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Mikael Laredo, MD[1]; Ludivine Oliveira Da Silva, MD[2]; Fabrice Extramiana, MD, PhD[4]; Nicolas Lellouche, MD, PhD[5]; Émilie Varlet, MD[|6]; Denis Amet, MD[6]; Vincent Algalarrondo, MD, PhD[7]; Xavier Waintraub, MD[1]; Guillaume Duthoit, MD[1]; Nicolas Badenco, MD[1]; Carole Maupain, MD[1]; Francoise Hidden-Lucet, MD[1]; Philippe Maury, MD, PhD[8]; Estelle Gandjbakhch, MD, PhD[1]; GPUR Groupe Parisien Universitaire en Rythmologie Investigators.

Affiliations:

[1]Sorbonne Université, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Institut de Cardiologie, Paris, F-75013, France.

[3]University Hospital of Martinique, Martinique, France.

[4]AP-HP, University Hospital Bichat, Department of Cardiology, Paris, France.

[5]AP-HP, University Hospital Henri Mondor, Department of Cardiology, Creteil, France.

[6]AP-HP, Hôpital Européen Georges Pompidou, Department of Cardiology, Paris, France.

[7]AP-HP, Hôpital Antoine Béclère, Department of Cardiology, Clamart, France.

[8]Division of Cardiology, University Hospital Rangueil, Toulouse, France

Brief Title:

Electrical Storm Ablation in ARVC

Word count: 4973

Source of funding:

None

Disclosures:

The authors report no conflict of interest relevant to the present study to disclose.

Address for correspondence:

Dr. Mikael Laredo

Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière,

47-83 boulevard de l'Hôpital, 75013 Paris.

Email : mik.laredo@gmail.com Phone: +33 1 42 16 30 54; Fax: +33 1 42 16 30 56

Structured Abstract

Background

Therapeutic strategies for electrical storm (ES) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) are not well defined.

Objective

To report the acute and long-term results of ventricular tachycardia (VT) radiofrequency catheter ablation (RFCA) as treatment for ES in patients with ARVC.

Methods

This multicenter study retrospectively enrolled 23 consecutive patients with ARVC (mean age 43.6±16.7 years; all male) who underwent 24 RFCA procedures for ES between 2003 and 2015.

Results

Thirteen (57%) patients had a previous VT RFCA;14 (61%) had right ventricular dysfunction and 7 (30%) left ventricular ejection fraction ≤ 50%. The clinical VT was inducible in 19 (79%) procedures. Epicardial ablation was performed in 4 (17%) procedures. The median number of targeted VTs was 1 [1–6]. Complete acute success (no VT inducible) was achieved in 11 (46%) procedures and partial acute success (clinical VT nor inducible) in 11 (46%). After a median follow-up of 3.9 years [1 month–10 years], ES recurred in 2 patients and end-stage heart failure developed in 4 (17%), leading to 1 death and 3 heart transplantations. At 1-year follow-up, the probability of freedom from VT recurrence was 75% and did not significantly predict long-term survival. At last evaluation, 8 (35%) patients were free of non-beta-blocker anti-arrhythmic drugs as compared with 1 (4%) at baseline ($p = 0.02$).

Conclusion

Catheter ablation was efficient to prevent ES recurrence in patients with ARVC. However,

these patients were at high risk of evolution toward ARVC-related heart failure that was not associated with VT recurrence.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), a type of arrhythmogenic cardiomyopathy is a rare inherited disease associated with progressive fibrofatty myocardial remodeling affecting mostly the right ventricle (RV)[1,2]. Structural alterations associated with ARVC predispose to reentrant ventricular tachycardia (VT), and patients may experience a high burden, especially those at advanced disease stage[3]. Implantable cardioverter-defibrillators (ICDs) can efficiently prevent sudden cardiac death; however, VT events among ICD carriers with ARVC are frequent and are associated with ICD firing and increased cardiovascular morbidity[3].

Electrical storm (ES) is a life-threatening complication of structural heart diseases associated with advanced disease stage, with poor short- and long-term prognosis, that requires specific therapeutic interventions[4,5]. Patients with ARVC may experience ES, but the clinical implications and prognostic significance in this setting are less well understood.

Multiple studies have demonstrated a benefit of radiofrequency catheter ablation (RFCA) for treating ARVC-associated VT[6–8], which is therefore recommended in addition to ICD[9,2]. Several reports also suggest that RFCA is effective in reducing the ventricular arrhythmia burden in the context of ES, when evaluated in various heart diseases[4,10]. However, the benefits of RFCA as a treatment for ES in ARVC has not been specifically assessed. In this multicenter observational study, we analyzed the clinical and electrophysiological characteristics of ARVC-related ES and report the outcomes of RFCA.

Methods

Patients and definitions

Patients who underwent catheter ablation for ES from 2003 to 2015 in 7 tertiary care French centers were retrospectively included (n=23) if they 1) had a definite diagnosis of ARVC according to the 2010 revised Task Force Criteria (TFC)[11]; 2) presented ES defined by at least 3 separate sustained VT episodes or ventricular fibrillation episodes within 24 hr, documented by 12-lead electrocardiography (ECG), Holter monitoring or ICD interrogation; 3) and were referred for radiofrequency ablation as an urgent treatment for ES. Any ICD therapy (antitachycardia pacing or shock) was considered a sustained VT episode. In cases of unsuccessful antitachycardia pacing or shock, further therapies related to the same episode were not counted as an individual VT episode.

Patient screening involved reviewing all consecutive VT RFCA procedures in each center during the inclusion period, identifying those performed for ARVC-related VT (n=121 across the 7 centers), and selecting procedures that were specifically performed as urgent treatment for ES in the days or weeks after ES.

ARVC was prospectively diagnosed according to the current consensus documents and was retrospectively assessed for final diagnosis according to the 2010 revised TFC[11] at the time of data collection. The TFC criteria regarding the arrhythmia refer to an evaluation before the ES event.

Severe RV systolic dysfunction was defined by RV ejection fraction < 40% on MRI or RV angiography and/or RV fractional area change < 33% on transthoracic echocardiography in the apical 4-chamber view (major TFC). Diffuse RV involvement was arbitrarily defined by the presence of ≥ 3 akinetic or dyskinetic RV regions including RV apex, outflow tract,

free wall and peritricuspid region and diagnosed by echocardiography, MRI or RV angiography.

Patients with available samples underwent mutation screening for desmosomal genes *PKP2*, *DSG2*, *DSP*, *JUP* and *DSC2* by Sanger or next-generation sequencing after informed written consent. All patient data were anonymized prior to data collection. No authorization approval from our Institutional Committee on Human Research was required for this retrospective study, in accordance with French law.

Electrophysiological study and catheter ablation

Electrophysiological studies (EPS) and catheter ablation procedures (n=24) were performed under continuous invasive pressure monitoring. Programmed ventricular stimulation was performed in patients in sinus rhythm at the beginning of the procedure, according to standard protocols by using intravenous isoproterenol infusion if necessary. Ablation strategies included VT activation mapping with characterization of the VT critical isthmus and ablation targeting mid-diastolic potentials, pace-mapping based on the clinical VT 12-lead ECG morphology and substrate mapping based on delineation of scar areas identified by bipolar voltage mapping and maximal elimination of late potentials or Local Abnormal Ventricular Activities in sinus rhythm or ventricular pacing. Ablation strategies were chosen at the discretion of the electrophysiologist according to the patient's history, number of previous ablation procedures, VT characteristics and clinical tolerance. For the purpose of the study, ablation strategies were retrospectively classified as VT mapping (activation, entrainment and pace-mapping), substrate mapping and mixed VT + substrate mapping.

Electro-anatomical mapping systems (CARTO, Biosense Webster Inc., Diamond Bar, CA, or NavX, St. Jude Medical Inc., St. Paul, MN) were used in 19/24 procedures and a multipolar electrode diagnostic catheter was used in 3/24 procedures. When indicated,

epicardial access was obtained by a percutaneous subxiphoid puncture. Procedures were performed with 4-mm conventional or irrigated-tip radiofrequency catheters. Induced VTs were considered clinical when the 12-lead ECG morphology was identical to the clinical VT with the same rate ± 20 bpm. Complete acute success was defined as no sustained VT induced at final EPS, partial acute success as no clinical VT induced, acute procedural failure as the ability to induce a sustained clinical VT. Procedural success was considered undetermined when no VT was induced at the beginning of the procedure or when no final EPS was performed.

Follow-up and endpoints

Patients were followed routinely by their treating electrophysiologist or cardiologist. VT recurrence was defined as the recurrence of any documented sustained VT lasting ≥ 30 sec or any appropriate ICD therapy including anti-tachycardia pacing. Recurrence of ES followed the same definition as for the initial presentation. Medical records and stored electrograms from ICD interrogations were reviewed at each center to identify VT recurrence and assess ICD therapies.

Data collection

Data regarding demographics, medical history, clinical evaluation, 12-lead ECG, genetic analyses, echocardiography and computed tomography imaging, ICD interrogations, electrophysiology studies and catheter ablation procedures were retrieved from medical records at each center.

Statistical analyses

Continuous data are reported as mean ± SD or median [range] for normally or non-normally distributed data. Categorical variables are presented as number (%). Comparative statistics involved the exact Fisher test. Survival curves were created with the Kaplan-Meier method,

with comparisons involving the Log-Rank test. Univariate regression analyses were performed with the Cox proportional-hazards model, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). All tests were two-sided, with $p < 0.05$ denoting statistical significance. All statistical analyses involved using IBM SPSS v23 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Overall, 23 consecutive patients with ARVC (mean age at diagnosis 43.6±16.7 years) underwent 24 RFCA procedures for ES were retrospectively enrolled (Table 1). All patients had a definite ARVC diagnosis according to the 2010 revised TFC[11]. Individual TFC criteria are available in Supplementary Table 1 and ES episode descriptions are in Supplementary Table 2. Patients presented ES at a mean of 7.3 ± 9.6 years after ARVC diagnosis. Three (13%) patients had a history of resuscitated sudden cardiac death. Overall, 17 (74%) patients had previously experienced at least one episode of sustained VT, 18 (83%) had previous ICD placement, and 13 (57%) had previous VT catheter ablation (median 1, range [0–7]). Results from genetic analysis were available for 15 (65%) patients; 10/15 (67%) carried an ARVC-related pathogenic mutation (Table 1). Twelve (52%) patients presented incessant not-well tolerated VT despite repeated intravenous amiodarone boluses, electrical cardioversion or general anesthesia (Supplementary Table 2). The median number of ICD shocks related to ES was 13 (range 1–30). Most patients showed typical depolarization and repolarization abnormalities (Supplementary Table 1). Overall, 14 (61%) patients had severely impaired RV systolic function, 8 (35%) had at least mild LV systolic function impairment with LV ejection fraction (LVEF) ≤ 50%, and one had severe LV dysfunction (LVEF = 20%).

Procedural characteristics and acute results

In most cases, a single monomorphic VT was responsible for the ES [20 (83%) procedures], whereas multiple sustained monomorphic VTs could be induced by ventricular programmed stimulation in 15 (63%) procedures (Table 2 and Supplementary Table 2 for individual electrophysiogical data). Median clinical VT rate was 171 bpm (range 130–230). Endocardial+epicardial mapping and ablation was performed in 4 (17%) procedures. In one patient with severely depressed LVEF, the RFCA procedure was performed under extracorporeal membrane oxygenation support for incessant hemodynamically unstable VT. Irrigated radiofrequency was used in 21 (88%) procedures and non-irrigated radiofrequency in 3 (12%). Ablation strategies consisted of VT mapping [7 (29%)], substrate mapping [8 (33%)] and mixed VT and substrate mapping [9 (38%)]. The median number of targeted VT was 1 [range 1–6] and targeted RV areas 1 [1–5]. More than one RV area was targeted in 9 (38%) patients and 10 (42%) procedures. Targeted RV areas included RV free wall [12 (50%)], RV outflow tract [7 (29%)], RV sub-tricuspid region [9 (38%)], RV septum [2 (8%)] and left ventricle [2 (8%)] (Supplementary Table 2). Complete acute success was achieved in 11 (46%) procedures and partial acute success in 11 (46%). An undetermined result was reported in 2 (8%) procedures. There was no acute procedural failure. Acute procedural complications included one minor groin hematoma and one femoral arteriovenous fistulae requiring percutaneous treatment.

Long-term outcomes

During a median follow-up of 3.9 years (range 1 month–10 years), ES recurred in 2 patients (see Supplementary Table 3 for detailed individual outcomes). The first patient underwent redo RFCA for ES at 2.5 years after the initial procedure but died 2.8 years later in the post-

operative course of heart transplantation (HT) that was performed for end-stage heart failure. The other had ES recurrence 1.5 years after the initial ES; he underwent redo RFCA and remained free of VA recurrence in a subsequent follow-up period of 1 year. The cumulative probability of freedom from ES recurrence at 1 and 5 years after the initial ES RFCA procedure was 100% and 85% (Figure 1A & Supplementary Table 4 for 95% CIs of survival rates). Six patients had VT recurrence during follow-up. All VT recurrences were monomorphic and triggered appropriate ICD therapies (details in Supplementary Table 3). Five patients underwent redo VT ablation, including 4 who remained free of VT recurrence at the end of follow-up. The cumulative probability of freedom from VT recurrence at 1 and 5 years after the initial ES RFCA procedure was 77% and 66% (Figure 1B). Complete acute procedural success was not significantly associated with freedom from VT recurrence after the initial ES ablation procedure (HR = 0.27, 95% CI [0.05–1.43], p = 0.13). Baseline LVEF and presence of RV systolic dysfunction were not associated with VT recurrence. After the initial ES catheter ablation procedure, 4 patients had ICD placement, so all patients had an ICD during follow-up. At the end of follow-up, 8 (35%) patients were not taking non-beta-blocker anti-arrhythmic agents as compared with 1 (4%) at baseline (p = 0.02).

Three patients died during follow-up (2 immediately after HT and 1 from hemorrhagic stroke while awaiting HT) and 1 patient survived HT. These 4 patients had end-stage heart failure related to ARVC with severe biventricular systolic dysfunction. The cumulative probability of survival without death or HT at 1 and 5 years after initial ES catheter ablation was 90% and 84% (Figure 2A). Neither VT recurrence during follow-up (HR 2.32, 95% CI [0.32–16.74], p = 0.40) (Figure 2B) nor complete acute procedural success (HR 0.96, 95% CI [0.13–6.86], p = 0.97) was significantly associated with death or heart transplantation during follow-up, Among the 4 patients who died or underwent HT, 2 did not show VA recurrence after the initial RFCA. Baseline LVEF was significantly associated with risk of death or HT

(HR for a 1% LVEF increase: 0.90, 95% CI [0.81–60.99], p = 0.045) (Figure 2C). The detailed course of adverse events during follow-up is in Supplementary Table 3.

Discussion

This is the first study to report outcomes after RFCA performed for ES in patients with ARVC. RFCA was safe and effective to prevent ES recurrence, with no periprocedural adverse outcomes and only 2 ES recurrences. In addition, 1) patients presenting ES frequently had ARVC with overt RV structural alterations and a significant history of ventricular arrhythmias with previous VT ablations, 2) usually one monomorphic VT was responsible for the ES event, 3) complete procedural success was achieved in 11 (46%) procedures and elimination of the clinical VT could be achieved in 22 (92%), 4) the 5-year estimated VT recurrence rate was 34%, and 5) we found a 24% 5-year estimated rate of mortality or HT after an ES event — mortality consecutive to heart failure related to ARVC structural dysfunction and that was not associated with the long-term arrhythmic outcome after RFCA.

Clinical features associated with ES in ARVC

In our series of ARVC patients presenting ES and referred for RFCA, we found a high prevalence of electrical and structural abnormalities as compared with large cohorts of ARVC patients[12,13]. Most patients had severe RV systolic dysfunction, 35% had LV dysfunction, 43% showing epsilon-wave and 53% previous VT RFCA. All were male, and the mean age at ES was 43.6 years, when most ARVC patients are symptomatic[14]. Overall, 66% of screened individuals had a pathologic mutation in desmosomal genes, which is higher than what is usually found in ARVC cohorts and associated with worse prognosis[12]. These high-risk features were also more frequent than in a recent large cohort of ICD carriers[15]. However,

patient characteristics were overall comparable to studies enrolling ARVC patients undergoing VT ablation[8,16], except in terms of the frequency of ECG depolarization abnormalities and previous VT ablation, which were more frequent in our patients and suggests that ARVC patients experiencing ES have a more extensive electrical substrate than those with isolated VT.

The study of Carbuciccio *et al*. reported outcomes of ES ablation among 95 patients (76% with ischemic cardiomyopathy and 13 [14%] with ARVC][10]. Mean age was higher than in our series (64±13 years), 38% of patients had several clinical VTs and 11% required periprocedural hemodynamical support. In our ARVC series, a single VT was responsible for most of the ES; we did not observe any patient with repetitive polymorphic VT; and only 1 patient had > 5 inducible VTs. Hemodynamic instability was rare, which is probably related to the conserved or mildly impaired LV function in most ARVC patients.

Procedural outcomes

We report a relatively low rate of complete acute procedural success, 46%, as compared with the 72% in the largest series of ES ablation[10] and the 71% to 77% in a recent series of VT ablation in ARVC[8]. The low rate may have several explanations: first, our series included rare patients across a 12-year period that saw major progresses in RFCA techniques. Particularly, a combined endocardial+epicardial approach, associated in several studies with improved acute procedural success and long-term freedom from VT recurrences[7,8,17,18], was performed in only 18% of our cases because of the inclusion period. Epicardial ablation likely would have enhanced our acute and late success rates. Nonetheless, recent evidence has shown a negative correlation between the extension of RV endocardial scarring and the presence of arrhythmogenic epicardial scar because of disease progression from the epicardium to the endocardium[19]. Considering the severity of RV involvement in our series, a first-line

epicardial approach would probably have been less profitable than in a regular case of VT RFCA in ARVC. Also, epicardial access may be deleterious in patients with ES by compromising the chance of inducing the clinical VT and by increasing the risk of hemodynamic instability during VT mapping. That being said, there is sufficient evidence to favor an initial endocardial+epicardial approach in stable patients presenting ES, and it should be particularly considered in patients with early-stage ARVC or when evidence for extensive epicardial substrate or clinical VT originating from the epicardium is known from a previous VT ablation. Second, 3D electroanatomic mapping systems, which significantly improve VT RFCA[7] in ARVC, were unavailable at the time of RFCA in 25% of our cases. Finally, our patients had marked RV structural alterations, which are correlated with scar extension and diffuse arrhythmogenic substrate[20].

All our patients were amenable to RFCA, including those with several previous ablations and biventricular dysfunction, and no severe complications were observed, including no hemodynamic deterioration. Although we obtained a relatively low rate of complete acute success, clinical VT could not be induced in most patients (92%) and only 2 patients experienced ES recurrence after RFCA. This finding may suggest that inability to induce clinical VT is a reasonable endpoint to prevent ES recurrence. Catheter ablation is a Class I indication as an urgent first-line treatment for ES[21] regardless of the heart disease, and should also be considered as such in ARVC.

Long-term survival after ES in ARVC

ES is an independent predictor of death among various heart diseases[5]. However, the mechanisms by which ES leads to increased mortality remain poorly understood, and its clinical significance in ARVC as compared with other heart diseases is poorly established. In a recent meta-analysis of 471 ES patients from 39 publications, only 22 had ARVC, which

precluded generalizing findings to patients with ARVC[4]. A key question is whether RFCA improves long-term survival after an ES event in ARVC, or if RFCA only permits a palliative benefit of alleviating the VT burden. In the study of Carbuciccio *et al.*, long-term survival was worse for patients for whom RFCA resulted in partial success or procedural failure, with a significant occurrence of sudden cardiac death related to untractable ES recurrence[10]. In the above-mentioned meta-analysis, arrhythmic sudden death accounted for 23% of long-term mortality[4]. These findings suggest that VA recurrence after RFCA for ES contributes to survival to some extent. In our study specifically addressing ARVC, we found no association between long-term survival and procedural success or VT/VF recurrence during follow-up. Fatal outcomes were all related to ARVC-related structural dysfunction, and we found no temporal association between VT recurrence and mortality or HT. These results are in line with a recent multicenter observational study finding no difference in survival in RFCA- versus AAD-treated patients despite a significantly reduced VT burden in the former group[22]. Also, a prospective study including patients with ES occurring in various forms of cardiomyopathies showed that patients with ES shared many similarities with those presenting severe decompensated heart failure and a comparable prognosis[23]. ES clinical presentation and accessibility to RFCA seems more favorable in ARVC than in the overall ES landscape, but eliminating the arrhythmic substrate responsible for ES may have little impact on the progressive structural deterioration. For ARVC patients with advanced disease, ES might be considered an epiphenomenon of disease progression toward end-stage heart failure.

Limitations

The main limitations of our study are its retrospective nature and the long inclusion period. The low number of included patients over a 12-year inclusion period in a specialized center certainly does not reflect the ES incidence in ARVC, data that would have been interesting to

report but given the nature of our study, cannot be provided. The patient screening methodology that we used identified patients who underwent VT ablation specifically for ES treatment and not those who were managed medically. A recent retrospective study of 31 ICD carriers reported an annual incidence of ES of 31% [24], so the definition of ES itself encompasses diverse and arrhythmia profiles that range from 3 separate episodes of well-tolerated VT to the critical situation of incessant VT, which was the most frequent scenario in our study. The RFCA strategies and techniques were heterogenous, considering that they were performed in 7 different centers over 12 years, beginning in 2003. Much progress has been made in the field of VT ablation over the last decade, including refinement of electroanatomic mapping, substrate identification and epicardial ablation; therefore, our acute and late results might have been improved if RFCA procedures were performed in a contemporary setting. Also, we lack quantitative data regarding ICD data at baseline and during follow-up, which would have been helpful to assess the reduction in VT burden provided by RFCA. Finally, the small study population warrants caution in interpreting descriptive and survival statistics.

Conclusions

Patients with ARVC experiencing ES exhibited features of structurally advanced disease and frequently had a long history of ventricular arrhythmias, but ES was characterized by relatively good hemodynamic tolerance and single monomorphic VT in most cases. Despite a relatively low complete procedural success rate, RFCA was effective in preventing ES recurrence. Long-term mortality was significant and was associated with the ARVC-related structural dysfunction rather than the arrhythmic outcome. Further studies are needed to define the optimal first-line strategy for ES ablation in the setting of ARVC.

Acknowledgments

This work was supported by grants from the “Fédération Française de Cardiologie”, “Société Française de Cardiologie” and “Ligue contre la Cardiomyopathie.”

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Figure title and legends

Figure 1. Long-term arrhythmic outcomes in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) after catheter ablation for electrical storm (ES). A) Kaplan-Meier representation of cumulative probability of freedom from ES recurrence after the initial ES ablation procedure. B) Kaplan-Meier representation of cumulative probability of freedom from ventricular tachycardia (VT) recurrence after the initial ES ablation procedure.

Figure 2. Long-term survival in patients with ARVC after catheter ablation. A, B, C) Kaplan-Meier representation of cumulative probability of survival without death and heart transplantation after the initial ES ablation procedure with and without VT recurrence and LVEF > 50% and ≤ 50%. Vertical bars represent the 95% confidence interval of the estimated probability.

Table 1: Characteristics of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) undergoing catheter ablation as urgent treatment for electrical storm (ES) (n=23)

Age at procedure, years	43.6 ± 16.7
Time from diagnosis to ES, years	3.4 (-4.4–39.2)
Male sex	23 (100)
Definite ARVC diagnosis (TFC)	23 (100)
Pathogenic mutation	
PKP2	6 (26)
DSG2	1 (4)
DSP	1 (4)
PKP2 + *DSP VUS*	2 (9)
None	5 (12)
Unknown	8 (35)
ECG abnormalities	
Inverted T-waves beyond V2	17 (74)
Epsilon wave	10 (43)
QRS width in V1, ms	108 ± 20
Structural abnormalities	
LVEF	56 (20–70)
LVEF ≤ 50%	7 (30)
RVEF	45 (29–63)
RV systolic dysfunction*	14 (61)
Diffuse RV involvement	16 (70)
ICD before ablation	19 (83)
Previous VT ablation	12 (52)

Anti-arrhythmic drugs	
Beta-blocker alone	6 (26)
Flecainide	10 (43)
Amiodarone	4 (17)
Flecainide + sotalol	1 (4)
Sotalol	1 (4)
None	1 (4)
ES clinical tolerance	
Syncope	12 (52)
Hemodynamic failure	4 (17)

Data are n (%), median (range) or mean ± SD.

*: defined by RVEF < 40% with RV angiography or fractional area change < 33% with transthoracic echocardiography.

Table 2: Arrhythmia characteristics and results of electrophysiological study for each ES catheter ablation procedure (n=24)

Clinical VT	
Number of documented VTs	1 (1–2)
>1 documented VT	4 (17)
Clinical VT morphology*	
LBBB, inferior axis	12
LBBB, superior axis	10
RBBB	2
Electrophysiological study and catheter ablation	
Clinical VT cycle length	348 ± 51
>1 induced VT	15 (63)
Use of a 3D electroanatomic mapping system	18 (75)
Number of induced VTs	2 ± 1.36
Number of targeted VTs	1 (1–6)
Number of targeted sites	1 (1–5)
Radiofrequency time, s	790 (180–6150)
Procedure duration, min	180 (120–360)

Data are n (%), median (min-max) or mean ± SD.