

## Role of ventricular tachycardia ablation in arrhythmogenic right ventricular cardiomyopathy

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### Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by progressive fibro-fatty replacement of the myocardium that represents the substrate for recurrent sustained ventricular tachycardia (VT). These arrhythmias characterize the clinical course of a sizeable proportion of patients and have significant implications for their quality of life and long-term prognosis. Antiarrhythmic drugs are often poorly tolerated and usually provide incomplete control of arrhythmia relapses. Catheter ablation is a potentially effective strategy to treat frequent VT episodes and ICD shocks in ARVC patients. The aims of this review are to discuss the electrophysiological and electroanatomic substrates of ventricular tachycardia in patients with ARVC and to analyze the role of catheter ablation in their management with particular reference to selection of patients, technical issues, potential complications and outcomes.

### Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare inherited heart muscle disease characterized by progressive fibro-fatty replacement of the myocardium that represents the substrate for ventricular arrhythmias and sudden cardiac death (SCD), mostly in young individuals and athletes.<sup>1-4</sup> It is a genetically determined cardiomyopathy, often caused by mutations in genes encoding for desmosomal proteins, which are cellular structures specialized for cell-to-cell adhesion.<sup>5</sup> Desmosomal defects are responsible for impaired cell connections that lead over time to myocyte death, with subsequent repair by fibrofatty replacement. This pathophysiological process typically spreads from the epicardium to the endocardium, and predominantly affects the right ventricle (RV), resulting in wall thin-

ning and aneurysmal dilatation, typically located at the angles of the *triangle of dysplasia*, i.e. the apex, inflow and outflow tract of the RV. In the classical form of ARVC, the left ventricle (LV) is affected to a lesser extent than the RV; however, disease variants characterized by equal or greater involvement of the LV are also observed.<sup>6-8</sup>

The natural history of ARVC is characterized by a spectrum of ventricular arrhythmias ranging from premature ventricular complexes to sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).<sup>3,9</sup> The pathogenesis of ventricular arrhythmias relies on the disease phase; in younger, often previously asymptomatic patients, SCD is mainly due to VF, in the context of active phases of acute myocyte death and reactive inflammation.<sup>10</sup> By contrast, older patients with a long-lasting disease more often experience scar-related hemodynamically stable VT, due to a reentry mechanism around a myocardial scar.<sup>11</sup>

The overall incidence of cardiac arrest attributable to VF varies among different series, ranging from 0.08% per year,<sup>12</sup> to 3.6% per year.<sup>13</sup> Prevention of SCD is the mainstream of ARVC therapy, and implantable cardioverter-defibrillator (ICD) therapy represents the only effective choice to achieve this aim. Many observational studies and registries of large population of ARVC patients have established the safety and efficacy of ICD therapy in interrupting lethal tachyarrhythmias and improving the survival of selected high risk ARVC patients.<sup>14-16</sup>

Another important objective of clinical management of ARVC is the improvement of symptoms and quality of life by reducing/abolishing palpitations, VT recurrences, or ICD discharges. Currently available treatment options are the pharmacological therapy and catheter ablation. While the efficacy of antiarrhythmic drugs is controversial and over the last decades no new molecules have been introduced, catheter ablation has evolved from being a poorly available and often unsuccessful treatment, to an effective therapy for most ARVC patients with recurrent sustained ventricular arrhythmias.<sup>17</sup>

The aim of this review is to provide insights into the electrophysiological and electroanatomic substrates of VT in patients with ARVC and to analyze the role of catheter ablation in their management.

### Indications and patient selection

Management of ARVC patients with recurrent VT and frequent ICD therapy can

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be challenging, but has significant implications for their quality of life and long-term prognosis. Antiarrhythmic drugs are often poorly tolerated and usually provide incomplete VT control.<sup>17</sup> Catheter ablation of scar-related VT has significantly improved VT recurrence-free survival, particularly since epicardial mapping and ablation have been implemented, in addition to the more common endocardial approach.<sup>18</sup> According to the recent International Task Force consensus statement,<sup>17</sup> catheter ablation is considered a potentially effective strategy to treat frequent VT episodes and ICD shocks in ARVC patients. It is therefore recommended in patients with incessant VT or frequent appropriate ICD interventions on VT, despite maximal pharmacological therapy, and may be considered in patients who do not desire or cannot tolerate antiarrhythmic drugs. However, catheter ablation has not demonstrated to prevent SCD and should not be considered an alternative to ICD implantation in ARVC patients with a history of sustained VT, with the possible exception of selected cases with a drug refractory, hemodynamically stable, single morphology VT.<sup>17</sup>

### Electroanatomic mapping in ARVC: understanding the VT substrate

Over the last twenty years, advances in electrophysiologic knowledge and techniques enabled a more detailed understanding of the complex arrhythmic substrate in patients with ARVC and VT. Among the tools available for direct imaging of ventricular myocardial lesions, bipolar three-dimensional electroanatomic voltage mapping (3D-EVM) accurately identifies the

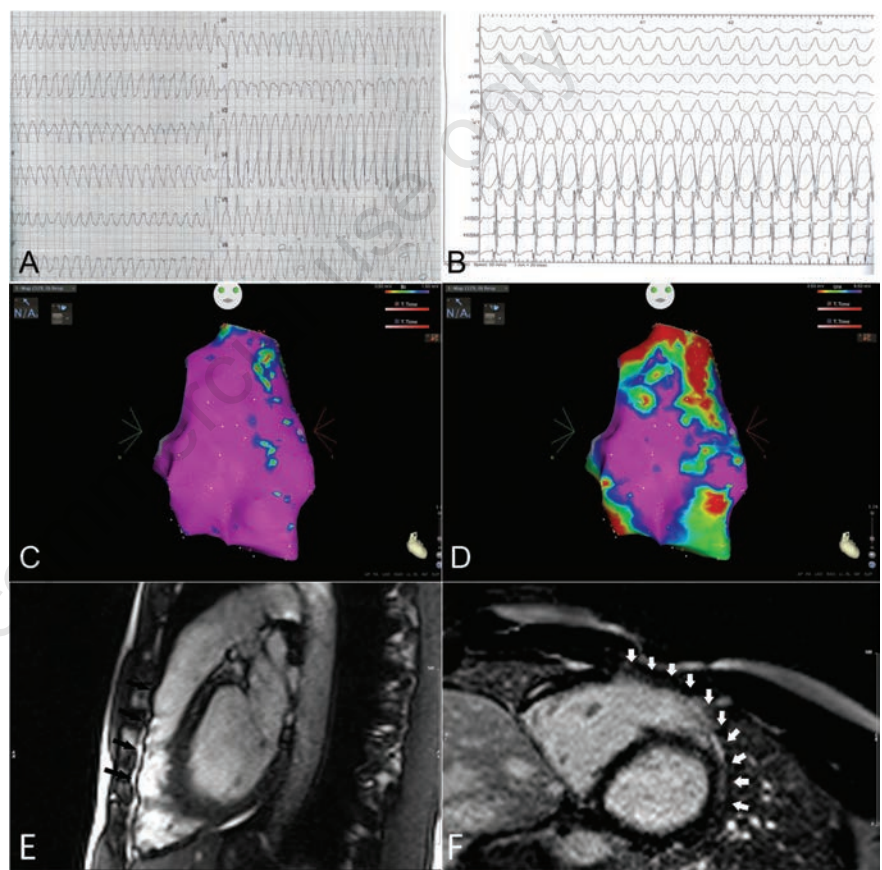
presence, location, and extent of the pathological substrate of ARVC by detection of low-voltage regions, that reflect the electric consequences of transmural myocyte loss and fibrofatty replacement, observed at histopathological examinations (Figure 1).<sup>19</sup> A good concordance between the presence and location of RV low-voltage areas identified by 3D-EVM and akinetic/dyskinetic regions detected by echocardiography or angiography was demonstrated.<sup>20</sup> Moreover, 3D-EVM is significantly more sensitive than cardiac magnetic resonance to identify RV scar lesions.<sup>20,21</sup> As abnormal bipolar EVM is specific for ARVC, it can provide additional value for differential diagnosis between ARVC and other RV disease.<sup>22</sup>

Abnormal RV endocardial regions (so-called electroanatomic scars) are defined by areas  $\geq 1$  cm<sup>2</sup> with low bipolar voltages ( $< 1.5$  mV), and fractionated potentials (*i.e.*  $> 3$  deflections, amplitude  $\leq 1.5$  mV, duration  $> 70$  ms).<sup>23</sup> Low voltage regions in patients with ARVC distinctively involve the RV free wall and particularly the anterolateral, infundibular, and inferobasal (sub-tricuspidal) region, resembling the distribution of fibrofatty scars observed in pathologic specimens.<sup>24</sup> Low-voltage abnormalities can also be found on the apex, but typically spares the RV septum.<sup>22</sup> By using mapping catheters with multiple poles and very small inter-electrode distance (*e.g.* Orion catheter<sup>TM</sup>, Boston Scientific or PentaRay<sup>TM</sup>, Biosense Webster) it is possible to create a voltage map with a very high density of points. This may allow to record electrical activities within areas of very low voltage (*dense scar*), revealing surviving myocardial bundles that may represent the substrate for re-entrant circuits within the scar that may otherwise be overlooked.<sup>25</sup> Besides its diagnostic value, bipolar 3D-EVM also carries prognostic significance, as one study demonstrated that the presence and extent of bipolar low voltage areas is an independent predictor of arrhythmic events, over and above classical risk factors like clinical history, arrhythmic background and ventricular dysfunction,<sup>19</sup> and another study that the fragmented electrograms are significantly associated with arrhythmic events during follow-up.<sup>26</sup>

Endocardial bipolar EVM can fail to detect low-voltage areas in about 25-30% of ARVC patients with VT,<sup>19,27</sup> and endocardial ablation approach provides only a modest freedom from VT recurrence.<sup>27</sup> This is related to the pathogenesis of the disease: as proved by autopsy and pathology studies, the wavefront of fibrofatty myocardial replacement progresses from the epicardium to the endocardium, so that the scar tis-

sue can either involve the whole thickness of ventricular wall or be confined to epicardial/midmural layers, sparing the endocardial regions.<sup>28</sup> Epicardial substrate in ARVC can be better identified by epicardial voltage mapping, which is particularly useful to guide catheter ablation in patients that have failed the endocardial approach. Abnormal epicardial bipolar low-voltage areas (amplitude  $< 1.0$  mV) are normally larger than the corresponding endocardial low-voltage areas, with extensive networks of late activation and fractionated potentials.<sup>18</sup> Epicardial fat or major coronary vessel can be misclassified as abnormal, since they show low signal amplitude. To limit the

possibility to misinterpret these structures as low-voltage areas, the contiguous abnormal regions should demonstrate not only low amplitude electrograms, but also discrete late potentials and/or broad multi-component ( $> 80$  ms) or split signals. The presence of late potentials is specific for identification of the epicardial substrate of VT because they are not observed in patients without structural heart disease.<sup>29</sup> Signs that could suggest the need for epicardial approach for VT mapping and ablation include a delayed intrinsicoid activation of the QRS complex of VT on surface ECG,<sup>30</sup> the presence of isolated epicardial scar at cardiac magnetic resonance, and/or prior



**Figure 1.** Representative example of a 27 year-old male who suffered hemodynamically unstable sustained ventricular tachycardia while he was running (A). The clinical tachycardia was re-induced by programmed ventricular stimulation with two extrastimuli, suggesting a re-entrant mechanism (B). The tachycardia morphology (left bundle branch block/inferior axis) suggests the origin from the right ventricular outflow tract. Antero-posterior view of right ventricular bipolar endocardial voltage mapping with the Ensite Precision system, set to show in red areas of low voltages ( $< 0.5$  mV) and in purple areas of normal voltages ( $> 1.5$  mV) (C). The exam demonstrated only limited low voltages areas, corresponding to transmural fibrofatty scar, below the pulmonary valve and in the right ventricular free wall. Instead, unipolar voltage mapping (3.5-5.5 mV) revealed large low voltage areas, suggesting subepicardial fibrofatty replacement, involving the subtricuspid, apical and outflow tract regions (*i.e.* the so called *triangle of dysplasia*) (D). Cardiac magnetic resonance demonstrated multiple areas of systolic bulging of the right ventricular outflow tract (black arrows) (E) and late gadolinium enhancement (suggesting fibro-fatty replacement) of the anterior right ventricular wall extending to the subepicardial layer of the antero-lateral left ventricular segment (white arrows) (F).

failed endocardial ablation. As an alternative to the invasive epicardial mapping, analysis of unipolar endocardial signals, having a larger field-of-view, can provide information about the presence of epicardial abnormality as well as identify a greater amount of low-voltage areas in those with abnormal bipolar EVM, suggesting a more extensive epicardial substrate (Figure 1D). By comparing bipolar epicardial mapping and unipolar endocardial mapping it has been demonstrated that a threshold of <5.5 mV at unipolar endocardial mapping accurately correlates with subepicardial scar regions.<sup>31</sup>

## Ablation technique

The procedure of VT ablation in ARVC should be performed with almost the same general principles used in all scar-related VT ablations, but with higher chances of needing an epicardial approach. Since it has been proved that general anesthesia reduces VT inducibility, causes excessive hypotension during VT and, when combined with muscle relaxants, drops sensitivity of high-output phrenic nerve mapping,<sup>32,33</sup> conscious sedation is preferred over general anesthesia during the endocardial procedure. RV endocardial voltage mapping should be created in sinus rhythm with standard 0.5-1.5 mV voltage cutoffs.<sup>34</sup> It is crucial to provide adequate catheter contact during mapping, to confirm the observed

low voltage areas. During mapping, the identification of fractionated signals and late potentials must be registered: for this purpose, modern ablation catheters with contact force sensors are particularly useful. Pace-mapping is also recommended to identify additional sites of interest. Once the RV endocardial mapping is completed, programmed ventricular stimulation can be performed to induce the VT. Electrocardiographic morphologies of induced VT should be compared to clinical arrhythmias and to pace-mapping morphologies. The standard ablation technique involves activation and entrainment VT mapping to identify the tachycardia circuit, but this technique could be problematic due to hemodynamic instability or changes in morphology caused by catheter manipulation. As an alternative, a substrate-based ablation targeting *channels* and delayed/fractionated potentials within low voltages areas can be performed. Radiofrequency energy is usually applied with an open irrigated tip catheter using powers up to 40 W, for 60-90 sec, with a goal of 12 to 15 Ohm impedance drop or 10% decrease from the baseline impedance.<sup>35</sup> Epicardial approach is required whenever inducible VT is still present after endocardial ablation or in case of early relapse, and is generally performed with pericardial access, under general anesthesia. Mapping, electrophysiological study and ablation technique are quite similar to those described for the endocardium. The

induced VTs are usually less hemodynamically tolerated so that an ablation targeting the substrate (*i.e.* abolishing area of low voltages and complex/fractionated potentials) is usually performed. Coronary angiography should be performed prior to epicardial ablation, to maintain a safe distance of the ablation site from main epicardial coronary vessels.<sup>36</sup> Potential complications of epicardial ablation are cardiac tamponade, damage to coronary arteries and phrenic nerves, RV perforation, pulmonary embolism and liver laceration.<sup>35</sup> Careful attention to blood pressure and constant monitoring of catheter position and pericardial effusion, are crucial.

## Outcomes

Table 1 summarizes the main results of VT ablation in various series reported in the literature. Overall, acute success was achieved in 60-80% of patients with a rate of major complications <5%, whereas the recurrence rates during long-term follow-up of 3-5 years after a single ablation are very high, even with a combined subendocardial/subepicardial approach.

The use of a combined endocardial/epicardial approach has markedly improved acute success, which in some modern series reaches 100%. As already mentioned, ARVC lesions progress from the epicardium to the endocardium, and the presence of subepicardial myocardial scars may partly

**Table 1. Major series reporting ventricular tachycardia ablation outcome in arrhythmic cardiomyopathy.**

Author (year)	Patients n (men)	Ablation technique			Complete acute success (%)	Procedure-related complications	Follow-up	
		Electro-anatomic map	Irrigated tip	Epicardial map/abl			Mean (months)	VT recurrences (%)
Mussigbrodt 2017	45 (30)	Yes	Yes	Yes	84	5 (TIA, tamponade x2, PE x2 1 fatal)	31	44*
Souissi 2016	49 (44)	Yes	Yes	Yes	71	3 (tamponade, femoral AV fistula, intestinal perforation)	64	81 at 5 years 31 at 1 years*
Santangeli 2015	62 (45)	Yes	Yes	Yes	77	5 (PE x2, pericardial effusion, RV puncture, CT)	56	29*
Philips 2012	86 (45)	Yes	Yes	Yes	82	2 (death, MI)	88	85
Berruezo 2012	11 (9)	Yes	Yes	Yes	100	1 (tamponade)	11	9
Garcia 2009	13 (10)	Yes	Yes	Yes	92	0	18	23
Nogami 2008	18 (13)	Yes	No	No	72	0	61	33
Dalal, 2007	24 (11)	Yes	No	No	77	1 (death)	32	85
Satomi 2006	17 (13)	Yes	No	No	88	0	26	24
Verma 2005	22 (15)	Yes	Yes	No	82	1 (tamponade)	37	36
Miljoen 2005	11 (8)	Yes	No	No	73	0	20	45
Marchlinski 2004	19 (18)	Yes	Yes	No	74	0	27	11
Reithmann 2003	5 (3)	Yes	No	No	80	0	7	20
Ellison 1998	5 (4)	No	No	No	42	0	17	0

\*The end-point was ventricular tachycardia-free after the last ablation. AV, artero-venous; CT, constrictive pericarditis; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischemic attack; RV, right ventricular; VT, ventricular tachycardia. Modified with permission from Corrado D, et al. *Circulation* 2015;132:441-53.



explain the failure of conventional endocardial catheter ablation. Garcia *et al.*<sup>18</sup> first reported the feasibility and efficacy of epicardial ablation in ARVC patients after previously failed endocardial VT mapping/ablation procedures. In these patients, the extent of electroanatomical scar area at voltage mapping was larger on the epicardial side of the RV wall than on the endocardium. Complete success was achieved in 85% of cases (partial success in 92%) and 77% of patients were free from VT during 18 months of follow-up. On the other hand, subepicardial ablation is more technically demanding than the traditional subendocardial approach and poses additional risks such as the risks correlated to the pericardial puncture (in the absence of pericardial fluid) and to the presence of epicardial coronary arteries. As such, it should be performed only in experienced centers.

Modern studies providing long term follow-up on large number of patients,<sup>37,38</sup> reported very high recurrence rates after the first procedure despite a combined endo/epicardial approach, although the cumulative freedom from VT following procedures using 3D-EVM and/or epicardial approach was significantly greater than conventional ablation. The most likely reason is the progressive nature of the disease with modification of the arrhythmic substrate over time. At variance with post myocardial infarction scar, which remains relatively stable over time, the fibrofatty scar of ARVC evolves leading to the occurrence of multiple reentry circuits and new arrhythmogenic foci over time. However, recent studies<sup>38-40</sup> reported that long-term VT-free survival can be achieved in the majority of ARVC patients, provided that multiple procedures are performed.

## Conclusions

In patients with recurrent, symptomatic VT, catheter ablation has emerged as a valuable treatment option, especially in experienced centers and in cases when antiarrhythmic drug therapy is either ineffective or non-tolerated. However, compared to other diseases, ablation of VT in ARVC may be more challenging because of the subepicardial substrate and the evolving nature of the disease. Although acute success is today very good thanks to advancements in substrate characterization with 3D-EVM, the use of irrigated-tip catheters with contact force sensors and epicardial approach, rates of recurrence during long-term follow-up remain high and multiple procedures are often needed to achieve good long-term results. Accordingly, VT

ablation of ARVC remains a symptomatic therapy that should not be looked upon as an alternative to ICD therapy for prevention of sudden death.

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