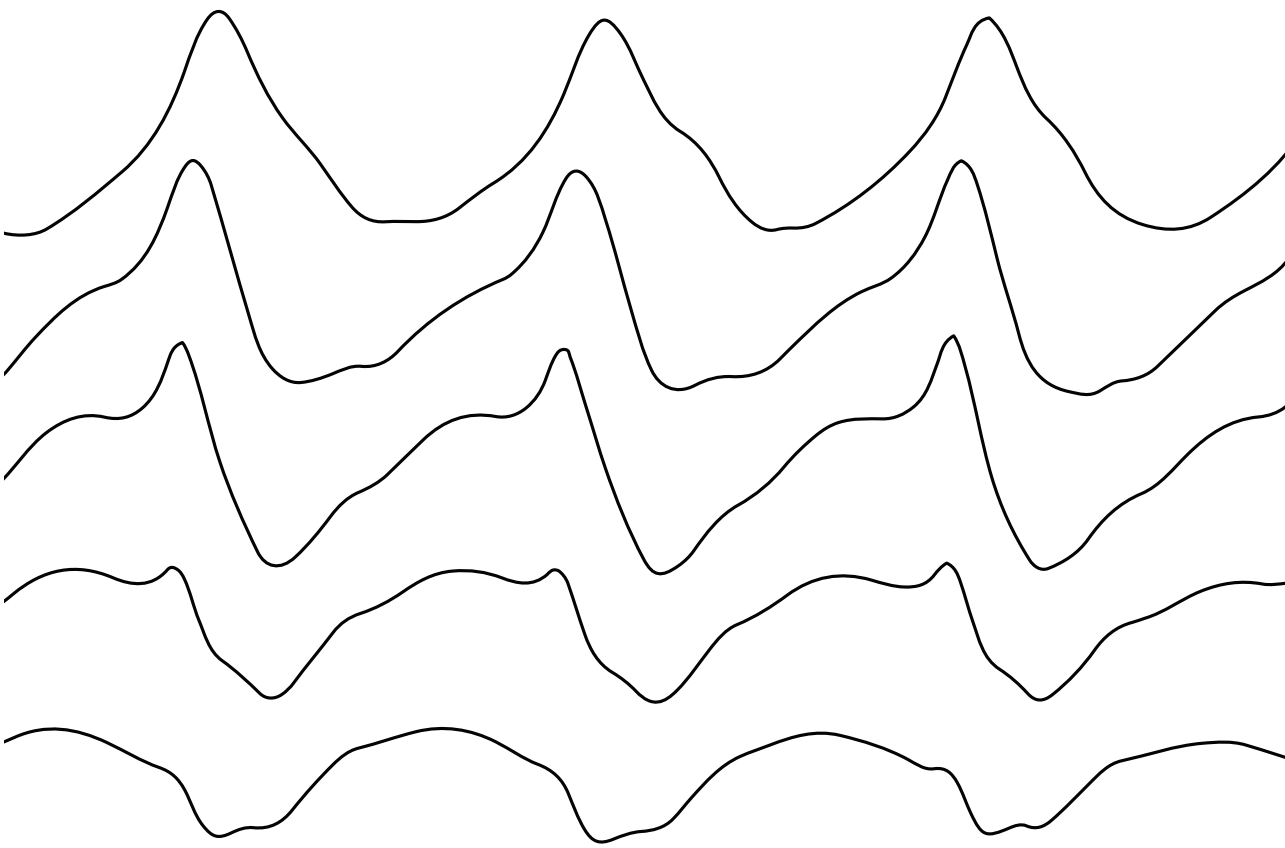
New insights and methods in the treatment of scar related arrhythmias

Astrid Armanda Hendriks



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Nieuwe Inzichten en Methoden
in de Behandeling van Litteken
Gerelateerde Aritmieën

Astrid Armanda Hendriks

New Insights and Methods in the Treatment of Scar Related Arrhythmias

Nieuwe Inzichten en Methoden in de Behandeling van Litteken Gerelateerde Aritmieën

THESIS

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I dedicate this thesis

To my grandfather

For Dienesh and Ravi

Contents

Introduction and outline of thesis

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chapter 1

Background

Ventricular tachycardia (VT) typically occurs several years after a patient survives a myocardial infarction (MI). VT may present as a single episode or as a clustering of multiple episodes known as electrical storm (ES). ES is a state of electrical instability and is characterised by 3 or more episodes of VT or ventricular fibrillation (VF) within 24 hours.[1] The implantable cardioverter defibrillator (ICD) can effectively terminate ventricular arrhythmia, however it will not eliminate or modify the trigger or substrate of ES.[2] Mortality in the early and subacute phase of ES is high.[3] Treatment of ES can be very complex and entails the administration of anti-arrhythmic drugs (AAD), suppression of sympathetic tone and sometimes urgent catheter ablation (CA). Furthermore patients with ES are in need of a tailored approach. A select patient group presenting with ES benefits from a CA intervention.[4] CA has shifted from a last resort treatment towards an early treatment strategy.[5] CA is reported to decrease the likelihood of subsequent ICD shocks. It prolongs the time to VT recurrence and decreases VT burden.[6-8]

Catheter ablation

Episodes of monomorphic VT in patients with post MI scar are characterised by re-entry. Post MI scar is complex and leads to VTs emanating from re-entry path with multiple and interconnected circuits with numerous entrances, exits and dead-end tracts.[9,10] Therefore besides targeting the critical isthmus of a clinical VT, targeting the substrate during CA is also of critical importance.
Optimizing the outcome of VT ablation remains a challenge. Longterm outcome is hampered by diagnostic inaccuracy, ablation approach and ablation technique. Diagnostic accuracy can be improved by better visualisation of the substrate and

identification of critical parts of the scar. A substrate ablation approach leads to an improved outcome compared to an approach targeting the critical isthmus of the VT only.[11] Multiple forms of substrate ablation have been described such as: substrate homogenisation, elimination of abnormal potentials and scar de-channeling. All aiming to thoroughly abolish any abnormal electrical activity.[12] An incomplete substrate approach may subsequently lead to incomplete abolition of VTs. Combined endo -epicardial ablation in post MI VT was shown to be beneficial especially in the setting of transmural scars.[13] Despite endo -epicardial ablation, ablation lesions do not necessary penetrate the complete myocardial wall and midmyocardial VT circuits may be left untouched.[14] Finally, for optimal outcome in VT ablation improving lesion formation is needed. Optimal wall contact during ablation is mandatory. Excursion of the ventricle, especially during tachycardia, may lead to an unstable catheter position. An unstable catheter position results in intermittent impaired energy delivery and subsequent inadequate lesion formation.[15] Wall contact during myocardial contraction can be maintained by remote magnetic navigation (RMN).[16] Effective lesion formation is enhanced by the knowledge of good contact with the myocardial wall.[17] Optimal contact is equally important in adequate three-dimensional electro-anatomic mapping (EAM).[18] Ideally, contact force (CF) sensing is integrated in RMN as both entities could magnify the benefit of remote magnetic navigation. Contact feedback only became available recently with the development of the e-Contact Module (ECM).

Visualising the substrate

Performing a cardiac magnetic resonance (CMR) remains a challenge in patients implanted with an ICD, however it is not impossible. The ICD artefact most commonly affects the basal left anterior free wall.[19] Computed tomography (CT) has the advantage of not being limited by ICD artefacts. Relatively preserved wall thickness on CT correlates with ridges within areas of pronounced wall thinning in the scar. These areas of preserved wall thickness have been recognized as the arrhythmogenic substrate of scar-related VT.[20]
In patients with VT after MI both modalities of imaging help to identify, delineate and characterize the scar. An electro-anatomical map (EAM) aids to define the scar and the border zone of the scar. Yet, scar is 3-dimensional and a voltage map is limited in spatial resolution.[21] Moreover arrhythmogenic substrate may be found in heterogeneous tissue with normal voltages.[22] In the era of revascularized MI, limited and inhomogeneous substrate is more frequently seen. In addition, inhomogeneous substrate is often more difficult to diagnose with bipolar EAM. Borderzone channels of inhomogeneous scar may be better depicted by contrast enhanced CMR.[23]
With pre-procedure imaging, imaging modalities can guide towards the best ablation approach. Integrating imaging in the procedure and visualising myocardial scar real time, facilitates VT ablation by focusing on the area of interest and providing more accurate substrate characterization.

A substrate approach

A substrate approach precludes the need for support devices during hemodynamically intolerant scar related VT ablation. Also ongoing scar related intra-atrial re-entry tachycardia during ablation, in patients with corrected congenital heart disease, can result in hemodynamic instability. Not only patients with scar related VT benefit from a substrate ablation approach, but also patients with scar from corrected congenital heart disease and atrial arrhythmias may be treated with scar dechanneling.

Aim and outline of thesis

The present thesis aims to contribute to the current attitude and approach to scar related arrhythmia. We investigate the role of remote magnetic navigation, contact force, a substrate approach and image-integration in patients with scar related atrial and ventricular arrhythmias.

In **Part 1**, the outcome of ventricular tachycardia (VT) ablation is studied, and how remote magnetic navigation (RMN) and contact force (CF) can influence the outcome. **Chapter 2** provides a detailed overview on the role of catheter ablation for ventricular tachycardias for the treatment of patients with electrical storm. **Chapter 3** highlights the triggers and mechanism leading to ES and their consequent treatment options. Conservative treatment and early and delayed catheter ablation in the outcome of patients with electrical storm is compared in **Chapter 4**. In **Chapter 5** and **6**, CF is compared to RMN in a population with idiopathic ventricular arrhythmia (VA) and a population with all different types of VA respectively. CF is integrated in RMN and the benefit of the e-contact module in ischemic VT is discussed in **Chapter 7**.

Part 2 descripes imaging, endo- epicardial VT ablation and their common denominator. The role of imaging guided ablation for scar-related VT will be systematically discussed and in **Chapter 8** imaging guided and non imaging guided VT ablation is compared in a meta-analysis. In **Chapter 9** a study design is presented, a combined endo- epicardial ablation as a first procedure is randomised to a stepwise approach in a population with ischemic VT. **Chapter 10** shows a case series of potential life-threatening complications of epicardial VT ablation.

In **Part 3**, the focus is on the substrate. **Chapter 11** paraphrases the role of delayed-enhancement magnetic resonance imaging in atrial fibrillation ablation. Substrate ablation as described in **Chapter 12**, can be used in the treatment of intra-atrial re-entrant tachycardia (IART) for patients after congenital heart surgery. In **Chapter 13** it is shown how IART can deteriorate the hemodynamic status of a patient with a Fontan circulation, and how a percutaneous left ventricular assist device aids to an IART ablation.

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chapter 1

part 1

Outcome of VT ablation, and the role of magnetic navigation and contact force

In the eye of the storm, however, it is uttermost serene

Remember that the storm is a good opportunity for the pine and the cypress to show their strength and their stability.

Ho Chi Minh

The role of catheter ablation of ventricular tachycardias in the treatment of patients with electrical storm

2

chapter 2

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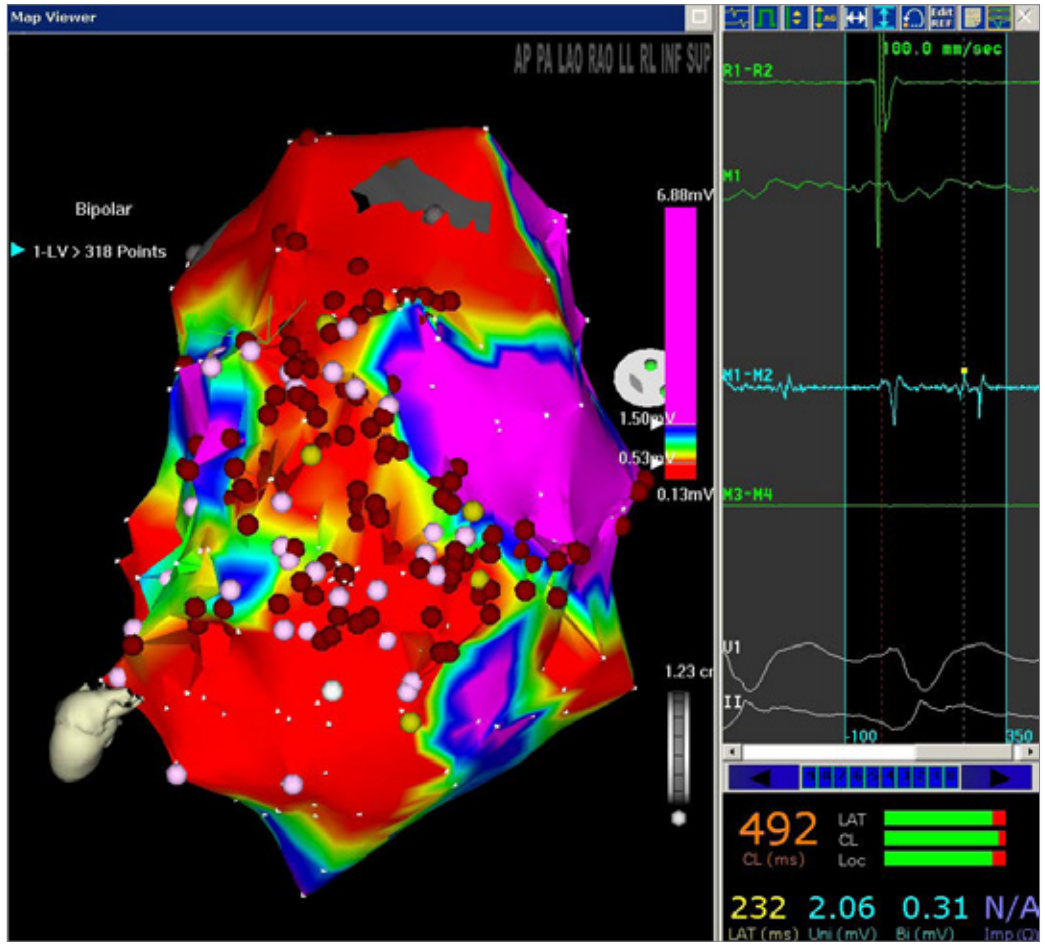
Abstract
Electrical storm due to the development of repetitive sustained ventricular tachycardias (VT) is a potentially life-threatening clinical entity. Acute catheter ablation can be lifesaving. Electrical storm (ES) can be characterized as a period of severe cardiac electrical instability manifested by recurrent ventricular arrhythmias. ES adversely affects short and long term prognosis. The highest mortality risk is in the first 3 months after the occurrence of the index event as shown by the AVID trial. The appearance of a ventricular tachycardia (VT) storm is associated with a rather high mortality despite the presence of an internal cardioverter defibrillator. Catheter ablation (CA) in VT storm is evolving as a standard of care therapy. The increased utilization of CA is partly driven by data suggesting that ICD shocks may be associated with increased mortality, partly due to the limited possibilities and adverse events of medical therapy. The aim of this review is to summarize recent advances in CA of VTs in emergency setting.

Background
Since electrical storm due to the development of life threatening sustained ventricular tachycardias is a cardiac emergency, acute catheter ablation can be lifesaving. Electrical storm (ES) can be characterized as a period of severe cardiac electrical instability manifested by recurrent ventricular arrhythmias.[1] The development of ES has a strong negative impact on the outcome of patients. The highest mortality risk is in the first 3 months after the occurrence of the index event as shown by the AVID trial.[2] Although the presence of implantable cardiac defibrillator decreases mortality, it is also not without risks. Indeed, the increased utilization of catheter ablation (CA) is partly driven by data suggesting that ICD shocks may be associated with increased mortality, partly due to the limited possibilities and adverse events of medical therapy. Every defibrillator shock therapy multiplies the mortality risk by direct cell injury.[3,4,5] Other mechanisms how ES directly affects patient prognosis is by progressive deterioration of cardiac function from prolonged low-output states, and/or an adverse haemodynamical effect of antiarrhythmic medication[6] and thus, CA may become a life-saving procedure for these patients.

Mechanism of VT in electrical storm
The term "electrical storm" indicates a state of cardiac electrical instability manifested by several distinct episodes of VTs within a short period of time.[1] In patients with an ICD, ES is best defined as 3 or more appropriate VT detections in 24 hours, treated by antitachycardia pacing, shock or eventually untreated, but sustained in a VT monitoring zone. Incessant VT, defined as VT starting shortly (after ≥1 sinus cycle and within 5 minutes) after a technically successful therapy, represents a serious form of electrical storm. Ventricular monomorphic tachycardia is the most common arrhythmia in patients with an electrical storm, and reentry is the most common underlying mechanism.[7]
Scarring—i.e. the development of fibrous tissue is the anatomical and electrophysiological substrate. It is therefore also the target for CA. Other targets can be premature ventricular contractions (PVC), since those can trigger sustained arrhythmias.[8] The study Hayashi et al. that investigated ES in acute heart failure, described PVC arising from the Purkinje fibers that not only triggered VF but also for about 30% of the monomorphic VTs.[9] Likewise early post-myocardial infarction (MI) incessant VT is mostly triggered by PVC.[10,11] In these patient categories targeting the PVCs resulted in a reasonable ablation success.[9,10,11]

VT ablation in electrical storm
In electrical storm catheter ablation has been considered as a realistic and valid treatment option.[7] Carbuccio et al.[12] have shown the superiority of CA to conventional medical therapy (92% and 66%, respectively). CA is lifesaving; it also improves quality of life and reduces the recurrent VA episodes.[13] A systematic review by Nayar et al. included 39 studies with 471 ventricular arrhythmia (VA) storm patients concluded that ventricular arrhythmia storm ablation has high acute success rates, with a low rate of recurrent storm.[14] They found high acute success rate of invasive management of VA storm, with 91% of patients having elimination of the clinical VA and 72% of patients having all inducible VA eliminated. Ninety-four percent of the patients were free from VA storm on follow-up.
For the better success rates sometimes multiple procedures (1.3 + 0.4 per patient) are needed.[14] In the study of Carbuccichio et al. one to three procedures were needed to suppress clinical VTs in 89% of patients.[12] Among the patients with all clinical VTs abolished during the ablation, no recurrence of electrical storm

Figure 1 Three dimensional electro-anatomical map



Three dimensional electro-anatomical map of a LV ventricle in a patient with a large scar (red). LAVAs (local abnormal ventricular activities) are tagged with white colors. The patient had multiple morphologies of ventricular tachycardias. Extensive scar ablation (dark red dots) in an emergency setting rendered all tachycardias non-inducible.

occurred during the follow-up period, and the mortality was significantly lower compared to those who showed persistent inducibility of ≥1 VT at the end of the procedure. Interestingly enough, Kozeluhova et al. found non-inducibility of the VT at the end of the study was not predictive of ES or VT recurrences during follow-up which might be explained by the inclusion of not only monomorphic VT but also polymorphic VTs.[6] Despite a remarkable initial success rate in VT ablation patients in ES, only a moderate long term efficacy at follow-up has been reported.[15] Especially non-ischaemic dilated cardiomyopathy, is reported to be an independent predictor of failure of CA procedure in patients with ES.[12] Arya et al. reported an excellent survival rate after successful CA procedures in patients with non-ischemic dilatated cardiomyopathy. Probably more aggressive ablation strategies targeting all inducible VTs may be appropriate as it improves long term freedom from VTs.[16] The same group evaluated Long term efficiency of CA using remote navigation in

VT ablation in patients with ischemic heart disease and ES. During a mean followup of 7.8 months, 21 patients (70%) had no recurrence of VTs and received no appropriate ICD therapy. Multisite stimulation induction method was found very useful in assessment of the success of CA procedure.[17] The authors concluded that a significantly more aggressive ablation strategy, including epicardial mapping and ablation of all inducible VTs, may improve the ablation outcome especially among those who had an initially failed ablation procedures.[17] Di Biase et al. compared endocardial surface with limited substrate ablation to endocardial and epicardial scar homogenization in patients with an electrical storm and an underlying ischemic cardiomyopathy. A significant difference in outcome was observed after 25 months (p = 0.006) in favour of the endo/epicardial homogenization group.[13] Limited substrate ablation abolishes circuits relevant to the arrhythmia burden at the time of the procedure, but more extensive ablation endo- and epicardial substrate homogenization may be more successful at long term.[12]

CA for hemodynamically unstable VTs

Acute cardiac decompensation can be either a cause or a consequence of ES. Unstable and decompensated patient is an important sub-entity of ES.[18] Urgent radiofrequency catheter ablation in the setting of an acute heart failure (AHF) decompensation in patients with monomorphic VT was found safe, with the exception for a temporary exacerbation of pulmonary congestion in 20% of the patients.[9] Urgent RFCA for drug-resistant sustained ventricular tachyarrhythmias during AHF decompensations is a feasible therapeutic option.[8] In this study PVCs were found responsible for the ventricular arrhythmias and targeted for ablation. In monomorphic VT percutaneous left ventricular assist device-assisted VT ablation is a reasonable alternative to substrate mapping for haemodyanamically unstable, medically refractory VT in high-risk patients.[19] Of all ES studies 23% of all patients required major invasive haemodynamic support during the procedure.[14] Hemodynamic support is crucial for this patient population.
It can be achieved in the form of counter pulsation balloon pump, Impella device or by LVAD.[19,20]

Long term prognosis after CA of electrical storm patients

VT free long term survival may be improved by early invasive intervention. Deneke et al. performed catheter ablation within 24h after admission of the patient with electrical storm and showed a high cumulative mid-term survival (median 15 months) of 91%.[21] CA for VT in the early post infarction period may also be a feasible treatment.[11] In the study of Saggu et al. 5 patients short after myocardial infarction underwent catheter ablation within 48 hours for the treatment of VTs. CA is fairly called a “lifesaving” approach with an acceptable efficacy and safety profile and a low complication rate (1%).[14] The risk of death has been found the greatest at 3 months after ES.[2] Severely depressed LVEF, a higher degree of LV dilation, renal insufficiency, and ES recurrence after previous CA procedure were identified as predictors of adverse outcome within the first 6 months after the procedure.[6] In AHF decompensated VT patients, AHF after RFCA was ameliorated in 93% of the patients.[9] Nevertheless heart failure is the dominant cause of death in the long term in patients having a successful procedure.[14] In this subset of patients, the magnitude of the cardiac damage is too extensive and chronic heart failure far advanced.[6] Looking at it this way ES may rather be an epiphenomenon of progression of heart failure and even successful CA does not guarantee a good prognosis. High arrhythmia rate heralds pre-terminal pump failure, yet failure of the

CA procedure carries an even higher mortality.[14]

Conclusion

In conclusion, progressively increasing number of studies support that CA is very effective in suppressing ES and it may be a life-saving therapy for a very troubled patient population.

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The treatment of electrical storm, an educational review

3

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Abstract
Electrical storm is characterised by a state of severe electrical instability that occurs in a rare combination of circumstances, and may lead to multiple implantable cardioverter defibrillator shocks and haemodynamic instability, and possible death. The main goal of treating electrical storm is to eliminate the trigger and modify the substrate of the arrhythmia. The aim of this educational review is to provide information for a better understanding of the underlying mechanisms and therefore help to improve the treatment of electrical storm patients.

Introduction

Electrical storm is a state of electrical instability and is characterised by several episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF). The implantable cardioverter defibrillator (ICD) can effectively terminate ventricular arrhythmia (VA); however, it will not eliminate or modify the trigger or substrate of electrical storm.[1] Electrical storm patients usually present as a severe medical emergency characterised by multiple ICD shocks and haemodynamic instability. Because of the infrequent nature and unpredictability of electrical storm associated with a potential lethal outcome many physicians feel uncertain in the acute setting. Mortality in the early and subacute phase is high.[2,3] Several factors are associated with a negative outcome in electrical storm patients: severely impaired left ventricular ejection fraction (LVEF),[4] pre-existing advanced New York Heart Association class, cardiogenic shock[5] and older age.
Electrical storm can be a distressing experience for patients and their families, leading to significant psychological consequences. Effective management of electrical storm is crucial, and a collaborative hospital network with a dedicated electrical storm team has been suggested as beneficial.[6,7] Treatment of electrical storm can be very complex and consists of the administration of antiarrhythmic drugs (AADs), suppression of sympathetic tone, device re-programming and sometimes urgent catheter ablation (Table 1).

Table 1 Learning objective

1	How the mechanism and trigger of electrical storm can guide electrical storm treatment
2	To learn about the importance of the sympathetic nervous system in the initiation and maintenance of electrical storm
3	To tailor AAD treatment considering efficacy, drug-related pro-arrhythmia and other side effects
4	How to programme an ICD to avoid recurrent shocks
5	To learn about the indication and timing of catheter ablation

AAD: anti-arrhythmic drug; **ICD**: implantable cardioverter defibrillator.

Definition of electrical storm: diversity in the literature

The clinical syndrome of electrical storm has been defined empirically. In the past a variety of definitions were used. In those early definitions the VT episodes ranged between two and 20 within 24 hours.[5,8] At present, in the era of ICDs the most commonly accepted definition is three or more separate arrhythmia episodes leading to ICD therapy occurring over a single 24-hour time period.[9] The episodes of VT must be separate, meaning that the persistence of VT following unsuccessful ICD therapy is not considered as a second episode.[10] Incessant VT is a condition in which a sustained VT resumes within 5 minutes after successful ICD therapy and continues for over 12 hours. No study to date has determined a certain threshold burden of ICD therapy that begins to confer an adverse outcome.

Mechanisms underlying electrical storm

Crucial for the occurrence of electrical storm is an interplay between the autonom-

ic nervous system, cellular milieu and a predisposing electrophysiological substrate. Both the trigger and the substrate may change over time influenced by the progression of scarring, left ventricular remodelling and the progression of heart failure. The critical role of an increased activation of the sympathetic nervous system in initiating and maintaining electrical storm is demonstrated in electrical storm patients who have exacerbation of heart failure.[11]

Electrical storm: disease or symptom

Although electrical storm directly affects the patients' prognosis, by preventing the next episode of electrical storm the mortality does not necessarily decrease.[12] Electrical storm often represents part of the natural history of advanced cardiac disease and may predict a serious deterioration in the underlying processes. It can even be debated if electrical storm is a marker for mortality in the near future and accordingly functions as a major bystander. This raises the question of whether all electrical storm patients would be potential candidates for catheter ablation. It is also a valid question as to whether a severe disbalance in the cellular milieu could outweigh a modification of the substrate? At the other end of the spectrum is those presenting with a first episode of electrical storm, who may benefit much more from a catheter ablation intervention and have a possible survival benefit.[13] Therefore, every patient that presents with even a single ICD shock should be considered as a possible electrical storm, whereas it may be preceded by multiple episodes of VT successfully treated by antitachycardia pacing (ATP).

Treatment of electrical storm: corresponding to the mechanism and trigger

Searching for and correction of reversible factors

In the majority of cases, no clear cause for electrical storm can be identified. Triggers such as electrolyte imbalance, acute ischaemia, exacerbation of heart failure, adjustment of or non-compliance to anti-arrhythmic medication[1] and recent introduction to biventricular pacing have been identified.[14] They should be actively searched for and promptly corrected in each electrical storm patient. Flow limiting coronary artery disease and volume overload should be adequately treated. Decreased left ventricular wall stress can be achieved with non-invasive and invasive haemodynamic support including a left ventricular assist device (LVAD), venoarterial extracorporeal membrane oxygenation (ECMO) and continuous flow percutaneous ventricular assist devices. Fever is a more rare trigger of electrical storm, and is especially important in patients with Brugada syndrome, in whom unsuppressed fever may lead to medically resistant incessant polymorphic and possibly fatal VT.[15]

Device programming

Shocks delivered for self-limiting haemodynamically tolerable arrhythmias ought to be avoided. Detection time can be prolonged and ATP can be given as an initial therapy.[16] Augmentation of ATP attempts, when feasible, is encouraged especially when shown previously to be successful.[17] During an electrical storm an effort should be made to avoid further conscious shocks[18],and temporary disabling of shock therapy may be considered.

Anti-arrhythmic drugs

Frequently, the first step in the treatment of electrical storm is the administration of beta-blockers. Beta-blockers play a fundamental role in the management of electrical storm by blocking the sympathetic system. Adding beta-blockers intravenously in electrical storm patients already on oral beta-blocker therapy may help to keep

an electrical storm episode under control.[19] Propranolol, a lipophilic unselective beta-blocker that penetrates the central nervous system, has been demonstrated to be effective in suppressing VAs as compared to metoprolol and amiodarone.[20] In the presence of structural heart disease amiodarone is one of the most frequently used drugs for the treatment of electrical storm. Procainamide, a class 1C AAD, has demonstrated its superiority compared to amiodarone for the treatment of haemodynamically tolerated monomorphic VT in the PROCAMIO trial.[21] However, it has been investigated only in patients without manifest heart failure and without severely depressed LVEF, in whom it is considered safe. The incidence of IV-amiodarone-refractory electrical storm is approximately 30%. IV-amiodarone-refractory VT storms are frequently induced by triggering premature ventricular contractions (PVCs) with a narrow QRS complex[22], and may be successfully suppressed with additional administration of mexiletine, a class 1B AAD.[23] Reperfusion often leads to the development of automaticity or delayed afterdepolarisations originating from the Purkinje network,[24] which in fact is sodium channel mediated.[25] Lidocaine, a class 1B AAD is used in the setting of acute ischaemia.[26]

There is no consensus on the optimal drug treatment for refractory malignant VA, and AADs may be given in a manner of trial and error. Drug combinations are sometimes necessary to alter electrical instability. AADs carry the risk of increasing the cycle length of re-entry VAs and make VT more stable, which may precipitate to incessant VT. AADs should be given individually, taking into account not only the efficacy but also the increased risk of drug-related proarrhythmia and other side effects.

Overdrive pacing and sedation

Temporary (atrial) overdrive pacing may help to interrupt an incessant or re-occurring VA, especially in conditions such as Brugada and early repolarisation syndrome.[26] Overdrive pacing helps by preventing PVCs from occurring and reduces early afterdepolarisation.[27]

As the sympathetic nervous system plays a major role in the initiation but also the maintenance of VAs[11], sedation and/or intubation may be needed in order to suppress the sympathetic tone. A complete sympathetic blockade can be performed by left cardiac sympathetic denervation.[28]

Radiofrequency catheter ablation

In the majority of electrical storm patients the episodes are characterised by a monomorphic VT based on re-entry. Therefore catheter ablation, targeting the substrate in which re-entry has formed, is an important treatment option for electrical storm. In a pooled meta-analysis[29] of 471 electrical storm patients who underwent catheter ablation, catheter ablation had a high success rate with a low rate of recurrent electrical storm. Acute procedural success was 72% and procedural failure was 9%. During a follow-up of 15 months, 60% of patients were free of VA recurrences and 94% were free of electrical storm. Since then ablation of VT has evolved, and new approaches and technologies, such as the substrate approach[30], remote magnetic navigation[31], and a combined endo-epicardial substrate ablation[32], have improved the outcome of VT ablation (Table 2).[33]

There is also a role for catheter ablation in patients who suffer from recurrent VF episodes. In 29 patients with ischaemic heart disease, recurrent VF was triggered by monomorphic ventricular extrasystole that originated from the fibrous peri-infarction zone. In eight patients with drug refractory electrical storm, ablation of the ventricular extrasystole was successfully performed, and control of electrical storm was achieved.[34]

Table 2 Outcome of ventricular tachycardia ablation in electrical storm patients

	Number of electrical storm patients	Population	Control group	Follow-up duration, months	Free of recurrence, %	Survival, %
Nayyar et al., 2013[30]	471	Meta-analysis 68% ICM 37% incessant VA	NA	15	60	83
Di Biase et al., 2012[31]	92	ICM	Limited substrate ablation vs. endo-epicardial homogenisation	25	Limited substrate: 53 endo-epi: 81 *P=0.006*	Limited substrate: 98 endo-epi: 98 *P= NS*
Izquierdo et al., 2012[12]	23	ICM Catheter ablation: 83 MT: 66	MT: 23	28	Catheter ablation: 68 MT 71 *P=NS*	Catheter ablation: 70 MT: 48 *P=NS*
Özcan et al., 2016[39]	44	ICM, drug refractory electrical storm	NA	28	55	82
Muser et al., 2017[40]	267	ICM and non-ICM 22% endoepicardial ablation	NA	45	67	71
Jin et al., 2017[32]	54	ICM, ablation with RMN	NA	17	50	80
Morawski et al., 2017[13]	28	81% ICM	MT: 42	28	MT: 26 Catheter ablation: 43 *P=NS*	Catheter ablation: 86 MT: 62 *P=0.03*
Kumar et al., 2017[41]	287	64% ICM	ICM vs. non-ICM	12	ICM: 51 Non-ICM: 36 *P=0.007*	ICM: 75 Non-ICM: 72 *P=NS*

ICM: ischaemic cardiomyopathy; **MT:** medical therapy; **NA:** not applicable; **RMN:** remote magnetic navigation.

Compared to medical therapy catheter ablation reduces the number of subsequent VT episodes especially when VT ablation is performed within one month of electrical storm.[35] VT ablation in patients with a LVEF of 25% or greater is shown most beneficial.[12] Freedom from recurrent VT after catheter ablation has been associated with an improved survival.[13,36] Morawski et al.[13] showed that in a first time electrical storm population, VT ablation was significantly more effective than any other form of therapy in reducing death at any time, even though the recurrence rate was not lower in the catheter ablation group. Yet, it is also known that patients with electrical storm have an increased risk of non-cardiac death. In other studies a mortality benefit from VT ablation in electrical storm patients was not shown.[2]
This underlines the importance of the selection of patients as potential candidates for ablation. The timing of catheter ablation, the approach and support should be tailored. Patients with incessant drug refractory VT who fail on haemodynamic support can benefit from a rescue VT ablation.[37] Patients with advanced heart failure and unstable VTs are at highest risk of haemodynamic collapse during the ablation procedure; they can benefit from mechanical support during catheter ablation.[38] Alternatively, the ablation can be confined to a substrate approach only. Consequent fluid overload related to irrigated catheter ablation may precipitate acute decompensation[39], and preventive measures such as LVAD or ECMO may still be indicated in patients with severely depressed left ventricular function. In a small proportion of patients there is such a limited reserve in cardiac output that limited ablation should be aimed for, targeting only the critical isthmus of the clinical VT.

Conclusion

Electrical storm is a critical condition and even after successful catheter ablation patients continue to bear an increased burden of morbidity and mortality. Early recognition and referral to a tertiary electrophysiology centre is mandatory. Electrical storm should be treated by a team that offers a structured and tailored approach.

Key points

1. Early recognition of electrical storm and referral to a tertiary electrophysiology centre is mandatory.
2. Electrical storm should be treated by an experienced team that offers a structured and tailored approach.
3. An increased activation of the sympathetic nervous system is critical in the initiation and maintenance of electrical storm.
4. Electrical storm often represents part of the natural history of advanced cardiac disease and may be a predictor of serious deterioration of the underlying disease.
5. By treating electrical storm we attempt to eliminate the trigger and modify the substrate of the ventricular arrhythmia.
6. Treatment of electrical storm is complex and consists of the administration of anti-arrhythmic drugs, suppression of sympathetic tone, device re-programming and catheter ablation.
7. Anti-arrhythmic drugs should be given individually, taking into account not only the efficacy but also an increased risk of drug-related pro-arrhythmia and other side effects.
8. Electrical storm is a critical condition and even after successful catheter ablation patients continue to bear an increased risk of morbidity and mortality.

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Conservative treatment and delayed catheter ablation fail to improve outcome of patients with electrical storm: a comparative study

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Abstract

Background - Current guidelines on electrical storm (ES) recommend urgent catheter ablation (CA) in patients with structural heart disease. However, studies on ES may include a highly selected group characterised by a referral bias for ablation and therefore limited outcome data is available to show superiority and support immediate CA. The aim of the present study is to show real world data on the outcome of ES and the influence of timing of CA.

Methods - ES patients were selected from a prospective implantable cardioverter defibrillator (ICD) database. ES was defined as > 3 appropriate ICD therapy within 24h. VT recurrences were compared between patients who underwent early CA, late CA and patients who had conservative treatment (CNT). Early CA occurred within 90 days of the first ES.

Results - In 2544 ICD patients, 129 were identified that fulfilled the definition of ES. Patients had a median follow-up of 6.4 years [IQR 3.9 - 9.2]. Sixteen patients had CA for ES, in 6 early and in 10 late. CA for ES led to a 6-fold ICD therapy reduction as compared to an increase of 1.5 in CNT. Patients with early CA had a lower number of ICD therapy on follow-up: 1 [0-20] versus 63 [12-135] in patients with late CA (p = < 0.05).

Conclusions - CA for ES in the absence of reversible triggers in a highly selected patient group may reduce the burden of ICD - therapy on follow-up as compared to CNT if undertaken within 90 days.

Introduction

Electrical storm (ES), a state of electrical instability manifested by several episodes of ventricular tachycardia (VT) in a short period of time, leads to high morbidity and mortality.[1,2] ES often occurs in the setting of a critically ill patient.[3,4] An implantable cardioverter defibrillator (ICD) can terminate VT, however it will eliminate neither the trigger nor the substrate of the arrhythmic storm3 and ICDs do not provide definite protection against sudden cardiac death (SCD).[5] Current guidelines recommend urgent catheter ablation (CA) in patients with scar related heart disease.[6] Urgent CA however, often carries a logistic challenge. Yet, the guidelines that advocate early intervention is based on a single publication.[7] In this article on patients with ES who underwent CA there was no analysis performed in order to provide data on timing of ablation, apart from a group who underwent CA < 24h for drug refractory VT in refractory cariogenic shock. Few comparative studies between conservative treatment (CNT) and ablation for ES have been performed.[8,9] Studies on ES may represent a highly selected group characterized by a referral bias for ablation. Consequently there is limited outcome data available to show superiority and support for immediate catheter ablation. More importantly, clear recommendations have been provided for the optimal timing of intervention for ES despite the current lack of available data on proper timing of ES ablation. There is an urgent need for more data to justify, replace or support current guidelines.
The aim of the present study is to show real world data from an ICD database on the outcome of ES and the influence of timing of ablation.

Methods

Study Cohort

The study population was included from the ICD registry of the cardiology department of Erasmus MC. All ICD carrying patients in Erasmus MC are prospectively followed and all of those patient who had ES between January 2005 until March 2017 were included in the present study. In total 2544 ICD patients were screened. ES patients were selected from the ICD database taking all events into consideration. ES was defined as > 3 ICD -therapies within 24h with the episodes of VT separated by more than 5 minutes.[2,10] If patients had more than one ES, the first ES after ICD implantation was seen as the index ES. Type and timing of intervention after ES was studied.

Ethical approval

This was a retrospective cohort analysis of patients with a clinical indication for ICD - therapy. The need for written informed consent was waived.

Intervention

Medical therapy and/or ablation and timing of the ablation was decided at the discretion of the treating physician, influenced by current guidelines and insight.

Ablation Protocol

VT ablation was performed for patients not responding to AAD or as a first-choice for recurrent or incessant arrhythmia. All CA procedures were performed in accordance with institutionally approved local medical treatment protocols of the Erasmus Medical Center.
Ablation was performed targeting VTs induced by programmed electrical stimulation (PES) and modifying the electrical substrate. CA was performed either manu-

ally or using remote magnetic navigation (Stereotaxis, Inc., St. Louis, MO, USA.) when available.
The left ventricle was accessed through a transaortic or transseptal approach. Electroanatomic maps were obtained while patients were in sinus rhythm (CARTO 3, Biosense Webster Inc, Diamond Bar, CA; or EnSite, St. Jude Medical, Minneapolis, MN). Bipolar voltage criteria were used to identify scar (< 0.5 mV), scar-border zone (0.51–1.49 mV) and healthy tissue (> 1.5 mV).
If not incessant, VT was induced by PES and activation or entrainment mapping was performed to locate exit sites and critical isthmuses. Pace-mapping was used for hemodynamically unstable VTs. Substrate modification was based on the elimination of local abnormal potentials. PES was used at the end of the procedure to assess ablation success. Successful ablation was defined as no inducible VT.

Follow-up
Follow-up started at the time of the occurrence of the index ES. In-clinic device interrogation was performed on regular visits scheduled every 3–6 months and after symptomatic events. The ICD settings were left at the discretion of the physician and were influenced by the most recent guidelines at the time of presentation. In addition to in-clinic interrogation, some patients used remote monitoring of their implanted ICD system. All ICD - therapies were analyzed for appropriateness. Patients were monitored for recurrent ES. Early CA was defined as ablation that took place within 90 days of the first ES.

Endpoints
We analyzed the following parameters: mortality, heart transplantation, recurrences, number of recurrences and ES during follow-up. VT and ES recurrences were compared between patients who underwent CA and those with CNT. If patients had more than one ES, time to ablation was calculated for the index ES. The outcome of CA related to timing was analyzed.

Statistical analysis
After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Median and interquartile ranges (IQR) were computed for continuous variables with non-normal distribution. Descriptive statistics for categorical data were expressed in absolute numbers and percentages. Comparison of continuous variables between groups was made by unpaired Student's t -tests. In the case of non-normal distribution of data, the Mann–Whitney U-test and for related samples the Wilcoxon test was used. When comparing frequencies, the chi-square test, ANOVA and Kruskal Wallis test were used, as appropriate. Event-free survival rates were determined using the Kaplan Meier method and differences were evaluated by the log-rank test. A 2-sided P-value of < 0.05 (2-tailed) was considered significant. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results
Among 2544 ICD patients, 129 patient who had ES were included in the registry and had a follow-up duration of 6.4 years.

Study population
In this ES cohort of 129 patients, ischemic, dilated and hypertrophic cardiomyopathy were present in respectively 54, 25 and 6% (Table 1). Other underlying etiologies were arrhythmic right ventricular cardiomyopathy (n = 1), corrected congenital heart disease (n = 7) and channelopathies (n =7). In 48% of the patients ICDs were implanted for primary prevention. ES occurred a median of 438 days after ICD implantation [IQRS 55-1331] (Table 2). ES was the first occurrence of arrhythmia in 36% of the patients. On average, 3 ICD - therapies occurred during ES with a maximum of 49 ICD - therapies. The median CL of the first ES episodes was 315ms (319 ms in CNT and 366ms in the ablation group) (p = 0.02). Of all 129 first ES episodes, 11 (7%) were VF. There were not significantly more VF episodes in the CNT group: 8.9% versus 6.3% in the ablation group. (p = NS), However slow VT occurred more often in the ablation group (11 versus 45% in the ablation group, p < 0.01).
Age, ejection fraction (EF), New York Heart Association functional classification (NYHA) class, number of patients with ischemic heart disease, use of class III anti-arrhythmic drugs (AAD) and co-morbidities were not significantly different between the conservative, early and late ablation treatment group. ES was stabilised with medical therapy in 41 patients (3 in the ablation group), in 80% the prescribed AAD was Amiodarone. During follow-up an anti-arrhythmic drug was used in 78% of all the ES patients, and in 79% of the patients treated with CA.

Course of electrical storm
During a follow-up of 6.4 years [IQR 3.9 - 9.2], 74% of the patients had recurrent ICD - therapies after ES with a median number of 4 ICD - therapies (Table 3). ES re-occurred in 46% of the patients. Patients who had ICD - therapy before the first ES had a median of 11 [1-40] VA recurrences versus 1 [0-6] VA recurrences without ICD - therapy before the first ES (p = < 0.05). Patients who had an ICD for primary prevention had a median of 3 [IQRS 0- 11] VA recurrences after ES versus a median of 10 [IQRS 1-37] VA recurrences in patients with an ICD for secondary prevention (p < 0.05). Thirty-eight percent of the patient in this cohort died during follow-up and 6% received a heart transplant.

ES trigger and cause of death
The trigger for ES was known in 29% of the cases. In 18 patients the trigger for ES was either acute decompensation of chronic heart failure, terminal heart failure, lowering or cessation of anti-arrhythmic drugs, or electrolyte imbalances. In few cases the initiation of biventricular pacing with left ventricular stimulation, sepsis or heart surgery was thought to be the triggering factor.
Forty-nine patients (38%) died during a median of 6.4 ± 3.1 years of follow-up. Two patients died at the same day as the ES and 4 patient died within 30 days of ES. In only 2 cases death was directly attributed to ES. One patient had refractory ventricular fibrillation during follow-up. Terminal heart failure was the cause of death in 10 patients. Four patients died of multi organ failure due to sepsis. Other causes were cancer (1 patient), trauma (1 patient) and rejection to heart transplant (1 patient). In the remaining cases the cause of death was unknown.

Catheter ablation for ES
Sixteen patients had an ablation for ES, with an average interval of 373 days after the first ES. Nine patients had an earlier episode of VT before the occurrence of ES. Patients who underwent late CA (Table 2) had more total number of ICD - therapies (p = 0.04), a higher number of previous ICD - therapies (p < 0.01), but not more ICD - therapies during ES. Eight patients had substrate modification. In 2 cases the PVC that triggered VF or polymorphic VT was the target of ablation, 1 in the early ablation group and 1 in the late ablation group. All other CA procedures targeted monomor-

phic VT. In 6 out of 16 cases ablation was performed with remote magnetic navigation. On ablation was performed with the aid of a hemodynamic support device (Impella). Acute procedural success was 94%. Ablation was unsuccessful in 1 case and in 2 cases only partly successful. In 3 patients a repeat VT ablation was required, in 1 of the 3 cases the focus was not reached from the endocardium at the initial unsuccessful baseline procedure and during repeat ablation 2 weeks later was successfully targeted epicardially.

Ablation versus conservative treatment
Patients treated by CA for ES had 12.3 ICD - therapy/year before the CA procedure (Figure 1). After CA the year-burden of ICD - therapy decreased to 2.4 ICD - therapies/year ($P < 0.05$). Patients who had CNT for ES had 1.2 ICD - therapies/year before ES and after ES it increased to 3.0 ICD - therapy/year after (P = NS).

Timing of intervention by ablation
In 6 and 10 patients ablation took place within 90 days (early ablation) and after 90 days (late ablation) of the index ES, respectively. If patients had an early ablation for ES (Table 3) 60% of the patients had a recurrence and 0% of the patients had a repeat ES on follow-up versus 90% and 40% respectively in the late ablation group (p = NS). Patient with an early ablation had a significant lower median number of ICD - therapies of 1 [0-20] versus 63 [12-135] in patients with a late ablation ($p < 0.05$). Figure 2 demonstrates the Kaplan Meier survival curves for mortality, recurrence and ES recurrence. Recurrence free survival is significantly different (p = 0.05) within the 3 groups in favour of early ablation.

Table 1 Baseline characteristics

	all ES patients (%) - 129	**early ablation group** (%) - 6	**late ablation group** (%) - 10	**CNT group** (%) -113	*p-value*
age	59 SD ± 15	58 ± 7	63 ± 8	59 ± 16	0.77
iCMP	69 (54)	3/6 (50)	6 (60)	60 (53)	0.90
LVEF	30 [25-35]	27 [22-30]	30 [28-40]	30 [25-36]	0.46
median QRS duration	126 [108 - 153]	122 [103-141]	138 [99-167]	125 [108-153]	0.71
median nyha class	2 [1-3]	2 [1.8-2.3]	2 [2-2]	2 [1-3]	0.94
ICD for primary prevention	62 (48)	2 (33)	2 (20)	58 (51)	0.13
atrial fibrillation	38 (30)	2 (33)	1 (10)	25 (22)	0.52
CKI*	20 (16)	0 (0)	3 (30)	17 (15)	0.26
DM	16 (12)	0 (0)	4 (40)	34 (30)	0.22
amiodarone at baseline	26 (20)	3 (50)	2 (20)	21 (19)	0.18

CKI: chronic kidney injury; **DM:** diabetes mellitus; **CMP:** ischemic cardiomyopathy; **LVEF:** left ventricular ejection fraction; **NYHA:** New York Heart Association functional classification

**CKI* chronic kidney injury : defined as creatinine > 120

Baseline characteristics in all ES patients, in the different subgroups and a p- value was calculated within the 3 subgroups

chapter 4

Table 2 ICD data at baseline and during follow-up

	all ES patients (%) - 129	**early ablation group** (%) - 6	**late ablation group** (%) - 10	**CNT group** (%) -113	*p-value*
Timing of first ES after ICD implantation (days)	483 [IQRS 55-1331]	787 [14-2241]	358 [39-990]	489 [66-1332]	0,62
median number of ICD-therapy before ES	1 [IQR 0-4]	3.5 [0-26]	22 [IQR 0-88]	1 [0-4]	< 0.01
number of patients with first shock = shock during ES (%)	47 (36)	2 (33)	2 (20)	43 (38)	0.5
median number of ICD-therapy during ES	3 [3-8]	4 [3-8]	4 [IQR 3-14.5]	4 [3-7]	0.87
median CL of arrhythmia during index ES (ms)	315 [IQR 280-350]	380 [289 -482]	348 [IQR 323-391]	310 [280-340]	0.02
number of patients with VF during first first episode of ES (%)	11 (9)	1 (17)	0 (0)	10 (89)	0.48
number of patients with slow VT during first episode of ES (%)	19 (15)	3 (50)	4 (40)	12 (11)	< 0.01
median total number of ICD-therapy	18 [IQR 8 - 39]	10 [8-30]	72 [IQR 39-142]	16 [8-35]	0.04

ES: electrical storm; **VT:** ventricular tachycardia

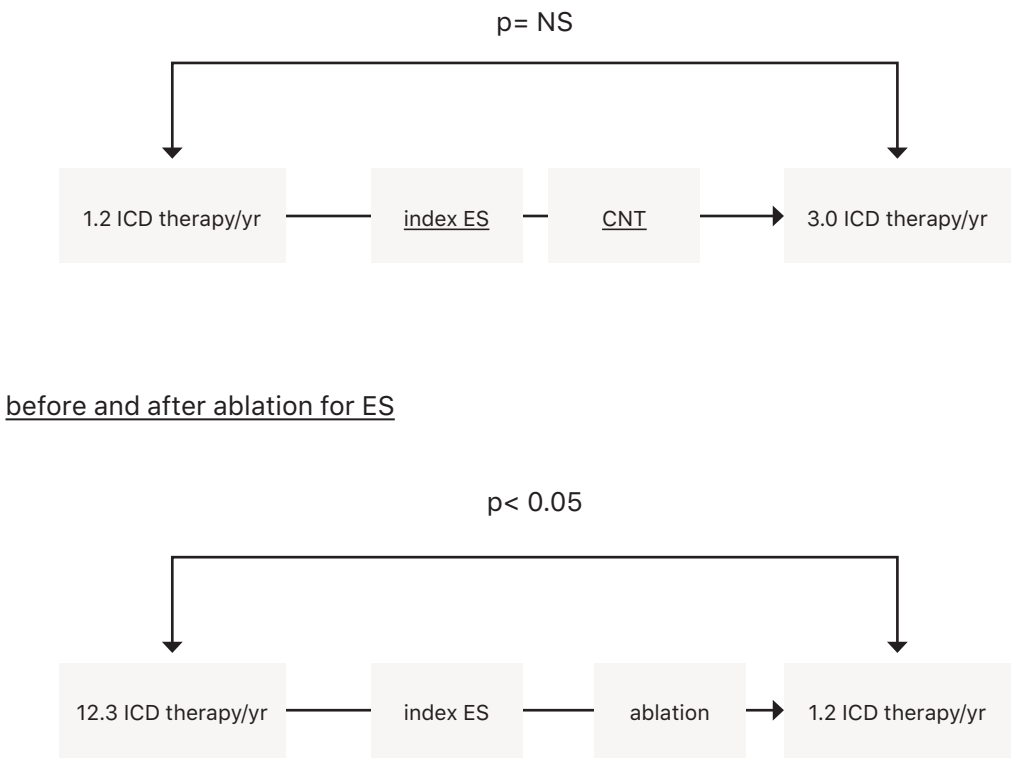
Table 3 Follow-up after electrical storm

	all ES patients (%) - 129	**early ablation group** (%) - 6	**late ablation group** (%) - 10	**CNT group** (%) -113	*p-value*
- mean FU duration (yr) - SD	6.4 ± 3.1	6.1 ± 3.3	6.2 ± 4.1	6.4 ± 3.1	0.96
ICD-therapy					
patients with recurrence of ICD -therapy	95 (74)	4 (60)	9 (90)	82 (73)	0.45
patients with recurrence ES	52 (40)	0 (0)	4 (40)	48 (43)	0.12
median number of ICD-therapy after index ES	4 [0-21]	1 [0-20]	63 [12-135]	4 [0-19]	< 0.05
other					
mortality	49 (38)	1 (17)	4 (40)	44 (39)	0.55
heart transplantation	8 (6)	0 (0)	1 (10)	6 (5)	0.72

CNT: Conservative treatment; **ES:** electrical storm; **ICD:** implantable cardioverter defibrillator; **SD** standard deviation; **yr** year

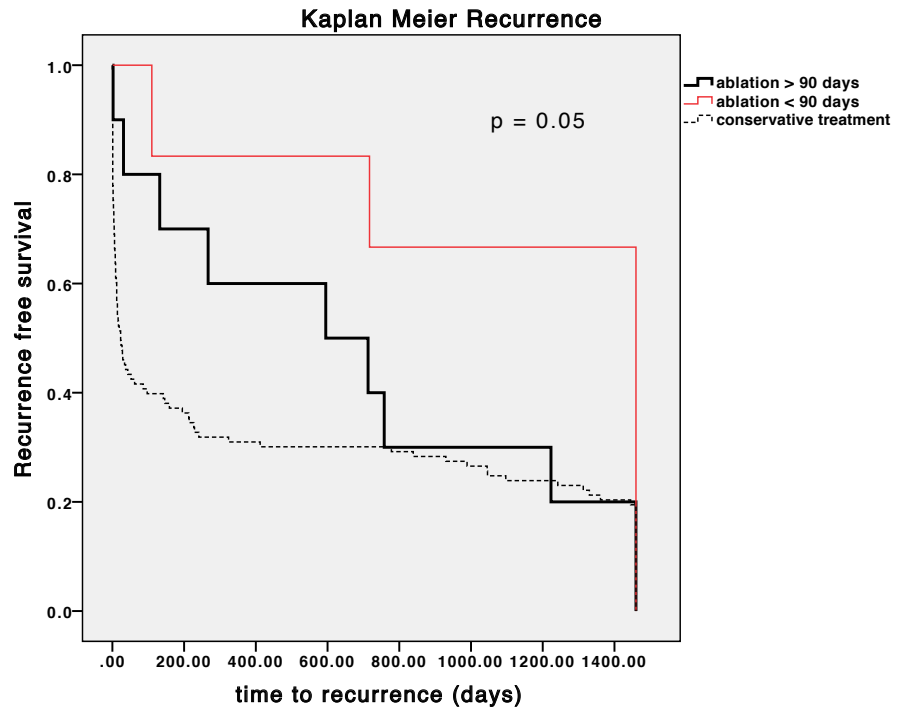
Follow-up data in all ES patients, in the different subgroups and a p- value was calculated within the 3 subgroups

Figure 1 shock reduction early versus late ablation



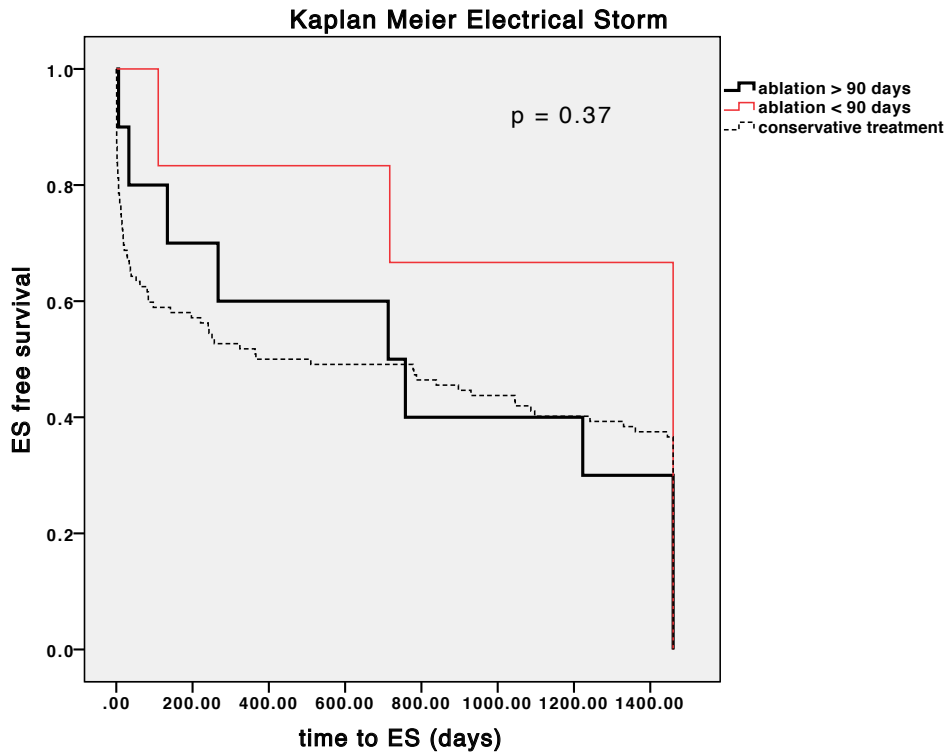
shock reduction per patient-year
CNT: conservative treatment; **ES:** electrical storm

Figure 2 Kaplan Meier survival curves
A. Kaplan Meier Recurrence



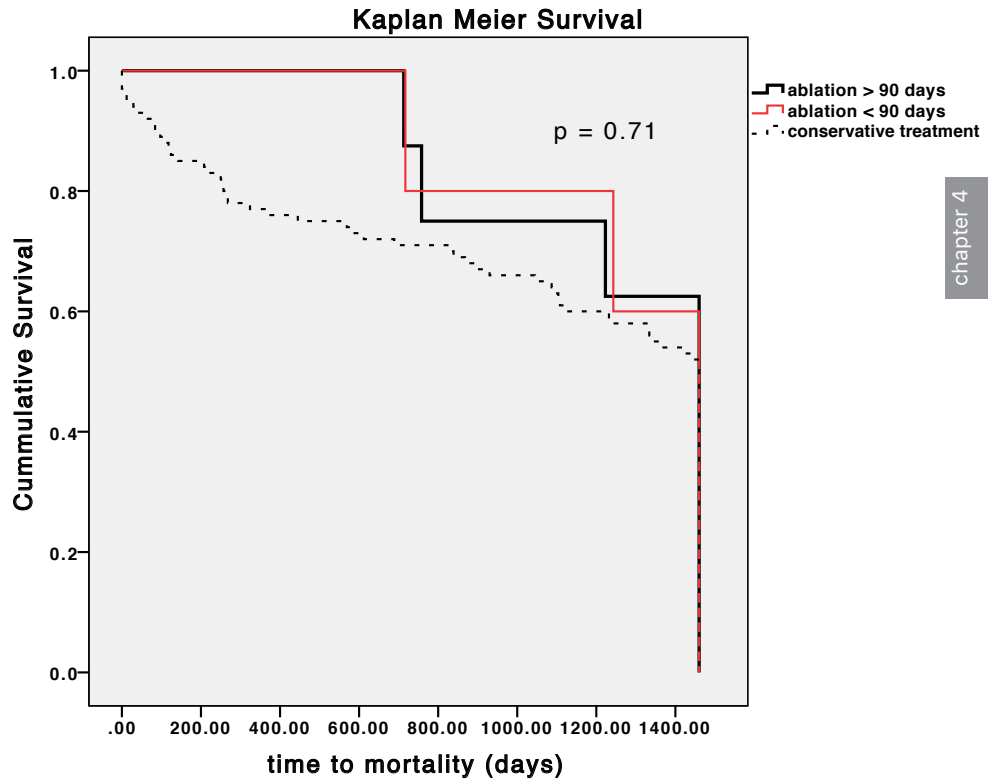
Number of patients	**128**	10	**45**	6	**40**	3	**34**	3	> 90 days
		6		5		4		4	< 90 days
		112		34		33		27	CNT
Cumulative recurrence	**0**	0	**74**	4	**77**	5	**78**	5	> 90 days
		0		1		1		1	< 90 days
		0		69		71		72	CNT

B. Kaplan Meier recurrence of Electrical Storm



Number of patients	**129**	10 6 113	**68**	6 5 57	**61**	4 4 53	**56**	6 4 46	> 90 days < 90 days CNT
Cumulative ES	**0**	0 0 0	**46**	4 1 41	**48**	4 1 43	**49**	4 1 44	> 90 days < 90 days CNT

C. Kaplan Meier Survival



Number of patients	**129**	10 6 113	**105**	10 6 89	**97**	8 5 84	**84**	7 4 73	> 90 days < 90 days CNT
Cumulative recurrence	**0**	0 0 0	**18**	0 0 18	**22**	0 0 22	**23**	1 0 22	> 90 days < 90 days CNT

Discussion

The present study a real life outcome data study demonstrating the natural evolvement of ES. CA for ES leads to a 6-fold shock reduction as compared to an increase of 1.5 fold in case of CNT for ES. If ablation for ES takes place within 90 days of the first ES, invasive treatment may lead to a lower ICD - therapy burden.

Main findings compared to previous results

The incidence of ES in this study, a mixed population of primary and secondary prevention, was 5.1% during a median follow-up of 6.4 years.In comparison to previous studies the incidence was low, also set against the observed patient population. In the VANISH trial an incidence of ES in 25-33% was seen during a follow-up period of 28 months. Patients after MI were included when they had experienced an ICD shock, 3 or more ATP or ES in the previous 6 months. In the MADIT-II[21], a study on ICD for primary prevention, 4% of patients developed ES during an average follow-up of 20.6 months. After 2014 there has been a considerable change in ICD programming after the MADIT-RIT study[22] impacting primary prevention patients. Also heart failure therapy has intensified in the previous decade, including the use of resynchronisation devices.
In our cohort ES adversely affects outcome. Mortality amongst this population is high, 38% in 6.4 years. In the MADIT-2 sub-study 2-year mortality was as high as 54%, in a population with cardiomyopathy of ischemic origin and severely impaired EF. Factors such as impaired left ventricular EF[13], pre-existing NYHA class, cardiogenic shock[14], age and other co-morbidities influence the outcome of patients with ES. We found that if patients had their ICD for secondary prevention or had ICD - therapy before the first ES, a significant higher percentage of the patients had recurrences on follow-up. In the AVID trial[15], the development of ES was a relatively late phenomenon, with the initial episode occurring 9.2±11.5 months after ICD implantation. In the current study it was even longer: 16 months (2-44). This probably indicates earlier referral for primary implantation for an ICD.

Ablation treatment for ES

VT ablation compared to CNT did not reduce the number of patients with recurrence, neither did VT ablation effect mortality. Nonetheless shock burden was significantly reduced after ablation. Late ablation for ES had a comparable outcome as CNT. This latter observation probably derives from a selection of patients with highest ventricular arrhythmia (VA) burden in the late ablation group. Patients with single ICD - therapy events before ES and ICD implanted for secondary prevention had significantly higher number of ICD - therapies during follow-up. In previous studies besides ICD implanted for secondary prophylaxis, lower left ventricular EF, serum creatinine were independent predictors for ES recurrence.[13]

Rationale for early VT ablation for electrical storm

CA for ES in the absence of reversible triggers reduces the burden of ICD - therapy if performed within 90 days. Search for contingent conditions that may have precipitated ES is crucial. In the current study potential triggers were found in a minority.
Our results are in line with previous trials that show a longer VT free survival16 when ES patients have CA within 30 days compared to a delayed ablation. Evidence for prophylactic ablation for unclustered arrhythmic events to reduce the burden of shock[17, 18] and maintaining longer VT free survival[19] has previously been published. Yet, there is limited evidence for superiority of a rescue ablation (< 24h)[7] compared to conventional stabilization in the majority of ES patients. Further research to confirm our results is warranted.

Electrical storm prognostic value or symptom

It remains a question whether ES contributes to higher mortality in a direct manner or rather is an epiphenomenon of advanced heart disease or systemic illness. Most of the deaths on follow-up were non-SCD, which points in the direction of ES being a marker of progression of underlying disease.
Patients with early VT recurrence had higher mortality than those without VT recurrence during follow-up.[20] Previous studies found that successful VT ablation in patients after ES improves survival.[2] However, survival of patients with ES even in the absence of VT recurrences during follow-up were lower compared to patients without either ES and VT recurrences after a single arrhythmic event, suggesting that non-arrhythmic factors still act on these patients and might lead to death.

Limitations of the Study

There are several limitations to note. The current study is limited by historical evolving treatment of ES, more evolving ablation techniques and ICD programming that constitutes with the current standard of care. Including only patients who had > 3 ICD therapy < 24hours, patients with ES and VT under the therapy zone of the ICD may have been missed. We cannot exclude a bias in selection for the relative small number of subjects that had CA. The relatively low incidence of ICD therapies before ES may have influenced decision to follow CNT. Therefore the limited number of patients that underwent CA may hamper generalizability.
Currently, substrate homogenisation has become an established therapy for VT ablation.[21] In recent years ICD programming has evolved to prevent shocks, by delayed ICD - therapy and ATP first.[12,22] The study ensures detection of all recurrent treated VTs, but not the monitored or unmonitored VTs. Lastly the studied population was heterogeneous therefore our conclusions cannot be directly extrapolated to the individual patient. Large differences in the burden of ICD interventions amongst the different study groups could also be addressed to different type of patients in term of electrical instability and those selected for late CA could be patients who were beholding the highest electrical instability. The observed difference in outcome in different timing for CA in patients with ES, should be verified in a randomised controlled fashion with a larger number of patients. Yet, at present this is the largest real outcome study that compares ablation to CNT for ES.

Conclusion

Ablation for ES in the absence of reversible triggers may reduce the burden of ICD -therapy if performed within 90 days after the first ES.

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chapter 4

5

Procedural and long-term outcome after catheter ablation of idiopathic outflow tract ventricular arrhythmias: comparing manual, contact force, and magnetic navigated ablation

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Abstract

Aims
Currently, comparative data on procedural and long-term clinical outcome of outflow tract (OT) idiopathic ventricular arrhythmia (IVA) ablation with manual (MAN), contact force (CF), and magnetic navigation system (MNS) ablation are lacking. The aim of this study was to compare the procedural and long-term clinical outcome of MAN, CF, and MNS ablation of OT IVAs.

Methods and results
Seventy-three patients (31 MAN, 17 CF, and 25 MNS patients; consecutive per group) with OT IVA, who underwent catheter ablation in our centre were analysed. Procedural success rates (success at the end of the procedure), procedural data and long-term follow-up data were compared. Baseline patient demographics were comparable. Procedural success rates were similar (MAN 81%, 71% CF, and MNS 92%; P = 0.20). Median fluoroscopy time was shorter in the MNS group: MAN 29 (16–38), CF 37 (21–46), and MNS 13 (10–20) min (P = 0.002 for MNS vs. CF and MAN). The overall complication rate was: MAN 10%, CF 0%, and MNS 0% (P = 0.12). Median follow-up was: MAN 2184 (1672–2802), CF 1721 (1404–1913), and MNS 3031 (2524–3286) days (P <0.001). Recurrences occurred in MAN 46%, CF 50%, and MNS 46% (P = 0.97). Repeat procedures were performed in MAN 20%, CF 40%, and MNS 33% (P = 0.32).

Conclusion
Procedural and long-term clinical outcome of OT IVA ablation are equal for MAN, CF, and MNS. MNS has a favourable procedural safety profile due to the shorter fluoroscopy time compared with MAN and CF.

What's new?

- This is the first study directly comparing the procedural and long-term clinical outcome of catheter ablation of exclusively outflow tract idiopathic ventricular arrhythmias between manual (MAN), contact force (CF), and magnetic navigation system (MNS) catheter ablation.
- The major findings of this study are that there are no significant differences in procedural or long-term success rates between these three groups and that fluoroscopy time is shorter for MNS compared with MAN and CF.

Introduction
Idiopathic ventricular tachycardias (VTs) account for approximately 10% of all VTs.[1] Additionally, depending on the measurement duration and the method of detection, premature ventricular contractions (PVCs) in patients without structural heart disease can be found in about 4–50% of the population.[2,3] They are commonly located in one of the cardiac outflow tracts (OT).[1] Idiopathic ventricular arrhythmias (IVAs) generally have a benign course.[1] However, they can be highly symptomatic and frequent arrhythmias can result in the development of tachycardiomyopathy.1 Therefore, it is important to consider that treatment with catheter ablation leads to a better quality of life and reversal of tachycardiomyopathy.[4,5] Catheter ablation of VTs is an important and increasingly performed treatment and has a high procedural success rate for both VTs and PVCs.[1,6] Recent technological advances have been made to increase the safety and efficacy of this treatment. The use of a magnetic navigation system (MNS) has been shown to result in higher procedural success rates and a better safety profile compared with manual (MAN) ablation due to the flexible nature of the MNS catheters.[7,8] Additionally, contact force (CF) sensing ablation catheters have been developed to reduce cardiac perforations and have been shown to enhance lesion formation in ablation of atrial fibrillation.[9] Data on IVA ablation with CF are sparse and there are very few comparative studies on longterm clinical outcome of these techniques. The aim of this study is to compare the procedural and long-term clinical outcome of MAN, CF, and MNS OT IVA ablation.

Methods
Patients
This prospective registry included 73 patients, consecutive per group, who underwent catheter ablation for OT IVAs either with MAN, CF, or MNS ablation before 2014. A total of 31 patients were included in the MAN group, 17 in the CF group, and 25 in the MNS group. There are two separate electrophysiology laboratories at our centre: one equipped with the MNS system and one without. For all patients the index procedure was a first procedure. Paediatric patients were defined younger than the age of 18 years. A medical ethical committee, the METC, approved data collection as prospective registry.

Electrophysiology studies — ablation strategy
The procedures were performed by the same group of senior electrophysiologists and with the assistance of two fellows over the entire study duration. In our centre, all operators are equally trained in both manual and remote MNS ablation. All ablation procedures were performed in accordance with institutionally approved local medical treatment protocols from the Erasmus MC, Thoraxcenter, Rotterdam. Informed consent was obtained from all patients before the ablation procedure. Within 48 h post-procedure, a resting 12-lead electrocardiogram, laboratory tests, a chest X-ray, and two-dimensional echocardiography were obtained from all patients. Standard periprocedural medication protocols were followed in all patients. Patients were instructed to discontinue antiarrhythmic drugs (except amiodarone) for a period of at least four half-lives prior to the planned ablation procedures. After a successful procedure the use of antiarrhythmic drugs was halted. The procedures were performed during a fasting state, with use of local or general anaesthesia.
As clinically indicated at the discretion of the operator, market-approved diagnostic, and ablation catheters were used. Left-sided access was achieved via retrograde aortic route or trans-septal puncture based on the operators' preference

and the exact location of the arrhythmia. All procedures were performed using a three-dimensional mapping system. Standard ablation andmapping techniques were applied based on hospital protocol at the operators' discretion. For induction, programmed stimulation was performed using up to triple extra-stimuli pacing from the right ventricular apex, right ventricular outflow tract (RVOT), or left ventricle. Isoproterenol was administered in a dosage ranging between 1.3 mg/min and 2.7 mg/min. As a first step usually an activation map was created (preferably with a local activation timing pre-QRS of -30ms). This was then followed by pace mapping (the site with a paced 12-lead QRS morphology identical (12/12) to an inducible monomorphic VT or PVC was assumed to be the exit site of that particular VA) for verification.
Additionally, early presystolic discrete potentials were targeted when present. There were no differences between ablation strategies in the MAN, CF, or MNS ablation groups. Crossovers were excluded from the study. The following definitions of endpoints of procedural success were applied: if the VT was inducible, non-inducibility was the endpoint; if only PVCs were present, then the complete termination of clinical PVCs or presence of <5 PVCs per hour from different locations was required. The presence of a pacemaker (PM) or implantable cardioverter-defibrillator (ICD) was not considered a contraindication for MNS guided ablation procedures, which is consistent with the product labelling for the MNS.[8]

Magnetic navigation system-guided ablations
The procedures in the MNS group were performed with the NiobeVR II Magnetic Navigation System (Stereotaxis, Inc., Saint Louis, MO, USA) in an EP lab equipped with a Siemens Axiom Artis (Siemens, Erlangen, Germany) fluoroscopy system. All patients were treated with a NaviStar RMT ThermoCool catheter (Biosense Webster, Inc., Diamond Bar, CA, USA). Electroanatomical mapping was performed using the CARTO RMT (BiosenseWebster, Inc., Diamond Bar, CA, USA) system.[8]

Manual- and contact force-guided ablations
The manual catheter ablation procedures took place in an EP lab equipped with a Philips Allura Xper (Philips, Eindhoven, the Netherlands) fluoroscopy system. Electroanatomical mapping was performed either with the EnSite NavX system (St. Jude Medical, Inc.) or CARTO (Biosense Webster Inc.). The ablation catheters that were used included the following: Biosense Webster Navistar Thermocool D and F curve and St. Jude Cool Path Duo.[8] Contact force ablation was performed in the same lab using the same equipment as mentioned for MAN ablation. Ablation catheters that were used included the following: Thermocool Smarttouch CF (Biosense Webster Inc., Diamond Bar, California, USA) and TactiCath (Endosense/ St Jude Medical, St Paul, Minnesota, USA). A target contact force of between 10 and 20 g was pursued for all ablations.

Data collection and analysis
The parameters that were analysed for all groups include the following: procedural success rate, fluoroscopy time, procedure time, total radiofrequency (RF) application time, RF application number, and major and minor procedure related complications. The procedural success rate was assessed based on the conclusions in the procedural reports. At follow-up, recurrences and repeat procedures were assessed. Fluoroscopy time was recorded from the fluoroscopy system in both rooms.

Procedure
Time was specified as the interval between subcutaneous injection of lidocaine to the groin and removal of catheters from the patients' body, including a 30-min waiting period for every case. Any adverse event registered by the operator during the procedure, by the attending cardiologist prior to hospital discharge or by the general physician during follow-up was examined by a trained electrophysiologist and was considered as a complication if the event could be ascribed to the procedure. Major complications were defined as pericardial effusion and/or tamponade, permanent AV block, PM/ICD damage requiring device or electrode replacement, stroke, major bleeding, or death. Minor complications were defined as minor bleeding, transient ischaemic attack, new permanent bundle branch block, transient ST-elevation, pericardial effusion without the need for intervention, an audible steam pop without consequences and temporary AV block.[8]

Follow-up
Routine follow-up visits were scheduled at the outpatient clinic of our department for all patients 3 months after the procedure and subsequently every 6 months. 24-h Holter recordings were employed during these visits for documentation of recurrent arrhythmias. For long-term follow-up, patient records were analysed and all patients were contacted by phone and interviewed concerning recurrences and/or repeat ablation procedures (performed in other institutions).

Statistics
The normality of distribution was assessed using the Shapiro–Wilk test. Descriptive statistics are presented as mean ± standard deviation for continuous variables if normally distributed, or otherwise as median with 25th and 75th percentiles, where appropriate. Data were compared by one-way ANOVA, Kruskal–Wallis test, or Mann–Whitney test, as appropriate.
Categorical data were expressed as percentages and compared with Fisher's exact test. Statistical analysis was performed using SPSS version 21 (IBM Corp., Somers, NY, USA). Statistical significance was defined as P-value of <0.05 (two-tailed).

Results

Demographics and procedural results
Baseline characteristics including age, gender distribution, number of paediatric patients, medication use, and left or right OT VA did not significantly differ between the three groups, except for beta-blocker use, which was higher in the CF group compared with the MNS group (P = 0.007) (Table 1). There was no significant difference in procedural success rates between the groups (Table 2). Fluoroscopy time was significantly shorter in the MNS group compared with the MAN and CF group (P= 0.002 for MNS vs. MAN and CF). Procedure time, application time, number of applications, and hospital stay were equal in all three groups (Table 2). The application time was not significantly different between MAN and CF [499 (128–870) vs. 200 (120–270) s; P= 0.57] or MAN and MNS [499 (128–870) vs. 291 (183–431) s; P = 0.15].

Complications
The complication rates are reported in Table 2. There were no significant differences in overall, minor, or major complication rates. In total, one major complication (tamponade after perforation, with full recovery after pericardiocentesis) occurred, which was in the MAN group. Minor complications occurred in two patients (7%),

both from the MAN group (Table 2). In both instances an audible steam pop occurred without consequences and a normal CT afterwards.

Long-term follow-up

Median follow-up was 2184 (1672–2802) days for the MAN group, 1721 (1404–1913) days for the CF group, and 3031 (2524–3286) days for the MNS group (P <0.001). In total, five patients were lost to follow-up. In the MAN group, one patient was unable to answer our telephone inquiry due to Alzheimer's disease. In the CF group, two patients were lost to follow-up; both patients did not respond to our efforts to contact them. In the MNS group, two patient were lost to follow-up; one patient due to loss of contact after emigration and one patient deceased because of acute myeloid leukaemia. The number of recurrences and repeat procedures were equal in the three groups (Table 2, Figures 1 and 2). Six patients had an early recurrence during the admission period after a reported successful procedure.
Of those, three patients were in the MAN group, one was in the CF group and two were in the MNS group. Repeat procedures were successful in 67% (4 out of 6) patients in the MAN group, 83% (5 out of 6) patients in the CF group, and 100% (8 out of 8) patients in the MNS group. The ablation technique used for the repeat procedures was MAN in 28% (5/18), CF in 39% (7/18), MNS in 28% (5/18), and cryoablation in 6% (1/18). Of two repeat procedures the ablation technique was not reported. Repeat procedures with MAN were successful in 80% (4/5) of procedures, with CF in 86% (6/7), with MNS in 100% (5/5), and with cryoablation also in 100% (1/1) of procedures. Overall, there were no major complications during repeat procedures. During repeat procedures one minor complication (post-ablation pericarditis) occurred after a CF procedure. In two repeat procedures occurrence of complications was not reported.

Table 1 Demographic data

	MAN	CF	MNS	*p-value*
Patient total (n)	31	17	25	25
Patient age (years)	48 ± 16	45 ± 18	49 ± 13	0.72
Sex (male)	18 (58%)	8 (47%)	10 (40%)	0.40
Paediatric	2 (7%)	2 (12%)	0 (0%)	0.25
ASA	4 (13%)	3 (18%)	3 (12%)	0.86
Acenocoumarol	2 (7%)	0 (0%)	0 (0%)	0.25
AADs				
Class III	5 (16%)	0 (0%)	1 (4%)	0.10
Beta blocker	15 (48%)	12 (71%)	7 (28%)	0.024*
VA region				0.51
RVOT	23 (74%)	15 (88%)	20 (80%)	
LVOT	8 (26%)	2 (12%)	5 (20%)	

Patient characteristics and comparison of ablation results between the MAN and MNS groups.
Descriptive statistics are presented as mean ± SD for continuous variables.
*P < 0.05 for MNS vs. CF.

AADs: antiarrhythmic drugs; **ASA**: acetylsalicylic acid; **CF**: contact force; **LVOT**: left ventricular outflow tract; **MAN**: manual; **MNS**: magnetic navigation system; **RVOT**: right ventricular outflow tract; **SD**: standard deviation; **VA**: ventricular arrhythmia.

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Table 2 Procedural data

	MAN *(n= 31)*	CF *(n= 17)*	MNS *(n= 25)*	*P-value*
Procedural success	25 (81%)	12 (71%)	23 (92%)	0.20
Ablation data				
Approach (% of group total)				0.55
Antegrade	22 (71%)	15 (88%)	20 (80%)	
Transseptal	1 (3%)	1 (6%)	0 (0%)	
Retrograde	7 (23%)	1 (6%)	5 (20%)	
Epicardial	1 (3%)	0 (0%)	0 (0%)	
LVOT: below/above aortic valve	5 (63%)/3 (38%)	1 (50%)/1 (50%)	3 (60%)/2 (40%)	0.95
Application number	11 (4–21)	7 (3–17)	7 (4–9)	0.35
Application time (s)	499 (128–870)	200 (120–270)	291 (183–431)	0.46
Fluoroscopy time (min)	29 (16–38)	37 (21–46)	13 (10–20)	0.001*
Procedure time (min)	175 (123–221)	165 (146–180)	150 (120–173)	0.31
Hospital stay (days)	3 (2–5)	3 (2–4)	2 (2–3)	0.51
Complications				
Overall	3 (10)%	0 (0%)	0 (0%)	0.12
Minor	2 (7%)	0 (0%)	0 (0%)	0.25
Major	1 (3%)	0 (0%)	0 (0%)	0.50
Long-term follow-up				
Follow-up time (days)	2184 (1672–2802)	1721 (1404–1913)	3031 (2524–3286)	<0.001
Recurrences	12 (46%)	5 (50%)	10 (46%)	0.97
Repeat procedures	6 (20%)	6 (40%)	8 (33%)	0.32

Comparison of ablation results between the MAN, CF, and MNS groups. Descriptive statistics are presented median with (25th and 75th percentile). *P < 0.05 for MNS vs. MAN and CF.

CF: contact force; **LVOT:** left ventricular outflow tract; **MAN:** manual; **MNS:** magnetic navigation system

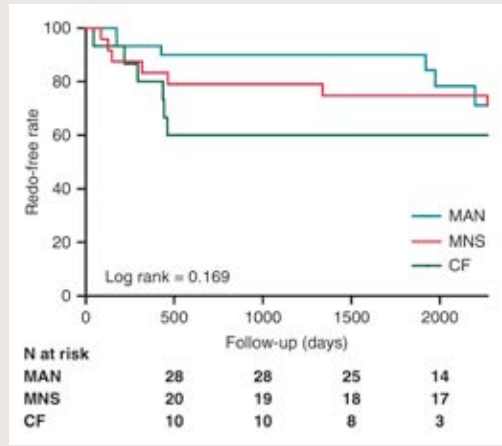

Figure 1 Repeat procedure-free rate and time to repeat procedure. **CF**: contact force; **MAN**: manual; **MNS**: magnetic navigation system

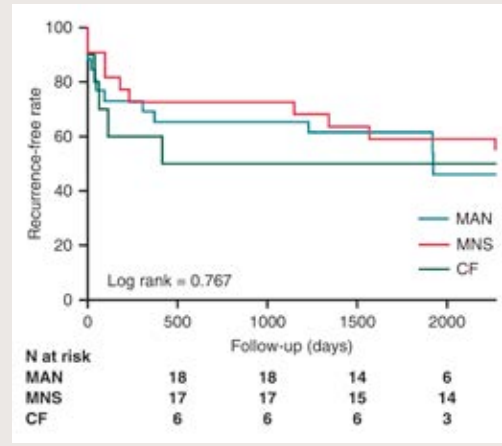

Figure 2 The recurrence-free rate and time to recurrence. **CF**: contact force; **MAN**: manual; **MNS:** magnetic navigation system

Discussion

This is the first study directly comparing the long-term clinical outcome of exclusively OT IVA ablation between MAN, CF, and MNS catheter ablation. The major findings of this study are that there are no significant differences in procedural or long-term success rates between these three groups and that fluoroscopy time is shorter for MNS compared with MAN and CF.

Manual catheter ablation success rates and complications

In literature, conflicting success rates are reported for manual catheter ablation of IVAs. Procedural success rates between 54% and 100% have been reported.[10,11] Reported mid-term success rates also vary, ranging between 55% and 100%.[12,13] In our present study, the procedural success rate of manual catheter ablation was 81%. These varying success rates may reflect differences in follow-up methods, definitions of success, and inclusion bias. Additionally, it may also demonstrate the heterogeneity in IVA presentation, from easily accessible and frequently seen locations such as the RVOT to more complex regions like the aortic cusps.

Minor complications during manual catheter ablation are reported in literature to be between 0% and 20%,[13,14] while major complications occur in 0–6%.[11,15] In our study, minor complications occurred in 7% of the MAN group and major complications in 3%.

Contact force ablation

A recent innovation regarding manual catheter ablation is the use of contact force sensing catheters. These catheters were designed to improve catheter—tissue contact by providing direct and quantified feedback to the operators of the applied pressure on the endo- or epicardium in order to enhance lesion formation and to simultaneously improve safety by guarding against excessive applied force.

The advantage of CF ablation is the additional force information that is obtained during the ablation. A disadvantage, however, is the increased stiffness of CF catheters. A recent meta-analysis comparing 19 studies showed that for ablation of atrial

fibrillation, the use of CF catheters vs. non-CF MAN catheters resulted in a significantly lower occurrence of acute pulmonary vein reconnections and recurrences as well as a reduced major complication rate and improved procedure parameters during 1 year follow-up.[9] However, very few data exist on CF ablation of VAs. One study from our centre demonstrated that CF ablation of idiopathic VAs in general showed no improvement on complication rate, acute success rate or recurrence rate during long-term follow-up compared with MAN or MNS ablation.[16]
In the current study, we found no improvement of procedural success or recurrences and repeat procedures when we compared CF with MAN or MNS ablation. Additionally, the CF group complication rate was equal compared with MAN ablation.

Magnetic navigation system ablation
One of the main advantages of MNS over MAN ablation reported in literature is safety. Upon publication, not a single myocardial perforation during ablation with theMNS has been reported, which is due to the soft and flexible quality of the catheter. Furthermore, after completion of an initial learning curve, the use of MNS most likely shortens procedure time, which in turn may prevent operator fatigue, shortens fluoroscopy time (as supported by the data in this report) and helps to reach less easily accessible areas in the heart during mapping.[7,17] Another advantage during mapping is the fact that the flexible catheter rarely induces mechanical PVCs, which makes identifying focal localizations of ventricular arrhythmias less challenging.[18]
A report on endocardial voltage maps for the diagnosis of arrhythmogenic right ventricular dysplasia comparing MAN and MNS acquired maps, showed MNS maps were more accurate because of better defined low voltage regions and higher surface areas and volumes of the RV.[19] Emphasis on procedural safety is important in general, but even more so in the treatment of usually non-lethal conditions such as IVAs. The ratio of treatment benefit vs. treatment risk in these cases needs to be weighed extra carefully. This makes a system like the MNS particularly useful for treating IVAs.
Additionally, as noted in the literature and again demonstrated in this study, most IVAs are ablated in the RVOT, which is a vulnerable area due to a relatively thin wall and neighbouring structures such as the bundle of his, the left main coronary artery, the left anterior descending artery, and the right and left coronary ostia.[1,20] Precision steering and reproducibility of mapping sites by using stored vectors helps to avoid these structures and to navigate back to previously determined safe and effective ablation targets.[17]

Clinical outcome
Our data did not show a significant difference in procedural success rates between the three groups. As mentioned earlier, apart from a study which showed no significant differences between MAN and CF regarding acute and long-term success of idiopathic VA ablation in general,[16] very few data exist on CF ablation of VAs. A recent randomized controlled study comparing MAN and MNS ablation of RVOT arrhythmia in 30 patients similarly showed no significant difference in procedural success.[14] One report comparing MAN and MNS ablation for all VT entities, which included a subgroup of IVA, did show a significant difference in procedural success (MAN 62% vs. MNS 84%), although the IVA subgroups were unevenly distributed in number (21 vs. 49) and included a variety of both OT and non-OT VT locations.[8] Our report did not show any significant differences in long-term clinical outcome; recurrences and repeat procedures were similar in all three groups.

Limitations of the study
This study is not a randomized trial and contains a relatively small patient cohort. Nonetheless, it should be taken into account that for the studied population of idiopathic VA patients this sample size is very reasonable. Additionally, follow-up was long and consecutive patients were included in both groups in compensation of the nonrandomized nature of this study.

Conclusion
Procedural and long-term clinical outcome of IVA ablation are equal for MAN, MNS, and CF. MNS has a favourable procedural safety profile due to the shorter fluoroscopy time compared with MAN and CF. To confirm our conclusions, more prospective and randomized studies with larger patient cohorts should be performed.

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6

Safety and Clinical Outcome of Catheter Ablation of Ventricular Arrhythmias Using Contact Force Sensing: Consecutive Case Series

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Abstract

Background
Poor catheter-to-myocardial contact can lead to ineffective ablation lesions and sub-optimal outcome. Contact force (CF) sensing catheters in ventricular tachyarrhythmia (VT) ablations have not been studied for their long-term efficacy.

Purpose
The aim of this study was to compare CF ablation to manual ablation (MAN) and remote magnetic navigation (RMN) ablation for safety and efficacy in acute and long-term outcome.

Methods
A total of 239 consecutive patients who underwent VT ablation with the use of MAN, CF, or RMN catheters were included in this single-center cohort study from January 2007 until March 2014. The primary endpoints were procedural success, acute major complications, and VT recurrences at follow-up. The median follow-up period was 25 months.

Results
Acute successwas achieved in 182 out of 239 procedures (76%). Acute success in-manual ablation, CF ablation and RMN ablation was 71%, 71%, and 86%, respectively (P = 0.03). Major complications occurred in 3.3% and there were less major complications (P = 0.04) in the RMN group. After an initial successful procedure, 66 of 182 patients (36%) had a recurrence during follow-up. This was not significantly different between groups. Using an intention-to-treat analysis, 124 patients (52%) had a recurrence. The recurrence rate was lowest in the RMN group.

Conclusion
The use of CF sensing catheters did not improve procedural outcome or safety profile in comparison to non-CF sensing ablation in this observational study of ventricular arrhythmia ablations.

Introduction
Catheter ablation of ventricular tachycardia (VT) has become standard therapy.[1-3] Meanwhile, there is a persistent demand for novel technologies to reduce complications and to improve success rates. Poor catheter-to-myocardial contact can lead to ineffective lesions and suboptimal outcomes. Information on contact force (CF) has shown to be an important determinant for the success of radiofrequency (RF) catheter ablation of atrial fibrillation.[4,5] It has been suggested that CF sensing also improves the acute outcome of VT ablation in small cohorts and improves safety.[6-8] However, there is a lack of data on the long-term clinical outcomes of with VA ablation using CF sensing catheters.
Remote magnetic navigation (RMN) in VT ablation has shown to be superior to manual catheter ablation, especially in nonstructural heart disease.[9,10] However, there has not been a direct comparison of visual and tactile feedback for VT ablation. The aim of this study is to compare CF ablation, manual (MAN) ablation, and RMN ablation for safety and efficiency in acute and long-term outcomes. Our primary hypothesis was that the use of CF catheters improves safety and efficacy compared to manual ablation.

Methods
Study Population and Data Collection
All patients who underwent ablation for ventricular arrhythmias (including patients with VT and ventricular extrasystoles [VES]) between January 2007 until March 2014 were included in this study. All data were collected prospectively with the exception of the CF data, which was collectedlater. The local ethics committee approved the study.

Preprocedural Protocol
All catheter ablation procedures were performed in accordance with institutionally approved local medical treatment protocols of the Erasmus Medical Center. Written informed consent for the procedure was obtained from all patients. Thrombus in the left ventricle was excluded by the use of a 2-dimensional transthoracic echocardiography. Antiarrhythmic drugs were discontinued for at least 4 half-lives prior to the procedure with the exception of amiodarone. In the case of an emergency VT procedure antiarrhythmic drugs were not ceased.

Procedural Protocol
The procedures were performed under local or general anesthesia. The choice of access (retrograde transaortic or transseptal) to the left ventricle was left up to the preference of the operator. Transseptal punctures were always guided by intracardiac echocardiography (ICE). Programmed electrical stimulation (2 drive trains at 400 and 600 milliseconds, up to 3 extrastimuli) was performed before and after the ablation to induce VT and to determine success, respectively. The procedures were performed using EnSite NavX 3D (St. Jude Medical Inc., St. Paul, MN, USA) mapping or the CARTO system (Biosense Webster, Inc., Diamond Bar, CA, USA). The following CF ablation catheters were used: Thermocool Smart Touch catheter (Biosense Webster) and EndosenseTacticath SA (St. Jude Medical Inc.). Contact between the catheter and the myocardium for each mapping point was measured in average and the maximum force and expressed in grams (g). The area under the real time force is measured as force time integral expressed in gram seconds (gs).
In patients with a focal origin of the VES or VT, ablation targets were the site of the earliest activation and/or the site of identical pace mapping. In patients with fascicular VT, ablation targets are the diastolic potential in the descending limb of the fascicular circuit or the presystolic fused Purkinje potential at the VT exit. In patients with

scar-related VT, ablation target include presystolic electrical activity within the infarct zone that demonstrates concealed entrainment (critical isthmus) or the exit sites. For substrate VT ablation, a combination of voltage mapping, pace mapping, and electrogram mapping is used. Scar homogenization was usually performed to abolish late-activated channels within scar and VT exit sites. Established peak-to-peak bipolar voltage criteria were used for identifying scar (0.5 mV), scar-border zone (0.51–1.49 mV) and healthy tissue (1.5 mV). For irrigated catheters, the electrode-tip temperature limit is usually set at 42 °C, with a power of 30–45 W, and irrigation flow of 30 mL/min. The ablation time is usually 60 seconds or shorter, depending on the location and effect. The catheter selection was dependent on logistics and the clinical judgment of the operator. Crossover to another ablation technique was allowed at the discretion of the operator. Crossover from manual catheter navigation to RMN ablation was not possible due to logistical reasons.

Postprocedural Protocol

Within 48 hours of the procedure a resting 12 lead electrocardiogram, laboratory tests, and chest radiograph were performed. All patients were seen for regular follow-up at 3 months after the ablation. For idiopathic VT or VES, a 24-hour Holter recording was scheduled for the 3-month follow-up visit and thereafter when symptomatic.

Complications

Acute complications were defined as complications occurring before the end of the procedure. All complications up to 30 days after the index procedure were identified. Complications were subdivided in minor and major complications. Minor complications included groin hematomas, AV fistula, pericardial effusion not requiring intervention, transient ischemic attack, and temporary AV block. The following complications were considered major complications: pericardial effusion requiring intervention, persistent AV-block, stroke, arterial venous fistula requiring surgery, and major bleeding. We also specifically studied ablation-related complications that excluded complications related to the vascular access.

Recurrence Rates

Recurrence was defined as any VT documented during follow-up. If antiarrhythmic drugs were necessary to remain free of VT it was considered a recurrence. When available, the morphology and the cycle length of the VT were studied. Medical charts from emergency room visits, discharge letters, ICD interrogation, electrocardiograms and, Holter recordings were studied. Time to recurrence from the index procedure and number of ICD therapy (shock and/or antitachycardia pacing ATP]) were analyzed. In case of an ablation of ventricular extrasystole (VES), recurrence was defined as VES on Holter recording < 95% reduction compared to preablation beats per 24 hours, with a morphology identical to the ablated VES.

Statistical Analysis

Data was analyzed using SPSS 15.0 (SPSS Inc., Chicago,IL, USA). We analyzed the following parameters: acute procedural success, complications, and recurrences during follow-up. Acute procedural success was defined as noninducibility of the clinical ventricular arrhythmia. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Median and interquartile ranges (IQR) were computed for continuous variables with non-normal distribution. Comparison of continuous variables between groups was made by unpaired Student's t-tests. In the case of nonnormal distribution of data, the Mann–Whitney U-test was used. Descriptive statistics for categorical data were expressed in absolute numbers and percentages. When comparing frequencies, the chi-square test or ANOVA test was used, as appropriate. Event-free survival rates were determined using the Kaplan–Meier method for both intentionto-treat analysis and for patients after an acute successful procedure. A 2-sided P-value of <0.05 (2-tailed) was considered significant.

Results

Baseline and Procedural Characteristics

A total of 239 consecutive patients were included in this study. The baseline characteristics of the study population are depicted in Table 1. There were 41 patients in the CF group, 112 patients in the MAN group, and 86 patients in the RMN group. Patients in the CF group more often had VES ablation, outflow tract ablation, and a transaortic route in comparison to the other groups. Patients in the MAN group less often had a redo ablations and outflow tract ablations in comparison to the other groups. Patients in the RMN group more often had a structural normal heart in comparison to the other groups. The median number of RF applications was lowest in the RMN group (Table 2). Procedural time was similar for all groups.

Procedural Outcome

Acute success was obtained in 76% of all procedures (Table 3). The highest acute procedural success was achieved in the RMN group. When stratified by the presence or absence structural heart disease, it is clear that RMN had a better outcome in patients with a structural normal heart (Figure 1, Table 1).

Crossover

In 1 patient of the RMN group and 4 patients of the CF group there was a crossover to a non-CF catheter. The reason for switching in the RMN group was the need for cryoablation. Reasons for switching from CF sensing catheters to a non-CF sensing catheter were the use of cryoablation (n = 2); ineffective ablation (n = 1); and damage to the catheter (n = 1). Cryoablation was used in 3 patients due to the location of the VA (coronary sinus and posterior fascicle) and due to intolerability of RF in 1 patient.

Complications

Major complications occurred in 3.3% of all procedures, and 0.4% of the major complications were acute (Table 3). There were significantly more major complications in the CF group (P = 0.04). Four out of 8 complications (50%) were due to the vascular access site and were not related to the CF catheter itself. One patient in the CF group died within 48 hours after a failed VT ablation due to refractory heart failure. In this patient the procedure was done under left ventricular assist device (LVAD), which had been indicated for cardiogenic shock.

Recurrence Rate

The median follow-up duration was 25 months [IQR 14- 35]. By using an intention to treat analysis, 124 patients (52%) had a recurrence (Table 3). The Kaplan–Meier analysis demonstrated that the RMN group had the lowest recurrence rate (Figure 2, log-rank P = 0.016). When looking at the outcome of 182 patients who had an initial successful procedure, 66 patients (36%) experienced a recurrence. There was no difference in recurrence rate between the different groups (Table 3).

Table 1 Baseline Characteristics

	ALL	CF	MAN	RMN	*P-value*
Total	239	41	112	86	
Male	174 (73%)	25 (61%)	88 (79%)	61 (71%)	0.09
Age (SD)	52.3 ± 16.7	55.5 ±16.2	53.2 ± 17.7	52.4 ± 15.8	0.70
Pediatric	12 (5%)	2 (5%)	7 (6%)	3 (4%)	0.68
VES	88 (35%)	21 (51%)	33 (30%)	31 (36%)	0.04
Redo	48 (20%)	10 (24%)	11 (10%)	27 (31%)	0.001
OT	84 (35%)	27 (58%)	25 (22%)	36 (41%)	0.001
Fascicular	24 (10%)	1 (2%)	12 (11%)	11 (13%)	0.18
Left sided	128 (54%)	17 (42%)	68 (61%)	43 (50%)	0.14
- Transaortic route	113 (88%)	2 (12%)	59 (87%)	39 (91%)	0.03
- Transseptal puncture	13 (10%)	15 (88%)	9 (13%)	2 (5%)	0.03
Ischemic	82 (34%)	15 (37%)	48 (43%)	19 (22%)	0.009
Non-SHD	126 (53%)	19 (46%)	47 (42%)	60 (70%)	< 0.001
SHD, nonischemic	31 (13%)	7 (17%)	16 (15%)	7 (8%)	0.24
ICD	103 (43%)	15 (37%)	62 (55%)	26 (30%)	0.001
OAC	22%	17%	26%	12%	0.05
B-blockers	54%	63%	56%	46%	0.15
Class I AAD	19%	24%	23%	13%	0.23
Class III AAD	38%	37%	48%	23%	0.01

AAD: antiarrhythmic drugs; **OAC**: oral anticoagulation; **OT**: outflow tract; **VES**: ventricular extrasystole; **SHD**: structural heart disease

Table 2 Procedural Characteristics

	ALL Median [IQR]	CF Median [IQR]	MAN Median [IQR]	RMN Median [IQR]	*P-value*
Procedural time (seconds)	180 [120–220]	120 [90–180]	190 [135–220]	150 [120–220]	0.39
Application number	11 [5–26]	15 [6–25]	12 [6–42]	8 [4–20]	0.02
Application time (seconds)	472 [215–1147]	482 [213–962]	700 [300–1920]	400 [190–1065]	0.10

Table 3 Acute Success, Complications and Recurrences, CF, MAN, and RMN

	ALL	CF	MAN	RMN	*P-value*
Acute success	**182 (76%)**	**29 (71%)**	**79 (71%)**	**74 (86%)**	**0.03**
-Structural heart disease	87 (77%)	16 (73%)	50 (78%)	21 (81%)	0.80
-Nonstructural heart disease	95 (75%)	13 (68%)	29 (62%)	53 (88%)	0.005
Complications	**26 (11%)**	**8 (19%)**	**13 (12%)**	**5 (5.8%)**	**0.06**
-Major	8 (3.3%)	4 (10%)	3 (2.7%)	1 (1.2%)	0.04
-Major acute	1 (0.4%)	1 (2.4%)	0 (0%)	0 (0%)	0.57
-Major catheter ablation related	4 (1.7%)	1 (2.4%)	2 (1.8%)	1 (1.2%)	0.31
-Major vascular access related	4 (1.7%)	2 (4.9%)	1 (0.9%)	1 (1.2%)	0.38
- Minor	18 (7.5%)	4 (9.6%)	10 (8.9%)	4 (4.7%)	0.44
FU time, months	25 [14–35]	18 [12–27]	25 [17–37]	29 [15–39]	0.001
Recurrences (intention-to-treat)	124 (52%)	24 (59%)	64 (57%)	36 (42%)	0.07
- Structural heart disease	69 (61%)	15 (68%)	38 (59%)	16 (62%)	0.72
- Nonstructural heart disease	55 (44%)	9 (29%)	26 (47%)	20 (33%)	0.07
Time to recurrence (months) [IQR]	0.5 [0–3]	1 [0–3]	0 [0–3]	3 [0–10]	0.09
Recurrence after acute successful procedure	66 (36%)	12 (41%)	30 (38%)	24 (32%)	0.53

CF: contact force; **MAN**: manual; **RMN**: remote magnetic navigation; **IQR**: interquartile range

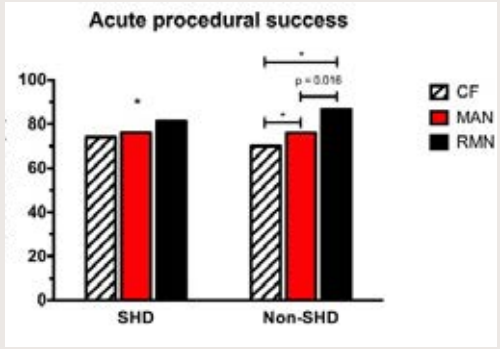

Figure 1 Acute procedural success in the 3 groups stratified by the presence of structural heart disease. *P = not significant. **CF:** contact force; **MAN:** manual; non-**SHD**: nonstructural heart disease; **RMN:** remote magnetic navigation; **SHD:** structural heart disease.

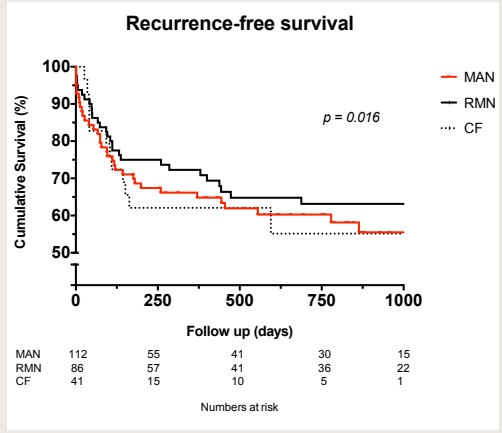

Figure 2 Recurrence-free survival stratified by the 3 groups (intentionto-treat analysis). **CF**: contact force; **MAN**: manual; **RMN**: remote magnetic navigation.

Discussion

This is the first study that investigates the long-term clinical outcome in VT ablation using CF catheters. In this ventricular arrhythmia cohort, CF did not improve results in terms of complications, acute success, or recurrence during follow-up. RMN was superior with regard to acute success, reduction of major complications, and recurrence rate using an intention-to-treat analysis.

Main Findings

A wide range of acute success of VT ablation has been reported, varying from 41 to 99%.[11-15] One of the first prospective multicenter studies was reported in 2000.[14] Over time there has been a remarkable evolution of mapping and ablation techniques, and also the indication for VT ablation has become wider. These are factors that possibly affect procedural success. In the present study, patients were included as early as 2007 up to 2014 and there was an acute success rate of 76%. Other studies over the last years have reported a long-term efficacy of VT ablation ranging from 27 to 49% during a follow-up of 8 to 48 months, which is comparable to the 36% recurrence rate in our cohort. Our group has previously shown a positive effect of RMN on the outcome of VT ablation in patients with structural heart disease.[9] With the current data, CF was not superior to RMN or MAN ablation.

Rationale for CF in VT Ablation

The TOCCATA study was one of the first catheter ablation studies in atrial fibrillation patients that showed a clinical benefit of CF on clinical outcome.[4] Recently, 2 clinical studies from Mizuno and Titz et al.[7,8] studied CF in VT ablation and found that continuous information on contact force resulted in less inefficient or excessive lesion formation. The 2 studies, however, were limited in their number of cases (17 and 10, respectively) and lacked proof of clinical outcome. Our observations did not confirm the extrapolated theoretical improvement of lesion formation into an improved long-term outcome or a better safety profile. In general, catheter force related complications in VT ablation such as perforation and tamponade are rare.[13,16]

Secondly, the lack of an integrated feedback loop in CF ablation may be critical in the current results. An optimal endocardial lesion in the ventricles in an animal model needed a total force of 30–40 g,[6] substantially higher than the averageand even maximum force in the present study. Despite being informed, the operator might not know how to interpret and integrate the given information. In the animal study of Sacher et al. a dramatic decrease was observed in the number of RF applications that do not result in adequate lesion formation with the addition of CF information.[6] An in vivo study of Mizino et al. calculated the best cut-off value for CF in ventricular ablation is at least 8 g when compared to other parameters of lesion formation.[7] Although CF sensing may be useful to prevent exertion of excess force on the myocardium, there is no consensus regarding how CF sensing may be useful to guide the formation of effective lesions in VT ablation.

Remote Magnetic Navigation Versus Contact Force

The average contact force in the current study is relatively low. However, we also know that RMN does not provide high contact force.[17] Therefore, it is unlikely to be the reason for the relatively low success. Of note, CF has primarily been used as a safety tool, not an efficacy tool. A possible explanation for the higher acute success in RMN-guided VT ablation is enhanced maneuverability.[18,19] It has the ability to reach anatomical structures which are otherwise difficult to access. Also, improved catheter stability in RMN is an important advantage.[20] The better long-term outcome of RMN in the intention-to-treat analysis can probably be explained by the higher acute procedural success rate.

Force Behavior During Ventricular Tachycardia

Low CF during ablation in atrial fibrillation has proven to be associated with a higher recurrence rate.[4,21] In contrast to the ablation of atrial arrhythmias the excursion of the ventricle during a VT ablation especially during tachycardia itself might lead to a less stable catheter position. An unstable catheter position results in intermittent impaired energy delivery and subsequent inappropriate lesion formation. This might explain why the use of CF in atrial arrhythmia is well established, while the benefit is not so clear for VT ablations. Ideally, CF sensing in the future can be integrated in robotic navigation as both entities could magnify the benefit of CF.[22]

Limitations of the Study

Although this study was able to provide data on followup from a substantial number of patients who underwent VT ablation, it was not randomized. The study cohort was heterogeneous; the indication for ablation varied from VES, idiopathic VT to scar relatedVT. Baseline characteristics significantly differed between groups. Another limitation of the study was that ICD recordings were only available for a minority of patients for follow-up. In the other patients, Holter and clinical events were used. Considering the inherent limitations of an observational study, all conclusions must be drawn with caution.

Conclusion

The use of CF sensing catheters did not improve procedural outcome or safety profile in comparison to non-CF sensing ablation in this observational study of ventricular arrhythmia ablations. RMN was superior with regard to acute success, reduction of major complications, and recurrence rate using an intention-to-treat analysis.

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7

Contact feedback improves long-term outcomes of remote magnetic navigation guided ischemic ventricular tachycardia ablation

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Abstract

Introduction
Remote Magnetic Navigation (RMN)-guided catheter ablation (CA) is a feasible treatment option for patients presenting with ischemic ventricular tachycardia (VT). Catheter-tissue contact feedback, enhances lesion formation and may consequently improve CA outcomes. Until recently, contact feedback was unavailable for RMN-guided CA. The novel e-Contact Module (ECM) was developed to continuously monitor and ensure catheter-tissue contact during RMN-guided CA.
Objective: The present study aims to evaluate the effect of ECM implementation on acute and long-term outcomes in RMN-guided ischemic VT ablation.

Method
This retrospective, two-center study included consecutive ischemic VT patients undergoing RMN-guided CA from 2010–2017. Baseline clinical data, procedural data, including radiation times, and acute success rates were compared between CA procedures performed with ECM (ECM+) and without ECM (ECM–). One-year VT-free survival was analyzed using Cox-proportional hazards models, adjusting for potential confounders: age, left ventricular function, VT inducibility at baseline and substrate based ablation strategy.

Results
The current study included 145 patients (ECM+ N=25, ECM– N=120). Significantly lower fluoroscopy times were observed in the ECM+ group (9.5 (IQR 5.3–13.5) versus 12.5 minutes (IQR 8.0–18.0), P=0.025). Non-inducibility of the clinical VT at the end of procedure was observed in 92% ECM+ versus 72% ECM– patients (P=0.19). ECM guidance was associated with significantly lower VT-recurrence rates during 1-year follow-up (16% ECM+ versus 40% ECM–; multivariable HR 0.29, 95%–CI 0.10–0.69, P=0.021, reference group: ECM–).

Conclusion
Contact feedback by the ECM further decreases fluoroscopy exposure and improves VT-free survival in RMN-guided ischemic VT ablation.

Introduction
Catheter ablation (CA) is an important treatment option for patients with ischemic heart disease presenting with ventricular tachycardia (VT).[1, 2] CA is reported to decrease the likelihood of subsequent ICD shocks, prolongs the time to VT recurrence and decreases VT burden in patients diagnosed with ischemic VT.[3-5]
Several CA techniques are currently available for ischemic VT ablation. Some studies reported superiority of remote magnetic navigation (RMN) over manual guided VT ablation, exhibiting lower procedure and fluoroscopy times, higher acute success rates, lower VT recurrence rates and less adverse events.[6-8]
CA techniques are rapidly evolving and there is a continuous search for novel technologies to improve long-term success and reduce complication rates.[2] As the quality of contact between the catheter tip and the myocardial tissue is believed to be of vital importance for lesion formation[9], there has been a focus on the development of technologies providing contact feedback. Contact force (CF) sensing catheters appeared to be beneficial in manual guided atrial fibrillation ablation.[10] However, in an observational study of VT ablations, the use of CF sensing catheters was still inferior to RMN-guided CA with respect to procedural outcome, long-term outcomes and safety.[7] A possible explanation for the lack of benefit of CF sensing catheters in manual VT ablation is the loss of tissue contact during ventricular contraction which can be maintained with RMN. In RMN-guided CA, contact feedback only recently became available with the development of the e-Contact Module (ECM). The present study aims to evaluate the effect of the ECM on RMN-guided ischemic VT ablation outcomes. Our primary hypothesis is that use of the ECM benefits lesion formation, resulting in lower VT recurrence.

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Methods

Study design
This study is a retrospective, two-center study investigating ischemic VT ablation procedures performed with RMN. Index procedures performed with the ECM (ECM+) were compared with index procedures performed without ECM (ECM–). Primary endpoint was the freedom of VT recurrence during 12-months of follow-up (FU). We also analyzed the following secondary endpoints: procedural parameters (including radiation times), acute procedure success, complication rates, the redo procedure rates and all-cause mortality at 12-months of follow-up (FU). Additionally, the ICD therapy burden during the 12 months anticipating and the 12 months following the index procedure were evaluated, as well as the proportion of ECM guided applications applied in optimal or suboptimal contact. The local ethical committees approved data collection (MEC-2018-1114 and WO 15.142). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Procedural informed consent was obtained from all the patients prior to the electrophysiological study (EPS).

Study population
All consecutive patients undergoing the first RMN-guided CA procedure for VT with an ischemic substrate in one of the two participating centers between January 2010 until December 2017 were included in this study. Patients with VTs caused by a non-ischemic cardiomyopathy were not eligible for inclusion. Participating centers were the Onze Lieve Vrouwe Gasthuis (OLVG, Amsterdam, the Netherlands) and the Erasmus Medical Center (Erasmus MC, Rotterdam, the Netherlands). Patients were eligible for VT ablation based on the most recent guidelines and recommendations at the time of procedure.[1, 2]

Definitions
Index procedures were defined as the first RMN-guided VT ablation procedure performed in a patient in one of the participating centers within the mentioned time frame. All repeat VT ablation procedures following the index procedure were considered redo procedures. Acute procedure success was defined as non-inducibility of the clinical VT at the end of procedure. Recurrence of VT was regarded when a patient had a recurrence of a sustained VT, or VT treated with implantable cardioverter defibrillator (ICD) therapy (either anti-tachy pacing (ATP) or shock). Total procedure time was defined as the time from first puncture until the removal of catheters. Mapping time was defined as the time from start mapping (first point taken) until completion (last point taken), whereas ablation time was defined as time from first application until last application. Minor complications were pericardial effusion not requiring intervention and access site complications. Major complications were cardiac tamponade, hemorrhagic shock, stroke and procedure-related death. Chronic kidney disease was considered when a patient had an estimated Glomerular Filtration Rate (eGFR) using the CKD-EPI formula of 59 ml/min/1.73m2 or lower (i.e. chronic kidney disease (CKD) stage IIIa or higher).

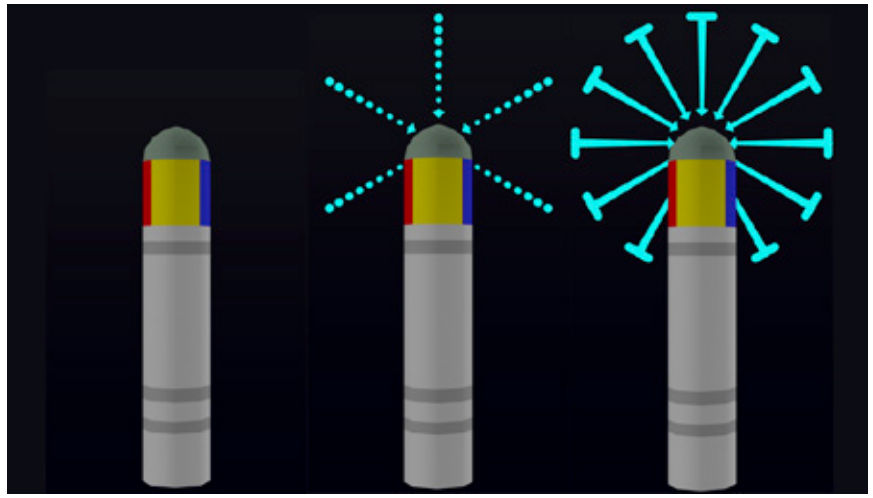
Data collection
Baseline demographic and clinical characteristics were collected from the institutional electronic patient dossiers (HiX version 6.1 (ChipSoft BV, Amsterdam, NL) or Epic Hyperspace 2017 (Epic Systems Corporation, Verona, WI, USA)). Procedural data was derived both from the electronical medical files, as well as from the procedural log files recorded with the EP-workmate (St. Jude Medical Inc., St. Paul, MN, USA), the Niobe II or Niobe ES Magnetic Navigation System (Stereotaxis Inc., St. Louis, MO, US) and the Odyssey Cinema system (Stereotaxis Inc., St. Louis, MO, USA). All patient information was de-identified.

Procedural protocol
All CA procedures were performed in accordance with institutionally approved local medical treatment protocols of the OLVG and EMC. Ablation was performed targeting VTs induced by programmed electrical stimulation (PES) and/or modifying the electrical substrate. The left ventricle (LV) was accessed through a transaortic or transseptal approach based on the operator's preference. In all patients, electroanatomic maps were obtained while patients were in sinus rhythm with the Carto 3D mapping system as standard of care (CARTO 3 (Biosense Webster Inc., Diamond Bar, CA, USA). Bipolar voltage criteria were used to identify scar (<0.5 mV), scar-border zone (0.51–1.49 mV) and healthy tissue (>1.5 mV). If not incessant, VT was induced by PES and activation or entrainment mapping was performed if VT was hemodynamically tolerable, to locate critical isthmuses and exit sites. The main target of scar-related VT ablation was the critical isthmus of hemodynamically stable sustained VT identified using conventional diagnostic criteria (i.e. middiastolic potentials). Another target was the exit of the VT circuit identified during activation mapping or pace mapping. In the case of hemodynamically unstable or noninducible sustained VT, substrate ablation was performed focused on areas within the scar demonstrating fractionation or late potentials during sinus rhythm. It was up to the operator's preference to perform substrate ablation in hemodynamically stable VT as well in addition to targeting critical isthmus and exit sites. Ablation was performed using the following radiofrequency settings: right ventricle (RV): 40-45W, 20ml/min, max 43°C; LV: 50-55W, 30ml/min, max 43°C. PES was performed at the end of the procedure to evaluate the effect of the applied therapy. RMN (Stereotaxis, Inc., St. Louis, MO, USA.) was used in all cases.

Follow-up
Following the index procedure, all patients were checked at the out-patient clinic at regular intervals. Standard follow-up visits were: 6 months and 12 months after the procedure, including ICD check-up. Voluntary follow-up patients were: 3 months and 9 months after procedure. Some patients were seen even more frequently when they experienced VT recurrences. Some patients had their FU at referral hospitals. This data was also collected and included in the present study.

e-Contact Module
The ECM, a recently developed hardware and software module compatible with the Niobe ES RMN system, incorporates 16 types of data of three categories to determine whether the catheter is in contact with cardiac tissue or not. The following types of data are used to determine whether the catheter is in (optimal) contact with cardiac tissue: 1) electrical impedance measurements; 2) cardiac induced motion of the catheter tip; and 3) the torque being applied by the magnetic field. To confirm the different threshold levels of contact, qualitative assessments based on observations during pre-clinical studies were made while visually observing contact using intra-cardiac ultrasound. The contact assessment is visualized to the user as a starburst near the catheter tip and as a blue line on the contact tracing (Figure 1). When there is minimal contact, the starburst is small, whereas in optimal contact the starburst is bolder. Without any contact, there is no starburst. The ECM was installed in the EMC in April 2016 and in the OLVG in July 2017.

Figure 1 The e-Contact Module



The figure shows the three types of output of the e-Contact Module.

Left: When the catheter is not in contact with myocardial tissue, the ablation catheter is displayed without starburst.
Middle: When the catheter is placed in contact with myocardial tissue, a starburst appears at the tip of the ablation catheter.
Right: When the catheter is in optimal contact, a dense starburst is shown at the catheter tip.

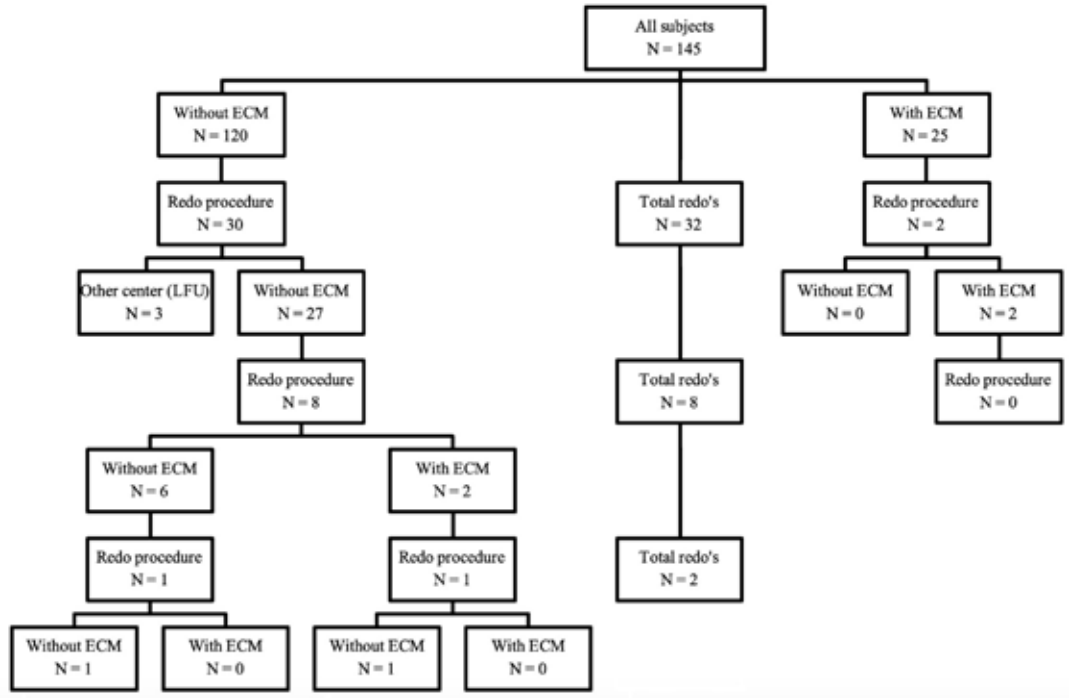
Quality of Contact
As contact is established by the ECM by a mathematical algorithm, calculated from 16 variables, as described above, this algorithm could be used to evaluate the quality of contact of all RF applications applied in patients included in the study. For every single RF application, its time being applied in either optimal, suboptimal or without contact with myocardial tissue was derived from the procedural log files recorded by the ECM and the Stereotaxis systems.

Statistical analysis
Normality was assessed by the Kolmogorov-Smirnov test, or when appropriate, Shapiro-Wilk test. Mean and standard deviation (SD) were calculated for normally distributed continuous variables. Median and interquartile range (IQR) were computed for continuous variables with non-normal distribution. Descriptive statistics for categorical data were expressed in absolute numbers and percentages. Continuous variables were compared between groups by the unpaired Student's T-tests. For variables with non-normal distributions, the Mann-Whitney U-test was used. For comparing frequencies, the Chi-square test was used, or, when appropriate, Fisher's exact test. Univariable and Multivariable Cox proportional hazards models were used to examine the relationship between treatment group and long-term outcomes, adjusting for potential confounders. In all ECM+ patients, Cox proportional hazards models were also used to evaluate the relationship between the quality of contact as measured by the ECM and the long-term outcomes. A 2-sided P-value of <0.05 was considered significant. Data were analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA).

Results
This study included 187 RMN-guided VT ablation procedures, of which 145 were index procedures and 42 were redo procedures (Figure 2). Of the 145 index procedures, 120 were performed without ECM (ECM–) and 25 with ECM (ECM+) guidance. In total, the OLVG included 91 patients (63%) and the Erasmus MC 54 patients (37%). In the OLVG, 5 patients (6%) were treated with ECM guidance, whereas in the Erasmus MC it was used in 20 patients (80%). In the OLVG, procedures were performed by 2 operators in total. The first operator from this center performed 95% of procedures, which was comparable between study groups. In the second center, 5 operators in total performed the procedures over time. First operator performed the majority of procedures (57%), the second operator performed 4%, the third 4%, the fourth 20% and the fifth 15% of procedures, which were also comparable between groups.

Demographic and baseline clinical data
Demographic and baseline clinical data are presented in Table 1. The mean age was 67.9 ± 9.6 years. The majority of patients had a poor LVEF <30% (N=82 (57%)). At baseline, 83 (58%) patients were on amiodarone therapy. In total, 136 (94%) patients had an ICD. Baseline demographic and clinical data were not significantly different between groups, except for PCI being more frequently performed in the ECM+ group (ECM– 55% versus ECM+ 80%, P=0.019).
Descriptive procedural parameters are presented in Table 2. Epicardial ablation was performed in 3 patients (3%). The ECM was not applied to the epicardium in this study. In all ECM+ patients (N=25, 100%) an ablation strategy including substrate ablation was applied versus in 83% of the ECM– patients (P=0.024). In the 21 patients (14%) were no substrate ablation was performed, the ablation strategy focused on elimination of critical isthmuses and/or exit sites only.

Figure 2 Study population



Procedural outcome
Mean total procedure time was 200 ± SD 76 minutes and was comparable between groups (P=0.12), as is shown in Table 3. The mean application duration was 1943 ± SD 1064 seconds. There was no significant difference between groups (ECM– 1823 ± SD 1117 seconds versus ECM+ 2119 ± SD 979 seconds, P=0.29). Fluoroscopy time was significantly lower in ECM+ patients (9.5 (IQR 5.3 – 13.5) minutes versus 12.5 (IQR 8.0 – 18.0) minutes, P=0.025). Moreover, the ablation time was significantly lower in ECM+ group (83 ± SD 49 versus 112 ± 60 minutes, P = 0.028), whereas the mapping times were comparable between groups. Non-inducibility of the clinical VT at the end of the procedure was observed in 115 patients (79%), whereas non-inducibility of all VT was observed in 84 patients (56%). The non-inducibility rates were comparable between groups (P=0.19 and P=0.27, respectively).

Long-term outcome
At 12-months FU, VT recurrence was observed in 48 (40%) ECM– patients, compared to 4 (16%) ECM+ patients (P=0.023), as illustrated in Table 3. Moreover, ECM– patients were more frequently admitted to the hospital because of VT recurrence (39 (33%) ECM– versus 3 (12%) ECM+, P=0.040). We observed a tendency towards more redo procedures performed in ECM– patients when compared to ECM+, although this was statistically not significant (30 (25%) versus 2 (8%) respectively, P=0.06). Anti-arrhythmic drugs were stopped during FU in 22 patients (16%), which consisted predominantly of therapy with amiodarone and was compa-

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rable between groups. Twelve month FU data was incomplete in 22 patients (15%), which was comparable between groups (ECM– 18 patients (15%) versus ECM+ 4 patients (15%), P = 0.90).

CA procedures performed with ECM guidance (ECM+) were associated with improved VT-free survival during the 12 months of follow-up, when compared to ECM– (multivariable HR 0.29, 95%-CI 0.10–0.69, P=0.021, with ECM– as the reference group) (Table 4a and Figure 3). Age, gender, LVEF, VT inducibility at baseline EPS and an ablation strategy using substrate ablation, did not show a significant relation with the outcome. As a sensitivity analysis, center of procedure, medical history of PCI, non-inducibility of clinical VT at end of procedure and non-inducibility of all VT at end of procedure, were consecutively also added to the univariate and multivariate models, and did not show any significant associations with the primary outcome either (data not shown). There was no significant difference between groups in all-cause mortality (multivariable HR 1.47, 95%-CI 0.37–5.88, P=0.59, with ECM– as the reference group) (Table 4b), or in the redo procedure rates (multivariable HR 0.51, 95%-CI 0.11–2.33, P=0.39, with ECM– as the reference group) (Table 4c). Age, gender, LVEF and an ablation strategy using substrate ablation, procedurecenter and medical history of PCI, did not show a significant relation with all-cause mortality and redo procedure rate. However, VT inducibility at baseline EPS was significantly related to a lower redo procedure rate (multivariable HR 0.43, 95%-CI 0.12–0.97, P=0.044, with VT non-inducibility at baseline EPS as the reference group).

ICD therapy burden

In 120 patients who had an ICD implanted, the ICD therapy burden in the 12 months anticipating and 12 months following the index procedure was evaluated. In 16 patients, no pre-operative ICD data was available, as the ICD was implanted during the same hospital admission as the VT ablation procedure. Additionally, 9 patients did not have an ICD at all. Post-procedurally, a significant lower proportion of ECM+ patients experienced ICD shocks, as compared to ECM– patients (4% versus 24%, P = 0.048). A median reduction of 2.0 (IQR 0.0 – 10.0) ATP episodes and a median reduction of 1.0 (IQR 0.0 – 3.0) shock were observed after the VT ablation procedure (Table 5), which were comparable between groups.

Quality of contact

The quality of catheter-tissue contact during all ECM+ procedures was calculated and analyzed. The majority of the total application duration was applied in optimal contact (71% (IQR 42 – 83)). A small part of the total application duration was applied without contact (6% (IQR 1 – 17)), whereas 21% (IQR 7 – 29) of the total application duration was applied in suboptimal contact. There was no significant relation between the type of contact and the 12-months VT recurrence rates (applications applied without any contact: univariate HR 1.02, 95% CI 0.98 – 1.06, P = 0.407; applications applied in suboptimal contact: univariate HR 0.94, 95% CI 0.86 – 1.04, P = 0.227; applications applied in optimal contact: univariate HR 1.00, 95% CI 0.96 – 1.04, P = 0.958). There were no significant associations between LV approach (transaortic or transseptal) and the measured quality of contact.

Safety data

Major and minor complication rates were not significantly different between groups (major: 3% versus 0%, P=0.42; minor: 8% versus 12%, P=0.56). Major complications were CVA (1 patient, who had post-procedural hemianopia and dysartria which improved significantly 5 days after the procedure), a complete AV block (1 patient, who already had an DDD-ICD implanted) and RV tab during attempting pericardial access. The RV tab was initially dry and therefore the procedure was continued, however a few hours after completion of the procedure the patient developed cardiac tamponade for which pericardiocentesis was performed (1 patient, who recovered without sequelae). The majority of minor adverse events were access site complications.

Table 1 Demographic and baseline clinical data

	ECM– N=120	**ECM+** N=25	**Total** N=145	*P-value*
Age (years) *	67.5 ± 9.9	69.8 ± 7.7	67.9 ± 9.6	0.27
Female	24 (20%)	3 (12%)	27 (19%)	0.35
BMI (m/kg2) †	26.9 (24.2 – 30.8)	26.0 (23.5 – 29.3)	26.4 (24.2 – 30.5)	0.44
Hypertension	46 (38%)	9 (36%)	55 (38%)	0.83
Diabetes	20 (17%)	6 (24%)	26 (18%)	0.39
Atrial Fibrillation	40 (33%)	11 (44%)	51 (35%)	0.31
COPD	23 (19%)	5 (21%)	28 (19%)	0.85
Chronic Kidney disease (stage ≥ IIIa)	56 (48%)	15 (60%)	71 (50%)	0.27
eGFR (ml/min/1.73m2)	61 ± 19	60 ± 26	61 ± 20	0.85
Hemodialysis	2 (2%)	0 (0%)	2 (1%)	0.51
NYHA class I	30 (42%)	9 (45%)	39 (42%)	0.79
NYHA class II	18 (25%)	7 (35%)	25 (27%)	0.37
NYHA class III	24 (33%)	4 (20%)	28 (30%)	0.25
NYHA class IV	0 (0%)	0 (0%)	0 (0%)	1.00
Ischemic CMP	120 (100%)	25 (100%)	124 (100%)	1.00
Thrombolysis	12 (10%)	3 (12%)	15 (10%)	0.78
PCI	65 (55%)	20 (80%)	85 (59%)	0.019
CABG	37 (31%)	11 (44%)	48 (33%)	0.20
ICD	111 (93%)	25 (100%)	136 (94%)	0.16
VT storm	29 (24%)	4 (16%)	33 (23%)	0.38

LVEF				
Normal (≥55%)	5 (4%)	0 (0%)	5 (3%)	0.30
Mildly Reduced (45-54%)	22 (18%)	3 (12%)	25 (17%)	0.45
Reduced (30-44%)	27 (23%)	6 (24%)	33 (23%)	0.87
Poor (<30%)	66 (55%)	16 (64%)	82 (57%)	0.41
(D)OAC	79 (66%)	18 (72%)	97 (67%)	0.55
Beta-blocker	98 (82%)	20 (80%)	118 (81%)	0.85
Ca-antagonist	5 (4%)	1 (4%)	6 (4%)	0.97
Amiodarone	66 (56%)	17 (68%)	83 (58%)	0.27
Sotalol	10 (8%)	3 (12%)	13 (9%)	0.56
Class 1a	4 (3%)	1 (4%)	5 (4%)	0.89
Class 1b	2 (2%)	2 (8%)	4 (3%)	0.08
Class 1c	0 (0%)	0 (0%)	0 (0%)	1.00

* Mean ± SD † Median (IQR)
BMI: body mass index; **CABG**: coronary artery bypass grafting; **CKD-EPI**: chronic kidney disease epidemiology collaboration; **CMP**: cardiomyopathy; **COPD**: chronic obstructive pulmonary disease; **(D)OAC**: (direct) oral anticoagulant; **ECM**: e-Contact Module; **eGFR**: estimated Glomerular Filtration Rate (using the CKD-EPI formula); **ICD**: implantable cardioverter defibrillator; **LVEF:** left ventricular ejection fraction; **PCI**: percutaneous intervention

Table 2 Baseline procedural data

	ECM– N=120	**ECM+** N=25	**Total** N=145	*P-value*
Approach				
Right sided - Transvenous	3 (3%)	0 (0%)	3 (2%)	0.42
Left sided - Transseptal	8 (7%)	3 (12%)	11 (8%)	0.36
Left sided - Transaortic	105 (88%)	22 (88%)	127 (86%)	0.95
Both Right and Left (transaortic)	4 (3%)	0 (0%)	4 (3%)	0.36
VT inducibility at baseline EPS	106 (88%)	18 (75%)	124 (86%)	0.18
Mapping during VT	76 (63%)	15 (60%)	91 (63%)	0.75
Number of VT morphologies*	2.0 (1.0 – 3.0)	1.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)	0.10
VT cycle length (msec)*	391 ± 101	398 ± 70	392 ± 97	0.81
Location of ablation				
RV	7 (6%)	0 (0%)	7 (5%)	0.22
LV	117 (98%)	25 (100%)	142 (98%)	0.42
Epicardial	3 (3%)	0 (0%)	3 (2%)	0.42
Substrate modification	99 (83%)	25 (100%)	124 (86%)	0.024

* Median (IQR)
ECM: e-Contact Module; **LV:** left ventricle; **RV:** right ventricle; **VT =** ventricular tachycardia

Table 3 Acute and long-term outcomes

	ECM– N=120	**ECM+** N=25	**Total** N=145	*P-value*
Acute outcomes				
Total procedure time (min)*	206 ± 79	175 ± 56	200 ± 76	0.12
Total ablation time (sec)	1823 ± 1117	2119 ± 979	1943 ± 1064	0.29
Total fluoroscopy time (min)†	12.5 (8.0 – 18.0)	9.5 (5.3 – 13.5)	11.0 (7.2 – 17.3)	0.025
Non-inducibility clinical VT	92 (77%)	23 (92%)	115 (79%)	0.19
Non-inducibility all VT	66 (55%)	19 (76%)	85 (59%)	0.15
12 month outcomes				
VT recurrence	48 (40%)	4 (16%)	52 (36%)	0.023
Hospital admission for VT recurrence	39 (33%)	3 (12%)	42 (29%)	0.040
Redo procedure	30 (25%)	2 (8%)	32 (22%)	0.06
All-cause mortality	9 (8%)	3 (12%)	12 (8%)	0.46

* Mean ± SD † Median (IQR)
ECM: e-Contact Module; **VT:** ventricular tachycardia

Table 4a Cox Proportional Hazard models for VT recurrence

VT-recurrence	Univariable model			Multivariable model		
	Hazard ratio*	95% CI	P-value	Hazard ratio*	95% CI	*P-value*
ECM guidance	0.34	0.12 – 0.95	0.040	0.29	0.10 – 0.69	0.021
Age	1.01	0.99 – 1.04	0.35	1.01	0.98 – 1.04	0.48
LVEF <45%	1.66	0.75 – 3.70	0.21	1.85	0.83 – 4.17	0.14
VT inducibility at baseline EPS	0.62	0.30 – 1.27	0.19	0.53	0.25 – 1.14	0.10
Substrate modification	0.80	0.39 – 1.64	0.55	1.02	0.49 – 2.17	0.95

Table 4b Cox Proportional Hazard models for All-cause mortality

All-cause mortality	Univariable model			Multivariable model		
	Hazard ratio*	95% CI	P-value	Hazard ratio*	95% CI	*P-value*
ECM guidance	1.56	0.42 – 5.88	0.50	1.47	0.37 – 5.88	0.59
Age	1.03	0.97 – 1.10	0.40	1.03	0.96 – 1.09	0.42
LVEF <45%	0.37	0.05 – 2.86	0.34	2.50	0.32 – 20.00	0.38
VT inducibility at baseline EPS	0.81	0.18 – 3.70	0.78	0.97	0.20 – 4.55	0.97
Substrate modification	0.94	0.20 – 4.35	0.94	0.92	0.19 – 4.55	0.92

Table 4c Cox proportional Hazard models for Redo procedure

Redo procedure	Univariable model			Multivariable model		
	Hazard ratio*	95% CI	P-value	Hazard ratio*	95% CI	*P-value*
ECM guidance	0.48	0.11 – 2.04	0.32	0.51	0.11 – 2.33	0.39
Age	0.99	0.95 – 1.03	0.60	0.98	0.94 – 1.02	0.30
LVEF <45%	1.09	0.37 – 3.23	0.88	1.12	0.38 – 3.33	0.83
VT inducibility at baseline EPS	0.47	0.17 – 1.27	0.14	0.34	0.12 – 0.97	0.044
Substrate modification	2.27	0.88 – 5.88 0.17 – 1.13	0.09	0.41	0.15 – 1.12	0.08

* Hazard ratios were calculated using the following reference groups: no ECM guidance (ECM–), normal LVEF, VT non-inducibility at baseline EPS, no substrate modification performed.
ECM: e-Contact Module; **EPS**: electrophysiology study; **LVEF**: left ventricular ejection fraction; **VT**: ventricular tachycardia

Table 5 ICD therapy burden

	ECM– N=120	**ECM+** N=25	**Total** N=145	*P-value*
12 months pre-procedure				
Documented VT	95 (100%)	25 (100%)	120 (100%)	1.00
If yes, number of VT episodes*	5.0 (2.0 – 15.0)	6.0 (4.0 – 18.0)	5.0 (3.0 – 14.8)	0.52
ATP performed	69 (73%)	19 (76%)	88 (73%)	0.29
If yes, number of ATP episodes	5.0 (3.0 – 14.0)	6.0 (5.0 – 39.0)	5.0 (3.0 – 17.0)	0.10
shock performed	66 (70%)	13 (52%)	79 (66%)	0.10
If yes, number of shocks	2.0 (1.0 – 4.0)	2.0 (1.0 – 8.0)	2.0 (1.0 – 5.0)	0.19
12 months post-procedure				
Documented VT	48 (50%)	4 (16%)	52 (43%)	0.023
If yes, number of VT episodes	3.0 (1.0 – 10.5)	21.0 (5.0 – 99.3)	3.0 (1.0 – 12.5)	0.05
ATP performed	31 (33%)	4 (16%)	35 (29%)	0.22
If yes, number of ATP episodes	3.0 (1.5 – 8.0)	21.0 (4.3 – 99.3)	3.0 (2.0 – 10.0)	0.39
shock performed	23 (24%)	1 (4%)	24 (20%)	0.048
If yes, number of shocks	2.0 (1.0 – 5.0)	1.0 (1.0 – 1.0)	2.0 (1.0 – 4.5)	0.09
Reduction				
VT episode reduction	3.0 (1.0 – 10.3)	5.0 (1.5 – 18.0)	4.0 (1.0 –11.0)	0.23
ATP episode reduction	2.0 (0.0 – 7.5)	5.0 (0.8 – 39.0)	2.0 (0.0 – 10.0)	0.09
Shock reduction	1.0 (0.0 – 3.0)	1.0 (0.0 – 3.5)	1.0 (0.0 – 3.0)	0.80

* Median (IQR)
ECM: e-Contact Module; **VT**: ventricular tachycardia; **ICD**: implantable cardioverter defibrillator; **ATP:** anti-tachy pacing; **CA**: catheter ablation

Figure 3A Cumulative VT free survival of patients treated with e-Contact Feedback (ECM+) versus patients treated without e-Contact Feedback (ECM-)

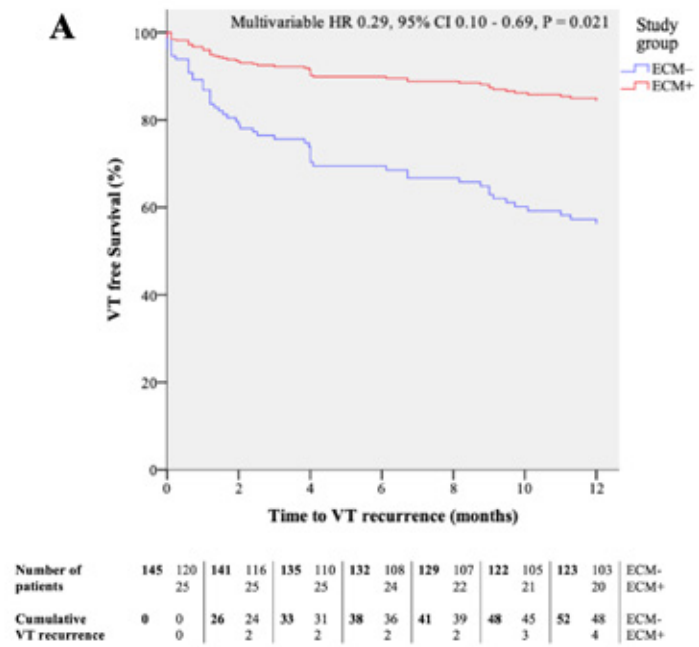


Figure 3B Cumulative survival of patients treated with e-Contact Feedback (ECM+) versus patients treated without e-Contact Feedback (ECM-)
Feedback (ECM-)

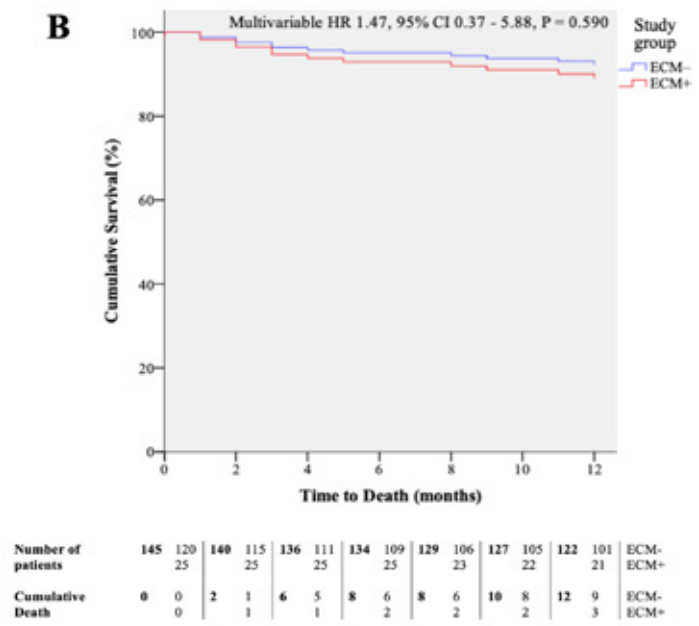
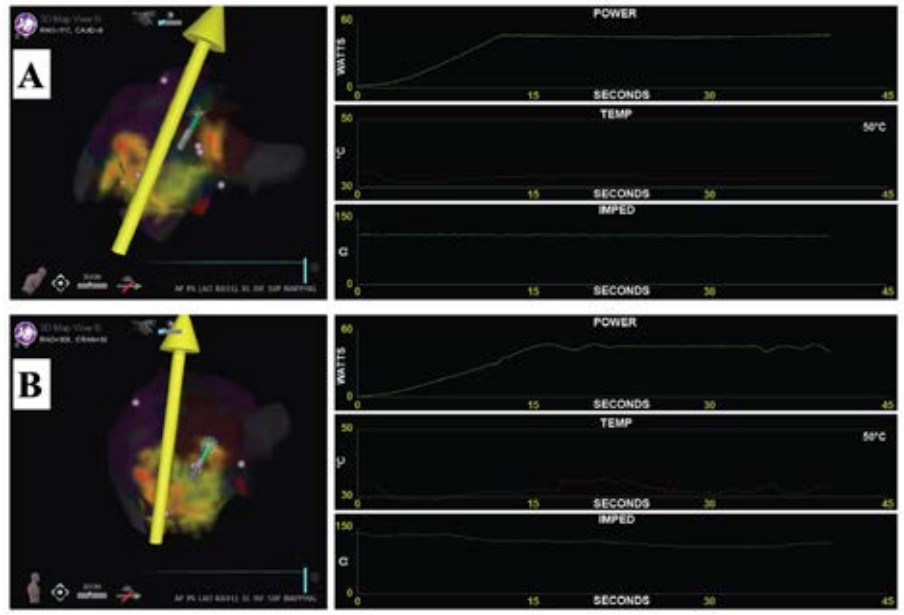


Figure 3A shows the survival curves of VT-recurrence and all-cause mortality, which were evaluated by Cox proportional hazards models. Figure 3A displays the VT-free survival during 12 months of follow-up. A significant higher VT-free survival was observed in patients treated with ECM guidance (ECM+) (multivariable HR 0.29, 95% CI 0.10 – 0.69, P=0.021, for VT recurrence with ECM– as the reference group).

Figure 3A shows the all-cause mortality during 12 months of follow-up, as evaluated by Cox proportional hazards models. The all-cause mortality was not significantly different between patients treated with the ECM connected (ECM+) and those treated without ECM (ECM–) (multivariable HR 1.47, 95% CI 0.37 – 5.88, P=0.586, for all-cause mortality with ECM– as the reference group).

ECM: e-Contact Module; **HR**: hazard ratio; **LVEF**: left ventricular ejection fraction; **VT:** ventricular tachycardia

Figure 4 Case example



This figure is a case example of one of the patients from our cohort treated with ECM guidance. At the left end, CARTO electroanatomic maps of the left ventricle are displayed. The electroanatomic maps are displayed more transparent, whereas previous ablation points are displayed in less-transparent yellow and orange (i.e. the 'Ablation History" feature of the Stereotaxis system). On the right, ablation parameters of the currently performed application are displayed, including temperature, power and impedance (recorded by the Claris system). Panel A displays an application applied in suboptimal contact. The suboptimal catheter-tissue contact is shown to the user by the ECM as a small starburst at the catheter tip. One can appreciate that during this specific application the impedance was stable. On the contrary, Panel B shows an application applied in optimal catheter-tissue contact (visualized by a dense starburst at the catheter tip), where we observed a gradual impedance drop during ablation, which is related to improved lesion quality.

Discussion

This is the first study to assess the clinical outcome of contact feedback in RMN-guided CA. Our results suggest that contact feedback by the ECM improves VT free survival in RMN-guided ischemic VT ablation.

The importance of catheter-tissue contact

Effective lesion formation is a major determinant of outcome in VT ablation. In addition to traditional indices of power and RF duration, lesion continuity, catheter stability and contact have emerged as key elements influencing effective lesion formation.[11] Different contact matters are of importance, including contact homogeneity across a line of ablation, spatiotemporal dynamics of contact governed by cardiac and respiratory motion and contact directionality.[11] Moreover, contact is of critical importance in adequate three-dimensional electro-anatomic mapping, another determinant of substrate ablation outcome.[12] This is illustrated by when a normal region is mislabeled as low-voltage scar due to poor tissue contact. Improved contact permits to define the areas of reduced potentials[12] and increases the sensitivity of late potential detection.[13] The present study observed that implementation of a novel contact assessing technology during RMN-guided ischemic VT ablation, resulted in higher VT-free survival. Consistently, less ICD shocks and less hospital admissions for VT recurrence were observed. Real-time contact feedback potentially improves the efficacy of VT ablation by virtue of more accurate maps[12] and optimizing lesion formation.[11] First of all, by optimizing mapping, as points were predominantly taken when the ECM showed that there was optimal catheter-tissue contact. Secondly, by enhancing RF ablation, as the RF application was only started when the ECM showed there was optimal contact and catheter position was continuously optimized during ablation. It would be interesting to further investigate the ECM's determination of size, definition and resolution of low-voltage areas in future studies involving scar related VT.

Remote Magnetic Navigation versus Manual guided VT ablation

Where manual ablation catheters are still confined to uni- or bidirectional movement using pull wires[8], magnetic navigation ensures enhanced maneuverability of the ablation catheter that makes reach of difficult anatomical structures possible.[14,15] Magnetic guided ablation by itself aids to achieve more adequate lesion formation by enhanced catheter stability and consequently improved contact with the myocardial wall.[16, 17] This is of critical importance in cardiac regions with greater wall motion excursion such as the ventricle. RMN facilitates titration of CF between the catheter and the myocardial tissue. Most studies comparing manual with RMN-guided VT ablation, reported superiority of RMN, with respect to procedure and fluoroscopy times, acute success rates and adverse events.[7, 8] Moreover, in VT ablation of patients with non-structural heart disease, RMN reported significantly lower VT recurrence rates during long-term FU.[6] The present study reported lower procedure, fluoroscopy and mapping times, when compared to prior studies evaluating RMN guided ablation of scar related VT in general.[18] Moreover, we observed even significant further reduction of VT recurrence, ablation time and fluoroscopy exposure after implementation of the ECM. In our opinion this illustrates the technological advances made in RMN guided ablation over time and highlights that the ECM was rapidly embedded in daily practice by the operating electrophysiologists.

The e-Contact Module

CF in manual guided CA is determined electromechanically based on the amount of mechanical deformation or diffraction of light experienced by the catheter tip.[19] In contrast to CF sensing catheters in manual guided CA, the ECM does not inform on the quantity of force applied. In RMN's ECM, contact in fact is calculated by a combination of factors including the vector of the ablation catheter, wall motion and impedance. The ECM in RMN-guided ablation takes into account the angle between the tip of the catheter and myocardial surface that affects the pattern of the systodiastolic contact. In larger scars contact measurements may be less reliable, there wall motion may be distorted due to akinesia or dyskinesia and impedance is altered due to changes in conduction properties. Yet, the ECM incorporates 16 variables to gauge contact that aids to high accuracy. The results of the present study, are in our opinion a confirmation of the accuracy of this novel feature, assisting to the composition of accurate maps and advancing effective lesion formation.

The quality of contact

This study also evaluated the measured quality of contact of every single RF application. According to the ECM, we observed that 92% of the total RF application time was applied in contact with myocardial tissue, of which >70% was applied in optimal contact. Six percent of the total RF application time was applied without any contact with the myocardium. Interestingly, even though not all applications were applied in optimal contact, we observed improved outcomes. Real-time contact feedback of the ECM, allows operators to constantly optimize catheter position while ablating reducing cumulative application time in suboptimal catheter position. Whether this explains the improved 12-month outcome in this study, should be verified in future studies where the operator is blinded versus unblinded to the ECM. Moreover, it would be interesting to investigate the effect of other parameters, such as LV approach, on the measured quality of contact.

Limitations

The present study's retrospective nature and the lack of blinded adjudication might have introduced bias, although this was mitigated by the use of objective measures. The present study included all procedures performed since the implementation of ECM. As the operators had to learn how to incorporate the ECM's feedback in their procedural approach, this learning curve might have negatively affected our results. Nevertheless, we observed a significantly better long-term outcome in procedures performed with ECM. Nowadays substrate ablation is being performed as per standard of care in all patients, whereas in the earlier days sometimes the procedure focused on elimination of critical isthmus and exit sites only. Moreover, insights on substrate ablation methodology changed over time. Possibly, it led to an improved abolition of channels[20, 21] and this could have biased our results. However, substrate ablation as potential confounder was added to the Cox proportional hazard models and did not show a significant relation with the outcomes.

Conclusion

Contact feedback by the ECM appears to improve 1-year outcome in RMN-guided ischemic VT ablation, resulting in a higher 1-year VT free survival. Moreover, implementation of the ECM significantly reduces fluoroscopy exposure and ablation times. These observations are most likely the result of improved accuracy of mapping and advanced ablation lesion formation due to the contact feedback provided by the ECM.

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part 2

Catheter ablation of ventricular tachycardia, imaging and epicardial substrate

Everything you can imagine is real

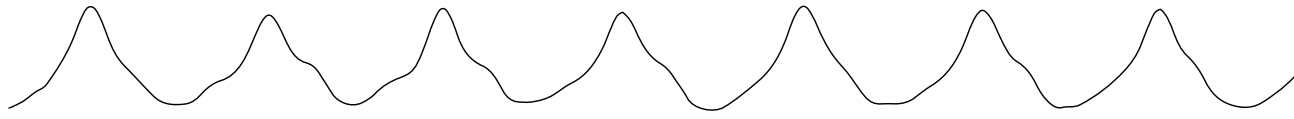
Picasso

I believe in intuition and inspiration. Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution. It is, strictly speaking, a real factor in scientific research.

Albert Einstein

Imaging guided versus non imaging guided ventricular tachycardia ablation - a review

8



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Abstract

Background
Magnetic resonance imaging (MRI) and computed tomography (CT) in patients with ventricular tachycardia (VT) after myocardial infarction (MI) helps to delineate scar from healthy tissue. Imaging- guided VT ablation has not yet been studied on a large scale.

Objective
The aim of the meta-analysis was to compare the long-term outcome of image-guided VT ablation to a conventional approach for VT after MI.

Methods
Eight electronic bibliographic databases were searched to identify all relevant studies from 2012 until 2018. The search for scientific literature was performed for studies that described the outcome of VT ablation in patients with an ischemic substrate. The outcome of image guided ablation was compared to the outcome of conventional ablations.

Results
Of the 2990 citations reviewed for eligibility, 38 articles enrolling a total of 7748 patients - were included into the meta-analysis. Five articles included patients with image-guided ablation. VT-free survival was 82% [74-90] in the image-guided VT ablation group versus 59% [54-64] in the conventional ablation group ($p < 0.001$) during a mean follow-up of 35 months. Overall survival was 94% [90-98] in the image guided versus 82% [76-88] in the conventional VT ablation ($p < 0.001$).

Conclusions
Image-guided VT ablation in ischemic VT was associated with a significant benefit in VT free and overall survival as compared to conventional VT ablation. Visualizing myocardial scar facilitates substrate guided ablation procedures, pre-procedurally and by integrating imaging in the procedure, and may consequently improve long-term outcome.

Introduction
Magnetic resonance imaging (MRI) and computed tomography (CT) advancing ventricular tachycardia (VT) ablation have an important role in diagnosing structural heart disease. In patients with VT after myocardial infarction (MI) these modalities of imaging help to identify, delineate and characterise the scar. Electro-anatomical map can be used to define the scar and border zone. However, scar is 3dimensional and a voltage map is limited in spatial resolution.[1] Moreover arrhythmogenic substrate may be found in heterogeneous tissue with normal voltages.[2] Channels that correlate with critical VT isthmuses can be identified by searching the scar for abnormal potentials. This may be time consuming and often incomplete. High-resolution MRI has been demonstrated to be able to delineate areas of surviving myocardial tissue within the scar that correlate with VT channels.[3] MRI preceding VT ablation can accurately predict recurrences in the presence of scar[4] and is a promising tool to identify ablation strategy in case of transmural scar.[5] Currently randomised and large scale trials lack on the long term outcome of image guided VT ablation. The aim of the current meta-analysis is to perform a large scale analysis, comparing the long term outcome of image-guided VT ablation to a conventional VT ablation approach.

Methods
Data sources and search strategy
This review was conducted in accordance with the PRISMA and MOOSE guidelines (Appendix 1, 2). The purpose of our study was to identify all studies that use imaging modalities to focus on scar that is performed prior to ablation for ischemic VT. We searched Embase.com, Medline via Ovid, Web-of-science Core collection, the Cochrane Central registry of trials, Scopus, CINAHL via EBSCOhost and Google Scholar from January 2012 until January 2018. The search strategy was created with the assistance of a medical librarian (WB). The search strategy combined terms for ventricular tachycardia and catheter ablation, and terms for myocardial scar due to previous ischemic injury. The search results were limited to English language articles. The detailed search methodology for all databases is provided in Appendix 3.

Study selection and data extraction criteria
Studies were included if they: (i) were observational studies or randomized controlled trials (ii) reported on long-term follow-up of patients that had undergone percutaneous CA for ischemic VT, (iii) provided data on recurrences with a follow-up duration of > 1 year. Articles that focused on patients with structural heart disease other than ischemic scar were excluded. Also if the studied population was heterogeneous and we were not able to extract the outcome of the patients with an ischemic VT, the study was excluded. Individual case reports, editorials, review articles and conference meeting abstracts were not included. We compared image-guided VT ablation to non image-guided VT ablation. If imaging was performed preceding VT ablation but did not influenced the ablation procedure it was seen as non image-guided VT ablation.
Two reviewers (AAH, ZK) independently evaluated the titles and abstracts according to the inclusion and exclusion criteria. For each potentially eligible study, two reviewers assessed the full-text. In cases of disagreement, a decision was made by consensus or, if necessary, a third reviewer (TSZT). was consulted.
A predesigned data extraction form was used to collect relevant information on baseline characteristics, ablation method, imaging, procedural data and follow-up.

Risk of bias assessments for the included clinical studies
The risk of bias within each individual study was evaluated by two reviewers (AAH, ZK) based on the nine-star Newcastle–Ottawa Scale (NOS) using three pre-defined domains namely: selection of participants, comparability and ascertainment of outcomes of interest. The NOS attributes a maximum of four points for selection, two points for comparability, and three points for outcome. Studies that received a score of nine points were judged to be at low risk of bias; studies that scored seven or eight stars were considered at medium risk; those that scored six or less were considered at high risk of bias (appendix 4).

Data Synthesis and Analysis
The unpaired Student's t -tests was used for demographic comparison of continuous variables between groups. We used metaprop command to pool proportions and we presented a weighted sub-group and overall pooled estimates with inverse-variance weights obtained from a random-effects model. Heterogeneity was quantified using the I2 statistic, classified as low (I2 ≤25%), moderate (I2 >25% and <75%), or high (I2 ≥75%). Additionally, Q-statistic was used to assess the presence of heterogeneity. PQ statistic ≥0.05 was considered to indicate no significant heterogeneity among the included studies. Study characteristics including the location of the study, duration of the study, age, male sex, left ventricular function, the presence of VT storm at baseline and the percentage of patients using amiodarone were pre-specified as characteristics for assessment of heterogeneity and were evaluated using stratified analyses and random-effects meta-regression if 10 or more studies were included in the meta-analysis. Publication bias was evaluated through a funnel plot and asymmetry was assessed using the Egger's test. All tests were two-tailed and p-values of 0.05 or less were considered statistically significant. STATA release 14 (Stata Corp, College Station, Texas) was used for all statistical analyses.

Results

Identification of relevant studies
The search strategy identified 2454 (1307 citations after excluding articles from before 2012), out of which 63 articles were found relevant following initial screening based on titles and abstracts. After full-texts reading, 25 articles were further excluded based on extraction of ischemic VT data and the follow-up criteria. A total of 38[2], 4-40 articles were included that describe the outcome of VT ablation. Five[4-8] of the 38 articles were image-guided. Figure 1 shows the selection process.

General characteristics of the included studies
Table 1 shows the key characteristics of the included studies.

Baseline characteristics
A total number of 7748 patients with VT from ischemic scar were included in this meta-analysis (Table 2). Image-guided VT ablation had taken place in 224 patients. The majority of the non-image guided articles were authors from the USA whereas the majority of the image-guided articles were authors from Europe. The average age was 65 years and 89% was male. The average ejection fraction was 33%. Electrical storm was the reason for VT ablation in 16-100% of the population in the 23 studies that reported on it.
Substrate ablation was applied in 50% of the included articles. Eighty percent of the image-guided VT ablation articles primarily used a substrate approach. In 7 articles a targeted ablation was applied and in one article[9] there was a direct comparison between targeted and a substrate approach. Three articles - all non-image guided - in the non-imaging guided ablation used remote magnetic navigation (49-100% of the patients). Seven articles - all non-image guided - commented on using assist devices in patients with non-hemodynamically tolerable VTs. Fifty-five and 94% of the patients in the image guided ablation group and the conventional VT ablation group respectively were ICD carriers (p = 0.02) at baseline. Fifty-eight percent had reported amiodarone use at the time of ablation. No studies were judged at low bias of risk. Among the observational studies, studies were judged to be at median or high risk of bias. Among the randomised controlled trials, studies were all judged at median bias of risk.

Techniques used in image guided VT ablation
Different type of image guided ablation was reported. One article[5] reported to use imaging to plan the ablation strategy, 2 articles[7,8] used imaging to integrate in the ablation procedure and 2 articles[4,6] reported on doing both. One of the articles that integrated imaging in the procedure used Automatic Detection of Arrhythmic Substrate (ADAS).[8]

Procedural difference in characteristics between image-guided and non image-guided VT ablation
Characteristics between the image-guided and non image-guided VT ablations were similar except for a significant difference in percentage of patients who had epicardial access, 37 in the image-guided VT ablation versus 6 in the non image-guided VT ablation group (p < 0.01) (Table 2).

Procedural data
Procedural duration was on average 4.5 hours in the image guided ablation versus 3.7 hours in the conventional ablation (p = 0.09). There was no significant difference between radiofrequency time and fluoroscopy time in image guided VT ablation versus conventional ablation (Table 2).

Longterm outcome in VT ablation
Sixty-one percent [IQR 54 - 67] of the patients were free of VT recurrences during a mean follow-up duration of 35 months with an overall survival of 84% [IQR 80-88].

Outcome of image-guided VT ablation
The image-guided VT ablation reported a higher VT free survival of (82% [IQR 76-88]) compared to the non image-guided VT ablations (59% [IQR 54-64]) (p < 0.001) (Figure 2). Overall survival was 94% [IQR 90-98] in the image guided versus 82% [IQR 77-87] in the conventional VT ablation (p < 0.001) (Figure 3). High between-study heterogeneity (random- effects model i2 93.56%, p < 0.001) could not be explained by any of the investigated between-study characteristics (Supplement 1).

Table 1 Characteristics of included studies

A. Image-guided

Publication			Method of study	Patients - with ischemic VT	FU duration
author	year	country		image- guided	- months
Neijm[4]	2015	USA	OS, Co, SC	8	17
Acosta[5]	2016	Spain	OS, Co, SC	58	23
Yamashita[6]	2016	France	OS, Co, SC	67	17
Yamashita[7]	2016	France	OS, Co, SC	54	28
Andreu[8]	2017	Spain	Os, Co, SC	37	20

B. non image-guided

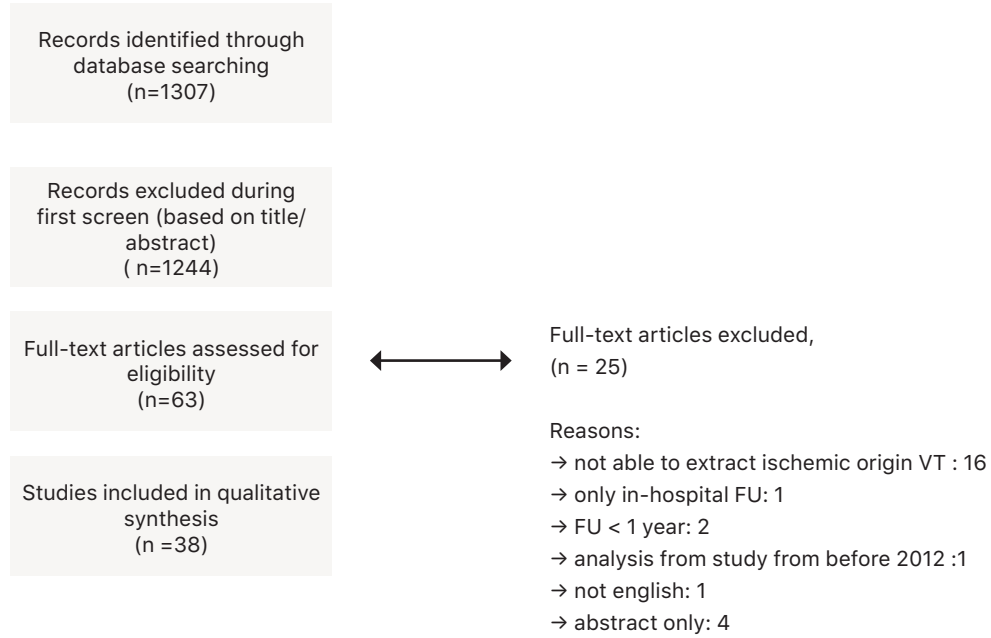
Publication			Method of study	Patients - with ischemic VT	FU duration
author	year	country		Non image-guided	- months
Di Biase[9]	2012	Hungary, Italy, USA	OS, Co, MC	92	25
Dinov[10]	2012	Germany	OS, Co, SC	102	14
Arenal[10]	2013	Spain	OS, Co, SC	59	38
Ghanem[12]	2013	Egypt	OS, Co, SC	22	12
Tung[13]	2013	USA	OS, Co, SC	69	12
Aryana[15]	2014	USA	OS, Co, MC	36	19
Goya[16]	2014	Japan	OS, Co, SC	51	41
Mork[17]	2014	Denmark	OS, Co, SC	90	39
Saggu[18]	2014	India	OS, Co, SC	5	46
Silberbauer[20]	2014	Italy	OS, Co, SC	160	47
Tilz[21]	2014	Germany	OS, Co, SC	12	40
Avila[2]	2015	Spain	OS, Co, SC	46	32
Clemens[22]	2015	Check Republic	OS, Co, SC	31	46
de Riva[23]	2015	the Netherlands	OS, Co, SC	91	23
Di Biase[23]	2015	China, Europa, USA	RCT, MC	118	12
Izguierdo[24]	2015	Spain	OS, Co, SC	50	13
Luther[25]	2015	UK	OS, Co, SC	24	24
Pioretti[26]	2015	USA	OS, Co, SC	87	54
Siontis[27]	2015	Europa, USA	OS, Co, MC	1412	56
Tsiarchis[40]	2015	Italy	OS, Co, SC	100	52
Tung[29]	2015	USA	OS, Co, MC	1095	12
Yokokowa[14]	2015	USA	OS, Co, SC	906	35
Acosta[30]	2016	Spain	OS, Co, SC	44	46
Dinov[31]	2016	Germany	OS, Co, SC	50	12
Frankel[32]	2016	Italy, Japan, USA	OS, Co, MC	1095	12
Fukunaga[33]	2016	Japan	OS, Co, SC	51	40
Ozcan[34]	2016	North America	OS, Co, SC	44	28
Sapp[35]	2016	Europe, USA	RCT, MC	132	28
Skoda[36]	2016	Chech Republic, Germany, USA	OS, Co, MC	53	12
Jin[37]	2017	China, Denmark	OS, Co, MC	54	17
Kuck[38]	2017	Germany	RCT, MC	60	28
Kuroki[39]	2017	Japan	OS, Co, MC	109	24
Tzou[40]	2017	USA, Japan	OS, co, MC	1174	12

CO: cohort; **MC:** multi-center; **ND**: no data; **OS**: observational study; **SC:** single-center; **RCT:** randomised controlled trial

Table 2 Baseline characteristics of included patients

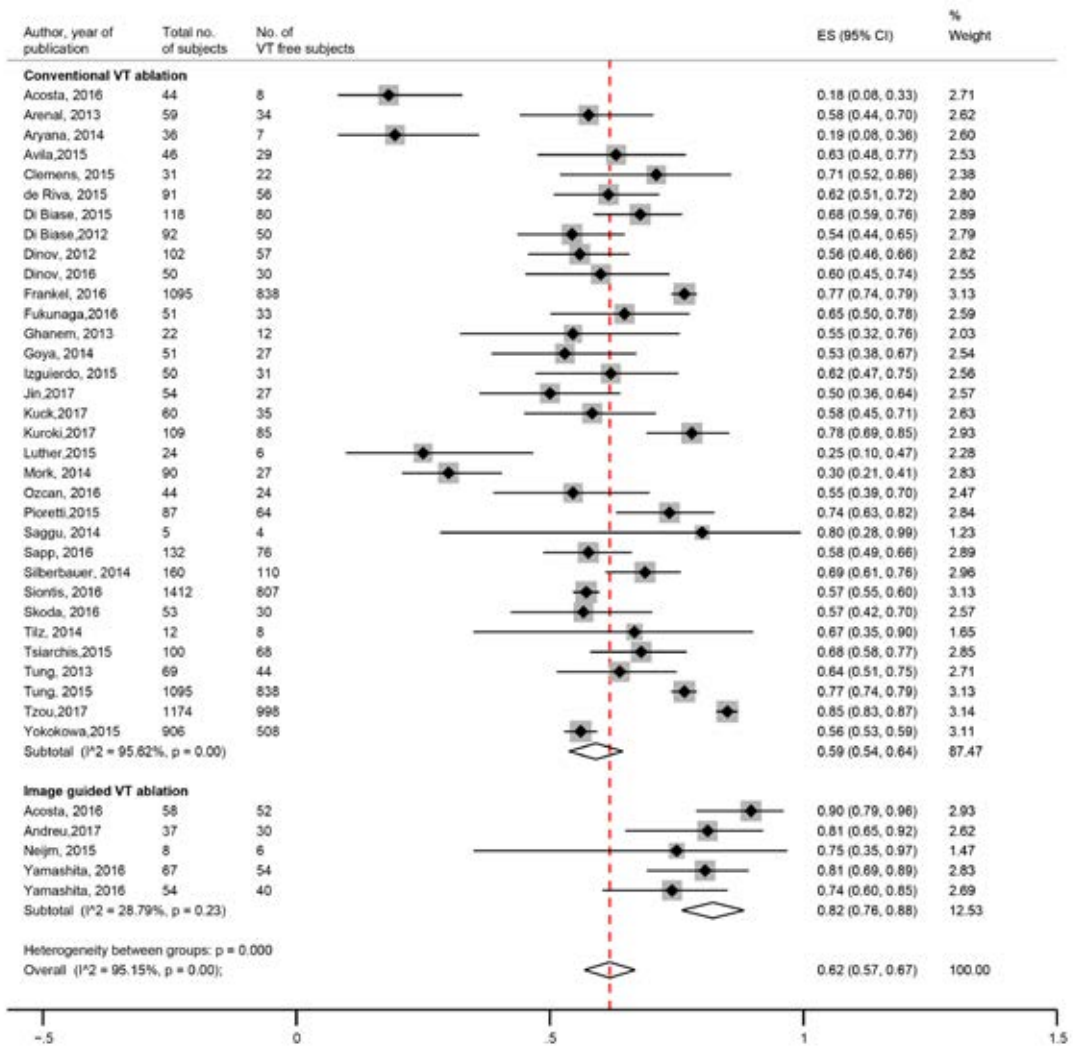
		number of studies	image-guided	non image-guided	*p-value*
age		38	64	66	0.07
EF		38	34	32	0.09
			- %	- %	
male		36	94	90	0.40
infarct location	anterior	21	43	40	0.80
	inferoposterior	20	52	46	0.66
nyha class III + IV		18	11	34	0.07
electric storm		23	49	36	0.45
diabetes mellitus		22	19	30	0.13
hypertension		27	70	60	0.11
amiodarone therapy		34	68	54	0.41
Prior VT ablation		23	32	15	0.14
epicardial access		34	37	6	< 0.01
ICD carrier		31	55	94	0.02
			- min	- min	
procedural duration		28	269 [250 -]	220 [194 - 265]	0.09
radiofrequency time		13	34 [32 -]	38 [24 -67]	0.93
radiation exposure		24	54 [34 -]	28 [15 -38]	0.18

Figure 1 Flowchart of studies for outcome ventricular tachycardia ablation



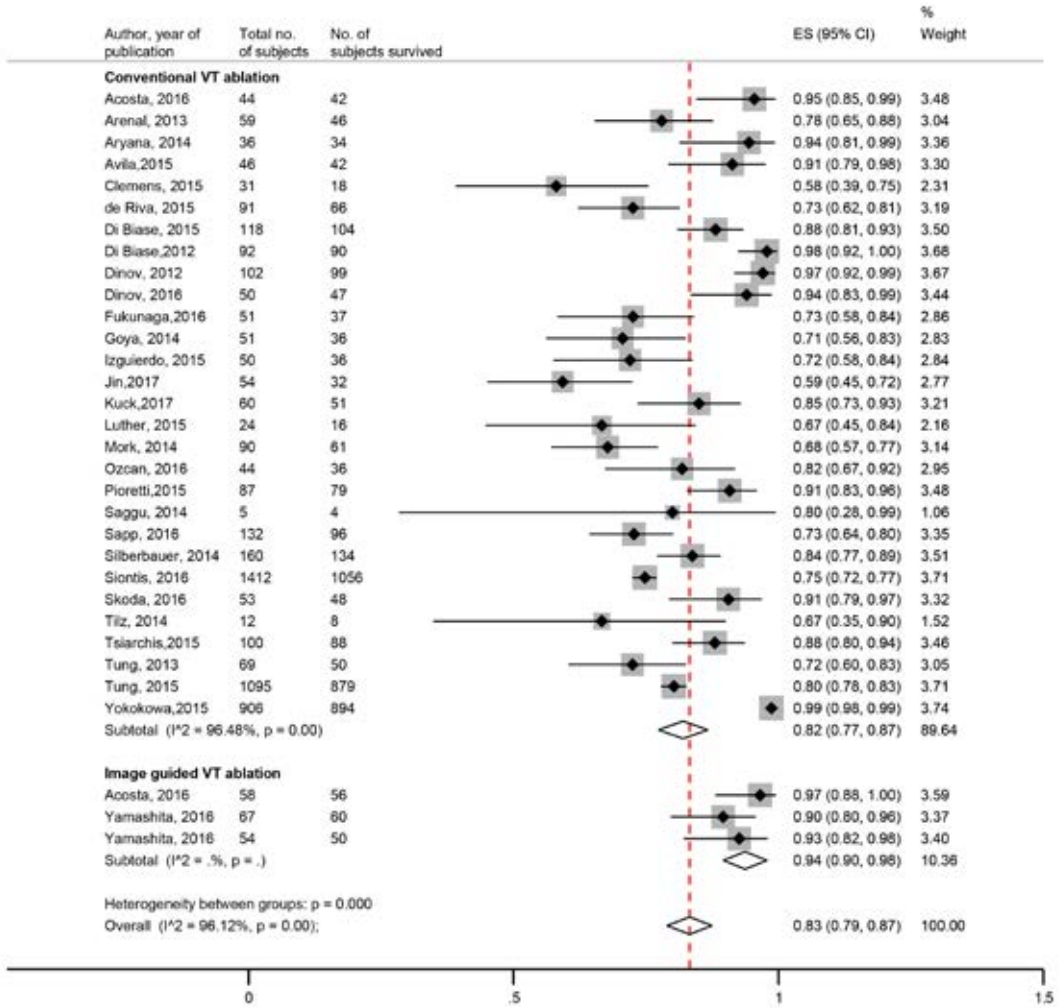
chapter 8

Figure 2 Forrest plot of VT free survival image-guided versus non image-guided



CI: confidence interval, **ES:** effect size, **VT:** ventricular tachycardia

Figure 3 Forest plot survival – image-guided versus non-image-guided



CI: confidence interval, **ES:** effect size, **VT:** ventricular tachycardia

Discussion

The current meta-analysis shows an improved VT free and overall survival in patients with ischemic VT by using image-guided VT ablation compared to conventional VT ablation. This is the first study that demonstrates true large scale benefit. Visualising myocardial scar and integrating imaging in the procedure facilitates VT ablation by focussing on the area of interest and providing more accurate substrate characterization.

Imaging derived scar versus electro-anatomical map

Generally, there is a good correlation between bipolar voltage mapping and CT and MRI derived scar.[6,41] Increased transmurality of the scar on MRI correlated well with reduced bipolar low voltage on the endocardium[42], suggesting the presence of low voltage in the epicardium.
However, voltage mapping may fail to accurately delineate the extent of diseased myocardium because of limitations such as catheter contact issues, reduced sensitivity to far-field signal of the mid-myocardium[43], and the interposition of epicardial fat.[44] Epicardial fat may lead to false-negative low voltage on epicardial voltage mapping, CT accurately visualises epicardial fat and differentiates it from scar.[44]
Scar is a 3-dimensional structure and consequently a voltage map has a limited spatial resolution. Moreover, bipolar voltage map may show absence of low voltage in the presence of an intramural scar and therefore may be missed. It is potentially unmasked with unipolar recordings, but may be best visualised with MRI. In the presence of an intramural scar VT recurrences occur more frequently.[4] Recognizing the presence of intramural scar, high output endocardial ablation, bipolar ablation or a radiofrequency needle ablation catheter may reach the mid-myocardium and successfully ablate the VT circuit.[45]

Limitations of MRI

There are certain limitations on the use of cardiac MRI in VT ablation. Currently there is no consensus on nor standardisation of image postprocessing.[46] Another limitation is the presence of artefacts that derive from ICDs, most commonly affecting the basal left anterior free wall. The presence of devices not only limits the interpretations of scar tissue on MRI but also affect the reliability of contrast enhanced imaging due to provoked hyper-intense off-resonance artefacts mimicking scar tissue.[47] The wideband inversion recovery late gadolinium enhancement (LGE) MRI technique can potentially overcome this type of artefact.[48]
Furthermore errors can arise with image integration as well. Geometry can change due to respiratory and cardiac motion, and conformational changes can occur between the time of MRI and the ablation procedure due to for example differences in volume or rhythm.[47] Partial-volume effects on the standard thickness short-axis slices for example can lead to overestimation of borderzone areas.[49]
In EP procedures this is a known phenomenon. During electro-anatomical mapping (EAM) the mean maximum amplitude of cardiac and respiratory motion was 10.2 ± 2.7 mm and 8.8 ± 2.3 mm respectively.[50] This may be especially critical in the identification of conduction channels.
Using real time MRI minimalizes conformational changes. Non-contrast-enhanced T1 weighted imaging with long TI decay times is promising as it was shown to be an effective method for visualizing necrosis within radiofrequency ablation lesions. Enhancement is more specific and stationary than that from contrast LGE MRI. Scar tissue appears dark in the non-contrast-enhanced images, allowing to differentiate between acute RF ablations and chronic scar.[51]

Cardiac motion correction by cardiac triggering improves precision in myocardial T1 mapping.[52]

Imaging guided ablation strategy

Epicardial ablation in ischemic VT is usually restricted to patients with previous failed endocardial ablation attempts. Yet, there is a relation between complete VT substrate elimination and better ablation outcomes.[11] The importance of complete substrate ablation is in the assumption that substrate not related to clinical or inducible VT can activate and become a VT isthmus during follow-up. Epicardial borderzone channels in post MI transmural scar are seen in 63%.[3] However, if epicardial ablation is used as a first-line ablation, a significant proportion of patients undergoing epicardial mapping do not exhibit an epicardial arrhythmogenic substrate.[9] And therefore tools are needed to avoid unnecessary pericardial explorations. Acosta et al.[5] showed that if patients with a transmural scar on MRI had endocardial ablation, a significant lower recurrence free survival compared to complete substrate ablation resulted.

Characterize the scar

A large area of scar heterogeneity predicts recurrence of VT after VT ablation.[4] Also successful ablation appears to be in localised areas of heterogeneity, and incomplete ablation in these areas predicts VT recurrence in animal models.[53] The delayed components of the conducting channel electrograms reflect the presence and activation of viable fibers embedded in fibrosis.[54] Borderzone channels display a 3D structure within the myocardial wall that can be depicted by contrast enhanced MRI.[3] Critical sites of ischemic VT are confined to areas of high signal intensity. Channels on MRI correlate with areas of survival myocardial tissue which help to better locate the target ablation sites and find critical channels in the areas of normal voltage.[8, 55] Identification of conductive channels channels on EAM aided by pixel intensity maps improved when based on 3D imaging with 1.4 x 1.4 x 1.4-mm resolution compared to conventional 2-dimensional clinical imaging with 5-mm slice thickness.[3] Identification of conduction channels in the electro-anatomical map can be improved when using a cutoff value of 60% of the maximum pixel signal intensity, both for core and borderzone. Using CT, thicker ridges within areas of pronounced wall thinning in the scar, seen as relatively preserved wall thickness, are recognized as the arrhythmogenic substrate of scar-related VT.[56]
Critical VT isthmus sites in patient with prior MI are located in close proximity to the area on MRI where transition between >75% transmural scar and the core-borderzone occurs.[57] Critical isthmus sites around the core-borderzone transition suggest that the signal intensity threshold of a maximal 50% may indicate a critical mix between fibrosis and viable myocytes that allow for slow conduction and thereby, re- entrant VT. Currently however, 3D imaging and postprocessing methods may still be limited at detecting fractionated and late potential regions within EAM dense scar.[3]

Image-integration

Real time integration of VT substrate helps focusing on diseased vs healthy areas of the myocardium. Yamashita et al.[6] showed that despite a similar number of mapping points a higher number of local abnormal ventricular activities (LAVA) sites could be identified in patients who had ablation guided by imaging data. Mapping more efficiently focuses towards the critical areas when guided by imaging data and leads to better long-term freedom of VT.[7,8]

Clinical implications

Guidance of imaging for VT ablation is not mentioned in the current ventricular arrhythmia guidelines.[58] The current meta-analysis suggests benefit in VT free and overall survival by the use image guidance in VT ablation for patients with ischemic heart disease. Larger scale randomized studies are needed to confirm our results, in addition we are in need of studies that teach us about cost-effectiveness of image-guided VT ablation.

Limitations

Despite the fact the this is the largest image-guided VT ablation cohort so far there are several limitations to note, some inherent to performing a meta-analysis. First, some data on patient level was unavailable in the included studies, which precluded a detailed evaluation to identify the impact of particular baseline demographic characteristics (i.e., number of ICD shocks before the ablation), type of imaging used (CT or CE-CMR) and procedural factors (use of magnetic navigation or contact force) on the outcome of freedom of VT. Additionally we were not able to extract data on the correlation between ablation strategy (substrate versus a targeted arrhythmia approach) and longterm outcomes in all of the eligible studies. There were significantly less patients with an ICD at the time of inclusion in the image-guided group even though ejection fraction was similar. A possible explanation for the low % of patients who had an ICD implanted at baseline is a selection bias, patients without an implanted ICD during their presentation with VT were possible more prone to ondergo MRI before ablation. ICD patients benefit from a continuous monitoring system, it could influence the detection of VT during follow-up. We cannot exclude that ICD was implanted during follow-up. Higher VT free and overall survival has been seen in patients treated with a substrate approach including epicardial ablation compared with a limited ablation.[9] Patients with image guided VT ablation more often had a substrate approach and had a higher percentage of epicardial access, which itself could be an explanation for the lower number of recurrences in this group. Yet, determining ablation strategy is one of the potential benefits from image guided VT ablations.[5] There was minimal publication bias as indicated by conventional funnel plots and Egger test (Supplement 2), however these approaches are limited by their qualitative nature. The majority of the included studies were observational in nature, with higher risk of selection bias. Randomised controlled trials are needed to convince the effectiveness of imaging data for VT ablation procedures. Limited scanning capacity and additional costs could hinder implementation. Currently, we cannot be confident that our results are merely a reflection of the contribution of image guided ablation.

Conclusion

Image-guided VT ablation was found to be associated with a significant benefit in VT free and overall survival as compared to conventional VT ablation. Visualizing myocardial scar may facilitate substrate guided ablation procedures, pre-procedurally and by integrating imaging in the procedure, and consequently may improve long-term outcome.

Appendix 1 PRISMA checklist

Checklist item			
Section/ topic	**#**		**Reported on page #**
TITLE			
Title	1	Identify the report as a systematic review and a meta-analysis	1
ABSTRACT			
	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 Appendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review)	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8 Appendix 4 Suppl. 1
Summary measures	13	State the principal summary measures	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5 Suppl. 1

Section/ topic	#		Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-8 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11 Table 1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 Suppl. 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11 Table 1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl. 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Suppl. 1
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13, 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Appendix 2 MOOSE checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Magnetic resonance imaging (MRI) and computed tomography in patients with ventricular tachycardia (VT) after myocardial infarction helps to delineate scar from healthy tissue. MRI preceding VT ablation can prognosticate an increased recurrence rate in the presence of intramural scar and is a promising tool to identify an epicardial ablation strategy in case of transmural scar. No meta-analysis that compares the long-term outcome of imaging guided ventricular tachycardia ablation to conventional ventricular tachycardia ablation, has been published.
√	Hypothesis statement	The usage of imaging guided ventricular tachycardia ablation improves long-term freedom from ventricular tachycardia recurrence as compared to conventional ventricular tachycardia ablation.
√	Description of study outcomes	We included studies that estimated the outcome of ventricular tachycardia ablation in patient with an ischaemic substrate
√	Type of exposure or intervention used	VT ablation with and without the guidance of imaging
√	Type of study designs used	Eligible study designs included randomized controlled trials (RCTs), cohort, case-control studies.
√	Study population	Only studies carried out in adults (>18 years old) were included.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators are indicated in the authors list.
√	Search strategy, including time period included in the synthesis and keywords	Search strategy and time periods are detailed in page 7 of the manuscript and in Figure 1 and the full search strategy is available in Appendix 3.
√	Databases and registries searched	Medline, Embase, Google Scholar, Scopus, CINAHL EBSCOhost, Web-of-Science, Cochrane Central
√	Search software used, name and version, including special features	We did not employ a search software. Endnote was used. to merge retrieved citations and eliminate duplications.
√	Use of hand searching	We hand-searched bibliographies of retrieved systematic reviews and meta-analysis for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. Citations for the included studies are included in the text and table 1. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed restrictions to English language.
√	Method of handling abstracts and unpublished studies	Systematic reviews were used to identify further references.
√	Description of any contact with authors	Authors of included studies were contacted to retrieve missing full texts and to identify any missing studies.

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of search strategy should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	A predesigned data collection form was prepared to extract the relevant information from the included full texts, including study design, imaging technique, ablation strategy and whether endo/epicardial ablation was performed in a first set-up.
√	Assessment of confounding	We performed qualitative analyses to evaluate differences between studies
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review.
√	Assessment of heterogeneity	We were able to pool the data statistically.
√	Description of statistical methods in sufficient detail to be replicated	Under Data Synthesis and Analysis there is a detailed description of the statistical analyses.
√	Provision of appropriate tables and graphics	We included 2 main tables, 3 graphs, 4 appendices, and 2 supplements
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2 and 3
√	Table giving descriptive information for each study included	Tables 1 and 2
√	Results of sensitivity testing	Suppl. 1
√	Indication of statistical uncertainty of findings	95% confidence intervals or SD's were presented if available
Reporting of discussion should include		
√	Quantitative assessment of bias	Not applicable
√	Justification for exclusion	We excluded studies that had no or an unclear definition of outcome, or data extraction was not feasible.
√	Assessment of quality of included studies	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review.

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Due to the lack of standardisation of follow-up, it is difficult to provide unifying statements within a larger number of manuscripts hampered by large levels of heterogeneity.
√	Generalization of the conclusions	The generalizability of our findings has been enhanced by the involvement of data, including USA and Europe. However, there is a clear lack of evidence from the African and most of theWest Pacific Region.
√	Guidelines for future research	Further work is necessary to standardize the follow-up of patients who underwent image guided ventricular tachycardia ablation
√	Disclosure of funding source	Nothing to disclose.

Appendix 3 data search

Embase.com
('heart ventricle arrhythmia'/exp OR (((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) NEAR/3 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt):ab,ti) AND ('ablation therapy'/exp OR 'ablation catheter'/de OR 'catheter ablation'/de OR 'radiofrequency ablation'/de OR 'radiofrequency ablation device'/de OR 'cryoablation'/de OR (ablati* OR cryoablati* OR rfa):ab,ti) AND ('ischemia'/de OR 'ischemic heart disease'/exp OR infarction/exp OR 'heart muscle ischemia'/exp OR scar/de OR (ischemi* OR ischaemi* OR infarct* OR postinfarct* OR scar):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

Medline Ovid
(("Arrhythmias, Cardiac "/ AND "Heart Ventricles"/) OR "Ventricular Fibrillation"/ OR "Tachycardia, Ventricular"/ OR (((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) ADJ3 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt).ab,ti,kf.) AND ("Ablation Techniques"/ OR "Catheter Ablation"/ OR (ablati* OR cryoablati* OR rfa).ab,ti,kf.) AND ("ischemia"/ OR "Myocardial Ischemia"/ OR "Myocardial Infarction"/ OR Cicatrix/ OR (ischemi* OR ischaemi* OR infarct* OR postinfarct* OR scar).ab,ti,kf.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane CENTRAL
((((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) NEAR/3 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt):ab,ti) AND ((ablati* OR cryoablati* OR rfa):ab,ti) AND ((ischemi* OR ischaemi* OR infarct* OR postinfarct* OR scar):ab,ti)

Web of Science
TS=(((((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) NEAR/2 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt)) AND ((ablati* OR cryoablati* OR rfa)) AND ((ischemi* OR ischaemi* OR infarct* OR postinfarct* OR scar)))

AND DT=(article) AND LA=(english)

Google scholar
"ventricle|ventricular|rvot|lv|rv|lvot tachycardia|tachyarrhythmia|arrhythmia" ablation|cryoablation|rfa ischemia|ischaemia|ischemic|ischaemic|infarction|infarct

Imaging VT studies

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('heart ventricle arrhythmia'/exp OR (((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) NEAR/3 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt):ab,ti) AND ('ablation therapy'/exp OR 'ablation catheter'/de OR 'catheter ablation'/de OR 'radiofrequency ablation'/de OR 'radiofrequency ablation device'/de OR 'cryoablation'/de OR (ablati* OR cryoablati* OR rfa):ab,ti) AND ('imaging'/de OR 'cardiac imaging'/de OR 'diagnostic imaging'/de OR 'nuclear magnetic resonance imaging'/exp OR 'nuclear magnetic resonance'/de OR 'computer assisted tomography'/exp OR 'positron emission tomography'/de OR (imaging OR image* OR (magnet* NEAR/3 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* NEAR/3 tomograph*) OR ct OR ((cat OR pet) NEAR/3 scan*) OR cmr OR cmri OR ((positron* OR emissi*) NEAR/3 tomogra*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline Ovid
("Tachycardia, Ventricular"/ OR (((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) ADJ3 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt).ab,ti.) AND ("Ablation Techniques"/ OR "Catheter Ablation"/ OR (ablati* OR cryoablati* OR rfa).ab,ti.) AND ("Cardiac Imaging Techniques"/ OR "Diagnostic Imaging"/ OR exp "Magnetic Resonance Imaging"/ OR exp "Tomography, X-Ray Computed"/ OR exp "Tomography, Emission-Computed"/ OR (imaging OR image* OR (magnet* ADJ3 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* ADJ3 tomograph*) OR ct OR ((cat OR pet) ADJ3 scan*) OR cmr OR cmri OR ((positron* OR emissi*) ADJ3 tomogra*)).ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane
((((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) NEAR/3 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt):ab,ti) AND ((ablati* OR cryoablati* OR rfa):ab,ti) AND ((imaging OR image* OR (magnet* NEAR/3 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* NEAR/3 tomograph*) OR ct OR ((cat OR pet) NEAR/3 scan*) OR cmr OR cmri OR ((positron* OR emissi*) NEAR/3 tomogra*)):ab,ti)

Web of science
TS=(((((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) NEAR/2 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt)) AND ((ablati* OR cryoablati* OR rfa)) AND ((imaging OR image* OR (magnet* NEAR/2 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* NEAR/2 tomograph*) OR ct OR ((cat OR pet) NEAR/2 scan*) OR cmr OR cmri OR ((positron* OR emissi*) NEAR/2 tomogra*))))

Scopus
TITLE-ABS-KEY(((((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) W/2 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt)) AND ((ablati* OR cryoablati* OR rfa)) AND ((imaging OR image* OR (magnet* W/2 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* W/2 tomograph*) OR ct OR ((cat OR pet) W/2 scan*) OR cmr OR cmri OR ((positron* OR emissi*) W/2 tomogra*))))

CINAHL EBSCOhost
(MH "Tachycardia, Ventricular" OR TI (((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) N2 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt) OR AB (((ventric* OR idioventric* OR rvot OR lv OR rv OR lvot) N2 (tachycard* OR tachyarrhythm* OR fibrillat* OR arrhythm*)) OR vt)) AND (MH "Ablation Techniques" OR MH "Catheter Ablation" OR TI (ablati* OR cryoablati* OR rfa) OR AB (ablati* OR cryoablati* OR rfa)) AND (MH "Cardiac-Gated Imaging Techniques" OR MH "Diagnostic Imaging" OR MH "Magnetic Resonance Imaging+" OR MH "Tomography, X-Ray Computed+" OR MH "Tomography, Emission-Computed+" OR TI (imaging OR image* OR (magnet* N2 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* N2 tomograph*) OR ct OR ((cat OR pet) N2 scan*) OR cmr OR cmri OR ((positron* OR emissi*) N2 tomogra*)) OR AB (imaging OR image* OR (magnet* N2 resonan*) OR ceMRI OR ceMR OR mri OR nmr OR mr OR (comput* N2 tomograph*) OR ct OR ((cat OR pet) N2 scan*) OR cmr OR cmri OR ((positron* OR emissi*) N2 tomogra*))) NOT (MH animals+ NOT MH humans+)

Google scholar
"ventricle|ventricular|rvot|lv|rv|lvot tachycardia|tachyarrhythmia|arrhythmia" ablation|cryoablation|rfa imaging|image|"magnetic resonance"|mri|nmr|"computed|-computer tomography"|"positron emission tomography"

Appendix 4 Newcastle- Ottawa Quality Assessment Scale

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection
1) Is definition of NCDs adequate?
a) Yes, according to a clear and widely used definition *
b) Yes, eg record linkage or based on self-reports
c) No description
2) Representativeness of the cases
a) Consecutive or obviously representative series of cases *
b) Excluded cases are random *
c) No description of the excluded cases or potential for selection biases or not stated
3) Comparison with a reference group
a) The results are compared with a reference from community or with the status of the cases prior to the disease *
b) The results are compared with the results from other patients
c) No description/no comparison available
4) Definition of reference

chapter 8

a) Individuals with no NCD or sample from general population or the same individuals before NCD suffering*
b) Non community comparator is described
c) No description of source

Comparability
1) Comparability of the results on the basis of the design or analysis
a) The results are described in age and sex sub groups (sex is not applicable for female diseases) *
b) The results are additionally adjusted for/described in different socioeconomic factors or disease related confounders*

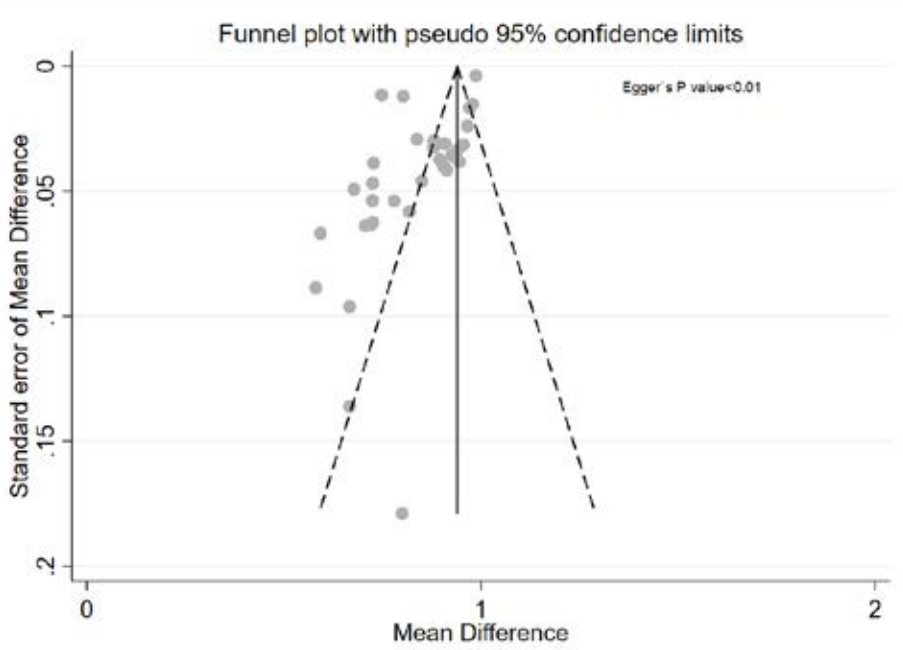
Exposure (costs, productivity, households)
1) Ascertainment of exposure
a) Secure record (e.g. surgical records, hospital records, and administrative records, national…) *
b) Structured interview were blind to case/control status *
c) Interview not blinded to case/control status
d) Written self-report or medical record only
e) No description
2) Same method of ascertainment for NCDs and comparators
a) Yes *
b) No
c) No comparator group exist
3) Non-Response rate
a) All participants included or same rate for both groups or respondents and non-respondents have the same characteristics*
b) Non respondents described
c) Rate different and no designation
d) Response rate not described

Supplement 1 Sensitivity analysis of studies included in meta-analysis

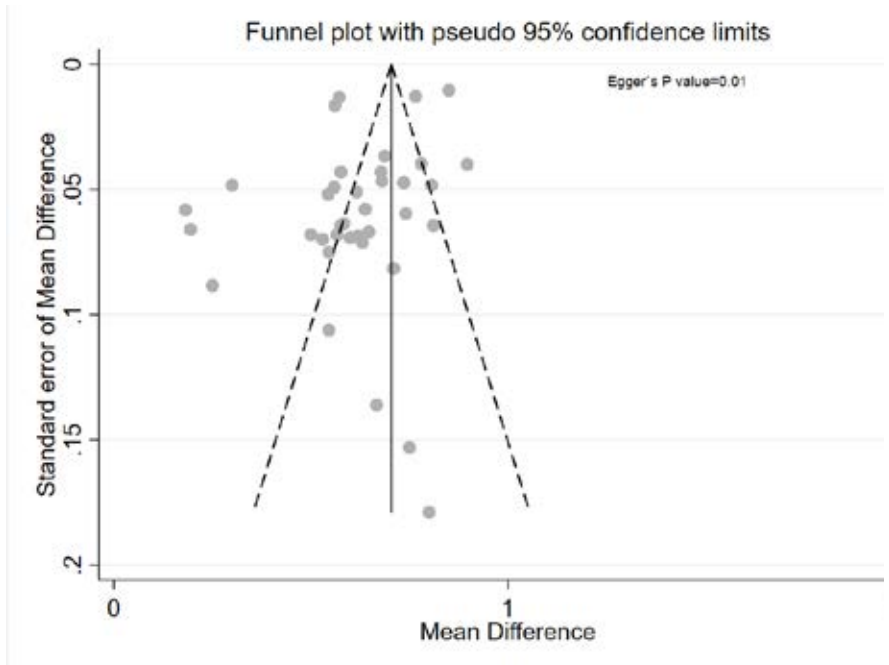
Subgroups by Study Characteristics		Number of studies	Proportion (95% CI)	I^2 for heterogeneity	*P-value for heterogeneity*
Proportion of VT free subjects					
Median percentage of male population	≤90%	17	0.56 (0.48-0.65)	96.7%	0.3
	>90%	16	0.62 (0.55-0.69)	92.5%	
Median age	≤66	16	0.62 (0.55-0.69)	95%	0.2
	>66	17	0.57 (0.52-0.62)	80.4%	
Median duration of follow-up	≤28 months	19	0.60 (0.54-0.66)	94.1%	0.6
	>28 months	14	0.58 (0.51-0.64)	88.4%	
Median Ejection Fraction	≤32%	20	0.56 (0.51-0.61)	84.5%	0.2
		13	0.64 (0.57-0.71)	94.1%	
Location	Europe	15	0.55 (0.46-0.63)	87.2%	0.4
	Asia	5	0.65 (0.53-0.78)	69.3%	
	North America	6	0.58 (0.45-0.71)	96.8%	
	Multinational	7	0.65 (0.54-0.76)	98.1%	
Proportion of VT subjects survived during the follow-up period					
Median percentage of male population	≤90%	16	0.83 (0.78-0.89)	95.9%	0.5
	>90%	13	0.81 (0.76-0.87)	86.4%	
Median age	≤66	12	0.81 (0.75-0.88)	91.6%	0.8
	>66	17	0.82 (0.76-0.89)	97.1%	
Median duration of follow-up	≤28 months	15	0.83 (0.77-0.88)	92.4%	0.8
	>28 months	14	0.81 (0.73-0.89)	97.5%	
Median Ejection Fraction	≤32%	20	0.83 (0.78-0.89)	97.73%	0.98
	>32%	8	0.78 (0.68-0.88)	88.5%	
Location	Europe	15	0.83 (0.77-0.88)	85.5%	0.5
	Asia	3	0.72 (0.64-0.81)	0%	
	North America	6	0.87 (0.77-0.97)	98%	
	Multinational	5	0.79 (0.67-0.92)	97.6%	

NOTE: meta-regression was not performed in group of image guided VT ablation due to small number of available studies (n=5)

Supplement 2 funnel plot
A. overall survival



B. VT free survival



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9

Ventricular tachycardia in ischemic cardiomyopathy; a combined endo-epicardial ablation as the first procedure versus a stepwise approach (EPILOGUE) - study protocol for a randomized controlled trial

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Abstract

Background
The role of epicardial substrate ablation of ventricular tachycardia (VT) as a first-line approach in patients with ischemic heart disease is not clearly defined. Epicardial ablation as a first-line option is standard for patients with nonischemic dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Several nonrandomized studies, including studies on patients with ischemic heart disease, have shown that epicardial VT ablation improves outcome but this approach was often used after a failed endocardial approach. The aim of this study is to determine whether a combined endo-epicardial scar homogenization as a first-line approach will improve the outcome of VT ablation.

Methods/Design
The EPILOGUE study is a multicenter, two-armed, nonblinded, randomized controlled trial. Patients with ischemic heart disease who are referred for VT ablation will be randomly assigned to combined endo-epicardial scar homogenization or endocardial scar homogenization only (control group). The primary outcome is recurrence of sustained VT during a 2-year follow-up. Secondary outcomes include procedural success and safety.

Discussion
This study is the first randomized trial that evaluates the role of a combined endo-epicardial scar homogenization versus endocardial scar homogenization for the treatment of ischemic scar-related VT.

Trial registration: NL4816807814v02

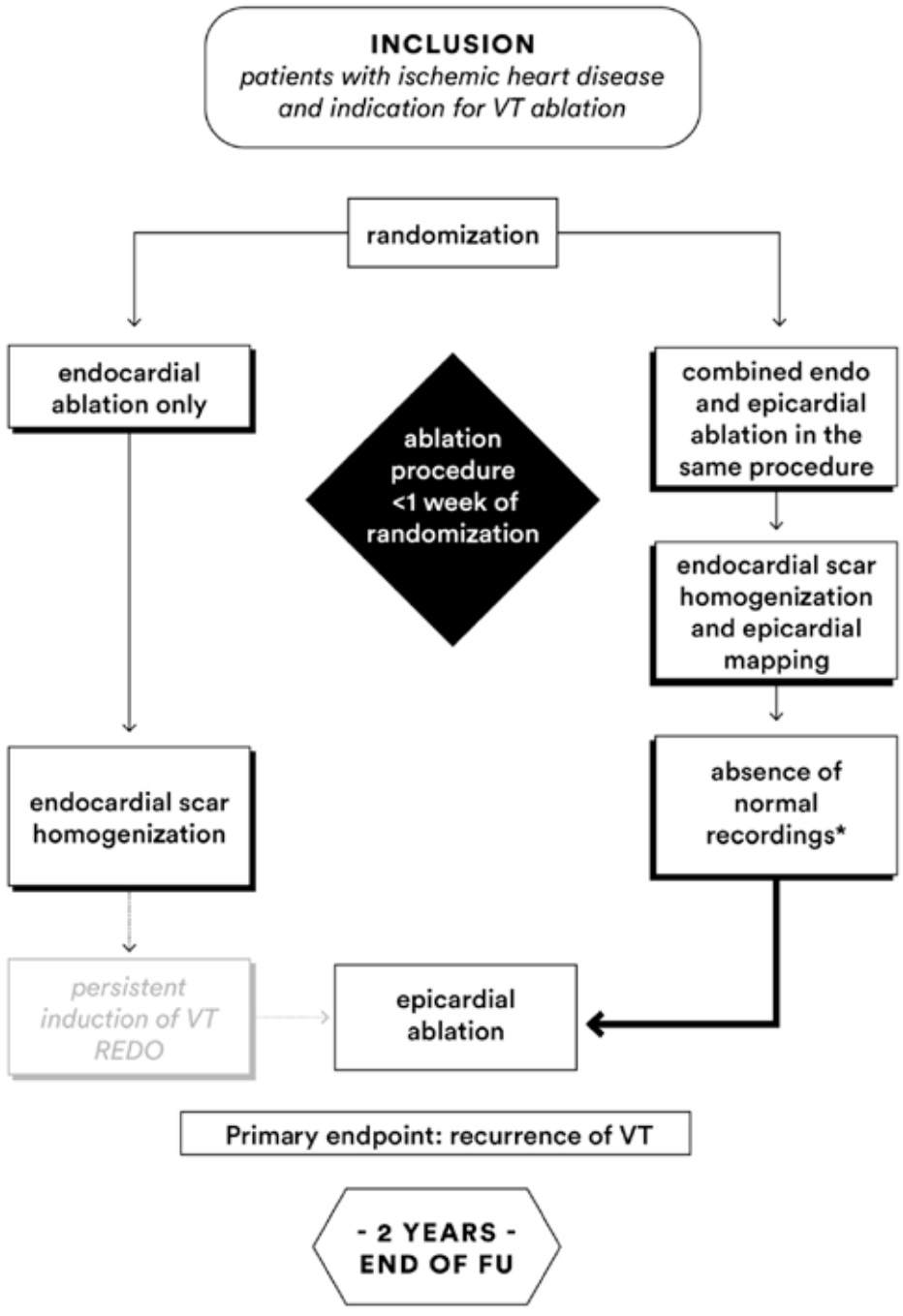
Background
Ventricular tachycardia (VT) is an important clinical sequela after a myocardial infarction and may be associated with sudden cardiac death.[1] The introduction of the implantable cardioverter defibrillator has provided an important tool in the prevention of sudden cardiac death. However, a significant proportion of patients experience multiple appropriate implantable cardioverter defibrillator shocks due to sustained VT. Catheter ablation of VT is useful to reduce the burden of VT. The threshold for VT ablation has lowered in recent years, mainly as a result of technological advancements and increased experience.[2–4] The endocardial approach has been the preferred first-line approach for VT ablation in patients with ischemic heart disease. Recent studies suggest that 12–17% of all VTs in a mixed population of ischemic and nonischemic cardiomyopathies have an epicardial origin.[5,6] Epicardial VTs have been observed in 10% of post-infarction VTs.[7] These numbers may be underestimated, considering the moderate outcomes of endocardial VT ablations.[8,9] In experienced centers, epicardial VT ablation has an acceptable risk-to-benefit ratio.[6,10] Current recommendations for scar-related VT suggest that patients with ischemic heart disease can benefit from an epicardial approach if an endocardial ablation fails.[11] The aim of this randomized trial is to determine whether combined endo-epicardial scar homogenization as a firstline approach will improve the outcome of VT ablation in comparison with endocardial scar homogenization only.

Methods/design
Study design
The EPILOGUE study is a multicenter, two-armed, nonblinded, randomized controlled trial. Patients will be randomized to endocardial scar homogenization or endoepicardial scar homogenization (Figure 1). The study period is 2 years after the index procedure. All participating centers are tertiary referral centers for VT ablation with experience in epicardial ablation.

Study population
All patients with a history of ischemic heart disease who are referred for VT ablation will be considered for inclusion. Patients can be included if they meet all of the following inclusion criteria:
- Age ≥18 years;
- History of ischemic heart disease;
- Presence of or planned for implantable cardioverter defibrillator soon after VT ablation.

Patients will be excluded if they meet any of the following criteria:
- Presence of unstable angina;
- Acute myocardial infarction <30 days (or in case of incessant VT, <14 days);
- Absence of visualization of coronary anatomy (coronary angiogram or computed tomography);
- Presence of significant coronary stenosis clinically relevant for intervention;
- Presence of mobile left ventricular thrombus;
- Presence of aortic or mitral mechanical valve prosthesis;
- Previous pericarditis;
- Previous coronary artery bypass graft;
- Other factors that could potentially lead to pericardial adhesion (e.g., thoracic radiation therapy);
- Contra-indication for general anesthesia.

Figure 1 EPILOGUE study flow chart



*Normal recordings are defined as not more than three sharp and discrete deflections from baseline, amplitude >1.5 mV, duration >70 ms or amplitude-to-duration ratio >0.046.
FU: follow-up; **VT:** ventricular tachycardia

Ethics
The study protocol was approved in February 2015 by the Medical Ethical Committee (2014–248) Erasmus Medical Center, Rotterdam, The Netherlands. Informed consent will be obtained from each participant.

Primary and secondary outcomes
The primary outcome of this study is recurrence of sustained VT (defined as appropriate implantable cardioverter defibrillator therapy or VT >30 s duration) within 2 years. We will use a blanking period of 1 week after the ablation procedure. The secondary outcome parameters will be acute procedure success and procedure-related major complications. Procedural success will be defined as complete success if there is noninducibility of any sustained monomorphic VT. Partial success will be defined as noninducible clinical VT but inducible polymorphic VT, or VT with a cycle length <200 ms. Procedural failure will be defined as a spontaneous occurrence of VT or inducible clinical monomorphic VT.
Furthermore, the following data will also be determined: procedure time, fluoroscopy time, radiofrequency ablation time, time to recurrence of the ventricular arrhythmia, number of appropriate implantable cardioverter defibrillator therapies on follow-up, number of VT-related hospitalizations, freedom of antiarrhythmic drugs on follow-up, repeated (epicardial) ablation procedures, evidence of an incessant VT or VT storm during follow-up, and mortality.

Study groups
This study has two study arms, the endocardial approach only and the combined endocardial and epicardial approach (combined approach). Crossover is not allowed during the first procedure. When a patient is randomized to the combined approach and the epicardial access is unsuccessful, this is considered a screening failure.

Randomization
Patients are randomized to either the endocardial approach or the combined endocardial and epicardial approach. Randomization is performed using a computer-generated program (ALEA). The person carrying out randomization will not be the treating physician or involved in the selection procedure. The patient and the electrophysiologist who will be performing the procedure will not be blinded for the method of approach.

Electrophysiology procedure and catheter ablation
Pre-procedural preparation
In general, anticoagulation therapy will be discontinued before the procedure (unless the operator decides otherwise). When performing the pericardial puncture, the international normalized ratio should be <2.0. Transthoracic echocardiography will be used to exclude a thrombus in the left ventricle. If the transthoracic echocardiography is inconclusive, contrast transthoracic or transesophageal echocardiography will be used. Antiarrhythmic medications will be stopped 5 days before the procedure. In case of an emergency VT ablation, the operator can choose to do the ablation while continuing antiarrhythmic drugs. Patients who undergo an epicardial ablation will receive general anesthesia; otherwise conscious sedation and local anesthesia will be used. The epicardial ablation is performed with a surgical team as backup.

Pericardial access
In patients undergoing epicardial ablation, before ablation and systemic heparinization, subxiphoid pericardial access will be obtained by fluoroscopic guidance (lateral plane). Using a Tuohy needle, small amounts of contrast are injected while carrying out the puncture. Guided by fluoroscopy, a guide wire is inserted into the pericardial space and an Arrow sheath is placed. An appropriate sized guiding catheter is inserted to keep the sheath open. During ablation, we will use an irrigated tip catheter. The baseline flow should be reduced to 1 ml/min. Fluid will be drawn from the pericardial space frequently during the ablation. At the discretion of the operator, epicardial phrenic nerve capture will be performed if the origin of the VT is located in the area of the phrenic nerve. When capture is performed, a balloon is inserted and inflated to avoid phrenic nerve damage during ablation. At the end of the procedure, a pericardial drain is inserted for 24–48h. The operator will administer an intrapericardial steroid injection. Colchicine should be prescribed for up to 1 month, commencing on the first day after the procedure. The first day post procedure Colchicine is dosed 1 mg twice daily followed by a maintenance dose of Colchicine 0.5 mg twice daily.

Mapping
Endocardial mapping will be performed in all patients. A multipolar diagnostic catheter will be placed in the coronary sinus. A quadripolar diagnostic catheter will be introduced via the femoral vein to the right ventricular apex. Left ventricle mapping will be performed via the retrograde aortic or transseptal approach. The procedure will be performed under intravenous anticoagulation with heparin, with a target activated clotting time >250 s. Electroanatomical maps will be obtained using CARTO 3 (Biosense Webster, Diamond Bar, CA, USA) or EnSite NavX (St. Jude Medical, St. Paul, MN, USA). This includes activation (if applicable) and voltage maps. The bipolar voltage thresholds used to consider dense scar and border zone will be 0.5 and 1.5 mV, respectively. We will aim to acquire a very dense map, especially around scar areas. Areas of fractionated or late potentials will be annotated. Programmed ventricular stimulation will be performed, and will involve three extra stimuli from two different right ventricular sites, high-rate pacing, and intravenous isoproterenol (at the discretion of the operator). In hemodynamically unstable VTs mechanical circulation support (Impella, intra-aortic balloon pump) can be considered.

Ablation protocol (both groups)
If a hemodynamically tolerated VT is induced during the electrophysiological study, a standard activation or entrainment mapping is carried out. The ablation will continue until the VT is no longer inducible. Additionally, endocardial scar homogenization will be performed. Based on the substrate map, ablation will be empirically extended throughout the entire scar endocardially. Also delayed and fractionated electrograms will be targeted for ablation. If clinical VT is still inducible in the endocardial ablation-only group, an epicardial VT ablation will be performed in a 'redo' procedure. Epicardial mapping and ablation will be performed as described in the combined approach.

Combined endocardial and epicardial group ablation
After obtaining pericardial access, a substrate map is constructed to identify abnormal electrograms. Activation mapping during VT – if possible – is done to prove epicardial involvement. Normal electrogram recordings show not more than three sharp and discrete deflections from baseline, amplitude >1.5 mV, duration <70 ms or amplitude-to-duration ratio >0.046.[9] Before epicardial ablation, a coronary angiogram will be performed to avoid coronary artery damage. In addition to targeting abnormal potentials, epicardial homogenization will be performed. Ablation is continued until all abnormal potentials are gone.

Clinical outcome and follow-up
Patients will be seen periodically up to 2 years (at 1, 3, 9, 12, and 24 months) after the index procedure. All implantable cardioverter defibrillator therapies and clinical events are reported. The implantable cardioverter defibrillator will be programmed to detect VTs slower than the clinical VTs. Recommended implantable cardioverter defibrillator programming consists of a ventricular fibrillation zone with a cut-off rate of 220 beats per minute and a therapeutic VT zone with a cut-off cycle length of 60 ms below the slowest documented VT. To register VTs with rates below the detection limit, a monitor zone will be programmed with a cut-off rate of 120 beats per min. Detection duration will be 24/32 beats or 5 s in the ventricular fibrillation zone and 26 beats or 10 s in the therapeutic VT zone.
The analysis of recurrence of VT depends on the clear differentiation of VT from supraventricular tachycardia events. For reliable adjudication of arrhythmic events, implantable cardioverter defibrillator episodes with available electrograms are mandatory. In the case of singlechamber devices, the recommended setting is storage of both near-field and far-field (shock) electrogram sources. In addition, electrogram storage must be available before arrhythmia onset.

Adverse events
In compliance with medical ethics committee regulations, it is compulsory to register all serious adverse events. Death, acute myocardial infarction, coronary artery damage, type III and V major bleeding, abdominal bleeding, tamponade of more than 80 cm^3, late tamponade, and an ischemic cerebral event are considered major adverse events. Dry right ventricle puncture, drainable hemopericardium, postprocedural precordial pain, phrenic nerve injury and type II minor bleeding[12] are considered minor adverse events.

Safety monitoring
Two committees and one monitor will be appointed to monitor patient safety. A data safety monitoring board will review study progress and has the authority to end the study if significant benefits or adverse effects in either study arm are suspected. The board members are three experienced electrophysiologists and a statistician. The clinical events committee will study all serious adverse events for a causal relationship between events and the EPILOGUE study. A monitor will evaluate protocol compliance by taking random samples in all participating centers.

Statistical analysis
Continuous variables between groups will be compared using Student's t test or the Mann–Whitney test for continuous variables, where appropriate. Categorical variables between groups will be compared with the chi-square test or Fisher's exact test, where appropriate. The primary outcome parameter will be analyzed using Kaplan–Meier survival curves and tested with a log-rank test. A two-sided P value of 0.05 will be considered statistically significant for all analyses. Statistical analysis will be performed using SPSS version 20.

Sample size calculation
Sample size was calculated based on the following assumptions: a 29% difference in primary outcome event rate (recurrence of VT) between the endocardial and epicardial group (15%) and the control group (44%) after a follow-up time of 2 years[9]. We calculate that a sample size of 86 patients is required to achieve an 80% power to detect a significant difference with a (two-tailed) alpha error of 5%. Allowing for a dropout rate of 10%, we calculated that we would require 100 subjects.

Discussion
Mechanism of scar-related ventricular tachycardia
Sustained VT in the presence of coronary artery disease is most often the result of prior myocardial infarction[13]. Scar areas form the substrate for macro-reentry which is the most frequent mechanism underlying VT. Targets for ablation are the area of low bipolar voltage that corresponds to the subendocardial projection of the scar, and potential targets within the scar that represent critical diastolic isthmuses during VT.

Role of epicardial ablation
In 73% of unsuccessful endocardial ablations, evidence of an epicardial substrate of VT was found.[14] To reach procedural success in VT ablation, Cesario et al.[15] found that 40% of the patients were in need of an epicardial ablation. A recent retrospective observational study from Tung et al.[16] compared the outcomes of patients who underwent epicardial ablation with the outcomes of patients who did not. The pericardial space could not be accessed in 7% by the percutaneous technique. The study demonstrated that at 12 months those with an ischemic substrate for VT who underwent a combined endocardial and epicardial ablation had improved freedom from VT compared with those who underwent endocardial-only ablation (85% versus 56%; P = 0.03). In a multicenter study by Della Bella et al.[5], 67% of a subgroup of patients with ischemic VT etiology were in need of a stepwise approach. It could be speculated that an endocardial and epicardial approach as a first-choice ablation strategy in this subgroup might have avoided a substantial number of repeat procedures and improved outcome.

Epicardial ablation in ischemic cardiomyopathy
Multiple studies on epicardial VT ablation in scar-related VT have been published[5, 9, 15, 17, 18]; however, few have compared endocardial ablation with a combined endocardial and epicardial ablation. In 33 post-infarct patients[17], epicardial mapping was performed when endocardial ablation failed. These 33 patients were retrospectively compared with patients who had had an endocardial ablation only. There was found to be no difference in outcome. However, only 6% of the patients had had an epicardial ablation. A recent study from Di Biase et al.[9] compared limited endocardial substrate ablation with combined endocardial and epicardial scar homogenization in patients with an electrical storm and ischemic cardiomyopathy. There was a lower VT recurrence rate in those who underwent endocardial and epicardial scar homogenization during a mean follow-up of 25 months (19% versus 47%; P = 0.006). A limitation of this study is that because these researchers used a historical control group, the technique of ablation (limited substrate ablation versus scar homogenization) differed between groups.

Safety of epicardial ablation
The reported complication rates associated with epicardial ablation range from 0.6 to 4.1%.[5,6] Procedure-related death in most studies was 0%.[5,6,16] However, a study from Hamburg reported two procedure-related deaths in 59 patients undergoing epicardial VT ablations.[14] Thus, life-threatening complications might occur. Other reported major complications were:[5,6,9,16]
- Hepatic bleeding;
- Pericardial bleeding requiring a drain;
- Phrenic nerve palsy;
- Pleuro-pericardial fistula;
- Coronary artery damage;
- Cardiac tamponade;
- Pericardial inflammatory reaction.

To prevent pericardial inflammation and subsequently adhesions, the use of colchicine after epicardial ablation is mandatory in our study.[19]

Study design
The study of Di Biase et al.[9] was a retrospective comparison of two techniques. Although there was a well-written prospective protocol, the two well-known techniques are difficult to compare. In the absence of a large scar or in the presence of dense scars, patients did not undergo epicardial ablation. Only 14 out of 43 patients (33%) in the endocardial and epicardial scar homogenization group underwent epicardial VT ablation. In the current study both groups will undergo scar homogenization. Patients randomized to the combined approach will undergo epicardial ablation unless there is a complete absence of abnormal recordings. The EPILOGUE study is the first randomized controlled study to compare a combined approach with a stepwise approach for VT ablation in patients with ischemic cardiomyopathy.

Limitations
This study is an open study that may subsequently lead to bias. However, the primary endpoint is recurrence of VT, an objective endpoint. Patients who have had a coronary artery bypass graft will be excluded from this study, thereby excluding a relevant part of the scar-related VT population. Open heart surgery is a known risk factor for adhesions and has shown to limit epicardial VT ablation.[16] When considering that VT ablation is not yet general practice, the inclusion rate may be low. This approach may change in following years as a consequence of improved understanding of the underlying pathophysiology or mechanism of VT.

Trial status
Inclusion of eligible candidates in the EPILOGUE study has not yet started; enrolment is expected to start in May 2015.

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chapter 9

Damage to the left internal mammary artery during epicardial ventricular tachycardia ablation: a case series

10

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Introduction

Epicardial ventricular tachycardia (VT) ablation is increasingly performed in patients with recurrent VT, in whom epicardial arrhythmogenic substrate is suspected. It is a preferred approach if the substrate for VT is located epicardially, such as in patients with arrhythmogenic right ventricular cardiomyopathy and nonischemic dilated cardiomyopathy. Moreover, endo -epicardial substrate homogenisation may also be useful as a first-line therapy in patients with VTs after myocardial infarction[1,2], especially in the presence of a transmural scar.[3] Complications in epicardial VT ablation can occur during pericardial puncture or can be caused by the ablation catheter. The most common cardiac complications are right ventricular perforation leading to pericardial bleed (4.5%)[4], and coronary vessel damage. Furthermore, because of the proximity of surrounding extracardiac structures and anatomic variance one should be cautious for intra-abdominal, pleural and vessel complications. We report two cases who had pericardial access for epicardial VT ablation that resulted in damage to the left internal mammary artery (LIMA).

Case Report

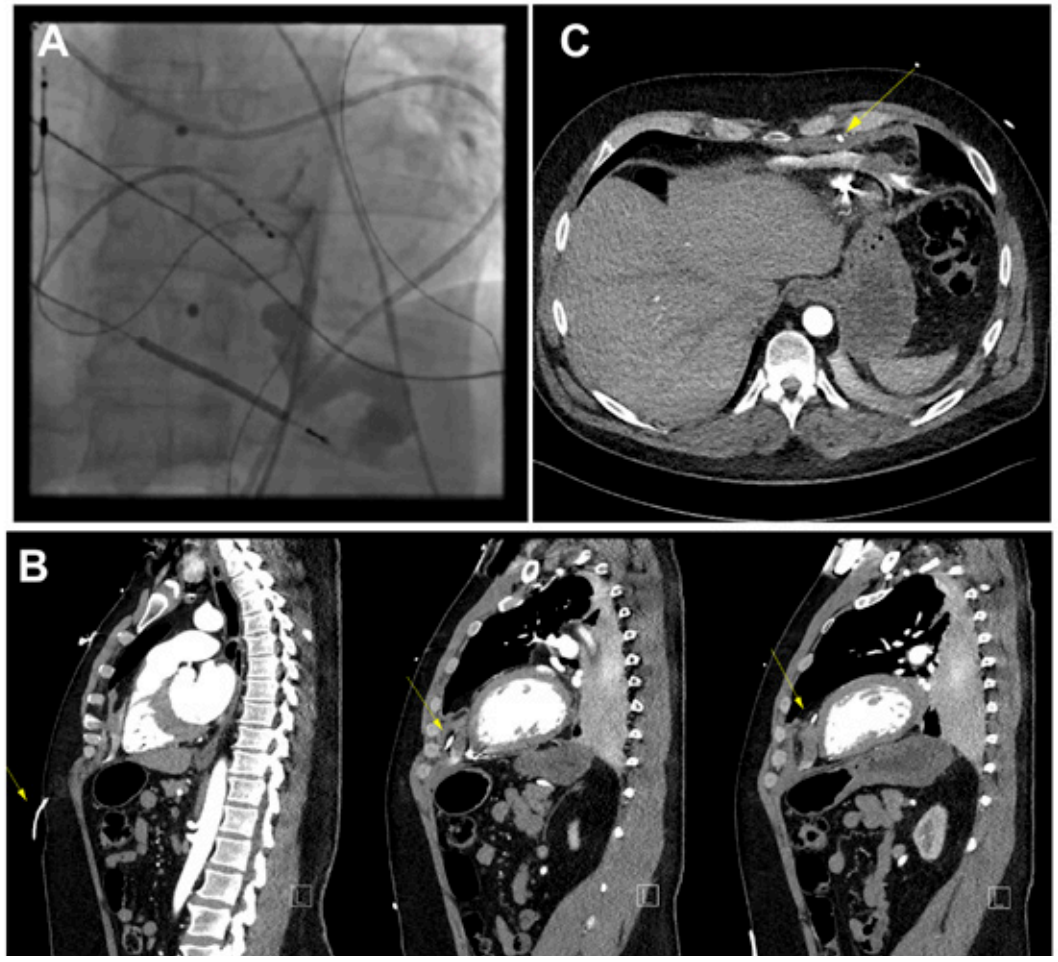
Patient 1

We present a case of a 48 year old male who was seen for second opinion after multiple appropriate ICD shocks for VT, that mostly occurred during exercise. Four years before he had received an internal cardioverter defibrillator (ICD) for secondary prophylaxis. His ejection fraction was moderately reduced. Coronary angiogram revealed no epicardial stenosis, cardiac magnetic resonance imaging showed a scar with the characteristics of a previous myocardial infarct in the inferoposterior region. He consented for a VT ablation and was planned for endo - epicardial scar homogenisation in the context of the Epilogue trial[5]. After endocardial access, pericardial access via an anterior xiphoid puncture[8] was obtained without difficulty. Both the endo -and epicardial voltage did not show areas of low voltage. VT induction led to haemodynamic instability for which rescue electrical cardioversions were needed. The best depicted location by pacemap was the inferior epicardium, however during activation map this area was late. Therefore we did not proceed with radiofrequency ablation.
After replacing the arrow sheath for a pericardial drain (Perivac, Boston Scientific), blood was noticed. Contrast injection through a drain with proximal side holes, demonstrated extravasation in the thorax and not the pericardium (Figure 1A). He remained clinically stable. A CT scan confirmed a pericardial drain positioned at an anterior position of the heart, that brushed a side branch of the LIMA (Figure 1B /C). Within a few hours after the procedure the drain production stopped and was removed without complications. With amiodarone therapy he remained free of VT. In the absence of scar on 3D voltage map a new diagnostic effort was made and a genetical form (RMB20 mutation) of dilated cardiomyopathy was recognised.

Patient 2

The second case is a 62-year old male known with a myocardial infarction and a moderate impaired LV had recurrent VTs for which he received an ICD. He was scheduled for an endo-epicardial VT ablation[5] because of recurrent sustained VT. Angiography did not reveal novel coronary artery stenosis. Amiodarone and oral anticoagulation were withheld. VT ablation was performed under general anaesthesia. To accomplish pericardial access a subxiphoid anterior puncture was

Figure 1 damage to the LIMA patient 1

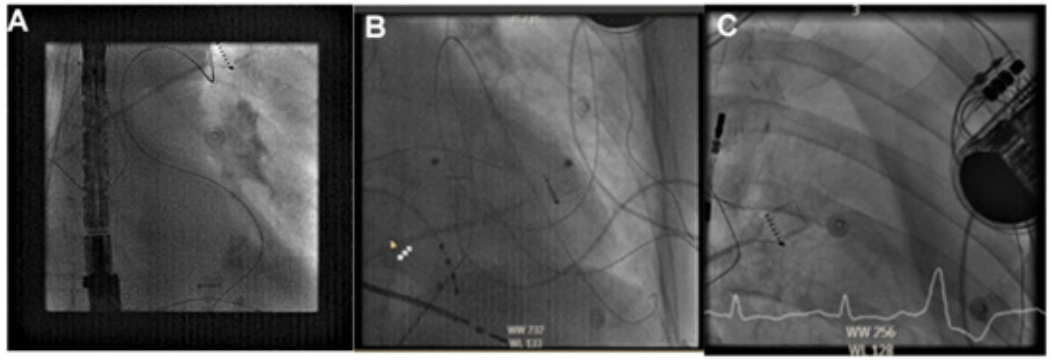


A. Fluoroscopy reveals contrast extravasation extra pericardial
B. The CT (sagittal view) demonstrates the anterior course of the pericardial drain
C. The CT (axial view) shows that the pericardial drain is directly adjacent to the LIMA and courses through its side branch (arrow).

undertaken, using a Tuohy needle. During the first puncture the guidewire aligned the cardiac silhouette, however it took off higher than the normal pericardial folds (Figure 2A). Advancing the guidewire further confirmed a localisation in the pleural space (Figure 2B). In a second attempt, the needle unintendedly moved up over the epicard, resulting in a pleural puncture. A third attempt resulted in successful pericardial access. Heparin was given and activated clotting time > 250 seconds was targeted. Sequential endo -and epicardial electroanatomical maps (CARTO 3 RMT, Biosense Webster) revealed a large area of low voltage signals and identified various late potentials (Figure 3A /B). During mapping increasing inotropic support was necessary to treat hypotension. At a critical isthmus a few RF applications were given. Because of therapy resistant hypotension the procedure was impeded.

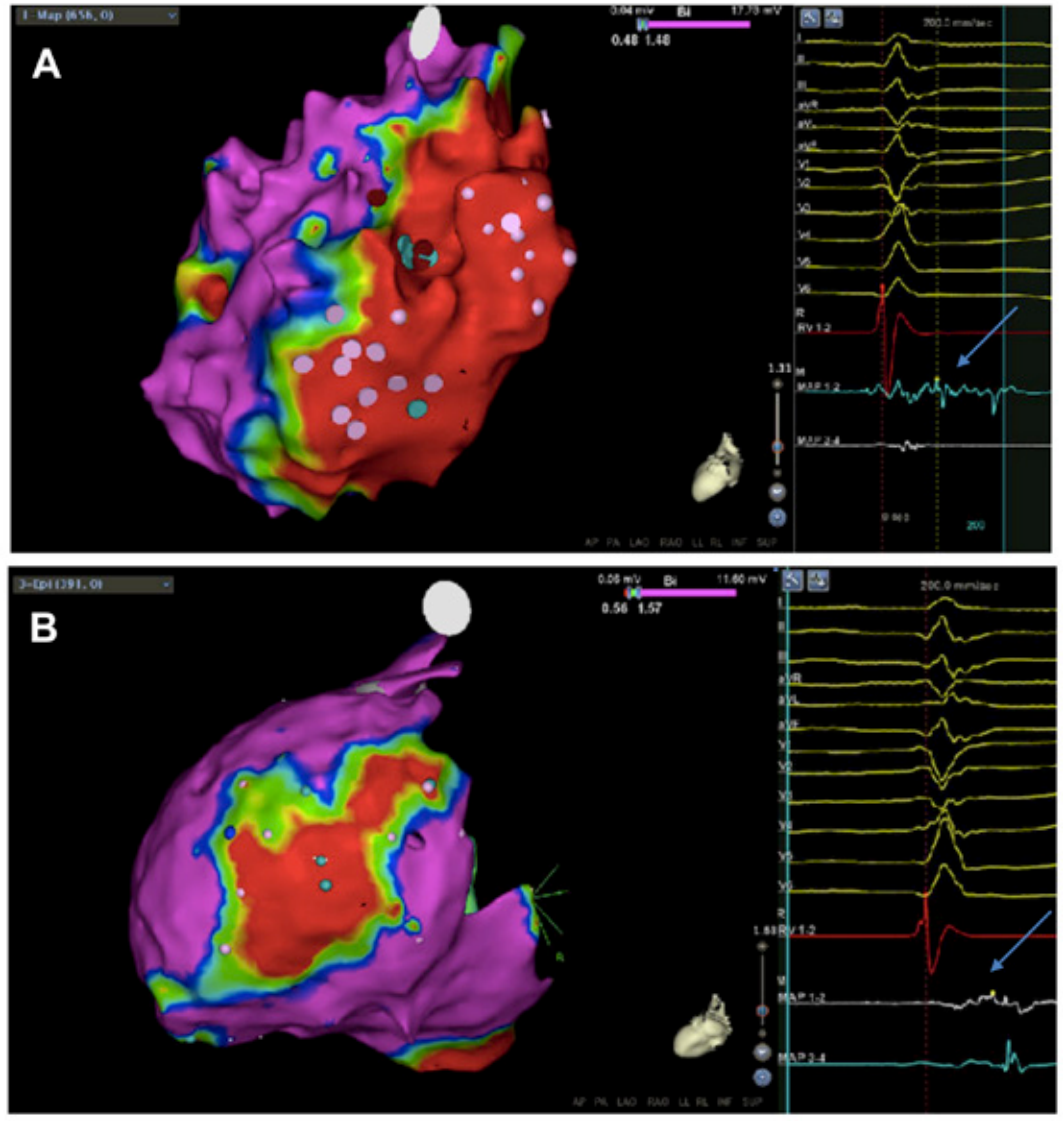
Repeated fluoroscopy revealed extensive pleural fluid on the left thorax (Figure 2C). Immediate drainage of the pleural space resulted in 2 litres of blood. On the operation room emergency lateral thoracotomy was performed. A laceration of the LIMA near the 6th intercostal space, was identified and repaired with a single suture. At follow-up he developed recurrent exudative pleural fluid.

Figure 2 fluoroscopy during and after pericardial puncture patient 2



During the first puncture (patient 2) the guidewire aligned the cardiac silhouette. However it took off higher than the normal pericardial folds (**Figure A**). Advancing the guidewire further confirmed its localisation in the pleura space (**Figure B**). On fluoroscopy extensive pleural fluid on the left thorax is seen (**Figure C**).

Figure 3 endo -and epicardial voltage map patient 2



A. Endocardial map showing an area of low voltage, posterior view and on the right intracardiac electrogram revealing an abnormal potential

B. Epicardial map showing an area of low voltage, posterior view, and on the right an intracardiac electrogram revealing an abnormal potential.

Discussion

A LIMA laceration, a complication of a pericardial puncture can stay temporarily concealed and may lead to a potential life threatening condition.
We would like to emphasize the importance of understanding the anatomy and recognising the person to person variability when performing epicardial VT ablation. The angle of a successful pericardial puncture is dependent on the rotation of the heart and the type and quantity of tissue that is crossed. Body mass index, pulmonary disease and history of abdominal operations are risk elevating factors.
As an alternative, an anterior approach directly accesses the fibrous pericardium without going through the diaphragm, can be used. A conventional inferior pericardial puncture has been safely used, however still contains a limited risk of right ventricle and liver trauma.[6,7] Few complications so far have been described.[8] Since the runoff of the LIMA is more anteriorly, an anterior puncture in general may contain a higher risk of LIMA perforation.
CT is very helpful in delineating the structural relationship of pericardium with other chest and abdominal organs. CT preceding epicardial VT ablation may prevent injury to unexpected structures during pericardial puncture.

Conclusion

Pericardial puncture may be complicated by a laceration of the LIMA. An anterior approach preferred to avoid right ventricular puncture, can potentially increase the incidence of LIMA damage. Caution is needed during needle advancement when approaching the pericardium to avoid a higher than usual puncture or needle take off.

Key teaching points

1. One of the complications of a pericardial puncture is laceration of the LIMA.
2. An anterior approach is preferred to avoid right ventricular puncture.
3. An anterior approach may be related to a higher incidence of LIMA damage.
4. When approaching the pericardium caution is needed during needle advancement to avoid a higher than usual puncture or needle take off.
5. A very anterior puncture can can be avoided when the puncture needle is aimed at a minimum angle of 20° towards the anterior RV silhouette. A pre-procedural CT scan can aid to avoid LIMA puncture in case of difficult anatomy.
6. A pericardial drain with proximal side holes outside the pericardium is commended to detect extra pericardial bleed that otherwise is left unnoticed.

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chapter 10

part 3

Scar related atrial arrhythmias

The scar reminds me of what I can be

Lawson

What deep wounds ever closed without a scar? The hearts bleed longest, and heals but to wear That which disfigures it.

Lord Byron

The Role of Atrial Fibrosis Detected by Delayed-Enhancement MRI in Atrial Fibrillation Ablation

11

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Abstract

Introduction
Atrial Fibrillation (AF) is associated with remodeling of the atrial tissue, which leads to fibrosis that can contribute to the initiation and maintenance of AF. Delayed-Enhanced Cardiac Magnetic Resonance (DE-CMR) imaging for atrial wall fibrosis detection was used in several studies to guide AF ablation. The aim of present study was to systematically review the literature on the role of atrial fibrosis detected by DE-CMR imaging on AF ablation outcome.

Methods
Eight bibliographic electronic databases were searched to identify all published relevant studies until 21st of March, 2016. Search of the scientific literature was performed for studies describing DE-CMR imaging on atrial fibrosis in AF patients underwent Pulmonary Vein Isolation (PVI).

Results
Of the 763 citations reviewed for eligibility, 5 articles (enrolling a total of 1040 patients) were included into the final analysis. The overall recurrence of AF ranged from 24.4 - 40.9% with median follow-up of 324 to 540 days after PVI. With less than 5-10% fibrosis in the atrial wall there was a maximum of 10% recurrence of AF after ablation. With more than 35% fibrosis in the atrial wall there was 86% recurrence of AF after ablation.

Conclusion
Our analysis suggests that more extensive left atrial wall fibrosis prior ablation predicts the higher arrhythmia recurrence rate after PVI. The DE-CMR imaging modality seems to be a useful method for identifying the ideal candidate for catheter ablation. Our findings encourage wider usage of DE-CMR in distinct AF patients in a pre-ablation setting.

1. Introduction
Atrial Fibrillation (AF) is the most common supraventricular tachy-arrhythmia, which reduces quality of life and overall survival.[1,2] Although Pulmonary Vein Isolation (PVI) is established as a standard rhythm control strategy for AF ablation, its long-term efficacy despite significant improvements in catheter ablation technology remains controversial.[3-9] Several studies identified that AF is associated with electrical, structural and contractile remodeling of the atrial tissue.[10-13] It has been proven that the electrical remodeling process finally results in loss of atrial myocytes and increased level of collagen component, which leads to the fibrosis of the atrial wall.[12] Fibrotic atrial regions are thought to contribute not only to the initiation but also to the maintenance of AF.[10-13] The mechanism responsible for post-fibrillatory contractile dysfunction (loss of contractility) is still not completely understood. However, the atrial contractile dysfunction after prolonged fibrillation seems to be mainly associated with the depressed L-type Ca2+ current.[13] As for structural remodeling, the AF-related structural changes involve: 1) Increase in cell size, 2) Perinuclear glycogen accumulation, 3) Myolisis (central loss of sarcomeres), 4) Connexin expression alteration, 5) mitochondrial shape changes, 6) fragmention of sarcoplasmatic reticulum, 7) changes in quantity and localization of structural cellular proteins, 8) Homogenous nuclear chromatic distribution.[13] The structural changes in AF might be a result from adaptation to chronic Ca2+ overload and metabolic stress. Positive feedback- loops of atrial remodeling during AF is suspected. Down- regulation of L-type Ca2+ channels is considered responsible for electrical and contractile remodeling. The loss of contractility and increase in compliance result in the stretch of the atrial myocardium, which is a stimu lus for structural remodeling of the atria.[13] The Delayed- Enhanced Cardiac Magnetic Resonance (DE-CMR) imaging is a non-invasive, quantitative technique for localizing and evaluating the extent of atrial fibrosis and/or ablationinduced atrial tissue changes.[14] The DE-CMR imaging modality can identify tissue remodeling or fibrosis in the atria as these areas have a slower washout kinetic of contrast compared to normal atrial tissue, which results in increased signal intensity on T1-weighting imaging.[14] Several studies investigated the extent of atrial fibrosis by using DECMR imaging for guidance of AF ablation and exploring its impact on clinical outcome.[14-20] However, to date no report exists that systematically reviewed the role of DECMR imaging modality in AF ablation procedures. The aim of the study was to systematically review the available evidence on the role of atrial fibrosis detected by DE-CMR imaging in prediction of arrhythmia recurrence after Catheter Ablation (CA) of AF.

2. Methods
2.1. Data Sources and Search Strategy
This review was conducted in accordance with the PRISMA and MOOSE guidelines (Appendix 1, 2). We aimed to identify all published articles discussing the role of atrial fibrosis detected by DE-CMR imaging in CA of AF. We searched Embase.com, Medline via Ovid, Web-ofscience, Scopus, Cinahl (EBSCOhost) and the Cochrane Central from inception until the 21st of March, 2016. Additional references were obtained from PubMed, the subset as supplied by publisher, containing recent references, and the first relevant results from Google scholar. The search strategy was created with the assistance of a medical librarian (WB). The search results were limited to English language articles. The detailed search methodology for all databases is provided in Appendix 3.

2.2. Study Selection and Eligibility Criteria

We included studies that reported the outcome data of patients underwent percutaneous PVI for AF after detection of atrial fibrosis by DE-CMR imaging. Only those articles on patients who underwent CA for AF, who had had preablation DE-CMR imaging focusing on atrial fibrosis, and which also reported the follow-up of AF recurrence were included. The articles that focus on DE-CMR imaging results of patients with structural heart disease were excluded e.g. dilated cardiomyopathy, hypertrophic cardiomyopathy, congenital heart disease. Individual case reports, editorials, review articles and conference meeting abstracts were not included.

2.3. Data Extraction Process

Firstly, two authors (ZK, AAH) independently reviewed the included articles and analyzed the following data: degree of atrial fibrosis, type of AF, CA type, catheter type, procedural and fluoroscopy time, follow-up time, ablation success rate. Secondly, the authors cross-checked their findings to ensure accuracy. Finally, if there was no complete agreement, a third author was called to break the tie (TST). Only patients with good MRI quality by consensus of at least 2 observers defined by the core laboratories of the original study groups were included into the final analysis. Detailed description of "poor MRI quality" was not provided in the original articles.

2.4. Risk of Bias Assessments for the Included Studies

Study quality was assessed by two independent reviewers (ZK, AAH) based on the nine-star Newcastle–Ottawa Scale (NOS) using three pre-defined domains: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Studies that received a score of nine stars were considered to be at low risk of bias; studies that scored seven or eight stars were considered at medium risk; those that scored six or less were considered at high risk of bias.

2.5. Outcome Assessment and Statistical Methods

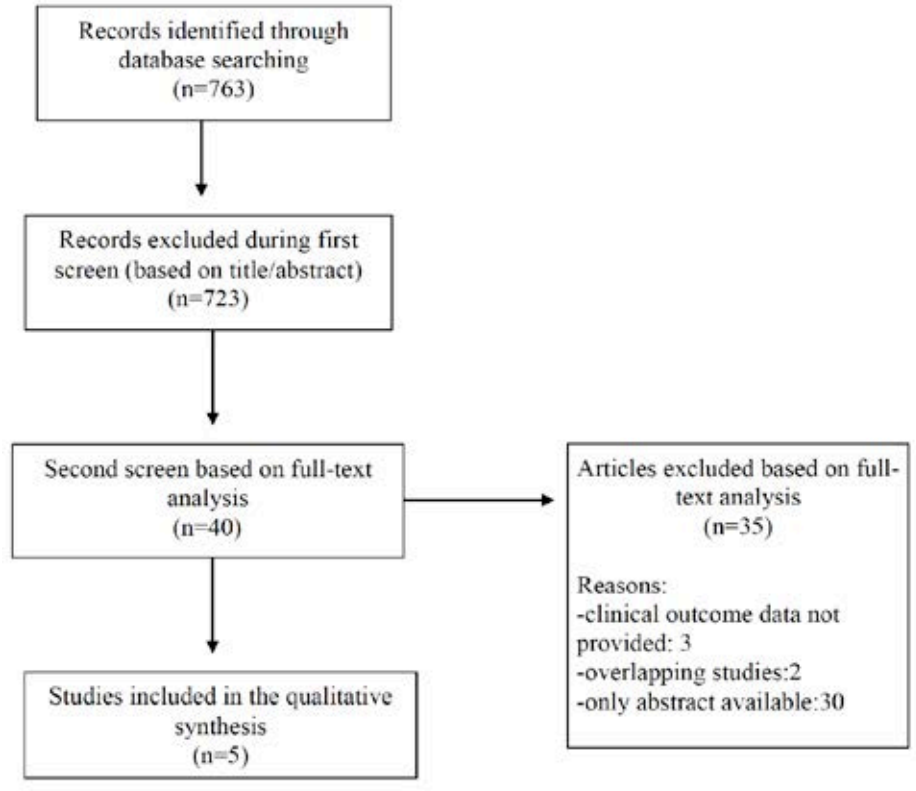
For each study, we identified whether an association was reported, and when applicable, effect sizes were reported. Continuous variables are presented as mean ± SD. Categorical variables are presented as frequencies and percentages. A Cox proportional hazard ratio was used to evaluate the arrhythmia recurrence.

3. Results

3.1. Identification of Relevant Studies

The search strategy identified 763 citations, out of which, following initial screening based on titles and abstracts, fulltexts of 40 articles were evaluated further. A total of 5 studies without overlapping patient population discussing the degree of atrial fibrosis using DE-CMR imaging performed prior PVI for AF were included.[16-20] (Figure 1)

Figure 1 Flowchart of studies



Flowchart for outcome of atrial fibrosis detection using delayed-enhancement magnetic resonance imaging before atrial fibrillation ablation.

3.2. General Characteristics of the Included Studies

Table 1 shows the key characteristics of the included studies. In aggregate, in all included studies, 1040 patients who had DE-MRI and underwent ablation for AF were included in this review. All 5 included studies were prospective with observational design. Out of 5 studies 4 single-center, and 1 multi-center were analyzed. The intensity of the follow-up within 1 year after the index procedure was comparable among the included studies (Table 1). Four studies reporting the outcome data of PVI ablation conducted a clinical visit with at least 7-days Holter-monitoring 3 times per year, furthermore symptom driven event monitoring was also performed. In the study Khurram et al. a clinical and phone visit were scheduled at 6, 12-months of follow-up.[20] If a patient was suggestive of an arrhythmia recurrence 24-h Holter-monitoring or 30-day event monitoring were performed.[20] The recurrence of AF was defined as documented symptomatic or asymptomatic atrial fibrillation, atrial tachycardia or atrial flutter more than 30 seconds duration after 3-month blanking period. Patients with poor MRI quality were excluded in the reviewed studies, which ranged from 3.5[20], 9.6[16], to 17.3[17] percentage of patient population. The value of MRI was

chapter 11

Table 1 Comparison of the extent of pre-ablation atrial fibrosis and the ablation outcome data derived from the included articles.

Publication	C.Mahnkopf 2010, USA	U.Canpolat 2014, Turkey	N. F. Marrouche 2014, USA, SPA, GER, FRA	N. Akoum 2015, USA	I.M.Khurram 2016, USA
Study design	Prospective, singlecenter	Prospective, singlecenter	Prospective, multicenter	Prospective, singlecenter	Prospective, singlecenter
Ablation strategy	PVI, posterior wall, septal debulking	PVI, CFAE, posterior wall	PVI, CTI	PVI, posterior wall, interatrial septum, mitral istmus	PVI, additional lines
Ablation source energy	RF	Cryo, redo with RF	RF, cryo	RF	RF
Patient number	333	41	272	172	165
Paroxysmal AF (n)	Nd	41	168	92	71
Persistent AF (n)	Nd	0	92	80	94
Follow-up (days)	324 ± 234	540	325	346 ± 82	306 ± 171
Average pre-ablation fibrosis (%)	Nd	Nd	Nd	14,6 ± 8,4	35,9 ± 14,8
Recurrence rate (%)	40,9	21,9	33	34,9	38,2
Follow-up methodology					
Clinical visit	3, 6, 12 months	3, 6, 12 months	3, 6, 12 months	3, 6, 12 months	3, 6 months
Holter monitoring	8d Holter 3, 6, 12 months	24h Holter 3, 6, 12 months	Ambulatory monitoring 3, 6, 12 months	7d Holter 3, 6, 12 months	Nd
Additional investigation based on symptoms	ECG	Holter	Nd	ECG	24h Holter or 30d event monitoring

Nd: No Data

Table 2 Correlation between the extent of left atrial fibrosis and arrhythmia recurrence after successful pulmonary vein isolation for atrial fibrillation.

Extent of the Left Atrial Wall Fibrosis								
Publication	**< 5%**	**< 10%**	**< 20%**	**< 30-35%**	**> 5-10%**	**> 20%**	**> 30%**	**> 35%**
Mahnkopf 2010	0/21 (0%)	—	52/162 (32%)	95/310 (30%)	117/312 (38%)	65/171 (38%)	—	22/23 (96%)
Canpolat 2014	—	0/25 (0%)	4/29 (14%)	—	—	9/12 (75%)	—	—
Marrouche 2014	—	7/49 (15%)	42/156 (27%)	79/236 (33%)	79/236 (33%)	49/104 (28%)	12/24 (51%)	—
Akoum 2015	9/68 (13%)	—	22/126 (17%)	54/163 (33%)	37/110 (24%)	28/46 (61%)	—	6/9 (67%)
Khurram 2016	—	—	—	30/86 (35%)	—	—	—	67/79 (85%)
Total	9/68 (13%)	7/74 (8%)	120/473 (25%)	258/795 (33%)	265/652 (41%)	151/333 (45%)	12/24 (50%)	95/111 (86%)

N: Number; **pts:** Patients; **Afib:** Atrial Fibrillation

limited for patients with a high body mass index and uncontrolled fast heart rate. All studies were at medium risk of bias. The quality assessment of the involved studies is reported in Supplement 1 and 2.

3.3. Assessment of left Atrial Wall Fibrosis

Quantification of Left Atrial (LA) remodeling was obtained using the methodology described by Oakes et al.[15] Fibrosis was reported as a percentage of the atrial surface area with delayed-enhancement using CMR imaging. Contrast enhancement is a result of altered washout kinetics of gadolinium relative to normal myocardial tissue, indicative of increased fibrosis of the myocardium.[21] Two studies[16,18] used the UTAH scoring system for determining fibrosis of the atrial wall. Utah stage I was defined as < 5% LA wall enhancement. Utah stage II as > 5% and < 20%, Utah stage III as > 30% and < 35%, and Utah stage IV as > 35%. In further three reviewed studies different cut-off values were used for analysis of left atrial fibrosis.[17,19,20] The percentage of LA wall fibrosis in these studies ranged from 5%[16,18], 10%[17,19], 20%[16-19], 30%[17] and 35%[16,18,20] based on MRI imaging (Table 2).

3.4. Correlation Between Atrial Wall Fibrosis and Arrhythmia-Free Survival After Ablation for AF

Overall recurrence of AF ranged from 24.4 - 40.9% with median follow-up of 324 to 540 days after PVI. With less than 5 - 10% fibrosis in the atrial wall there was a maximum of 10% recurrence of AF after ablation. With more than 35% fibrosis in the atrial wall there was 84% recurrence of AF after ablation. Using a cut-off value of 20% there was respectively 25 versus 45% recurrence during follow-up for less versus more fibrosis.

4. Discussion

The noninvasive DE-CMR imaging modality to detect fibrotic left atrial tissue in AF patients may allow a better patient selection for CA in certain cases. The present systematic review reveals that all included studies uniformly report a correlation between higher rate of AF recurrence after successful ablation among patients with more extensive atrial fibrosis identified by pre-ablation DE-CMR imaging. Patients with more extensive pre-ablation left atrial enhancement were more likely to suffer AF recurrence after successful PVI compared to those with minimal or moderate degrees of contrast enhancement.[16-20] Despite three out of five included studies derived from the same group of investigators, the quantitative evaluation of fibrosis extent in percentage showed a wide range of variety, which also might have a positive aspect providing the opportunity to study the recurrence in different settings and in relation with different fibrosis degree.

4.1. Correlation Between the Extent of LA Wall Fibrosis and the Type of Atrial Fibrillation

Atrial fibrillation is a progressive disease and the causality between fibrillation and fibrosis is thought to be bidirectional.[15] Although one can reason as AF begets AF, that the longer a patient is in AF the more LA fibrosis is expected, this was not confirmed by all imaging studies.[22] The study by Mahnkopf et al. pointed out that the amount of LA enhancement was independent from the AF duration, comorbidities, and the baseline type of AF.[16] The DECAAF study also demonstrated a weak correlation between AF phenotype (paroxysmal, persistent, longstanding persistent) and the degree of fibrosis.[17] Khurram et al. hypothesized that the association of AF recurrence with baseline Left Gadolinium Enhancement (LGE) extent would be dependent on AF type. However, they found no evidence of statistical interaction or effect modification between LGE extent and type of AF prior ablation.[20]

4.2. Predictors of AF Recurrence After Successful PVI

The result of Oakes et al. demonstrated that not only the extent but also the location of the Left Atrial (LA) enhancement appeared to be an independent predictor of AF recurrence. Patients with contrast enhancement in all LA regions had higher recurrence rate, while those responded successfully to ablation had limited enhancement focused to posterior wall and the septum.[15] Akoum et al. reported in 2011 that the overall ablation scar in the LA predicted the AF recurrence independently in patients with mild or moderate fibrosis.[14] The same group concluded in 2015 that the residual fibrosis remaining after ablation was a significant predictor of arrhythmia recurrence after ablation irrespective of AF type and PV encirclement.[18] Patients with baseline anterior wall fibrosis, usually not targeted by ablation were more likely to have higher residual fibrosis and higher AF recurrence rate compared to those with baseline fibrosis in the posterior left atrium and PV antral region.[20] In the study by Canpolat et al. the extent of LA fibrosis and the early recurrence were found an independent predictor of AF recurrence after ablation. One percent increase in LA fibrosis increased the risk of AF recurrence with 1,127 fold, while early recurrence increased the recurrence risk with 1,442 fold.[19]

4.3. Pulmonary Vein Encirclement Detection After Ablation by DE-CMR

While CA of AF aims to achieve complete isolation of PVs as a procedural endpoint, the intra-procedural achievement of conduction block does not always result in longterm block.[23] It has been reported that gaps identified with DE-CMR in PV regions after ablation correlated with PV electrical reconnections.[24] In the analysis from the DECAAF study the overall chronic complete encirclement of all PVs with PVI was achieved in 7, 3% (12/163) of pa tients. Circumferential PV scarring was not an important factor of arrhythmia recurrence in paroxysmal AF patients. The proportion of patients where complete 4PVs encirclement failed (92,7%) was significantly higher compared to those who represented with AF recurrence (36%). It suggests that complete encirclement of all PVs is not a critical factor in determining procedural success. Taken together the results on PV encirclement with the role of residual fibrosis as a significant predictor of AF recurrence, advocates the larger role of atrial substrate elimination in rhythm control of AF.[22] This is in accordance with observation by Narayan et al. who reported that ablation of PV antral regions may coincidentally lead to elimination of focal sources and rotor centers that maintain the arrhythmia.[25]

4.4. Strengths and Limitations

To the best of our knowledge, this is the first systematic review attempted to evaluate the role of DE-CMR detected LA wall fibrosis on AF ablation outcome. One of the reasons for this is that the available literature fulfilling our inclusion criteria is novel, with more than half of included studies were published in the past two years. Our searching methodology ensured that we included the most relevant articles in our review enrolling more than one thousand patients. However, this study has a number of limitation. Firstly, despite all efforts made to undertake a comprehensive search of the published English literature, the possibility of publication bias due to under-reporting of negative findings cannot be excluded. Secondly, it is important that the assessment of the effect of different ablation methodologies such as (segmental, circumferential etc.) “PVI-only” and/or additional linear line ablations due to the considerable heterogeneity from the original studies made it impossible to establish a relation between the method of ablation and the clinical outcome. Thirdly, the included studies were also heterogeneous concerning the type (cryoballon, radiofrequency) of ablation. Probably, these facts can also influence the rate of arrhythmia recurrence after ablation. Finally, high-quality randomized controlled trials with adequate sample sizes and standardized long-term follow-up are needed to assess the role of atrial wall fibrosis detected by DE-CMR imaging on clinical outcome of CA for AF.

4.5. Clinical Implication

The DE-MRI may become an additive tool in guiding physicians in recommending CA for patients with AF. This method could give a helping hand in defining the most promising candidates not only for the primary but also for redo ablation procedures. However, saying MRI can predict responders to AF ablation can we ethically withhold the therapy to those with a high LA fibrosis density if a little less than halve are recurrence free after ablation? Alternatively, one can argue additional lines, targeting rotors or complex fractionated atrial electrograms in addition to PVI in the presence of extensive fibrosis. On the other end of the spectrum, in patients with longstanding persistent AF and very limited fibrosis AF ablation could become a more feasible therapy. Knowledge on limited fibrosis lowers the probability of ablation failure.

Conclusion

In conclusion, the identification of LA wall fibrosis using DE-CMR modality may aid to an appropriate patient selection for atrial fibrillation ablation. Our findings encourage wider usage of DE-MRI in distinct AF patients in a preablation setting.

Appendix 1 PRISMA checklist

Section/topic	#	Checklist Item	Reported on Page #
Title			
Abstract	1	Identify the report as a systematic review and a meta-analysis	1
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligi- bility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5, Suppl. 1,2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA

Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-8 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-12 Table 1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl. 1,2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-12 Table 1,2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl. 1,2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13 Figure 1, 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Appendix 2 MOOSE checklist.

Criteria	Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include	
Problem definition	Delayed-enhanced cardiac magnetic resonance (DE-CMR) imaging for atrial wall fibrosis detection was used in several studies to guide AF ablation. The aim of present study was to systematically review the literature on the role of atrial fibrosis detected by DE-CMR imaging on AF ablation outcome.
Hypothesis statement	The usage of DE-CMR imaging modality may help in identifying proper candidates for pulmonary vein isolation (PVI)
Description of study outcomes	We included studies that described DE-CMR imaging on atrial fibrosis in AF patients who (PVI).
Type of exposure or intervention used	DE-CMR imaging was used in all patients before PVI for atrial fibrillation
Type of study designs used	Eligible study designs included randomized controlled trials (RCTs), cohort, case-control studies.
Study population	Only studies carried out in adults (>18 years old) were included.
Reporting of search strategy should include	
Qualifications of searchers	The credentials of the investigators are indicated in the authors list.
Search strategy, including time period included in the synthesis and keywords	Search strategy and time periods are detailed in page 5 of the manuscript and in Figure 1 and the full search strategy is available in Appendix 3.
Databases and registries searched	Google Scholar, PubMed, Embase.com, Medline via Ovid, Web-of-science, Scopus, Cinahl (EBSCOhost) and the Cochrane Central
Search software used, name and version, including special features	We did not employ a search software. Endnote was used. to merge retrieved citations and eliminate duplications.
Use of hand searching	We hand-searched bibliographies.
List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. Citations for the included studies are included in the text and Table 1. The citation list for excluded studies is available upon request.
Method of addressing articles published in languages other than English	We placed restrictions to English language. Systematic reviews were used to identify further references.
Method of handling abstracts and unpublished studies	Systematic reviews were used to identify further references.
Description of any contact with authors	Authors of included studies were contacted to retrieve missing full texts and to identify any missing studies.
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
Rationale for the selection and coding of data	A predesigned data collection form was prepared to extract the relevant information from the included full texts, including study design, type of atrial fibrillation, type of catheter ablation, extent of atrial fibrosis.

Assessment of confounding	
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case- control and cohort studies included in this reviews
Assessment of heterogeneity	We were not able to pool due to large levels of heterogeneity evaluated visually and statistically
Description of statistical methods in sufficient detail to be replicated	For each study, we defined whether an association was reported, and when applicable, effect sizes were reported.
Provision of appropriate tables and graphics	We included 1 main figure, 2 main tables, and 3 appendices, 2 supplements
Reporting of results should include	
Graph summarizing individual study estimates and overall estimate	Figure 2, 3
Table giving descriptive information for each study included	Table 1
Results of sensitivity testing	The heterogeneity of the outcomes across the different studies thwarted our ability to provide pooled estimations
Indication of statistical uncertainty of findings	95% confidence intervals or SD's were presented if available
Reporting of discussion should include	
Quantitative assessment of bias	Not applicable
Justification for exclusion	We excluded studies that had no or unclear definition of outcome, or data extraction was not feasible.
Assessment of quality of included studies	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case- control and cohort studies included in this review.
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Due to the lack of standardisation of follow-up, it is difficult to provide unifying statements within a larger number of manuscripts hampered by large levels of heterogeneity.
Generalization of the conclusions	The generalizability of our findings has been enhanced by the involvement of data, including region of the Americas, Europe. However, there is a clear lack of evidence from West Pacific Region, and the African and Asian, Australian Region.
Guidelines for future research	Further randomized controlled studies with long-term follow-up are necessary to investigate the role of DE-CMR imaging on detecting atrial fibrosis in AF patients
Disclosure of funding source	Nothing to disclose.
Disclosure of funding source	Nothing to disclose.

Appendix 3 Data search strategy

Embase.com	575	570
Medline Ovid	130	18
Web of science	184	67
Scopus	285	17
Cochrane	5	2
PubMed publisher	14	10
Cinahl EBSCO	31	3
Google scholar	100	76
Total	1375	763

Embase.com 575 (Fibrosis/de OR 'heart muscle fibrosis'/de OR (fibrosis)) AND ('atrial fibrillation'/exp OR (((atrial OR atrium) NEAR/3 fibrillat*) OR AF)) AND ('nuclear magnetic resonance imaging'/de OR 'nuclear magnetic resonance'/exp OR 'cardiovascular magnetic resonance'/de OR ('magnetic resonance' OR mri OR CMR OR (mr NEAR/3 imag*) OR (multimodalit* NEAR/3 imag*))) NOT ([animals]/lim NOT [humans]/lim)

Medline Ovid 130 (Fibrosis/ OR (fibrosis)) AND ("Atrial Fibrillation"/ OR (((atrial OR atrium) ADJ3 fibrillat*) OR AF)) AND (exp "Magnetic Resonance Imaging"/ OR "Magnetic Resonance Spectroscopy"/ OR ("magnetic resonance" OR mri OR CMR OR (mr ADJ3 imag*) OR (multimodalit* ADJ3 imag*))) NOT (exp animals/ NOT humans/)

Cochrane 5 ((fibrosis)) AND ((((atrial OR atrium) NEAR/3 fibrillat*) OR AF)) AND (('magnetic resonance' OR mri OR CMR OR (mr NEAR/3 imag*) OR (multimodalit* NEAR/3 imag*)))

Web of science 184 TS=(((fibrosis)) AND ((((atrial OR atrium) NEAR/2 fibrillat*) OR AF)) AND (("magnetic resonance" OR mri OR CMR OR (mr NEAR/2 imag*) OR (multimodalit* NEAR/2 imag*))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine) NOT (human* OR patient*)))

Scopus 285 TITLE-ABS-KEY(((fibrosis)) AND ((((atrial OR atrium) W/2 fibrillat*) OR AF)) AND (("magnetic resonance" OR mri OR CMR OR (mr W/2 imag*) OR (multimodalit* W/2 imag*))) AND NOT ((animal* OR rat OR rats OR mouse OR mice OR murine) AND NOT (human* OR patient*)))

Cinahl EBSCO 31 (MH Fibrosis OR (fibrosis)) AND (MH "Atrial Fibrillation" OR (((atrial OR atrium) N2 fibrillat*) OR AF)) AND (MH "Magnetic Resonance Imaging+" OR MH "Magnetic Resonance Spectroscopy" OR ("magnetic resonance" OR mri OR CMR OR (mr N2 imag*) OR (multimodalit* N2 imag*))) NOT (MH animals+ NOT MH humans)

PubMed publisher 14 (Fibrosis[mh] OR (fibrosis[tiab])) AND ("Atrial Fibrillation"[mh] OR (atrial fibrillat*[tiab] OR atrium fibrillat*[tiab] OR AF[tiab])) AND ("Magnetic Resonance Imaging"[mh] OR "Magnetic Resonance Spectroscopy"[mh] OR ("magnetic resonance"[tiab] OR mri[tiab] OR CMR[tiab] OR mr imag*[tiab] OR (multimodalit*[tiab] AND imag*[tiab]))) NOT (animals[mh] NOT humans[mh]) AND publisher[sb]

Google scholar Fibrosis "atrial|atrium fibrillation" "magnetic resonance"|mri|CMR|"mr|multimodality imaging|images|image".

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Extensive scar modification for the treatment of intra-atrial re-entrant tachycardia in patients after congenital heart surgery

12

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Abstract

Background
Catheter ablation (CA) is an important therapeutic option for atrial tachycardias in patients with congenital heart disease (CHD). As a result of extensive scarring and surgical repair, multiple intra-atrial re-entrant tachycardia (IART) circuits develop and serve as a substrate for arrhythmias. The best ablation approach for patients with multiple IARTs has not been investigated. Here, we compared substrate-based ablation using extensive scar modification (ESM) to conventional ablation.

Methods
The present study included patients with surgically corrected CHD that underwent IART ablation. ESM was defined as substrate ablation based on a dense voltage map, aimed to eliminate all potentials in the scar region. The control group had activation mapping based ablation (AMBA). A clinical composite endpoint (CCE) was assessed. Points were given for type, number and treatment of IART recurrence.

Results
In 40 patients 63 (ESM 13) procedures were performed. Acute procedural success was achieved in 78%. Procedural duration was similar in both groups. Forty-nine percent had a recurrence within 1 year. During a 5-year follow-up [2.5 - 7.5 years] 46% required repeat CA. Compared to baseline CCE significantly decreased by 46% after 12 months (P = 0.001). Acute procedural success, procedural parameters, recurrence and repeat ablation were similar between ESM and AMBA.

Conclusion
CA using ESM for IARTs occurring after surgically corrected CHD illustrated similar short and long-term outcomes and procedural efficiency compared to CA using AMBA. The choice of ablation approach for multiple IART should remain at the discretion of the operator.

Introduction
Atrial arrhythmias have a major impact on the quality of life in patients with congenital heart disease (CHD). Surgical incisions in the atrium and atrial fibrosis form the substrate of intra-atrial reentrant tachycardia (IART). The presence of extensive scar may cause multiple IART circuits.[1,2,3] During catheter ablation (CA) the mapping of all the critical isthmuses of these circuits can be time consuming. Moreover, even after a successful ablation of all identified critical isthmuses the long-term results are hampered by a high recurrence rate.[4,5] A scar-related approach has been used with success in patients with scar-related ventricular tachycardia[6] and even in atrial fibrillation.[7]
One of the most important limitations of longterm success in this population is complex scar with multiple re-entrant circuits. To the best of our knowledge there have not been studies performed addressing this small but very significant patient group. Extensive scar modification (ESM) is a treatment option for multiple IART circuits using the same scar. We hypothesized that ESM compared to activation map based ablation (AMBA) for the treatment of IART in patients with CHD reduces procedure times and improves efficiency of procedural outcomes.

Methods
Study population and data collection
Forty-eight consecutive patients with a surgically corrected congenital defect and atrial arrhythmias were screened. Forty of these patients had entrainable tachycardias and were included into the study. These 40 patients underwent 63 ablation procedures for scar related IART between May 2006 and May 2016 in our center. IART was defined as an arrhythmia from which the central obstacle was a surgical scar or any anatomical barrier other than the tricuspid annulus.[8] If more than 3 different IARTs were present we defined it as multiple.
All CA procedures were performed in accordance with institutionally approved local medical treatment protocols. The local ethical committee approved data collection (MEC-2016-705). Procedural informed consent was obtained from all the patients prior to the electrophysiological study. All patient information was de-identified.

Procedural protocol
Anti-arrhythmic drugs were discontinued for at least 4 half lives prior to the procedure with the exception of amiodarone. The procedures were performed under local or general anaesthesia. The procedures were guided using EnSite NavX 3D (St. Jude Medical Inc., St. Paul, MN) mapping or CARTO system (Biosense Webster, Inc., Diamond Bar, California). Only detailed extensive maps were included in the study. Intracardiac bipolar electrograms filtered at 30 to 500 Hz were recorded by a computerized electrophysiological recording system. In all CAs for IART the chamber of origin was determined. When a left sided IART was suspected a deflectable decapolar catheter was inserted into the coronary sinus and functioned as a reference mapping catheter.
Per definition re-entry is the mechanism in patients with IART, and mapping is aimed to map the whole cycle length. IARTs were separated from another based on both morphology and cycle length.
The target of ablation was identified by activation and/or voltage mapping. Irrigated catheters were used for the majority of the procedures. The electrode-tip temperature limit was set at 43°C, with a power ranging from 30 to 45 W, and needed irrigation flow of 20-30 mL/min. The catheter selection was dependent on clinical judgment of the operator. Remote magnetic navigation (RMN) (Stereotaxis, Inc., St.

Louis, MO, USA) was used in 58% of the cases.
If the patient was not in atrial tachycardia (AT) at the beginning of the procedure, AT was induced, most commonly with rapid atrial pacing or atrial extra-stimuli. An electroanatomic map was created during atrial tachycardia. The only exception for creating a biatrial map was if AMBA was performed and the whole atrial cycle length could be mapped in the chamber of origin and tachycardias remained non-inducible after ablation. Double potentials depicted the target location. Entrainment pacing was used to identify and/or confirm atrial tachycardia circuits. Sites with a post pacing interval minus atrial tachycardia cycle length within 30 ms were considered to lie within the circuit. Hereafter in the presence of multiple re-entry circuits and at the preference of the operator a conventional AMBA or ESM approach was chosen.

Activation mapping based approach
A line was created across the critical isthmus, usually between areas of scar of between a scar and an anatomical structure (e.g. the inferior vena cava, superior vena cava or tricuspid annulus). Pacing was performed to prove bidirectional block. Localized re-entry was treated with discrete ablation lesions. After termination of an IART, we attempted to re-induce the IART using the stimulation protocol as described previously.

Extensive scar modification
Using a detailed 3D bipolar voltage map an effort was made to identify the sites of surgical incisions and sutures. Substrate mapping was performed during sinus rhythm with standard settings defined as normal tissue greater than 0.5 mV and very low-voltage area as 0.1 mV.[9] Dense scar was defined as areas with amplitudes less than the baseline noise level of the recording system (amplitude of < 0.05 mV). Maps were considered complete when both atria were extensively mapped and all scar borders were clearly defined. After mapping the ablation was extended throughout the entire scar.[9] Ablation was continued until the scar was unexcitable which was proven with pacing manoeuvers. A final result of ESM is illustrated in Figure 1.

Post-procedural protocol
All patients underwent continuous rhythm monitoring for 48 hours, a resting 12-lead electrocardiogram, laboratory tests and chest radiograph after the procedure. Regular follow up was performed at 3 months after the ablation and thereafter depending on the underlying symptoms and pathology for every 3 to 12 months. A 24-hour Holter recording was performed when a patient experienced recurrence symptoms.

Outcome definitions
We analyzed the following outcome date per strategy (substrate - ESM versus non substrate - AMBA): acute procedural success, early AT recurrences, median time to AT recurrence and redo and His bundle ablations during follow-up. Acute procedural success was defined as termination and non-inducibility of all IART. Any AT during follow-up was considered a recurrence. Early recurrences were defined as recurrences within 1 year after ablation. If during an electrophysiology study the arrhythmia was an isthmus dependent atrial flutter without the involvement of scar, it was not considered a repeat ablation.
A clinical composite endpoint (CCE) was calculated at baseline, at 6 months and 12 months follow-up. The CCE was a score per subject and therefore only focused on the index procedure (first procedure in our center, or first procedure after May 2006). Points (1-4) were given for 3 categories: electrocardiographically documented occurrence of IART, acute and longterm treatment (Table 4). Review of medical records and procedure notes was performed to ascertain the dates of occurrence of cardioversion and emergency room visit or hospital admission for management of arrhythmia or symptoms of the arrhythmia.

Statistical analysis
Data was analyzed using SPSS 15.0 (SPSS INC., Chicago, IL, USA). Descriptive statistics for categorical data were expressed in absolute numbers and percentages. Student t test, chi-square test, and Fisher exact test were used to compare differences across groups. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Median and interquartile ranges (IQR) were computed for continuous variables with non-normal distribution, and the Mann-Whitney U test to compute statistical significance. Wilcoxen signed rank test was used to calculate differences in significance for the CCE at different points in time. A two-sided P-value < 0.05 (two tailed) was considered significant.

Results

Clinical characteristics
Sixty-three procedures for IART in a total of 40 patients with surgically repaired CHD were included in this analysis (1 procedure n = 21, 2 procedures n = 15, 3 procedures n = 4). Thirteen procedures were a substrate approach. Two patients with an AMBA index procedure (Supplement 2A) underwent ESM during a repeat procedure. Two patients with an ESM index procedure (supplement 2B) underwent an AMBA approach during the repeat procedure.
A median number of 2 sustained IART episodes were recorded in the 6 months before ablation. Four patients had incessant IART at the index procedure. Thirty-one percent used Amiodarone at baseline. Six procedures were performed in paediatric patients.
In 13 IART ablation procedures the approach was ESM, in 50 procedures it was AMBA. In 43 out of 63 procedures multiple IARTs could be induced. There were no differences in baseline characteristics between the 2 groups (Table 1). The congenital cardiac anomalies in this cohort are described in Table 2 according to the presence of multiple IART and ESM. Transposition of the great arteries was present in 12 cases, Ebstein or tricuspid atresia in 8 cases and tetralogy of Fallot in 5 cases. Six out of 40 patients had a Fontan operation and 10 patients were following a Mustard operation.

Procedural data
Number of applications (26 - IQR 18 - 69), time (1124 seconds - IQR 627 - 2385) and procedural duration (240 minutes - IQR 163 - 298) were similar in both groups (Table 3).

Complications
There were 6 complications, 1 in the ESM group and 5 in the AMBA group (8 and 9% respectively in ESM and AMBA) (P = NS). Four were vascular peripheral complications: there were 2 haematomas, 1 arterio-venous fistula and 1 thrombus in the common femoral artery in relation to a percutaneous left ventricular support device. There was 1 cerebral vascular event in a patients that had an AMBA approach.

One ablation led to altered impedance of the pacemaker lead.

Outcome of the procedures

Acute procedural success was reached in 78% (Table 5) of the IART population. Forty-nine percent of the total patients had a recurrence within 1 year. One patient was lost to follow-up. The median time to recurrence was 120 days [IQR 30 - 525]. In case of a successful procedure (50): the 1-year recurrence rate was 45%. In case of an unsuccessful procedure (13): there was a 1-year recurrence rate of 57% (P = 0.55). The CCE in the overall group was reduced by more than one-third after 6 and 12 months (Figure 2). After 6 and 12 months 66% and 68% of the patients improved. This was a significant change compared to baseline (Table 6). Three patients required reinstitution and 2 patients needed an increase of antiarrhythmic drugs at 12 months after the index procedure, while 7 patients were able to discontinue their antiarrhythmic drugs altogether. Of the 16 patients with an early recurrence of IART, 4 had non-sustained AT episodes.

Substrate modification versus a conventional approach

There was no significant difference in procedural success between both approaches. ESM compared to AMBA was similar with regard to early and late recurrence and repeat procedures. The CCE after 6 and 12 months was not significantly different between the two groups (Table 7).

Repeat procedure

During a median follow-up of 5 years [IQR 2.5 - 7.5] a repeat procedure was considered necessary in 29 patients, 46% of the patients in both groups. One of the patients had multiple IARTs and one had a single IART which foci could not be reached during the index ablation. Both patients had AMBA as an ablation strategy. In 4 patients a His bundle ablation with pacemaker implantation was needed, and in 6 patients cavo-tricuspid isthmus ablation (CTI) after IART ablation was necessary to control recurrence (Figure 2). The underlying congenital heart disease in the patients who required CTI was pulmonary stenosis, double outlet ventricle, atrial septal defect (2) and tetralogy of Fallot (2).

Discussion

Table 1 Baseline characteristics

	Total N = 63 procedures	**ESM** N = 13 procedures	**AMBA** N = 50 procedures	*p-value*
male	40 (64)	9/13 (69)	31/50 (62)	0.75
median age [IQR]	34 [25-47]	33 [26 - 43]	35 [25 - 47]	0.66
median age at correction (years) [IQR]	5 [2 -11]	5 [1 - 10]	5 [3 - 12]	0.44
pediatric	7/63 (11)	1/13 (6)	6/50 (12)	1.00
number of sustained episodes 6 months before the the procedure [IQR]	2 [1 - 3]	1.5 [0 - 2.75]	2 [1 - 3]	0.65
Pacemaker for SN dysfunction at baseline	17 (27)	1 (8)	16 (32)	0.16
index procedure is a repeat procedure*	31 (49)	9 (69)	22 (44)	0.129
Medication				
betablocker	16 (25)	1 (8)	15 (30)	0.16
verapamil	1 (2)	0 (0)	1 (2)	1.00
class 1C AAD	1 (2)	0 (0)	1 (2)	1.00
sotalol	24 (38)	7 (54)	17 (34)	0.21
amiodarone	19 (30)	5 (39)	14 (28)	0.51
Procedure				
multiple IART morphologies	40 (63)	13 (100)	27 (68)	0.006
HD support device	3 (5)	2 (15)	1 (2)	0.51
RMN	40 (64)	8 (62)	32 (64)	1.00
Follow-up				
median duration of follow-up (years) [IQR]	5 [2.5 - 7.5]	5 [3 - 7]	5 [1.5 - 8]	0.98

* In 13 of the repeat procedures the index procedure was performed before 2006 or in another center

AMBA: activation map based ablation; **AAD:** anti-arrhythmic drugs; **ESM:** extensive scar modification; **HD:** hemodynamic; **RMN:** remote magnetic navigation; **SN:** sinus node

chapter 12

Table 2 Patient characteristics congenital heart defects

CONGENITAL HEART DEFECTS	all - 40	multiple - 26	ESM - 9
tricuspid atresia	6	5	1
ebstein	2	2	1
transposition of the great arteries	12	7	1
double outlet left ventricle	5	4	1
Tetralogy of Fallot	5	3	2
atrial septal defect / venous sinus defect	5	3	1
- *concomitant atrial septal defect*	5	3	1
atrioventricular septal defect	2	1	0
hypoplastic left ventricle	1	1	1
cor triatriatum	1	1	0
pulmonary stenosis, valvular or sub or supravalvular	5	3	0
congenital aortic stenosis, valvular and subvalvular	1	1	0
SURGERY CORRECTION CONGENITAL HEART DEFECT			
Fontan	6	6	3
Mustard	10	5	1

The distribution of anomalies among all procedures, procedures with multiple intra-atrial re-entry tachycardias (multiple) and extensive scar modification (ESM) procedures

Table 3 procedural parameters

	all median [IQR]	ESM median [IQR]	AMBA median [IQR]	*p-value*
applications number	26 [18 - 69]	31 [23 - 68]	24 [15 - 71]	0.43
application time (sec)	1124 [627 - 2385]	1100 [851 - 2494]	1148 [459 - 2400]	0.39
procedural duration (min)	240 [163 - 298]	240 [165 - 329]	225 [158 - 293]	0.73

AMBA: activation map based ablation; **ESM:** extensive scar modification

Table 4 Clinical composite endpoint count

Points	documented IART	acute treatment	long term treatment
0	none	none	none, betablocker, verapamil, digoxin
1	non sustained only	1 ECV	class I, sotalol
2	1 sustained	> 2 ECV	class III
3	incessant	hospitalisation for symtpoms of heart fialure, syncope of cardiac arrest	His, redo ablation

ECV: electrical cardioversion

Table 5 Procedural outcome

	all	ESM	AMBA	*p-value*
acute success	50/63 (79)	11/13 (85)	39/50 (78)	0.719
early recurrence	29/63 (46)	4/13 (31)	25/50 (50)	0.349
repeat procedure	29/62* (46)	6/13 (46)	23/49* (46)	1.00

* 1 patient was lost to follow-up

AMBA: activation map based ablation; **ESM**: extensive scar modification

Table 6 Composite endpoint - changes over time

	all	ESM	AMBA
Baseline versus 6 months (p/s)	25 improved 10 worsened 3 unchanged *p = 0.002*	6 improved 2 worsened 0 unchanged *p = 0.139*	19 improved 8 worsened 3 unchanged *p = 0.006*
Baseline versus 12 months (p/s)	26 improved 9 worsened 3 unchanged *p = 0.001*	6 improved 1 worsened 1 unchanged *p = 0.073*	20 improved 8 worsened 2 unchanged *p = 0.04*
6 months versus 12 months (p/s)	6 improved 7 worsened 25 unchanged *p = 0.751*	1 improved 1 worsened 6 unchanged *p = 0.655*	5 improved 6 worsened 19 unchanged *p = 0.787*

AMBA: activation map based ablation; **ESM**: extensive scar modification; **p/s:** per subject

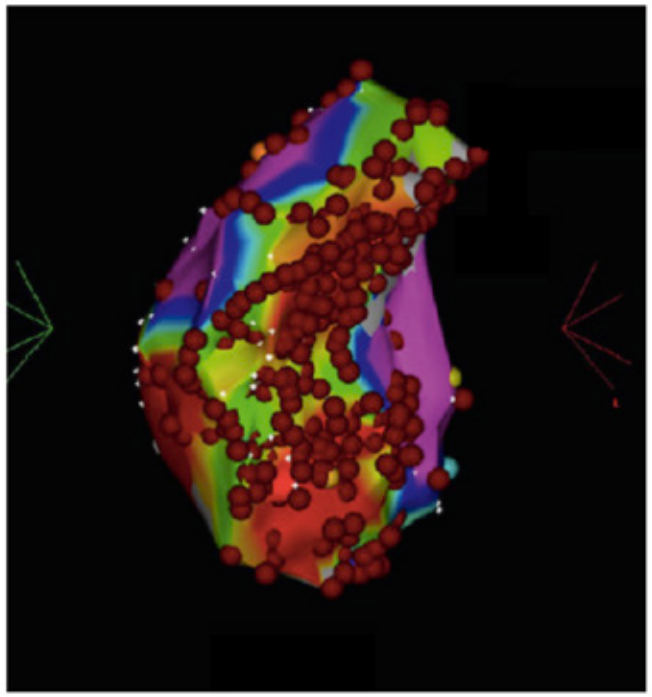
Table 7 Composite endpoint

	Baseline (p/s)	**6 months** (p/s)	**12 months** (p/s)
ESM	4.25	2.38	2.13
AMBA	4.07	2.33	2.30
p-value	0.785	0.570	0.687

* in 2 subjects no data on composite endpoint, one in the ESM and one in the AMBA group

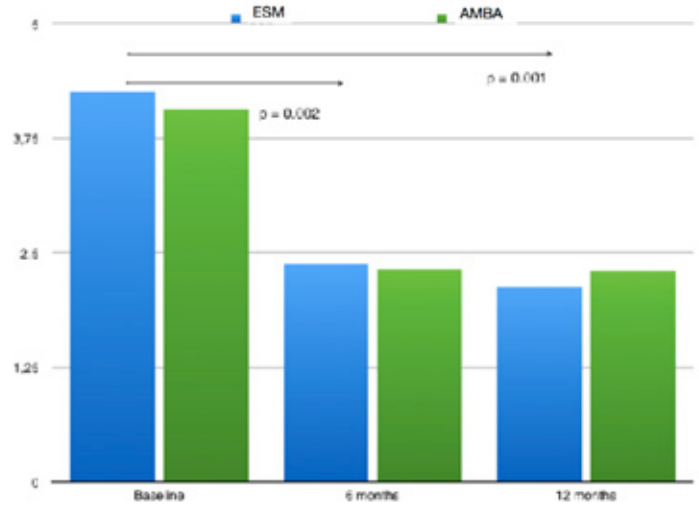
AMBA: activation map based ablation; **ESM**: extensive scar modification

Figure 1 An illustration of a patient with atrial extensive scar modification



This is an illustrations of a CARTO map of a patient who underwent extensive scar modification. Bipolar voltage scale was in the range of 0.1 - 0.5 mV. The dots represent a location of ablation. In case of dragging every 15 seconds a subsequent dot is placed.

Figure 2 Clinical composite endpoint
Clinical composite endpoint in p/subject in the ESM and AMBA group at baseline, 6 months and 12 months



AMBA: activation map based ablation; **ESM**: extensive scar modification

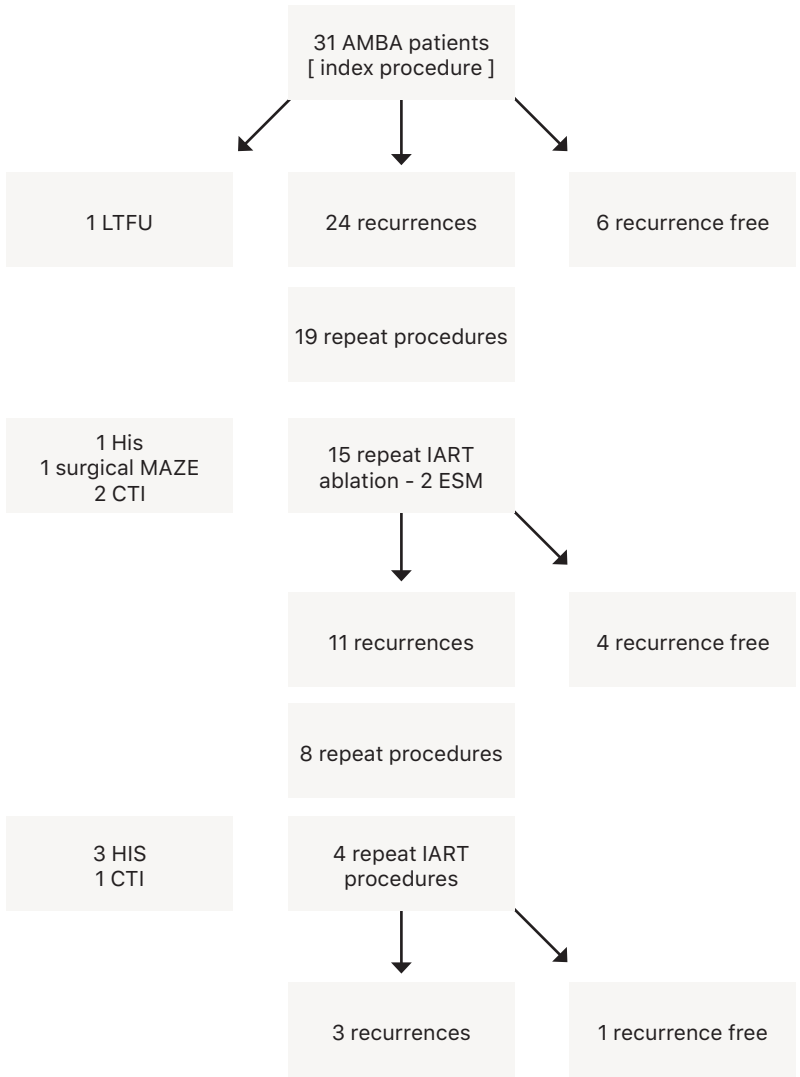
Supplement 1 Clinical composite endpoint countbaseline, 6 months and 12 months

Points	**documented IART**	**acute treatment**	**long term treatment**
0	none	none	none, betablocker, verapamil, digoxin
1	non sustained only	1 ECV	class I, sotalol
2	1 sustained	≥ 2 ECV	class III
3	incessant	hospitalisation for symptoms of heart failure, syncope of cardiac arrest	His, repeat ablation

ECV: electrical cardioversion; **IART**: intra-atrial re-entrant tachycardia

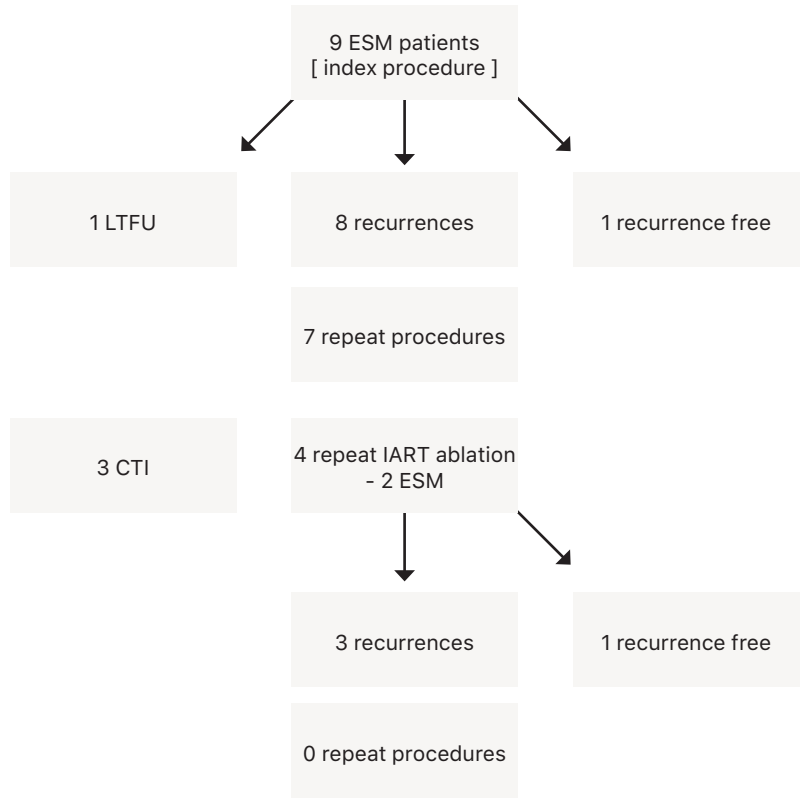
Supplement 2 recurrences and repeat procedures per strategy in AMBA and ESM

A. AMBA



AMBA: activation map based ablation; **CTI**: cavo-tricuspid isthmus; **ESM**: extensive scar modification; **His**: his bundle ablation; **IART**: intra-atrial reentrant tachycardia; **LTFU**: lost-to follow-up; **Maze:** maze surgical ablation

B. ESM



AMBA: activation map based ablation; **CTI:** cavo-tricuspid isthmus; **ESM**: extensive scar modification; **His**: his bundle ablation; **IART**: intra-atrial reentrant tachycardia; **LTFU**: lost-to follow-up; **Maze:** maze surgical ablation

Supplement 2 contains a flow chart describing the recurrences and repeat procedures throughout the complete follow-up of patients with activation map based ablation (AMBA) and extensive scar modification (ESM) respectively, thereafter in case of recurrence it shows again the chosen strategy. If this ablation strategy was IART it is specified whether it was AMBA or ESM and if there were recurrences.

To the best of our knowledge this is the first study that analyzed different ablation approaches in a difficult patient population. The major finding of this study is that ESM compared to AMBA in patients with intra-atrial re-entry tachycardia as a result of congenital heart surgery is not different with regards to short and long-term outcome and procedural efficiency.

Outcome IART ablation
IART ablation in the present study has an acute success of 78% and leads to a significant reduction in arrhythmia burden after 6 and 12 months. A high recurrence rate after ablation and even after repeat ablation in patients with IART is a standard in today's practice.[4,5]
Complex atrial anatomy, markedly enlarged, scarred right atria with wall thickening and high right atrial pressure are factors associated with pour ablation outcome.4 In the contrary, IART that are CTI dependent are associated with a better long-term outcome after ablation. These type of IART were excluded in the present study
Even if IART episodes are not eliminated entirely by ablation, the procedure can often provide substantial improvement by reducing the frequency of episodes and eliminating the need for ongoing drug therapy[11] illustrated by a significant drop in composite endpoint score after ablation. Triedman et al.[12] reported similar results to the current study regarding the frequency of clinical events pre-ablation and post-ablation periods and found a subsequent significant decrease in clinical events.
In our study, alike other studies[13], multiple atrial tachycardias are present in more than half of the patients referred for IART ablation. The clinical value of multiple arrhythmias during an ablation procedure is not completely known, also considering that one arrhythmia frequently dominates. Recurrences during the follow-up however, frequently means the development of novel onset atrial tachyarrhythmias[1,2,3] even in the absence of multiple atrial arrhythmias at baseline.

Challenges in the ablation of IART
The circuit of the IART predominantly uses a central obstacle formed by the right lateral patch or right lateral atriotomy scar[14], and is less frequently formed between the scar and IVC, SVC or TV.[15] Multiple IART circuits may develop due to incisional scar and obstacles in the atria.[1,2,3] Rather than mapping all the IART individually, ESM can be applied as an alternative. In the present study ESM was equally effective compared to AMBA in treating IART. The equal number of RF applications and duration of RF between the two groups may be a representation of multiple unsuccessful ablation points in conventional ablation. A combination of ESM and AMBA is not performed in the present study, yet it is likely to assume it can become a successful future ablation approach, especially in case of a frequently re-occurring clinical IART with identical morphology.

Scar modification in VT ablation
Shorter procedural and fluoroscopy times are needed for a direct substrate VT ablation strategy compared to ablation guided by entrainment maneuvers.[6] Higher scar heterogeneity is related to a higher arrhythmogenic potential of the ventricular scar[16], which rationalizes scar modification in VT ablation. In a recent multicenter randomized study that compared scar modification with clinical VT ablation in ischemic cardiomyopathy, a significantly larger freedom from VT recurrence is seen at one year.[6] Moreover a larger percentage of patients were able to discontinue anti-arrhythmic drugs after substrate ablation.

Scar modification in the atria
Possible drawbacks of scar modification approach are the lack of an established endpoint to verify individual or multiple point lesion efficacy, need for remapping to assess for complete elimination of abnormal electrograms, and ablation of bystander regions.[17] In the atria the latter might be of less importance. In VT ablation abundant ablation leading to a reduced ventricular function is of critical importance. On the contrary a large ablation area in a scarred atrium will not deprive cardiac output substantially. A theoretical disadvantage of ESM is a higher chance of complications with more extensive ablation. The current study does not support this potential hazard.
In ESM there is no need for arrhythmia induction. This can be an advantage not only in case of non-inducibility, but also for hemodynamic instability. Especially patients with an univentricular heart can become hemodynamically unstable during mapping and ablation.[18] Substrate mapping would abolish the need for a hemodynamic support device.

Candidates for ESM
The recurrence risk is particularly high among Fontan patients who tend to have the largest number of IART circuits, the largest atrial dimensions and most atrial hypertrophy.[4,19] Therefore potential candidates for ESM are patients with RA-PA Fontan connections. On the contrary in Mustard patients the cavotricuspid isthmus usually is the target.[20] Our ESM cohort is represented by a heterogeneous group of congenital heart disease. Also surgically corrected ASD and TOF patients, who usually have limited areas of low-voltage are represented. In the current study invasiveness of congenital heart surgery did not correlate with the arrhythmia burden and the presence of multiple IARTs. Disease progression is a possible explanation for the presence of multiple IART. If multiple re-entrant circuits are present in ASD and TOF more extensive areas of low voltage should be suspected and ESM can be a feasible approach.

Limitations of the study
The main limitation of the study is that it is a single-center retrospective analysis with a low number of patients who have ESM. Not all patients with a recurrence had an electrophysiology study, therefore we cannot be sure about the mechanism of the recurrent atrial tachycardia. In some analysis patients were used repeatedly as unique events which adds potential bias. One should be cautious to draw conclusions on the specific congenital population referred for IART ablation there the analysis included a heterogeneity of anomalies. The follow-up duration in this study is representative of standard clinical practice. A single recurrence or the time to a first recurrence in this population does not represent the most important clinical outcome marker. In this article we have made an effort to give an insight in the reduction of arrhythmia burden.

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Conclusions

In the ablation treatment of intra-atrial re-entry tachycardias in patients after congenital heart surgery, extensive scar modification illustrated similar outcome compared to a conventional mapping approach, even in the presence of multiple intra-atrial re-entry tachycardias. Based on the outcome of this study we don't recommend operators to change their current approach. Longterm recurrence rates remain high so further studies are needed to develop the best treatment strategy.

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Percutaneous ventricular assist device for circulatory support during ablation of atrial tachycardias in patients with a Fontan circulation

13

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Percutaneous ventricular assist device for circulatory support during ablation of atrial tachycardias in patients with a Fontan circulation

Case series

Sr. Editor:

In the current paper we describe two patients with Fontan circulation in whom a haemodynamically unstable atrial arrhythmia was successfully ablated with the aid of a continuous flow percutaneous ventricular assist device (pVAD).

A 34 year old male patient was referred to our clinic for an ablation for symptomatic frequently recurring intra atrial re-entrant tachycardias (IART). He was diagnosed with tricuspid atresia, atrial and a ventricular septal defect. At the age of 8 a Fontan circulation had been created and resulted in a pulmonic homograft between the right atrium (RA) and a hypoplastic right ventricle (Bjork modification). Pre-procedure examination revealed moderately reduced left ventricular (LV) function and a mildly stenosed homograft. The first ablation procedure was discontinued due to haemodynamic instability. During the repeat procedure we decided to use haemodynamic support with the use of a pVAD (Impella 3.5 CP catheter - Abiomed Inc., Danvers, MA, USA), that was placed via the right femoral artery in a retrograde approach across the aortic valve in the LV (figure 1A). A dense bipolar voltage map (figure 1B) of the RA identified multiple locations of scarring. An IART was induced and ablation was performed during tachycardia. During ablation on the lateral wall the tachycardia terminated. However, multiple different IART's could be re-induced. After ablation of all channels in the scar no IART could be induced at the end of the procedure .
Initially, during atrial tachycardias the patient was haemodynamically unstable. With a continuous blood flow of 2.7L per minute the tachycardias were tolerated, but only after correction of the preload.
There has not been a recurrence during a follow-up of 30 months.

A 21 year old male born with a tricuspid valve atresia underwent a bidirectional Glenn anastomosis at nine months. Completion of the Fontan circulation followed at the age of 2 when the RA was connected to the pulmonary artery.
He was referred for catheter ablation because of multiple episodes of drug resistant IART. The patient had deteriorated LV function and subsequently overt congested heart failure. Considering he was haemodynamically unstable during his tachycardias we used haemodynamic support with an Impella 3.5 CP catheter (Abiomed Inc., Danvers, MA, USA) that was placed via the left femoral artery. Bipolar voltage map illustrated an area of low-voltage on the lateral wall of the RA, most probably the result of the atriotomy. Entrainment mapping suggested that the area of low-voltage on the lateral RA wall was part of the induced IART circuit. Consequently an ablation line in the target area led to termination of the IART. With the use of the pVAD and preload correction by administrating 1.5L lactated ringer's solution to obtain a left ventricular end diastolic pressure of more than 12 mmHg, he maintained stable haemodynamics (Figure 2) and a urine production of > 200ml per hour.
He continued on Sotalol twice daily, and experienced a single episode of atrial tachycardia in the subsequent year. Additionally his ventricular function improved, symptoms of heart failure have ceased and his functional class remained stable. To the best of our knowledge this is the first report illustrating percutaneous circulatory LV support as a human implant during complex atrial arrhythmia ablation in univentricular physiology.

Despite extended periods of haemodynamic instability during ablation end-organ perfusion can be safely maintained by using circulatory support devices such as continuous flow pVAD. Haemodynamic support in VT ablation is widely accepted[1], but uncommon during the ablation of atrial arrhythmias. Instability during ablation may vary according to the type of arrhythmia and underlying structural morphology. In both single ventricle patients, with the use of pVAD, resulting in a blood flow of 2.7L /min and 3.5L/min respectively, stable blood pressure and cardiac output was maintained. This allowed for extensive mapping and ablation[2] during prolonged periods of atrial arrhythmia without developing haemodynamic compromise as suffered by one of our patients in a previous ablation attempt.

Arrhythmias are a well-known long-term complication of surgically repaired congenital heart defects such as after Fontan operation.[3] The pathophysiology is a complex interplay between cardiac anatomy, chamber enlargement from abnormal pressure and volume loads, cellular injury from cardiopulmonary bypass and fibrosis at sites of suture lines and patches.[4] Cardiac failure due to loss of sinus rhythm was already recognised by Fontan in his first report.[5]

In conclusion, in single ventricle patients with a Fontan type repair the use of pVAD combined with adequate preload results in a stable cardiac output, facilitating mapping and ablation of atrial arrhythmias.

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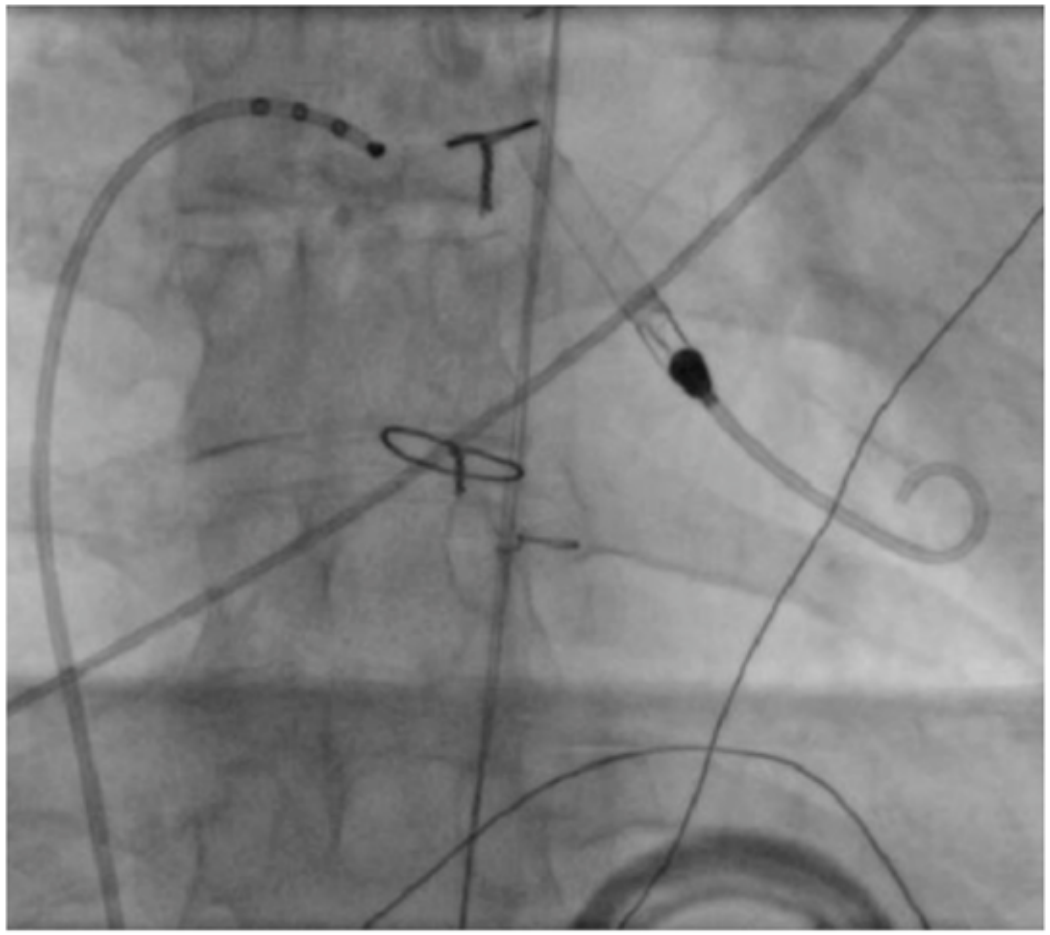
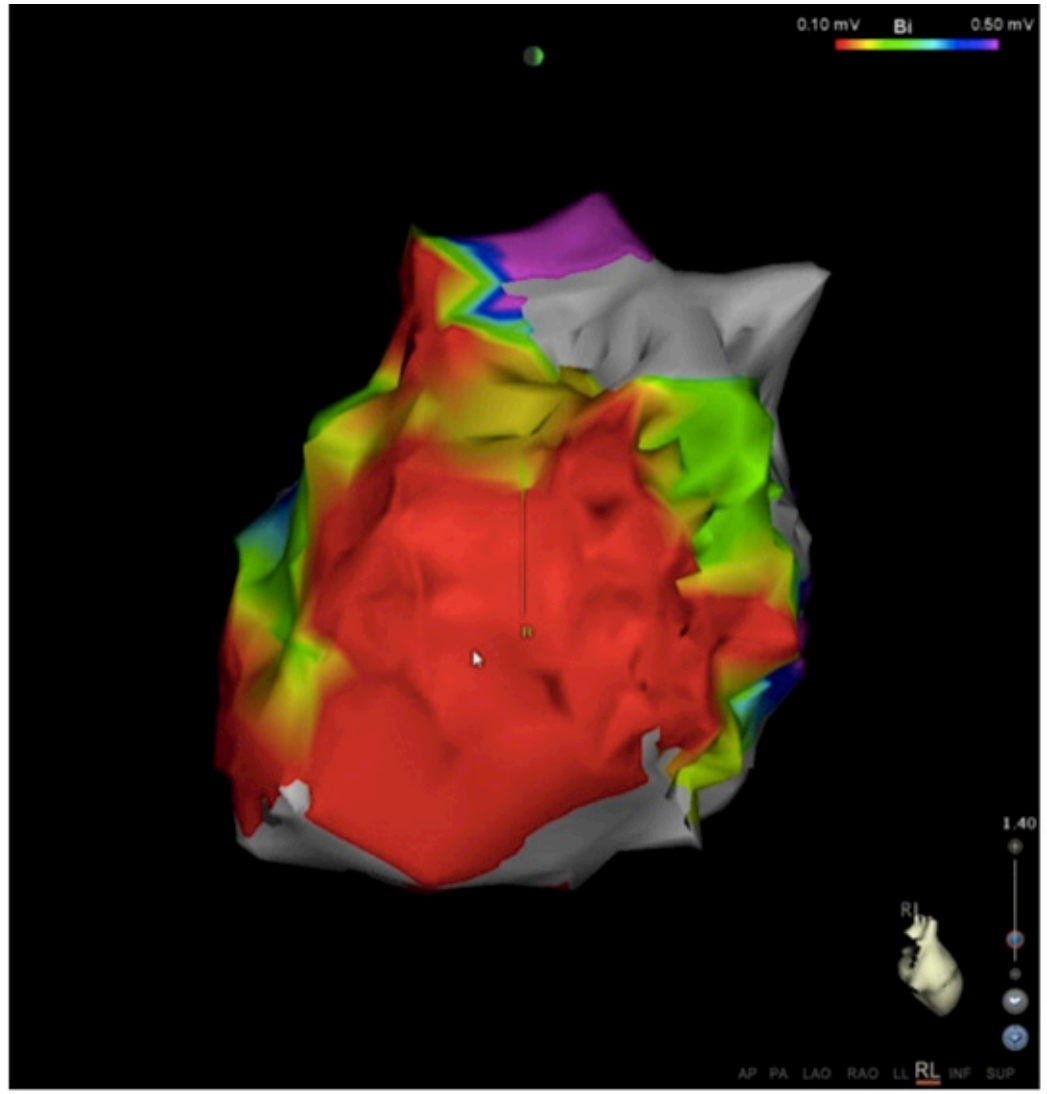
Figure 1 Radiographic image during the procedure (A), bipolar voltage map (B), case 1



A. Percutaneous ventricular assist device is placed via the right femoral artery in a retrograde approach across the aortic valve in the left ventricle.



B. Bipolar voltage map showing extensive scarring in the right atrium (right lateral view).

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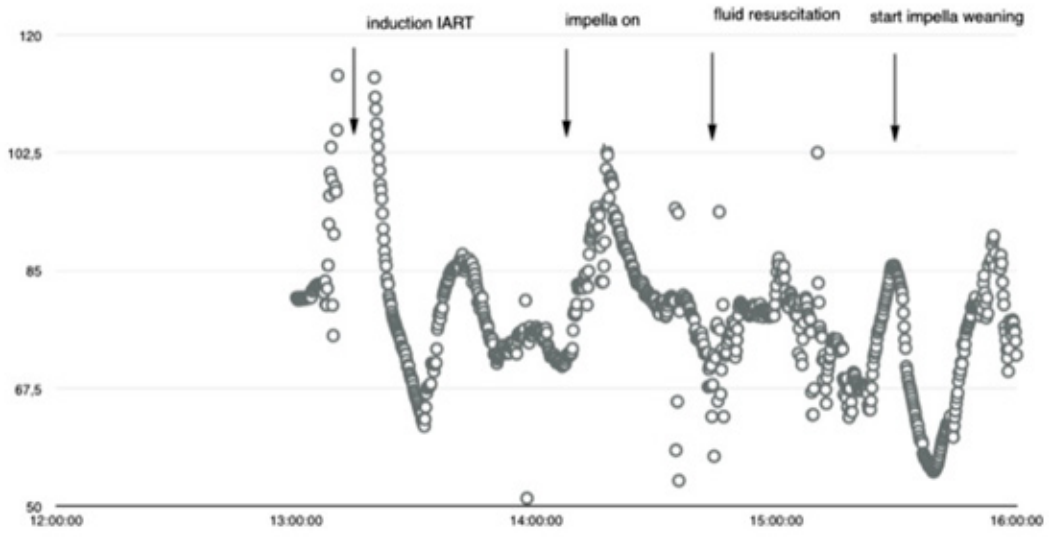
Figure 2 Mean arterial pressure during ablation, case 2



X-axis time in hours, Y-axis blood pressure in mmHg
During ablation the tachycardias were well tolerated under impella support, but only after correction of the preload.

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part 4

Summary and discussion

Beauty lies in the eye of the beholder

Plato

A lot of us grow up and we grow out of the literal interpretation that we get when we're children, but we bear the scars all our life. Whether they're scars of beauty or scars of ugliness, it's pretty much in the eye of the beholder.

Stephen King

Summary

Scar related arrhythmias, whether they arise from myocardial infarction or cardiac surgery, represent a major health burden. The substrates of these arrhythmias are subject to the complexity of a scar. Scar related ventricular tachycardia (VT) can be life threatening and treating VT may be life saving. Freedom of VT recurrence after ablation ranges between 40 and 88% during a mean follow-up period of 12-28 months.[1-4] VT ablation has advanced from a targeted ablation only, limited to inducible and stable tachycardias, to a combination of targeted and substrate ablation applicable for almost all VT patients. Targeted ablation abolishes circuits relevant to the arrhythmia burden at the time of the procedure, but more extensive ablation may target potential future VTs.[5] Refinement of techniques for induction, mapping and ablation all aid to improve VT ablation outcome.
The aim of this thesis was to investigate the outcome of catheter ablation on scar related arrhythmias. We studied the role of remote magnetic navigation, contact force, a substrate approach and image-integration.

Outcome of VT ablation, and the role of magnetic navigation and contact force
In **Chapter 2** we discussed the role of catheter ablation for VT in the treatment of patients with electrical storm. An increasing number of studies support the finding that catheter ablation is effective in suppressing electrical storm and it may be a direct life-saving therapy for the affected patient population. In **Chapter 3** we provided an educational review on electrical storm. Electrical storm often presents as part of an advanced cardiac disease and may predict a serious deterioration in the underlying processes. Both the trigger and the substrate of electrical storm may change over time. This may be influenced by progression of scarring, heart chamber remodelling and progression of heart failure. Electrical storm directly affects the patients' prognosis. However, by preventing the next episode of electrical storm mortality does not necessarily decrease.[6]
Catheter ablation for electrical storm has led to a 6-fold ICD - therapy reduction as compared to an increase in ICD - therapy of 1.5 in time when treating electrical storm with medication alone. In **Chapter 4** we conclude that ablation for electrical storm in the absence of reversible triggers may reduce the burden of ICD-therapy, only if performed within 90 days after the first episode of electrical storm.

Procedural and long-term clinical outcome of idiopathic outflow tract ventricular arrhythmias ablation in **Chapter 5** were equal for manual ablation, remote magnetic navigation and contact force guided ablations. Remote magnetic navigation was shown to have a favourable procedural safety profile due to the shorter fluoroscopy time compared with manual and contact force guided ablations. In **Chapter 6** we have described the first study that investigated the long-term clinical outcome in VT ablation using contact force catheters. The use of contact force sensing catheters did not improve procedural outcome or safety profile in comparison to non-contact force sensing ventricular arrhythmia ablation. However, remote magnetic navigation was superior with regard to acute success, reduction of major complications, and lower recurrence rate. The excursion of the ventricle during a VT ablation especially during tachycardia itself might lead to a less stable catheter position.
An unstable catheter position results in intermittent impaired energy delivery and subsequent inappropriate lesion formation. Moreover there is no way for the operator to produce a real-time response to contact force data requiring precise control over the catheter tip. This may explain why contact force in VT ablation is not well established. More complete substrate ablation may be obtained by ways of enhanced maneuverability[7,8,] improved accessibility to difficult anatomical structures[8], greater catheter stability[9,10] and preventing operator fatigue.
Adding contact measurement to remote magnetic navigation would possibly overcome the disadvantage of not being in contact with the myocardial wall throughout the whole ventricular contraction period. The awareness of inadequate contact may lead to more detailed mapping and limits errors on the presumption of false channels. Improved contact allows for a better demarcation of the low voltage areas[11] and increases the sensitivity of late potential detection.[12]
Implementation of contact feedback in **Chapter 7**, using e-contact in remote magnetic navigation for an ischemic VT ablation population resulted in a higher 1-year VT free survival. The e-contact module significantly reduced fluoroscopy exposure. These observations were most likely the result of improved accuracy of mapping and advanced ablation lesion formation due to the contact feedback.

Catheter ablation of ventricular tachycardia, imaging and epicardial substrate
Bipolar voltage map may show absence of low voltage in the presence of a small, patchy and non-transmural scar[13] and consequently a VT substrate may be missed. The VT substrate is potentially unmasked with right ventricular extrastimulation[14], and may be better visualized with CT or DE-CMR. Visualizing myocardial scar pre-procedurally may facilitate substrate guided ablation procedures. In the presence of an intramural scar, VT recurrences occur more frequently.[15]
By recognizing the presence of intramural scar, and by methods such as high output endocardial ablation, bipolar ablation or radiofrequency needle ablation, the mid-myocardium may be reached and the VT circuit may still be successfully ablated.[16] A meta-analysis on imaging guided versus non imaging guided VT ablation is presented in **Chapter 8**. We concluded that image-guided VT ablation in ischemic VT was associated with a significant benefit in VT free and overall survival as compared to conventional VT ablation.
Endo- epicardial substrate homogenization may be useful as a first-line therapy in patients with VTs after myocardial infarction[17,18], especially in the presence of a transmural scar.[19] In **Chapter 9** we proposed a study protocol for a randomized controlled trial: VT in ischemic cardiomyopathy; a combined endo- epicardial ablation as the first procedure versus a stepwise approach (EPILOGUE). It is the first randomized trial that evaluates the role of a combined endo- epicardial scar homogenization versus endocardial scar homogenization for the treatment of ischemic scar-related VT. We investigate whether risks[20] outweigh the benefit of an epicardial ablation. Even with the preferred anterior approach, that lowers the risk of RV puncture and liver damage[21,22], other life threatening complications are seen, such as laceration of the left internal mammary artery. In **Chapter 10** we described a case series on a pericardial puncture complicated by damage to the left internal mammary artery. We concluded that the anterior approach was preferred to avoid right ventricular puncture and to obviate the potential increased incidence of damage to the left internal mammary artery.

Scar related atrial arrhythmias
Substrate based ablation has been primarily used for ventricular arrhythmia, however can be applied to atrial arrhythmias such as atrial fibrillation and atrial tachycardias in the presence of scar or fibrosis.[23] The role of atrial fibrosis detected by delayed-enhancement cardiac MRI (DE-CMR) in atrial fibrillation ablation is

analysed in **Chapter 11**. Our analysis suggests that more extensive left atrial wall fibrosis prior ablation predicts higher arrhythmia recurrence rate after pulmonary vein isolation. DE-CMR imaging modality seems to be a useful method for identifying the ideal candidate for catheter ablation. Our findings encourage wider usage of DE-CMR in distinct atrial fibrillation patients in a pre-ablation setting.
Surgery in the atrium leaves scar tissue that can give rise to arrhythmia by ways of a re-entry mechanism. As a result of abundant scaring, often multiple atrial tachycardia morphologies are seen.[24,25,26] **Chapter 12** revealed a study on atrial substrate modification for the treatment of intra-atrial re-entrant tachycardia in patients after congenital heart surgery. In catheter ablation for intra-atrial re-entry tachycardias after congenital heart surgery, substrate homogenisation compared to activation map based linear ablation was non-inferior in short -and longterm outcome. Especially if multiple intra-atrial re-entry tachycardias are present, substrate homogenisation is a reasonable alternative. In addition, in substrate homogenisation there is no need for arrhythmia induction. This can be an advantage not only in case of non-inducibility, but also for hemodynamic instability during tachycardia. Induction of tachycardias that result in circulatory deterioration prevents adequate mapping and ablation. A report illustrating percutaneous circulatory left ventricle support during complex atrial arrhythmia ablation in single-ventricle is described in **Chapter 13**. Only with the use of circulatory support devices, end-organ perfusion can be safely maintained during ablation with extended periods of hemodynamic instability. However, in single-ventricle patients with a Fontan-type repair, the use of percutaneous ventricular assist devices only when combined with adequate preload resulted in stable cardiac output.

Discussion + future perspectives

The optimal timing of VT ablation remains to be determined. After the first sustained ventricular arrhythmia? Or after multiple episodes of VT storm? Any sustained VT without a reversible cause could mean a potential deterioration in arrhythmic stability. But when is late, too late? When VT is merely a result of general poor condition, VT ablation may be disadvantageous.

In the era of targeting scar instead of a single arrhythmia circuit[27], there are different endpoints for VT ablation. Firstly, termination by ablation of the ongoing VT translates to a high rate of VT isthmus identification. Secondly, when the clinical VT remains non-inducible after ablation and when no VT at all is inducible at the end of the procedure we speak of partly and complete procedural success respectively. Theoretically an entire substrate may be abolished. If we consider elimination of all abnormal potentials a marker for abolishing the substrate, we know that when complete elimination of all mappable abnormal potentials is reached, it is associated with a good clinical outcome.[28] Whereas today's clinical practise is an anatomical scar modification, the future may indicate a more physiological scar modification approach.[30] Undoubtedly, what we cannot obtain after VT ablation of scar related arrhythmia, is a healthy heart.

In this period of time we are dealing with revascularized myocardial infarctions, and consequently with smaller and more inhomogeous scar as compared to an era in which we treated patients with VT from non-revascularized infarctions. These types of scars are associated with fast and poorly tolerated VT[29] and absence of low voltage on electro-anatomical maps.[13] Knowledge of the substrate can come from pre - and periprocedural imaging which can function as a plan of approach and potentially as a roadmap. Ten percent of the patients with ischemic VT have inducible VT from the epicardium and at least 30% have low voltage in the epicardium on bipolar electro-anatomical maps.[31]

If good long term effect can be reached in a single procedure, performing multiple procedures should be avoided. Yet, is a single time of abolishing endocardial and epicardial VT circuits in the substrate enough to take away the threat of future VT's? In other words, does scar after ablation stay in a steady-state, or is it an everlasting changeable entity? Ventricular remodelling in heart failure leads to electrophysiologic changes, which in the early stages may be a modifiable process.[32] These electrophysiologic changes include abnormal calcium homeostasis, repolarization, and gap junction remodelling, all mechanisms that trigger ventricular arrhythmia.[33]

The Epilogue trial will teach us whether all patients with ischemic substrate benefit from complete substrate ablation. The issue with pericardial access at a first approach is the risk of adhesions, complicating a future epicardial VT ablation. If there is no second chance, and the substrate is changing, wild cards shouldn't be used early. Yet, patients with poor left ventricular function, ventricular arrhythmia and heart failure, generally have poor life expectancy and we believe optimal timing for complete scar homogenisation should be seen in the light of the individual patient.

Part 4

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Addendum

I Nederlandse Samenvatting

Litteken gerelateerde aritmieën (ritmestoornissen), zowel afkomstig van een doorgemaakt myocardinfarct (hartinfact) als na hart chirurgie, zijn een belangrijk onderwerp in de hedendaagse gezondheidsproblematiek. Het substraat van deze aritmieën is onderhevig aan de complexiteit van het litteken. Litteken gerelateerde ventrikel tachycardieën (kamerritmestoornissen) (VT) kunnen levensbedreigend zijn en het behandelen van een VT kan levensreddend zijn. Gedurende een gemiddelde follow-up periode van 12-28 maanden na een VT ablatie (behandeling van een kamerritmestoornis) is er uitblijven van VT recidief in 40-88% van de patiënten.[1-4] Katheter ablatie wordt van oudsher beperkt tot het behandelen van de klinische VT, alleen toepasbaar op induceerbare en stabiele tachycardieën. Hedendaags heeft VT ablatie zich ontwikkeld tot een combinatie van een beperkte en een substraat (litteken) ablatie die toepasbaar is op bijna alle VT patiënten. De beperkte ablatie heft circuits op die relevant zijn voor de ritmestoornis die op het moment van de procedure voorkomt, maar een uitgebreidere ablatie kan in potentie ook VTs die ontstaan uit toekomstige circuits, voorkomen.[5] De uitkomst van VT ablatie is verbeterd door verfijning van opwekken van de ritmestoornis, van het mappen (origine van de ritmestoornis bepalen) en van de ablatie techniek.
Het doel van het huidige proefschrift was om de uitkomsten van katheter ablatie voor litteken gerelateerde aritmieën te onderzoeken. Wij onderzochten de rol van magneet gestuurde ablatie, ablatie met behulp van katheters die contact met het myocard (hartspier) meten (contact force katheters), een substraat aanpak en ablatie met integratie van beeldvorming.

Resultaten van VT ablatie, en de rol van magneet gestuurde navigatie en contact force
In **Hoofdstuk 2** bediscussiëren we de rol van katheter ablatie voor VT in de behandeling van patiënten met een VT storm (3 of meer kamerritmestoornissen < 24u). Een toenemend aantal studies laten zien dat katheter ablatie effectief is in het bedwingen van elektrische instabiliteit, en het een levensreddende therapie kan zijn voor een zeer zieke patiënt populatie. In **Hoofdstuk 3** verstrekken we een educatieve review over VT storm. VT storm kan een uiting zijn van het natuurlijk beloop van vergevorderde hartziekte en kan een waarschuwingssignaal zijn voor verslechtering van de aandoening zelf. De trigger en het substraat van een VT storm kunnen veranderen, zij zijn onderhevig aan progressie van verlittekening, remodelering van de ventrikel en van het hartfalen an sich. Een VT storm beïnvloedt direct de prognose van de patiënt. Daarentegen wordt door middel van het voorkomen van de volgende episode, niet direct de mortaliteit verlaagd.[6] Katheter ablatie voor VT storm leidde tot 6x minder ICD therapie (shocks en anti-tachy pacing), dit in vergelijking met 1.5x meer ICD therapie gedurende follow-up als een VT storm conservatief behandeld werd. In **Hoofdstuk 4** concluderen we dat ablatie voor VT storm in de afwezigheid van omkeerbare triggers, multipele ICD shocks zou kunnen voorkomen, mits de ablatie procedure wordt verricht binnen 90 dagen van het eerste voorkomen van de VT storm.

De procedurele en lange termijn klinische uitkomsten van ablatie voor idiopatische uitstroombaan ventriculaire aritmie (kamerritmestoornissen uit de uitstroombaan van de hartkamers zonder andere oorzaak) in **Hoofdstuk 5** waren gelijk voor manuele ablatie, magneet gestuurde ablatie en contact force ablatie. Magneet gestuurde ablatie heeft een beter procedureel veiligheidsprofiel doordat er een kortere doorlichtingstijd is in vergelijking met manuele en contact force geleide ablaties. In **Hoofdstuk 6** wordt de eerste studie beschreven die de lange termijn klinische uitkomsten van VT ablatie laat zien gebruik makend van contact force katheters. Het gebruik van contact force katheters heeft niet geleid tot verbetering van procedurele uitkomsten of verbetering van de veiligheid, in vergelijking met niet contact force gestuurde ablatie voor ventriculaire aritmie. Daarentegen was magneet gestuurde ablatie superieur in acuut succes, het optreden van majeure complicaties en recidieven. De beweging van de ventrikel tijdens een VT ablatie, vooral ten tijde van de tachycardie zelf kan leiden tot een minder stabiele katheter positie. Een instabiele katheter positie resulteert in intermitterend onvoldoende afgeven van energie aan het weefsel en zodoende suboptimale laesies. Bovendien is het niet mogelijk om onvertraagd te reageren op de contact force data en daarmee de precise controle te hebben over de catheter tip. Dit zou de verklaring kunnen zijn waarom contact force geen grote rol heeft in VT ablatie. Magneet gestuurde VT ablatie kan leiden tot completere substraat ablatie door een tal van factoren: betere manoeuvreerbaarheid[7,8], het beter kunnen bereiken van anatomische structuren[9], stabielere katheter positie[10], en het voorkomen van vermoeidheid bij de operateur.
Het toevoegen van contact meting aan magneet gestuurde ablaties geeft de mogelijkheid te corrigeren wanneer er foutief verondersteld wordt dat er contact is met het myocard ten tijde van ablatie. Bovendien kan het weten of er wel of niet adequaat contact is, tot meer gedetailleerd mappen leiden en kan het fouten voorkomen met betrekking tot het veronderstellen van niet bestaande 'channels' (resterend elektrisch geleidend weefsel in een litteken). Verbetering van contact geeft de mogelijkheid om gebieden van lage voltage te definiëren[11] en het verbetert de sensitiviteit van het detecteren van late potentialen.[12] Implementatie van contact feedback, gebruik makend van de e-contact module in magneet gestuurde ablatie in VTs uitgaande van een oud myocardinfarct, resulteerde in een hogere 1 jaars VT vrije overleving wat beschreven is in **Hoofdstuk 7**. De e-contact module reduceerde blootstelling aan röntgenstraling significant. Accuratere mapping en geavanceerde ablatie laesie formatie (het maken van een nieuw litteken) door contact feedback zijn mechanismes die ten grondslag zouden kunnen liggen aan de betere lange termijn resultaten met e-contact.

Katheter ablatie van ventriculaire tachycardie, beeldvorming en het epicardiale substraat
Wanneer er sprake is van een klein, en niet-transmuraal (niet de hele hartwand omvattend) litteken kan het er toe leiden dat er geen laag gevolteerd gebied zichtbaar is op de bipolaire voltage map[13] en als gevolg daarvan kan een VT substraat gemist worden. Substraat ablatie procedures kunnen worden vergemakkelijkt door het visualiseren van het myocardiale litteken, preprocedureel maar ook door beeldvorming te integreren in de procedure. Dit kan uiteindelijk de lange termijn uitkomsten van de ablatie procedure verbeteren. In de aanwezigheid van een intramuraal (midden in de hartwand) litteken, is er vaker sprake van een recidief VT na endocardiale ablatie (ablatie vanaf de binnenkant van het hart).[15] Door de aanwezigheid van een intramuraal litteken te erkennen, kunnen methodes worden toegepast zoals 'high output' endocardiale ablatie, bipolaire ablatie en ablatie middels een radiofrequente naald.[16] In **Hoofdstuk 8** wordt een meta-analyse gepresenteerd gericht op VT ablatie die geleid is door beeldvormende technieken versus VT ablatie niet geleid door beeldvormende technieken. De conclusie is dat ablatie geleid door beeldvorming in VT na een myocardinfarct is geassocieerd met een significante verbetering in VT vrije overleving en überhaupt overleving.
Endo-epicardiale (binnenkant en buitenkant van het hart) substraat ablatie kan bruikbaar zijn als een eerste-lijns behandeling in een patiënt met VT na een hartinfarct[17-18], vooral als er sprake is van een transmuraal infarct.[19] In **Hoofdstuk 9** presenteren we een protocol voor een gerandomiseerd onderzoek: VT in ischemische cardiomyopathie, een gecombineerde endo-epicardiale ablatie in de eerste procedure versus een stapsgewijze aanpak (EPILOGUE). Het EPILOGUE onderzoek is het eerste gerandomiseerde onderzoek dat de

Part 5

rol van een gecombineerde endo- epicardial litteken ablatie onderzoekt en vergelijkt met het ableren van alleen het endocardiale litteken. We onderzoeken of de risico's[20] opwegen tegen de voordelen van een epicardiale ablatie. Zelfs met een geprefereerde anterieure (meer aan de voorzijde) aanpak, die het risico op punctie van de rechter kamer en lever schade verkleint[21,22], kunnen zich weer andere levensbedreigende complicaties voordoen, zoals beschadiging van de linker arteria mammaria interna (LIMA). In **Hoofdstuk 10** beschrijven we een tweetal casussen waarbij een pericard (hartzakje) punctie gecompliceerd werd door beschadiging van de LIMA. Een anterieure aanpak kan in potentie de incidentie van LIMA schade doen toenemen.

Litteken gerelateerde atriale aritmieën
Ablatie gebaseerd op het substraat werd in eerste instantie toegepast op ventrikel tachycardieën, desalniettemin kan deze ook toegepast worden op atriale aritmieën zoals atriumfibrilleren (boezemfibrilleren) of atriale tachycardieën (georganiseerde boezemritmestoornis), vooral wanneer het voorkomen hiervan geassocieerd is met de aanwezigheid van litteken (fibrose).[23] Geanalyseerd in **Hoofdstuk 11** is de rol van atriale fibrose in atriumfibrilleren gedetecteerd door middel van delayed-enhanced cardiale MRI (DE-CMR). Onze analyse suggereert dat uitgebreidere fibrose van het linker atrium te zien voorafgaande aan een ablatie, een hogere recidief kans voorspelt van atriumfibrilleren na pulmonaal vene isolatie (ablatie voor boezemfibrilleren). De DE-CMR beeldvormende techniek lijkt een haalbare methode om de ideale kandidaat voor katheter ablatie te selecteren. Onze bevindingen moedigen gebruik van de DE-CMR aan in een pre-ablatie setting in een geselecteerde groep patiënten met atriumfibrilleren.

Na chirurgie in het atrium blijft litteken weefsel achter, ten gevolge daarvan kunnen zich aritmieën voordoen en meestal gaat het om re-entry (vast circuit waar de ritmestoornis gebruik van maakt). Uitgebreide verlittekening resulteert vaak in een atriale tachycardie met multipele morfologieën (verschijningsvormen).[24,25,26] Atriale substraat modificatie voor de behandeling van intra-atriale re-entry tachycardieën na chirurgie voor aangeboren hartaandoeningen wordt beschreven in **Hoofdstuk 12**. Substraat modificatie in vergelijking met lineaire ablatie gebaseerd op activatie maps waren non-inferieur op de uitkomsten op korte en lange termijn, bij patiënten die katheter ablatie ondergingen voor een intra-atriale re-entry tachycardie na aangeboren hart chirurgie. Vooral als er sprake is van multipele intra-atriale re-entry tachycardieën, is substraat modificatie een goed alternatief. Daarnaast is er bij substraat modificatie geen noodzaak tot opwekken van de aritmie. Dit kan voordelen hebben, niet alleen als de ritmestoornis niet opwekbaar is, ook wanneer er hemodynamische instabiliteit (lage bloeddruk) tijdens de tachycardie is. Mappen en ook ablatie kan onvoldoende bewerkstelligd worden indien er sprake is van een circulatoir gecompromitteerde situatie (verminderde doorbloeding van de organen) na het opwekken van de tachycardie. **Hoofdstuk 13** betreft een tweetal casussen waar dit wordt geïllustreerd, waarin patienten met een univentriculair hart ondersteund worden door een percutaan circulatoir steun device van de linker ventrikel, wanneer zij een ablatie ondergaan van een complexe atriale aritmie. Gedurende langere periodes van hemodynamische instabiliteit kan eind-orgaan perfusie alleen bewerkstelligd worden met het gebruik van een circulatoir steun device. Echter in patiënten met een Fontan-type reparatie en een univentriculair hart resulteerde het gebruik van een percutaan ventriculair steun device, alleen wanneer gebruikt in combinatie met een adequate preload (vulling), in een goede cardiac output.

Discussie en toekomst perspectief

Het blijft een belangrijk vraagstuk wat de meest optimale timing van VT ablatie is. Na de eerste episode van een sustained ventriculaire aritmie? Na multipele episodes van VT storm. Kan elke sustained VT zonder een reversibele oorzaak een potentieel verval betekenen van aritmische stabiliteit? En wanneer is laat te laat? VT ablatie kan zelfs in het nadeel werken van de patiënt, wanneer VT slechts een uiting is van een algeheel slechte conditie.

In een tijd waar het aanpakken van het litteken de standaard is geworden in plaats van het aanpakken van een enkel VT circuit, zijn andere eindpunten bruikbaar.[27] Allereerst leidt het door ablatie beëindigen van een ongoing VT vaak tot de identificatie van de kritische isthmus. Ten tweede, als de klinische VT niet meer induceerbaar is na de ablatie of wanneer er geen enkele VT meer induceerbaar is aan het einde van de procedure spreken we van respectievelijk gedeeltelijk of volledig succes. Theoretisch gezien kan een volledig substraat uitgeschakeld worden. Als we het elimineren van alle abnormale potentialen als een marker zien voor het uitschakelen van het substraat, is het daadwerkelijk geassocieerd met een goede klinische uitkomst.[29] Wat we ongetwijfeld niet kunnen bereiken na VT ablatie voor litteken gerelateerde aritmieën, is een gezond hart.

In de laatste decennia hebben we te maken gekregen met gerevasculariseerde myocard infarcten, met als gevolg kleinere en inhomogene littekens. Deze type littekens zijn geassocieerd met snelle VT's die hemodynamisch slecht verdragen worden[29] en in de afwezigheid zijn van lage voltage op electro-anatomische maps.[13] Kennis over het substraat kan verkregen worden door middel van pre en periprocedurele beeldvorming, deze kan de procedure vergemakkelijken door te fungeren als een plan van aanpak en kan potentieel ook dienen als een roadmap. Tien procent van de patiënten met ischemische VT's hebben ten tijde van elektrofysiologisch onderzoek induceerbare VTs vanuit het epicardium en ten minste 30% heeft lage voltage in het epicardium op de bipolaire maps.[31]

Als een enkele procedure een goed lange termijn effect kan doen bereiken, zou het ondernemen van multipele procedures voorkomen dienen te worden. Hoewel, is een enkele keer uitschakelen van endo en epicardiale VT circuits in het substraat wel genoeg om toekomstige VT's te behandelen? In andere woorden blijft een litteken na ablatie in een soort steady-state, of is het een steeds veranderende entiteit. Ventriculaire remodeling in hartfalen heeft elektrofysiologische veranderingen tot gevolg, welke in de vroege fase een mogelijk reversibel proces betreft.[32] Abnormale calcium homeostase, remodelering van repolarisatie en gap juncties zijn voorbeelden van de verschillende elektrophysiologische veranderingen die op deze verschillende wijzen ventrikel aritmie kan triggeren.[33]

Of alle patiënten met een ischemisch substraat baat hebben bij volledige substraat ablatie zal duidelijk worden na het bekend worden van de resultaten van de Epilogue studie. Wanneer pericardiale toegang is verkregen bij een eerste poging tot VT ablatie is er het risico op adhesies, wat een toekomstige epicardiale VT ablatie zou kunnen compliceren. Als er geen tweede kans is, en er sprake is van een veranderend substraat, dan zal de troef niet te vroeg ingebracht moeten worden. Aan de andere kant, wanneer er sprake is van ventriculaire aritmieën en hartfalen bij patiënten met een sterk verminderde linker ventrikel functie, is de levensverwachting onafhankelijk van de aritmie sterk verminderd. De optimale timing voor complete scar homogenistatie, zo geloven wij, dient dan ook te worden bepaald in het licht van de individuele patiënt.

II List of publications

Hendriks AA, Szili Torok T. The role of catheter ablation of ventricular tachycardias in the treatment of patients with electrical storm. Journal of Cardiovascular Emergencies 2015;1(1):8-11 doi: 10.1515/jce-2015-0002.

Hendriks AA, Akca F, Dabiri Abkenari L, Khan M, Bhagwandien R, Yap SC, Wijchers S, Szili-Torok T. Safety and Clinical Outcome of Catheter Ablation of Ventricular Arrhythmias Using Contact Force Sensing: Consecutive Case Series. J Cardiovasc Electrophysiol. 2015 Jul 20. doi: 10.1111/jce.12762.

Hendriks AA, Khan M, Geller L, Kardos A, de Vries LJ, Yap SC, Wijchers SA, Theuns DA, Szili-Torok T. Ventricular tachycardia in ischemic cardiomyopathy; a combined endo-epicardial ablation as the first procedure versus a stepwise approach (EPILOGUE) - study protocol for a randomized controlled trial. Trials. 2015 Oct 29;16:487. doi: 10.1186/s13063-015-1005-6.

Szili Torok T, de Vries LJ, Özcan EE, Hasdemir C, Kis Z, Kardos A, Géczy T, Kovacs I, Benedek I, Oosterwerff E, Hendriks AA, Khan M, Yap SC. Disappearance of Idiopathic Outflow Tract Premature Ventricular Contractions After Catheter Ablation of Overt Accessory Pathways. J Cardiovasc Electrophysiol. 2016 Oct 6. doi: 10.1111/jce.

de Vries LJ, Hendriks AA, Szili-Torok T. The "Dead-End Tract" and Its Role in Arrhythmogenesis. J. Cardiovasc. Dev. Dis. 2016, 3(2), 11; doi:10.3390/jcdd3020011

Kis Z, Noten AM, Martirosyan M, Hendriks AA, Bhagwandien R, Szili-Torok T. Comparison of long-term outcome between patients aged < 65 years vs. ≥ 65 years after atrial fibrillation ablation. J Geriatr Cardiol. 2017 Sep;14(9):569-574.

Wierda E, Hendriks AA, Amoroso G, Mol D, van Doorn DJ, Khan M. A rare case of acute myocardial infarction during extraction of a septally placed implantable cardioverter-defibrillator lead. HeartRhythm Case Rep. 2017 Nov 14;4(3):127-129.

de Vries LJ, Hendriks AA, Yap SC, Theuns DAMJ, van Domburg RT, Szili-Torok T. Procedural and long-term outcome after catheter ablation of idiopathic outflow tract ventricular arrhythmias: comparing manual, contact force, and magnetic navigated ablation. Europace 2018 May 1;20(suppl_2):ii22-ii27.

Hendriks A, De Vries L, Witsenburg M, Yap SC, Van Mieghem N, Szili-Torok T. Percutaneous ventricular assist device for circulatory support during ablation of atrial tachycardias in patients with a Fontan circulation. Rev Esp Cardiol 2018 Jun;71(6):493-495.

Hendriks AA, Szili-Torok T. The treatment of electrical storm, an educational review. Eur Heart J Acute Cardiovac Care. 2018 Aug;7(5):478-483.

Khan M, Hendriks AA, Yap SC, Berger WR, de Ruiter GS, Szili-Torok T. Damage to the left internal mammary artery during epicardial ventricular tachycardia ablation: a case series. Heart rhythm case report. 2018 Aug 14;4(11):534-537.

Kis Z, Hendriks AA, Muka T, Bramer WM, Kovacs I, Szili-Torok T. The Role of Atrial Fibrosis Detected by Delayed-Enhancement MRI in Atrial Fibrillation Ablation. Curr Med Imaging Rev. 2020;16(2):135-144.

Noten AME, Hendriks AA, Yap SC, Mol D, Bhagwandien R, Wijchers S, Kardys I, Khan M, Szili-Torok T. Contact feedback improves 1-year outcomes of remote magnetic navigation-guided ischemic ventricular tachycardia ablation. Int J Cardiol. May 12:S0167-5273(20)30564-7.

Hendriks AA, Kis Z, Akca F, Yap SC, Wijchers SA, Bhagwandien RE, Szili-Torok T. Extensive scar modification for the treatment of intra-atrial re-entrant tachycardia in patients after congenital heart surgery. Cardiol Young. 2020 Jul 23:1-7.

Hendriks AA, Kis Z, Glisic M, Bramer WM, Szili-Torok T. Pre-procedural image-guided versus non-image-guided ventricular tachycardia ablation-a review. Neth Heart J. 2020 Sep 15. doi: 10.1007/s12471-020-01485-z.

III Curriculum Vitae

Astrid Armanda Hendriks was born on the second of may 1985 in Groningen, the Netherlands. She obtained her medical degree at the university of Maastricht in 2009. Her singular interest was cardiology therefore she started her residency at the OLVG in 2011. Arrhythmias have fascinated her for longer than she can remember. In order to fulfil her purpose she went on to pursue a PhD in electrophysiology. A collaboration with Erasmus Medical Center in 2013 resulted in the current thesis "New insights and methods in the treatment of scar related arrhythmias". Once she completed her residency in 2018, she further went on to commit to a fellowship in electrophysiology.

IV Acknowledgement

Leonard van Woerden - you have been a major inspiration for your never ceasing interest in the human physiology. Your practise first as a neuropsychiatrist and later as a neurologist has lived to move you up to 96 years of age. You have been both a role model and a coach. Thank you!

Johan Koets - You have stayed and will alway be a drive and a guidance to me. Hopefully there will be an opportunity to meet.

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Dienesh Dwarka Chaubé - You are the melody and the beat simultaneously. And I consider myself lucky to have this dance with you. Thank you for your everlasting endurance and support.

Ravi Chaitanya Dwarka Chaubé - Small as you are today, as big your impact is on me. You are my light. As if it is all reflected back on you.

Marjolijn Hendriks - van Woerden - Thank you for giving me your fire, thank you for having taught me to fight.

Charlotte Gabriel - The world is not big enough to get you out of my sight.
Rachida El Moussaoui - You absolutely radiate, you empower.

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Tamás Szili-Török - It has been a pleasure having you as my co-promotor, teacher and mentor. I am very proud to have worked with you and hopefully it is only the beginning of a nice collaboration.

V Summary of PhD training activities

Name PhD student: Astrid Hendriks M.D.
Erasmus MC Department, Electrophysiology
Research School: COEUR

PhD period: 2015-2020
Promoter: Prof. Felix Zijlstra
Supervisor: Tamás Szili-Török

PhD training	Year	CT points
statistical course	2015 (March)	1,5
echocardiography AMC	2015 (April)	1,0
TEE	2015 (May)	0,3
stralingshygiëne	2016 (March)	0,6
electrocardiography CVOI	2015 (December)	0,3
CRT old and new CVOI	2016 (February)	0,3
Pacemaker/ICD course CVOI	2016 (April)	0,6
ICD advanced course Medtronic	2016 (November)	0,6
CVOI beeldvormingsavonden ritmestoornissen en elektrofysiologie	2016 (December)	0,3
electrophysiology basic Medtronic	2017 (June)	0,6
CRT advanced course Biotronik	2017 (March)	0,6
electrophysiology advanced Biotronik	2018 (March)	0,6
National and International conferences		
NHRA jaarcongres brady & tachy	2014 (September)	
Europace Milan	2014 (June)	1,2
American Heart Orlando	2015 (November)	1,2
Cardiostim Nice	2016 (June)	1,2
Europace Vienne	2017 (June)	1,2
ESC Barcelona	2017 (August)	1,2
VT/VF symposium Berlin	2017 (December)	1,2
EHRA Barcelona	2018 (March)	1,2
Heart rhythm Boston	2018 (May)	1,2
EMHEF symposium Maastricht	2018 (October)	0,6
EHRA Lisbon	2019 (March	0.9
Seminars and workshops		
SVT Workshop (Rotterdam)	2016 (March)	0,6
SCRN Inaugural Meeting (Amsterdam)	2016 (October)	0,6
EHRA cardiac pacing, ICD and cardiac resynchronisation (Vienna)	2017 (March)	0,6
SCRN Annual Meeting (Lisbon)	2017 (October)	0,6
CARTO training (Amersfoort)	2018 (November)	0,3
Analyzing electrograms from RV and LV structures (Enschede)	2018 (November)	0,6
EHRA atrial fibrillation (Madrid)	2019 (May)	0,9
EHRA advanced EP with the focus on VT ablation (Prague)	2019 (September)	0,9
EHRA Interventional Electrophysiology (Paris)	2020 (February)	0,9

PhD training	Year
Presentations	
AHA Poster Presentation (1X) Orlando Safety and Clinical Outcome of Catheter Ablation of Ventricular Arrhythmias Using Contact Force Sensing: Consecutive Case Series	2015 (November)
Cardiostim Poster Presentation (1X) Nice The predictive value of discrete prepotentials in catheter ablation of outflow tract arrhythmias	2016 (June)
Europace Poster Presentation (2X) Vienne The role of imaging guided ablation for scar-related ventricular tachycardia – a systematic review Extensive scar de- channelization in the atria for the treatment of intra- atrial tachycardia in patients after congenital heart surgery	2017 (June)
VT/VF symposium Oral Presentation (1X) Berlin Long-term outcome of scar-related ventricular tachycardia ablation guided by imaging integration	2017 (December)
EHRA Poster Presentation (3X) Barcelona Unexpected serious collateral damage during pericardial puncture for epicardial ventricular tachycardia ablation – a case series Conservative treatment and delayed catheter ablation fail to improve outcome in patients with electrical storm, a comparative study Imaging guided versus non imaging guided ventricular tachycardia ablation - a meta-analysis	2018 (March)
Heart rhythm Poster Presentation (1x) Boston Conservative Treatment Fails To Improve Outcome Of Patient With Electrical Storm: A Comparative Study With Catheter Ablation	2018 (May)