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Ventricular tachycardia ablation in structural heart disease: long term results

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Abstact

Introduction: Ventricular tachycardia (VT) occur in the setting of structural heart disease, adversely affecting patients' prognosis and quality of life. Current therapies such as an implantable cardioverter defibrillator or anti-arrhythmic drugs are sub-optimial in reducing VT recurrence. Despite advances in mapping technology, radiofrequency catheter ablation (RCA) presents sub-optimal outcomes with 5-year recurrence rates above 50%.

Objectives: The main objectives of this study were to compare the safety and efficacy of RCA in patients submitted to VT ablation in the context of ICM and NICM.

Methods: Single-centre retrospective study of consecutive patients submitted to VT ablation of substrate-guided and activation-guided VT using multipolar catheters (PentaRay™, Orion™, or HDGrid™) and 3D mapping systems (Carto™, Rhythmia™, or Ensite Precision™). Maps in structural heart disease were evaluated in order to identify intra-cicatricial channels (areas of bipolar voltage <1.5mV) in which sequential propagation of local abnormal ventricular activities (LAVAs) were observed, during or after QRS. The ablation strategy aimed at the abolition of all intra-cicatricial LAVAs, directing the radiofrequency applications primarily to the entrances of the channels. Safety was evaluated by 30-day mortality rate after VT ablation. Efficacy was evaluated by freedom from all-cause mortality, appropriate ICD shocks or CV hospitalization at 36 months.

Results: 102 patients were enrolled, 75 ICM and 27 NICM patients (94.1% male, 66.7±10.8 years of age, mean follow-up 31.2±21.2 months). There was a similar safety profile between ICM and NICM (4% vs. 3.7%, *P* = 0.95) and a similar efficacy at 36 months (58.7% vs 33.3%, p=0.12). Appropriate ICD shocks at 36 months were significantly reduced in patients in whom activation-mapping complemented substrate ablation vs substrate-based ablation alone (5.7% vs 21.2%, p<0.05.

Conclusion: There was a similar safety and efficacy profile between ICM and NICM patients referred for VT ablation. These results emphasize the importance of VT ablation

in non-ischemic patients with structural heart disease and recurrent ventricular tachycardia.

Keywords: Ventricular tachycardia, Ablation, Structural heart disease.

Resumo

Introdução: A taquicardia ventricular (TV) ocorre no contexto de doença cardíaca estrutural, afetando negativamente o prognóstico e a qualidade de vida dos doentes. Tratamentos atuais, como implantação de um cardioversor desfibrilador implantável ou medicação antiarrítmica são abordagens subótimas na redução da recorrência de TV. Apesar de avanços na tecnologia de mapeamento, a ablação por cateter de radiofrequência (ARC) apresenta resultados limitados, com taxas de recorrência aos 5 anos acima de 50%.

Objetivos: O principal objetivo deste estudo foi comparar a segurança e eficácia da ARC em doentes submetidos a ablação de TV no contexto de Miocardiopatia isquémica (MCI) e miocardiopatia não isquémica (MCNI).

Métodos: Estudo retrospetivo unicêntrico de doentes submetidos a ablação de TV guiada por substrato e guiada por ativação utilizando cateteres multipolares (PentaRay™, Orion™, ou HDGrid™) e sistemas de mapeamento 3D (Carto™, Rhythmia™, or Ensite Precision™). Mapas em miocardiopatia estrutural foram avaliados para identificar canais intracicatriciais (áreas de voltagem bipolar <1,5mV) nos quais se observou propagação sequencial de atividades ventriculares anormais locais (LAVAs), durante ou após o QRS. A estratégia de ablação visava a abolição de todos os LAVAs intracicatriciais, direcionando as aplicações de radiofrequência principalmente para as entradas dos canais. A segurança foi avaliada pela taxa de mortalidade em 30 dias após a ablação de TV. A eficácia foi avaliada pela ausência de mortalidade por todas as causas, choques apropriados do CDI ou hospitalização cardiovascular aos 36 meses.

Resultados: 102 doentes foram incluídos, sendo 75 MCI e 27 MCNI (94,1% do sexo masculino, 66,7±10,8 anos, seguimento médio de 31,2±21,2 meses). Houve um perfil de segurança semelhante entre MCI e MCNI (4% vs. 3,7%, P = 0,95) e uma eficácia semelhante em 36 meses (58,7% vs 33,3%, p = 0,12). Choques apropriados do CDI em 36 meses foram significativamente reduzidos em doentes nos quais o mapeamento de ativação complementou a ablação de substrato versus ablação baseada em substrato isolada (5,7% vs 21,2%, p <0,05).

Conclusão: Houve um perfil de segurança e eficácia semelhante entre os deontes MCI e MCNI encaminhados para ablação de TV. Esses resultados evidenciam a importância da ablação da TV em doentes não isquémicos com cardiopatia estrutural e taquicardia ventricular recorrente.

Palavras-chave: Taquicardia ventricular, Ablação, Doença cardíaca estrutural.

Introduction

Ventricular arrhythmias (VA), in particular sustained monomorphic ventricular tachycardia (VT), occur in the setting of structural heart disease, adversely affecting patients' prognosis and quality of life. Besides addressing adequate treatment for the underlying structural heart disease, there are three main treatment options: implantable cardioverter defibrillator (ICD), antiarrhythmic drugs (AAD) and invasive radiofrequency catheter ablation (RCA). Despite decreasing sudden cardiac death, ICDs do not prevent VT recurrences or shocks. In fact, ICD shocks are associated with higher all-cause mortality and increased hospitalizations for heart failure(H. C. M. Kamphuis et al., 2003; Moss et al., 2004a; Poole et al., 2008a). Additionally, recurrent ICD shocks are painful, resulting in impaired quality of life. Therefore, strategies to prevent ICD shocks are needed. Adjunctive antiarrhythmic drugs, reduce the risk of ICD shocks and VT recurrence, but are associated with significant long-term toxicity leading to drug discontinuation. RCA is an effective alternative to prevent VT storm and ICD shocks in patients who are refractory or intolerant to antiarrhythmic drugs. Our group recently demonstrated that catheter ablation in ischemic heart disease can reduce risk of VT storm and ICD therapies(Lima da Silva et al., 2020). However, clinical outcomes for VT catheter ablation remain sub-optimal**(Josephson & Anter, 2015)**, with 1-year VT-free survival of 70%(Tung et al., 2015) and declining to 54% at 5 years(Muser et al., 2017).

Complex VT circuits and noninducible, nonsustained, or hemodynamic instability during VT precluding activation mapping are some of the reasons for failure of endocardial ablations**(Sosa & Scanavacca, 2005)**. Consequently, endocardial substrate-based ablation strategies targeting low voltage, fractionated electrograms and late potentials have been developed with varied results**(Santangeli & Marchlinski, 2016)**. Studies addressing the outcomes in nonischemic cardiomyopathy (NICM) patients are fewer, include smaller groups of patients, and have reported worse outcomes. (Marchlinski et al., 2000)

In this study we aimed to compare the safety profile and the long-term efficacy of RCA of VT in ischemic cardiomyopathy (ICM) and NICM patients.

Methods

Study Design and population

This was a retrospective single-centre study of patients enrolled at the Santa Maria University Hospital (Lisbon, Portugal) referred for VT ablation in patients with structural heart disease between February 2015 and February 2021. VT ablation procedures were performed with 3D high-density mapping systems as described below. Enrollment included patients older than 18 years of age with at least 1 episode of sustained VT or appropriate ICD therapies refractory to antiarrhythmic therapy, meeting the current ESC guidelines for VT ablation(Priori et al., 2015).

The study was performed according to the principles outlined in the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines of the European Commission.

All patients provided written informed consent, and the study protocol was approved by the institutional ethics committee.

Study Objectives

The main objectives of this study were to compare the safety and efficacy of RCA in patients submitted to VT ablation in the context of ICM and NICM.

Safety was evaluated by 30-day mortality rate between ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) patients post VT ablation. Efficacy was evaluated by freedom from all-cause mortality, appropriate ICD shocks or CV hospitalization between ICM and NICM patients at 36 months.

Additional study objectives included evaluation of procedural complications (classified as life-threatening or delaying hospital discharge), VT inducibility in the end of the electrophysiology (EP) procedure, duration of the procedure, radiofrequency ablation time, and the recurrence of ICD appropriate shocks in substrate-based ablation and substrate complemented with activation mapping ablation.

Electrophysiology procedure

EP procedures were performed in the fasting state, under deep sedation or general anesthesia, with continuous invasive monitoring of arterial pressure, arterial oxygen saturation, and acid/base balance. ICD therapies were inactivated.

A quadripolar nonsteerable catheter was placed in the RV apex, and a decapolar steerable catheter in the coronary sinus if the patient had no cardiac resynchronization therapy. LV access was gained through an anterograde transseptal or a retrograde aortic approach. If clinical and/or preprocedural imaging suggested an epicardial circuit, epicardial access was performed using a Tuohy needle by the Sosa method.

After LV access was obtained, a bolus of heparin was administered intravenously and repeated as necessary to achieve an activated clotting time of 250-300s.

Substrate mapping

Mapping of the left ventricle (LV) or right ventricle (RV) used a high density 3-dimensional electroanatomical mapping (EAM) system (CARTO™ system with multipolar PentaRay™ catheter, Biosense Webster; RHYTHMIA™ system with multipolar INTELLAMAP ORION™ catheter, Boston Scientific; and Ensite Precision with multipolar HDGrid™ catheter, Abbott).

Substrate mapping was acquired with and least one of the following: intrinsic QRS complexes (sinus rhythm, atrial pacing or atrial fibrillation), RV pacing (quadripolar nonsteerable catheter in RV apex or with the implanted catheter in patients with an ICD or pacemaker) and/or LV pacing (in patients with CRT). Maps in structural heart disease were evaluated in order to identify intra-cicatricial channels (areas of bipolar voltage <1.5mV) in which sequential propagation of local abnormal ventricular activities (LAVAs) were observed, during or after QRS. LAVA was defined as sharp high-frequency ventricular potentials occurring during or after the far-field ventricular electrogram(Jaïs et al., 2012).

Activation mapping

After substrate mapping, VT was induced by programmed stimulation from the RV apex or from the protected isthmus (previously evaluated by the substrate mapping) at cycle lengths of 600 or 400 ms and up to 3 extrastimuli down to the ventricular effective refractory period or 200 ms. Induced VTs were classified as clinical or nonclinical based on comparison to the 12-lead ECG of the clinical VTs or based on the cycle length on ICD tracings. Activation map was recorded of any sustained and hemodynamically stable monomorphic VT circuits. Activation maps during VT or PVC were automatically annotated. Regions of low amplitude signal where the far-field signal was annotated were manually adjusted.

Catheter ablation and procedural endpoints

RCA was delivered with a sensor enabled open-irrigated catheter [ThermoCool SmartTouch™ Catheter (Biosense Webster Inc.); IntellaNav™ Catheter (Boston Scientific), TactiCath™ Catheter (Abbott)] at 30–50 W endocardial and 25–35 W epicardial.

Substrate-based ablation aimed at the abolition of all intra-cicatricial LAVAs. After ablation, the LV/RV were remapped and additional substrate ablation was performed if residual LAVAs were identified. In the presence of sustained and hemodynamically stable monomorphic VT circuits, VT isthmus ablation was performed complementing substrate-based ablation. Procedural endpoints were VT noninducibility and LAVA elimination in the end of the procedure.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median and interquartile range for normal and non-normal distributions, respectively. Continuous variables were compared among patient groups using the unpaired Student's t-test or Mann–Whitney test for normal and non-normal distributions, respectively. Categorical

variables were compared among patient groups using χ^2 tests. Freedom from all-cause mortality, appropriate ICD shocks or CV hospitalization were evaluated with the Cox proportional hazards model and Kaplan-Meier analysis, with the hazard ratio and 95% confidence interval (CI) reported. For all statistical tests, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics™ version 24 (IBM, Armonk, NY).

Results

Baseline Characteristics

Between June 2015 and April 2021, 102 patients with structural heart disease referred for VT ablation were enrolled (94.1% male, 66.7±10.8 years of age, mean follow-up 31.2±21.2 months, 47.1% in electric storm, 50.0%/17.6% NYHA functional class II/III, mean LVEF 33.9±11.3%). The etiology of structural heart failure was ischemic cardiopathy in 75 patients (73.5%) and non-ischemic cardiopathy in 27 patients (26.5%). The etiology of the underline cardiopathy in NICM patients was dilated cardiomyopathy 66.7%, myocarditis in 22.2%, right ventricular arrhythmogenic cardiomyopathy in 7.4% and sarcoidosis in 3.7%. Complete baseline characteristics are provided in Table 1.

Safety and procedural outcomes

There was no difference in the 30-day mortality rate between ICM and NICM patients post VT ablation (4% vs. 3.7%, *P* = 0.95). In addition, procedural-related complications were also similar in ICM and NICM ablation (9.3% vs 14.8%, p=0.39). Main complications are presented in Table 2.

The majority of patients in the ischemic group were ablated endocardially, with only 4 patients (5.3%) with ischemic VT requiring an additional epicardial ablation. In contrast, in the NICM group, significantly more patients (12 patients, 44.4%) required additional epicardial ablation (*P*<0.001).

In the end of the EP procedure, noninducibility of any VT was achieved in 52 ICM patients (69.3%) and in 18 NICM patients (67.7%; *p*=0.77). The procedure time was significantly longer in the ICM group compared with the NICM group (276±98min versus 127±56 min, respectively; *p*<0.001). Radiofrequency ablation time was similar between groups (52±26min in ICM versus 52±40 min in NICM, p = 0.91).

Long-term clinical outcomes

During the follow-up, 32/102 (31.4%) patients died, 20/102 (19.6%) had appropriate ICD shocks, and 33/102 (32.4%) were hospitalized due to cardiovascular causes.

At 36 months after VT ablation, efficacy evaluated by freedom from all-cause mortality, appropriate ICD shocks or CV hospitalization was similar between ICM and NICM patients (44/75 [58.7%] vs 9/27 [33.3%], HR 1.58 95% CI [0.89-2.83], p=0.12), demonstrated in Figure 1. Individual outcomes were also similar between ICM and NICM, all-cause mortality occurred in 16/75 (21.3%) vs 9/27 (33.3%), p=0.22, appropriate ICD shocks in 9/75 (12%) vs 7/27 (29.6%), p=0.07, and CV hospitalization in 20/75 (26.7%) vs 9/27 (33.3%), p=0.42, respectively.

Substrate-based ablation complemented with activation mapping ablation

In 35/102 (34.3%) patients, clinical VT was inducible and mapped during EP study (34.7% in ICM and in 33.3%, p=0.87). Appropriate ICD shocks at 36 months were significantly reduced in patients in whom activation-mapping complemented substrate ablation vs substrate-based ablation alone (2/35 [5.7%] vs 13/66 [21.2%], HR 0.23 95% CI [0.05-0.99], p<0.05).

Discussion

The 36-month results of this retrospective study highlighted the safety profile of VT ablation procedures in ICM and NICM and its similar efficacy in long-term results with freedom from all-cause mortality, appropriate ICD shocks or CV hospitalization in 58.7% vs 33.3%, p=0.12. VT recurrence evaluated by appropriate ICD shocks was also similar between ICM and NICM (12% vs 29.6%, p=0.07). In addition, this study demonstrated that activation mapping complementing substrate mapping in VT ablation may increase long term results, mainly by reducing appropriate ICD shocks (5.7% vs 21.2% at 36 months, p=0.04).

VT frequently results from an underlying reentrant circuit around areas of myocardial patchy scar or at scar borders. Reentry is facilitated by anatomical barriers (fibrosis), functional barriers with reduced density/function of gap junctions and by anisotropy. Due to the long mapping times, difficulty to induce clinical VT during EP procedure, short VT duration and/or hemodynamic instability, clinical VT activation mapping is often difficult to achieve. Thus, substrate mapping has evolved over the past decade as an alternative to activation mapping. VT ablation relying on this methodology focuses on the identification and elimination of LAVAs, which can be found during sinus rhythm or pacing and potentially act as critical protected isthmuses during VT.

RCA has been increasingly used in the treatment of VT, either in ICM and NICM, with several studies evaluating its safety profile at the population-level (Dinov et al., 2014; Sapp et al., 2016a). These studies show a procedural-related complications of 6.8% in ICM and 8% in NICM, similar to our findings of 9.3% in ICM and 14.8% in NICM (p=0.39). Despite not statistically significant, the higher complication rate regarding NICM may result from a higher epicardial approach in the EP procedure (5.3% in ICM vs 44.4% in NICM, p<0.001) that comprises a higher risk. Larger studies are required to determine whether certain patient factors are independently associated with a higher risk of RCA complications.

As a result of the safety profile in both ICM and NICM VT ablation procedures, current guidelines recommend RCA as adjunctive treatment to prevent recurrent ICD therapies for patients with recurrent VT refractory or intolerant to antiarrhythmic drugs. (Sapp et al., 2016) . However, despite acute success, RCA presents sub-optimal outcomes with 5-year

recurrence rates of 46% in ICM and 59.5% in NICM (Dinov et al., 2014). Our results demonstrate a similar efficacy in long-term results of VT ablation in ICM and NICM with freedom from all-cause mortality, appropriate ICD shocks or CV hospitalization in 58.7% vs 33.3%, p=0.12. In contrast with previous trials documenting a higher VT recurrence rate in NICM than ICM after VT ablation (57% vs 40.5% at 12 months, p=0.01) (Dinov et al., 2014), our study shows similar VT recurrence in NICM and ICM at 36 months (29.6% vs 12%, p=0.07). The substrate in NICM VT is frequently more atypical, with an outspread spectrum than ischemic VT, involving the epicardium and being difficult to be identified. Our results are in line with the literature with a higher prevalence of epicardial substrate in NICM vs ICM (44.4% vs 5.3%, p<0.001). Recent development of advanced imaging methods such as contrast computed tomography or cardiac magnetic resonance imaging may better locate the substrate before EP study and its integration with EAM may help to identify the area of interest. Our results emphasize the importance of considering VT ablation in symptomatic patients with structural heart disease, even with a non-ischemic etiology.

Other significant aspect is that appropriate ICD shocks at 36 months were significantly reduced in patients with activation-mapping complemented substrate ablation vs substrate-based ablation alone (5.7% vs 21.2%, p<0.05). These results follow studies in the same area which demonstrate that activation mapping of VT is superior in reducing recurrent ICD shocks which have been associated with an increase in all-cause mortality, in heart failure hospitalization and impaired quality of life(Kamphuis, 2003; Moss et al., 2004; Poole et al., 2008) . However, we could only induce and perform activation mapping of the clinical VT in 34.7% in ICM and in 33.3%, p=0.87. In fact, the majority of VTs are noninducible/nonsustained during the EP study or are not hemodynamically tolerated, precluding VT activation mapping. Rapid and hemodynamically non-tolerated VTs have become more prevalent during the past 2 decades due to early coronary interventions for acute myocardial infarction. This led to smaller infarct size, and as a consequence, smaller re-entrant circuits and shorter VT cycle lengths. Thus, it is of the utmost importance to implement additional techniques to enable activation-mapping of short-duration or hemodynamic unstable VT, in order to complement substrate-based ablation and improve prognosis. Noninvasive 3D mapping systems may overcome these challenges by rapidly mapping an unstable or short-lived VT or PVC (H. C. M. Kamphuis et al., 2003; Moss et

al., 2004a; Poole et al., 2008a). However, there have been limited studies to evaluate the accuracy of noninvasive 3D mapping systems in VT activation mapping and the potential benefits to complement invasive EAM that should be evaluated in further studies.

Limitations

The main limitation of this study was the retrospective analysis of the outcomes and the small patient sample size, which may have limited the statistical power of some outcome metrics. Another important limitation is the widespread of time during the inclusion of the patients, from 2015 to 2021. Although all EP studies were performed with high-density mapping 3D systems, more recently the integration of advanced imaging techniques may have improved VT ablation outcomes that may become under-valued in the final results.

Conclusion

In this retrospective study of patients with structural heart disease referred for VT ablation, we demonstrate a good safety profile of the electrophysiology procedure and a similar efficacy of VT ablation in ischemic and non-ischemic structural heart disease patients. Thus, VT ablation should also be considered in non-ischemic patients with structural heart disease and recurrent ventricular tachycardia.

Population Characteristics	**ICM group** (N=75)	**NICM group** (N=27)	**P value**
Age, years (mean ± standard deviation)	68.9±9.3	60.6±12.3	<0.05
NTproBNP (mean ± standard deviation)	4338.3±7253.4	3364±3642.9	0.58
LV EF (mean ± standard deviation)	33.7±11.0	34.8±12.2	0.65
Female gender, n (%)	4 (5.3%)	2 (7.4%)	0.694
Comorbidities			
Hypertension, n (%)	64 (85.3%)	10 (37%)	<0.05
Peripheral artery disease, n (%)	9 (12%)	0 (0%)	0.60
Diabetes, n (%)	23 (30.7%)	6 (22.2%)	0.404
CKD (GFR < 60mL/min/1.73m^2), n (%)	39 (38.7%)	8 (29.6%)	0.05
Obesity (BMI > 30), n (%)	18 (24%)	5 (18.5%)	0.56
AF, n (%)	29 (37.3%)	10 (37%)	0.88
Electric Storm, n (%)	30 (40%)	18 (66.7%)	0.02
NYHA Functional Class			
I, n (%)	20 (26.7%)	9 (33.3%)	0.43
II, n (%)	41 (54.7%)	10 (37%)	
III, n (%)	13 (17.3%)	5 (18.5%)	
IV, n (%)	1 (1.3%)	3 (11.1%)	
Medical Therapy[*]			
Amiadarone at admission, n (%)	56 (74.7%)	22 (81.5%)	0.47
Beta-blocker at admission, n (%)	68 (90.7%)	25 (92.6%)	0.76
Previous ICD/CRT-D			
Primary prevention, n (%)	20 (26.7%)	13 (48.1%)	0.08

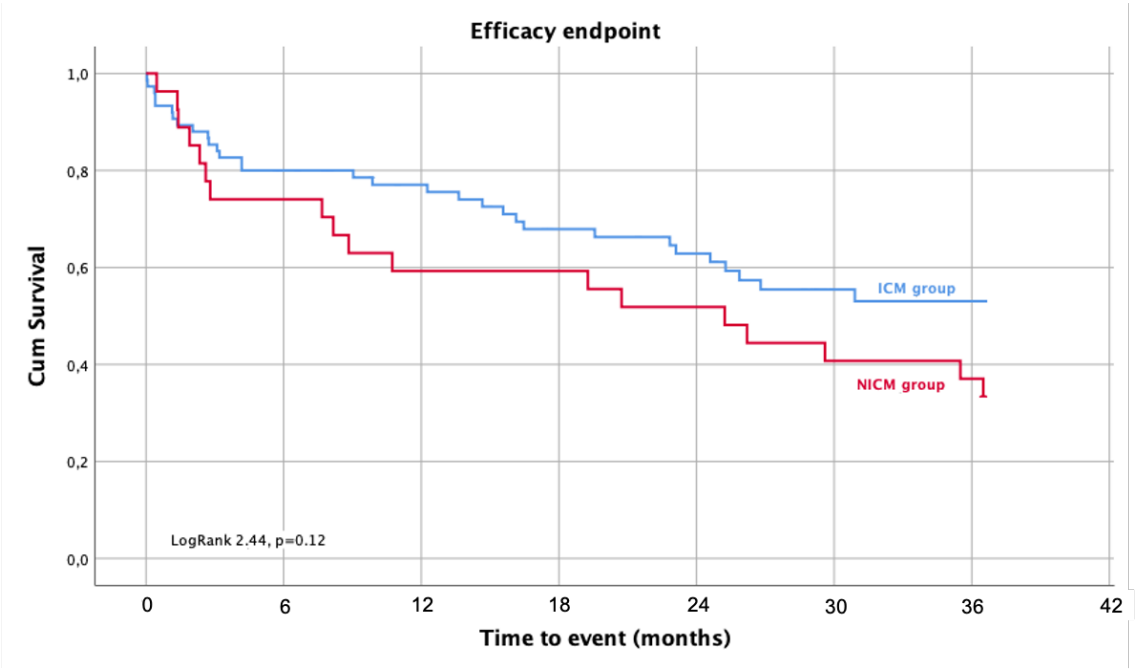
Secundary prevention, n (%)	39 (52%)	8 (29.6%)	

Table 1: Characteristics of the patients at baseline. ICM, Ischemic Cardiomyopathy; NICM, Non-ischemic Cardiomyopathy; LV, Left Ventricle; EF, Ejection Fraction; CKD, Chronic Kidney Disease; AF, Auricular Fibrillation; NYHA, New York Heart Association; ICD, Implantable Cardioverter Defibrillator; CRT-D, Cardiac Resynchronization Therapy Defibrillator.

Procedure complications	**ICM Group** (N=75)	**NICM Group** (N=27)
Third degree atrioventricular block, n (%)	1 (1.33%)	0 (0%)
Cardiogenic shock, n (%)	1 (1.33%)	1 (3.7%)
Aortic dissection, n (%)	1 (1.33%)	0 (0%)
Hematoma requiring transfusion, n (%)	1 (1.33%)	0 (0%)
Cardiac tamponade, n (%)	2 (2.33%)	2 (7.4%)
Pericarditis, n (%)	0 (0%)	1 (3.7%)
Peripheral artery pseudoaneurism	1 (1.33%)	0 (0%)

Table2: Complications after EP procedure. ICM, Ischemic Cardiomyopathy; NICM, Non-ischemic Cardiomyopathy;

Figure 1. Cumulative efficacy survival (all-cause mortality, appropriate ICD shocks or CV hospitalization.



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