coved-type ST segment, n (%)	5 (21)	2 (29)	3 (18)	0.659
Median ST elevation (IQR) in mV	0 (0–0)	0 (0–0.5)	0 (0–0)	0.534
Median AT (IQR) in ms	63 (53–69)	56 (53–64)	64 (52–101)	0.318
AD, median (IQR)	8 (2.3–17)	9 (4–14)	5 (1–19)	0.455
Median RT (IQR) in ms	303 (261–386)	275 (236–301)	330 (263–418)	**0.047**
Median ARI (IQR) in ms	234 (199–342)	201 (193–246)	240 (205–356)	0.166
Maximal ARI, median (IQR) in ms	317 (217–391)	363 (237–391)	255 (213–390)	0.619
Minimal ARI, median (IQR) in ms	205 (182–245)	170 (154–196)	222 (200–320)	**0.004**
Δ ARI, median (IQR) in ms	32 (6–140)	145 (68–216)	17 (3–48)	**0.001**
Δ RT, median (IQR) in ms	133 (108–222)	201 (160–235)	115 (65–177)	**0.019**

Values are presented as median (interquartile range) or n (%).
RVOT: right ventricular outflow tract; PVCs: premature ventricular contractions; AD: activation duration; AT: activation time; RT: recovery time; ARI: activation recovery interval.
[a] p values were calculated using the Mann-Whitney-*U* test for continuous variables and the Fisher test for categorical variables.

repolarization of the monophasic action potential coincided with positive slope of the T wave.

The first important finding in our study was the observation of ST elevation on the endocardial and epicardial unipolar electrograms more frequently in patients with PVCs from the RVOT that in controls. The difference only reaches statistical significance in the endocardium, and one possible explanation for this may have to do with the small sample size. We have previously described the presence of ST elevation in the 12 lead ECG of patients with PVCs from the RVOT that corresponded to the presence of low voltage in the RVOT assessed with electroanatomical mapping [2]. With the ECGI we had the ability to evaluate the presence of ST elevation in the RVOT itself and confirmed this finding. We do not know the reason or the implications of this ST elevation in the genesis of the disease. However, we can speculate that it may have to do with the dispersion of the repolarization as is the case of Brugada [9] or early repolarization syndromes [10]. The presence of ST elevation was associated with ARI dispersion in both Brugada and early repolarization syndromes. These two clinical entities were studied with ECGI to assess the repolarization properties of the epicardium. In the case of Brugada syndrome the authors described the presence of ST elevation and negative T waves in association with an ARI dispersion and prolongation of the RT [9]. In the early repolarization syndrome, the same authors also found ST elevation at local epicardial reconstructed unipolar electrograms at sites with ARI dispersion however in this case, associated with a shortening of the RT and ARI [10]. The ECGI used in these two studies only evaluates epicardial electrograms. Rudic et al. [14] with an ECGI identical to ours studied the epicardial and endocardial repolarization in patients with Brugada syndrome. They reported the presence of ST elevation and T wave inversion in the unipolar electrograms recorded both in the epicardial and endocardial surface of the RVOT [14]. The authors also reported increased AT in the endocardium and significantly prolonged ARI in the epicardium in comparison to controls.

Table 3
Endocardial versus epicardial differences in overall sample.

	Endocardium (n = 24)	Epicardium (n = 24)	P value[a]
Negative T wave, n (%)	22 (92)	15 (63)	**0.039**
Coved-type ST segment	11 (46)	5 (21)	0.070
ST elevation, n (%)	14 (58)	6 (25)	**0.008**
Median ST elevation (IQR) in mV	1 (0.12–1)	0 (0–0)	**0.036**
Median AT (IQR) in ms	55 (46–66)	63 (53–69)	<**0.0001**
AD, median (IQR)	0 (0–075)	8 (2.3–17)	<**0.0001**
Median RT (IQR) in ms	396 (360–439)	303 (261–386)	**0.001**
Median ARI (IQR) in ms	335 (319–354)	234 (199–342)	**0.001**
Δ ARI, median (IQR) in ms	0 (0–2.50)	32 (6–140)	**0.001**
Δ RT, median (IQR) in ms	0.0 (0.0–1.75)	133 (108–222)	<**0.0001**

Values are presented as median (interquartile range) or n (%).
AD: activation duration; AT: activation time; RT: recovery time; ARI: activation recovery interval.
[a] p values were calculated using the Wilcoxon test for continuous variables and the McNemar test for categorical variables.

When comparing our endocardial and epicardial results, the finding of an AT shorter in the endocardium or an RT shorter in the epicardium was predictable. It is well known that depolarization starts in the endocardium and the repolarization starts in the epicardium [21] and therefore, some of our findings are expected. Likewise, since the ARI is the difference between the RT and the AT, it was shorter in the epicardium as anticipated. When comparing groups, the AT was not significantly different between the group with PVCs from the RVOT and controls either in the epicardium or the endocardium. However, the median RT was shorter both in the endocardium and the epicardium. Median ARI was also shorter in patients with PVCs from the RVOT but did not reach statistical significance probably due to the small sample dimension.

The reason for this shorter RT is unknown. We hypothesize that just as it is possible that the refractory period may decrease in result of rapid

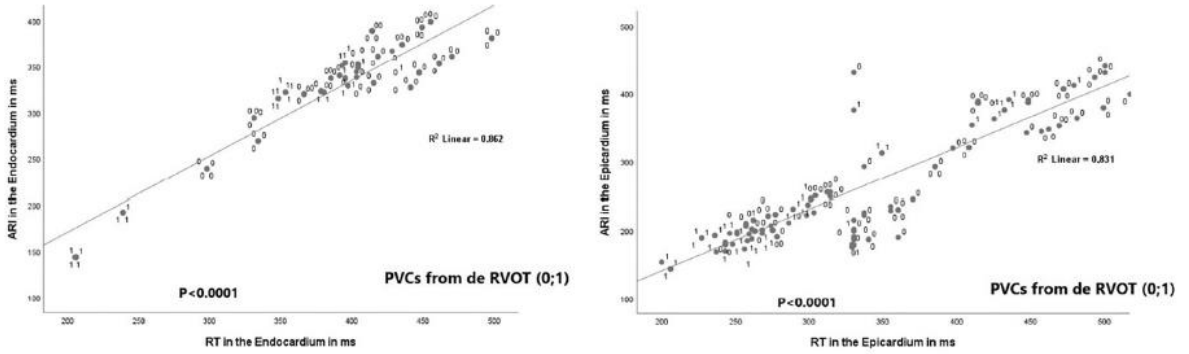

Fig. 5. Association between the RT and the value of ARI in the endocardium and epicardium in all segments analysedanalyzed.ARI: activation recovery time; RT: recovery time; PVC: premature ventricular contractions; RVOT: right ventricular outflow tract.0: control patients; 1: patients with PVCs from the RVOT. The rest of the paragraphs are the legends of supplementary figures A1, A2, A3 and A4 each paragraph for each supplementary figure.

pacing [22], it is conceivable that the constant ectopic activation by the PVCs may induce a reduction of the refractory period of the RVOT with time, as a form of electrical remodeling.

Recently Sakamoto et al. [23] described the presence of abnormal repolarization properties in patients with frequent PVCs from the RVOT assessed by the presence of T-wave changes and QRST time integral. This phenomenon involves changes in repolarization properties resulting from abnormal activation sequence [24]. Those T-wave abnormalities were more pronounced in patients with a PVC burden higher than 10.000 PVCs per day, as is the case of our study group, and progressively returned to normal a few weeks after successful ablation. The authors [23] attributed these T-wave changes to cardiac memory. They reported a statistically significant difference in the amplitude of the T-wave in lead V2 when compared to normal subjects and this difference attenuates after successful ablation. Patients with PVCs from the RVOT had also much lower QRST time integral values in V2 than normal subjects [23], although the authors did not comment on those findings.

So, it is possible that the findings obtained from the epicardial reconstructed electrogramas might be associated with the T-wave changes described by these authors and be a consequence of the PVCs. But it could be the other way round, and the repolarization abnormalities being the cause and not the consequence of the PVCs. In fact, the work from Zhang et al. [10] showed that in patients with early repolarization, a shorter RT was present in the epicardial surface. PVCs were present in two of those patients, and in both, the origin of the PVCs was in the area with ST elevation and repolarization abnormalities.

Idiopathic PVCs from the RVOT are thought to be due to delayed after depolarizations (DADs) [25], but this theory has never been proved. DADs result from an increase in intracellular Ca2+, so a critical factor should be the APD. Longer action potentials are associated with more Ca2+ overload and facilitated DADs [24]. Considering the fact that ARI correlates with the APD one would have expected that in patients with PVCs from the RVOT the ARI would be higher than in controls, and we found the opposite.

The most striking finding in our study was the presence of a dispersion of the RT and ARI in the epicardium in patients with PVCs from the RVOT. Hamon et al. [26] studied in a porcine model, the effect of PVCs from the RVOT on electrical stability and on dispersion of repolarization and found a significant increase in the dispersion of the repolarization on the sinus beats immediately after the PVCs, that progressively returned to normal in the subsequent sinus beats. Those authors also studied the effect of PVCs on the cardiac neurons that respond to both afferent and efferent cardiovascular stimuli and demonstrated that almost half of those neurons (46%) responded to PVCs. This fact indicates that PVCs pose a strong and unique stress to intrinsic cardiac nervous system neurons. The RT and ARI dispersion that we observed in our patients may result from the stress to intrinsic cardiac nervous system neurons, imposed by the presence of PVCs from the RVOT [26].

Limitations

There has been some concern regarding the accuracy of the electrograms obtained with the ECGI at least with the epicardial ECGI. Recently, Bear et al. [27] performed a validation study in five anesthetized, closed-chest pigs comparing the reconstructed epicardial unipolar electrograms obtained from ECGI with the electrograms directly recorded from the epicardium. The authors concluded that the ECGI provides qualitative information on the origin and spread of epicardial activation, but resolution was poorer than previously thought. Cluitmans et al. [28] also performed a validation study in four anesthetized closed-chest dogs assessing both the depolarization and the repolarization. The authors found a better accuracy of reconstructed activation times than of recovery times and pointed out the improvement obtained by incorporating the local spatiotemporal characteristics of the reconstructed electrograms, which we have not performed. Still, several studies in humans have validated the ECGI system for depolarization and repolarization in different diseases. With our epicardial and endocardial system, the number of studies is inferior, and invasive validation of this system for repolarization has not been performed, except for some limited data presented in the work by Rudic et al. [14]. The results of our study should therefore be interpreted with caution and more validation studies are needed prior to its widespread use to assess repolarization.

Conclusions

In conclusion, the RVOT in patients with frequent PVCs shows abnormal electrophysiological characteristics.

The reason for these abnormalities is still unknown but we may speculate that the PVCs are in their origin. The abnormalities of repolarization may represent a form of electrical remodeling in response to the abnormal depolarization, or on the contrary, they may be the cause of the PVCs. Either way that is worthy of bigger studies not only before ablation but in the follow-up, to assess the evolution of this abnormalities after successful ablation. Finally, we found the presence of a dispersion of repolarization in the epicardium of the RVOT, however the level of ARI and RT dispersion necessary to pose additional risk of ventricular arrhythmias is still not known.

Declaration of competing interest

M. Budanova, S. Zubarev are clinical application specialists of EP Solutions Company.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2019.08.046.

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Electrocardiographic imaging (ECGI): What is the minimal number of leads needed to obtain a good spatial resolution?

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ABSTRACT

Aims: Assess the minimal number of ECGI leads needed to obtain a good spatial resolution.
Methods: We enrolled 20 patients that underwent ablation of premature ventricular or atrial contractions using Carto and ECGI with AMYCARD. We evaluated the agreement regarding the site of origin of the arrhythmia between the ECGI and Carto, the area and diameter of the earliest activation site obtained with the ECGI (EASa and EASd). Based on previous studies with pacemapping, we considered a good spatial resolution of the ECGI when the EASd measured on the isopotential map was less than 18 mm. In presence of agreement the ECGI was reprocessed: a) with half the number of electrode bands (8 leads per electrode band) and b) with 6 electrode bands.
Results: The initial map was obtained with 23 (22-23) electrode bands per patient, corresponding to 143 (130-170) leads. Agreement rate was 85%, the median EASa and EASd were: 0.7 (0.5-1.3) cm^2 and 9 (8-13) mm. With half the number of electrode bands including 73 (60-79) leads, agreement rate was 80%, the EASa and EASd were: 2.1 (1.5-6.2) cm^2 and 16 (14 -28) mm. With only six electrode bands using 38 (30-42) leads, agreement rate was 55%, EASa and EASd were: 4.0 (3.3-5.0) cm^2 and 23 (21-25) mm.
The number of leads was a predictor of agreement with a good spatial resolution, OR (95% CI) of 1.138 (1.050–1.234), $p = .002$. According to the ROC curve, the minimal number of leads was 74 (AUC 0.981; 95% CI: 0.949–1.00, $p < .0001$).
Conclusion: Reducing the number of leads was associated with a lower agreement rate and a significant reduction of spatial resolution. However, the number of leads needed to achieve a good spatial resolution was less than the maximal available.

Introduction

Electrocardiographic imaging (ECGI) is a cardiac electrophysiology imaging tool that noninvasively allows the reconstruction of epicardial and endocardial potentials, from electrocardiographic body-surface electrocardiograms. The accuracy of the ECGI has been demonstrated in previous studies in terms of activation mapping as well as substrate characterization [1–5]. However, all those studies included a limited number of cases. The full adoption of ECGI as a clinical tool, instead of an investigational method, must be based on studies that clearly demonstrate its benefit on the outcomes. The benefit may be evaluated in terms of better success rate, procedure related parameters like reduction of procedure time or fluoroscopy time. This kind of studies are scarce [6] and thus, head to head studies comparing efficacy with and without ECGI along with cost effectiveness studies must be performed. One of the criticisms of the method is the large number of torso leads needed to obtain the noninvasive reconstruction [7]. According to those authors, that requirement is responsible for an increase in ablation costs and work burden, precluding its widespread utilization. Another limitation of the method that is also pointed out, is its interference with the placement of the electro anatomical mapping system's patches and external defibrillator patches [8].

The concept of ECGI is built upon mathematical equations aimed at solving the inverse problem of the electrocardiogram [9,10]. The inverse problem is ill-posed, meaning that small errors in the ECGI acquisition and processing, like noise, geometry errors, inaccurate conductivity

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values can produce infinite errors in the solution [11]. This fact is one of the reasons for the requirement of such a high number of torso leads.

The aim of this study was to evaluate the spatial resolution of the ECGI, and assess the minimum number of leads required to obtain a good spatial resolution.

Material and methods

Patient population

From February 2018 to July 2019, we retrospectively studied consecutive patients presenting to our center for ablation of symptomatic premature ventricular contractions (PVCs) or premature atrial contractions (PACs) that had an ECGI performed before ablation using cardiac computed tomography (CT). The accuracy of the ECGI was evaluated according to the type of arrhythmia, PVCs or PACs.

Non-invasive electrocardiographic imaging

The ECGI was performed with the non-invasive epicardial and endocardial electrocardiographic imaging Amycard 01C system (EP Solutions SA, Switzerland), before the catheter ablation. This method has been previously described [12]. However, briefly it consists of a multichannel ECG amplifier recorder that analyses up to 224 leads from up to 28 electrode bands, with 8 leads each, placed on the patient's torso. They were recorded with a 0.05- to 500-Hz bandpass filter, digitized with the sampling rate of 1000 samples/s and exported to the Amycard 01C software. Additionally, a 50 Hz frequency noise filter was used. Afterwards, with the electrode bands in place, an ECG-gated CT scanning of the heart and thorax with intravenous contrast, was performed with a third-generation 192-slice dual-source SOMATOM Force (Siemens Healthcare). Scanning of the torso and heart was performed simultaneously. The CT data was imported in the DICOM format into the Amycard 01C software, and a 3-dimensional torso and heart model were obtained from the CT. Body surface ECG data was processed by Amycard system, using its inverse problem solution software [13] in combination with heart and torso anatomy, allowing for reconstruction of unipolar electrograms at approximately 2500 points on epicardium and endocardium. The earliest activation site was visually estimated using isopotential map by an experienced user. The ECGI was done without isoprenaline in all patients.

Invasive Electroanatomic Mapping and Ablation

Patients were studied in a fasting non sedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. Isoprenaline was administered intravenously, as needed, and titrated to a dose capable of inducing PVCs or PACs. All patients underwent invasive electroanatomical mapping with the Carto 3 system version 6 (Biosense Webster) using the Niobe magnetic navigation system (Stereotaxis) working with the monoplane fluoroscopy system AXIOM ArtisTM (Siemens) as previously described [14]. An irrigated tip Navistar RMT Thermocool catheter (Biosense Webster) was used with a 4-mm distal tip electrode and a 2-mm ring electrode with an interelectrode distance of 1 mm.

The activation map was created by mapping several points during each PVCs or PACs while using a surface ECG lead as reference or an intracardiac electrogram in case of PACs. Activation times were assigned based on the onset of bipolar electrograms. In the case of PVCs bipolar pace mapping was also performed. The ablation site was selected based on the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous PVCs. Energy was delivered from an EP Shuttle RF generator (Stockert) between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 s, to a maximum temperature of 43 °C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the EAS. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. Success was defined as abolition of PVCs or PACS under isoprenaline infusion until thirty minutes after ablation.

Evaluation of agreement between non-invasive and invasive maps and spatial resolution of the non-invasive map

Localization of PVCs or PACs based on non-invasive and invasive electroanatomic mapping was performed using a segmental model of the atria and ventricles (Fig. 1). The assessment of the segment of origin of the arrhythmia based on the invasive activation map was performed by two experienced electrophysiologists and based on the non-invasive isopotential map by an experienced user.

We evaluated the agreement between the site of origin of the arrhythmia obtained with the ECGI and with Carto. In case of agreement between both maps, the area and maximal diameter of the earliest activation site obtained with the ECGI isopotential map, respectively (EASa) and (EASd), were directly measured using the system software.

We assessed these parameters obtained with the maximal number of torso leads. To avoid bias related to factors other than the number of leads we excluded from further analysis patients with non-agreement in the first map.

In patients with agreement between the non-invasive and invasive map, the ECGI was reprocessed upon exclusion of half the electrode bands used in the initial analysis. Electrode bands were switched on/off alternately starting at the first one connected (Fig. 2). After ECGI reprocessing, agreement with Carto map as well as the EASa and EASd were assessed again. We did the same procedure using only 6 electrode bands in a single configuration: 2 electrode bands applied to the anterior chest wall, 2 to the posterior wall and one to each side of the chest (Fig. 2). When reducing the number of electrode bands, we defined agreement if the EAS was located in the same segment or in contiguous segments.

Taking pace mapping results of Azegami et al. [15] in account, good spatial resolution was considered if the EASd was less than 18 mm. The association between number of leads used for the non-invasive map, as well as the type of arrhythmia, and achievement of good spatial resolution was analysed. The minimal number of leads needed to obtain good spatial resolution was assessed.

Statistical analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc., Chicago, Illinois). Data is presented as median and lower and upper quartile (Q1-Q3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann Whitney test for independent samples and with the Wilcoxon test for repeated measurements. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples and with the McNemar test for related samples. Binary logistic regression was used to evaluate the value of covariables as predictors of agreement with a good spatial resolution. The assumption of linearity for continuous variables was tested and confirmed with the Box-Tidwell test. We included in the multivariate analysis the variables presenting a P value <.25 in univariate analysis.

Non-parametric receiver operator characteristic curves (ROC) and areas under the curve (AUC) were obtained independently of logistic regression, to determine the discriminative power of the number of leads as predictor of agreement with a good spatial resolution. The optimal cut-point value was calculated to provide a rate of false positives of 0% (specificity of 1).

For all tests, a two-tailed p-value <.05 was considered as statistically significant.

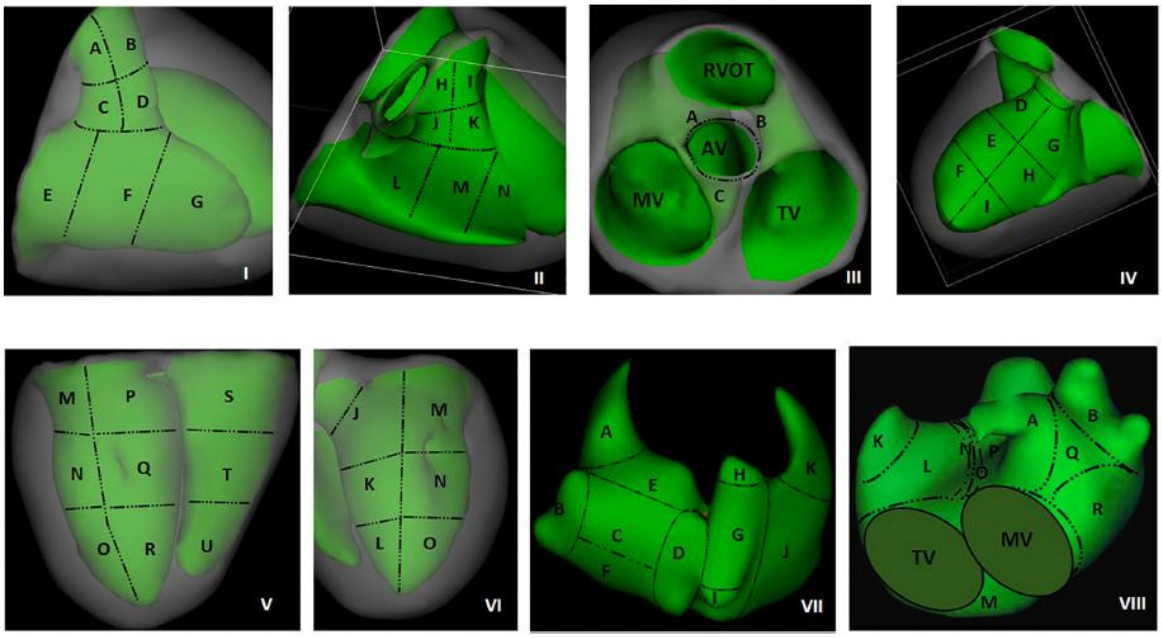

Fig. 1. Ventricular and atrial segmentation. I- A: RVOT posterior free wall sup; B: RVOT anterior free wall sup; C: RVOT posterior free wall inf; D: RVOT anterior free wall inf; E: RV basal free wall; F: RV mid-free wall; G: RV apical free wall. II- H RVOT posteroseptal sup; I RVOT anteroseptal sup; J: RVOT posteroseptal inf; K: RVOT anteroseptal inf; L: RV basal septum; M: RV mid-septal; N:RV apical septum. III- A: left aortic cusp; B right aortic cusp; C: non coronary cusp. IV- D LV anterobasal septum; E: LV mid-superior septum; F: LV superior-apical septum; G LV postero-basal septum; H: LV mid-inferior septum; I: LV infero-apical septum. V-M:LV latero-basal; N: LV mid-lateral; O: LV latero-apical; P: LV inferobasal;Q: LV mid-inferior; R: LV infero-apical; S: RV infero-basal; T:RV mid-inferior; U: RV infero-apical. VI- J: LV anterobasal; K: LV mid-anterior; L: LV anteroapical; M:LV latero-basal; N: LV mid-lateral; O: LV latero-apical. VII- A: LAA; B: LPV; C: LA posterior wall; D: RPV: E: LA roof; F: LA inferior wall: G: RA posterior wall; H: SVC I: IVC; J: RA lateral wall; K: RAA; VIII- A: LAA; B: LPV; K: RAA; L: RA anterior wall; M: coronary sinus ostium; N: RA septum; O: LA septum; P: LA anterior wall; Q: LA ridge; R: LA lateral wall.

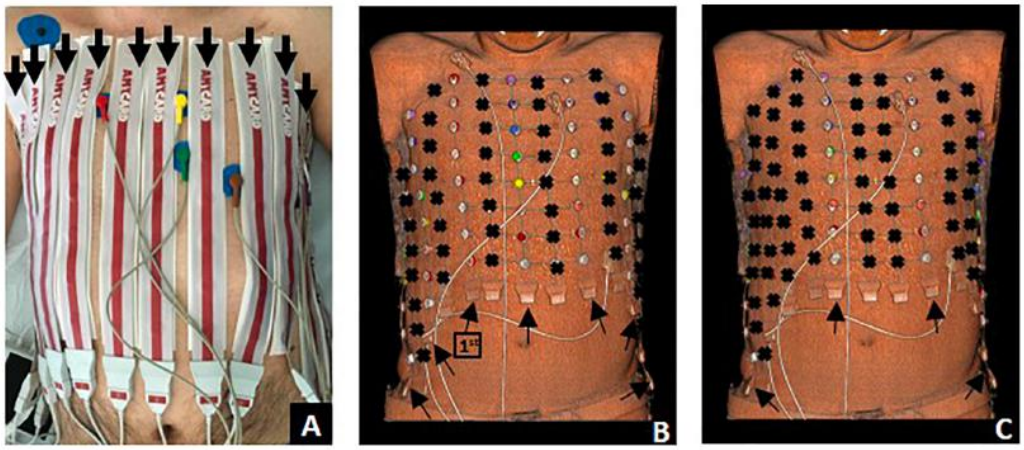

Fig. 2. Electrode binding. Panel A. Amycard electrode bands (arrows) with eight leads each. Panel B. Connection of alternate electrode bands (arrows). Disconnected electrode bands (without arrows) showing excluded leads (x). Panel C. Connection of only six electrode bands two anterior, two posterior and one each side of the torso (arrows). Disconnected electrode bands (without arrows) showing excluded leads (x).

Table 1
Baseline demographic characteristics in patients with PVCs and PACs.

	Overall sample ($n = 20$)	PVCs ($n = 14$)	PACs ($n = 6$)	P value
Age in years, median (Q1-Q3)	58 (49–67)	54 (49–63)	66 (52–69)	0.153
Male gender, n (%)	12 (60)	9 (64)	3 (50)	0.642
Height in cm, median (Q1-Q3)	171 (166–176)	171 (168–175)	170 (162–183)	0.904
Weight in Kg, median (Q1-Q3)	77 (71–85)	76 (72–84)	81 (65–86)	0.547
BSA, median (Q1-Q3) †	1.89 (1.78–1.98)	1.87 (1.80–1.98)	1.93 (1.73–2.03)	0.968
BMI, median (Q1-Q3) †	25.6 (23.7–28.1)	25.6 (23.9–28.1)	25.6 (22.6–29.8)	0,659

PVCs: premature ventricular contractions; PACs: premature atrial contractions; BSA: body surface area; BMI: body mass index.

Ethics

All patients signed the informed consent form and the study was approved by the Ethical Committee of the Hospital da Luz. The study is in compliance with the Helsinki Declaration.

Results

Patient population

A total of 23 patients were enrolled in this study, three patients were excluded because they did not undergo catheter ablation. Among the 20 patients studied, 12 were male, median age 58 (49–67) years. Fourteen patients had PVCs and six patients had PACs. No patient had structural heart disease. The demographic characteristics and the comparison between groups are depicted in Table 1.

Non-invasive electrocardiographic imaging

The median number of electrode bands used for the initial map was 23 (22—23) corresponding to 143 (130–170) leads, not significantly different in patients with PACs or PVCs (Table 2). Due to inadequate high levels of noise a median number of 41 (12–56) leads were disconnected and excluded from the calculation, corresponding to a 23 (6–30) % reduction of the expected number of leads according to the number of electrode bands applied to the patient's torso.(Fig. 3).

Mapping and ablation

Sixteen out of twenty patients (80%) underwent successful ablation, 10 (71%) in the PVC group and 6 (100%) in the PAC group, $p = .267$. Six patients had foci in the right ventricular outflow tract (RVOT), two in the left ventricular outflow tract (LVOT), one in the RV basal free wall, one in the RV basal septum, 2 in the RA posterior wall, one close to the coronary sinus ostium, one in the RA septum and two in the LA ridge.

In the four patients with unsuccessful PVC ablation the foci identified with Carto were located in the RVOT septal wall in two patients, in the RV basal septum in one and in the RV basal free wall in the other.

Evaluation of agreement and spatial resolution of the non-invasive map

There was agreement between the non-invasive and the invasive map regarding the site of origin of the arrhythmia in 17 patients (85%), 11 with PVCs and 6 with PACs. In the 3 patients without agreement the origin of the PVCs according to Carto was in the RVOT septal wall in two and in the right ventricular basal septum in one. It is noteworthy that in two of them, the ablation was unsuccessful.

The median number of leads used for the non-invasive map in case of agreement was not significantly different from the number in case of its absence, respectively, 144 (100–180) and 143 (135–170) leads, $p = .874$. When using all available leads the EASa in patients with agreement was 0.7 (0.5–1.3) cm^2, and the EASd was 9 (8–13) mm. When half of the electrode bands were disconnected, the agreement was not significantly lower, 80% versus 85%, $p = .9999$. However, the EASa was significantly wider: 2.1 (1.5–6.2) versus 0.7 (0.5–1.3) cm^2, $p < .0001$ and so was the EASd: 16 (14–28) versus 9 (8–13) mm, $p < .0001$ (Table 2).

When we left just 6 electrode bands connected, corresponding to 38 (30–42) leads, we found a significant reduction in the accuracy of the non-invasive map with an agreement of 55% versus 85%, $p = .031$. This reduction was higher in the group of PACs (Table 2). The EASa was also significantly broader, 4.0 (3.3–5.0) cm^2 versus 0.7 (0.5–1.3)

Table 2
ECGI data in patients with PVCs and PACs.

	Overall sample (n = 20)	PVCs (n = 14)	PACs (n = 6)	P value
ECGI map with all electrode bands				
No of leads, median (Q1-Q3)	144 (130–170)	155 (134–174)	120 (111–150)	0.051
Agreement with Carto, n (%)	17 (85)	11 (79)	6 (100)	0.521
EASa in cm^2, median (Q1-Q3) †	0.7 (0.5–1.3)	0.6 (0.5–0.9)	1 (0.6–1.9)	0.149
EASd in mm, median (Q1-Q3) †	9 (8–13)	9 (8–11)	11 (9–15)	0.149
Good spatial resolution, n (%)	17 (85)	11 (80)	6 (100)	0.521
ECGI map obtained with half the number of electrode bands				
No of leads, median (Q1-Q3)	73 (60–79)	76 (61–80)	69 (59–77)	0.312
Agreement with Carto, n (%)	16 (80)	11 (79)	5 (83)	1.000
EASa in cm^2, median (Q1-Q3) †	2.1 (1.5–6.2)	1.8 (1.4–2.5)	4.6 (2.5–6.9)	0.149
EASd in mm, median (Q1-Q3) †	16 (14–28)	15 (13–18)	24 (18–30)	0.145
Good spatial resolution, n (%) †	10 (59)	9 (81)	1 (17)	0.035
ECGI map obtained with six electrode bands				
No of leads, median (Q1-Q3)	38 (30–42)	38 (32–44)	35 (29–41)	0.494
Agreement, n (%)	11 (55)	10 (71)	1 (17)	0.005
EASa in cm^2, median (Q1-Q3) †	4.0 (3.3–5.0)	4.2 (3.2–5.0)	4.0	–
EASd in mm, median (Q1-Q3) †	23 (21–25)	23 (20–25)	23	–
Good spatial resolution, n (%) †	1 (6)	1(9)	0 (0)	–

[a] in case of agreement; PVCs: premature ventricular contractions; PACs: premature atrial contractions; EASa: area of the earliest activation site; EASd: diameter of the earliest activation site; Max: maximal; No: number.

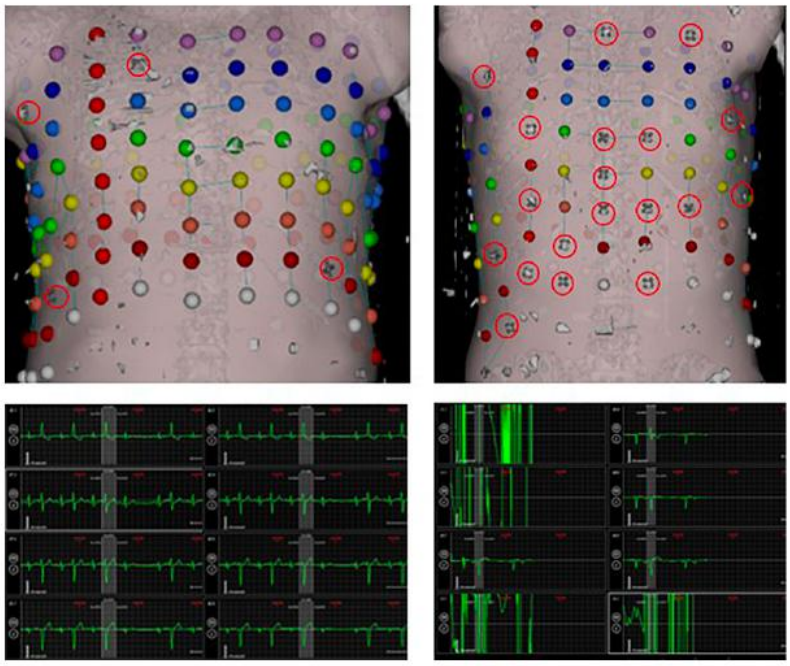

Fig. 3. Torso leads electrocardiographic recording. Left superior panel showing a good quality recording, only 4 leads disconnected (red circle) due to noise. Right superior panel showing a bad quality recording with a high percentage of disconnected leads due to noise. Inferior panels showing torso leads with a good ECG recording (left) and bad ECG recording (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cm^2, $p = .003$ and so was the EASd, 23 (21–25) mm versus 9 (8–13) mm, $p = .003$. (Fig. 4).

With the maximal number of available leads we found a good spatial resolution in 85% of the patients. When disconnecting half the electrode bands we decreased the percentage of patients with good spatial resolution from 17/20 (85%) to 10/17 (59%), $p = .016$ corresponding to a 30% reduction. This decrease was higher in patients with PACs (Table 2). When further reducing the number of torso electrode bands to six, we had a good spatial resolution in 1 out of 17 patients (6%), $p < .0001$, corresponding to a reduction of 92% in both groups with PVCs and PACs.

Evaluation of the minimal number of leads necessary to obtain agreement with a good spatial resolution

In univariate analysis the number of leads was a predictor of agreement with a good spatial resolution, OR (95% CI) of 1.138 (1.050–1.234), $p = .002$, but the type of arrhythmia was not, PVCs versus PACS, OR (95% CI) of 2.750 (0.842–8.982), $p = .094$. The adjusted OR (95% CI) for the number of leads was 1.223 (1.059–1.413), $p = .006$.

According to the ROC curve the minimal number of leads required to have agreement with a good spatial resolution with a 100% specificity, was 74 leads (AUC 0.981; 95% CI: 0.949–1.00, $p < .0001$) (Fig. 5). This cut-off value was associated with a positive predictor value (PPV) of 100% and negative predictor value (NPV) of 88%.

Discussion

The first important finding of this study was the difference between the maximal number of available leads, and the actual number of leads used for the initial non-invasive ECGI map. This fact is due in part to the limited space in the patient's torso, making it impossible in the majority of cases to use the maximum number of electrode bands. Secondly, it is due to exclusion of leads displaying high noise levels due to bad contact with the skin. Therefore, the initial map was obtained with fewer leads than expected. The accuracy was very good with an overall 85% agreement with the Carto map. Initial studies performed by Lux et al. [16,17] using body surface mapping for the localization of myocardial infarction or ischemia, have been able to show that the use of the 192 available leads resulted in spatial redundancy and the reduction of the number of leads to 30 did not lead to a lower resolution. These results were based on the selection of the leads with higher information content recordings. However, we must keep in mind that ECGI has its own specificities and the aim of our study was not to assess the best configuration of leads but rather to assess the accuracy of ECGI when reducing the number of leads.

The accuracy of the ECGI measurements is dependent on the quality of the body surface recordings and the exactness of the cardiac chambers' reconstruction [8,10]. Bear at al [18] demonstrated that filtering of the torso potentials with removal of high-frequency noise resulted in smoother reconstructed electrograms and significantly higher accuracy of the ECGI.

We used additional noise filtering and baseline correction, excluding the leads whenever the signal was not perfect after filtering. Additionally, we had extreme care in obtaining accurate torso and heart reconstructions. This may explain why despite the lower number of leads used in our study the accuracy was still high. Furthermore, the gold standard in this study was the Carto activation map and in two out of three patients without agreement, the ablation was unsuccessful at the location indicated by the Carto map. Remarkably, in the three cases without agreement the origin of the arrhythmia was in the RVOT in two and in the RV septum in one.

It has been shown before that the accuracy of the ECGI for ventricular outflow tracts and septum is still not perfect [1,6,19]. This is a consequence of the ill-posed solution of the problem which is not unique. Different potentials at the surface of the heart may correspond to a similar morphology at the surface of the torso. As a result of this drawback,

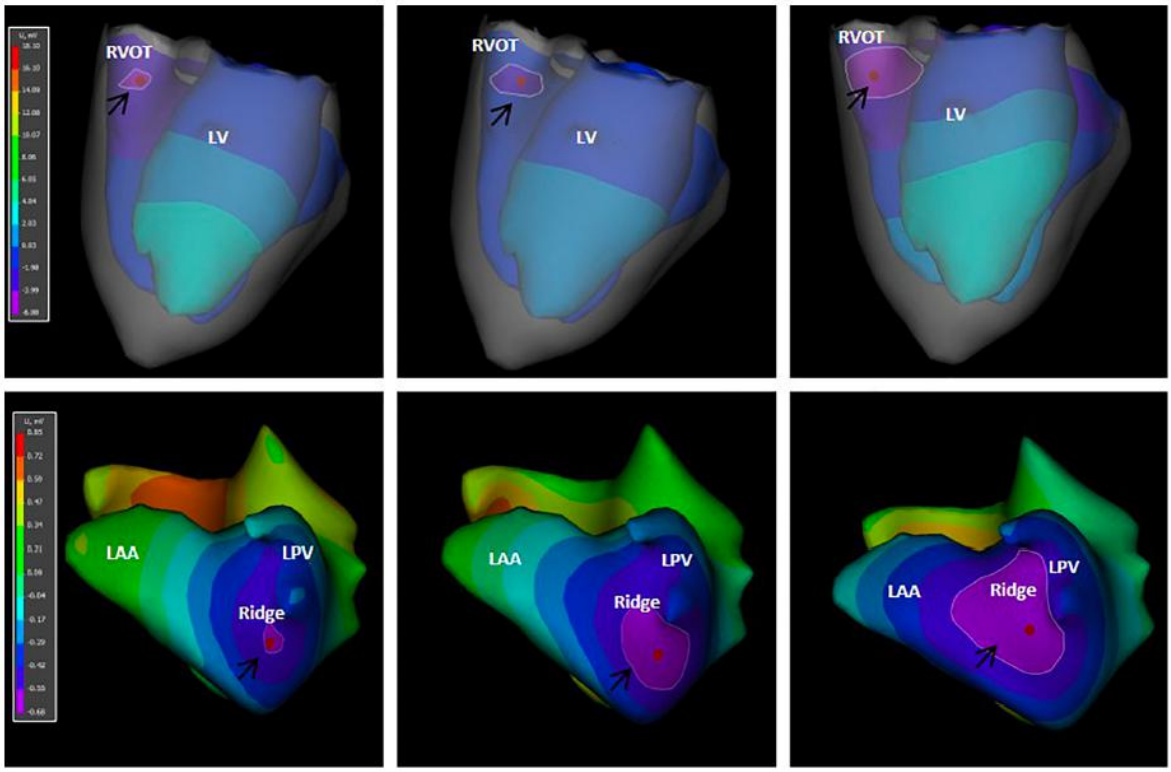

Fig. 4. Spatial resolution according to number of leads. Superior panel: patient with PVCs. From left to right, EASa (black arrow) with all 22 electrode bands, with 11 and with 6 electrode bands. Inferior panel: patient with PACs. From left to right, EASa with all 22 electrode bands, with 11 and with 6 electrode bands. EASa: area of the earliest activation site; LAA: left atrium appendage; LV: left ventricle; LPV: left pulmonary veins PVC: premature ventricular contractions; PACs: premature atrial contractions; RVOT: right ventricular outflow tract.

the spatial resolution of the ECGI may be reduced in complex anatomical sites as is the case of the ventricular outflow tracts. Furthermore, the inverse problem for *endo*-epicardial reconstruction is even more difficult than just for epicardial reconstruction. This is due to the more complex endocardial surface of the heart compared to the simple convex epicardial surface [10]. For this reason, the septal activation is

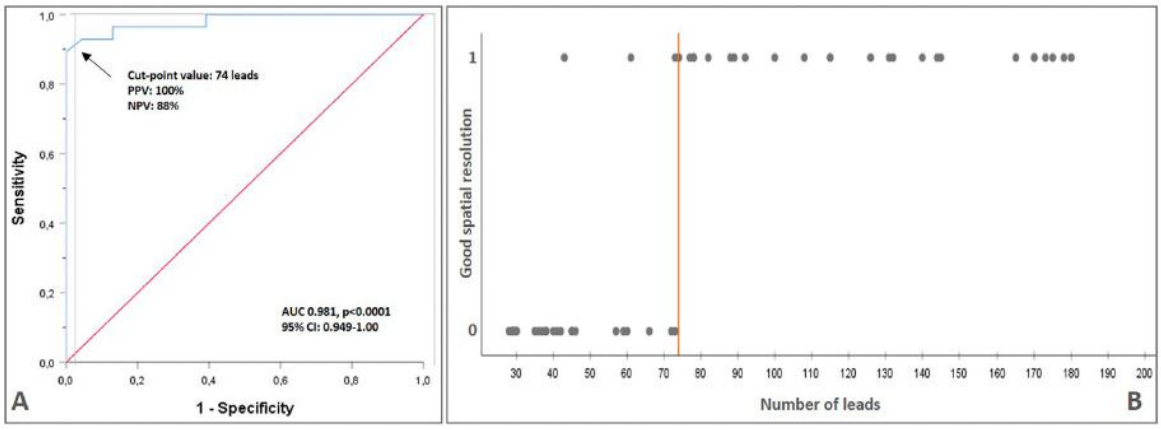

Fig. 5. Good spatial resolution by number of leads analysis. Panel A: ROC curve for good spatial resolution analysis by number of leads. PPV: positive predictive value; NPV: negative predictive value. AUC: area under the curve; ROC: receiver operator characteristic. Panel B: Scatter plot displaying the number of leads plotted against the x-axis and the binary variable (presence or absence of a good spatial resolution) plotted against the y-axis. For number of leads above 74 (red vertical line) all exams display good spatial resolution. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

another weakness of all ECGI systems either epicardial [6] or endo-epicardial [1,19].

The second finding of our study was the good spatial resolution of the non-invasive map with a very narrow median EAS area of 0.7 cm^2 and median diameter of 9 mm. This spatial resolution may be considered high based on previous studies using invasive activation and pace mapping [15,20]. Those studies have assessed the spatial resolution of invasive activation mapping by measuring on the isochronal map, the area of the isochrone encompassing the first 10 ms of the activation time. They have observed that the use of isoprenaline may expand the area of EAS from 1.2 ± 0.7 cm^2 as described by Bogun et al. [20] to 3.0 ± 1.6 cm^2, due to the increase in the conduction velocity away from the origin of the arrhythmia [15]. Unlike the invasive activation map, the ECGI was performed without isoprenaline since the map can be constructed with just one beat and this can explain the very good spatial resolution. In patients with infrequent PVCs or VT that is not inducible, pace mapping is currently the alternative method for identifying the site of origin. However, the spatial resolution of this method is bad. Sites with the best pace mapping matches were located an averaged 18 ± 5 mm (range: 11–26 mm) away from the effective ablation site [15]. Furthermore, pace mapping fails to reproduce the morphology of arrhythmias arising in the RVOT in approximately 20% of patients and therefore is not a reliable guide for ablation [20]. Regarding atrial pace mapping, Man et al. [21] demonstrated that pacing sites as far apart as 32 mm in the coronary sinus and 17 mm in the right atrium can result in P waves that are very similar or identical in appearance.

The third finding of our study was expected, and refers to the association between the number of leads used for the map and the spatial resolution. Nevertheless, when we used half the electrode bands, the agreement with Carto map was not reduced in the case of PVCs and has shown a small decrease from 100% to 83% in the group with PACs. The spatial resolution was still acceptable in the case of PVCs, with an EASd of 15 (13–18) mm and still better than the spatial resolution of the pace mapping [15]. In comparison, the spatial resolution of PACs was worse although not statistically significant, and still in line with the resolution of atrial pace mapping [21]. When we further reduced the number of electrode bands to six, the accuracy of the method was significantly reduced in both the PVCs and PACs group. Recently, Misra et al. [7] reported the initial experience with an ECGI system, based on the 12-lead electrocardiogram and patient's specific myocardial model from MRI or CT. It is designed to obtain an *endo*-epicardial map of ventricular arrhythmias and unlike our system, does not analyze the surface ECG but rather the surface vectorcardiogram. The reported accuracy in case of PVCs was 11/13 (85%) for perfect or near matches, the former considered if the EAS was in the same segment and the latter if it was in contiguous segments in comparison with the invasive electroanatomical mapping. It is important to emphasize, that in our study, in the initial analysis we only accepted perfect matches.

Although demonstrating good accuracy, the ECGI systems still show a major limitation. The reconstruction of septal activation is still a drawback, and this occurs with epicardial [6] as well as *endo*-epicardial systems like ours [19]. In a recent work, Potyagaylo et al. [22] using the vectorcardiogram analysis with the Amycard ECGI system obtained a better non-invasive imaging of septal ventricular sources.

Finally, we observed that the minimal number of leads needed to obtain agreement with good spatial resolution was 74, which corresponds to 33% of the maximal number of leads available with this system.

With our study we demonstrated that it is feasible to get accurate maps with a good spatial resolution with less leads and this is particularly true in patients with PVCs. We do not intend to encourage the reduction of leads. However, we may hypothesize that there is no need for such a high number of leads as 224. That would certainly decrease the cost of the procedure. Secondly, it would make it easier to perform non-invasive and invasive studies simultaneously. Applying less electrode bands, could allow for simultaneous use of electroanatomical or defibrillator patches, and make investigation more comfortable and user-friendly. There is a still a long way to definitely establish the ECGI as a clinical tool for catheter ablation, and the simplification of the method is certainly a useful path.

Limitations

ECGI in this study was performed with the Amycard 01C software version. Patients in whom cardiac imaging was obtained with MRI were excluded from analysis, because this software version does not import MRI images. Later versions of the software do not have this pitfall. Nevertheless, with the third-generation CT used in our study the radiation dose was very low, below 1 mSv as previously reported [23]. However, as the study was performed with CT, in patients with focal arrhythmias and in the absence of structural heart disease, we cannot extrapolate our results to ECGI performed with MRI, other arrhythmias or patients with structural heart disease. When defining the minimal number of leads, we did not specifically assess the preferential thoracic position of the connected leads, a predefined configuration of the electrode bands was used. The impact of number of leads might have been different with other configurations.

The gold standard to evaluate the origin of the arrhythmia was the Carto activation map and therefore, in case of unsuccessful procedures it is not certain that the site pointed out by the Carto system is the origin of the arrhythmia.

Conclusions

Reducing the number of leads was associated with a lower agreement rate and a reduction of spatial resolution. This finding is more pronounced in case of PACs. However, the number of leads needed to achieve agreement with a good spatial resolution is far less than the maximal available.

Grant support

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Declaration of Competing Interest

Margarita Budanova, Stepan Zubarev and Mikhail Chmelevsky are consultants of EP Solutions. Joana Pinho is technical support of Biosense Webster.

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Europace 2022 Volume 24 Supplement 1 i41

9.3.1 - Electrocardiography (ECG)

40535
Electrocardiographic imaging a valid tool or an inaccurate toy?

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Background and aim: Electrocardiographic imaging (ECGI) is capable of performing an activation map with a single beat. However, previous studies using the epicardial-only system, have suggested a bad accuracy for the assessment of the epicardial breakthrough. Recent systems using endo-epicardial analysis have shown promising results. The aim of this study was to assess the accuracy and reproducibility of two endo-epicardial ECGI systems using different cardiac sources one based on the extracellular-potential, and the other on the equivalent double layer model, respectively the AMYCARD (EP Solutions SA, Switzerland) and VIVO (Catheter Precision, NJ USA) systems.

Methods: We studied 11 consecutive patients referred for ablation of frequent idiopathic premature ventricular contractions at our center that had an ECGI performed using both systems on the same day. The AMYCARD system uses a dense array of body-surface electrocardiograms with up to 224 leads and VIVO uses just the 12-leads ECG. Both systems use a patient-specific heart torso geometry obtained with a CT-scan or cardiac magnetic resonance. The localisation of the PVCs based on ECGI was done using a segmental model with 22 segments on the left ventricle, to include the classical 17 segment model plus the aortic cusps and the papillary muscles, and 12 segments on the right ventricle including 4 on the right ventricular outflow tract (RVOT): (anterior, lateral, right septum and left septum). A perfect match was defined as a predicted location within the same anatomic segment, whereas a near match as a predicted location within the same segment or a contiguous one.

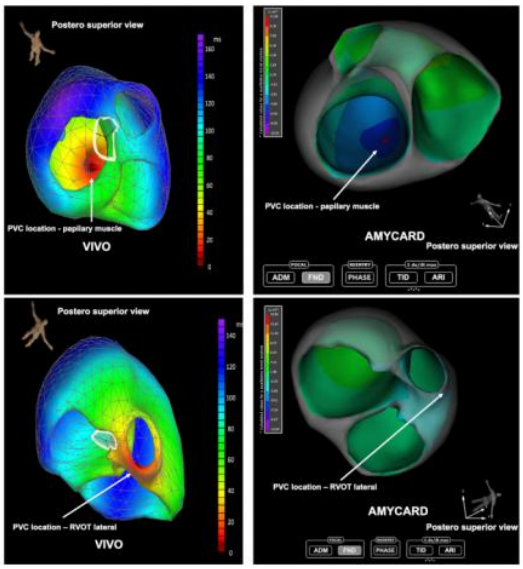
Results: The median (Q1-Q3) number of leads used for the AMYCARD was 131 (118-144). Seven patients underwent ablation and in 4 ablation is pending. The predicted locations and the ablation site are depicted on the Table. We found a perfect match between both systems in 73% (Figure) and near match in 91% of cases. In patients that underwent ablation the systems localised the site of origin of the PVCs within the same segment or the contiguous segment in all patients with VIVO and in six out of seven with AMYCARD.

Conclusions: ECGI is an accurate diagnostic tool with reproducible results regardless the cardiac source used for analysis.

Patient Nº	Ablation segment	VIVO segment	Amycard segment	Success
1	RCC	RCC	RORS	1
2	ROA	ROA	RORS	1
3	ROLS	ROLS	ROLS	1
4	PPM	PPM	PPM	0
5	LAB	LCC	LCC	1
6	ROLS	ROLS	ROLS	1
7	ROLS	ROLS	ROLS	1
8	np	ROL	ROL	np
9	np	PPM	PPM	np
10	np	RORS	ROLS	np
11	np	ROLS	ROLS	np

LAB: left anterior basal; LCC: left coronary cusp; np: non performed; PPM: posterior papillary muscle; RCC: right coronary cusp; ROA: right outflow tract anterior; ROL: right outflow tract lateral; ROLS: right outflow tract left septum; RORS: right outflow tract right septum

9.3.1 - Electrocardiography (ECG)



Electrocardiographic imaging accuracy and coherence between two different systems

Parreira L, Carmo P, Mesquita D, Marinheiro R, Marques L, Mancelos S, Hitchen R, Chmelevsky M, Zubarev S, Ferreira A, Goncalves P, Marques H, Adragao P

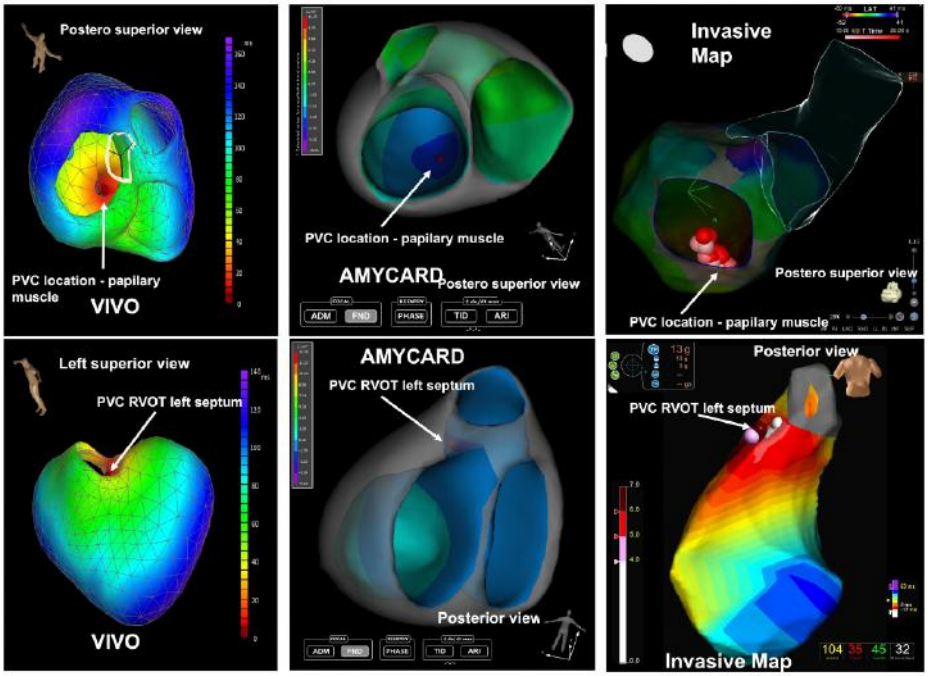
Background and aim: Previous studies reporting on electrocardiographic imaging (ECGI), using an epicardial-only system, have suggested a bad accuracy. The aim of this study was to assess the accuracy and coherence of two endo-epicardial ECGI systems using different cardiac sources.

Methods: We performed 61 ECGI procedures in 48 patients referred for ablation of frequent idiopathic premature ventricular contractions (PVCs) at our center. The Amycard (EP Solutions SA, Switzerland) system is based on the extracellular potential, was used in 26 patients, the VIVO (Catheter Precision, NJ USA) systems based on the equivalent double layer model in 9, and both in 13 patients. The first uses a dense array of body-surface electrocardiograms with up to 224 leads and the second one just the 12-leads ECG. Both use a patient-specific heart torso geometry obtained with a CT-scan or cardiac magnetic resonance. The localization of the PVCs based on ECGI was done using a segmental model with 22 segments on the left ventricle, to include the classical 17 segment model plus the aortic cusps and the papillary muscles, and 12 segments on the right ventricle including 4 on the right ventricular outflow tract (RVOT). A perfect match (PM) was defined as a predicted location within the same anatomic segment, whereas a near match (NM) as a predicted location within the same segment or a contiguous one.

Results: 42 patients underwent ablation, successful in 76%. The origin of the PVCs was the RVOT in 22 patients, right ventricle in 5, coronary cusps in 3, left ventricle in 3, LV summit in 3, LVOT in 2, papillary muscles in 2, moderator band in 1 and aortomitral continuity in 1. The agreement between the predicted site and the invasive mapping with both systems is depicted in the table. The percentage of PM and NM was not significantly different. In the 13 patients that had the ECGI performed with both systems, we found a NM in 100% and a PM in 70%. (Figure).

Conclusions: ECGI is an accurate diagnostic tool with reproducible results regardless the cardiac source used for analysis.

	AMYCARD (n=36)	VIVO (N=19)	P value
Perfect match between ECGI and Invasive map, n (%)	28 (78)	18 (95)	0.141
Near match between ECGI and Invasive map, n (%)	35 (97)	19 (100)	1.000



Non-invasive Prediction of Response to Cardiac Resynchronization Therapy using EP Solutions 3D Activation Mapping – a Multicenter Single-Blind Study

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ABSTRACT

Background

Pacing at a site remote from late activated left ventricle has been reported as possible reason for lack of response to cardiac resynchronization therapy (CRT). By using a noninvasive 3D activation mapping system to localize both latest electrical activated site (LEAS) and pacing site at left ventricle (LVPS), we tested the hypothesis that a LVPS closer to LEAS increases the likelihood of ventricular response.

Methods

111 consecutive CRT patients from 5 clinical centers in Europe were included in the study. All patients underwent a chest and heart computed tomography (CT) and acquisition of body surface potentials using 28 strips of 8 electrodes each, applied to the patient's torso. Subjects were classified as CRT Responders or non-Responders based on reduction of the left ventricular end-systolic volume; more than 15% reduction were classified as response. LEAS during native heart rhythm was identified. The distances d_P along the epicardial surface between LEAS and LVPS, identified on CT images, were measured in all patients.

Results:

All patients had CRT devices implanted 6 to 24 months prior to study enrollment, most had LBBB and 38% had ischemic heart disease.74 (67%) Responders and 37 (33%) non-Responders were included in the study. LEAS positions were found to be patient specific. Distances d_P between LEAS and LVPS varied widely from 2 to 137 mm. Mean d_P for Responders was approximately half of that for non-Respondents. The distance d_P was found to be a strong independent predictor of non-response ($p < 0.01$). A cutoff of d_P=47 mm yielded clear delineation between Responders and non-Responders (sensitivity 87 %, specificity 92%, PPV: 84%, NPV: 93%).

Conclusion:

The distance d_P between LEAS and LVPS identified with noninvasive 3D activation mapping system correlated strongly with CRT outcome. The results form the basis for using this low-risk, low-cost and noninvasive approach to prospectively plan and guide LV lead placement and thus further improve CRT outcomes.

Mesquita, Parreira L. Arritmias ventriculares idiopáticas. In Victor Gil ed. Cardiologia, LIDEL, 1ª edição, Lisboa:690-69

Arritmias Ventriculares idiopáticas

Dinis Mesquita, Leonor Parreira

As ectopias e as taquicardias ventriculares (mantidas e não mantidas) em corações estruturalmente normais são raras, observando-se um predomínio significativo destas em doentes com doença cardíaca adquirida. Estudos pós-*mortem* documentam ausência de alterações estruturais cardíacas em 2-54% de casos de morte súbita, pelo que a probabilidade de serem mais frequentes do que o descrito e insuficientemente reconhecidas é elevada. [1, 2] As séries que descrevem estas disritmias, reportam uma maior benignidade nas taquicardias ventriculares com origem no ventrículo direito, existindo um predomínio do sexo feminino e uma menor idade de apresentação (média de 32 anos). Comparativamente, as taquicardias ventriculares esquerdas, são mais frequentes no sexo masculino e em idades superiores (média 43 anos), observando-se um prognóstico menos favorável e uma maior associação a doença estrutural. [1]

Epidemiologia

As taquicardias ventriculares idiopáticas contabilizam cerca de 10% dos doentes em seguimento por taquicardias ventriculares [3]. Para além das ectopias e taquicardias ventriculares com origem nas câmaras de saída ventriculares e em outros focos miocárdicos (habitualmente do anel tricúspide ou anel mitral), estão descritos outros síndromes arrítmicos em corações estruturalmente normais: as taquicardias fasciculares, as taquicardias interfasciculares, as taquicardias de músculos papilares, as taquicardias de reentrada ramo-a-ramo e as taquicardias focais de fibras de *Purkinje*.

Estão também descritas arritmias malignas, potencialmente associadas a morte súbita em corações estruturalmente normais que ao contrário das anteriores são geralmente polimórficas e associadas a canalopatias. É o caso da taquicardia polimórfica catecolaminérgica, das taquicardias associadas ao síndrome de QT longo, do síndrome de Brugada e síndrome do QT curto, que serão tratadas no capítulo específico dos Síndromes Genéticos.

Neste capítulo abordaremos as arritmias ventriculares monomórficas, nomeadamente as arritmias das camaras de saída e as taquicardias ventriculares fasciculares.

Avaliação do doente para exclusão de doença cardíaca estrutural

Na avaliação de um doente com arritmias ventriculares é fundamental excluir a presença de cardiopatia estrutural. Para isso, alem de uma história clínica e interrogação sobre os antecedentes familiares será necessário a realização de um electrocardiograma de 12 derivações, e de um ecocardiograma 2D e modo M para excluir patologia estrutural ou alterações eletrocardiográficas associadas a ocorrência de arritmias ventriculares. Uma prova de esforço é também importante para avaliar o comportamento da arritmia com o esforço e para excluir isquemia. O registo de *Holter* de 24 horas permite avaliar a carga arrítmica. Na suspeita de cardiopatia isquémica a Angio TC ou mesmo a coronariografia poderão estar indicadas. Finalmente, a ressonância magnética nuclear com gadolínio, especialmente se houver suspeita de doenças infiltrativas ou cardiopatia arritmogénica do ventrículo direito, que além de permitir avaliar a função ventricular de forma mais precisa, permite também detetar a presença de alterações estruturais não identificadas no ecocardiograma, ou presença de isquemia e de fibrose. [4,5].

Arritmias das câmaras de saída ventricular

Anatomia

A camara de saída do ventrículo direito (CSVD) e do ventrículo esquerdo (CSVE) formam uma anatomia complexa com uma série de estruturas sobrepostas, incluindo as artérias coronárias. A CSVD encontra-se anteriormente e para a esquerda da CSVE, localizando-se a válvula pulmonar num plano superior em relação à válvula aórtica. A cúspide coronária direita (CCD) localiza-se imediatamente atrás da parede posterior da CSVD e a porção anterior da cúspide coronária esquerda (CCE) contacta com a porção mais esquerda da CSVD. Por sua vez, a raiz da aorta ao nível dos seios de Valsalva na sua porção posterior, ou seja, a face posterior da CCE e a cúspide não coronária (CNC) encontram-se em continuidade com o anel mitral constituindo a zona designada de continuidade mitro-aórtica. Esta estende-se entre o trígono fibroso esquerdo, posterior à CCE e o trígono fibroso direito, posterior à junção entre a CNC e a CCD. Imediatamente abaixo desta junção localiza-se o feixe de *His*. Estão descritas extensões musculares tanto na artéria pulmonar como na aorta, à exceção desta zona fibrosa.

Apresentação

As arritmias ventriculares idiopáticas das camaras de saída correspondem a 70-90% das taquicardias sem cardiopatia estrutural [6]. Podem apresentar três formas de gravidade crescente:

extrassístoles ventriculares (ESV) frequentes, salvas de TVNM e taquicardia ventricular mantida (Figura 1), acreditando-se que partilhem o mesmo mecanismo. [6]

Classicamente descritas como tendo origem na CSVD, na era da ablação por cateter tem sido, no entanto, demonstrada a sua origem em outras localizações, nomeadamente na CSVE, incluindo o seio de Valsalva esquerdo e direito, na zona parahisiana e anéis mitral e tricúspide, podendo ainda ter origem epicárdica. A sua localização mais frequente é a CSVD onde se origina em 80% dos casos, seguido da CSVE. Cerca de 10% das arritmias tem origem epicárdica, algumas junto à grande veia cardíaca, na veia cardíaca média ou na junção entre a grande veia cardíaca e a veia interventricular anterior, área designada por *summit* do ventrículo esquerdo. Em todas estas localizações partilhando o mesmo mecanismo. [7]

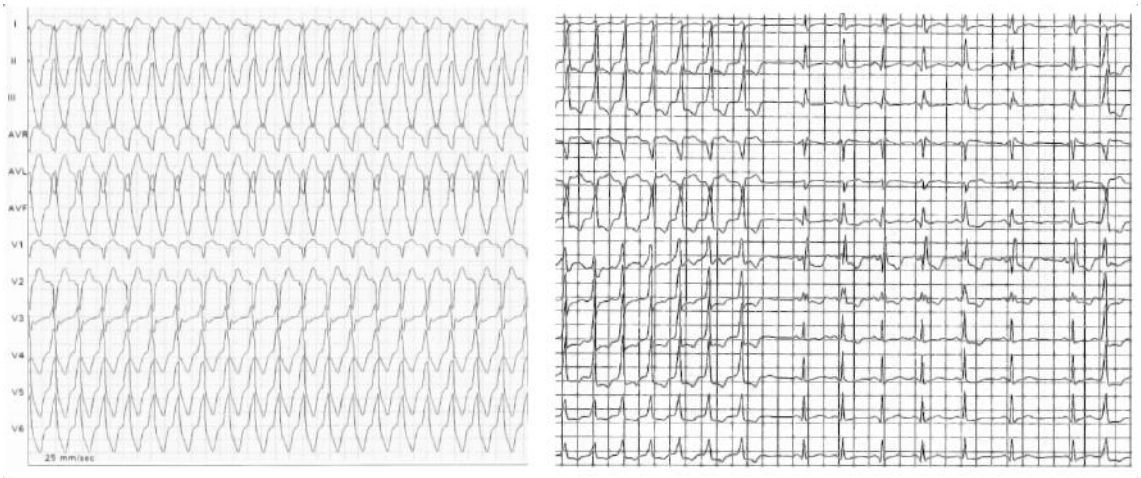

Figura 1

Taquicardia ventricular mantida com origem na CSVD (painel esquerdo) e salvas incessantes de TVNM com origem na CSVE (painel direito). CSVD: camara de saída do ventrículo direito; TVNM: taquicardia ventricular não mantida; CSVE: camara de saída do ventrículo esquerdo.

Mecanismo

O mecanismo subjacente é uma actividade *triggered* desencadeada por pós-despolarizações tardias mediadas por cAMP resultando num aumento do cálcio dentro da célula [8]. É agravada pelo estímulo adrenérgico e geralmente é induzida por estimulação continua auricular ou ventricular com ou sem perfusão de catecolaminas, ao contrário das taquicardias por reentrada que são mais facilmente induzidas por estimulação ventricular programada. A taquicardia é passível de ser interrompida por *overdrive pacing,* administração de bloqueadores beta adrenérgicos, bloqueadores dos canais de cálcio, manobra de Valsalva ou adenosina[8]. Este último facto é patognomónico deste tipo de TV, já que a adenosina é ineficaz no tratamento de TV por mecanismo de reentrada[9,10]. Por este motivo é também denominada TV sensível à adenosina

Sintomas

Os sintomas são muito variáveis e dependem do tipo de apresentação clínica. No caso das ESV ou salvas de ESV, os doentes queixam-se sobretudo de palpitações, dor precordial, dispneia e tonturas, embora muitos sejam assintomáticos. Em caso de TV mantida, a maioria dos doentes apresenta sintomas e embora raramente, a síncope pode ocorrer.

As arritmias agravam-se com o stress, cafeína, e exercício, sobretudo no período de recuperação.[11]

Diagnóstico Eletrocardiográfico

Existem múltiplos algoritmos desenvolvidos com o objetivo de predizer o local de origem da arritmia, com base no electrocardiograma de 12 derivações. Porém estes algoritmos apresentam uma baixa precisão e reprodutibilidade, o que se deve à baixa resolução espacial do ECG face à complexa anatomia da região das camaras de saída ventriculares. Além disso estes algoritmos não entram em consideração com as diferentes anatomias cardíacas e diferentes orientações do coração em relação à parede torácica.

De uma forma simplista podemos afirmar que arritmias com origem na parede livre da CSVD, sendo a localização mais anterior e direita, apresentam uma transição mais tardia nas derivações precordiais do que as que se originam na parede septal da CSVD ou na CSVE. Assim, uma transição em V2 indica em geral uma origem na CSVE e uma transição em V4 uma origem na CSVD. Porém uma transição em V3 poderá representar uma origem tanto na CSVD como na CSVE. Quanto mais para esquerda o foco se localiza, mais negativo o QRS na derivação DI, de tal modo que a origem na porção anterior do septo ou parede livre da CSVD, apresentam QRS mais positivo em DI do que as posteriores. As que se originam na continuidade mitro-aórtica, por isso mais posteriores e esquerdas têm um padrão de BCRD e com concordância positiva nas derivações precordiais. As arritmias com origem no *summit* do VE têm um padrão rS em DI e uma onda r empastada em V1 (Figura 2).

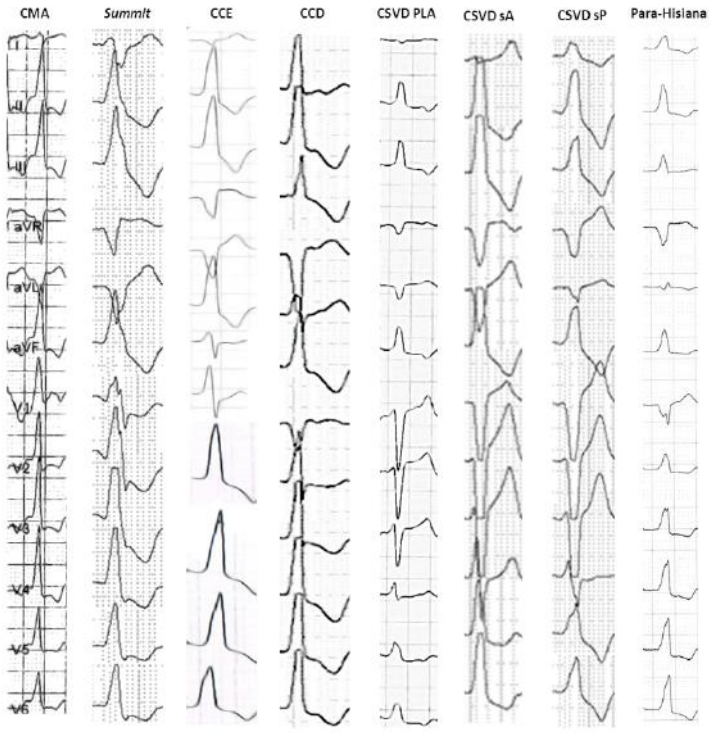

Figura 2

Electrocardiograma de 12 derivações típico das várias origens da arritmia de doentes com origem confirmada por mapeamento durante a ablação por cateter, com sucesso. Da esquerda para a direita origem na continuidade mitro-aórtica com concordância positiva em todas as derivações precordiais, no *summit* do ventrículo esquerdo com um padrão rS em DI e r empastado em V1. O padrão das cúspides coronárias com uma transição precordial muito precoce, mais na CCE. As arritmias com origem na CSVD têm uma transição precordial mais tardia sobretudo nas septais. As mais anteriores (CSVD PLA e CSVD sA) são menos positivas ou mesmo negativas em DI. Finalmente as para-Hisianas com a presença de QRS isolelétrico em aVL. CMA: Continuidade mitro-aórtica; CCE: cúspide coronária esquerda; CCD: cúspide coronária direita; CSVD PLA: camara de saída do ventrículo direito parede livre anterior; CSVDsA: camara de saída do ventrículo direito septo anterior; CSVD sP: camara de saída do ventrículo direito septo posterior.

Prognóstico

O prognóstico tem sido considerado benigno[12] com ausência de morte súbita em estudos com tempo de seguimento longo. No entanto recentemente tem surgido evidência que uma pequena percentagem destes doentes podem apresentar um quadro de taquicardia ventricular polimórfica ou fibrilhação ventricular,[13,14] ou evoluírem para uma situação de disfunção ventricular esquerda.[15] Esta taquicardiomiopatia como tem sido designada ocorre em doentes com salvas incessantes de ESV mas também tem sido descrita em situações de ESV isoladas, frequentes. Têm sido investigados marcadores de desenvolvimento de taquicardiomiopatia, nomeadamente o limiar de carga arrítmica[16]. Têm sido apontados valores que variam entre 16% e 24% do total de batimentos / 24 horas [17,18], no entanto os estudos são unânimes em afirmar que é necessária uma carga arrítmica superior a 10.000 ESV /24 horas por um período prolongado de tempo e que ainda assim esta entidade ocorre numa minoria de doentes.[8]

Terapêutica

Esta entidade tem uma apresentação pleomórfica, variando entre ESV isoladas assintomáticas até TV sincopal. O tratamento depende da presença de sintomas ou de disfunção ventricular esquerda. De forma aguda a adenosina é eficaz em terminar a TV.

Se o doente é assintomático e não existe evidência de cardiopatia estrutural, muitas vezes é suficiente tranquilizar e sugerir a restrição de fatores desencadeantes como o exercício em excesso e os estimulantes, e seguimento em consulta com avaliação periódica da função ventricular. No caso de sintomas ligeiros muitas vezes a terapêutica com bloqueadores beta adrenérgicos ou antagonistas dos canais de cálcio não diidropiridinicos é suficiente. Na ausência de resposta aos fármacos, em caso de sintomas mais graves ou em caso de preferência do doente, a terapêutica de ablação por cateter está indicada, já que se trata em geral de doentes jovens em relação aos quais a terapêutica muito prolongada com fármacos antiarrítmicos não é aconselhável. [19]

Ablação por cateter

A estratégia terapêutica utilizada depende do mecanismo da arritmia, da etiologia e presença de cardiopatia subjacente, e da capacidade de induzir a arritmia e de a manter o tempo necessário. As arritmias idiopáticas em geral são bem toleradas dado que se trata na maioria de doentes jovens e sem cardiopatia estrutural de base.

Por esse motivo a ablação é baseada no mapeamento da taquicardia, ao contrário das TV na cardiopatia estrutural em que na maioria dos casos se utiliza uma técnica de ablação do substrato sem necessidade de indução da arritmia.

No caso de ablação de TV ou de ESV efetua-se o mapeamento electroanatómico, com obtenção de um mapa com um padrão de activação centrifuga dado que se trata de uma arritmia focal. O electrograma unipolar intracavitário mostra um padrão QS e uma precocidade em relação ao QRS do electrocardiograma de superfície de pelo menos 20 mseg. (Figura 3)

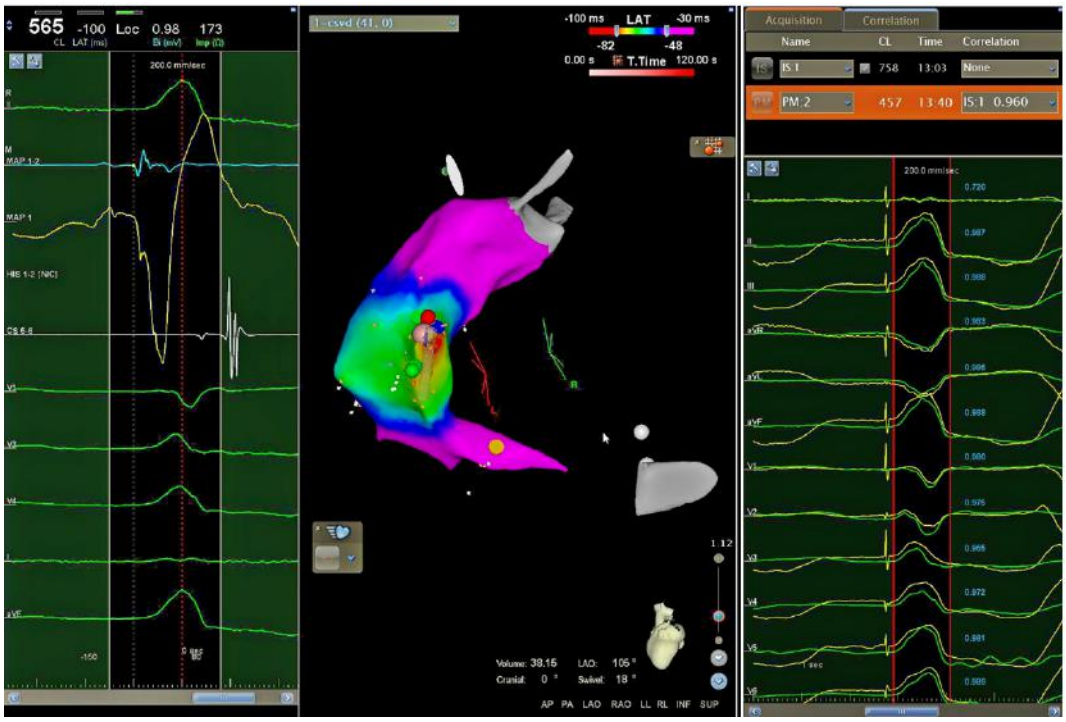

Figura 3

Mapeamento electroanatómico com o sistema Carto®. O mapa de ativação, (painel central) mostrando um padrão de ativação centrifugo com a zona mais precoce (cor vermelha) a nível do septo posterior da CSVD.

No painel da esquerda observa-se um padrão QS no local de ablação com uma precocidade elevada em relação ao início do QRS de superfície. No painel da direita *pacemapping* no local de ablação revelando uma concordância em todas as derivações.

A estimulação no local de ativação mais precoce origina um QRS com uma morfologia sobreponível à da arritmia clínica.

A ablação mostrou maior eficácia que os fármacos no alívio sintomático, no tratamento da TV mantida e na resolução da disfunção ventricular induzida por ESV frequentes [20,21,22,23,24]. A taxa de sucesso ronda os 90%, podendo, no entanto, ser inferior, na eventualidade de uma incapacidade de induzir a arritmia durante o procedimento ou se a origem se localizar em determinados locais, nomeadamente no *summit* do ventrículo esquerdo, na zona epicárdica ou intramural. A taxa de complicações é baixa tratando-se de um procedimento seguro.

Taquicardias Fasciculares Idiopáticas

Apresentação

As taquicardias fasciculares, ocorrem em corações morfologicamente normais, embora previamente se pensasse que estivessem associadas a uma variante anatómica mediante a conexão de um falso tendão ventricular esquerdo entre o septo basal e a parede póstero-inferior ventricular esquerda (relatos anátomo-patológicos documentam em alguns casos a existência

de fibras de *Purkinje* mescladas no miocárdio dos falsos tendões).[25] Descritas inicialmente por *Cohen et. al* e posteriormente por *Zipes et. al* em 1973, a sua sensibilidade ao verapamil foi mais tarde documentada por *Belhasen et. al*. Estas subdividem-se habitualmente em taquicardias fasciculares posteriores (90-95% dos casos), em taquicardias fasciculares anteriores (até 10% dos casos) e existindo ainda uma terceira variante de taquicardia fascicular, extremamente rara, com origem septal superior esquerda (<1%).[26] No global contabilizam cerca de 10-15% dos casos de taquicardias ventriculares em corações morfologicamente normais. [27]

Mecanismo

O mecanismo mais comum é uma macrorreentrada que utiliza o feixe posterior esquerdo do sistema de condução *His-Purkinje* (menos comumente o fascículo anterior) com condução por via retrógrada, ocorrendo a condução anterógrada por conexão anómala através de fibras de *Purkinje* ou de miocárdio adjacente (zona lenta do circuito, com propriedades de condução decrementais e com sensibilidade ao verapamil), onde a zona de entrada no circuito é habitualmente no septo basal. Maioritariamente, todo o feixe de *His* faz parte do circuito de macrorrentrada.[25,28] À semelhança de outras disritmias de reentrada, são indutíveis e terminadas com estimulação auricular e ventricular programada e respondem a manobras de *entrainment*.

Para além da taquicardia ventricular fascicular de reentrada, podem igualmente ocorrer extrassístoles ventriculares fasciculares ou taquicardias por mecanismo de automaticidade ou atividade deflagrada. Alguns autores, descrevem a taquicardia de músculos papilares como ocorrendo por intermédio de fibras de *Purkinje*.[28]

Sintomas e investigação etiológica

A apresentação clínica é extremamente variável. Os sintomas mais frequentes são as queixas de palpitações em doentes jovens e sem antecedentes médicos ou cirúrgicos patológicos. Não obstante, a pré-síncope, síncope ou paragem cardiorrespiratória (que pode ser a forma de apresentação) são outros sintomas associados (embora muito raramente). Sendo as palpitações o sintoma mais comum, em casos raros de taquicardia incessante, pode ocorrer taquicardiomiopatia (6% dos casos), habitualmente reversível com a resolução da disritmia.[1] Maioritariamente com surgimento espontâneo em repouso, o exercício físico, o *stress* e a descarga catecolaminérgica endógena podem igualmente ser fatores precipitantes da taquicardia.

Predominante no sexo masculino (60-80% dos casos) apresenta-se tipicamente em idade jovem (15-40 anos). [27]

Diagnóstico eletrocardiográfico

A apresentação eletrocardiográfica da taquicardia fascicular posterior esquerda é a de uma taquicardia regular de complexos relativamente estreitos (habitualmente largura de QRS de 100 até 140 mseg, com um *nadir* RS inferior a 60 mseg), padrão de bloqueio de ramo direito e eixo esquerdo (sugerindo saída do circuito no septo póstero-inferior, figura 4). As taquicardias fasciculares anteriores têm padrão de bloqueio de ramo direito mas com eixo direito (sugerindo saída do circuito na parede antero-lateral do ventrículo esquerdo).[26,28] O ECG basal destes doentes é habitualmente normal. Por sua vez, as taquicardias do septo superior esquerdo, tem QRS estreitos, padrão de bloqueio de ramo direito e o eixo eletrocardiográfico pode ser direito ou normal.

O diagnóstico destas taquicardias deve ser feito mediante a exclusão de cardiopatia estrutural. A dificuldade em distinguir estas taquicardias de disritmias supraventriculares com aberrância é frequente atendendo à morfologia e largura habitual dos QRS. A documentação de dissociação aurículo-ventricular no ECG ou em estudo eletrofisiológico expõe o diagnóstico. Igualmente a sua sensibilidade ao verapamil, permite distinguir o comportamento das taquicardias fasciculares de outras taquicardias ventriculares, embora possa agravar a dificuldade em diferenciá-las de aberrância de condução.

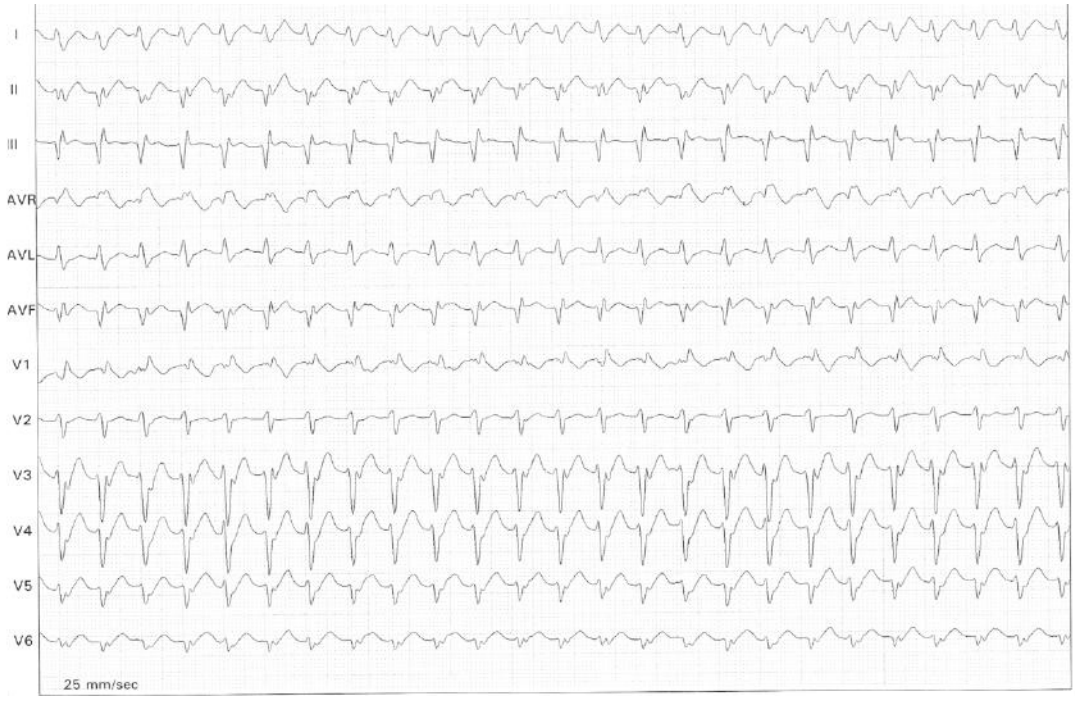

Figura 4.

Electrocardiograma de taquicardia fascicular posterior esquerda: largura de QRS de 110mseg e padrão de bloqueio de ramo direito. A taquicardia tipicamente tem desvio esquerdo do eixo elétrico e o nadir rS conforme observado, é inferior a 60 mseg.

Prognóstico

O prognóstico a longo prazo em doentes com taquicardia ventricular fascicular na ausência de doença cardíaca estrutural é habitualmente bom e com um curso clínico benigno. Em até 6% dos casos, a apresentação pode cursar com sintomas de insuficiência cardíaca em contexto de taquicardiomiopatia, que é habitualmente reversível após a resolução do quadro disrítmico. A paragem cardiorrespiratória e morte súbita arrítmica são formas extremamente raras de apresentação das taquicardias fasciculares. [1,27]

Terapêutica

Num doente que se apresente com taquicardia regular, a decisão terapêutica inicial deve tomar em linha de consideração a estabilidade hemodinâmica do doente e o seu risco de colapso cárdio-circulatório (apresentação em insuficiência cardíaca ou episódio recente de síncope). Em doentes que cumpram estes critérios de gravidade, a cardioversão elétrica urgente deve ser preconizada. Na ausência destes, a decisão passa habitualmente por terapêutica farmacológica, onde o diagnóstico diferencial da taquicardia se mostra premente. Em doentes com dúvidas diagnósticas, atendendo à largura do QRS e nos quais não é possível a certificação do ritmo, o manejo terapêutico deve seguir o algoritmo das taquicardias ventriculares pelo risco de colapso hemodinâmico em casos de diagnóstico erróneo.[19,29] Nos casos em que é possível aferir o diagnóstico, a terapêutica de eleição é a administração endovenosa de 10 mg de verapamil dado que as taquicardias fasciculares são dependentes da entrada lenta de cálcio nas fibras de *Purkinje* e demonstram uma excelente resposta à administração deste fármaco. A terapêutica com antiarrítmicos das classes IA e IC de *Vaughn-Williams*, são igualmente uma opção terapêutica para estes doentes (embora não sejam a primeira linha). Não existe habitualmente resposta terapêutica efetiva à adenosina ou aos beta-bloqueantes.[27]

Embora as taquicardias fasciculares sejam habitualmente sensíveis ao verapamil, demonstram uma reduzida taxa de resposta efetiva a longo prazo ao fármaco. Em doentes cuja terapêutica não é tolerada, que tenham recidiva de episódios de taquicardia ventricular ou cuja opção do doente seja esta, a terapêutica ablativa por cateter está recomendada com intenção curativa. [29] Em centros com experiência na ablação deste tipo de taquicardia, a ablação é recomendada como primeira linha terapêutica a longo prazo. [19] Esta pode ser efetuada de duas formas. Ablação do feixe do circuito de condução anterógrado pelo mapeamento dos potenciais diastólicos que precedem o QRS em pelo menos 25 até 110 mseg, mais tardios de uma forma em gradiente do apex para a base (potenciais de *Purkinje* e potenciais pré-*Purkinje*) ou em

alternativa, ablação do feixe posterior mediante o mapeamento dos potenciais *his-like* imediatamente inscritos antes do QRS (figura 5).[26,28]

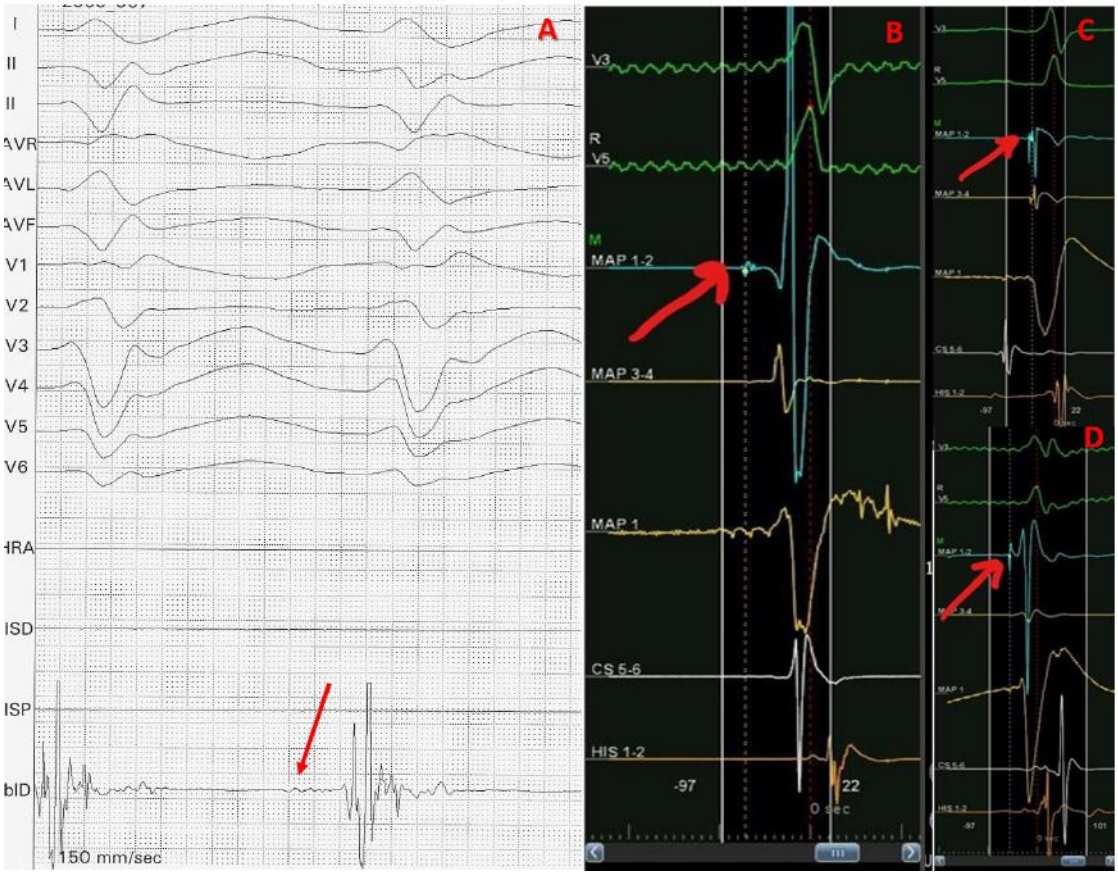

Figura 5

Potenciais encontrados durante mapeamento de taquicardia fascicular: A – Potencial Pré*Purkinje* (P1) evidente antes do QRS (seta) durante taquicardia fascicular posterior. B – Potencial Pré*Purkinje* (P1) durante ritmo sinusal (seta). C - Potencial do feixe anterior esquerdo de *His* durante ritmo sinusal (seta). C - Potencial do feixe posterior esquerdo de *His* durante ritmo sinusal (seta).

Esta última forma de ablação é idealmente realizada da zona médio-ventricular para a zona apical, ao longo do fascículo de forma a evitar a ocorrência de bloqueio de ramo esquerdo ou BAV completo (complicações raras neste tipo de ablação e habitualmente transitórias) e realizada em linha perpendicular ao maior eixo de ventrículo esquerdo e de condução nativa, idealmente a cerca de 1cm do ponto de saída, quando efetuada em ritmo sinusal.[28]

A ablação, com uma taxa de sucesso em 75-95% dos casos, pode ser conseguida mesmo na ausência de inducibilidade da taquicardia durante o estudo eletrofisiológico. São reportadas recorrências de 10-20% (Figura 6).[26,28,29]

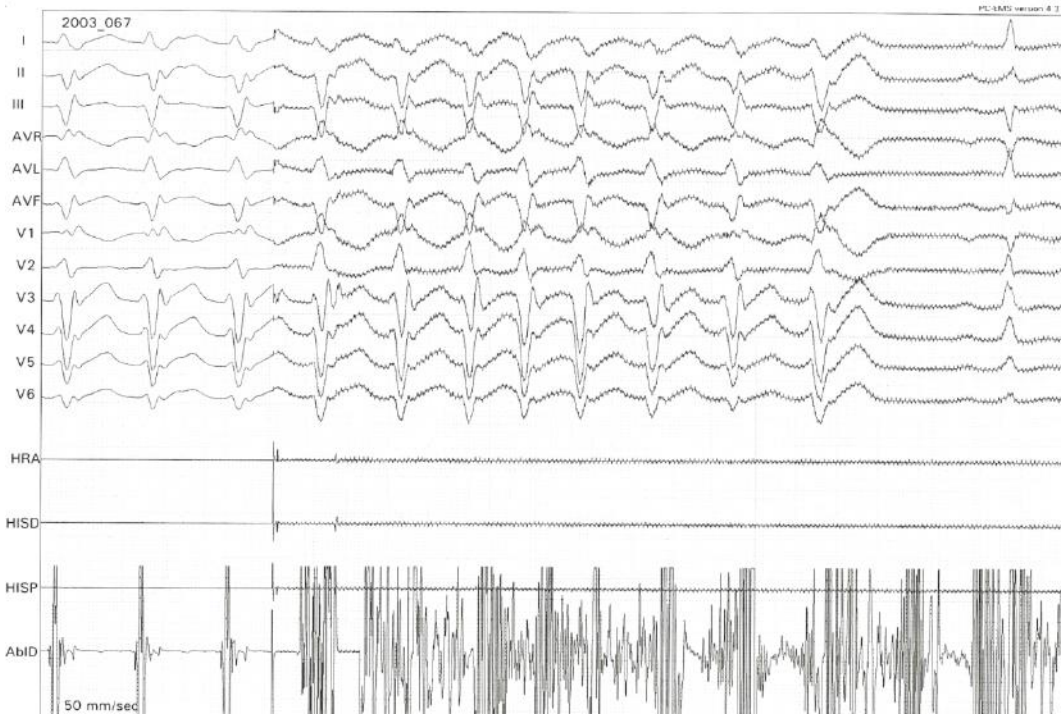

Figura 6

Aplicação de radiofrequência em zona do feixe posterior esquerdo de His durante taquicardia fascicular posterior esquerda (potenciais imediatamente inscritos antes do electrograma ventricular), com término da mesma durante as aplicações e conversão a ritmo sinusal.

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ORIGINAL ARTICLE

Premature ventricular contractions of the right ventricular outflow tract: Upward displacement of the ECG unmasks ST elevation in V1 associated with the presence of low voltage areas

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Abstract
Introduction and Aims: Frequent premature ventricular contractions (PVCs) originating from the right ventricular outflow tract (RVOT) are usually considered a benign entity and the ECG is typically normal. The aim of this study was to assess whether upward displacement of the ECG to the second intercostal space (ICS) would reveal any abnormal pattern.
Methods: A total of 18 consecutive patients with apparently normal hearts were studied, mean age 44±16 years, 12 women, who underwent catheter ablation of the RVOT due to frequent PVCs. A 12-lead ECG was performed in the standard position and repeated in a higher position, at the level of the second ICS. Three-dimensional bipolar electroanatomical voltage mapping (EVM) was performed in all patients and low voltage areas (LVAs) were defined as areas with amplitude <1.5 mV.
Results: The ECG in the second ICS was normal in eleven patients but in seven (39%) it revealed a pattern of ST-segment elevation in V1. EVM revealed the presence of LVAs in six patients (33%) which included the earliest activation site (EAS) in five. The ST elevation was associated with the presence of LVAs ($p<0.0001$) and with the LVAs at the EAS ($p=0.002$).
Conclusion: In this group of patients with apparently normal hearts and with frequent PVCs of the RVOT, upward displacement of the ECG revealed the presence of ST elevation in more than one third of patients, and the ST elevation was associated with the presence of LVAs in the RVOT.

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PALAVRAS-CHAVE
Eletrocardiograma de 12 derivações;
Extrasistoles ventriculares;
Arritmias ventriculares idiopáticas;
Mapa de voltagem;
Supradesnivelamento do segmento ST;
Ablação por cateter

Extrasistolia ventricular da camara de saída do ventrículo direito. ECG efetuado no segundo espaço intercostal revela supradesnivelamento do segmento ST que se associa com a presença de baixa voltagem no mapa electroanatómico

Resumo
Introdução e objetivo: A extrasistolia ventricular (ESV) frequente da camara de saída do VD (CSVD) é em geral uma patologia benigna e o ECG é tipicamente normal. O objectivo deste estudo é avaliar se o ECG efetuado no 2.° espaço intercostal (2.° EIC) permite detetar algum padrão anormal dada a maior proximidade com a CSVD.
Métodos: Estudámos 18 doentes consecutivos submetidos a ablação de ESV da CSVD, idade média 44±16 anos, 12 mulheres, com coração aparentemente normal. O ECG foi obtido na posição standard e repetido com as derivações V1 e V2 a nível do 2 EIC. Foi efetuado mapa eletroanatómico de voltagem bipolar (MEV). Foram estabelecidos como área de baixa voltagem (ABV) os eletrogramas com amplitude <1.5 mV.
Resultados: O ECG no 2.° EIC não mostrou alterações em 11 doentes, mas em sete (39%) observou-se um padrão de supradesnivelamento do segmento ST (supra ST) em V1. O MEV revelou a presença de ABV em seis doentes (33%), a qual incluía a zona de aplicação em cinco doentes. O supra ST em V1 associou-se com a presença de ABV (p<0,0001) e com ABV no local de ablação (p=0,002).
Conclusões: Neste grupo de doentes com ESV da CSVD e coração aparentemente normal, a realização do ECG no 2.° EIC permitiu identificar a presença de supra ST em V1 em mais de um terço dos doentes que se associou com a presença de áreas de baixa voltagem na CSVD.

Abbreviations

ARVC	arrhythmogenic right ventricular cardiomyopathy
cMRI	cardiac magnetic resonance imaging
EAS	earliest activation site
ECG	electrocardiogram
EVM	electroanatomical voltage mapping
ICS	intercostal space
LVA	low voltage area
MNS	magnetic navigation system
PVC	premature ventricular contraction
PVT	polymorphic ventricular tachycardia
RVOT	right ventricular outflow tract
VF	ventricular fibrillation

Introduction

Premature ventricular contractions (PVCs) are a common finding in the normal population. The prognosis depends on the presence of structural heart disease; idiopathic PVCs are considered benign. Recently, however, evidence has emerged that a small percentage of patients may present with polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF).[1,2]

Many potential markers have been studied, but none has so far been found that could predict this malignant outcome. It has been questioned whether all right ventricular outflow tract (RVOT) PVCs are in fact benign or whether some may represent an early stage of arrhythmogenic right ventricular cardiomyopathy (ARVC).

Initial studies with cardiac magnetic resonance imaging (cMRI) showed the presence of structural abnormalities, including localized wall bulging, focal wall thinning or fatty replacement in a high percentage of patients with PVCs and apparently normal hearts.[3] However, most recent cMRI studies using modern techniques like electrocardiogram (ECG) gating and contrast-enhanced cMRI with delayed contrast enhancement used for imaging of ventricular scars have shown no pathological findings in patients with idiopathic RVOT PVCs.[4]

It has been demonstrated that the presence of myocardial fibrosis is associated with the occurrence of arrhythmic events. Myocardial fibrosis can be assessed noninvasively with cMRI or invasively with bipolar electroanatomical voltage mapping (EVM). However, the presence of fibrosis may reflect a more advanced form of the disease, and it would be useful to find other as yet unknown signs that are detectable in earlier stages of the disease.

We decided to perform an ECG in a higher position to assess whether closer proximity to the RVOT might expose features absent in the standard ECG that could help to

identify patients who would present with abnormalities during the ablation procedure.

Methods

Patient selection

This prospective study included consecutive patients undergoing mapping and ablation of frequent RVOT PVCs (defined as more than 10 000/24 hours during Holter recording), refractory to medical therapy, between June 2014 and December 2016.

All patients underwent transthoracic echocardiography, including two-dimensional (2D), M-mode, and Doppler studies, and 12-lead ECG. When symptoms increased with exercise or when there was a suspicion the patient might have coronary heart disease, a treadmill exercise test was performed. cMRI was performed to rule out structural heart disease if any of the other exams were abnormal. Patients were excluded if structural heart disease was present, if they had undergone previous ablation or if the standard 12-lead ECG displayed evidence of conduction or electrical disease or abnormal QRS morphology. Patients with a PVC focus outside the RVOT were also excluded.

Study design

Demographic data, cardiovascular risk factors, symptoms, transthoracic echocardiograms, 24-hour Holter monitoring and medications were recorded, as well as treadmill exercise test and cMRI results when performed. All patients underwent a standard 12-lead ECG and a 12-lead ECG in the second ICS.

Twelve-lead electrocardiogram

All ECGs were recorded in the electrophysiology laboratory on AXIOM Sensis™ (Siemens Systems) or EP-WorkMate 1.2.0™ (St. Jude Medical) recorders. Patients underwent a standard 12-lead ECG that included recordings of both premature ventricular and sinus rhythm beats using standard paper speed and calibration. The V1 and V2 leads were placed in the fourth ICS in the right and left sternal locations, respectively. The upper limb leads were placed on the respective shoulders, and the lower limb leads were placed on the respective side of the abdomen. The ECG was then repeated with the V1 and V2 leads placed in the second ICS, maintaining the other lead positions. The 12-lead ECG morphology of PVCs in both ECG positions and the morphology of the QRS and ST intervals in sinus rhythm were analyzed in the standard and higher positions. Right precordial T-wave inversion was considered present when beyond V1. The precordial transition in sinus rhythm and during PVCs was defined as the precordial lead in which the QRS changed from predominantly negative to predominantly positive and the R/S ratio became >1.

Mapping and ablation

Mapping technique and measurements

Patients were studied in a fasting non-sedated state. All antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study.

Diagnostic catheters were positioned via the femoral vein with fluoroscopic guidance in the His position and in the great cardiac vein via the coronary sinus.

Isoprenaline was administered intravenously, as needed, and titrated to a dose that induced PVCs.

All patients underwent electroanatomical mapping by CARTO 3™ (Biosense Webster) or EnSite Velocity™ (St. Jude Medical) systems during sinus rhythm.

With CARTO 3 mapping, all procedures were performed using the Niobe™ magnetic navigation system (MNS) (Stereotaxis) working with the single-plane AXIOM Artis™ fluoroscopy system (Siemens) as previously described.[5] An irrigated-tip Navistar RMT Thermocool™ catheter (Biosense Webster) was used with a 4-mm distal tip electrode and a 2-mm ring electrode with an interelectrode spacing of 1 mm.

With the EnSite Velocity, all procedures were performed manually with the BV Pulsera™ (Philips) single-plane fluoroscopy system and using a FlexAbility™ irrigated-tip catheter (St. Jude Medical) with a 4-mm distal tip electrode and 1-4-1 interelectrode spacing.

The ablation catheter was introduced via the femoral vein and advanced manually to the right atrium and then advanced to the His bundle and RVOT, automatically in the MNS patients and manually in the EnSite patients, under fluoroscopic guidance. The ablation catheter was then placed at multiple sites on the endocardial surface of the RVOT to record bipolar intracardiac electrograms (filtered at 30 to 400 Hz). This information was used to generate three-dimensional (3D) electroanatomical maps of the RVOT with the electrophysiological information color-coded and superimposed on the geometry.

Activation mapping

The activation map was created by mapping several points within the RVOT during each PVC, using a surface ECG lead as a reference. Activation times were assigned on the basis of the onset of bipolar electrograms and displayed as color gradients on a 3D activation map. Bipolar activation times were manually reviewed and the earliest isochrone was defined as the earliest activation site (EAS). After generation of isochrone reconstructions of the RVOT, bipolar pace mapping was performed at multiple endocardial sites near the EAS. Pacing was performed at cycle lengths as close as possible to that of the coupling interval of the PVC. The ablation site was selected based on the earliest endocardial activation time and confirmed by pace mapping that provided at least an 11 out of 12 match between paced and spontaneous PVCs.

Electroanatomical voltage mapping

Bipolar voltage reference for normal and abnormal myocardium was based on values validated by intraoperative and catheter mapping and used in previous voltage mapping studies.[6]

The color display for depicting normal and abnormal voltage myocardium ranged from red, representing electroanatomical scar tissue (amplitude <0.5 mV), to purple, representing electroanatomically normal tissue (amplitude >1.5 mV). Areas with signal amplitudes <1.5 mV represented low voltage areas (LVAs).

Complete endocardial maps were obtained to enable reconstruction of the 3D geometry of the RVOT.

Magnetic navigation

The MNS uses two computer-controlled permanent magnets positioned on either side of the fluoroscopy table. These magnets create a magnetic field of 0.1 T. The position of the magnets is remotely controlled by a console, the Navigant workstation, which changes the orientation of the magnetic field according to the vectors chosen by the operator. The ablation catheter has three magnets in its distal portion that render it parallel to the magnetic field. Changes in the orientation of the magnetic field deflect the catheter, which is remotely advanced or retracted with the aid of a computerized motor drive, Cardiodrive™ (Stereotaxis). Magnetic field vectors can be stored in order to automatically navigate the ablation catheter to previous sites.

Ablation

Energy was delivered from an EP Shuttle™ radiofrequency generator (Stockert) between the distal electrode of the ablation catheter and a cutaneous patch for up to 120 s to a maximum temperature of 43 °C and a power output limit of 35 W. When the application was ineffective, additional applications were delivered to sites adjacent to the EAS with a good pace-map.

During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed.

Success was defined as elimination of PVCs under isoprenaline infusion for at least 30 min after ablation.

All patients were monitored in hospital for 24 hours after the procedure.

Follow-up

Follow-up was performed at outpatient visits. Clinical assessment was carried out one to three months after ablation and regularly every six months thereafter. At least one 24-hour Holter recording was obtained after the procedure.

Ethics

All patients gave their written informed consent and the study was approved by the institutional review board. The study is in compliance with the Helsinki Declaration.

Statistical analysis

IBM SPSS version 23 software (IBM SPSS Inc., Chicago, IL) was used for the statistical analysis. Data are expressed as means ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Baseline characteristics and outcomes were compared using the chi-square test for categorical variables and the t test for continuous variables. A value of $p<0.05$ was considered statistically significant.

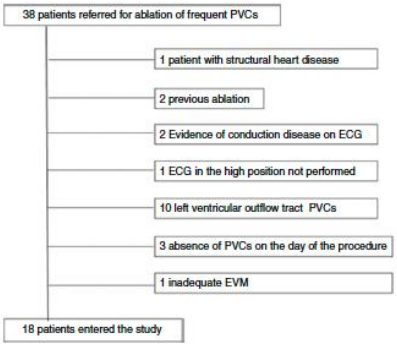

Figure 1 Flowchart of the study selection process. ECG: electrocardiogram; EVM: electroanatomical voltage mapping; PVC: premature ventricular contraction.

Results

Study population

Eighteen patients out of 38 were included in the study, mean age 45±16 years, 12 female (Figure 1). The patient characteristics are displayed in Table 1. Only one patient was asymptomatic; 17 patients complained of palpitations and one had a history of syncope, but none had documented episodes of sustained ventricular arrhythmias. Two patients had a family history of sudden death but none had a family history of ARVC. Physical examination, chest X-rays, and transthoracic echocardiography, including 2D, M-mode, and Doppler studies, were normal and demonstrated normal right ventricular size and function. Ten patients underwent treadmill exercise testing that showed a reduction of PVC frequency in nine patients and an increase in one, without evidence of ischemia. The 24-hour Holter recording showed a high PVC burden, with a mean of 24 823±9546 PVC/24 hours. Seven patients underwent cMRI, three of them because of precordial T-wave inversion on the 12-lead ECG, to rule out ARVC, two because of a family history of sudden death, one because of PVC increase during the exercise test and one because of syncope. The cMRI was normal in all. A flecainide test was administered to the patient with ST elevation and syncope to rule out Brugada syndrome, which was negative.

Standard 12-lead electrocardiogram

The precordial transition in sinus rhythm was beyond V3 in all patients, as was the precordial transition of the PVCs. In two patients the transition of the PVC was later than the transition in sinus rhythm, but in 16 patients it was earlier or in the same precordial lead.

Table 1 Baseline characteristics of the study groups.

	Overall sample (n=18)	Normal second ICS ECG (n=11)	ST elevation second ICS (n=7)	p
Demographic data				
Male gender, n (%)	6 (33)	4 (36)	2 (28)	NS
Age, years, mean ± SD	44.7±15.7	48±12.7	42.6±17.6	NS
Risk factors and history				
Family history of sudden death, n (%)	2 (11)	2 (18)	0	NS
Absence of risk factors, n (%)	14 (77)	9 (82)	5 (71)	NS
Strenuous exercise, n (%)	1 (5.6)	1 (14)	0	NS
Symptoms				
Asymptomatic, n (%)	1 (5.6)	0	1 (14)	NS
Syncope, n (%)	1 (5.6)	0 (0)	1 (14)	NS
Palpitations, n (%)	17 (94.4)	11 (100)	6 (86)	NS
Previous sustained VT, n (%)	0	0	0	NS
Duration of symptoms, months	40±30	45±30	32.2±31.1	NS
Medications				
Beta-blockers, n (%)	14 (77.8)	8 (72)	6 (86)	NS
Antiarrhythmics, n (%)	2 (11.1)	2 (18)	0	NS
Standard 12-lead ECG				
Right precordial T-wave inversion, n (%)	3 (16.7)	0	3 (43)	0.043
Sinus rhythm precordial transition at V3, n (%)	2 (11)	0	2 (28)	NS
Sinus rhythm precordial transition beyond V3, n (%)	16 (88)	11 (100)	5 (71)	NS
PVC precordial transition at V3, n (%)	4 (22)	2 (18)	2 (28)	NS
PVC precordial transition beyond V3, n (%)	14 (77)	9 (82)	5 (71)	NS
QRS duration (ms)	86.8±8.3	85.9±6.9	88.4±10	NS
Treadmill exercise test (n=10)				
Exercise-induced increase in PVC frequency, n (%)	1 (10)	1 (16)	0 (0)	NS
Exercise-induced reduction in PVC frequency, n (%)	9 (90)	5 (83)	4 (100)	NS
24-hour Holter recording				
No. of PVCs/24 hours	24 823±9546	24 274±10649	25 109±8297	NS
NSVT, n (%)	5 (27.8)	3 (27)	2 (28)	NS
cMRI (n=7)				
Normal, n (%)	7 (100%)	3 (27)	4 (57)	NS

cMRI: cardiac magnetic resonance imaging; ECG: electrocardiogram; ICS: intercostal space; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contraction; SD: standard deviation; VT: ventricular tachycardia.

Three patients had T-wave inversion in V1 to V3, but the ECG was otherwise normal in all.

Second intercostal space electrocardiogram

The upward shift of the precordial leads V1 and V2 to the second ICS resulted in the appearance of ST-segment elevation in seven patients (39%). The ST elevation was less than 2 mm, convex and followed by a negative T wave, but did not reach criteria for type 1 Brugada pattern (Figure 2). Five patients (28%) had an rSr' pattern in V1, not present on the standard ECG, and in two patients both features were present (Figure 2).

The pattern of the PVC changed little, becoming more negative with the loss of the initial r in leads V1 and V2, changing from rS to QS.

The clinical and non-invasive data for both groups with and without ST-segment elevation are displayed in Table 1. We found no differences except for a higher frequency of

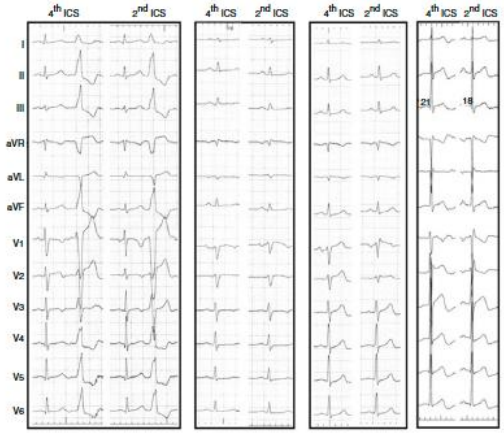

Figure 2 12-lead electrocardiogram (ECG) of four different patients comparing the tracings with V1 and V2 in the standard and high positions. From left to right, in the first patient V1 does not change, the PVC loses R in V1 and V2 in the second ICS. In the second patient the upper ECG displays ST elevation in V1, in the third patient ST elevation with rSr' pattern and in the fourth patient an rSr' pattern without ST elevation. ICS: intercostal space; PVC: premature ventricular contraction.

precordial T-wave inversion in the group with ST elevation (0% vs. 43%, p=0.043).

Mapping and ablation

Electroanatomical mapping was successfully acquired in all patients. The mean number of points used to obtain the RVOT map was 78±29. The activation map identified the EAS in the RVOT free wall in seven patients and in the RVOT septum in 11. In all patients there was an LVA at the level of the pulmonary valve. However, in six patients (33%) the LVA extend more proximally and in five patients the EAS was within the LVA (Figure 3). The acute success rate was 89% and there were no complications. The two patients with unsuccessful ablation are being followed on an outpatient basis and despite continuing to experience a high number of PVCs/24 hours, refused a second procedure.

We found an association between ST-segment elevation in the higher ECG and the presence of LVA (86% vs. 0% vs. p<0.0001) and the presence of EAS in the LVA (71% vs. 0%, p=0.002) (Table 2). The presence of an rSr' pattern did not correlate with the presence of LVA (2/5 [40%] vs. 4/13 [31%] (NS). The presence of LVAs or ST elevation did not correlate with acute success.

Follow-up

During a mean follow-up of 19.5±9.6 months, in the 16 patients in whom ablation was successful there were no recurrences. All patients remained free of symptoms. Antiarrhythmic drugs were suspended after ablation and only one patient continued beta-blocker therapy, for hypertension. All patients underwent 24-hour Holter recording and there was no recurrence of the ablated PVCs; in some cases there were still occasional PVCs, but with a different morphology. The number of PVCs/24 hours was dramatically reduced, from 24 823±9546 to 21±31.

Discussion

In the absence of structural heart disease, PVCs have generally been considered to have a benign prognosis.[7] However, recently there have been reports suggesting that a small percentage of patients may present with PVT or VF. Viskin et al.[1] reported the clinical history of three patients with apparently benign idiopathic PVCs of the RVOT who had episodes of PVT or VF during follow-up. Noda et al.[2] studied 16 out of 101 patients without structural heart disease who underwent ablation of RVOT PVCs and presented during follow-up with episodes of PVT or VF induced by PVCs.

It is important to assess whether the entity known as idiopathic RVOT PVCs may affect patients with some form of concealed structural heart disease at a very early stage, and if so, to identify the features that suggest that the patient may have a worse prognosis.

The specific marker of ARVC is the transmural loss of right ventricular myocardium and the presence of fibrofatty deposition is no longer considered diagnostic.[8] This loss of cardiac cells results in the appearance of areas of low voltage and electrical scar on EVM.[9,10] However, the results of EVM in patients with idiopathic RVOT PVCs are contradictory. In our study we demonstrated the presence of LVAs in the RVOT in 33% of patients. Boulos et al.[9] obtained different results. They compared the EVM of patients with idiopathic RVOT tachycardia to that of patients with ARVC and normal controls and concluded that patients with idiopathic VT and normal controls had similar EVM without LVAs, unlike the ARVC patients, who presented with LVAs. Other authors likewise demonstrated the presence of these LVAs in patients with idiopathic RVOT arrhythmias. Furushima et al.[11] performed EVM in 28 patients with apparently normal hearts and found LVAs immediately below the pulmonary valve in all patients, the width of the LVA being variable. Two patients had PVT/VF, and these were the ones with wider LVAs, although these patients did not undergo further investigation to rule out ARVC. The authors conclude that in the presence of a wider LVA, its potential arrhythmogenic impact must be borne in mind.

Corrado et al.[6] studied 27 patients out of 89 with RVOT arrhythmias and apparently normal hearts by EVM and endomyocardial biopsy. They found LVAs in seven patients (26%), an incidence very close to ours. Although without criteria for the diagnosis of ARVC according to the authors, these patients had symptoms or signs suggestive of potential structural disease, and yet only seven underwent cMRI, which was diagnostic of ARVC in four.

In our study, patients in whom structural heart disease was suspected due to T-wave inversion, syncope, family history of sudden death or worsening of arrhythmia during exercise underwent cMRI, which excluded ARVC.

EVM is an invasive procedure requiring cardiac catheterization, so it cannot be proposed as a routine method to assess patients with PVCs unless there is an indication for catheter ablation.

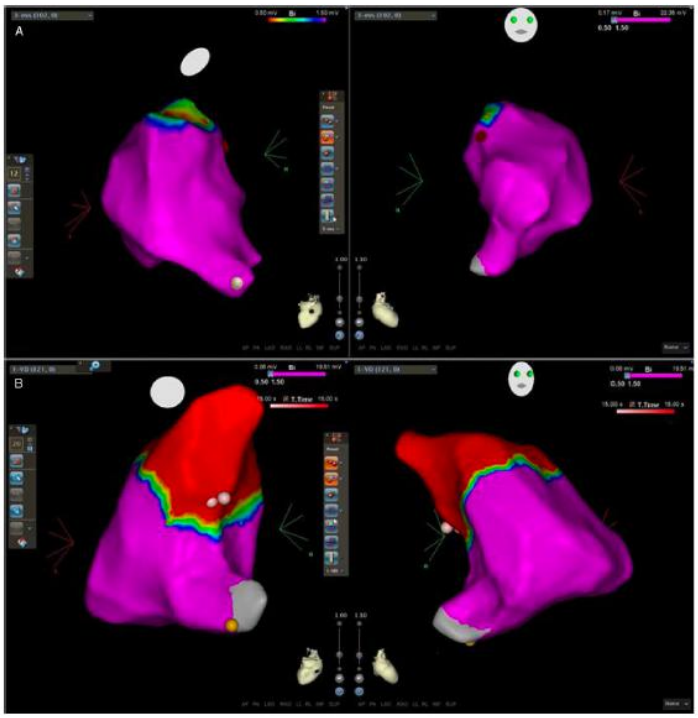

Figure 3 Three-dimensional electroanatomical voltage maps of the RVOT. (A): A patient with normal voltage map; (B): a patient with an LVA extending into the RVOT. Pink and red dots indicate the successful ablation site and yellow dots indicate the His bundle. Note that the ablation site lies within the LVA in the second patient. LVA: low voltage area; RVOT: right ventricular outflow tract.

Table 2 Mapping, ablation and follow-up data.

	Overall sample (n=18)	Normal second ICS ECG (n=11)	ST-elevation second ICS (n=7)	p
Mapping data				
Mapping system (CARTO/NavX), n	11/7	8/3	3/4	NS
Number of points	78±29	75±27	83.7±33.6	NS
EAS RVOT free wall, n (%)	7 (39)	4 (36)	3 (43)	NS
EAS RVOT septum, n (%)	11 (61)	7 (64)	4 (57)	NS
Presence of LVAs, n (%)	6 (33)	0	6 (86)	<0.0001
Ablation data				
EAS in the LVA, n (%)	5 (28)	0	5 (71)	0.002
Acute success, n (%)	16 (89)	9 (82)	7 (100)	NS
Complications, n (%)	0	0	0	NS
Follow-up data				
Duration of follow-up (months)	19.5±9.6	22±11	15.7±6.5	NS
Recurrence of PVCs, n (%)	0	0	0	NS
No. of PVCs on 24-hour Holter	21±31	16±6	37±45	NS
Beta-blockers, n (%)	1 (6)	0	1 (14)	NS
Antiarrhythmics, n (%)	0	0	0	NS

EAS: earliest activation site; ICS: intercostal space; LVA: low voltage area; PVC: premature ventricular contraction; RVOT: right ventricular outflow tract.

Recently, it has been demonstrated that upward displacement of leads V1 and V2 to the second ICS can improve the sensitivity of Brugada syndrome diagnosis due to the greater proximity to the RVOT.[12]

We decided to perform the ECG in the higher position since we were mapping the RVOT. In this position we identified a pattern of ST-segment elevation with or without an rSr' pattern that is absent in the standard ECG. The presence of an rSr' pattern has been described in the upper position in normal individuals.[13] Previous studies have also shown the presence of ST-segment elevation in V1-V2 at the second ICS identified as a Brugada type 2 or 3 pattern in athletes,[14] normal Asiatic populations[15] and normal European populations.[16] In these studies the reported incidence of ST elevation varies from 1.3%[15] to 4.3%[16] excluding the type 3 Brugada pattern. Chung et al.[14] found a higher incidence (12%), but they included the Brugada type 3 pattern, which is different from the morphology of our ST elevation, which was coved, although not reaching the criteria for Brugada type 1. All these studies showed a significantly lower incidence of ST elevation in the higher ECG than the 39% in our study, and it is important to underline that in these studies the subjects were not studied with cMRI to rule out structural heart disease.

The major finding of our study was the association between the presence of LVAs and ST-segment elevation in V1 in the ECG performed at the second ICS in patients with apparently normal hearts. To the best of our knowledge this is the first report of this association. Patients with ST elevation showed similar baseline characteristics to those without, with the exception of a higher incidence of T-wave inversion, but these patients underwent cMRI that ruled out the presence of ARVC.

The meaning of this ST elevation, and of the presence of LVA, remains unknown, however there seems to be an association between the two.

We do not know the long-term prognostic implications of these findings, but we found no impact on the acute success rate or short-term follow-up.

Krittayaphong et al.,[17] on the contrary, demonstrated that the presence of abnormalities on cMRI in patients with RVOT arrhythmias referred for catheter ablation without diagnostic criteria for ARVD was associated with a lower success rate and higher recurrence.

Although previous trials have demonstrated a correlation between the presence of scar on cMRI and on EVM,[18] they mostly involved the left ventricle. In the right ventricle, EVM demonstrated a higher sensitivity than cMRI for a diagnosis of LVAs.[19]

The definition of a condition as idiopathic is based on the absence of abnormalities in diagnostic tests and on lack of knowledge of its cause, but it does not imply absence of pathological abnormalities. In fact, Letsas et al.[20] recently demonstrated the presence of LVAs in the RVOT endocardium of asymptomatic type 1 Brugada patients using high-density endocardial voltage mapping despite the absence of delayed contrast enhancement on cMRI.

Thus we may speculate that in RVOT arrhythmias the presence of LVAs may be a marker of a very early stage of disease, not detected by current imaging techniques, and that ST elevation in V1 at the second ICS may be a surrogate marker of these LVAs.

Study limitations

The number of patients in our study was relatively small and there was no control group. cMRI was performed in only a small percentage of patients because it is not a routine examination for patients with PVC and apparently normal hearts, and when performed it was not repeated during follow-up.

EVM was perfoth two different systems with different methodologies. However, the electrogram analysis is similar and the threshold for defining low voltage is the same in both, and this has been validated previously. The mean follow-up time of 19 months is very short to assess the long-term success of the procedure and to demonstrate the benign outcome in this population.

Conclusion

In this group of patients with apparently normal hearts and with frequent PVCs of the RVOT, EVM during the ablation procedure displayed the presence of LVAs. Upward displacement of the ECG showed the presence of ST elevation in V1 in more than one third of patients, and this ST elevation was associated with the presence of LVAs in the RVOT.

Neither ST-segment elevation nor the presence of LVAs predicted the success or recurrence rate.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PLOS ONE

RESEARCH ARTICLE

Isolated diastolic potentials as predictors of success in ablation of right ventricular outflow tract idiopathic premature ventricular contractions

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Abbreviations: PVCs, Premature ventricular contractions; RVOT, Right ventricular outflow tract;

Abstract

Background and aims

Discrete potentials, low voltage and fragmented electrograms, have been previously reported at ablation site, in patients with premature ventricular contractions (PVCs) originating in the right ventricular outflow tract (RVOT). The aim of this study was to review the electrograms at ablation site and assess the presence of diastolic potentials and their association with success.

Methods

We retrospectively reviewed the electrograms obtained at the radiofrequency (RF) delivery sites of 48 patients subjected to ablation of RVOT frequent PVCs. We assessed the duration and amplitude of local electrogram, local activation time, and presence of diastolic potentials and fragmented electrograms.

Results

We reviewed 134 electrograms, median 2 (1–4) per patient. Success was achieved in 40 patients (83%). At successful sites the local activation time was earlier– 54 (-35 to -77) ms vs -26 (-12 to -35) ms, $p<0.0001$; the local electrogram had lower amplitude 1 (0.45–1.15) vs 1.5 (0.5–2.1) mV, $p = 0.006$, and longer duration 106 (80–154) vs 74 (60–90) ms, $p<0.0001$. Diastolic potentials and fragmented electrograms were more frequently present, respectively 76% vs 9%, $p <0.0001$ and 54% vs 11%, $p<0.0001$. In univariable analysis these variables were all associated with success. In multivariable analysis only the presence of diastolic potentials [OR 15.5 (95% CI: 3.92–61.2; $p<0.0001$)], and the value of local activation time [OR 1.11 (95% CI: 1.049–1.172 $p<0.0001$)], were significantly associated with success.

RF, Radiofrequency; ECG, Electrocardiogram; OR, Odds ratio; CI, Confidence interval; DADs, Delayed afterdepolarizations.

Conclusion

In this group of patients the presence of diastolic potentials at the ablation site was associated with success.

1. Introduction

The most common site of premature ventricular contractions (PVCs), in patients without structural heart disease, is the right ventricular outflow tract (RVOT) [1]. The intracardiac bipolar ventricular electrograms in the absence of structural heart disease, typically show a sharp deflection with normal amplitude and duration. Ablation based on activation mapping and/or pace-mapping is considered the standard technique for eliminating idiopathic PVCs arising from the RVOT [2]. Radiofrequency delivery should be performed at the site of the earliest ventricular activation. The ideal pace-map at ablation site is an identical QRS pattern in all 12 surface ECG leads (12/12 match).

Despite the high success rate [3] there are cases when complete eradication of the PVCs cannot be obtained. Many authors have looked for potential predictors of success, clinical and electrocardiographic or based in electrophysiological findings [4–6].

In our paper, we describe the presence of discrete isolated diastolic potentials, on the bipolar intracardiac electrograms at ablation site. These are low amplitude potentials, occurring after the T wave of the ECG in sinus rhythm that become pre-systolic, preceding the local bipolar ventricular electrogram during the PVCs. The meaning of these isolated diastolic potentials is unknown, and the aim of the present study was to evaluate their prevalence during RVOT PVCs ablation and their impact on the success of the procedure.

2. Methods

2.1. Patient selection

We studied 48 patients subjected to catheter ablation of idiopathic RVOT PVCs, between January 2010 and January 2018 in two Hospitals.

All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler echocardiography as well as 12-lead electrocardiograms (ECG). Whenever a structural heart disease was suspected, due to the presence of electrocardiographic or echocardiographic anomalies, the presence of syncope or a family history of sudden death, a cardiac magnetic resonance imaging was performed. When symptoms were triggered or aggravated by exercise, a treadmill stress test was performed to rule out ischemia and, in case of doubt, a computed tomography angiography was done to exclude coronary artery disease. Cardiac magnetic resonance imaging was also performed at the discretion of the attending physician.

Patients were excluded if a structural heart disease was present, if the patient had been subjected to previous ablation or if the PVCs focus was outside the RVOT.

2.2. Study design

We retrospectively analyzed all intracardiac electrograms at the site of RF delivery, to assess the presence of diastolic potentials. Other characteristics of the local bipolar electrogram were evaluated, including the local activation time in relation to the beginning of the QRS of the PVCs on the surface ECG, their amplitude, duration and the presence of fragmented

electrograms. The electrograms were evaluated by two senior electrophysiologists. For the purpose of this study we only considered RF applications that lasted at least 60 seconds.

We evaluated the association between the presence of diastolic potentials and procedure acute success rate, adjusted to the other variables.

2.3. Mapping and ablation

2.3.1. Mapping technique and measurements. Patients were studied in a fasting non-sedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study.

Diagnostic catheters were positioned via the femoral vein with fluoroscopic guidance in the His position and in the great cardiac vein via the coronary sinus.

Isoprenaline was administered intravenously, as needed, and titrated to a dose capable of inducing PVCs.

All patients underwent electroanatomical mapping by the CARTO 3 system (Biosense-Webster) or EnSite Velocity system (Abbott).

With the CARTO 3 system all procedures were performed using the Niobe magnetic navigation system (Stereotaxis) working with the monoplane fluoroscopy system AXIOM Artis (Siemens) as previously described by Parreira et al [7]. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster) was used with a 3.5-mm distal tip electrode and a 2-5-2 interelectrode distance.

With the EnSite Velocity system all procedures were done manually with the monoplane fluoroscopy system BV Pulsera (Philips) and using an irrigated tip Therapy Cool Path or Flexability catheter (Abbott) with a 4-mm distal tip electrode and a 1-4-1 interelectrode distance.

The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT in the magnetic navigation system patients or manually in the EnSite patients, under fluoroscopic guidance. The ablation catheter was then placed at multiple sites on the endocardial surface of the RVOT. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed. The bipolar electrograms were analyzed in regard of their timing in relation to the onset of the QRS on the surface ECG, their local amplitude, duration and presence of multiple components. The information was used to generate 3-dimensional electroanatomical activation and voltage maps of the RVOT, with the electrophysiologic information, color coded and superimposed on the geometry. The color display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude $>$ 1.5 mV), to red, representing electroanatomical scar tissue (amplitude $<$0.5 mV). Intermediate colors represented regions with electroanatomical low voltage.

2.3.2. Diastolic potentials. Diastolic potentials were defined as persistent low amplitude discrete potentials occurring at late diastole, after the end of the T wave of the surface ECG in sinus rhythm. These diastolic potentials became presystolic during the PVCs and were only recorded close to the ablation site (Fig 1).

2.3.3. Fragmented electrograms. Defined as bipolar electrograms at ablation site, with low amplitude, long duration and multiple peaks (Fig 2).

2.3.4. Activation mapping and ablation. The activation map was created by mapping several points within the RVOT during each PVCs while using a surface ECG lead as reference. Activation times were assigned based on the onset of bipolar electrograms. After isochronal reconstructions of the RVOT were generated, bipolar pace mapping was performed at multiple

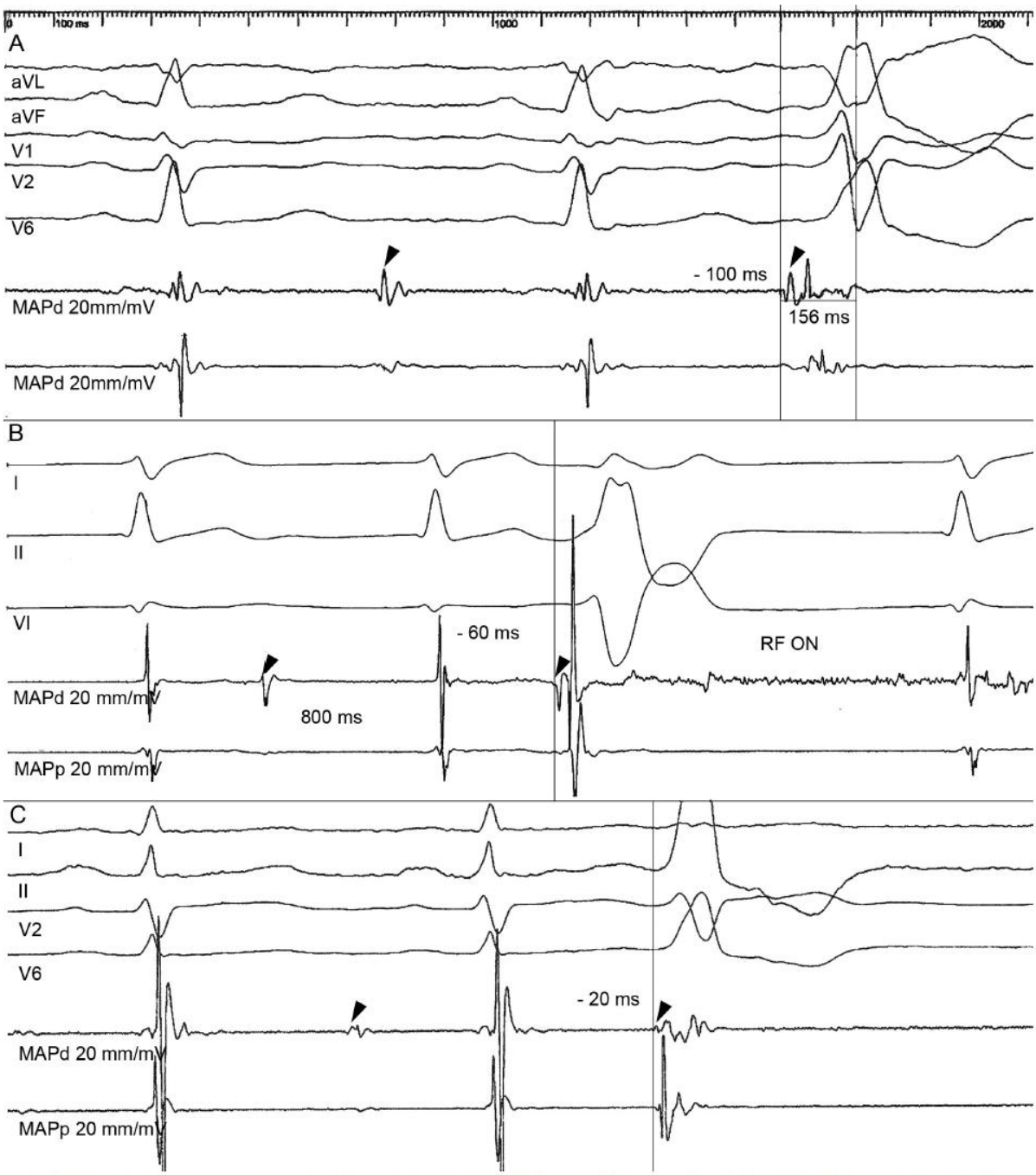

Fig 1. Diastolic potentials. Representative intracardiac electrograms at a successful ablation sites of 3 different patients. The MAPd exhibits the diastolic potentials (arrow head), occurring after the T wave of the surface ECG in sinus rhythm, becoming pre-QRS during the PVCs. The gain in the ablation catheter is 20 mm/1mV and sweep

speed is 100 mm/sec. (A), fragmented diastolic potential preceding the QRS by -100 ms; (B) sharp diastolic potential preceding the QRS by—60 ms. (C) dull diastolic potential preceding the QRS by -20 ms. In panel B and C the local electrogram in sinus rhythm displays normal amplitude and duration. In Panel A the local electrogram shows low voltage and prolonged duration.

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endocardial sites near the earliest activation site. Pacing was performed at cycle lengths as close as possible to that of the coupling interval of the PVCs.

The ablation site was selected based on the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least a 11 out of 12 match between paced and spontaneous PVCs.

Energy was delivered from an EP Shuttle RF generator (Stockert) between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 seconds, to a maximum temperature of 43˚C and a power output limit of 40 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site displaying a good pace-map matching. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed.

Success was defined as abolition of PVCs under isoprenaline infusion until thirty minutes after ablation.

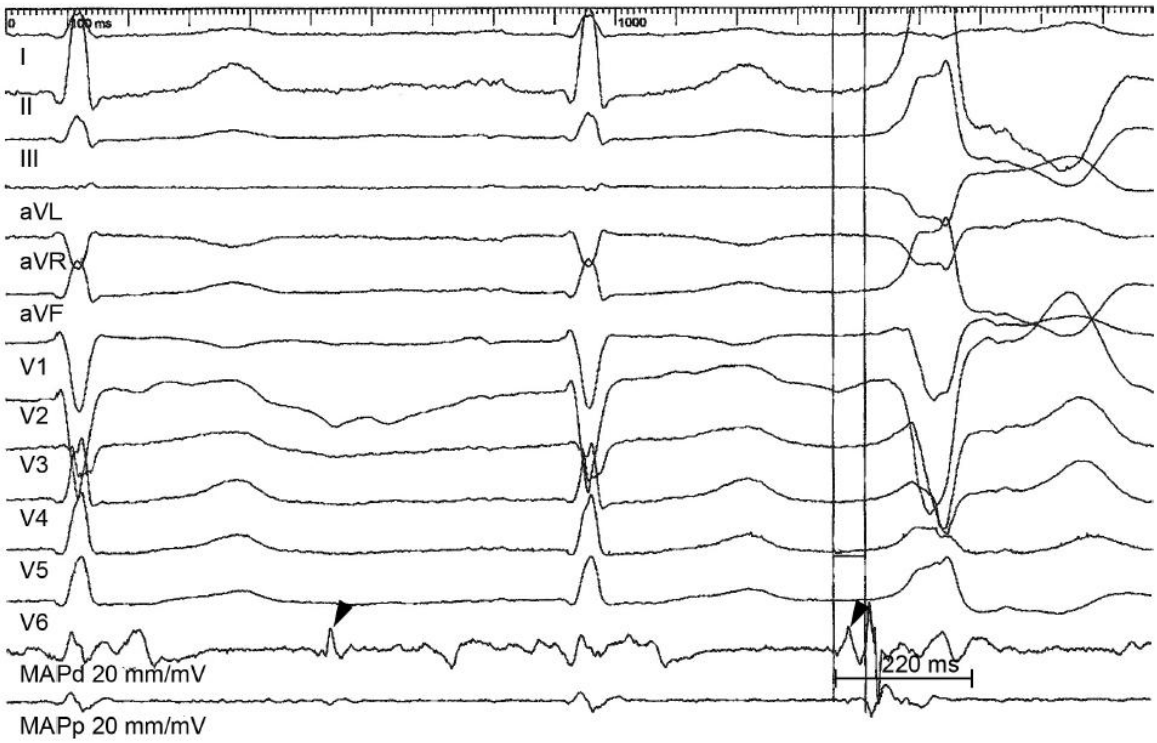

Fig 2. Fragmented electrograms. Intracardiac electrograms at successful ablation site. The bipolar electrogram on the ablation catheter (MAPd) exhibits a typical fragmented electrogram, diastolic potentials are also present (arrow heads). The fragmented electrogram shows low voltage and prolonged duration, 220 ms, but ending before the end of the QRS.

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All patients were monitored in hospital for 24 hours after the procedure.

2.4. Follow-up

Follow-up was performed on outpatient clinical visits. Clinical assessment was performed 1 to 3 months after ablation and regularly every 6 months thereafter. In patients that were followed by another physician the contact was performed by phone. All patients had a 24-hour Holter recording done after the procedure.

2.5. Statistical analysis

SPSS version 23 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data is expressed as median and interquartile range for continuous variables and as frequencies and percentages for categorical variables. Baseline characteristics were compared using the chi-square test for categorical variables and the Mann-Whitney-U test for continuous variables. Univariable and multivariable logistic regression analysis was used to calculate the odds ratios (OR) and 95% confidence intervals (CI). A value of $p < 0.05$ was considered statistically significant.

2.6. Ethics

All patients signed the informed consent form and the study was approved by the Ethics Committee for Health of Hospital da Luz and Ethics Committee for Health of Centro Hospitalar de Setúbal. The study is in compliance with the Helsinki Declaration.

3. Results

3.1. Study population

We reviewed 134 electrograms from forty-eight patients that entered the study, median age was 40 (31–56) years, eighteen males. Patient characteristics are displayed on Table 1.

Only four patients were asymptomatic while almost 90% of patients complained of palpitations. Seven patients had a history of syncope or near syncope, although none had documented episodes of sustained ventricular arrhythmias. Two patients had family history of sudden death, but none had family history of inherited arrhythmic disorders. Twenty-four patients were on beta-blockers and eleven were on antiarrhythmics other than amiodarone. Physical examination and transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler echocardiography were normal and demonstrated normal right ventricle size and function in all patients. The ECG displayed T wave inversion beyond V1 in 8 patients but arrhythmogenic right ventricular cardiomyopathy was ruled out according to the 2010 Task Force Criteria [8]. Twenty-eight patients underwent treadmill stress test that showed a reduction of the PVCs frequency in twenty-two (79%) patients and an increase in six (21%), without evidence of ischemia. Three patients underwent computed tomography angiography, with normal results. Fifteen patients underwent cardiac magnetic resonance imaging, without any relevant findings. A flecainide test was performed in one patient with ST elevation and syncope to rule out Brugada Syndrome. The 24-hour Holter recording showed a high PVCs burden with a median 18250 (15000–24000) PVCs/24 hours and the occurrence of runs of non-sustained ventricular tachycardia in six patients. The demographic and clinical characteristics did not differ whether the procedure was successful or unsuccessful.

3.2. Mapping and ablation

3.2.1. Activation mapping and ablation. The median number of acquired points in the RVOT were 67 (50–94). The activation map identified the earliest activation site in the RVOT

Table 1. Baseline characteristics of the studied patients.

	Overall sample (n = 48)	Successful procedure (n = 40)	Unsuccessful procedure (n = 8)	P value[a]
Demographic data				
Age (years)	40 (31–56)	40 (33–50)	53(19–61)	0.609
Male gender, n (%)	18 (38)	13 (33)	5 (62)	0.132
Risk factors and history				
Family history of sudden death, n (%)	2 (4)	2 (5)	0	0.9999
Absence of risk factors, n (%)	39 (81)	34 (85)	5 (63)	0.330
Strenuous exercise, n (%)	5 (10)	3 (8)	2 (25)	0.189
Symptoms				
Asymptomatic, n (%)	4 (8)	2 (5)	2 (25)	0.124
Syncope/near syncope n (%)	7 (14)	5 (13)	2 (25)	0.330
Palpitations, n (%)	43 (89)	37 (93)	6 (75)	0.189
Medications				
Betablockers, n (%)	24 (50)	21 (53)	3 (38)	0.701
Antiarrhythmics, n (%)	11 (23)	8 (20)	3 (38)	0.361
12 Lead ECG				
T wave inversion after V1, n (%)	8 (17)	6 (15)	2 (25)	0.605
Treadmill stress test (n = 28)				
Exercise induced increase in PVCs frequency, n (%)	6 (21)	6 (15)	0	0.542
24-Hour Holter recording				
N° of PVCs/24 hours	18250 (15000–24000)	18000 (15000–24000)	19250 (15750–23000)	0.857
NSVT n (%)	6 (12)	6 (15)	0	0.571
Mapping data				
Mapping system (CARTO/EnSite), n	35/13	29/11	6/2	0.9999
EAS RVOT free wall, n (%)	15 (31)	11 (27)	4 (50)	0.236
EAS RVOT septum, n (%)	33 (69)	29 (73)	4 (50)	0.236
Number of points in the map	67 (50–94)	64 (50–94	70 (52–95)	0.782
Number of RF pulses	2 (1–4)	2 (1–3.75)	4.5 (4–6)	0.0001

Values are presented as median (interquartile range) and number (%). EAS, earliest activation site; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular contraction; RF, radiofrequency; RVOT, right ventricular outflow tract.

[a] p values were calculated using Mann-Whitney-U test for continuous variables and the chi-square test for categorical variables.

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free wall in fifteen patients and in the RVOT septum in thirty-three. The median number of RF pulses was 2 (1–4). The acute success rate was 83% and there were no complications (Table 1). In the forty patients with a successful procedure, thirty (75%) had diastolic potentials at ablation site and ten (25%) did not. Success was achieved in all thirty patients with diastolic potentials and only in 56% of patients without. Forty-one RF pulses, out of the 134 analysed, were considered successful because they led to elimination of the PVCs. On one application the PVCs recurred after 30 minutes and a new RF pulse was applied at the same site with success (Table 2).

Successful RF applications had earlier local activation times—54 ms (-35 to -77) when compared to unsuccessful ones– 27 ms (-16 to-38). Diastolic potentials and fragmented electrograms were both more frequently present at successful sites, respectively 76% and 54% vs 9% and 11% at unsuccessful sites.

Comparing sites with diastolic potentials versus sites without diastolic potentials, the local activation time was earlier,– 54 (-34 to -74) ms vs -27 (-16 to -38) ms, $p<0.0001$, the median

Table 2. Mapping and ablation data.

	Overall sample (n = 134)	Successful (n = 41)	Unsuccessful (n = 93)	P value[a]
Ablation data				
LAT (ms)	-30 (-20 to -44)	- 54 (-35 to -77)	- 27 (-16 to-38)	<0.0001
Amplitude of local electrogram (mV)	1 (0.5–2)	1 (0.45–1.15)	1.5 (0.5–2.1)	0.006
Duration of local electrogram (ms)	80 (64–100)	106 (80–154)	74 (60–90)	<0.0001
Presence of diastolic potentials, n (%)	39 (29)	31 (76)	8 (9)	<0.0001
Presence of fragmented electrograms, n (%)	32 (24)	22 (54)	10 (11)	<0.0001
	Overall sample (n = 134)	**With DP (n = 39)**	**Without DP (n = 95)**	**P value[a]**
Ablation data				
LAT (ms)	-30 (-20 to -44)	- 54 (-34 to -74)	- 27 (-16 to -38)	<0.0001
Amplitude of local electrogram (mV)	1 (0.5–2)	1 (0.5–1.5)	1.1 (0.5–2)	0.037
Duration of local electrogram (ms)	80 (64–100)	120 (80–160)	74 (60–90)	<0.0001
Presence of fragmented electrograms, n (%)	32 (24)	21 (54)	11(12)	<0.0001
Success, n (%)	40 (30)	31 (80)	10 (11)	<0.0001

Values are presented as median (interquartile range) and number (%). DP, diastolic potentials; LAT: local activation time.

[a] p values were calculated using Mann-Whitney-U test for continuous variables and the chi-square test for categorical variables;

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amplitude of the local electrogram was significantly lower, 1 (0.5–1.5) vs 1.1 (0.5–2) mV, p = 0.037 and the duration of the ventricular electrogram was longer, 120 (80–160) vs 74 (60–90) ms, p<0.0001. Fragmented electrograms were more frequently present at sites with diastolic potentials, (54% vs 12%; p<0.0001).

When analysing with univariable logistic regression the association between the analysed ablation parameters and the acute success, we found that all parameters were associated with success. In multivariable analysis we found that only the value of the local activation time and the presence of diastolic potentials were independently associated with success. The preliminary main effects analysis for both variables showed a 11% increase in the possibility of success for each ms of earliness of local activation, [OR 1.11 (95% CI: 1.049–1.172 p<0.0001)]. The presence of diastolic potentials was associated with a sixteen times higher possibility of success [OR 15.5 (95% CI: 3.92–61.2; p<0.0001)] (Table 3).

However, these main effects are qualified by an interaction between both variables. The presence of diastolic potentials reduces the OR for the local activation time from 1.11 to 1.061, meaning that in the presence of diastolic potentials the earliness of the local activation is less

Table 3. Univariable and multivariable logistic regression analysis.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value[a]	OR (95% CI)	P value[a]
LAT (ms)	1.123 (1.075–1.173)	<0.0001	1.11 (1.049–1.172)	<0.0001
Amplitude of local electrogram ($mVx10^{-1}$)	0.940 (0.899–0.982)	0.006	0.949 (0.899–1.028)	0.198
Duration of local electrogram (ms)	1.031 (1.017–1.044)	<0.0001	0.996 (0.974–1.017)	0.692
Presence of diastolic potentials	32.9 (11.9–91)	<0.0001	15.5 (3.92–61.2)	<0.0001
Presence of fragmented electrograms	9.6 (3.9–23.6)	<0.0001	1.707 (0.296–9.848)	0.550

CI: confidence interval; LAT: local activation time; OR: odds ratio

[a] p values were calculated using univariable and multivariable logistic regression analysis

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important to achieve success. The OR for the presence of diastolic potentials decreases with the increasing earliness of local activation and varies from OR 52.45 for local activation time of -30 ms, OR 12.8 for local activation time of -40 ms, OR 3.1 for local activation time– 50 ms, with no effect for local activation times earlier than this value.

3.2.2. Diastolic potentials. The characteristics of the thirty-nine diastolic potentials present at RF application sites in thirty patients are presented in Table 4. In seven patients more than one RF application site displayed diastolic potentials.

None of these sites were above the pulmonary valve. The diastolic potentials varied in morphology, either fragmented, sharp or dull potentials (Fig 1), but they all had very low voltage, median 0.1 mV (0.1–0.3). The coupling interval to the end of the previous QRS was variable, but always after the end of the T wave in the surface ECG, median 360 ms (300–400). There was some irregularity in the inter diastolic potential interval that caused a similar variation in the interval between consecutive PVCs (Fig 3).

The interval between the diastolic potentials and the beginning of the QRS during PVCs varied from patient to patient and, in the same patient, from site to site. The diastolic potentials at successful sites were significantly earlier -60 ms (-31-94) versus -30 ms (-16-51); $p = 0.016$ when compared to unsuccessful sites.

Diastolic potentials were mostly present in areas of low voltage with the median local electrogram voltage in sinus rhythm being 1 mV (0.5–1.5). Despite the presence of low voltage areas, patients had apparently normal hearts, with normal cardiac magnetic resonance imaging (Fig 4).

All patients with diastolic potentials underwent a successful procedure, although success was not obtained in the first site in seven patients. This was probably because at these unsuccessful sites the diastolic potential was not early enough in relation to the beginning of the QRS. Further mapping at this zone lead to the finding of an adjacent site with an earlier diastolic potential, where RF application was successful. During RF energy delivery we observed the disappearance of the diastolic potentials in a minority of cases (20%), preceded by a progressive reduction in the amplitude.

3.3. Follow-up

During a median follow-up of 48 months (32–80), there were 4 recurrences, all within the first year. Antiarrhythmic drugs were added to these patients, with symptomatic improvement. The other thirty-five patients remained asymptomatic with Holter recordings after the procedure showing a median of 5 PVCs/24 hours (1–30).

4. Discussion

The most important finding in this study was the recording of isolated diastolic potentials on the intracardiac bipolar electrogram, at successful ablation sites, during sinus rhythm. They were always found within the RVOT, below the pulmonary valve, and were only recorded in a small area around the successful ablation site. These diastolic potentials became pre-systolic during the PVCs.

Discrete isolated pre-systolic potentials have been previously described in PVCs originating above the pulmonary valve. Timmermans et al [9] described, for the first time, the occurrence of PVCs successfully ablated in the pulmonary artery. In five out of six patients they recorded a sharp local potential preceding the QRS of the PVCs, occurring late, after the end of the local electrogram in sinus rhythm. The authors suggested that this might be due to a muscular connection between the pulmonary artery site and the RVOT. Subsequently, several investigators described the presence of the same discrete potentials in patients with PVCs from the outflow

Table 4. Characteristics of the diastolic potentials at RF delivery site.

Patient (RF pulse)	DP amplitude (mV)	QRS-DP (ms)	PVC DP–QRS (ms)	SR DP-QRS (ms)	Success RF pulse	Morphology	Local electrogram amplitude (mV)
1(1)	0.2	400	128	500	yes	Fragmented	1.3
2(1)	0.2	280	100	800	yes	Sharp	3.5
4(5)	0.1	380	10	300	yes	Dull	0.5
5(1)	0.1	360	94	430	yes	Dull	1
7(2)	0.1	400	74	450	yes	Dull	1
9(1)	0.1	400	72	400	yes	Fragmented	2
11(1)	0.1	400	60	500	yes	Fragmented	1.1
12(3)	0.1	360	10	330	no	Dull	1
12(4)	0.1	360	10	380	no	Dull	0.3
12(5)	0.1	360	52	300	yes	dull	0.3
14(1)	0.5	360	32	500	yes	Fragmented	3
17(1)	0.2	300	26	320	yes	Fragmented	0.6
21(2)	0.6	220	50	340	yes	Sharp	1.5
22(1)	0.3	340	64	380	yes	Fragmented	0,4
23(1)	0.2	400	40	400	no	Sharp	2.2
23(2)	0.3	400	30	500	no	Sharp	1.5
23(3)	0.1	400	96	450	yes	Sharp	0.2
24(2)	0.1	360	70	360	no	Dull	1.7
24(4)	0.1	360	80	400	yes	Dull	0.5
25(2)	0.2	320	80	350	yes	Fragmented	1
27(2)	0,1	400	30	420	yes	Fragmented	1
29(3)	0.6	400	42	320	no	Sharp	0,5
29(4)	0.5	400	52	420	yes	Sharp	0.4
30(2)	0.2	180	60	200	yes	Dull	1
32(1)	0.3	420	100	400	yes	Dull	1.5
33(1)	0.2	240	60	450	yes	Sharp	1.2
35(2)	0.6	400	60	360	yes	Sharp	0.5
35(3)	0.3	400	14	320	yes	Sharp	0.5
38(3)	0.1	380	60	300	yes	Dull	0.3
39(2)	0.1	300	55	260	yes	Dull	0,5
41(1)	0.1	300	100	200	yes	Dull	0.5
42(1)	0.1	360	25	400	no	Dull	1
42(5)	0.1	360	100	400	yes	Dull	0,2
43(1)	0.1	200	22	200	no	Dull	2
43(2)	0.1	200	30	200	yes	Dull	1
44(4)	0.1	350	100	650	yes	Fragmented	2
45(4)	0.5	400	64	320	yes	Dull	0,1
46(1)	0.2	300	20	350	yes	Fragmented	0,4
48(1)	0.1	350	20	400	yes	Dull	0.5

DP: diastolic potential; QRS-DP: interval between the end of the previous sinus QRS and the DP; PVC DP-QRS: interval between the DP and the QRS of the PVC; SR DP-QRS: interval between the DP and the QRS in sinus rhythm; PVC: premature ventricular contraction; RF: radiofrequency; SR: sinus rhythm.

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tracts in which the site of origin was above the semi-lunar valves. Tada et al [10] found sharp, local potentials, in 12 patients with RVOT ectopy originating above the pulmonary valve and Srivathsan et al [11] described discrete arterial potentials in all 12 patients with outflow tract ventricular arrhythmias, also originating above the semi-lunar valves.

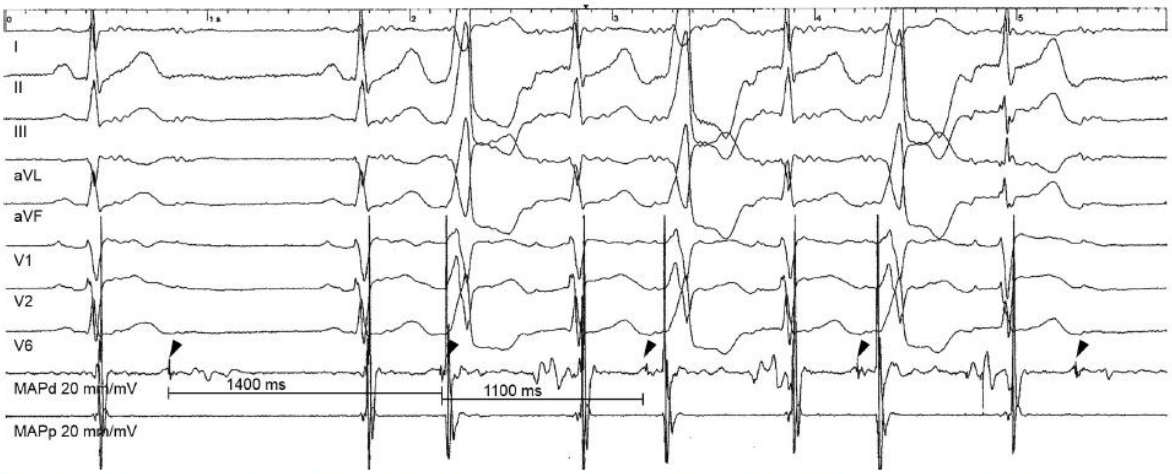

Fig 3. Variation in the inter diastolic potentials interval leading to a variation in the inter PVC interval. Intracardiac electrogram at successful ablation site. The bipolar electrogram on the ablation catheter (MAPd) exhibits sharp diastolic potentials (arrow head) after the T wave of the surface ECG in sinus rhythm, becoming pre-QRS during the PVCs. The variation of the interval between consecutive diastolic potentials is accompanied by a variation in the interval between the consecutive PVCs.

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However, the pre-systolic potentials described by those authors were only present when the origin of the PVCs was above the pulmonary valve. Thomsen et al [12] described, for the first time, the presence of similar discrete pre-systolic potentials in 24 patients with RVOT arrhythmias originating below the pulmonary valve. These pre-systolic potentials became late potentials during sinus rhythm, occurring at the end of the ventricular electrogram. According to Thomsen et al, they represent an area of conduction impairment, protecting an ectopic pacemaker by intermittent entrance block. We cannot rule out this mechanism in our patients, in fact, our diastolic potential may represent an ectopic focus protected by entrance block and intermittently capable of conducting to the adjacent myocardium. Supporting this hypothesis is the non-disappearance of the diastolic potentials after successful ablation in the majority of cases. This may suggest that we did not completely eliminate the focus, but instead may have created an exit block that rendered it incapable of propagating to a sufficient number of myocytes, in order to elicit a PVCs.

On the other hand, unlike the potentials described by Thomsen et al [12] our potentials occur late in diastole, after the end of the T wave, which corresponds to the phase 4 of the cardiac action potential [13].

Their occurrence during the phase 4 of the cardiac action potential suggests that they may result from delayed afterdepolarizations (DADs). This finding is in accordance with the generally accepted theory that the outflow tract ventricular tachycardia is caused by cAMP-mediated DADs and triggered activity [14]. The termination of the RVOT tachycardia in response to adenosine and to non-dihydropyridine calcium-channel blockers [15], along with its inducibility by rapid atrial/ventricular pacing or isoprenaline infusion, have been the clinical milestones for this theory. Other ventricular tachycardias that are thought to be due to triggered activity are the catecholaminergic polymorphic ventricular tachycardia and the ventricular tachycardia due to digitalis toxicity. The former is due to a mutation in the calcium ryanodine receptor gene (RyR2) or in the cardiac calsequestrin isoform 2 encoding gene (CASQ2) that leads to a cytosolic Ca^{2+} overload and DADs [16]. An inhibition of the Na^{+}/K^{+}-ATPase mediates the triggered activity due to digitalis toxicity [17].

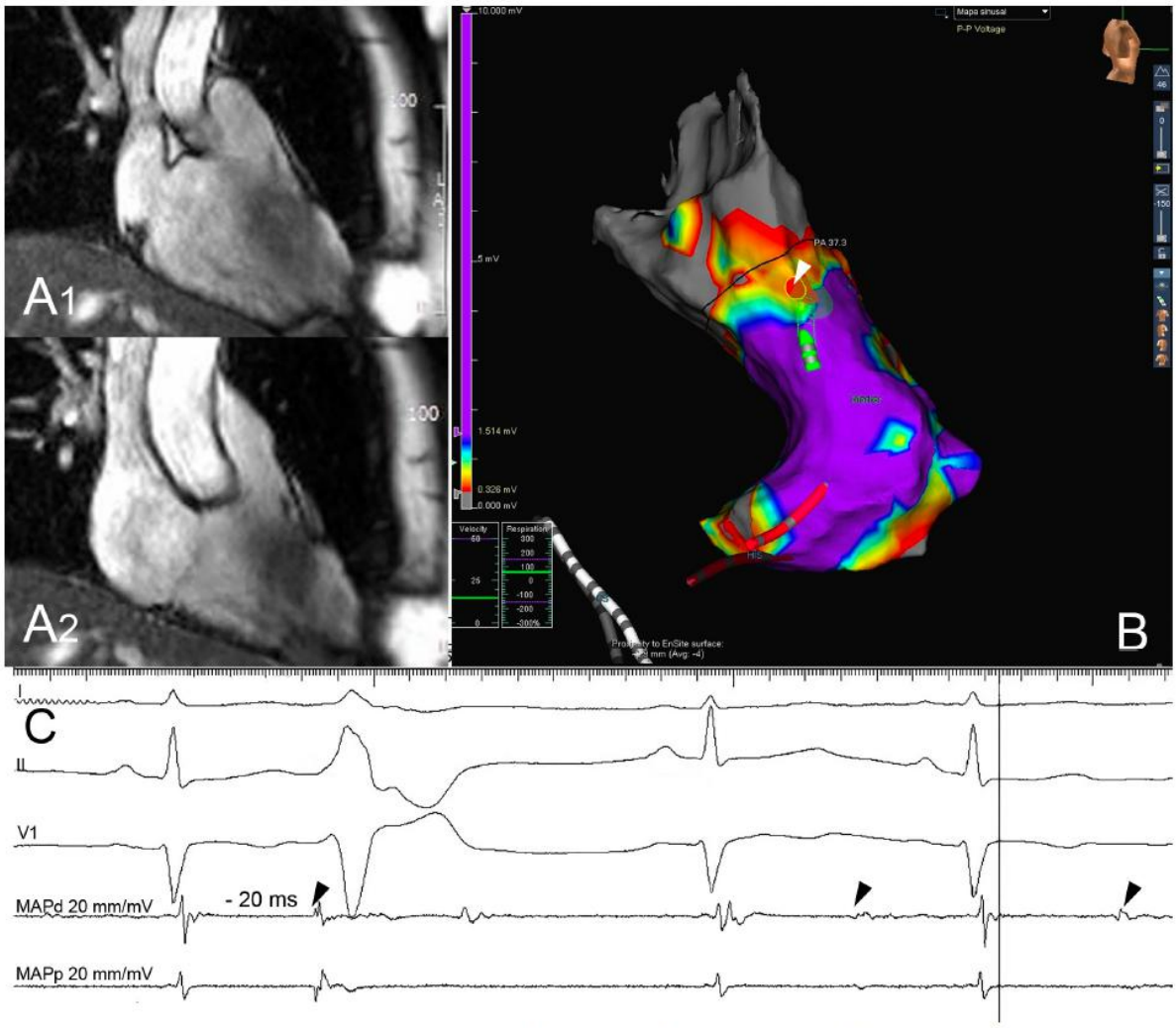

Fig 4. Low voltage areas. 35 years old female (patient 48) showing abnormal electrograms at ablation site despite apparent absence of structural heart disease. (A) Cardiac magnetic resonance steady-state free-procession (SSFP) cine imaging in the in-out view of the right ventricle in diastole (A1) and systole (A2) showing no abnormalities. (B) Electroanatomical voltage map in sinus rhythm. The black line indicates the pulmonary valve. The voltage map showing a wide area of low voltage below the pulmonary valve. The color map of voltage signals is explained in the methods. Purple indicates normal tissue while red indicates scar. Decapolar catheter in the coronary sinus and the His bundle catheter are displayed in white and red, respectively, at the bottom of the figure. The ablation catheter at the ablation site is indicated by the white arrow head. One RF ablation at this site caused the disappearance of the PVCs, indicated by the red dots. (C) The bipolar electrogram on the ablation catheter (MAPd) at successful ablation site exhibits very low voltage electrograms and dull diastolic potentials (black arrow heads) in sinus rhythm preceding the QRS by -20 ms during the PVC.

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Unlike these last two entities, in which the mechanism of the DADs is well known, in the RVOT tachycardia the precise mechanism for the occurrence of the DADs is not completely understood [18]. The demonstration of the presence of DADs in vivo has never been done, and the assumption that RVOT PVCs share the same mechanism of the RVOT tachycardia

has not been proven. Kim et al [19] hypothesized that outflow tract arrhythmias may represent a continuum with increasing severity and a common mechanism. However, in their paper they did not prove such statement.

We speculate that our diastolic potentials may represent a form of triggered activity that results in a potential with a very low amplitude, only recorded when the catheter is in close proximity to their origin. If we consider that they are the source of the PVCs, it would be expected that their location would be at the site of successful RF application. When this potential is able to propagate to a critical number of adjacent myocytes it elicits the occurrence of the PVCs. That may depend on the intensity of the DADs or on the degree of exit block. A detailed mapping of the area is fundamental in order to find the earliest diastolic potential in relation to the beginning of the surface QRS. That may explain why in some RF applications the presence of diastolic potentials at the ablation site was not enough to ensure success.

The hypothesis that these potentials may represent an area of very slow conduction similar the ones implicated in the reentry circuit of scar related ventricular tachycardia [20], is unlikely. Firstly, because although we recorded the diastolic potentials in areas of low voltage in some patients, in others the area was completely normal. A second reason is that reentry is unlikely to be the mechanism of RVOT PVCs.

We did not find, in the literature, any other reports of diastolic potentials identical to ours, except for a clinical case published by Saha et al [21], in 2016. It describes a patient with Brugada syndrome and arrhythmic storm that underwent catheter ablation. The authors present an image with diastolic potentials very similar to ours but do not address it in the text.

Regardless of the mechanism for the occurrence of diastolic potentials, we strongly believe that they are the source of the PVCs. Their timing in relation to the ventricular electrogram inverts during the PVCs from being very late in sinus rhythm to very early. This fact, along with the finding that variations in the inter diastolic potential intervals lead to variations in the intervals between consecutive PVCs, suggests that they are related to the PVCs instead of being a bystander.

The second important finding of our study was the observation that the diastolic potentials were recorded mostly on areas of low voltage and fragmented electrograms, suggesting that the DADs occur in diseased areas.

It is usually accepted that in the absence of structural heart disease the intracardiac electrograms display normal duration and normal voltage [22]. However, we observed areas of low voltage in the majority of our patients even though the echocardiogram and cardiac magnetic resonance imaging did not demonstrate any form of structural disease.

The presence of these low voltage areas may be due to the thinner myocardial wall of the RVOT. The local electrograms in the septum area of the right ventricle have the highest voltage, as opposed to the ones from the RVOT, which display the lowest values [23]. Still, the normal accepted value for the bipolar electrogram amplitude in the RVOT area is normally above 1.5 mV. The presence of such low voltage electrograms in our patients supports the hypothesis that some forms of apparently idiopathic outflow tract PVCs/VTs may be substrate-related arrhythmias, as previously described [24,25].

Liu et al [24] have recently described the presence of low voltage electrograms at the successful ablation sites, suggesting that there may be a substrate-based mechanism for the RVOT arrhythmias. These authors also report the occurrence of discrete late potentials only present at the low voltage areas. The potentials described by Liu et al are similar to the ones described above the pulmonary valves, occurring within or shortly after the local ventricular electrogram in sinus rhythm. In a previous study [25] we also identified areas of low voltage in the electroanatomical mapping in some of the patients with apparently idiopathic RVOT premature ventricular contractions.

The definition of an idiopathic situation results from the absence of abnormalities in the diagnostic tests performed and from the lack of knowledge of the cause, but it does not imply absence of pathological abnormalities. This is the case with the Brugada Syndrome, that was assumed to be an electric disease without anatomical substrate, and yet, recently some authors demonstrated the presence of delayed fragmented potentials in the epicardium of the RVOT that were successfully ablated [26]. We describe, in our paper, the presence of low voltage areas and fragmented electrograms, however, the fragmented electrograms we describe in our patients are not like the ones present in Brugada Syndrome, which are characterized by being very late. In fact, our fragmented electrograms terminate before the end of the QRS and the long duration of the local electrograms are mostly due to the fusion between the low voltage diastolic potentials and the fragmented electrograms.

In our group of patients, low voltage areas and diastolic potentials were not always present. This may imply failure to identify the area of interest, but it can also mean that RVOT PVCs may have different mechanisms or substrates.

The presence of low voltage areas and diastolic potentials may be considered a new target for ablation. Detailed mapping of these areas is needed in order to find the earliest diastolic potential in relation to the surface QRS of the PVCs.

Substrate mapping to identify areas of low voltage and searching for diastolic potentials may be a possible ablation strategy for ablation of RVOT PVCs in patients in whom the clinical arrhythmia cannot be elicited.

5. Limitations

This study was retrospective, and the total number of patients included was small. One possible important information might have been obtained by pacing the area where diastolic potentials were recorded and assessing the response to pacing.

A prospective study including more patients and a control group to validate the role of diastolic potentials in guiding outflow tract PVCs ablation is needed. The primary ablation target would be the earliest diastolic potential.

6. Conclusions

Diastolic potentials were frequently recorded in idiopathic outflow tract PVCs. They were present mostly at low voltage areas, suggesting that outflow tract PVCs may have an anatomic substrate. Catheter ablation at sites with diastolic potentials is associated with an increased success rate. Substrate mapping to identify areas of low voltage and searching for diastolic potentials may be a possible ablation strategy for ablation of RVOT PVCs.

Supporting information

S1 File. De-identified patient database.
(SAV)

S2 File. De-identified radiofrequency applications database.
(SAV)

Author Contributions

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Writing – review & editing: Leonor Parreira, Rita Marinheiro, Pedro Carmo.

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Idiopathic Premature Ventricular Contractions From the Outflow Tract Display an Underlying Substrate That Can Be Unmasked by a Type 2 Brugada Electrocardiographic Pattern at High Right Precordial Leads

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Background: Patients with premature ventricular contractions (PVCs) from the right ventricular outflow tract (RVOT) and apparently normal hearts, can have ST elevation similar to type 2 or type 3 Brugada pattern in the electrocardiographic (ECG) performed at a higher position. Cardiac magnetic resonance (CMR), has shown conflicting data regarding existence of structural abnormalities in patients with idiopathic PVCs from the RVOT.

Objective: Our aim was to evaluate the prevalence of low voltage areas (LVAs) in the RVOT of patients with PVCS from the outflow tract, and in a control group. Secondly, assess for the presence of a non-invasive ECG marker.

Methods: A 56 consecutive patients, 45 with frequent PVCs (>10000/24 h) LBBB, vertical axis, negative in aVL and 11 subjects without PVCs. Arrhythmogenic right ventricular cardiomyopathy was ruled out in all patients. An ECG was performed with V1–V2 at the level of the second intercostal space and the presence of ST-segment elevation with a Type 2 or 3 Brugada pattern (Type 2 BrP) was assessed. Bipolar voltage map of the RVOT was performed in sinus rhythm (0.5–1.5 mV color display). Areas with electrograms <1.5 mV represented the LVA. The area adjacent to the pulmonary valve usually displays voltage between 0.5 and 1.5 mV and is classified as transitional-voltage zone. Presence of LVAs outside this transitional-voltage zone were estimated. We compared two groups with and without ST-segment elevation and tested for the association between ECG pattern and LVAs.

Results: None of the patients in the control group had ST-segment elevation or LVAs. In the PVC group, no patient had type 1 Brugada pattern, 29 patients (64%) had type 2 or 3 ST-segment elevation (Type 2 BrP), and 28 (62%) had LVAs outside the transitional-voltage zone. LVAs were more frequent in patients with Type 2 BrP; 93% versus 4%, $p < 0.0001$. The ECG pattern was associated with the presence of LVAs, OR (95% CI): 202.50 (16.92–2423), $p < 0.0001$.

Conclusion: Low voltage areas were frequently present in the RVOT of patients with idiopathic PVCs. They were absent in controls and can be unmasked by the presence of Type 2 BrP in high right precordial leads.

Keywords: idiopathic arrhythmias, right ventricular outflow tract, low voltage, Brugada pattern, catheter ablation

INTRODUCTION

Idiopathic premature ventricular contractions (PVCs) arise from the outflow tracts in more than 80% of cases, more frequently the right ventricular outflow tract (RVOT) (Lerman, 2015). Cardiac magnetic resonance (CMR) imaging studies have shown conflicting data regarding the existence of structural abnormalities in the RVOT of those patients. Initial studies documented the presence of localized wall bulging, focal wall thinning or fatty replacement in a high percentage of patients (Globits et al., 1997). However, most recent studies using electrocardiographic (ECG) gating and imaging with late gadolinium enhancement (LGE) have shown absence of pathological findings in patients with idiopathic RVOT PVCs (Markowitz et al., 2014).

Detection of myocardial fibrosis can be assessed non-invasively with CMR using LGE (Bing and Dweck, 2019) but its detection depends on the type of fibrosis, whether replacement or interstitial fibrosis. In the initial phases of non-ischemic cardiomyopathy for instance, although a certain degree of diffuse fibrosis may be present, it goes undetected by LGE techniques and may be detected by T1 mapping (Puntmann et al., 2016).

Previous studies have shown presence of low voltage areas (LVAs) in the RVOT of patients undergoing catheter ablation of frequent PVCs despite normal CMR (Yamashina et al., 2009; Furushima et al., 2012; Letsas et al., 2019; Parreira et al., 2019a,b). These findings may suggest the presence of an underlying substrate too subtle to be identified by CMR techniques (Santangeli et al., 2011). The Brugada syndrome, caused by an inherited sodium channelopathy, is diagnosed in patients with Type 1 ST elevation, spontaneous or after drug provocation, at the standard or high position, and in patients with baseline Type 2 pattern that converts to Type 1 with drug provocation (Antzelevitch et al., 2005, 2017; Bayés de Luna et al., 2012; Priori et al., 2015). Patients with PVCs from the RVOT and apparently normal hearts can have ST elevation at V1 obtained at the level of the second intercostal space (ICS) similar to type 2 or type 3 Brugada patterns (Parreira et al., 2019b). That ECG pattern was associated with the presence of LVAs in the RVOT.

The aim of this study was to evaluate the prevalence of both the ST-segment elevation at high right ventricular leads and that of LVAs in the RVOT, in idiopathic patients with frequent PVCS from the outflow tracts and in a control group. Secondly, estimate the value of ST-segment elevation as a non-invasive ECG marker of low voltage in the RVOT.

MATERIALS AND METHODS

Patient Population

From 2016 to 2020, we retrospectively studied consecutive patients with symptomatic idiopathic frequent PVCs (>10000/24 h) with a LBBB, vertical axis, negative in aVL that were referred for catheter ablation by the same operator. Patients that did not undergo electroanatomical voltage map of the RVOT in sinus rhythm were excluded. The study was carried out in two hospitals. All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler study and standard 12-lead ECG. A second ECG was obtained with the right ventricular leads at the level of the second ICS. A treadmill exercise test was performed if symptoms appeared or were aggravated by exercise. All patients with PVCs had a CMR with Gadolinium to exclude the presence of RVOT anomalies.

Arrhythmogenic right ventricular cardiomyopathy was ruled out according to the Task Force Criteria (Marcus et al., 2010). A 24-h Holter recording was performed before ablation and the number of PVCs per 24 h and the presence of episodes of non-sustained ventricular tachycardia (NSVT), defined as >3 PVCs in a run were assessed. Patients with evidence of conduction delays, electrical diseases or abnormal QRS morphology, as well as patients with previous ablation were excluded.

A control group of consecutive patients without PVCs, that underwent catheter ablation of supraventricular tachycardias since 2019 and agreed to have a voltage map of the RVOT performed in sinus rhythm was also studied.

Study Design

We retrospectively assessed the presence of ST-segment elevation at the level of the second ICS, in patients with PVCs and in controls. According to the J-Wave syndromes expert consensus conference report (Antzelevitch et al., 2017) three different types of ST-segment elevation described as Brugada-type ECG patterns, may be observed during ECG recording: type 1 has a coved ST

segment elevation ≥2 mm, negative T wave and no isoelectric separation of T wave; type-2 has a saddleback appearance with an ST segment elevation of ≥2 mm, a trough displaying >1 mm ST elevation and then either a positive or biphasic T wave; type 3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. Type 2 and type 3 ECG are not diagnostic of the Brugada syndrome. The ST-segment elevation observed in our patients was classified according to the above classification. Patients were divided in two groups according to the presence of an ST-segment elevation similar to any of the patterns described above. Both groups with and without ST-segment elevation were compared regarding demographic and clinical characteristics, echocardiographic ECG and 24 Holter data and electroanatomical mapping and ablation data. The association between the presence of ST-segment elevation and presence of LVAs was analyzed.

Standard 12-Leads ECG and High Right Precordial Leads ECG

The ECG was performed with standard paper speed and calibration. After a standard 12-lead ECG recording the ECG was repeated, with V1 and V2 leads placed in the second ICS and maintaining the other lead's position. The duration of the QRS in sinus rhythm and the precordial transition of the sinus and ectopic beats, defined as the precordial lead where the QRS changes from predominately negative to predominately positive and the R/S ratio becomes >1 were assessed in the standard ECG both in sinus rhythm and during the PVC. The presence of T wave inversion beyond V1 was evaluated in standard and high right precordial leads ECG.

The ST-segment elevation was measured at the take-off point of the QRS-ST and the morphology of the ST segment was analyzed. All ECG recordings were evaluated by two independent reviewers blinded to the result of the voltage map.

Electroanatomic Mapping and Ablation

All patients underwent electroanatomical mapping with CARTO 3 (Biosense Webster) or EnSite Velocity (Abbott). With the former, all procedures were performed using the Niobe magnetic navigation system (Stereotaxis) working with the monoplane fluoroscopy system AXIOM Artis (Siemens) as previously described (Parreira et al., 2013). An irrigated tip Navistar RMT Thermocool catheter (Biosense Webster) was used with a 3.5-mm distal tip electrode and a 2-5-2 interelectrode distance. With the EnSite Velocity system all procedures were done manually with the monoplane fluoroscopy system BV Pulsera (Philips) and using an irrigated tip Therapy Cool Path or FlexAbility catheter (Abbott) with a 4-mm distal tip electrode and a 1-4-1 interelectrode distance. The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT in the magnetic navigation system patients or manually in the EnSite patients, under fluoroscopic guidance. The ablation catheter was then placed at multiple sites on the endocardial surface of the RVOT. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed. Two maps were created, a voltage bipolar map in sinus rhythm and an activation map during the PVC. In sinus rhythm the electrograms were analyzed in regard of their amplitude and the information was used to generate a 3-dimensional electroanatomical voltage map of the RVOT, with the electrophysiologic information, color-coded and superimposed on the geometry. The color display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude ≥1.5 mV), to red, representing electroanatomical scar tissue (amplitude <0.5 mV). LVAs were defined as areas with bipolar electrograms with an amplitude <1.5 mV. The level of RVOT/pulmonary valve junction was thoroughly determined based on electroanatomical voltage mapping by passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT. The voltage above the pulmonary valve is usually less than 0.5 mV. The area immediately below the level of the pulmonary valve displays intermediate colors, corresponding to a bipolar voltage between 0.5 and 1.5 mV, defined as the transitional-voltage zone (Yamashina et al., 2009). Presence of LVAs outside the transitional-voltage zone, were assessed.

The activation map was created by mapping several points during each PVCs while using a surface ECG lead as reference. The ablation site was selected based on the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous PVCs. Energy was delivered from an EP Shuttle RF generator (Stockert) between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 s, to a maximum temperature of 43°C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. Success was defined as abolition of PVCs under isoprenaline infusion until 30 min after ablation. All the intracardiac electrograms were reviewed by two senior electrophysiologists blinded to the results of the ECG.

Statistical Analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc., Chicago, IL, United States). Data is presented as median and lower and upper quartile (Q_1–Q_3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann Whitney test for independent samples. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples and with the McNemar test for related samples. Univariable logistic regression analysis and calculation of the respective odds ratios (OR) and 95% confidence intervals (CI) was used to evaluate the discriminative power of ST-segment elevation as a marker of LVA in the RVOT. The performance of ST-segment elevation as a diagnostic test including the positive and negative predictive value as well as specificity and sensitivity was based on 2 × 2 contingency table and chi

square test. For all tests a p value <0.05 was considered as statistically significant.

Ethics

All patients signed the informed consent form and the study was approved by the Ethical Committee of both hospitals. The study is in compliance with the Helsinki Declaration.

RESULTS

Patient Population

Fifty six patients were enrolled, 45 patients with PVCs and 11 patients in the control group of whom eight underwent ablation of atrioventricular nodal reentrant tachycardia, two of accessory pathways and one of typical atrial flutter. Both groups did not differ in relation to age or gender (**Table 1**). Patients in the PVC group were more frequently on beta blocker therapy, 73% versus 9%, $p < 0.0001$.

In the PVC group, all patients were symptomatic, 44 complained of palpitations, one patient had episodes of dizziness and five patients had a history of fainting, all typically vagal in nature. Two patients had family history of sudden death in one due to a myocarditis and in the other at the age of 64 years and preceded by chest pain. Physical examination, and transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler echocardiography were normal and demonstrated normal right ventricle size and function. The CMR did not show evidence of RVOT abnormalities in any patient.

Twenty patients underwent treadmill exercise test and twelve (60%) had a reduction of PVC frequency with exercise. The 24-h Holter recording showed a high PVC burden with a median of 20000 (14000–24000)/24 h and NSVT in 10 patients (22%).

Standard 12 Lead ECG and High Right Precordial Leads ECG

The mean duration of the QRS was 82 (80–90) ms and three patients in the PVC group displayed T wave inversion beyond V1, not significantly different between the PVC and control group (**Table 1**).

Type 2 BrP ST-segment elevation was absent in the standard ECG in both groups. Eighteen patients displayed T wave inversion beyond V1 in the high ECG, which represents a six-fold increase in comparison with the standard ECG ($p < 0.0001$). No patient in the control group showed T wave inversion beyond V1 (**Figure 1B**).

An ST-segment elevation was present in V1 recorded at the second ICS, in 29 patients (64%) in the PVC group and was absent in the control group, $p < 0.0001$. The ST-segment elevation was coved-type but <1 mm in 27 patients (example in **Figure 2A**) and classified as type 3, and ≥2 mm but without the coved-type morphology in two (example in **Figure 2B**), classified as type 2. No definite type 1 pattern was observed. Types 2 and 3 were classified together as Type 2 BrP.

Comparison Between Patients With and Without Type 2 BrP in High Right Precordial Leads ECG

The characteristics of patients with and without Type 2 BrP are depicted in **Table 2**. There were no significant differences regarding demographic data, clinical variables, PVC burden or presence of NSVT or standard ECG measurements. However, on the ECG performed in the high position, patients with Type 2 BrP showed T wave inversion beyond V1 more frequently (45% versus 19%, $p = 0.047$).

Electroanatomical Mapping and Ablation

PVC Group Versus Control Group

The electroanatomical mapping was successfully acquired in all patients, the median number of points per patient, collected in the RVOT to obtain the voltage map was 142 (98–300) and the results are displayed in **Table 3**. The number of points sampled was not significantly different between patients with PVCs and the control group, respectively 141 (102–300) versus 182 (120–317), $p = 0.529$. The electroanatomical system used in control group was predominantly Carto (90%), while in the PVC group it was used in approximately 50% of cases, $p = 0.036$. This occurred because Carto was the system used with Stereotaxis, our choice for mapping the RVOT in the control group due to safety issues.

In 40 patients the PVCs originated in the RVOT and in five the origin was in the left aortic cusp. Presence of LVAs outside the transitional-voltage zone were absent in all subjects from the control group (**Figure 1**) and present in 28 patients (62%) of the PVC group, $p < 0.0001$ (**Figure 2**).

Type 2 BrP as Risk Marker of Low Voltage Areas in Patients With PVCs

The number of points sampled for the RVOT map in the PVC group was 141 (102–300) not significantly different between patients with and without Type 2 BrP, respectively, 152 (104–313) versus 118 (99–190), $p = 0.066$ (**Table 3**). The electroanatomical system used was not significantly different in the two groups neither was the site of origin of the PVCs right versus left. Presence of LVAs outside the transitional-voltage zone were more frequent in the group with Type 2 BrP, 93% of cases versus 4%, $p < 0.0001$. The site of origin of the PVCs was in the LVA outside the transitional-voltage zone in 18 out of the 45 patients with PVCs (40%) (**Figure 3**). This percentage was significantly higher in patients with Type 2 BrP, respectively 59% of cases versus 4%, $p = 0.001$ (**Table 3**). The success rate was not significantly different in both groups. Type 2 BrP was a predictor of the presence of LVAs outside the transitional-voltage zone in the RVOT of patients with idiopathic PVCs, OR (95% CI) 202.50 (16.92–2423), $p < 0.0001$. The positive predictive value was 93%, negative predictive value 94%, sensitivity 96%, and specificity 88%.

DISCUSSION

The first finding of this study was the presence of a Type 2 BrP in 64% of patients with PVCs, on the ECG performed at

TABLE 1 | Baseline characteristics and comparison between PVC group and control group.

	Overall sample (*n* = 56)	PVC group (*n* = 45)	Control (*n* = 11)	*p* value
Demographic data				
Age in years, median (Q_1–Q_3)	50 (36–60)	48 (37–61)	50 (33–54)	0.773
Male Gender, *n* (%)	23 (41)	20 (44)	3 (27)	0.496
Risk factors, history and medications				
Hypertension, *n* (%)	7 (13)	6 (13)	1 (9)	1.000
Diabetes, *n* (%)	3 (5)	2 (4)	1 (9)	0.488
Syncope	5 (9)	5 (11)	0 (0)	0.571
Family history of sudden death	2 (4)	2 (5)	0 (0)	1.000
Beta blockers, *n* (%)	34 (61)	33 (73)	1 (9)	<0.0001
Standard 12 lead ECG				
QRS duration in ms, median (Q1–Q3)	82 (80–90)	84 (80–90)	80 (79–82)	0.062
T wave inversion beyond V1, *n* (%)	3 (5)	3 (7)	0 (0)	1.000
Type 2 BrP, *n* (%)	0 (0)	–	–	–
High right precordial leads ECG				
T wave inversion beyond V1, *n* (%)	18 (32)	18 (40)	0 (0)	0.011
Type 2 BrP, *n* (%)	29 (52)	29 (64)	0 (0)	<0.0001
24-h Holter Monitoring*				
Number of PVCs, median (Q1–Q3)*	–	20000 (14000–24000)	–	–
NSVT, *n* (%)*	–	10 (22)	–	–
Echocardiogram				
LVEF in %, median (Q_1–Q_3)	57 (56–60)	58 (56–60)	58 (57–59)	0.630

**In the PVC group. BrP, Brugada electrocardiographic pattern; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contractions.*

TABLE 2 | Baseline characteristics of patients with and Type 2 BrP in high right precordial leads.

	Overall sample (*n* = 56)	With Type 2 BrP (*n* = 29)	Without Type 2 BrP (*n* = 27)	*p* value
Demographic data				
Age in years, median (Q_1–Q_3)	50 (36–60)	45 (35–60)	50 (36–60)	0.896
Male Gender, *n* (%)	23 (41)	13 (45)	10 (37)	0.596
Patients with frequent PVCs, *n* (%)	45 (80)	29 (100)	16 (60)	<0.0001
Risk factors, history and medications				
Hypertension, *n* (%)	7 (13)	3 (10)	4 (14)	0.700
Diabetes, *n* (%)	3 (5)	1 (3)	2 (7)	0.605
Syncope, *n* (%)	5 (9)	1 (3)	4 (14)	0.185
Family history of sudden death, *n* (%)	3 (5)	0 (0)	3 (11)	0.106
Beta blockers, *n* (%)	34 (61)	21 (72)	13 (48)	0.100
24-h Holter Monitoring*				
Number of PVCs, median (Q1–Q3)*	20000 (14000–24000)	17595 (12774–24000)	20112 (15500–28500)	0.325
NSVT, *n* (%)*	10 (22)	6 (21)	4 (25)	0.726
Standard 12 lead ECG				
QRS duration in ms, median (Q1–Q3)	82 (80–90)	85 (80–90)	80 (80–90)	0.829
PVC precordial transition beyond V3, *n* (%)*	30 (68)	20 (69)	10 (63)	0.746
PVC transition earlier than SR, *n* (%)*	14 (31)	7 (24)	7 (44)	0.197
T wave inversion beyond V1, *n* (%)	3 (5)	3 (10)	0 (0)	0.237
High right precordial leads ECG				
T wave inversion beyond V1, *n* (%)	18 (32)	13 (45)	5 (19)	0.047
Echocardiogram				
LVEF in %, median (Q1–Q3)	57 (56–60)	57 (56–60)	60 (56–64)	0.254

**In the PVC group. BrP, Brugada electrocardiographic pattern; LVEF, left ventricular ejection fraction, NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contractions.*

TABLE 3 | Electroanatomical mapping and ablation data.

	Overall sample (n = 56)	PVC group (n = 45)	Control (n = 11)	p value
Electroanatomical mapping				
Number of points in the map, median (Q_1–Q_3)	142 (98–300)	141 (102–300)	182 (120–317)	0.529
Carto/EnSite	34/22	24/21	10/1	0.036
LVAs, n (%)	28 (50)	28 (62)	0 (0)	<0.0001
Electroanatomical mapping and ablation*	**Overall PVC group (n = 45)**	**With Type 2 BrP (n = 29)**	**Without Type 2 BrP (n = 16)**	**p value**
Number of points in the map, median ((Q_1–Q_3)*	141 (102–300)	152 (104–313)	118 (99–190)	0.066
Carto/EnSite*	24/21	13/16	11/5	0.212
PVCs from RVOT/LVOT*	40/5	26/3	14/2	1.000
LVAs, n (%)*	28 (62)	27 (93)	1 (4)	<0.0001
SOO in LVAs, n (%)*	18 (40)	17 (59)	1 (4)	0.001
Success, n (%)*	40 (89)	27 (93)	13 (81)	0.330

In the PVC group. BrP, Brugada electrocardiographic pattern; LVOT, left ventricular outflow tract; LVA, low voltage area; RVOT, right ventricular outflow tract; SOO, site of origin.

the level of the second ICS. According to the contemporary definition of Brugada syndrome, the diagnostic ECG displays a coved-type ST segment elevation of at least 2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the fourth, third or second ICS (Priori et al., 2015; Antzelevitch et al., 2017). The reason for using these higher positioned V1–V2 in the diagnosis of Brugada syndrome, is their closer proximity to the RVOT, now known to be the origin of the disease (Brugada et al., 2018). That is the reason why we used these higher leads in the present study, to record the electric activity form the RVOT. None of our patients, had a type 1 Brugada pattern (Antzelevitch et al., 2017). We did not perform drug challenge in our patients and that is in accordance with the latest guidelines (Antzelevitch et al., 2017). There was not a clinical suspicion of Brugada Syndrome in any of the patients and for the same reason a genetical testing is also not recommended (Antzelevitch et al., 2017).

Previous studies have reported the prevalence of Type 2 BrP in the general population. Holst et al. (2012) studied 340 healthy subjects and reported an incidence of type 1, 2, and 3 Type 2 BrP on the second ICS, respectively 0, 3.3, and 7.1%. Another work registered similar results in 504 healthy male volunteer subjects. The authors found an incidence of type 1, 2, and 3 Type 2 BrP on 0.8, 2, and 7.5%, respectively (Hunuk et al., 2013). In a population of 491 collegiate athletes a type 2 or 3 Type 2 BrP was seen in 58 (11.8%), and no definitive type 1 was observed (Chung et al., 2014). The much higher incidence of a type 2 or 3 Brugada ECG pattern mostly type 3 in our PVC patients, and its absence in the control group, raises the hypothesis that the two may be associated. Although type 3 ST-segment elevation is no longer regarded as a typical ECG Brugada pattern (Antzelevitch et al., 2017), it was present in a high percentage of our patients and it is not a normal finding either. The term Brugada phenocopy was proposed to describe conditions that induce Brugada-like ECG manifestations in patients without true Brugada syndrome (Baranchuk et al., 2012) and this may be the case.

The second finding in our study was the increase in the percentage of patients with T wave inversion beyond V1 when the ECG was obtained at the level of the second ICS in comparison with the standard ECG position. The diagnosis of ARVC is sometimes difficult, and T wave inversion in V1–V2 is considered a minor criteria (Marcus et al., 2010). If we accept that the T wave inversion at a higher ICS could have a similar value, then the number of ARVC "possible" cases would increase (Marcus et al., 2010). Unlike the ST-segment elevation the presence of T wave inversion was not associated with the presence of LVAs.

The third finding in our study was the presence of LVAs outside the transitional-voltage zone, that was absent in subjects without PVCs. The bipolar voltage above the pulmonary valve is typically less than 0.5 mV or even less than 0.1 mV (Furushima et al., 2012) due to the absence or scarcity of myocardium at that level. The voltage progressively increases as the catheter is withdrawn to the RVOT. The area immediately below the pulmonary valve displays a voltage between 0.5 and 1.5 mV and is described as the transitional-voltage zone (Yamashina et al., 2009). The length of this area is variable and according to the authors, longer in patients with malignant arrhythmias than in those with a benign course. In our study the LVAs were outside the transitional-voltage zone, into the RVOT body. Their presence was not significantly different in patients with a RVOT or LVOT origin. Probably, these results are due to the small number of patients with PVCs from LVOT. However, we cannot rule out the possibility that the PVCs from any of the outflow tracts represent the same disease with different manifestations.

The presence of LVA in patients with idiopathic PVCs is not a recent finding. In fact, a high number of previous studies have already demonstrated this finding, either with conventional ablation catheters (Yamashina et al., 2009; Furushima et al., 2012; Parreira et al., 2019a,b) or recently, with the use of a multipolar catheter to obtain a high−density endocardial voltage mapping (Letsas et al., 2019). The bipolar voltage depends amongst other things on the recording electrode size and the interelectrode spacing. One may argue that with high density/high resolution mapping the results could be different. We found the presence of LVA outside the transitional-voltage zone in 28 out of 45 patients (62%). Letsas et al. (2019) mapped the RVOT of patients

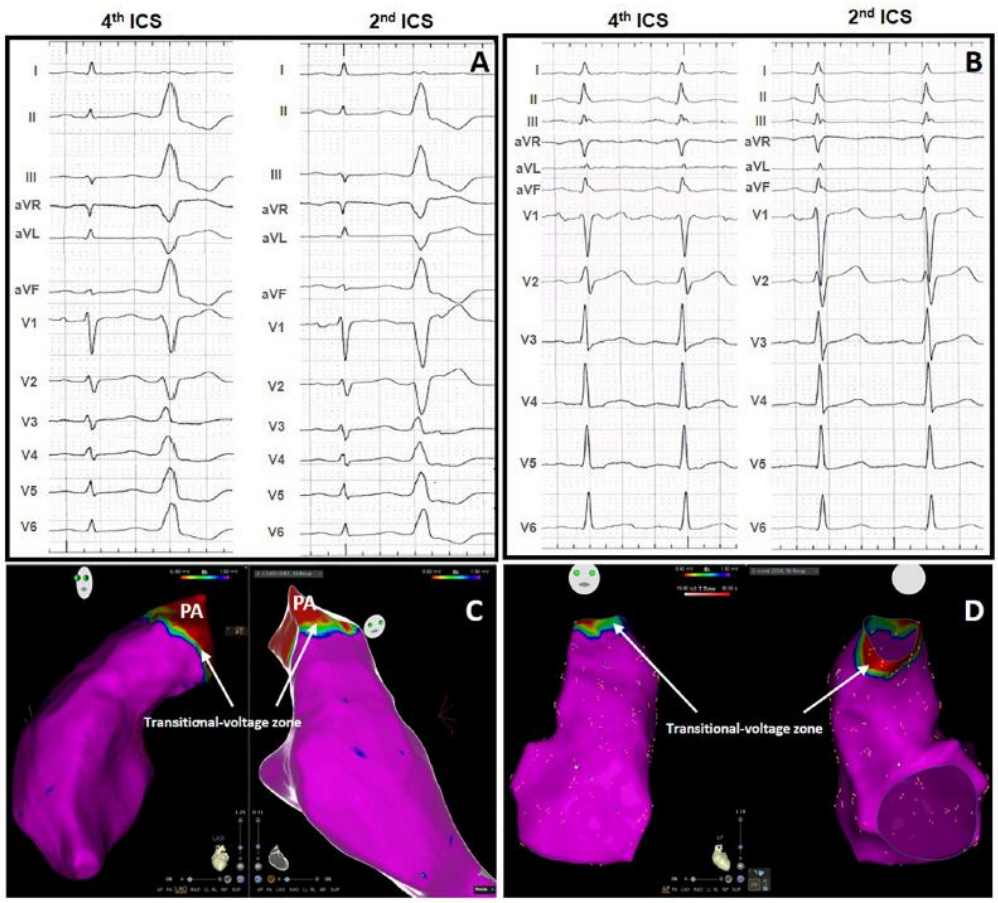

FIGURE 1 | Standard 12-lead electrocardiographic (ECG) and high right ventricular leads ECG without ST elevation in a patient with PVCs **(A)** and in a control subject without PVCs **(B)**. Normal voltage map without LVAs in the patient with PVCs **(C)** and in the control subject **(D)**. PA, pulmonary artery. Indicating the transitional-voltage zone (white arrows).

with idiopathic PVCs using a multipolar catheter with 2 mm electrodes for high density mapping (mean number of sampled points 1096.6 ± 322.3), and identified at least two low bipolar voltage areas less than 1 mV in 39 out of 44 patients (88%), a higher percentage than ours. These results prove that our high prevalence of LVAs is surely not the result of the lack of multipolar catheters. Those authors used an ablation strategy aiming at these LVAs in patients with low PVC burden as previously proposed by other group (Wang et al., 2016) with good success rates. The presence of LVAs did not match the results of the CMR in any of the studies. Detection of fibrosis using LGE has been well validated in ischemic cardiomyopathy and post-myocardial infarction, with an excellent agreement between CMR findings and the voltage map (Torri et al., 2019). However, that is not true for non-ischemic myocardiopathy. Myocardial fibrosis is a common final pathway in chronic myocardial disease but the type of interstitial fibrosis that occurs in the initial phases of non-ischemic myocardiopathy or ARVC is not reliably detected with LGE, and other techniques are being investigated (Puntmann et al., 2016; Bing and Dweck, 2019). On the other hand, we must not forget the true meaning of LVAs. In fact, low bipolar voltage is not synonyms of fibrosis. Bipolar voltage amplitude is influenced by many variables independently of the presence of fibrosis (Anter and Josephson, 2016). Boulos et al. (2005) studied the voltage map in patients with ARVC, normal subjects and idiopathic PVCs. They found a regional difference in the bipolar voltage throughout the right ventricle, and the RVOT displayed the lowest voltage (Boulos et al., 2005). However, it was well above the 1.5 mV cut-off value (mean 2.6 ± 0.4 mV) in normal subjects and significantly higher than the bipolar voltage in the dysplastic regions of patients with ARVC (0.60 ± 0.06 mV). So, independently of the points discussed above, the presence of

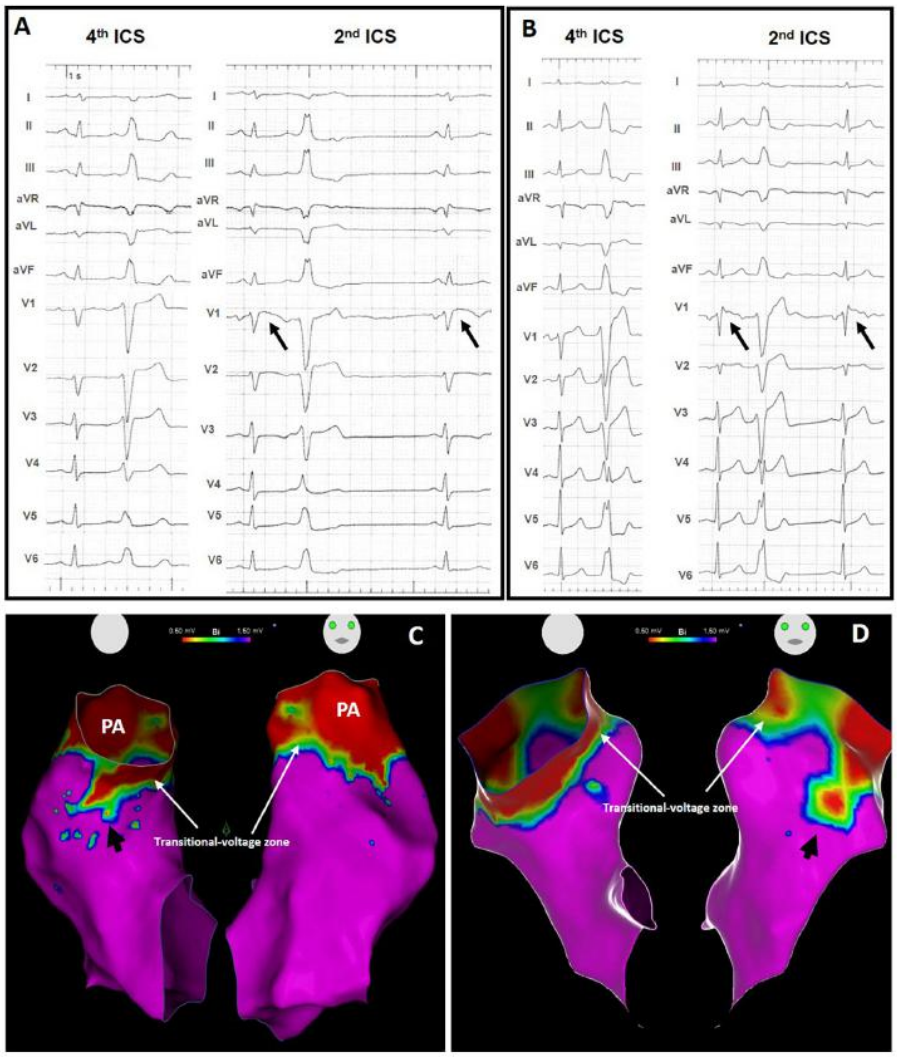

FIGURE 2 | Standard 12-lead ECG and high right ventricular leads ECG with Type 2 BrP (black arrows) in two patients with PVCs from the RVOT **(A,B)** and respective voltage map showing an area of low voltage outside the transitional-voltage zone (white arrows), in the septal wall **[(C)**, black arrow] and in the free wall **[(D)**, black arrow]. PA, pulmonary artery.

LVAs in the middle of normal voltage areas, must be considered an abnormal finding and hopefully a target for ablation as anticipated by the high percentage of cases in whom the site of origin of the arrhythmia was in the LVA, respectively in 18 out of 28 patients (64%) of cases.

The last finding was the association of the Type 2 BrP at higher V1 with the presence of LVAs in patients with apparently normal hearts. We have previously reported this finding with a smaller number of patients, and some limitations namely, the absence of a control group and the fact that CMR was not performed in all patients (Parreira et al., 2019a). The present study confirmed those preliminary results and we were able to demonstrate that the Type 2 BrP in the second ICS was a predictor of LVAs. The remarkably high odds ratio and wide CI is due to an extremely low prevalence of LVA in the absence of Type 2 BrP (one patient) and extremely low prevalence of absent LVAs in patients with Type 2 BrP (two patients). Presence of fibrosis as well as reduced connexin-43 signal was described in the RVOT of autopsies of patients with Brugada syndrome. The authors find therefore plausible

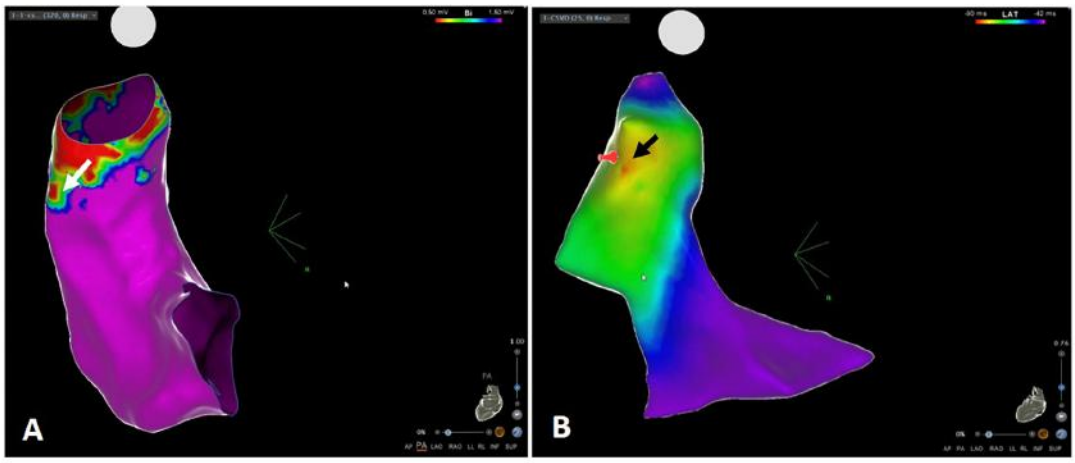

FIGURE 3 | (A) Voltage map of the RVOT displaying low voltage area (white arrow). **(B)** Activation map of the same patient showing site of origin of the PVCs (black arrow) in the area of low voltage. RVOT, right ventricular outflow tract.

that Brugada syndrome may reflect a generalized disease of myocardial of the RVOT predisposing it to fibrosis (Nademanee et al., 2015). The role of fibrosis in Brugada syndrome is uncertain, and the clinical phenotype concomitant with cardiac fibrosis remains a matter of ongoing scientific investigation (Brugada et al., 2018). Recently, the presence of LVAs has been reported in the endocardium of the RVOT of patients with Brugada ECG pattern (Letsas et al., 2018). The authors studied 10 asymptomatic patients with spontaneous type 1 Brugada pattern using high density mapping and found abnormal unipolar and bipolar electrograms displaying areas of low voltage despite normal CMR. None of our patients display a type 1 Brugada pattern but the electrocardiogram performed in a higher position was not normal either. Thus, we may speculate that in RVOT arrhythmias the presence of LVAs may be a marker of a very early stage of disease, not detected by current imaging techniques.

Low voltage areas may be pointed as a possible target for ablation and Type 2 BrP may be used as a non-invasive marker.

This study has some limitations. First, two different mapping systems were used to obtain the voltage map, and patients in the control group were mostly mapped with Carto and Stereotaxis. Nevertheless, the association between the presence of a Type 2 BrP and LVAs was proved with both systems. Secondly, we only considered patients that had a map of the RVOT done, so some of the patients with PVCs that went directly to LVOT mapping were excluded, leaving a small number of patients with the site of origin in the LVOT. A high-density voltage mapping was not performed. The median number of sampled points was 142 (98–300), which could hardly be considered insufficient for such a small area as the RVOT, and as proved by the similar results obtained with high-density mapping (Letsas et al., 2019).

We did not perform angiography to assess the level of the pulmonary valve. However, the LVAs that were analyzed in this study, were outside the transitional-voltage zone. The true level of the pulmonary valve is irrelevant for the interpretation of the results. Regarding the pattern of ST elevation observed in our patients, despite being abnormal, is not considered as a diagnostic Brugada ECG pattern according to the latest guidelines. However, we did not expect our patients to have Brugada Syndrome and for this reason we did not pursue further investigation.

Finally, patients did not repeat the ECG in the second ICS to evaluate if Type 2 BrP persisted after successful PVC ablation.

CONCLUSION

In conclusion, LVAs outside the transitional-voltage zone were frequently present in the RVOT of patients with idiopathic PVCs from the outflow tract. Those were absent in controls and could be unmasked by the presence of Type 2 BrP in high right precordial leads. The site of origin of the PVCs were within the LVA in a high percentage of cases. Low voltage areas may be a potential target for PVC ablation and Type 2 BrP is an accurate non-invasive marker of LVAs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hospital da Luz Lisboa and

Hospital Center of Setúbal. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LP contributed to the conceptualization, methodology, and writing. LP, RM, PC, DM, JF, PAm, MF, and AF contributed to the investigation. RM, DM, FC, DC, RC, and PAd contributed to the reviewing. All authors contributed to the article and approved the submitted version.

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Arrhythmias - Invasive Diagnostic Methods

Three-dimensional late gadolinium enhancement increases the diagnostic yield of cardiovascular magnetic resonance to detect low voltage in the right ventricular outflow tract

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Background: Cardiac magnetic resonance (CMR) using late gadolinium enhancement (LGE) fails to detect scar tissue in patients with electroanatomical abnormalities and biopsy-proven structural heart disease. It has shown conflicting data regarding existence of structural abnormalities in patients with idiopathic premature ventricular contractions (PVCs) from the right ventricular outflow tract (RVOT). Three- dimensional (3D) LGE enables high-spatial resolution more appropriate to the thin-walled right ventricle than two-dimensional (2D) LGE.

Objective: Our aim was to evaluate if the use of 3D-LGE would improve the performance of CMR to detect low voltage areas in the RVOT of patients with PVCs.

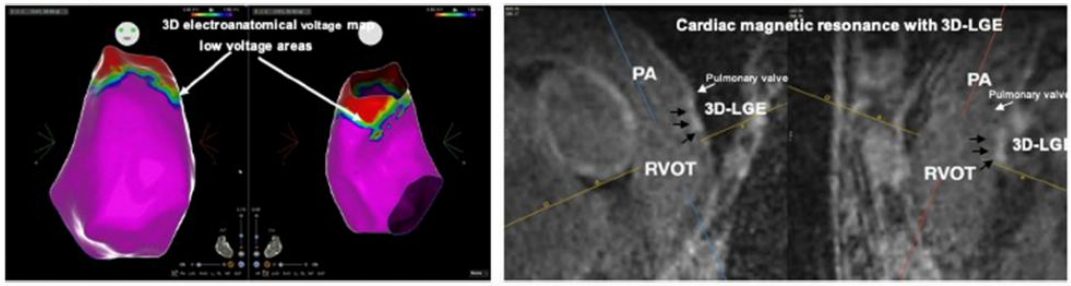
Methods: Since May 2020 we performed 3D-LGE CMR in 11 consecutive patients that underwent ablation of frequent PVCs. A control group of 11 consecutive patients that underwent catheter ablation by the same operator and had a 2D-LGE CMR performed before ablation was also studied. All patients had normal 2D-LGE CMR. A 3D electroanatomical bipolar voltage map of the RVOT was performed in sinus rhythm (0.5 mV-1.5 mV colour display). Areas with electrograms <1.5 mV represented the LVA. The area adjacent to the pulmonary valve usually displays voltage between 0.5 and 1.5 mV and is classified as transitional-voltage zone. Presence of LVAs outside this transitional-voltage zone were estimated. We compared the accuracy of CMR for detecting LVA in the two groups: 3D LGE and 2D LGE.

Results: The median number of points used for the voltage map was 344 (242-450). 18 patients (82%) displayed LVAs. The site of origin of the PVCs was the RVOT in 17 patients and the left ventricular outflow tract (LVOT) in 5. Comparison between groups is displayed in the table. 2D LGE CMR failed to demonstrate abnormalities of the RVOT in any of the patients that presented with LVAs. 3D CMR showed presence of fibrosis (Figure) in 3 out of 9 patients with LVAs (33%).

Conclusion: CMR using 3-D LGE techniques showed an increased power to diagnose structural abnormalities. This technique may be a better choice in initial stages of RVOT disease.

	All sample N = 22	3D-LGE CMR N = 11	2D-LGE CMR N = 11	p-value
Age in years, median (Q_1-Q_3)	47 (35-68)	62 (34-55)	42 (34-55)	0.243
Male gender, n (%)	8 (36)	3 (27)	5 (46)	0.330
PVCs RVOT/LVOT	17/5	9/2	8/3	0.500
N° points in the map, median (Q_1-Q_3)	344 (242-450)	350 (259-450)	300 (158-345)	0.076
Low voltage areas, n (%)	18 (82)	9 (82)	9 (82)	0.707

Abstract Figure.



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Premature ventricular contractions of the right ventricular outflow tract: is there an incipient underlying disease? New insights from a speckle tracking echocardiography study

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ABSTRACT

Context: Premature ventricular contractions (PVCs) originating in the right ventricular outflow tract (RVOT) are traditionally considered idiopathic and benign. Echocardiographic conventional measurements are typically normal.

Aims: To assess whether right ventricle longitudinal strain, determined by two-dimensional speckle tracking echocardiography, differ between RVOT PVCs patients (treated with catheter ablation) and healthy controls.

Methods: We retrospectively selected patients with PVCs from the RVOT who underwent electrophysiological study and catheter ablation between 2016 and 2019. Patients with documented structural heart disease were excluded. Transthoracic echocardiography was performed and right ventricle global longitudinal strain (RV-GLS), free wall longitudinal strain (RVFW-LS) and left ventricle global longitudinal strain (LV-GLS) were determined as well as conventional ultrasound measurements of RV and LV function.

Results: We studied 21 patients with RVOT PVCs and 13 controls. Patients with PVCs from the RVOT had lower values of RV-GLS and RVFW-LS compared with the control group (−19.4% versus −22.5%, $P = 0.015$ and −22.1% versus −25.5, $P = 0.041$, respectively). They also had lower values of LV-GLS, although still within the normal range (−19.1% versus −20.9%, $P = 0.047$). Regarding RVOT PVCs patients only, RV-GLS and RVFW-LS had no correlation with the PVCs burden prior to catheter ablation and they did not differ between the patients in whom the catheter ablation was successful and those in whom it was not. RV-GLS also had a positive correlation with RVOT proximal diameter ($r = 0.487$, $P = 0.025$).

Conclusions: In this group of RVOT PVCs patients, we found worse RV longitudinal strain values (and therefore sub-clinical myocardial dysfunction) when compared to healthy controls.

1. Introduction

Premature ventricular contractions (PVCs) originating in the right ventricular outflow tract (RVOT) are traditionally considered idiopathic and benign in the absence of structural heart disease [1]. However, there is evidence that a percentage of these patients may present with polymorphic ventricular tachycardia or ventricular fibrillation [2,3]. Cardiac magnetic resonance (CMR) imaging studies involving patients with idiopathic RVOT PVCs had contradictory results, with some reporting no pathological findings and others reporting structural abnormalities such as wall bulging, focal wall thinning and fatty replacement [4–6]. From an electro-anatomical mapping perspective, it has recently been demonstrated that patients with PVCs from the RVOT and apparently normal hearts have areas of low voltage electrograms in the RVOT [7]. Using non-invasive approaches, with endocardial and epicardial mapping systems to study the electrophysiological properties of the RVOT, it has been found that recovery time (RT) was shorter

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and activation recovery interval (ARI) dispersion across the epicardium was higher in patients with RVOT PVC versus control patients [8]. It is then reasonable to question if in RVOT PVCs patients, along with an apparent electrical remodeling process there is also an anatomical substrate behind the PVCs.

The quantification of right heart chamber size and function by echocardiography has been challenging due to the complex anatomy of the right ventricle (RV) [9]. Recently, two-dimensional speckle tracking echocardiography (2D-STE), an angle-independent technique that quantifies the amount of myocardial deformation, based on speckles (natural acoustic markers) and their motion in consecutive frames, has been under special attention. It was initially introduced to study the left ventricle (LV) function, but it is currently being applied to evaluate other cardiac chambers. It has the ability to detect subtle myocardial dysfunction earlier, in sub-clinical states, and has already proven its prognostic significance in different cardiomyopathies, such as hypertrophic cardiomyopathy [10]. Recent reports have shown that RV function can be accurately assessed by this method [11].

The aim of our study was to assess whether RV longitudinal strain, determined by 2D-STE, differs between RVOT PVCs patients and healthy controls.

2. Methods

2.1. Study population

We conducted a retrospective single-center analysis of 21 patients with frequent PVCs from the RVOT, defined as more than 10% of the total beats per 24 h, who underwent electrophysiological study and catheter ablation between 2016 and 2019. Patients with previous history of atrial fibrillation, documented structural heart disease (by transthoracic echocardiography and/or cardiac MRI), advanced lung disease or family history of sudden cardiac death or arrhythmogenic right ventricular cardiomyopathy (ARVC) were excluded. We also excluded patients with poor quality speckle tracking images defined as more than 2 segments with inappropriate tracking in a single view. We included, as a control group, 13 patients who underwent atrioventricular node reentrant tachycardia ablation in the same period of time, matched for age and sex, with a previous 24-hour Holter monitoring without PVCs.

2.2. Study design

We evaluated the demographic characteristics and cardiovascular risk factors of the patients such as hypertension, diabetes mellitus, dyslipidaemia and smoking. Patients underwent a standard 12-lead ECG that included recordings of both premature ventricular and sinus rhythm beats using standard paper speed and calibration. A 24-hour Holter monitoring was performed before the catheter ablation, and the presence and number of PVCs was assessed. The location from where the PVCs were ablated was registered. The acute success rate of the catheter ablation procedure was defined as the absence of RVOT PVCs for at least 30 minutes after the procedure. Transthoracic echocardiography was performed between 30 and 60 days after the catheter ablation procedure, using a Vivid E95 ultrasound system (GE Healthcare®, Horten, Norway) equipped with a 1.7/3.4 MHz tissue harmonics transducer. A complete echocardiographic study using standard views (parasternal long- and short-axis, apical 4-, 2- and 3-chamber, and RV-focused 4-chamber) was performed, during breath-holding and with stable electrocardiographic recording. Image contrast, frequency, depth and sector width were adjusted to optimize image acquisition. Three consecutive heart cycles (all of the patients were in sinus rhythm) were acquired. Data was digitally recorded for off-line analysis using dedicated software (EchoPAC 9.0, GE Healthcare®, Horten, Norway). Left ventricular ejection fraction (LVEF) was evaluated by the modified Simpson's biplane method, after determination of left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV). RVOT proximal and distal diameters were measured from the parasternal short-axis (PSAX) view (Fig. 1). Left atrial volume (LAV) was determined by the modified biplane method and right atrial (RA) area was measured in the 4-chamber view. Longitudinal RV function was assessed using tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (S'). End-diastolic and end-systolic RV areas were obtained and fractional area change (FAC) was calculated. Measurements were done according to the latest recommendations of the European Association of Cardiovascular Imaging (EACVI) [9]. For the speckle tracking analysis the reference frame coincided with the onset of the QRS. The frame rate was between 60 and 80 frames per second. The RV (in RV-focused 4-chamber view) and LV (in the 3 apical views) endocardial border was manually traced and the region of interest (ROI) was manually adjusted after analysis of tracking quality. RV global longitudinal strain (RV-GLS) was defined as the mean of the peak systolic strain in the 3 RV free wall segments and the ventricular septum (Fig. 2). RV free wall longitudinal strain (RVFW-LS) was defined as the mean of the peak systolic strain in the 3 RV free wall segments obtained from a 6-segment ROI. LV global longitudinal strain (LV-GLS) was defined as the mean of the peak systolic strain in the 16 LV segments. Analyses were performed in percentages.

2.3. Statistical analysis

SPSS version 22 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A Kolmogorov-Smirnov test was performed to test for the normality of continuous variables and in the presence of normality data is expressed as mean and standard deviation (SD) and, in its absence, as median and interquartile range [IQR]. Data is presented as frequencies and percentages for categorical variables. Categorical variables were compared with the use of the chi-square test. Continuous variables were compared with the use of Student's t-test or Mann Whitney test, as appropriate. Correlations between continuous variables were assessed by calculation of Pearson correlation coefficients. A value of $P < 0.05$ was considered statistically significant.

2.4. Ethics

The study was approved by the local Ethical Committee and is in accordance with the Helsinki Declaration. All participants or their legal representatives provided written informed consent.

3. Results

Twenty-one patients out of 37 were included in the RVOT PVCs group (Fig. 3) and 13 patients in the control group. Thirteen out of 21 patients had a cardiac MRI study done before the ablation procedure, which was normal in all of them. Median PVCs burden in the RVOT PVCs group prior to ablation was 16197 [9600–23213] PVCs in 24-hour Holter monitoring. The median time of PVCs before ablation was 18 [7–41] months. PVC precordial transition was in V3 in 3 patients (14%) and beyond V3 in 18 patients (86%). The ablation site was in the RVOT free wall in 5 patients (24%) and in the RVOT septum in 16 patients (76%). The acute success rate of the catheter ablation procedure, defined as absence of RVOT PVCs for at least 30 minutes after the procedure, was 86% (n = 18). The RVOT PVCs and the control group did not differ in relation to age,

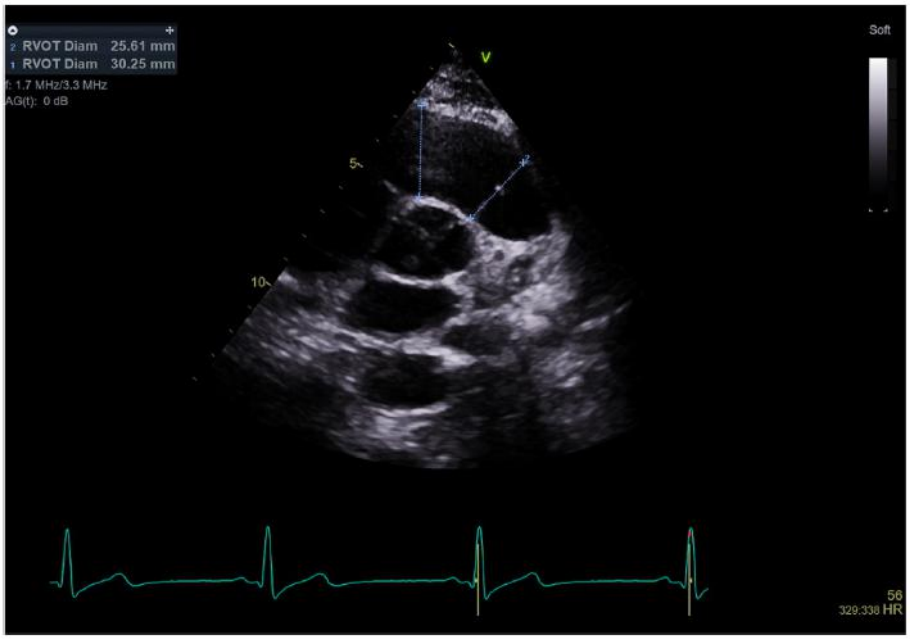

Fig. 1. Right ventricular outflow tract proximal and distal diameter.

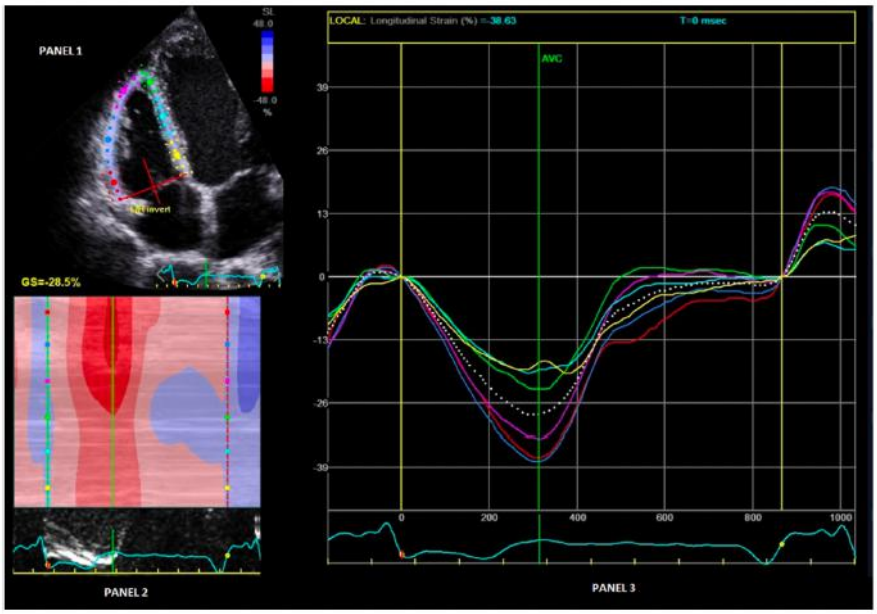

Fig. 2. Right ventricle global longitudinal strain. Panel 1: Colored Region of Interest (ROI). Panel 2: Colored M-Mode. Panel 3: Segmental Strain Curves. GS (Global Longitudinal Strain). AVC: Aortic valve closure.

gender, cardiovascular risk factors, body mass index, body surface area, heart rate, systolic and diastolic blood pressure during echocardiographic examination. Table 1 summarizes the baseline characteristics and Table 2 summarizes standard and strain echocardiographic parameters of RVOT PVCs patients and the control group. There were no significant differences between the groups concerning conventional echocardiographic measurements of RV and LV dimensions and function. Patients with RVOT PVCs

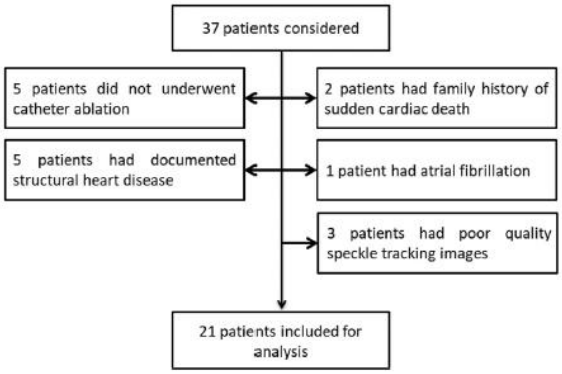

Fig. 3. Flowchart of the study selection process.

burden of PVCs prior to the catheter ablation procedure had no correlation with the RV-GLS, RVFW-LS and LV-GLS values obtained ($r = -0.046$, $P = 0.866$; $r = -0.266$, $P = 0.404$ and $r = -0.165$, $P = 0.528$, respectively). The time between PVCs diagnosis and ablation did not correlate with post-ablation RV-GLS, RVFW-LS and LV-GLS values ($r = 0.157$, $P = 0.496$; $r = 0.120$, $P = 0.659$ and $r = 0.404$, $P = 0.070$, respectively). In the RVOT PVCs group, when comparing RV-GLS and conventional echocardiographic measurements, we found that RV-GLS had a positive correlation with RVOT proximal diameter ($r = 0.487$, $P = 0.025$) (Fig. 4). RV-GLS also correlated with LV-GLS ($r = 0.572$, $P = 0.007$).

4. Discussion

Standard volumetric techniques and wall motion assessment usually used to asses LV function cannot be applied in the same manner to the RV due to its complex geometry, thin wall and

Table 1
Baseline characteristics in the two groups.

	RVOT PVCs (n = 21)	Controls (n = 13)	*P* value
Demographic data			
Age in years - mean (SD)	51 (17)	52 (15)	0.871
Male gender - n (%)	13 (62)	9 (69)	0.727
Hypertension - n (%)	6 (29%)	5 (38%)	0.549
Diabetes - n (%)	1 (5%)	0 (0%)	0.425
Dyslipidaemia - n (%)	4 (19%)	3 (23%)	0.778
Smoker - n (%)	2 (10%)	2 (15%)	0.606
Systemic hemodynamics/anthropometric data			
Body Mass Index in kg/m^2 - mean (SD)	25 (3)	23 (2)	0.058
Body Surface Area in cm^2 - mean (SD)	1,82 (0,18)	1,73 (0,14)	0.146
Systolic blood pressure in mmHg - mean (SD)	127 (13)	121 (13)	0.214
Diastolic blood pressure in mmHg - mean (SD)	72 (13)	67 (11)	0.316
Heart rate in beats per minute - mean (SD)	72 (14)	78 (15)	0.283

Table 2
Echocardiographic characteristics in the two groups.

	RVOT PVCs (n = 21)	Controls (n = 13)	*P* value
Conventional echocardiographic data			
LVEDV in ml - median [IQR]	78.8 [67.8–116.0]	86.0 [74.5–97.0]	0.800
LVESV in ml - median [IQR]	31.2 [26.2–45.2]	30.0 [27–37.3]	0.385
LVEF in percentage - mean (SD)	60.5 (6)	61.9 (6)	0.472
RVOT proximal diameter in mm - mean (SD)	32.1 (5)	30.1 (4)	0.287
RVOT distal diameter in mm - mean (SD)	24.0 (3)	21.9 (2)	0.061
TAPSE in mm - mean (SD)	23.1 (4)	23.3 (4)	0.846
S' RV in cm/s - mean (SD)	13.0 (3)	13.5 (4)	0.741
RVEDA in cm^2 - mean (SD)	19.7 (4)	18.5 (4)	0.435
RVESA in cm^2 - mean (SD)	10.9 (3)	10.1 (3)	0.485
RVFAC in percentage - mean (SD)	44.7 (6)	44.8 (6)	0.954
LAV indexed in ml/m^2 – median [IQR]	32.0 [25.1–38.0]	27.8 [25.9–33]	0.182
RA area in cm^2 - median [IQR]	15.4 [12.7–18.0]	13.8 [11.8–14.8]	0.251
2D Speckle Tracking echocardiographic data			
LV-GLS in percentage - mean (SD)	−19.1 (3)	−20.9 (2)	0.047
RV-GLS in percentage - mean (SD)	−19.4 (4)	−22.5 (2)	0.015
RVFW-LS in percentage - mean (SD)	−22.1 (6)	−25.5 (2)	0.041

had lower values of RV-GLS and RVFW-LS compared with the control group (−19.4% versus −22.5%, $P = 0.015$ and −22.1% versus −25.5, $P = 0.041$) as well as lower values of LV-GLS (−19.1% versus −20.9%, $P = 0.047$) (Table 2). Regarding RVOT PVCs patients only, RV-GLS, RVFW-LS and LV-GLS did not differ between the patients in whom the catheter ablation procedure was successful and those in whom it was not (−19.5% versus −18.9%, $P = 0.787$; −22.4% versus −20.8%, $P = 0.668$ and −18.5% versus −19.2%, $P = 0.677$, respectively). We also observed that the different contraction pattern. In this study 2D-STE, an angle independent technique that detects sub-clinical myocardial dysfunction was used to track the relative movement of myocardial speckles, in two-dimensional gray-scale images, over multiple time frames. Saberniak et al. compared RVOT PVCs patients with ARVC patients (the 2010 Task Force Criteria were used to make a diagnosis of ARVC) and found that RV-free wall strain and LV strain were lower in the latter group [12]. However, there was no control group of healthy, arrhythmia free patients, in their study. Some other studies

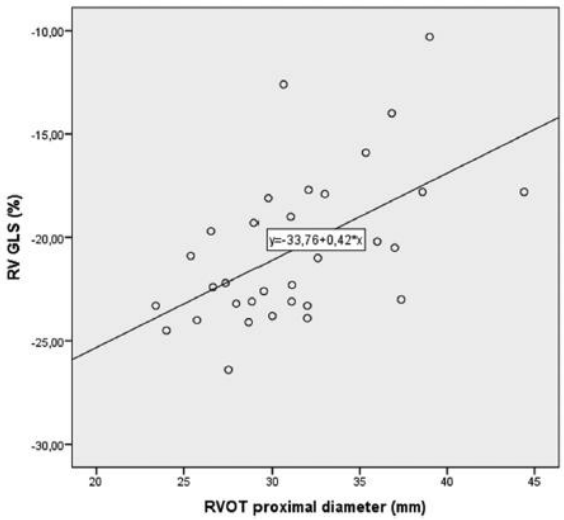

Fig. 4. Correlation between RVOT proximal diameter and RV-GLS.

have suggested that certain patients with RVOT PVCs may develop what has been called arrhythmia induced cardiomyopathy – LV and/or RV dysfunction caused by the presence of a high burden of PVCs [13]. This cardiomyopathy is not a tachycardiomyopathy [14]. Our echocardiographic findings cannot be explained by dyssynchrony either because they subside after the ablation procedure.

As previously stated, Parreira et al. group already demonstrated, in their group of RVOT PVCs patients, the existence of abnormal electrophysiological characteristics in the RVOT [8]. The major finding of our study is that RV-GLS and RVFW-LS are significantly lower in patients with RVOT PVCs compared with the control group. Besides, the RV-GLS and RVFW-LS values we obtained for our RVOT PVCs population ($-19.4 \pm 4\%$ and $-22.1 \pm 6\%$) were lower when compared to normal values described for healthy individuals. Muraru et al. group reported, in a study of 276 healthy volunteers, a lower limit of normal for 6-segment RV-GLS of −20.0% for men and −20.3% for women and a lower limit of normal for 3-segment RVFW-LS of −22.5% for men and −23.3% for women [15]. To the best of our knowledge, there are no echocardiographic studies that compared strain-derived parameters in RVOT PVCs patients with healthy subjects. Concerning strain values determined by CMR, Zghaib et al. group have previously proved, in ARVC patients, that lower regional strain could identify low voltage areas on endocardial and epicardial electroanatomical mapping and had a better correlation with VT substrate than late gadolinium enhancement sites [16].

We also found that LV-GLS was lower in the RVOT PVCs population compared with the control group, although it was still within the range of considered normal values for this 2D-STE parameter [17]. The lower RV-GLS, RVFW-LS and LV-GLS measurements were not correlated with the PVC burden before ablation nor with the acute success of the catheter ablation procedure. These results may suggest that the sub-clinical myocardial dysfunction detected might not be a consequence of the PVCs. However, without a baseline echocardiographic study before the occurrence of PVCs we cannot determine whether the mechanical abnormality is the result or the cause of the PVCs.

We also found a positive correlation between RV-GLS and RVOT proximal diameter determined in PSAX views – the lower the absolute values of RV-GLS the larger the dimension of the proximal RVOT (although the mean value of this diameter is still normal and outside the task force criteria for the diagnosis of ARVC). The reason for this is unknown. There are no echocardiographic reports in the literature describing morphologic abnormalities in the right heart of RVOT PVCs patients, although there are some CMR studies reporting abnormal findings. Gaita et al. observed that in a long term follow up of RVOT PVCs patients, 8 out of 11 had focal fatty replacement and other abnormalities of the right ventricle [18]. We may hypothesize that a larger RVOT is an early marker of an incipient cardiomyopathy. In fact, Krittayaphong et al. demonstrated that the presence of MRI abnormalities in patients with RVOT arrhythmias submitted to catheter ablation, without diagnostic criteria for ARVC, was associated with a higher recurrence rate [5]. Those findings could be an indicator of an abnormal anatomical substrate originating the PVCs.

Recently it has been proved that in Brugada syndrome, initially considered a purely electrical disease, patients have lower left and right longitudinal strain and more heterogeneous contractions than healthy controls, irrespective of the presence of previous events [19]. We can then say that the fact we haven't previously found imaging abnormalities doesn't necessarily mean there are no pathological findings associated with these conditions.

As study limitations, we note that our conclusions were based on a single center study, with a relatively small number of patients. The study and the control group were only matched for age and gender and that could have induced bias, although we believe that was not the case because both groups did not differ significantly in relation to cardiovascular risk factors. Besides, we cannot truly determine if the strain abnormalities were a precursor or an effect of RVOT PVCs. It would have been interesting to have a baseline study before the development of the PVCs and to assess the long-term outcome of the patients and the correlation with the imaging abnormalities found.

In conclusion, this group of RVOT PVCs patients with structurally apparent normal hearts, had worse RV longitudinal strain values (and therefore sub-clinical myocardial dysfunction) than healthy controls. Therefore, we recommend a closer follow-up by serial echocardiographic imaging and cardiac MRI in cases of persistence of strain abnormalities.

Declaration of competing interest

Authors declare no Conflict of Interests for this article.

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ORIGINAL ARTICLE

WILEY

Validation of an electrocardiographic marker of low voltage areas in the right ventricular outflow tract in patients with idiopathic ventricular arrhythmias

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Abstract

Background: Previous studies have reported the presence of subtle abnormalities in the right ventricular outflow tract (RVOT) in patients with apparently normal hearts and ventricular arrhythmias (VAs) from the RVOT, including the presence of low voltage areas (LVAs). This LVAs seem to be associated with the presence of ST-segment elevation in V1 or V2 leads at the level of the 2nd intercostal space (ICS).

Objective: Our aim was to validate an electrocardiographic marker of LVAs in the RVOT in patients with idiopathic outflow tract VAs.

Methods: A total of 120 patients were studied, 84 patients referred for ablation of idiopathic VAs with an inferior axis by the same operator, and a control group of 36 patients without VAs. Structural heart disease including arrhythmogenic right ventricular cardiomyopathy was ruled out in all patients. An electrocardiogram was performed with V1–V2 at the 2nd ICS, and ST-segment elevation ≥1 mm and T-wave inversion beyond V1 were assessed. Bipolar voltage map of the RVOT was performed in sinus rhythm (0.5–1.5 mV color display). Areas with electrograms <1.5 mV were considered LVAs, and their presence was assessed. We compared three groups, VAs from the RVOT ($n = 66$), VAs from the LVOT ($n = 18$) and Control group ($n = 36$). ST-elevation, T-wave inversion and left versus right side of the VAs were tested as predictors of LVAs, respective odds ratio (ORs) (95% confidence interval [CI]) and p values, were calculated with univariate logist regression. Variables with a $p < .005$ were included in the multivariate analysis.

Results: ST-segment elevation, T-wave inversion and LVAs were present in the RVOT group, LVOT group and Control group as follows: (62%, 17%, and 6%, $p < .0001$), (33%, 29%, and 0%, $p = .001$) and (62%, 25%, and 14%, $p < .0001$). The ST-segment elevation, T-wave inversion and right-sided VAs were all predictors of LVAs, respective unadjusted ORs (95% CI), p values were, 32.31 (11.33–92.13),

$p < .0001$, 4.137 (1.615–10.60), $p = .003$ and 8.200 (3.309–20.32), $p < .0001$. After adjustment, the only independent predictor of LVAs was the ST-segment elevation, with an adjusted OR (95% CI) of 20.94 (6.787–64.61), $p < .0001$.

Conclusion: LVAs were frequently present in patients with idiopathic VAs. ST-segment elevation was the only independent predictor of their presence.

KEYWORDS

catheter ablation, high right precordial leads, idiopathic ventricular arrhythmias, low voltage, right ventricular outflow tract, ST-segment elevation

1 | INTRODUCTION

The ventricular outflow tracts are the most frequent site of origin of idiopathic ventricular arrhythmias (VAs).[1] The idiopathic nature of the VAs refers to the absence of abnormalities on the currently available diagnostic tests, including cardiac magnetic resonance (CMR). However, several studies have been published, that report the presence of low voltage areas (LVAs) within the right ventricular outflow tract (RVOT) detected by invasive mapping, in patients with VAs originated from this location.[2–6] These LVAs are also associated with a lower conduction velocity[7] and a higher dispersion of the activation recovery interval a surrogate of the action potential.[8] The true nature of the LVAs is unknown and do not correspond to the identification of fibrosis on the CMR. The RVOT lays anteriorly and superiorly to the LVOT and its proximity to the 2nd intercostal space (ICS) tract increases the sensitivity of the electrocardiography to detect abnormalities when the right precordial leads are recorded at this level.[9] In a pilot study we demonstrated that the upward displacement of the electrocardiogram (ECG), unmasked the presence of ST segment elevation in V1 at the 2nd ICS absent in the standard ECG, in patients with premature ventricular contractions (PVCs) from the RVOT. This ECG marker was associated with the presence of LVAs across the RVOT,[10] but in this pilot study, CMR was not systematically performed, and a control group was absent. To overcome those limitations, we did a second study that included a larger sample with VAs from the right and left outflow tracts all with normal CMR, and a control group without VAs that had an ECG obtained at the 2nd ICS and a voltage map of the RVOT in sinus rhythm.[7] In this second study, ST-segment elevation was absent in the control group and present in 65% of patients with RVOT arrhythmias, but also in three out of five (60%) patients with VAs originating in the LVOT. This finding was surprising assuming that this was a marker of low voltage across the RVOT, thus unexpected in patients with arrhythmias with an origin outside the RVOT. So, the aim of the current study was to validate an electrocardiographic marker of LVAs in the RVOT in patients with idiopathic outflow tract VAs in a larger population, with a larger control group, and by including a larger number of patients with PVCs from the LVOT.

2 | MATERIALS AND METHODS

2.1 | Patient population

Since 2016 we prospectively performed an ECG with leads V1 and V2 at the level of the 2nd ICS to all patients referred for ablation of VAs with an inferior axis by the same operator at two centers. Those VAs included frequent PVCs, defined as more than 10 000 per 24 h, or sustained ventricular tachycardia (VT). A control group, of consecutive patients that underwent catheter ablation of supraventricular tachycardias since 2019 and agreed to have an electroanatomical map of the RVOT performed in sinus rhythm were also studied. Patients were excluded from the control group if there was any evidence of arrhythmias from the RVOT either in the patient's files or during ablation of the supraventricular arrhythmia (control group). All patients underwent transthoracic echocardiography with evaluation of left ventricular ejection fraction and left atrium diameter, and standard 12-lead ECG. CMR was performed to rule out structural heart disease in all patients with VAs. Patients were excluded if structural heart disease was present, in case of previous ablation or if the standard 12-lead ECG displayed evidence of conduction or electrical disease or abnormal QRS morphology. In the VA group patients were also excluded if a CMR was not performed before ablation. The CMR was performed to all patients with VA since 2019 and at the discretion of the attending physician between 2016 and 2019 on a 1.5 T scanner. The protocol comprised cine imaging (including views directed at the RVOT), and late gadolinium enhancement (LGE) performed 10 min after the intravenous administration of 0.2 mmol/Kg of gadolinium chelate (gadobutrol) with breath-hold 2-dimensional segmented phase-sensitive inversion-recovery sequences. Images were reviewed by a cardiologist with level 3 certification in CMR.

Arrhythmogenic right ventricular cardiomyopathy was ruled out according to the Task Force Criteria.[11] A 24-h Holter recording was performed before ablation in patients with VAs and the number of PVCs per 24 h and the presence of episodes of nonsustained ventricular tachycardia (NSVT), defined as >3 VAs in a run were assessed.

2.2 | Study design

All patients with VAs had a standard ECG and an ECG with V1 and V2 at the level of the 2nd ICS, performed before the procedure and the presence of ST-segment elevation in V1 or V2 and T- wave inversion beyond V1 in the precordial leads was recorded. Until 2019 only patients with right-sided VAs, had an invasive voltage map of the RVOT in sinus rhythm performed. After 2019 per protocol, all patients underwent RVOT mapping in sinus rhythm regardless the site of origin of the VA. All patients with VAs underwent invasive activation map and ablation. The patients from the control group all underwent ablation of supraventricular arrhythmias and had an ECG at the 2nd ICS before ablation and RVOT invasive voltage map in sinus rhythm. ST-segment elevation and T-wave inversion beyond V1, as well as LVAs in the voltage map, were assessed and compared in the three groups of patients as follows, patients with VAs from the RVOT, patients with VAs from the LVOT and control group. The groups were compared regarding demographic, clinical characteristics, and echocardiographic evaluated parameters. The burden and complexity of the VAs on the 24-h Holter was compared in the RVOT and LVOT VAs groups. The evaluation of ST-segment elevation and T-wave inversion as predictors of LVAs was performed adjusted to the site of origin of the PVCs.

2.3 | Standard 12-lead ECG and high right precordial lead ECG

The ECG was performed immediately before the ablation with standard paper speed and calibration. After a standard 12-lead ECG recording the ECG was repeated, with V1 and V2 leads placed at the level of the 2nd ICS maintaining the other lead's position. The presence of T wave inversion beyond V1 and ST-segment elevation ≥1 mm was assessed both on the standard ECG and on the high right precordial lead ECG. ST-segment elevation was measured at the take-off point of the QRS-ST and either presented a coved-type (Figure 1) or a saddleback pattern (Figure 2). All ECG recordings were evaluated by two independent reviewers blinded to the patient group or the result of the voltage map or activation map.

2.4 | Electroanatomic mapping and ablation

Patients were studied in a fasting nonsedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. In patients with VT, programed ventricular stimulation was performed to induce VT and isoprenaline was administered when needed. During endocardial mapping of the LVOT heparin was administrated to achieve an ACT of 250–300 s. All procedures in one center were performed with remote magnetic navigation (RMN) using the Niobe II Magnetic Navigation System (Stereotaxis, Inc.) with the CARTO 3 RMT (Biosense-Webster, Inc.) system. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster Inc.) was used with a 3.5-mm distal tip electrode and a 2-5-2 interelectrode distance as previously described.[12] At the second center all procedures were performed manually by the same operator using the EnSite Precision (Abbott) system, using an irrigated tip FlexAbility (Abbott) catheter with a 4-mm distal tip electrode and 1-4-1 interelectrode spacing until 2019 and a TactiCath catheter (Abbott) with a 3.5-mm distal tip electrode and a 2-2-2 interelectrode distance since then. The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT with the RMN system patients or manually, under fluoroscopic and then placed at multiple sites on the endocardial surface of the RVOT. Mapping of the LVOT endocardium and the aortic coronary cusps was performed using a transaortic approach in all patients. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed. Two maps were created, a voltage bipolar map of the RVOT in sinus rhythm and an activation map during the PVC.

2.4.1 | Sinus rhythm map

The RVOT voltage map was performed in sinus rhythm both in patients with VAs and in the control group. Only points with optimal contact were considered for the voltage mapping. The electrograms were analyzed in regard of their amplitude and the information was used to generate a 3-dimensional electroanatomical voltage map of the RVOT, with the electrophysiologic information, color-coded and superimposed on the geometry. The color display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude >1.5 mV), to red, representing electroanatomical scar tissue (amplitude <0.5 mV). LVAs were defined as areas with bipolar electrograms with an amplitude <1.5 mV. The level of RVOT/pulmonary valve junction was determined based on fluoroscopy and electroanatomical voltage mapping by thoroughly passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT until bipolar electrograms were absent in the distal pair of electrodes but present in the proximal pair. The voltage above the pulmonary valve is usually less than 0.5 mV. The area immediately below the level of the pulmonary valve displays intermediate colors, corresponding to a bipolar voltage between 0.5 and 1.5 mV, defined as the transitional-voltage zone.[2] The fill threshold used for mapping was 5–7. Presence of LVAs outside the transitional-voltage zone, were assessed.

2.4.2 | Activation map in VA and ablation

The activation map was created by mapping several points during the VA while using a surface ECG lead as reference. The ablation site was

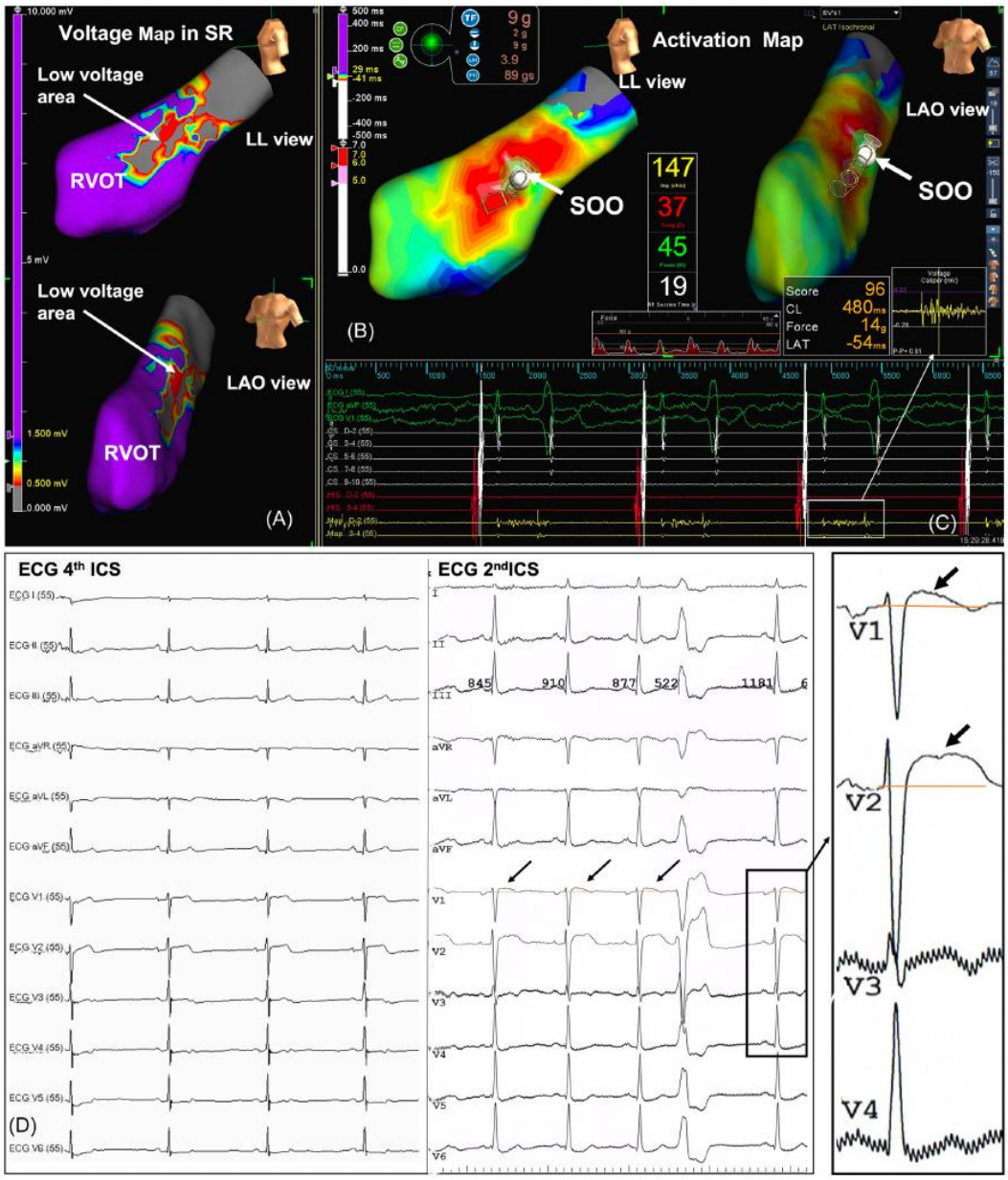

FIGURE 1 Patient with PVCs from the RVOT showing LVAs and coved-type ST-elevation. (A) Voltage map of the RVOT in SR showing LVAs (white arrow). (B) Activation map during PVCs showing the SOO (white arrows) and RF applications (pink dots). (C) Intracardiac electrograms at the ablation site. Electrogram at the distal tip (Map-D) amplified in the box above, displaying low voltage with a peak-to-peak amplitude of 0.6 mV. (D) 12 Lead ECG at the 4th ICS without ST-elevation (left) and at 2nd ICS showing coved-type ST elevation in V1 (black arrows), amplified in the right. ICS, intercostal space; LAO, left anterior oblique; LVA, low voltage area; PVC, premature ventricular contractions; RF, radiofrequency; RVOT, right ventricular outflow tract; SOO, site of origin; SR, sinus rhythm

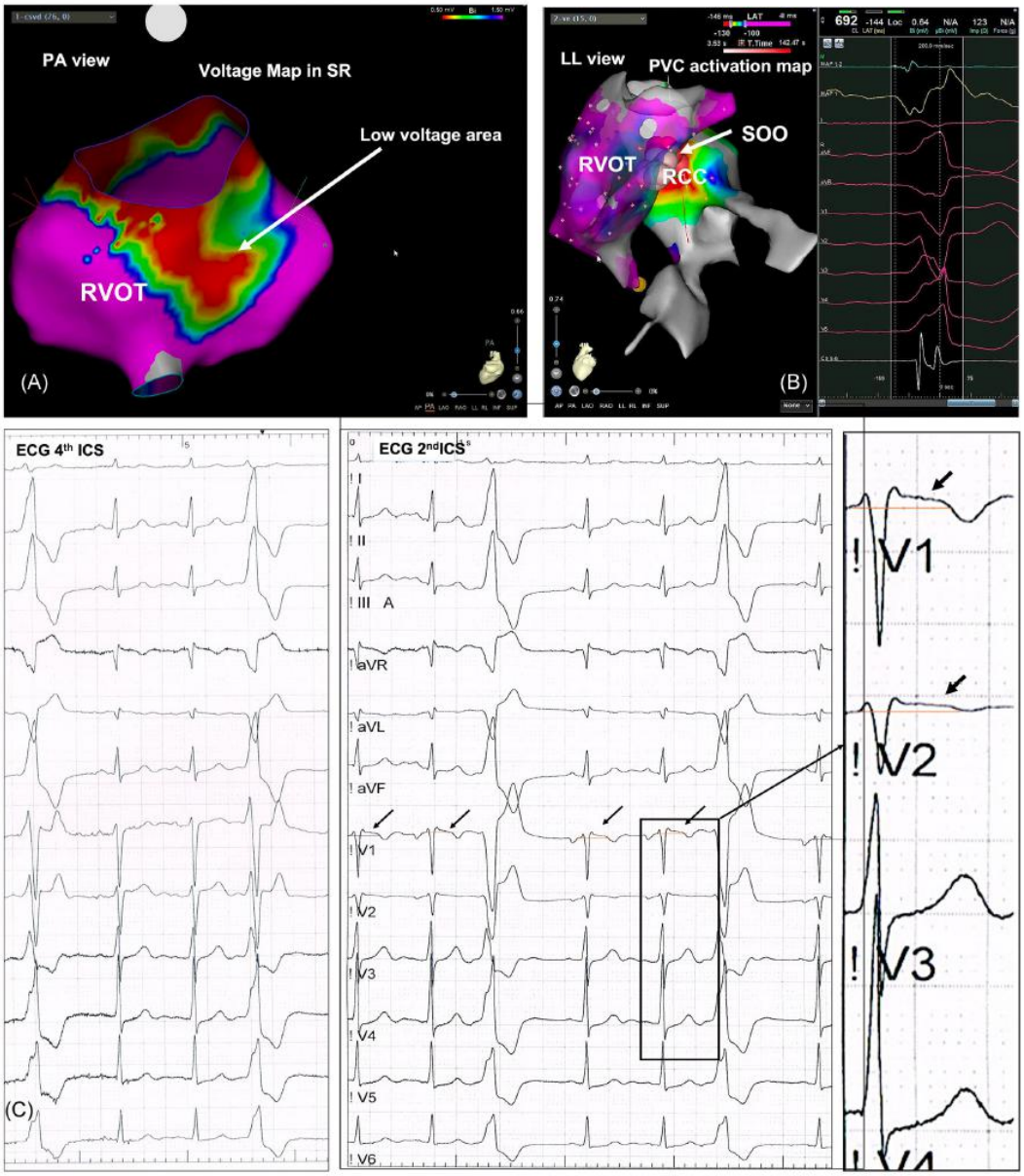

FIGURE 2 Patient with PVCs from the RCC showing LVAs and saddleback ST-elevation. (A) Voltage map of the RVOT in SR showing LVAs (white arrow). (B) Activation map during PVCs showing the SOO (white arrows) in the RCC and RF applications (pink dots) with RVOT overlaid in a transparent format on the right-side of the panel an image of the intracardiac electrograms at the ablation site. (C) 12 Lead ECG at the 4th ICS without ST-elevation (left) and at the 2nd ICS showing saddleback ST elevation in V1 (black arrows), amplified in the right. ICS, intercostal space; LL, left lateral; LVA, low voltage area; PA, posteroanterior; PVC, premature ventricular contractions; RCC, right coronary cusp: RF, radiofrequency; RVOT, right ventricular outflow tract; SOO, site of origin; SR, sinus rhythm

selected based on the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous VA. Energy was delivered between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 s, to a maximum temperature of 43°C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. Success was defined as abolition of PVCs or noninduction of VT under isoprenaline infusion until 30 min after ablation. The site of ablation and the success of the procedure were registered. All the intracardiac electrograms were reviewed by two senior electrophysiologists blinded to the results of the ECG.

2.5 | Statistical analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc.). Data is presented as median and lower and upper quartile (Q1–Q3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann–Whitney test for independent samples and Kruskal–Wallis test for multiple samples. Categorical variables were compared with the use of two-sided Chi-square or Fischer's exact test as appropriate for independent samples. Univariable logistic regression analysis and calculation of the respective odds ratios (OR) and 95% confidence intervals (CI) was used to evaluate the discriminative power of the evaluated parameters to predict the presence of LVAs. We included in the multivariate analysis those variables with a $p < .05$ in the univariate analysis. The performance of ST-segment elevation as a diagnostic test including the positive and negative predictive value as well as specificity and sensitivity was based on 2 × 2 contingency table and Chi-square test. For all tests a $p < .05$ was considered as statistically significant.

2.6 | Ethics

All patients signed the informed consent form, and the study was approved by the Ethical Committee of the two Hospitals. The study is in compliance with the Helsinki Declaration.

3 | RESULTS

3.1 | Patient population

We included 120 patients, median age 50 (39–62) years, 47 males (39%), 66 patients with VAs originating in the RVOT, 18 patients with VAs from the LVOT and 36 patients in the control group, of whom 29 underwent ablation of atrioventricular nodal reentrant tachycardia, two of occult accessory pathways, two of right atrial tachycardia and three of typical atrial flutter. The three groups did not differ in relation to age, gender, biometric parameters, risk factors presence of syncope or family history of sudden death (Table 1). Patients in the RVOT VAs group were more frequently on betablocker therapy than patients in the control group (60% vs. 25%, $p = .003$), and patients in the LVOT VAs group were more frequently treated with antiarrhythmic drugs than patients in the control group (33% vs. 8%, $p = .047$).

3.2 | Standard 12-Leads ECG and high right precordial leads ECG

We found no significant differences between groups regarding the ST-segment elevation or the presence of negative T-waves beyond V1 in the standard ECG. In the ECG performed at the level of the 2nd ICS, ST-segment elevation was present in 46 patients, 41 in the RVOT group, 3 in the LVOT and 2 in the control group both with a saddleback pattern previously described as Type 3 Brugada pattern,[13] this difference was statistically significant between the RVOT and the control groups (62% vs. 6%), $p < .0001$, but not between the LVOT and the control group. All patients with ST-segment elevation presented with either coved-type or saddleback pattern defined as Type 2 or 3 Brugada ECG pattern, but none presented with ECG diagnostic pattern for Brugada Syndrome, meaning a coved-type pattern with ≥2 mm in ≥1 right precordial lead (V1–V3).[14] The presence of T-wave inversion beyond V1 was significantly more frequent in the RVOT group comparing to the control group as well as in the LVOT group in comparison to the control group, respectively, 33% versus 0% and 29% versus 0%, $p = .001$.

3.3 | Electroanatomic mapping and ablation

3.3.1 | Sinus rhythm map

One hundred and fourteen patients underwent successful mapping of the RVOT. The mapping was performed with RMN in 75 patients (66%) of all cases. In the control group the percentage of cases performed with RMN was significantly higher than in RVOT and LVOT groups, respectively, 92% versus 56% versus 42%, $p < .0001$. The number of points acquired for the voltage map was 288 (97–401), not significantly different in patients with LVOT versus RVOT PVCs, 288 (90–403) versus 257 (146–397), 0.923 (Table 2). The RMN was the technique of choice to study the control group because due to the softer catheter tip and its higher safety profile[15] we were able to obtain the voltage map of the RVOT, median number of points 350 (330–480), with near zero fluoroscopy which was impossible to achieve with manual catheters. However, in the VAs group there were no significant

TABLE 1 Evaluated parameters and comparison between groups

	Overall sample ($n = 120$)	RVOT VA group ($n = 66$)	LVOT VA group ($n = 18$)	Control group ($n = 36$)	p value
Demographic data					
Age in years, median (Q_1–Q_3)	50 (39–62)	48 (39–63)	53 (44–66)	50 (35–59)	.312
Male gender, n (%)	47 (39)	24 (36)	9 (50)	14 (39)	.575
Weight in Kg, median (Q_1–Q_3)	67 (60–80)	65 (60–79)	71/65–81	64 (60–78)	.216
Height in cm, median (Q_1–Q_3)	165 (163–170)	165 (161–170)	165 (160–169)	167 (165–172)	.506
BMI in Kg/m^2, median (Q_1–Q_3)	24 (22–27)	24 (22–27)	24 (23–30)	23 (22–27)	.123
Risk factors, history and medications					
Hypertension, n (%)	25 (21)	11 (17)	4 (22)	10 (28)	.413
Diabetes, n (%)	6 (5)	3 (5)	1 (6)	2 (6)	.969
Syncope	7 (6)	6 (9)	1 (6)	0 (0)	.066
Family history of sudden death	3 (3)	1 (2)	2 (11)	0 (0)	.077
Betablockers, n (%)	58 (48)	40 (60)	9 (50)	9 (25)	.003[a]
Antiarrhythmic drugs, n (%)	18 (15)	9 (14)	6 (33)	3 (8)	.047[b]
Standard 12 lead ECG					
T wave inversion beyond V1, n (%)	2 (2)	2 (3)	0 (0)	0 (0)	.435
ST-segment elevation at V1 or V2, n (%)	2 (2)	2 (3)	0 (0)	0 (0)	.435
High right precordial leads ECG					
T wave inversion beyond V1, n (%)	27 (23)	22 (33)	5 (29)	0 (0)	.001[c]
ST-segment elevation at V1 or V2, n (%)	46 (38)	41 (62)	3 (17)	2 (6)	<.000[d]
Invasive voltage mapping in SR[e]					
RMN/manual ablation, n/n (%)	75/39 (66%)	37/29 (56%)	5/7 (42%)	33/3 (92%)	<.0001[c]
Presence of LVAs, n (%)	49 (43)	41 (62)	3 (25)	5 (14)	<.0001[d]

Abbreviations: BMI, body mass index; ECG, electrocardiogram; LVA, low voltage area; LVOT, left ventricular outflow tract; PVC, premature ventricular contractions; RMN, remote magnetic navigation; RVOT, right ventricular outflow tract; SR: sinus rhythm; VA, ventricular arrhythmia.

[a]Significant between RVOT and control group.

[b]Significant between LVOT and control group.

[c]Significant between RVOT and control group and LVOT and control group.

[d]Significant between RVOT and control group and between RVOT and LVOT group.

[e]Patients that underwent RVOT mapping in SR ($n = 114$).

differences regarding the use of manual versus RMN techniques. The use of AAD was not associated with LVAS, OR (95% CI), p value was .685 (0.234–2.002), $p = .489$. The presence of LVAs was found in five patients from the control group (Figure 3) and in three patients from the LVOT VAs group (Figure 2) Their presence was significantly higher in patients with RVOT (Figure 1) when compared with the control group (62% vs. 14%, $p < .0001$), but that was not the case for LVOT patients in comparison with the control group (25% vs. 14%). The number of points acquired for the voltage map was not significantly different in patients with LVAs in comparison with patients without, respectively, 365 (170–412) and 305 (118–393), $p = .07$. However, not all patients with RVOT VAs displayed LVAS, which were absent in 25 patients (38%), an example is shown in Figure 4.

3.3.2 | Activation map in VA and ablation

Six patients had sustained VT all with origin in the RVOT, and the remaining patients had frequent symptomatic PVCs, however, this difference was not statistically significant different between the RVOT and LVOT groups. The VA ablation was performed with RMN in 47 out of 84 patients (56%) of cases, the percentage for the two groups was not significantly different. The site of origin of the VA in the LVOT group was the left coronary cusp (LCC) in 5 patients, the right coronary cusp (RCC) in 3, the LV summit in 4, the LVOT below the aortic valve in 3, the aorto-mitral continuity in 2 and the commissure between the RCC and the LCC in one. The overall success rate of ablation was 88%. The presence of ST-segment elevation or LVAs was not associated with the success rate,

TABLE 2 Electrocardiographic variables and invasive mapping comparison between RVOT VA group and LVOT VA group

	Overall sample ($n = 84$)	RVOT VA group ($n = 66$)	LVOT VA group ($n = 18$)	p value
Standard 12 lead ECG				
ST-segment elevation at V1 or V2, *n* (%)	2 (2)	2 (3)	0 (0)	.455
T wave inversion beyond V1, *n* (%)	2 (2)	2 (3)	0 (0)	.455
High right precordial leads ECG				
ST-segment elevation at V1 or V2, *n* (%)	44 (52)	41 (62)	3 (17)	.001
T wave inversion beyond V1, *n* (%)	27 (32)	22 (33)	5 (28)	.655
24-h Holter recording				
Number of PVCs, in $n \times 10^4$, median (Q1–Q3)	2 (1.4–2.9)	2 (1.4–2.7)	2.2 (1.3–3.2)	.539
NSVT, *n* (%)	26 (31)	21 (32)	5 (28)	.742
Invasive voltage mapping in SR[a]				
No. points, median (Q1–Q3)	288 (97–401)	257 (146–397)	288 (90–403)	.923
RMN/manual ablation, *n*/*n* (%)	47/37	37/29 (56%)	5/7 (42%)	.969
Presence of LVAs, *n* (%)	44 (56)	41 (62)	3 (25)	.017

Abbreviations: ECG, electrocardiogram; LVA, low voltage area; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contractions; RMN, remote magnetic navigation; RVOT, right ventricular outflow tract; SR, sinus rhythm; VA, ventricular arrhythmia.

[a]Patients that underwent RVOT mapping in SR ($N = 78$).

respectively 89% for patients with ST-segment elevation vs 89% for those without, $p = 1.000$ and the same for the presence of LVAs.

3.4 | Comparison between left-sided and right-sided VA groups

The PVC burden and the presence of NSVT in the 24-h Holter recording was not significantly different in the two groups (Table 2). The presence of ST-segment elevation in the 2nd ICS was significantly more frequent in the group of patients with VAs from the RVOT, 62% versus 17%, $p = .001$. Also, the presence of LVAs were more frequent in this group 62 (%) versus 25%, $p = .017$.

3.5 | Predictors of the presence of LVAs

When evaluating the electrocardiographic findings we found an association between ST-segment elevation and the presence of negative T-wave beyond V1 at the 2nd ICS and the presence of LVAs, respective unadjusted OR (95% CI) of 32.31 (11.33–92.13), $p < .0001$, and 4.137 (1.615–10.60), $p = .003$. Also, the RVOT site of the VAs showed an association with LVAs, OR (95% CI) 8.200 (3.309–20.32), $p < .0001$ (Table 3). However, after adjustment with multivariate analysis the only independent predictor of LVAs was the ST-segment elevation with an adjusted OR (95% CI) of 20.94 (6.787–64.61), $p < .0001$. The ST-elevation as a noninvasive marker of LVAs has a sensitivity of 80%, specificity of 89%, positive predictor value of 85% and negative predictor value of 85%.

4 | DISCUSSION

The assumption that all VAs from the outflow tracts result from the same mechanism regardless the site, or the presentation, from frequent PVCs to sustained VT, is based on a single paper by Kim et al.[16] No further recent studies have confirmed these findings. Also, we may question if the left or right sided origin of the arrythmia may be of importance if one assumes that they share the same mechanism. However, there is an increasing amount of evidence suggesting the presence of a substrate within the RVOT in patients with VAs originating from the RVOT.[2–6] In the current study we found the presence of LVAs in 62% of cases using a quadripolar catheter and a point-by-point methodology, whereas Letsas et al.[5] mapped the RVOT with multipolar catheters and found a similar result, respectively, the presence of LVAs in 18 out of 28 patients (64%) of cases. The LVAs described by all those authors could not be detected by LGE CMR in none. This may be due to the small size of the LVAs, below the threshold capacity of detection with the currently available CMR techniques.[17,18] In fact, in a previous study we demonstrated that the use of three-dimensional LGE increased the diagnostic yield of CMR to detect LVAs when compared to conventional two-dimensional analysis, detecting fibrosis in three out of nine patients with LVAs (33%) of cases while two-dimensional analysis failed to demonstrate fibrosis in all.[19] Also, using speckle tracking echocardiography in 21 patients with PVCs from the RVOT and in 13 control patients we were able to demonstrate the presence of worse RV longitudinal strain values (and therefore subclinical myocardial dysfunction) in the PVC group when compared to healthy controls.[20] But on the other hand, the presence of LVAs does not

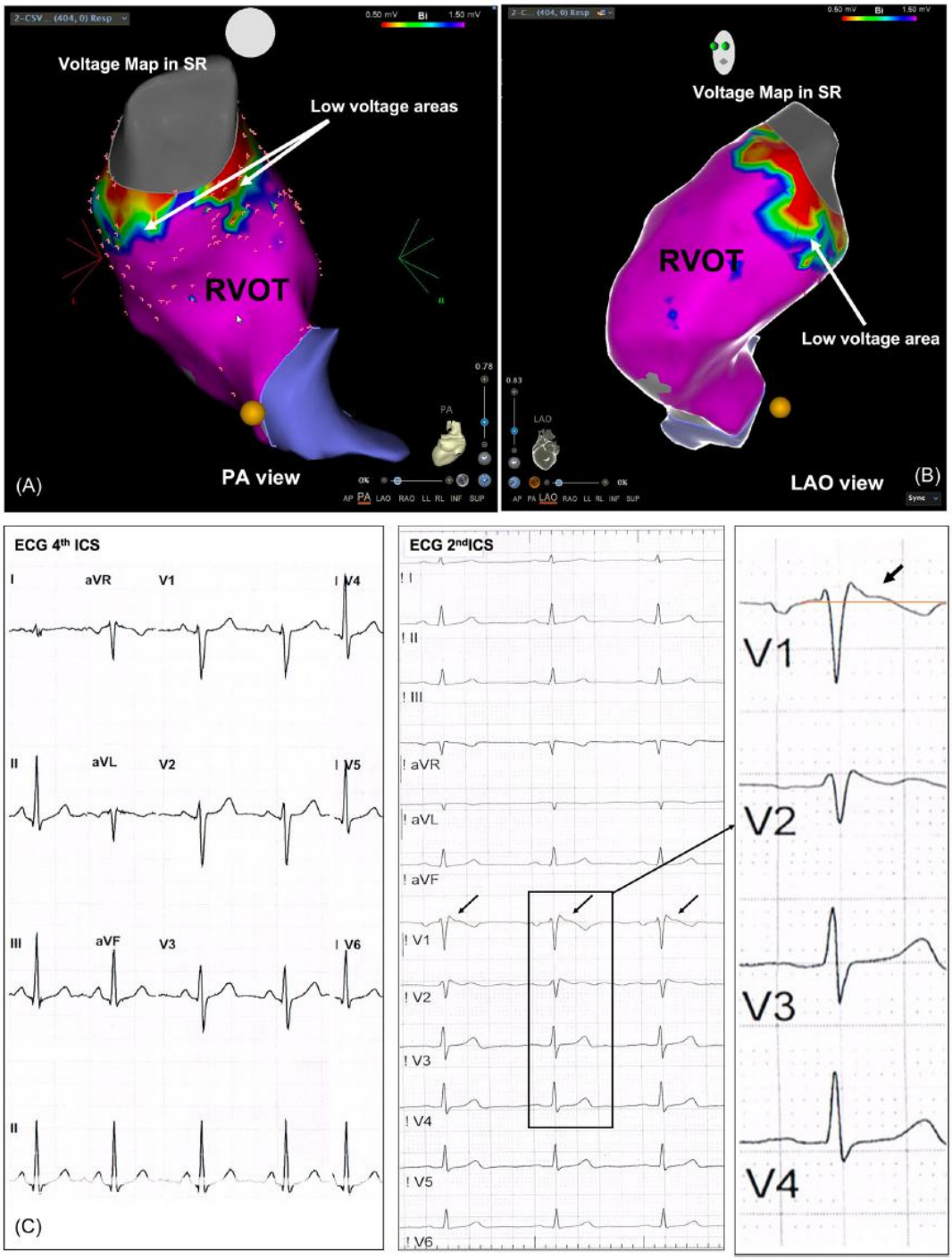

FIGURE 3 Patient from the control group showing LVAs and saddleback ST elevation. (A) Voltage map of the RVOT in SR showing LVAs (white arrow) in AP view. (B) Voltage map of the RVOT in SR showing LVAs (white arrow) in LAO view. (C) 12 Lead ECG at the 4th ICS without ST-elevation (left) and at the 2nd ICS showing saddleback ST elevation in V1 (black arrows), amplified in the right. AP, anteroposterior; ICS, intercostal space; LAO, left anterior oblique; LVA, low voltage area; RVOT, right ventricular outflow tract; SR, sinus rhythm

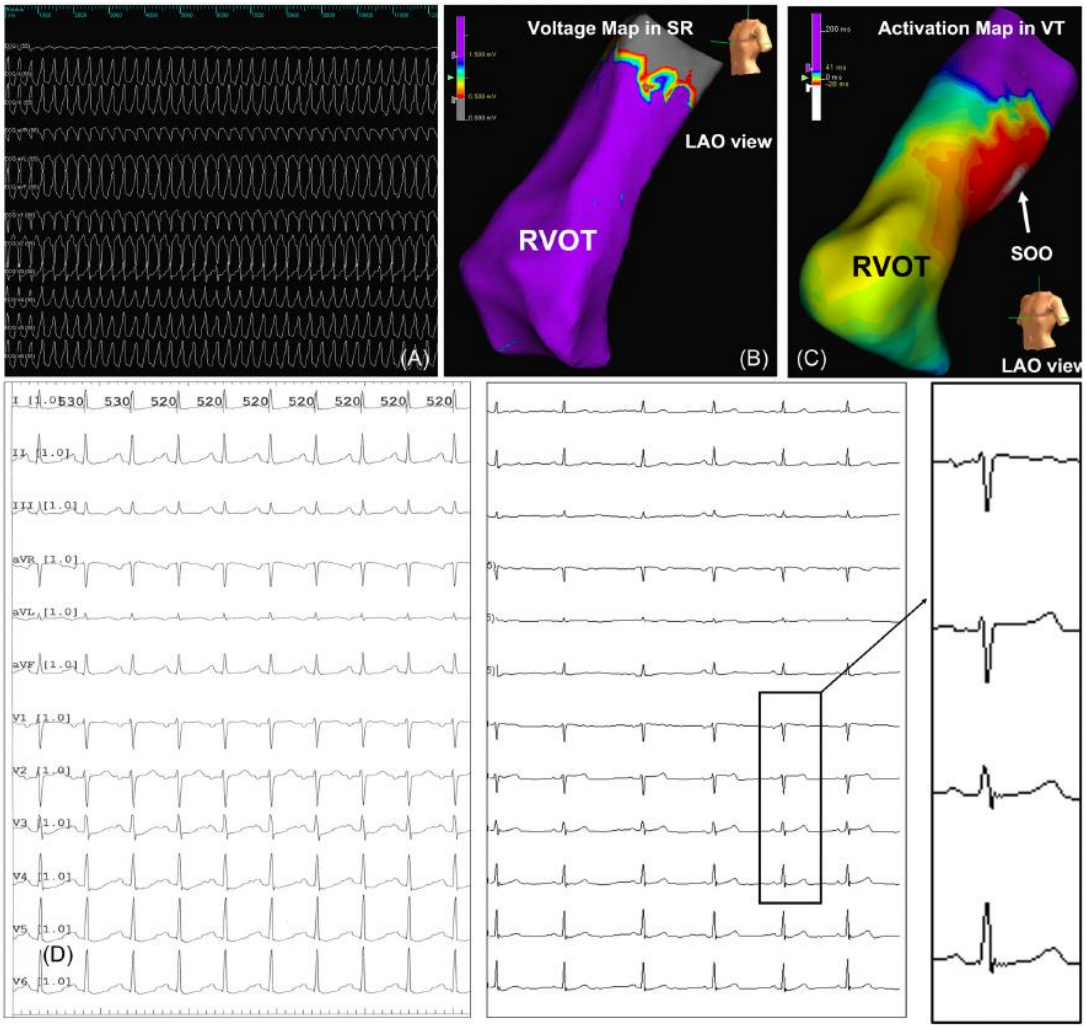

FIGURE 4 Patient with VT from the RVOT showing no LVAs or ST-segment elevation. (A) Standard 12 ECG during the procedure showing ventricular tachycardia with an inferior axis and a left bundle branch block. (B) Voltage map of the RVOT in SR showing absence of low voltage areas, all RVOT shows a purple color except the transition zone at the level of the pulmonary valve. (C) Activation map during VT showing the SOO (white arrow) in the RVOT anterior free wall (white area). (D) 12 Lead ECG at the 4th ICS (left) and at the 2nd ICS showing normal ST segment and absence of T-wave inversion from V1–V3, amplified in the right. ICS, intercostal space; LAO, left anterior oblique; LVA, low voltage area; RVOT, right ventricular outflow tract; SOO, site of origin; SR, sinus rhythm; VT, ventricular tachycardia

necessarily mean presence of fibrosis. The thickness of the RVOT wall is variable, and in areas where the wall may be thinner the voltage could be lower. The local electrograms in the septum area of the right ventricle have the highest voltage, as opposed to the ones from the RVOT, which display the lowest values.[21] So, it is possible that the LVAs may correspond to zones with a thinner RVOT myocardium. Nevertheless, the prevalence of these LVAs is extremely high in patients with arrhythmias from the RVOT in comparison with the general population, suggesting an association between the two. Additionally, these LVAs do not seem to display normal physiology. They are associated with slower conduction velocity and presence of deceleration zones as demonstrated by the slower velocity of wavefront propagation across the RVOT in patients with LVAs in comparison with patients with normal voltage.[7] Also, the electrophysiological properties of the RVOT in these patients are abnormal, we demonstrated with the use of noninvasive electrocardiographic imaging the presence of a dispersion of repolarization in the epicardium of the RVOT.[8]

TABLE 3 Binary logist regression analysis with crude and adjusted odds ratios OR (95% CI) showing the discriminative power of the evaluated parameters to predict the presence of LVAs[a]

Variables	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
ST elevation in V1 or V2 at the 2nd ICS	32.31 (11.33–92.13)	<0.0001	20.94 (6.787–64.61)	<0.0001
Negative T-wave beyond V1 at the 2nd ICS	4.137 (1.615–10.60)	0.003	2.077 (0.603–7.156)	0.247
RVOT site of VA	8.200 (3.309–20.32)	<0.0001	2.229 (0.669–7.422)	0.192
LVOT site of VA	0.406 (0.104–1.587)	0.195	–	–

Abbreviations: CI, confidence interval; LVOT, left ventricular outflow tract; LVA, low voltage area; OR, odds ratio; RVOT, right ventricular outflow tract; VA, ventricular arrhythmia.

[a]In the group of patients that underwent RVOT voltage map in SR.

And yet currently, there is no reliable method for the diagnosis of these minimal abnormalities identified as LVAs so far. So, the identification of a noninvasive marker of LVAs is important.

The findings in this study confirm the value of ST-segment elevation at the level of the 2nd ICS to detect the presence of LVAs. The much higher incidence of ST-segment elevation in our patients with RVOT VAs has been previously described by our group in a smaller population[6] and confirmed in this larger population. The percentage of ST-segment elevation in patients with LVOT VAs in the current study is lesser than in the former one, 60% versus 27%. The higher percentage formerly observed may have to do with the small sample size. The observation that the increase in the number of patients with LVOT VAs led to a significant reduction in the percentage of ST-elevation in the group can backup this statement. We can speculate that a further increase in the sample size would lead to additional reduction in this percentage rendering it similar to that of the general population. However, we cannot rule out the possibility that RVOT and LVOT VAs may be a global disease of the outflow tracts thus presenting similar pathological findings despite different clinical manifestation as RVOT or LVOT VAs. In opposition, the increase in the sample size of the group with RVOT VAs from 40 to 66 patients did not result in decrease in the percentage of ST-segment elevation, 67% in the previous study comparing to the 62% in the current one proving to be a consistent observation.

The prevalence of ST-elevation in our control group, with a morphology of Type 3 Brugada ECG pattern[13] was 6%, which is similar to the previous reported prevalence in the general population. Holst et al.[22] studied 340 healthy subjects and reported an incidence of Types 1, 2, and 3 Type 2 Brugada ECG pattern on the 2nd ICS, respectively, 0%, 3.3%, and 7.1%. Another work by Hunuk et al.[23] registered similar results in 504 healthy male volunteer subjects. The authors found an incidence of Types 1, 2, and 3 Brugada ECG pattern of 0.8%, 2%, and 7.5%, respectively. A flecainide test was not performed in any of the patients with ST-segment elevation, because a clinical suspicion of Brugada Syndrome was absent in all.[13]

It remains to be explained why some patients with arrhythmias from the RVOT do not display ST-segment elevation nor LVAs or why patients without VAs show LVAs within the RVOT. Regarding the former we can speculate that the mechanism for the arrhythmia may not be the same in all patients or at least the repercussion of the arrhythmia on the heart may differ among patients. Regarding the latter, we may speculate that the occurrence of the VAs depends on the presence of both the substrate and the triggers and so the occurrence of arrhythmias may never occur in the absence of the appropriate triggers, despite the presence of the substrate.[24]

Another interesting finding in this study was the high percentage of patients with T wave inversion beyond V1 when the ECG was obtained at the level of the second ICS. The diagnosis of ARVC is sometimes difficult, and T wave inversion in V1–V2 is considered a minor criterion.[11] If we accept that the T wave inversion at a higher ICS could have a similar value, then the number of ARVC "possible" cases would increase. However, despite its association with LVAs in univariate analysis, unlike the ST-segment elevation the presence of T-wave inversion was not independently associated with the presence of LVAs.

With this study we obtained consistent evidence of an association between ST-elevation and LVAs. In fact, it was the only independent predictor of LVAs. Their presence was not associated with a worse outcome, in fact the success rate was similar in patients with and without LVAs, they may however, be considered a possible substrate for RVOT arrhythmias and thus a target for ablation.

5 | LIMITATIONS

This study has some limitations. First, two different mapping systems were used to obtain the voltage map, and patients in the control group were mostly mapped with CARTO 3 RMT (Biosense-Webster, Inc.) and RMN with Niobe II Magnetic Navigation System (Stereotaxis, Inc.). Nevertheless, the association between the presence of ST-elevation and LVAs was similar with both systems in the VA groups. Second, the voltage map was mostly performed with noncontact force catheters, which only started being used since 2019. Third, the LVOT VAs group was smaller making it insufficient to interpret similar results as nonsignificant. However, considering the difference in the prevalence of ST-segment elevation and LVAs in the group with PVCs from the RVOT in comparison with that of the group with PVCs from the LVOT and the control group, allows the

acceptance of significance despite the small sample size. Fourth, the level of the pulmonary valve was assessed just with the fluoroscopy and electroanatomical mapping, so we cannot be sure if some of the LVAs especially in the control group are not just the normal low voltage in the transitional zone. Finally, we did not perform a pharmacological test in patients with ST-segment elevation, which would be the only way to definitely rule out Brugada pattern. However, none of the patients presented with any of the additional criteria required in the current Guidelines[13] to perform the test, so, from a clinical point of view and due to the nonnegligible risk, we opted to not perform the test. Thus, although the presence of LVAs as well as the presence of ST-segment elevation were significantly more frequent in patients with VA from the RVOT, we think that further studies are needed to confirm these results, before assuming they represent a substrate for VAs.

6 | CONCLUSIONS

LVAs within the RVOT were frequently present in patients with idiopathic VA from this location. ST-segment elevation at the level of the 2nd ICS was the only independent predictor of their presence and performed well as a marker of these LVAs showing a good positive predictive value and a good specificity.

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CONFLICTS OF INTEREST

Lia Marques is technical support of Abbott and Sofia Mancelos is technical support of Biosense-Webster. The other authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Prolonged Right Ventricular Outflow Tract Endocardial Activation Duration and Presence of Deceleration Zones in Patients With Idiopathic Premature Ventricular Contractions. Association With Low Voltage Areas

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Background and Aims: The wavefront propagation velocity in the myocardium with fibrosis is characterized by the presence of deceleration zones and late activated zones, that are absent in the normal myocardium. Our aim was to study the right ventricular outflow tract (RVOT) endocardial activation duration in sinus rhythm, and assess the presence of deceleration zones, in patients with premature ventricular contractions (PVCs) and in controls.

Methods: We studied 29 patients with idiopathic PVCs from the outflow tract, subjected to catheter ablation that had an activation and voltage map of the RVOT in sinus rhythm. A control group of 15 patients without PVCs that underwent ablation of supraventricular arrhythmias was also studied. RVOT endocardial activation duration and number of 10 ms isochrones across the RVOT were assessed. Propagation speed was calculated at the zone with the higher number of isochrones per cm radius. Deceleration zones were defined as zones with >3 isochrones within 1 cm radius. Low voltage areas were defined as areas with local electrogram with amplitude <1.5 mV.

Results: The two groups did not differ in relation to age, gender or number of points in the map. RVOT endocardial activation duration and number of 10 ms isochrones were higher in the PVC group; 56 (41–66) ms vs. 39 (35–41) ms, $p = 0.001$ and 5 (4–8) vs. 4 (4–5), $p = 0.001$. Presence of deceleration zones and low voltage areas were more frequent in the PVC group; 20 (69%) vs. 0 (0%), $p < 0.0001$ and 21 (72%) vs. 0 (0%), $p < 0.0001$. The wavefront propagation speed was significantly lower in patients with PVCs than in the control group, 0.35 (0.27–0.40) vs. 0.63 (0.56–0.66) m/s, $p < 0.0001$. Patients with low voltage areas had longer activation duration 60 (52–67) vs. 36 (32–40) ms, $p < 0.0001$, more deceleration zones, 20 (95%) vs. 0 (0%), $p < 0.0001$, and lower

wavefront propagation speed, 0.30 (0.26–0.36) vs. 0.54 (0.36–0.66) m/s, $p = 0.002$, than patients without low voltage areas.

Conclusion: Right ventricular outflow tract endocardial activation duration was longer, propagation speed was lower and deceleration zones were more frequent in patients with PVCs than in controls and were associated with the presence of low voltage areas.

Keywords: premature ventricular beat, idiopathic, right ventricular outflow tract, deceleration zone, low voltage areas

INTRODUCTION

It is usually accepted that PVCs from the outflow tracts result from triggered activity and occur in structurally normal hearts (Lerman, 2015). Most studies with cardiac magnetic resonance (CMR) have failed to demonstrate the presence of structural abnormalities. Still, studies with intracardiac mapping have shown the presence of low voltage areas (LVA) (Yamashina et al., 2009; Furushima et al., 2012; Letsas et al., 2019; Parreira et al., 2019a,c, 2020). Whether these LVAs correspond to a form of incipient manifestation of a disease of the RVOT remains unproved. Also, it was previously pointed out that patients with frequent PVCs had worse RV global longitudinal strain values (and therefore sub-clinical myocardial dysfunction) than healthy controls patients with structurally apparent normal hearts, irrespective of the absence of abnormalities on the CMR (Fonseca et al., 2021). Fibrosis is associated with late local activation and areas of slow conduction and slower wavefront propagation speed, known as deceleration zones (DZ) (Raiman and Tung, 2018; Aziz et al., 2019). It has been previously observed that the velocity of the wavefront propagation of the PVC across the RVOT is slower in patients with PVCs from the RVOT than from the left ventricular outflow tract (LVOT), but the authors attributed this finding to the presence of differences in myocardial fiber orientation (Herczku et al., 2012; Masuda et al., 2018). However, this finding might be due to subtle disease of the RVOT manifested by the presence of LVAs. Based on previous studies it has become clear that activation delay is a hallmark of arrhythmogenic right ventricular cardiomyopathy (ARVC) (Tandri et al., 2009).

The aim of this study was to assess the pattern of propagation of the endocardial activation in RVOT looking for the presence of DZs in patients with PVCs and in controls and evaluate the association with the presence of LVAs.

MATERIALS AND METHODS

Study Population

From July 2019 to December 2020, we prospectively studied consecutive patients with symptomatic idiopathic frequent PVCs (>10,000/24 h) with a LBBB or RBBB, vertical axis, negative polarity in lead aVL, that were referred for catheter ablation by the same operator. Independently of the site of origin of the arrhythmia all patients had an electroanatomical activation and voltage map of the RVOT obtained in sinus rhythm This study was carried out in two hospitals. All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler study and 12-lead electrocardiogram (ECG). All patients in the PVC group had a CMR with late gadolinium enhancement (LGE) to exclude the presence of structural heart disease.

Arrhythmogenic right ventricular cardiomyopathy was ruled out according to the Task Force Criteria (Marcus et al., 2010). A 24-h Holter recording was performed before ablation and the number of PVCs per 24 h and the presence of episodes of non-sustained ventricular tachycardia (NSVT), defined as >3 PVCs in a run were assessed. Patients with evidence of structural heart disease, conduction delays, electrical diseases or abnormal QRS morphology, as well as patients with previous ablation were excluded.

A control group of consecutive patients without PVCs, that underwent catheter ablation of supraventricular tachycardias since 2019 and agreed to have an electroanatomical map of the RVOT obtained in sinus rhythm was also studied.

Study Design

We assessed the duration of the endocardial activation (AD) on the RVOT in sinus rhythm as well as the presence of DZ in patients with PVCs and in controls. The presence of low voltage areas (LVAs) in sinus rhythm was also assessed. We tested for the association between the AD and DZs and the presence of LVAs.

Electroanatomic Mapping and Ablation

Patients were studied in a fasting non-sedate state. All beta-blockers and antiarrhythmic drugs were discontinued at least five half-lives before the electrophysiological study. Diagnostic catheters were positioned via the femoral vein with fluoroscopic guidance in the His position and in the great cardiac vein via the coronary sinus. During endocardial mapping of the LVOT heparin was administrated to achieve an ACT of 250–300 s. After the completion of the sinus rhythm map, isoprenaline was administered intravenously, as needed, and titrated to a dose capable of inducing PVCs.

All patients underwent electroanatomical mapping with CARTO 3 (Biosense-Webster) or EnSite Precision (Abbott). With the former, all procedures were performed using the Niobe magnetic navigation system (Stereotaxis) working with the monoplane fluoroscopy system AXIOM Artis (Siemens) as previously described (Parreira et al., 2013). An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster) was used with a 3.5-mm distal tip electrode and a 2–5–2 interelectrode distance. With the EnSite Precision system all procedures were done manually with the monoplane fluoroscopy

system BV Pulsera (Philips) and using an irrigated tip FlexAbility catheter (Abbott) with a 4-mm distal tip electrode and a 1–4–1 interelectrode distance. The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT in the magnetic navigation system patients or manually in the EnSite patients, under fluoroscopic guidance. The ablation catheter was then placed at multiple sites on the endocardial surface of the RVOT. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed. During sinus rhythm two maps were created, activation and voltage map and during PVC, activation map.

All the intracardiac electrograms were reviewed by two senior electrophysiologists.

Sinus Rhythm Activation and Voltage Map

The sinus rhythm maps were obtained without isoprenaline. With the Carto system, local activation time (LAT) was defined as the time of the maximum downslope of the unipolar distal electrogram displayed on the corresponding bipolar signal. With the Ensite system LAT was defined as the time of the first peak of the bipolar electrogram (Kim et al., 2020). Total RVOT AD was measured as the time interval from the earliest RVOT endocardial activation to the latest RVOT endocardial activation recorded during sinus rhythm. The geometry of the RVOT depicting the LAT recorded was constructed in real time with the electrophysiological information color coded and superimposed on the reconstruction. The data derived from the isochronal map and analysis were obtained offline, and therefore, the procedure results were not dependent on these data. Activation isochronal maps were displayed as 10 ms isochrones, those maps were generated automatically with the Carto3 system. In the case of Ensite Precision the RVOT isochronal map was always displayed as eight 10 ms isochrones, considering the earliest isochrone the one encompassing the first 10 ms of activation time in the RVOT, and the last isochrone covering the latest activation time above 80 ms. Six other 10 ms isochrones were considered for LAT between those two extreme values. The total number of 10 ms isochrones across the RVOT was measured as well as the maximum number of 10 ms isochrones per 1 cm radius (Aziz et al., 2019). The propagation speed was assessed in the areas of the highest number of isochrones per cm radius. These areas with higher isochrone confluence per cm represent the areas with a slower conduction, and therefore, were the ones chosen to evaluate whether propagation speed was outside the accepted normal values of 0.62 ± 0.06 m/s previously described in normal myocardium (Brugada et al., 1991). The areas with abnormal wavefront propagation speed, known as DZs were defined as zones with > 3 isochrones within 1 cm radius (Aziz et al., 2019).

The electrograms were also analyzed in regard of their amplitude and the information was used to generate a 3-dimensional electroanatomical voltage map of the RVOT, with the electrophysiologic information, color-coded and superimposed on the geometry. The color display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude $\geq$ 1.5 mV), to red, representing electroanatomical scar tissue (amplitude $<$ 0.5 mV). LVAs were defined as areas with bipolar electrograms with an amplitude $<$ 1.5 mV. The level of RVOT/pulmonary valve junction was thoroughly determined based on electroanatomical voltage mapping by passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT. The voltage above the pulmonary valve is usually less than 0.5 mV. The area immediately below the level of the pulmonary valve displays intermediate colors, corresponding to a bipolar voltage between 0.5 and 1.5 mV, defined as the transitional-voltage zone (Yamashina et al., 2009). Presence of LVAs outside the transitional-voltage zone, were assessed.

The sinus rhythm maps were obtained in patients with PVCs and in patients from the control group.

PVC Activation Map and Ablation

The activation map was created by mapping several points during each PVCs while using a surface ECG lead as reference. The ablation site was selected based on the earliest endocardial activation time in relation to the onset of the surface QRS, with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous PVCs. Energy was delivered from an EP Shuttle RF generator (Stockert) between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 s, to a maximum temperature of 43°C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. Success was defined as abolition of PVCs under isoprenaline infusion until 30 min after ablation.

Statistical Analysis

All analyses were performed using SPSS statistical software, version 26.0 (SPSS, Inc., Chicago, Illinois). Data is presented as median and lower and upper quartile (Q_1–Q_3) for continuous variables, as median and minimum and maximum (min-max) for ordinal variables and as absolute numbers and percentages for binary variables. Continuous variables and ordinal variables were compared with the use of Mann Whitney test for independent samples. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples. The ROC curve was used to assess the cut point value of AD that ensures the presence of LVAS and its specificity and sensitivity based on 2×2 contingency table and chi square test. For all tests a two-tailed $p < 0.05$ was considered as statistically significant.

Ethics

All patients signed the informed consent form, and the study was approved by the Ethical Committee of both hospitals. The study is in compliance with the Helsinki Declaration.

RESULTS

Study Population

Forty-four patients were enrolled, 29 patients in the PVC group and 15 patients in the control group of whom, twelve underwent ablation of atrioventricular nodal reentrant tachycardia, one of atrioventricular reentrant tachycardia and two of typical atrial flutter. Physical examination, 12-lead ECG and transthoracic echocardiography were normal. Both groups did not differ in relation to age, gender, or other clinical, standard electrocardiographic and echocardiographic parameters (**Table 1**). PVCs originated in the RVOT in 23 patients and in the LVOT in six. In the PVC group, all patients were symptomatic, all complained of palpitations and one patient had one syncopal episode typically vagal in nature. No patient had family history of sudden death. The 24-h Holter recording showed a high PVC burden with a median of 21164 (15,000–28,750) PVCs/24 h and presence of NSVT in 11 patients (38%). The CMR did not show evidence of RVOT abnormalities in any patient.

Electroanatomic Mapping and Ablation

Activation and Voltage Map in Sinus Rhythm

The electroanatomical mapping in sinus rhythm was successfully acquired in all patients, the median number of points per patient, collected in the RVOT to obtain the map was 387 (340–506) and was not significantly different between patients with PVCs and the control group, respectively 412 (343–533) vs. 345 (339–450), $p = 0.193$ (**Table 2**). The earliest RVOT endocardial activation occurred anteriorly in the free wall, while the latest endocardial activation was observed at the subpulmonary valve areas in all cases. The median AD, the median number of 10 ms isochrones and the maximum number of 10 ms isochrones per 1 cm radius was significantly higher in the PVC group than in the control group, respectively, 56 (41–66) vs. 39 (35–41) ms, $p = 0.001$; 5 (4–8) vs. 4 (4–5), $p = 0.001$; 4 (3–6) vs. 3 (3–3), $p < 0.0001$ (**Table 2**). The maximum number of 10 ms isochrones per 1 cm radius observed in the control patients was three (**Figure 1**). DZs were present in 20 patients (69%) and LVAs in 21 patients (72%) in the PVC group (**Figure 2**), but both were absent in control subjects,

TABLE 1 | Baseline characteristics and comparison between PVC group and control group.

	Overall sample (n = 42)	PVC group (n = 29)	Control group (n = 15)	*P* value
Demographic data				
Age in years, median (Q_1–Q_3)	53 (35–65)	51 (37–65)	56 (28–66)	0.710
Male Gender, n (%)	20 (46)	14 (48)	6 (40)	0.752
Body surface area in m^2, median (Q_1–Q_3)	1.81 (1.59–1.92)	1.79 (1.57–1.95)	1.82 (1.60–1.95)	0.757
Risk factors and medications				
Hypertension, n (%)	17 (39)	10 (35)	7 (47)	0.521
Diabetes, n (%)	8 (18)	6 (21)	2 (13)	0.695
Betablockers, n (%)	25 (58)	18 (62)	7 (50)	0.521
Antiarrhythmic drugs, n (%)	9 (21)	8 (28)	1 (7)	0.231
12 lead ECG				
QRS duration in ms, median (Q1–Q3)	87 (80–90)	89 (80–90)	83 (80–90)	0.288
T wave inversion beyond V1, n (%)	0 (0)	0 (0)	0 (0)	
24-h holter monitoring*				
Number of PVCs, median (Q1-Q3)*	–	21164 (15,000–28,750)		
NSVT, n (%)*	–	11 (38)		
Echocardiogram				
LVEF in%, median (Q_1–Q_3)	58 (56–59)	57 (56–60)	58 (57–59)	0.416
LAD in mm, median (Q_1–Q_3)	35 (30–40)	37 (30–41)	33 (31–41)	0.121

**In the PVC group; LAD, left atrial diameter in parasternal view; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contractions.*

TABLE 2 | Sinus rhythm activation and voltage mapping data.

	Overall sample (n = 44)	PVC group (n = 29)	Control group (n = 15)	*P*-value
Number of points in the map, median (Q_1–Q_3)	387 (340–506)	412 (343–533)	345 (339–459)	0.193
RVOT activation duration in ms, median (Q_1–Q_3)	42 (37–60)	56 (41–66)	39 (35–41)	0.001
N° of 10 ms isochrones in the RVOT, median (min-max)	5 (4–8)	5 (4–8)	4 (4–5)	0.001
Max. n° of 10 ms isochrones per 1 cm radius, median (min-max)	3 (3–6)	4 (3–6)	3 (3–3)	< 0.0001
Propagation speed* in m/s, median (Q_1–Q_3)	0.40 (0.29–0.65)	0.35 (0.27–0.40)	0.63 (0.56–0.66)	< 0.0001
Presence of DZs, n (%)	20 (46)	20 (69)	0 (0)	< 0.0001
Presence of LVAs, n (%)	21 (48)	21 (72)	0 (0)	< 0.0001

**At the 10 ms isochronal confluence zone; DZ, deceleration zone; RVOT, right ventricular outflow tract; LVA, low voltage area; PVC, premature ventricular contractions.*

$p < 0.0001$. The propagation speed at the areas of confluence of 10 ms isochrones was significantly slower in patients with PVCs than in controls, 0.35 (0.27–0.40) vs. 0.63 (0.56–0.66) m/s, $p < 0.0001$.

Association Between Duration of Endocardial Activation in the RVOT and Presence of LVAs in Patients With PVCs

In the PVC group, the presence of LVAs was more frequent in patients with PVCs from the RVOT than in patients with PVCs from the left side, 83 vs. 33%, $p = 0.033$.

The longer the AD the higher the likelihood of displaying LVAs in the RVOT. According to the ROC curve the cut point value is above 42 ms, with a sensitivity and specificity of 100%, $p < 0.0001$. Patients with LVAs had a longer AD than patients without LVAS, 60 (52–67) ms vs. 36 (32–40) ms, $p < 0.0001$. All patients with LVAs had ADs above 42 ms (**Figure 3**), they also displayed a higher number of 10 ms isochrones across the RVOT and maximum number of 10 ms isochrones per 1 cm radius (**Table 3**). In twenty out of twenty-one (95%) was possible to identify the presence of DZs that were absent in all patients without LVAs, $p < 0.0001$. DZs occurred in areas of normal voltage in just two patient (10%) **Figures 4, 5**. The propagation speed at the zone with the higher number of 10 ms isochrones was also slower in patients with LVAs than in those without, 0.30 (0.26–0.36) vs. 0.54 (0.36–0.66) m/s, $p = 0.002$.

We found no association between the PVC burden and the presence of LVAs or DZ. The median number of PVCs in patients with LVAs was 21000 (13,887–28,750)/24 h vs. 23717 (18,196–29,375)/24 h in patients without LVAs, $p = 0.301$. The median number of PVCs in patients with DZs was 19082 (13,330–28,750)/24 h vs. 23134 (18,797–31,470)/24 h in patients without DZs, $p = 0.295$.

PVC Activation Map and Ablation

In the PVC group the electroanatomical mapping was performed with Carto 3 in 11 patients and with Ensite Precision in 18 patients. The earliest activation site was located in the RVOT septum in 15 patients, the RVOT free wall in 8 patients, the left coronary cusp in two, the LVOT in three and the LV summit in one. The access to the LVOT was obtained by retrograde transaortic approach in all six patients. The earliest activation site was located within the LVAs in 15 (52%) patients. This percentage increased to 71% in the group with LVAs. The earliest activation site was located in a DZ in 10 (35%) patients (**Figures 6, 7**), that displayed low voltage in 70% of cases (**Table 4**), and outside a DZ in 19 (65%) patients (**Figures 8, 9**). At the earliest activation site, the precocity of the LAT in relation to the onset of the surface QRS was −41 [−33–(−51)] ms. The median procedure time, fluoroscopy time and RF time were, respectively, 120 (90–130) min, 6 (4–11) min and 440 (223–648) s. The comparison between patients with DZ and patients without DZ is presented in **Table 4**. Success was achieved in 25 patients (86%) and was not associated with the presence of LVAs or DZs.

DISCUSSION

The first important finding of this study was the demonstration of a longer duration of the endocardial activation across the endocardium of the RVOT in patients with PVCs in comparison with the control subjects. To the best of our knowledge this is

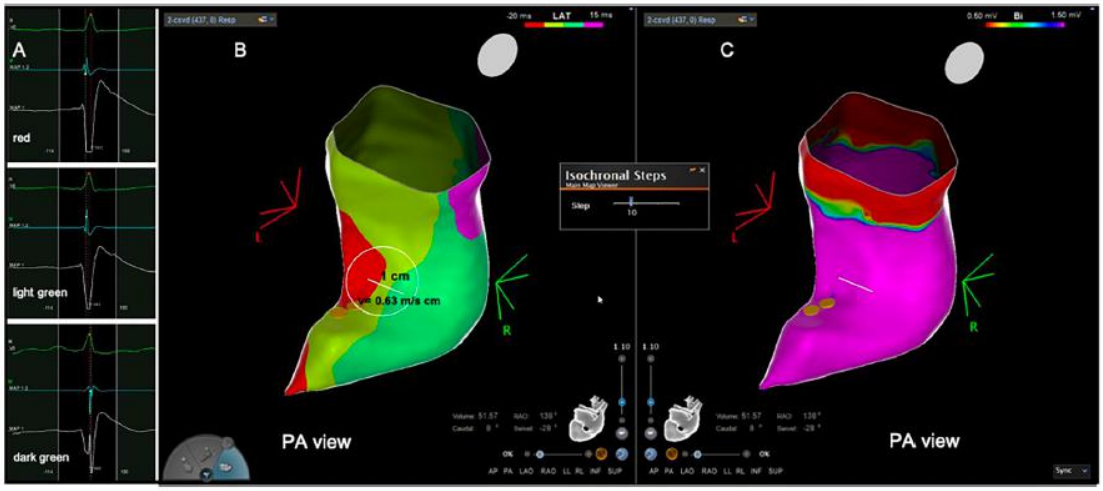

FIGURE 1 | Patient from the control group with normal activation and normal voltage. **(A)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. **(B)** RVOT isochronal map in sinus rhythm without DZ. **(C)** Voltage map in sinus rhythm without LVAs. Yellow dots in **(C)** His bundle tagging. DZ, deceleration zone; LVA, low voltage area; RVOT, right ventricular outflow tract.

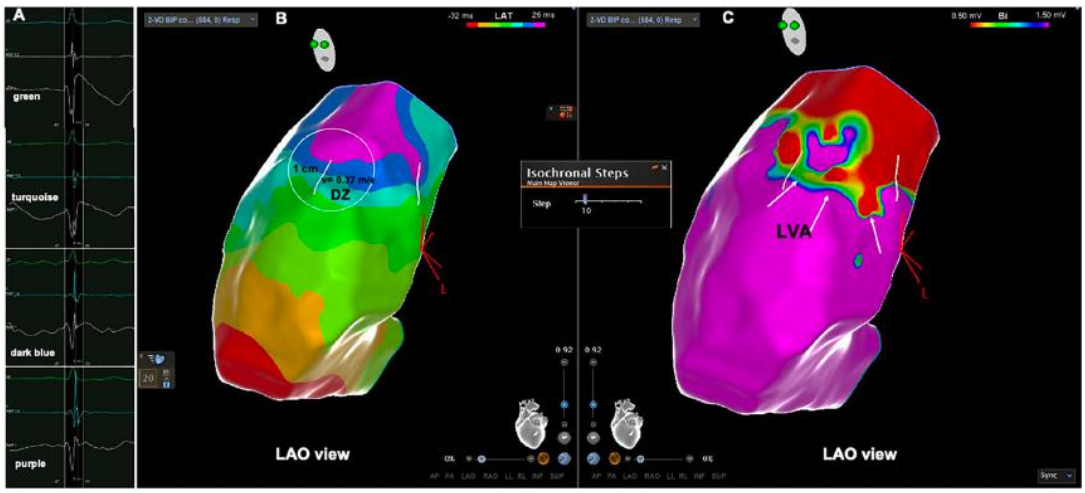

FIGURE 2 | Patient from the PVC group. **(A)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. **(B)** RVOT isochronal map in sinus rhythm with DZ in the RVOT free wall. **(C)** Voltage map in sinus rhythm with LVA at the same location. DZ, deceleration zone; LVA, low voltage area; RVOT, right ventricular outflow tract.

the first report assessing the propagation of the wavefront of endocardial activation in sinus rhythm in patients with PVCs from the RVOT in comparison with a control group without PVCs. In our group of patients, although the AD was significantly longer in the PVC group than in controls, it was nevertheless still within the normal range previously described by other authors (Tandri et al., 2009; Letsas et al., 2018). Tandri et al. (2009) studied a group of 25 patients with frequent left bundle branch block morphology premature ventricular complexes, 14 with ARVC and 11 with idiopathic PVCs. The authors evaluated the total right ventricular endocardial activation duration and observed that an AD higher than 65 ms was highly suggestive of ARVD and was never present in patients with idiopathic PVCs. The authors concluded that total right ventricular AD was a more sensible and earlier marker of disease than low voltage. Letsas et al. (2019) performed a high-density map of the RVOT in 8 patients with Brugada Syndrome and 20 patients with idiopathic PVCs. The mean RVOT endocardial activation time was significantly prolonged in patients with Brugada Syndrome in comparison with patients with idiopathic arrhythmias, 86.4 ± 16.5 vs. 63.4 ± 9.7 ms, $p < 0.001$. None of the above-mentioned authors have studied a population of normal subjects without PVCs, therefore, the value of 65 and 63.4 ms reported as normal might as well be augmented in relation to people without PVCs.

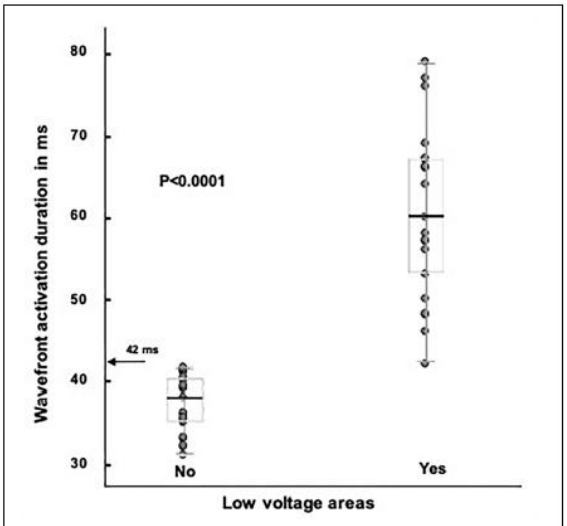

FIGURE 3 | Total RVOT endocardial activation time is significantly higher in patients with LVAs, $p < 0.0001$. The value of 42 ms was calculated with the ROC curve ($p < 0.0001$). None of the patients without LVAs had AD longer than 42 ms (arrow). LVA, low voltage area; RVOT, right ventricular outflow tract.

In a previous work using non-invasive mapping we observed the presence of abnormal electrophysiological characteristics in the RVOT in a group of seven patients with PVCs from the RVOT when compared with a control group. Although we could not demonstrate the presence of an activation delay, we found the presence of a higher dispersion of the activation recovery interval across the epicardium of the RVOT in patients with PVCs when compared to normal controls, suggesting once again the presence of an underlying substrate (Parreira et al., 2019b).

The second important finding of our study was the presence of DZs in the RVOT of patients with PVCs that were absent in the control group. Also, the median activation speed at the

TABLE 3 | Sinus rhythm activation data in the PVC group according to the presence of LVAs.

	Overall PVC Group (n = 29)	With LVAs (n = 21)	Without LVAs (n = 8)	*P*-value
Number of points in the map, median (Q_1–Q_3)	412 (343–533)	465 (366–533)	313 (214–544)	0.083
EAS in the RVOT, n (%)	23 (79)	19 (91)	4 (50)	0.033
RVOT activation duration in ms, median (Q_1–Q_3)	56 (41–66)	60 (52–67)	36 (32–40)	< 0.0001
N°of 10 ms isochrones in the RVOT, median (min-max)	5 (4–8)	6 (5–8)	4 (4–5)	< 0.0001
Max. n° of 10 ms isochrones per 1 cm radius, median (min-max)	4 (3–6)	4 (3–6)	3 (3–3)	< 0.0001
Propagation speed* in m/s, median (Q_1–Q_3)	0.40 (0.29–0.65)	0.30 (0.26–0.36)	0.54 (0.36–0.66)	0.002
Presence of DZ, n (%)	20 (69)	20 (95)	0 (0)	< 0.0001

**At the 10 ms isochronal confluence zone; EAS, earliest activation site; DZ, deceleration zone; LVA, low voltage area; RVOT, right ventricular outflow tract; PVC, premature ventricular contractions.*

FIGURE 4 | Patient from the PVC group with DZ outside the LVAs. **(A)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. **(B)** RVOT isochronal map in sinus rhythm with DZ in the RVOT free wall. **(C)** Voltage map in sinus rhythm with normal voltage at the DZ. DZ, deceleration zone; LVA, low voltage area; RVOT, right ventricular outflow tract.

areas with a higher confluence of isochrones, was significantly slower in the PVC group than in controls. The activation speed was particularly reduced at the zones with more than 3 isochrones per 1 cm radius (DZs) where it was half the previously accepted normal velocity of wavefront propagation (Brugada et al., 1991). The presence of DZs were associated with the presence of LVAs and were absent in patients without LVAs. Furthermore, the observed lower speed of the wavefront propagation, was worse in patients with PVCs that presented with LVAs than in those without LVAs. However, in 10% of cases the DZs occurred outside the LVAs and this was also described by Tandri et al. (2009) that observed that the presence of delayed activated areas was not always associated with decreased endocardial voltage and/or fractionated potentials. Even in the case of patients with structural heart disease as described by Aziz et al. (2019) DZ were present also in normal voltage zones. Voltage mapping is dependent on contact force, electrode area and orientation of the catheter tip in relation to the direction of the wavefront activation and so may be less accurate to evaluate substrate, whereas activation mapping is less dependent on these parameters (Aziz et al., 2019). But even the latter, is dependent on the methodology of LAT annotation and may be influenced by the presence of low amplitude pre-potentials, presence of multiple components or fractionated electrograms (Saba and Li, 2019).

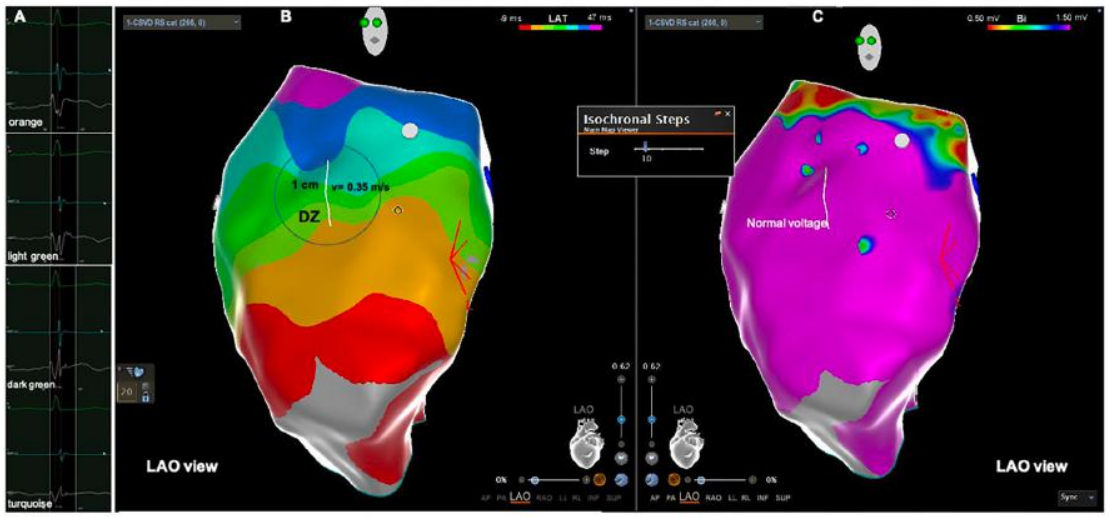

FIGURE 5 | Patient from the PVC group with DZ outside the LVAs. **(A)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. **(B)** RVOT isochronal map in sinus rhythm with DZ in the RVOT free wall. **(C)** Voltage map in sinus rhythm with normal voltage at the DZ. DZ, deceleration zone; LVA, low voltage area; RVOT, right ventricular outflow tract.

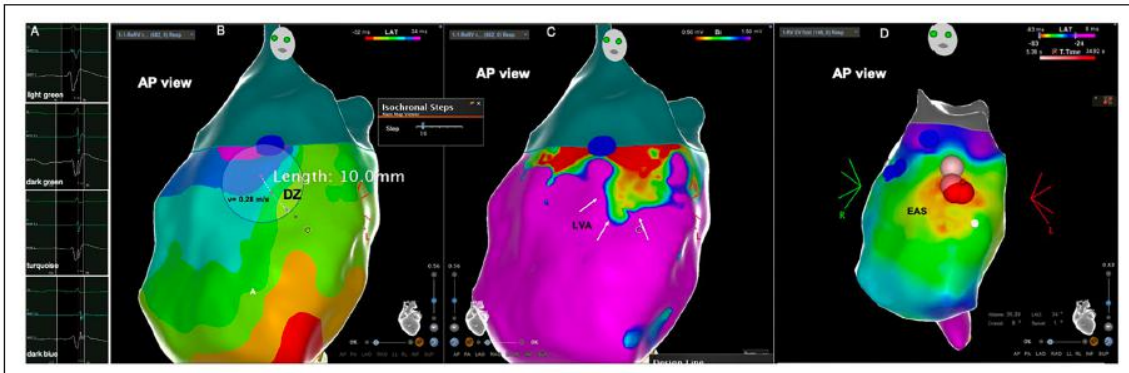

FIGURE 6 | Patient from the PVC group with DZ at a LVA and the earliest activation site located in that zone. **(A)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. **(B)** RVOT isochronal map in sinus rhythm with DZ in the RVOT free wall. **(C)** voltage map in sinus rhythm with LVA in the RVOT free wall. **(D)** Activation map during PVC showing the EAS at the DZ and LVA. Red and pink balls corresponding to radiofrequency application points. DZ, deceleration zone; EAS, earliest activation site; LVA, low voltage area; PVC, premature ventricular contractions; RVOT, right ventricular outflow tract.

Nevertheless, the absence of those findings in the control group speak against the hypothesis that the slower velocity and the DZ might be due to inaccurate measurements, or to the presence of the previously described anisotropic conduction in RVOT (Brugada et al., 1991).

Masuda et al. (2018) studied the velocity of propagation of the PVC in a group of 23 patients with idiopathic arrhythmias from the outflow tracts. Those authors assessed the propagation speed indirectly by measuring the areas encompassing the first 5, 10, 15, and 20 ms isochrones. Mapping of the RVOT during the PVC was performed using an ultra-high resolution electroanatomic mapping system. The wavefront propagation speed of the PVC over the RVOT was slower for PVCs originating from the RVOT than for PVCs originating from adjacent sites. The authors used this information to differentiate arrhythmias originating from the RVOT from the non-RVOT arrhythmias as previously described by Herczku et al. (2012) using a conventional mapping catheter in a point-by-point manner. Both groups explained their findings based on the myocardial fiber arrangement in the RVOT that leads to a different propagation speed according to the site of origin of the arrhythmia. Therefore, when the PVC originates in the LVOT

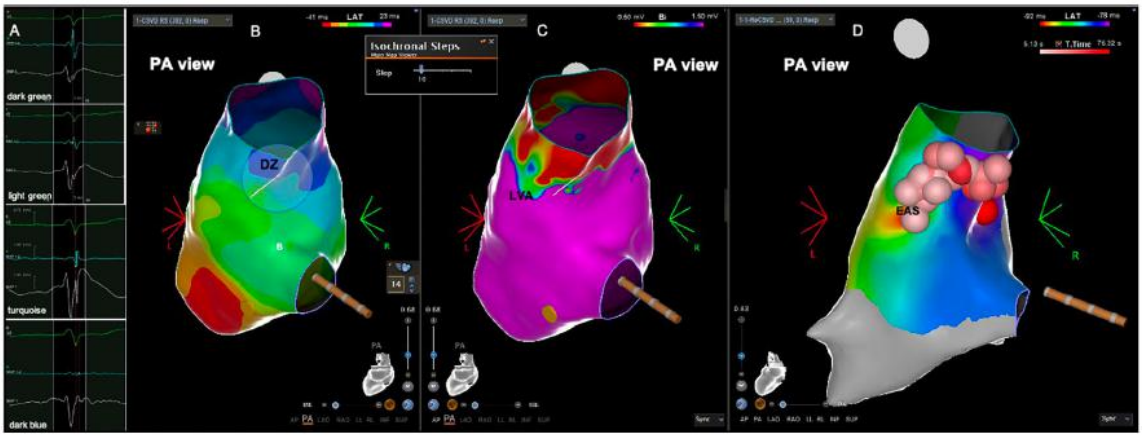

FIGURE 7 | Patient from the PVC group with DZ at a LVA and the earliest activation site located in that zone. **(A)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. **(B)** RVOT isochronal map in sinus rhythm with DZ in the RVOT posterior wall. **(C)** Voltage map in sinus rhythm with LVA in the RVOT posterior wall. **(D)** Activation map during PVC showing the EAS at the DZ and LVA. Red and pink balls corresponding to radiofrequency application points. DZ, deceleration zone; EAS, earliest activation site; LVA, low voltage area; PVC, premature ventricular contractions; RVOT, right ventricular outflow tract.

TABLE 4 | Activation mapping during PVCs and ablation data according to the presence of DZs.

	PVC group (n = 29)	With DZ (n = 20)	Without DZ (n = 9)	*p*-value
Carto/Ensite, n (%)/n (%)	11 (38)/18 (62)	7 (35)/13 (65)	4 (44)/5 (56)	0.694
PVCs from RVOT/LVOT, n (%)/n (%)	23 (79)/6 (21)	18 (90)/2 (10)	4 (44)/5 (56)	0.056
Presence of LVAs	21 (72)	20 (100)	1 (11)	< 0.0001
EAS in LVAs, n (%)	15 (52)	14 (70)	1 (11)	0.005
LAT at the EAS in ms, median (Q_1–Q_3)	−41 [−33–(−51)]	−42 [−35–(−50)]	−37 [−31–(−53)]	0.900
Procedure time in min, median (Q_1–Q_3)	120 (90–130)	120 (88–145)	120 (90–125)	0.934
Fluoroscopy time in min, median (Q_1–Q_3)	6 (4–11)	5 (4–10)	8 (4–12)	0.637
RF time in min, median (Q_1-Q_3)	440 (223–648)	430 (270–612)	565 (157–690)	0.760
Success, n (%)	25 (86)	17 (85)	8 (89)	1.000

EAS, earliest activation site; DZ, deceleration zone; LAT, local activation time; LVA, low voltage area; LVOT, left ventricular outflow tract; RF, radiofrequency; RVOT, right ventricular outflow tract; PVC, premature ventricular contractions.

it reaches the RVOT through multiple connections and the activation becomes faster in this case.

On the contrary, we believe that this slower conduction is related to the presence of a pathological substrate in the RVOT rather than a difference in the connections between the origin of the arrhythmia and the RVOT. In fact, in our study group the presence of a longer AD was significantly associated with the presence of LVAs. Previous studies have shown the presence of LVAs in the RVOT of patients undergoing catheter ablation of frequent PVCs despite normal CMR (Yamashina et al., 2009; Furushima et al., 2012; Letsas et al., 2019; Parreira et al., 2019a,c, 2020). The presence of LVAs did not match the results of the CMR in any of the studies. So, it may seem difficult to support that the activation delay represented by DZs is secondary to local fibrosis. However, very subtle interstitial fibrosis cannot be completely excluded, and our findings may suggest the presence of an underlying substrate too subtle to be identified by CMR techniques. In fact, the type of interstitial fibrosis that occurs in the initial phases of ARVC is not reliably detected with CMR with LGE (Puntmann et al., 2016). Using two-dimensional speckle tracking echocardiography (2D-STE) Fonseca et al. (2021) in a previous study have demonstrated that the right ventricle global longitudinal strain was significantly lower in patients with RVOT PVCs when compared with a control group, irrespective of the previous PVCs burden and success of the catheter ablation procedure. Concerning strain values determined by CMR, Zghaib et al. (2018) have previously demonstrated, in ARVC patients, that lower regional strain could identify low voltage areas on endocardial and epicardial electroanatomical mapping and had a better correlation with VT substrate than late gadolinium enhancement sites. These subtle morphological abnormalities may be the cause for the abnormal wavefront propagation observed in our population. These LVAs have been suggested as a target for ablation in case of low PVC burden during the procedure (Wang et al., 2016; Letsas et al., 2019). The way these findings might explain

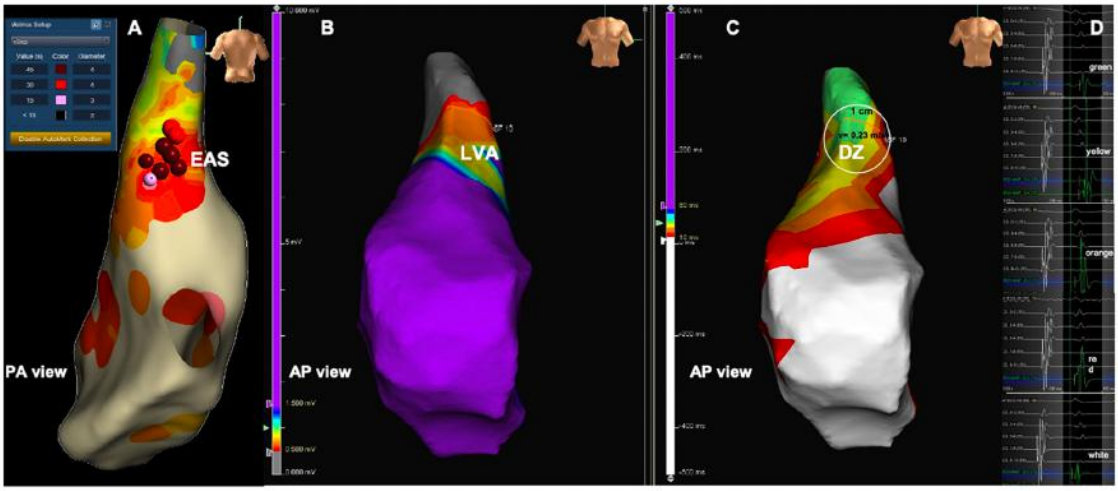

FIGURE 8 | Patient from the PVC group with DZ at a LVA but the earliest activation site located outside the DZ. **(A)** Activation map during PVC showing the EAS in the RVOT posterior wall. **(B)** Voltage map in sinus rhythm with LVA in the RVOT anterior wall. **(C)** RVOT isochronal map in sinus rhythm with DZ in the RVOT anterior wall. **(D)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. Red and pink balls in **(A)** corresponding to radiofrequency application points. DZ, deceleration zone; EAS, earliest activation site; LVA, low voltage area; PVC, premature ventricular contractions; RVOT, right ventricular outflow tract.

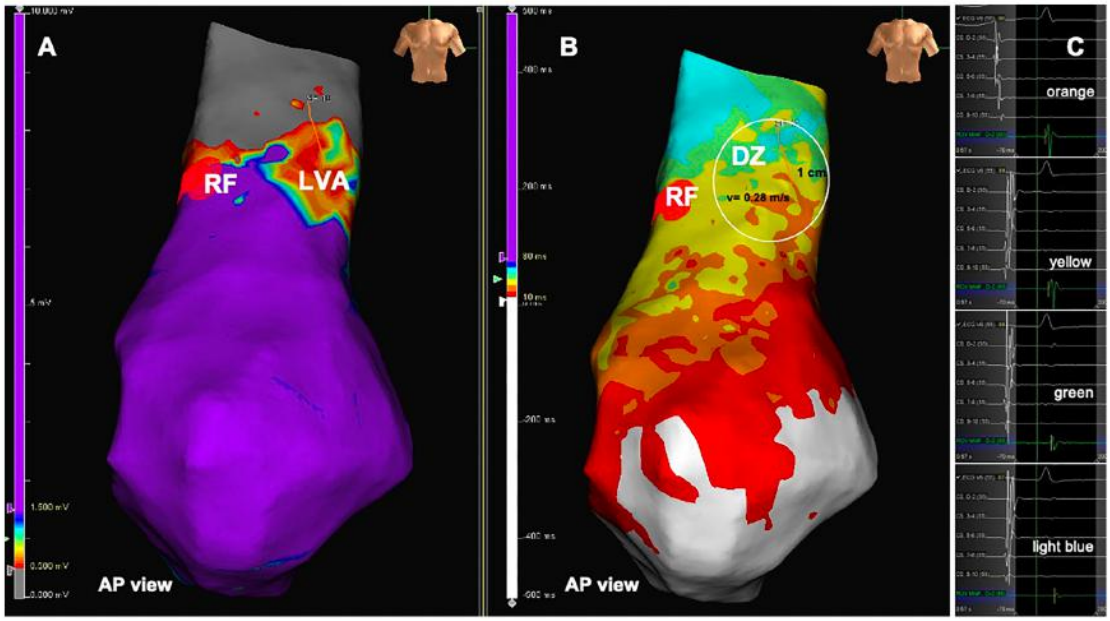

FIGURE 9 | Patient from the PVC group with DZ at a LVA but the earliest activation site located outside the DZ. **(A)** voltage map in sinus rhythm with LVA in the RVOT free, red dots at site of origin of the PVCs. **(B)** RVOT isochronal map in sinus rhythm with DZ in the RVOT free wall, red dots at the site of origin of the PVCs outside the DZ. **(C)** Intracardiac electrograms corresponding to the respective isochrones presented in the isochronal map. Red dots in **(A,B)** corresponding to radiofrequency applications. DZ, deceleration zone; EAS, earliest activation site; LVA, low voltage area; PVC, premature ventricular contractions; RF, radiofrequency applications; RVOT, right ventricular outflow tract.

the occurrence of the PVCs is controverse. Usually, conduction delay and deceleration zones are associated with re-entry (Aziz et al., 2019) and idiopathic PVCs are considered to be due to a triggered mechanism. However, we can speculate that not all patients with PVCs from the outflow tracts share the same mechanism. Probably some of them, maybe a minority are truly idiopathic with a triggered mechanism, but the majority display these conduction and voltage abnormalities that can be viewed as potential candidates for ablation. Wang et al. (2016) have shown that the SOO is located in low-voltage areas (amplitude < 0.5 mV) in 3% of patients, in transitional voltage zone (amplitude between 0.5 and 1.5 mV) in 89% of patients, and in high-voltage areas (amplitude > 1.5 mV) in 8% of patients. Likewise, Letsas et al. (2019) identified LVAs mainly located below or at the level of pulmonary valve in 39 of 44 patients and in 5 patients the voltage at the successful ablation site was normal.

In line with these previous studies, we have also noted that the earliest activation site was found to be located outside the DZ and LVAs in half the patients. Thus, it is difficult to accept that the DZ and LVAs are responsible for the PVCs in all cases. A second hypothesis to explain the presence of LVAs and DZs is that they are not the cause of the PVCs but rather the result of the electric remodeling triggered by the frequent PVCs. The median PVC burden in our group was 21164 PVC/24 h PVC. A higher PVC burden can be associated with an excess mortality in idiopathic patients (Parreira et al., 2021b), and a burden over 20,000 PVCs/24 h is associated with a higher risk of PVC-related cardiomyopathy (Nielsen et al., 2020). Fibrosis leads to conduction abnormalities and it may be the substrate for the presence of DZs, delayed activation and slower conduction, and these abnormalities may be a consequence of fibrosis and not implicated in the genesis of the PVCs. So, it remains to be demonstrated if the delayed activation and presence of DZs may denote the presence of a subtle substrate for the PVCs or the electrical and anatomical remodeling as a consequence of the high PVC burden. One way or the other, those patients should continue to be closely followed after ablatio to evaluate the evolution of the disease.

LIMITATIONS

Two mapping systems were used with different annotation methodologies. However, assuming that the methodology is consistent for all mapping points acquired with each system, the activation duration and the presence of DZ representing intervals rather than absolute values are perfectly comparable. Thus, although the minimal and maximal absolute values may be different between systems in absolute terms, the AD and 10 ms isochrones are independent of the annotation methodology.

Another limitation is the definition of DZs as more than three isochrones per 1 cm radius. This value was based on previous studies in patients with structural heart disease and may underestimate the presence of slow conduction in patients with idiopathic PVCs. However, in our group none of the normal subjects had less than three isochrones per 1 cm radius so considering abnormal a number above three seems adequate.

Finally, it would be interesting to investigate whether these abnormalities persist after ablation of the PVCs however, using invasive electroanatomical mapping to achieve that goal would be ethical unacceptable, leaving space for other techniques like for instance non-invasive mapping, echocardiographic longitudinal strain and CMR.

CONCLUSION

Patients with PVCs display a longer duration of the right ventricular outflow tract endocardial activation than controls, with presence of deceleration zones corresponding to zones with abnormal activation speed. Deceleration zones are present exclusively in patients with PVCs and occur mostly at LVAs. However, only half the patients present the SOO of the PVCs in those zones.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hospital Luz Ethical Committee and Hospital Center of Setubal Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LP: conceptualization, methodology, and writing. LP, PC, RM, DM, JF, AE, PAm, AF, and MF: investigation. RM, DM, RC, and PAm: reviewing. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

MAPPING THE REPOLARIZATION NONINVASIVELY WITH THE EPICARDIAL AND ENDOCARDIAL MAPPING SYSTEM- A VALIDATION STUDY

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Background and aims

The non-invasive endocardial and epicardial electrocardiographic imaging system (ECGI) is capable of displaying an automatic panoramic view of the ventricular repolarization. It is simple and can provide valuable information into the arrhythmia substrate. However, although this method has been extensively validated for the assessment of depolarization, regarding repolarization there is a lack of validation studies.

Purpose

The aim of this study was to validate the measurements obtained with the ECGI by comparison with the ones obtained invasively with the electroanatomical mapping system.

Methodology

POPULATION

- We studied the repolarization pattern in patients that underwent ablation of premature ventricular contractions of the right ventricular outflow tract (RVOT) and performed an ECGI exam before the procedure.

SEGMENTATION

- The RVOT was divided into 8 segments. (Figure 1)

ECGI

- ECGI was performed with the AMYCARD system, based on body surface electrocardiograms of a maximum of 224 electrodes and computed tomography imaging data. (Figure 2)

INVASIVE MAPPING

- Electroanatomical mapping with Carto 3 and Stereotaxis (Figure 3)

REPOLARIZATION EVALUATION

- Repolarization across the RVOT was measured by the activation recovery interval (ARI), calculated as the difference between the recovery time (RT) and the activation time (AT).
- The AT was defined as the time of maximal negative slope of the electrogram (EGM) during QRS, and the RT as the time of maximal positive slope of the EGM during T wave..
- These intervals were automatically obtained with the ECGI and manually calculated from the extracted invasive unipolar electrograms at the exact same site, using the MATLAB. We assessed the correlation between the measurements obtained with both methods. (Figure 4)

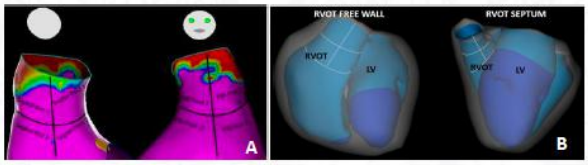

Figure1: Segmentation of the RVOT. Panel A: Carto; Panel B ECGI

Figure 2: ECGI

Figure 3: Stereotaxis and Carto mapping

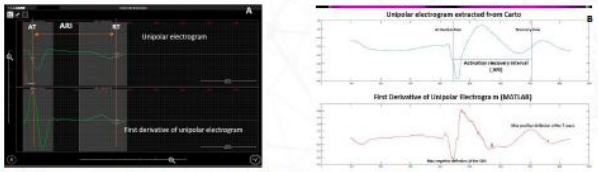

Figure 4: Automatic AT and RT calculation with the ECGI system by the analysis of the first derivative of the unipolar electrogram. Calculation of the AT and RT of the imported c«Carto Unipolar electrogram using MATLAB

Results

- We assessed the ARI in 64 segments in 8 patients, median age 50 (42-63) years, 4 males.
- The median absolute value of ARI measured with the ECGI was significantly higher than the ARI assessed from the intracardiac unipolar electrogram, respectively, 332 (320-364) ms and 312 (292-333) ms, p<0.001.
- However, we found a good correlation between both forms of measurement (R=0.614, p<0.001).

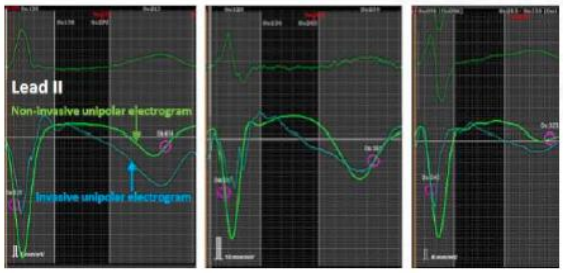

Figure 5: Three examples of ECGI and the Carto unipolar electrograms overlaying.

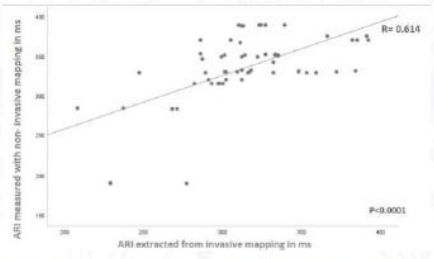

Figure 6: Correlation between ARI automatic measurements by ECGI and ARI calculated from intracardiac extracted electrograms

Conclusion

The automatic measurement of ARI with the ECGI showed a good correlation with the intracardiac measurements.