ESC European Society of Cardiology

Europace (2021) **00**, 1–9
doi:10.1093/europace/euab172

CLINICAL RESEARCH

Outcomes after catheter ablation of ventricular tachycardia without implantable cardioverter-defibrillator in selected patients with arrhythmogenic right ventricular cardiomyopathy

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Received 3 April 2021; editorial decision 19 June 2021; accepted after revision 22 June 2021

Aims The roles of implantable cardioverter-defibrillators (ICDs) and radiofrequency catheter ablation (RCA) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and well-tolerated monomorphic ventricular tachycardia (MVT) are debated. In this multicentre retrospective study, we aimed at reporting the outcome of selected patients with ARVC after RCA without a back-up ICD.

Methods and results Patients with ARVC who underwent RCA of well-tolerated MVT at 10 tertiary centres across 5 countries, without an ICD before and 3 months after RCA, without syncope or electrical storm, and with left ventricular ejection fraction ≥50% were included. In total, 65 ARVC patients [mean age 44.5 ± 13.2 years, 78% males] underwent RCA of MVT between 2003 and 2016. Clinical presentation was palpitations in 51 (80%) patients. One (2%) patient had >1 clinical MVT. At the ablative procedure, clinical MVTs (mean rate 185 ± 32 b.p.m.) were inducible in 50 (81%) patients. Epicardial ablation was performed in 19 (29%) patients. Complete acute success was achieved in 47 (72%) patients. After a median follow-up of 52.4 months (range 12.3–171.4), there was no death or aborted cardiac arrest, and VT recurred in 19 (29%) patients. Survival without VT recurrence was estimated at 88%, 80%, and 68%, 12, 36, and 60 months after RCA, respectively, and was significantly associated with the approach and the procedural outcome.

Conclusion In patients with ARVC, well-tolerated MVT without a back-up ICD did not lead to fatal arrhythmic event after RCA despite VT recurrences in some. Our data suggest that RCA may be an alternative to ICD in selected ARVC patients.

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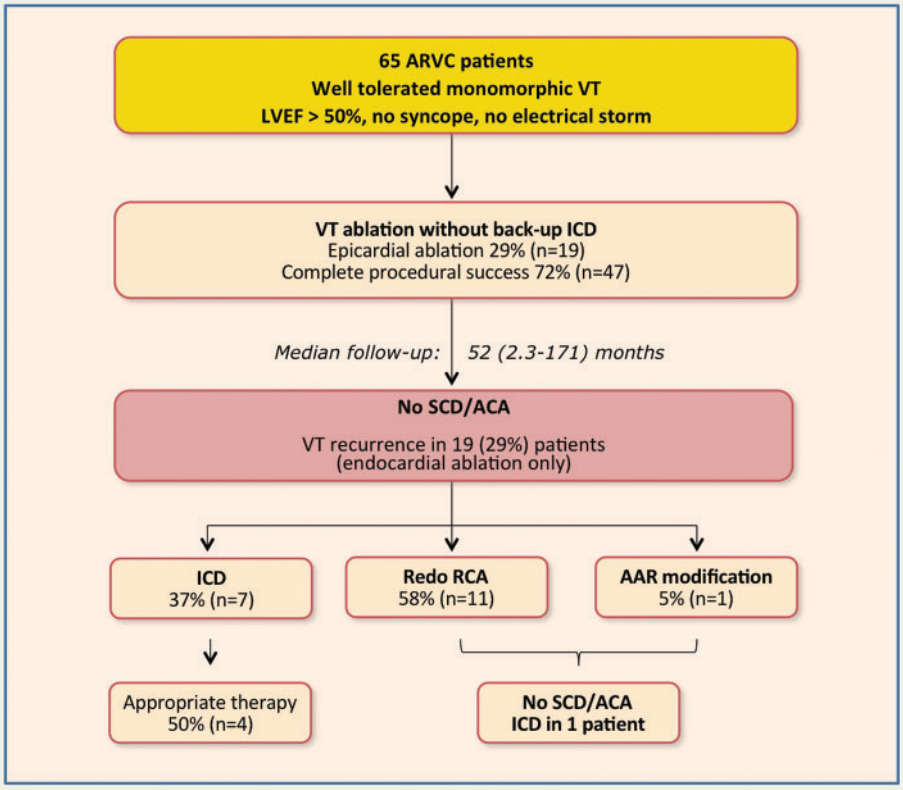
Graphical Abstract



Keywords Arrhythmogenic right ventricular cardiomyopathy • Sudden cardiac death • Monomorphic ventricular tachycardia • Catheter ablation • Implantable cardioverter-defibrillator • Epicardial ablation

What's new?

- Selected patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), well-tolerated monomorphic ventricular tachycardia may be managed safely by catheter ablation without an implantable cardioverter-defibrillator (ICD) back-up.
- Patients with a successful epicardial ablation are the best candidates for a no-ICD back-up therapeutic strategy.
- It is possible that the arrhythmic substrate underlying monomorphic ventricular tachycardia and malignant ventricular arrhythmias are different, and henceforth the corresponding patient populations within ARVC.
- Pending further prospective works, our data suggest that well-tolerated monomorphic ventricular tachycardia may not be a surrogate of sudden cardiac death in ARVC.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary cardiac muscle disease characterized by focal or diffuse cardiomyocyte loss and replacement with fibro-fatty tissue that affect primarily the right ventricle (RV) and progress from epicardial to endocardial myocardial layers.[1] The regional structural heterogeneity with areas of normal myocardium surrounded by scar tissue and slow-conduction areas, creating the ideal subtrate for macro-reentrant ventricular tachycardia (VT).[1,2] While the incidence of VT in ARVC is considerable and higher than in other forms of non-ischaemic cardiomyopathy, a very small proportion of patients will also experience sudden cardiac death (SCD) due to polymorphic VT or ventricular fibrillation (VF).[3] As implantable cardioverter-defibrillators (ICDs) are the most efficient therapy for SCD prevention, they are currently recommended in most high-risk situations, including in patients who have experienced monomorphic VT (MVT).[4] However, ICDs are associated with considerable morbidity related

to lead-related complications, device infections, and inappropriate therapies, especially in young population, such as ARVC patients.[3] Also, a significant number of ARVC patients worldwide do not access to ICD because of financial hardship.[5] In the last decades, major progress has been made in radiofrequency catheter ablation (RCA) techniques, and recent ARVC registries show good VT-free survival rates and drastic VT burden reduction after RCA.[2,6,7] Also, whether recurrent VT is a surrogate of SCD risk in ARVC is subject to debate, especially when other risk factors are lacking.[8] We, therefore, hypothesize that in selected patients with ARVC and well-tolerated MVT, it is safe to treat the arrhythmia by RCA without an ICD back-up.

Methods

Study population

Patients with a diagnosis of ARVC—according to the 2010 revised Task Force criteria (TFC) [9]—who underwent RCA between 2005 and 2018 for haemodynamically well-tolerated MVT, with preserved left ventricular systolic function [defined by left ventricular ejection fraction (LVEF) > 50% by cardiac magnetic resonance study or echocardiography] and who were not implanted with an ICD (prior to the procedure and in the 3 following months) were included. Patients who presented with syncope or electrical storm defined by ≥3 separate episodes of sustained VT within 24 h were excluded.

When baseline LVEF and right ventricular ejection fraction (RVEF) were evaluated by multiple modalities, the values obtained by magnetic resonance imaging (MRI), angiographic study, and echocardiography were selected in that order.

Electrophysiological study and catheter ablation

All patients provided written consent to the procedures, which were performed under general anaesthesia or conscious sedation at the operator's discretion. Programmed ventricular stimulation (PVS) was performed in patients in sinus rhythm at the beginning of the procedure, according to standard protocols (2 RV sites, up to 3 extra stimuli after 8 paced ventricular cycles of 600 and 400 ms) with use of intravenous isoproterenol infusion if necessary. Ablation strategies were based on activation mapping during VT with characterization of the VT critical isthmus and ablation targeting mid-diastolic potentials, pace-mapping, and/or substrate modification based on identification of scar areas by bipolar voltage mapping and elimination of local abnormal ventricular activities (LAVA) in sinus rhythm or ventricular pacing.[10] Ablation strategies were chosen at the discretion of the treating electrophysiologist at each centre according to current guidelines, available technologies, VT tolerance, and local expertise. For the purpose of the study, they were retrospectively classified as VT mapping (activation, entrainment, or pace-mapping), and substrate mapping (elimination of LAVA, scar modification, or linear ablation). Electro-anatomical mapping systems (CARTO, Biosense Webster Inc., Diamond Bar, CA, or NavX, St. Jude Medical Inc., St. Paul, MN, USA) were used to create bipolar and unipolar voltage maps in sinus or ventricular paced rhythm, with established voltage cut-offs to define scar.[11] When performed, epicardial access was achieved by a percutaneous subxiphoid puncture. Induced VTs were considered clinical when the 12-lead ECG morphology was identical to the clinical VT with the same rate ± 20 b.p.m.

Complete procedural success was defined as no sustained VT induced at final EPS including isoproterenol infusion, partial success as VT still inducible but clinical VT not inducible, and procedural failure as the ability to induce a sustained clinical VT. The result was considered undetermined when the clinical VT was not inducible at the beginning of the procedure or when no final PVS was performed.

Endpoints and follow-up

All-cause mortality, cardiovascular mortality, and SCD were collected, as well as occurrence of sustained VT (≥30 s) (including MVT, polymorphic VT, or VF) that required therapeutic intervention or otherwise that was documented on 12-lead ECG or Holter ECG monitoring. For Kaplan–Meier curve constructions, patients were censored at their last evaluation or when an ICD was implanted during follow-up. Outcomes of patients implanted with an ICD were nevertheless collected after ICD implantation.

Follow-up was carried out by treating physicians and included bi-annual out-patient visit with clinical evaluation, 12-lead ECG, and 24-h Holter monitoring. Recurrent VT was considered a relapse of the ablated VT when similar on 12-lead ECG morphology with identical rate ±20 b.p.m. No patient was lost to follow-up.

After evaluation and according to the General Data Protection Regulation and the French ethic and regulatory law, this study was approved and registered at the Toulouse University Hospital and covered by the MR-004 (CNIL number 2206723v0) regulation. Patients were informed that their anonymized data will be used for the study.

Statistical analyses

Continuous data are reported as mean ± SD or median (range) for normally or non-normally distributed data. Categorical variables are presented as *n* (%). Comparative statistics involved χ^2 or Fisher's exact test for qualitative variables, and *t*-test or the non-parametric Mann–Whitney test for quantitative variables, according to their distribution. 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

Baseline characteristics

Overall, 140 patients with ARVC and VT catheter ablation were screened across 10 international centres (Supplementary material online, *Table S1*). A total of 65 ARVC patients with LVEF >50%, who underwent RCA of well-tolerated MVT (no syncope or electrical storm) without ICD implantation before or during the first 3 months after RCA were included. Patient characteristics are summarized in *Table 1*. All patients met definite (53 patients, 90%) or borderline (6 patients, 10%) revised TFC criteria. Overall, 61 (94%) patients were probands, family history of ARVC was documented in 7 (11%) patients, and family history of SCD in 1 (2%). Most patients had ARVC-related ECG features (*Table 1*), but only 10 (16%) patients exhibited epsilon-waves. Nineteen patients (37%) had RV systolic dysfunction defined by RVEF <40% or fractional shortening <33%.

In all patients but one, the reason for which an ICD was not implanted was that the physicians did not recommend ICD implantation. One patient refused ICD implantation after being recommended by his electrophysiologist following RCA failure.

The clinical VT was monomorphic in each case, without associated documented polymorphic VT. Most patients presented with

Table 1 Patient characteristics ($n = 65$)

Age at RCA procedure, years	**44 ± 13**
Time since ARVC diagnosis, years	0.7 (−4.5 to 25.7)
Time from first VT episode to RCA, months	11.1 (0.1–312.8)
Male sex	51 (78)
TFC criteria[a,b]	
Definite	53 (90)
Borderline	6 (10)
TFC diagnostic score	5 (3–10)
≥2 major criteria	50 (67)
Pathogenic mutation[c]	21 (48)
PKP2	14 (66)
DSG2[d]	4 (19)
ANK2	2 (10)
PKP2 + *VUS DSP*	1 (5)
ECG abnormalities	
Inverted T-waves beyond V2[e]	28 (48)
Epsilon wave[f]	10 (16)
Maximal QRS width in V1–V3, ms[g]	108 ± 20
Pathological late potentials on signal average ECG[h,i]	31 (67)
Structural abnormalities	
RVEF[j]	45 (25–67)
LVEF	61 (50–71)
RVEF <40% or RVFAC <33%[k,l]	19 (37)
Mode of presentation	
Palpitations	52 (80)
Presyncope	9 (14)
Angina pectoris	1 (2)
Compensated heart failure	1 (2)
Asymptomatic	2 (3)
Anti-arrhythmic drugs[k]	
None	8 (14)
Class I	25 (42)
β-blockers alone	13 (22)
Amiodarone	5 (8)
Sotalol	8 (14)

Data are expressed as *n* (%), median (range), or mean ± SD.
ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; RCA, radiofrequency catheter ablation; RVFAC, Right Ventricle Fractional area change; RVEF, right ventricular ejection fraction; TFC, Task Force Criteria; VUS, variant of undetermined significance.
[a]$n = 59$ observations available.
[b]Such as defined by the 2010 revised TFC criteria.[13]
[c]Among 40 patients with genetic results available.
[d]Including one with homozygous *DSG2* mutation.
[e]$n = 58$ observations available.
[f]$n = 61$ observations available.
[g]$n = 55$ observations available.
[h]$n = 46$ observations available.
[i]$n = 47$ observations available.
[j]$n = 54$ observations available.
[k]$n = 59$ observations available.
[l]Defined by RVEF < 40% with RV angiography or fractional area change < 33% with transthoracic echocardiography.

palpitations only, although 9 (14%) presented with presyncope. Only one patient had more than one clinical VT morphology. The predominant morphology (98%) was left bundle branch block VT [superior axis: 15 (23%) patients; inferior: 40 (61%); left: 5 (8%); right: 4 (6%); null: 2 (3%)]. Most patients (86%) had failed anti-arrhythmic drug (AAD) or beta-blocker therapy prior to CA (*Table 1*).

Electrophysiological studies and catheter ablation procedures

Data from electrophysiological studies and RCA procedures are summarized in *Table 2* and the individual and per-centre dates and approaches for RCA and are shown in Supplementary material online, *Table S2* and *Figures S1* and *S2*. Epicardial mapping and ablation were performed in 19 (29%) procedures. A sustained VT was inducible in 54 (83%) patients. Induced VTs were well-tolerated haemodynamically in all but two patients, in whom the induced VT was the clinical VT. Ablation was performed at the VT critical isthmus identified by activation mapping in 17 (26%). Substrate-targeted ablation was performed in 48 (72%) patients. An example of epicardial VT mapping and ablation at the RV free wall is shown in *Figure 1*. Ablation sites included RV free wall in 31 (48%) patients [including 26 (40%) at the inferobasal aspect], RV outflow tract in 44 (68%), RV apex in 2 (3%), and RV septum in 1 (1%).

Complete procedural success was achieved in 47 (72%) procedures and partial success in 5 (8%). An undetermined result was reported in 10 (15%) procedures. Complete LAVA elimination was attempted in 41 (63%) patients and reached in 31 (48%). There were 3 (5%) patients with procedural failure. One of them had a pacemaker implanted immediately after RCA for atrioventricular block and his device was upgraded to an ICD at the time of VT recurrence, which was the well-tolerated clinical VT. The two others experienced clinical VT recurrence during follow-up without ICD implantation.

Acute complications occurred in 5 (7%) patients and included two patients with cardiac tamponade (one with and one without epicardial access), both managed by percutaneous drainage; one acute pulmonary embolism; one persistent atrioventricular block; and one femorocutaneous nerve injury.

Long-term outcomes

After a median follow-up of 52.4 months (range 2.3–171.4), no patient died or experienced aborted cardiac arrest (*Central Illustration*). A total of 19 (29%) patients experienced at least one recurrence of sustained VT during follow-up. Cumulative survival rate without sustained VT recurrence 12, 36, and 60 months after CA, was 88% [95% confidence interval (CI): 77–95], 80% (95% CI: 71–88), and 68% (95% CI: 50–80), respectively (*Figure 2A*). The per-centre VT-free survival rate is shown in Supplementary material online, *Figure S2*.

Among the 19 patients who underwent epicardial mapping and ablation, no patient experienced sustained VT recurrence (log-rank $P = 0.005$, *Figure 2B*). Lack of complete acute procedural success was significantly associated with VT recurrence during follow-up (*Figure 2C*, log-rank $P = 0.04$ and hazard-ratio 3.67, 95% CI 1.47–9.12, $P = 0.005$). Among the three patients with initial RCA failure, two had clinical VT recurrence, 85 and 60 months after RCA, respectively. One of them received an ICD.

There was a trend towards an association between VT recurrence and RV systolic dysfunction (HR for RVEF ≤ 35% 2.77, 95% CI 0.92–

Table 2 Arrhythmia characteristics and catheter ablation procedures ($n = 65$)

Arrhythmia	
Previous VT ablation	10 (15)
VT rate[a]	185 ± 32
VT morphology[b]	
LBBB-VT	59 (98)
RBBB-VT	1 (2)
> 1 clinical VT morphology	1 (2)
Approach	
Endocardial only	46 (71)
Endocardial + epicardial	19 (29)
Epicardial only	1 (2)
Electrophysiological study	
Number of induced VT[c]	1 (0–4)
>1 induced VT	16 (25)
Clinical VT inducible[c]	50 (81)
Catheter ablation	
Number of targeted RV sites, *n*	1 (1–3)
≥ 2 targeted RV sites	11 (17)
Irrigated radiofrequency	47 (73)
Procedural outcomes	
Full success	47 (72)
Partial success	5 (8)
Failure	3 (5)
Undetermined	10 (15)

Data are expressed as *n* (%), median (range), or mean ± SD.
LBBB, left bundle branch block; RBBB, right bundle branch block; RV, right ventricular; VT, ventricular tachycardia.
[a]Among 54 patients with data available.
[b]Among 60 patients with data available.
[c]Among 62 patients with data available.

8.35; $P = 0.07$) and between VT-free survival and complete LAVA elimination (HR 0.40, 95% CI 0.15–1.20; $P = 0.08$). No other baseline patient characteristic was associated with VT recurrence, as per results of univariate regression analyses.

The detailed course of patients who experienced VT recurrence is shown in Supplementary material online, *Table S3*. Recurrent VT was monomorphic in each case; 12-lead morphology was similar to the initial clinical VT in 10/19 (53%) patients and different in 1/19 (5%) (not documented in the remaining cases). Recurrent VT was associated with palpitations with otherwise good clinical tolerance in 15 (79%) patients and syncope in one (5%) (clinical tolerance not documented in the four remaining cases). In the single patient with a recurrent VT not comparable to the initial clinical VT, the recurrent VT had a comparable rate but a different axis (initial clinical VT: LBBB, left axis with late precordial transition, recurrent VT: LBBB, inferior axis). In one patient, monomorphic recurrent VT degenerated into polymorphic VT immediately following lidocaine infusion.

Recurrent VT was managed with redo catheter ablation in 11 (58%) patients, ICD implantation in 7 (42%), and AAD therapy modification in 1 (5%) patient. Overall, 12 patients had an ICD implanted during follow-up: eight with recurrent VT (including three after redo RCA failure, one with syncopal VT, one with lidocaine-induced polymorphic VT, one for high-grade atrioventricular block following redo RCA), and four without (one for unexplained syncope, one for change of referring institution, one for worsening of left ventricular dysfunction, reason not documented in one). Among these patients, 4 (33%) experienced appropriate ICD intervention during the remaining follow-up, which was anti-tachycardia pacing for MVT in all, followed by ICD shocks in 2. The median time of ICD implantation after RCA was 33 (range 4–161) months.

At last evaluation, 17 (29%) patients were off AAD therapy (vs. 15% before RCA, $P = 0.04$), 10 on beta-blocker alone (15%), 19 (29%) on Class I with beta-blockers, 3 (5%) on sotalol, 3 (5%) on amiodarone, and not documented in 13 (20%).

Discussion

This multicentre study is to date the largest series to reports the outcomes of patients with ARVC after RCA of VT without an ICD backup. The main finding is that we observed no death or aborted cardiac arrest despite a 30% VT recurrence rate after a median follow-up of more than 4 years after RCA. Other important findings include the absence of recurrent VT in all patients who underwent epicardial ablation and the significant association between procedural success, reached 72%, and VT-free survival.

Previously, in an observational study of 167 patients with mixed forms of structural heart diseases and LVEF over 30%—20 patients with ARVC—and VT managed by RCA without ICD therapy, Maury *et al.*[12] reported a 3.2% rate of SCD after a median follow-up of 32 months, with no death reported in the ARVC subgroup. More recently, Santangeli *et al.*[5] conducted a multicentre observational consisting of 32 ARVC patients—including a majority from East Asian ethnicity—who underwent VT RCA without background ICD therapy. The authors reported no arrhythmic death or aborted cardiac arrest after a 46-month median follow-up, with a VT-free survival rate of 81%. Our results are consistent with these data apart from some important aspects. First, in our study, the majority of patients was evaluated as being at low risk for lethal arrhythmia and was consequently not referred for an ICD, whereas ICD was recommended in all patients in Santangelli's study because of patient refusal or financial hardship. Second, we excluded patients with LV systolic dysfunction and prior syncope as they are particularly exposed to rapid or polymorphic VT in our experience[13] and since syncope and LV dysfunction are major criteria for SCD in current Consensus Statement.[4] Third, we report a slightly lower estimated VT-free survival rate compared to Santangeli's study (72% vs. 81% at 36 months). The lower rate of first-line epicardial ablation in our study—30% vs. 63%—likely contributes to this difference, especially considering that none of our patients who underwent epicardial ablation experienced VT recurrence. Also, in Santangeli's study, survival analysis began after the last RCA procedure, a methodological difference that, considering the 21% rate of redo ablation in our study, may have impacted VT-free rates. Last, when considering both Santangelli's study and the present one, the overall number of published patients with ARVC in whom ARVC was managed without an ICD despite VT is now higher than 100. This number is important as a single lethal event in this population may disqualify the proposed attitude.

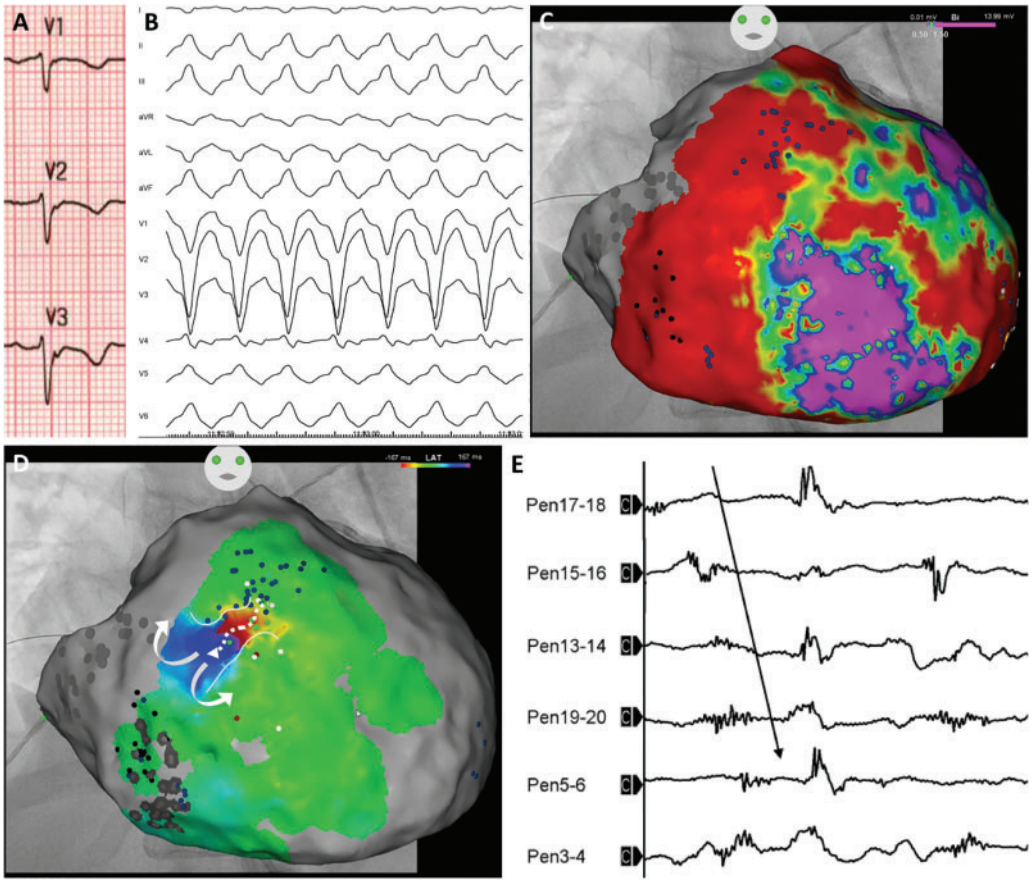


Figure 1 A 32-year-old man with *PKP2* mutation is referred for catheter ablation for recurrent well-tolerated MVT, without a back-up ICD. (*A*) Characteristic terminal activation delay is seen in right precordial leads. (*B*) Clinical VT of typical left bundle branch block morphology with late precordial transition. (*C*) Epicardial bipolar voltage mapping using standard cut-offs of 0.5–1.5 mV, displayed by the CARTO3 (Biosense Webster, Irvine, CA, USA) electro-anatomical mapping system, shows extensive scarring of the epicardial RV, affecting the entire peritricuspid region and extending toward the RV apex. (*D*) Local activation time mapping of the clinical VT suggests a macro-reentrant arrhythmia circuit with entrance, slow-conduction isthmus, and exit located at the epicardial RV free wall. (*E*) A duodecapolar mapping catheter positioned at the VT critical isthmus records mid-diastolic, fragmented electrograms with a gradient pattern covering >50% of the tachycardia cycle length. ICD, implantable cardioverter-defibrillator; MVT, monomorphic ventricular tachycardia; RV, right ventricular; VT, ventricular tachycardia.

Patients with ARVC are known to experience a high VT burden, with half of mutation-positive patients presenting with VT before 40 years of age.[3,14] In the recently published international prospective primary prevention ARVC registry from John Hopkins, 28% (5.6% per year) of patients presented with ventricular arrhythmias after 5 years of follow-up.[15] Earlier investigations also reported high annual VT incidences (2–10%).[8,16,17] All these studies included a majority of ICD-implanted patients, and thus incorporated a certainly significant proportion of ICD therapies treating episodes that may have otherwise been non-sustained, rapidly self-terminating, or even asymptomatic. In fact, the majority of series aiming at estimating VA incidence in ARCV include patients with an ICD and ICD-treated VAs are often considered as a surrogate for SCD.[8,15,17] However, not all ICD-treated VAs would have led to SCD, some VAs may self-terminate without need for ICD intervention and rapid-VT/VF may be induced by ICD interventions for initial slower VTs.[18]

Few data exist on the relative incidence of VT and of spontaneous rapid-VT/VF potentially causing SCD in patients without an ICD. In the North-American Multidisciplinary Study of ARVC following 108 patients with an ICD during a mean time of 3.3 years, 97% of VAs were MVT successfully treated by ATP, while only 2.6% were polymorphic VT/VF.[19] We previously published our experience in 137 ARVC patients without an ICD—31% with an history of VT and 18% with RCA—undergoing EPS for risk stratification.[13] During a median follow-up of 42 months, 14% of patients experienced sustained VT, while 4% of them presented rapid-VT/SCD. In the latter group, all patients had a history of syncope. In a multicentre study of 106 patients with ARVC and an ICD, 16% had shocks for VF or very rapid VT.[17] In the John Hopkins report including a majority of patients with an ICD, VT occurred in 27% of patients and rapid sustained VT/SCD occurred in 10%.[15] Whether rapid-VT/VF may rely on a different anatomical substrate than well-tolerated macro-reentrant VTs and whether some ARVC patients with sustained VT may however be at

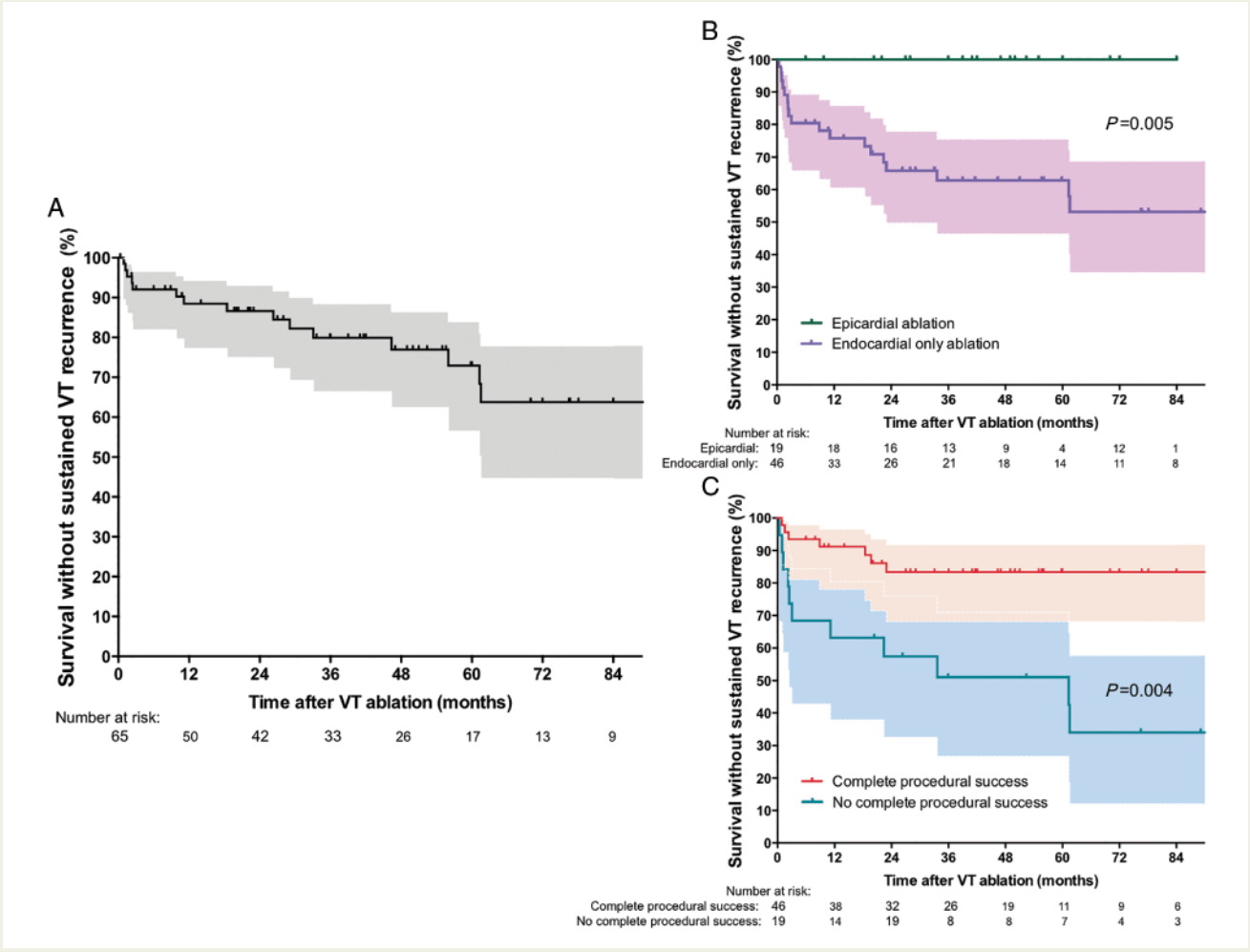


Figure 2 Long-term outcomes of catheter ablation of well-tolerated monomorphic VT in 65 patients with arrhythmogenic right ventricular cardiomyopathy and no back-up implantable cardioverter-defibrillator. (*A–C*) Kaplan–Meier curves representing the estimated cumulative survival without VT recurrence after catheter ablation. The dotted lines plot the 95% confidence interval of the Kaplan–Meier estimates. *P*-values refer to log-rank tests. VT, ventricular tachycardia.

very low risk for rapid-VT/VF is still unknown. The arrhythmic behaviour in ARVC is highly variable and the clinical paths may be different in patient with stable MVT compared to those with more malignant ventricular arrhythmia. Although studies on VT risk in ARVC do not provide strong comparative data between patients with stable MVTs and those with malignant VT, and do not analyse the temporal relationships between these two entities, our data suggest that carefully selected patients with well-tolerated VT treated by RCA are at low risk of SCD despite a significant VT recurrence rate following RCA. Further works aimed at attempting incidence, clinical characteristics, and substrate characterization of patients presenting with spontaneous rapid-VT/VF in ARVC are needed.

In ARVC, the frequency and clinical significance of LV involvement are increasingly recognized.[1] Data investigating a potential association between LV involvement and VA-risk are conflicting.[8,13,15] Nonetheless, patients with LV involvement are more likely to suffer from a more advanced disease or non-desmosomal 'arrhythmogenic cardiomyopathies' with a wide phenotypical and genotypical variability, such as *LMNA* or *PLN*-associated cardiomyopathies, which usually have a worse prognosis and a different arrhythmogenic substrate.[1] Additionally, the recent 2019 expert consensus document acknowledges LVEF <50% as a major risk factor for VT.[4] For these reasons, we did not consider patients with LV systolic function—even mild—for inclusion in our series as we consider these patients to be at high risk for SCD.

Dramatic progress in VT RCA has been achieved over recent years, especially in ARVC, where refinement of electro-anatomical mapping technologies allowing comprehensive substrate mapping and epicardial approach yields excellent results.[2,20] In our study, none of the patients who underwent epicardial ablation presented VT recurrence. The importance of epicardial approach in ARVC has been already demonstrated by many authors and should be part of the ablation strategy in most cases,[2,4,6,7] with a possible exception being end-stage ARVC with small epi-to-endocardium scar extent gradient, for which endocardial ablation may be sufficient.[20] Overall, first-line endo-epicardial

approach and substrate elimination should be recommended in patients selected for VT ablation without an ICD back-up, for which VT-free survival is the objective.

Assessing safety and efficacy of therapeutic strategies in rare patient populations, such as ARVC with VT is challenging, especially when it relates to SCD prevention. In this context, only large multicentre registries from referral centres can achieve an acceptable level of evidence. Our data support the view that ARVC patients with a successful VT ablation and without high-risk features, such as impaired LVEF, syncope or electrical storm as presentation, or poor VT clinical tolerance may be safely managed without a back-up ICD in experienced centres. Pending future works, this strategy may be proposed in carefully selected cases.

Limitations

The main limitation of this work originates from its retrospective design and the potential for selection bias. Despite consecutive patient enrolment at each centre, we cannot exclude that some patients meeting the inclusion criteria and potentially with a fatal event might not have been included, although this seems unlikely as all ablated patients are regularly followed at our institutions. Second, there was no standardized risk stratification across centres to recommend or not ICD implantation. Hence, we were unable to provide details regarding decision criteria for ICD implantation. Nonetheless, we think this does not compromise the study main objective to report outcomes of ARVC patients without an ICD back-up after VR RCA. Third, the study might have benefited from a comparison with similar patients implanted with an ICD, particularly to assess the risk/benefit profile of ICDs in this population and to medically treated patients to assess the effect of RCA on SCD prevention. However, retrospectively collecting two groups with comparable clinical characteristics and arrhythmic risk profile would have been very difficult. Fourth, the fact that this study encompasses a 13 years time of evolution in RCA techniques, including the development of epicardial mapping ablation that only a minority of patients benefited from for this reason, may have significantly affected long-term outcomes. The long inclusion period is also associated with variable indications for epicardial approach and various procedural factors that may have impacted procedural outcomes besides the approach. Fifth, MRI-based scar assessment lacked to characterize LV involvement in the study population. At last, with all included patients aged over 18 years, these results do not apply to the paediatric ARVC population.

Conclusions

Selected patients with ARVC, preserved left ventricular ejection fraction and well-tolerated MVT and without a back-up ICD did not experience fatal arrhythmic event after RCA, despite a significant VT recurrence rate. Patients with successful elimination of the epicardial substrate might be the best candidates for strategy consisting in VT RCA without a back-up ICD. Further studies will be essential to refine the respective places of ICD and VT RCA in the management of patients with ARVC and VT.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

Data availability

The data that support the findings of this study are available from the corresponding author, [author, M.L.], upon reasonable request.

References

1. Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. Clinical diagnosis, imaging, and genetics of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J Am Coll Cardiol* 2018;**72**:784–804.
2. Santangeli P, Zado ES, Supple GE, Haqqani HM, Garcia FC, Tschabrunn CM *et al.* Long-term outcome with catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol* 2015;**8**:1413–21.
3. Schinkel AF. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. *Circ Arrhythm Electrophysiol* 2013;**6**:562–8.
4. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC *et al.* HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;**16**:e373–407.
5. Santangeli P, Tung R, Xue Y, Chung F-P, Lin Y-J, Di Biase L *et al.* Outcomes of catheter ablation in arrhythmogenic right ventricular cardiomyopathy without background implantable cardioverter defibrillator therapy. *JACC Clin Electrophysiol* 2019;**5**:55–65.
6. Philips B, Riele A. T, Sawant A, Kareddy V, James CA, Murray B *et al.* Outcomes and ventricular tachycardia recurrence characteristics after epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm* 2015;**12**:716–25.
7. Laredo M, Da Silva LO, Extramiana F, Lellouche N, Varlet É, Amet D *et al.* Catheter ablation of electrical storm in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2020;**17**:41–48.
8. Corrado D, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A *et al.* Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2003;**108**:3084–91.
9. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia proposed modification of the task force criteria. *Eur Heart J* 2010;**31**:806–14.
10. Jais P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y *et al.* Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia. *Circulation* 2012;**125**:2184–96.
11. Kirubakaran S, Bisceglia C, Silberbauer J, Oloriz T, Santagostino G, Yamase M *et al.* Characterization of the arrhythmogenic substrate in patients with arrhythmogenic right ventricular cardiomyopathy undergoing ventricular tachycardia ablation. *Europace* 2017;**19**:1049–62.
12. Maury P, Baratto F, Zeppenfeld K, Klein G, Delacretaz E, Sacher F *et al.* Radiofrequency ablation as primary management of well-tolerated sustained monomorphic ventricular tachycardia in patients with structural heart disease and left ventricular ejection fraction over 30%. *Eur Heart J* 2014;**35**:1479–85.
13. Maupain C, Badenco N, Pousset F, Waintraub X, Duthoit G, Chastre T *et al.* Risk stratification in arrhythmogenic right ventricular cardiomyopathy/dysplasia without an implantable cardioverter-defibrillator. *JACC Clin Electrophysiol* 2018;**4**:757–68.
14. Groeneweg JA, Bhonsale A, James CA, Riele A. T, Dooijes D, Tichnell C *et al.* Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet* 2015;**8**:437–46.
15. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A *et al.* A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2019;**40**:1850–8.
16. Bhonsale A, James CA, Tichnell C, Murray B, Gagarin D, Philips B *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *J Am Coll Cardiol* 2011;**58**:1485–96.
17. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M *et al.* Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation* 2010;**122**:1144–52.

18. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol* 2006;**97**:1255–61.
19. Link MS, Laidlaw D, Polonsky B, Zareba W, McNitt S, Gear K *et al.* Ventricular arrhythmias in the North American multidisciplinary study of ARVC. *J Am Coll Cardiol* 2014;**64**:119–25.
20. Berruezo A, Acosta J, Fernández-Armenta J, Pedrote A, Barrera A, Arana-Rueda E *et al.* Safety, long-term outcomes and predictors of recurrence after first-line combined endoepicardial ventricular tachycardia substrate ablation in arrhythmogenic cardiomyopathy. Impact of arrhythmic substrate distribution pattern. A prospective multicentre study. *Europace* 2016; euw212.