REVIEW ARTICLE

Overcoming challenges in the management of arrhythmogenic right ventricular cardiomyopathy

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KEYWORDS

arrhythmogenic right ventricular cardiomyopathy, catheter ablation, electro-anatomic mapping, ventricular tachycardia

ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) appears in most patients to be an inherited disease characterized by fibrofatty replacement of myocytes extending from the epicardium to the endocardium in the right ventricle. The disease process results in life-threatening ventricular arrhythmias and ventricular dysfunction. In the absence of a gold-standard diagnostic test and despite the progress in imaging techniques, ARVC is often misdiagnosed and earlier detection of the disease is challenging. Preprocedural identification and localization of the substrate can be determined from the analysis of surface electrocardiography and cardiac magnetic resonance imaging. Typically, perivalvular arrhythmogenic substrate, defined by electroanatomic mapping, is present and can be isolated to the epicardium. Ablation targets are further identified with activation, entrainment, and local electrogram abnormalities based on detailed electroanatomic mapping. Extensive combined endo / epicardial ablation performed in experienced centers is frequently required to prevent ventricular tachycardia (VT). Catheter ablation significantly reduces recurrences of VT, appropriate implantable cardioverter-defibrillator shocks, and the use of antiarrhythmic drugs and cardiac transplant as a management strategy for refractory arrhythmias is rarely required. Progression of the disease is poorly understood and may require a distinct triggering mechanism. Biventricular involvement is more common than previously recognized. However, left ventricular involvement leading to significant terminal heart failure is fortunately uncommon and left ventricular tachycardias are also infrequent. Many questions remain regarding prevention and management of coexisting tricuspid valve regurgitation, atrial arrhythmias, and intracardiac thrombosis. Although data on genotype-phenotype correlations is growing, long-term follow-up studies of families with ARVC are still lacking. Ongoing research will contribute to better understanding of this pathological condition.

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Introduction Arrhythmogenic right ventricular cardiomyopathy (ARVC) appears in most patients to be an inherited disease involving predominantly the right ventricle (RV). The disease is characterized by fibrofatty replacement of myocytes involving the epicardium and extending to the endocardium and resulting in ventricular arrhythmias (VAs) and ventricular dysfunction.[1,2] Right ventricular free wall scarring and thinning with aneurysm formation situated at the vertexes of the triangle of dysplasia at basal infundibular and diaphragmatic areas adjacent to the tricuspid valve and less commonly the right ventricular apex can be observed.[3] At the cellular level, alteration of desmosomes is hypothesized to be associated with myocyte apoptosis and inflammation.[4-6] It has been suggested that these changes lead to fibrofatty replacement and result in impaired mechanical and electrical coupling producing conduction delay and associated arrhythmias.

ARVC was originally considered as a familial progressive degenerative or dysplastic desmosomal cardiomyopathy with autosomal dominant inheritance and variable penetrance.[7] However, only approximately 50% of patients who

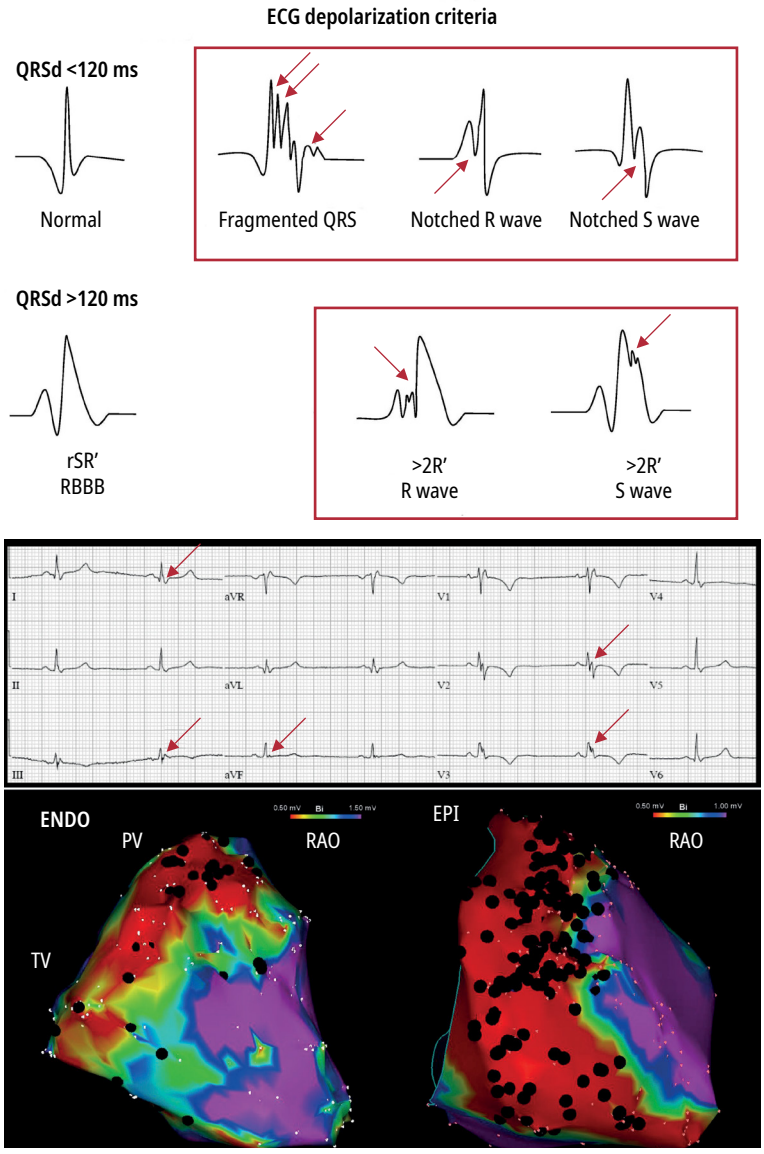

FIGURE 1 Electrocardiographic (ECG) depolarization abnormality criteria and right ventricular electroanatomic substrate; top: ECG depolarization abnormality criteria; bottom: baseline 12-lead ECG with anterior, inferior, and superior depolarization abnormalities (red arrows) and RV endocardial (ENDO) (0.5 to 1.5 mV) and epicardial (EPI) (0.5 to 1.0 mV) voltage maps in the right anterior oblique (RAO) projection in the same patient. There are extensive ENDO and EPI signal abnormalities including low voltage and late potentials (black tags) in the inferior free wall, 7 mid-free wall, and right ventricular outflow tract anatomic locations consistent with ECG regional abnormalities.
Abbreviations: PV, pulmonic valve; QRSd, QRS duration; RBBB, right bundle branch block ; TV, tricuspid valve (adapted with permission from Tschabrunn et al)[15]

present with ARVC Task Force Diagnostic Criteria (TFC) have the defined desmosomal gene abnormalities. Furthermore, the desmosomal gene abnormalities occur in approximately 15% of the general population with no apparent phenotypic expression. These observations should force us to question the exact role that genetic abnormalities play in many patients with the diagnostic phenotype. It is possible that the genetic abnormality, rather than causing a dysplastic or progressively degenerative process, is actually playing a primary role enabling or enhancing the disease manifestations and that unique inflammatory triggering or disease-causing mechanisms may occur even in the absence of a genetic predisposition. If this is an accurate reflection of the ARVC pathogenesis, it would have important implications regarding disease progression and recommendations regarding exercise restrictions. Excessive exercise may only precipitate disease progression in a genetically determined degenerative or dysplastic process. Clearly, we must keep an open mind on this subject.

The prevalence of ARVC is estimated at 1:5000 in the general population. ARVC accounts for 5% to 10% of sudden cardiac deaths in the population younger than 35 years.[8,9] The main goal of the management strategy in ARVC is the prevention of sudden cardiac death. Therefore, early detection of the disease and proper evaluation of the risk of lethal VA in order to institute preventive strategies are fundamental. However, despite undeniable improvements in diagnostic tools and therapies, sensitive diagnostic criteria are still lacking and many questions remain regarding optimizing and instituting treatment. We aim to review the current evidence and identify gaps in knowledge and challenges in ARVC diagnosis, localization of the arrhythmogenic substrate, and catheter ablation (CA) in ARVC. We will also discuss important considerations regarding disease progression and management of nonventricular arrhythmic events.

Diagnostic challenges and ARVC Task Force Criteria A definitive diagnosis of ARVC can be made based on histologic evidence of fibrofatty replacement of RV myocardium.[1,10] However, despite optimized electrogram guided techniques developed to overcome limitations due to the occasional patchy nature of the disease, biopsy of the RV free wall is not routinely performed. Clinical symptoms including syncope and palpitations are not systematically present and not specific. For this reason, the clinical diagnosis can often be missed. Consequently, the diagnosis of ARVC is currently based on information obtained from several objective diagnostic clues brought together in the ARVC Task Force Criteria.[11] Diagnosis can only be established if the standardized criteria from different diagnostic categories are fulfilled. The categories include depolarization and repolarization electrocardiography (ECG) abnormalities in V_1–V_3 and characteristic VA, abnormal signal-averaged ECG, RV function and morphology changes on imaging, characteristic histopathology, and family history.[11] The diagnostic value of each single criterion is required to be assessed in the context of combined criteria. Diagnosis is based on the presence of 2 major, 1 major and 2 minor, or 4 minor criteria. Emerging diagnostic modalities and advances in the genetics of ARVC lead to the revision of the initial TFC

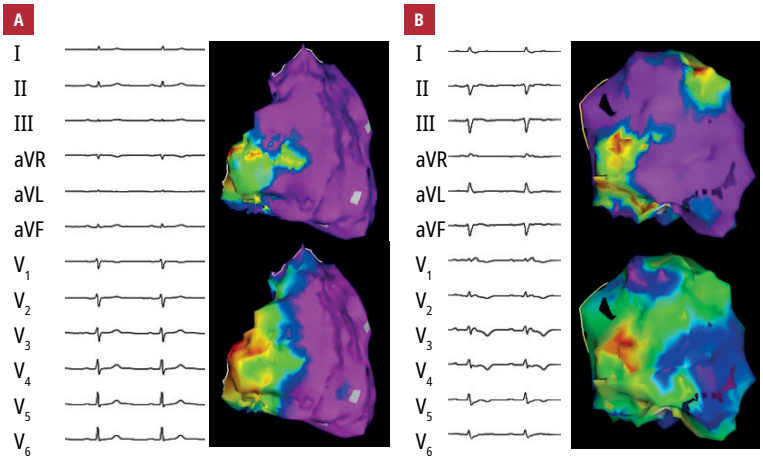

FIGURE 2 Twelve-lead surface electrocardiography (ECG) and representative of endocardial (ENDO) low-voltage abnormalities in right anterior oblique view for bipolar (<1.5 mV; on the top) and unipolar (<5.5 mV; on the bottom) recordings. **A** – a patient with no T-wave inversion. The abnormal area for ENDO bipolar recordings was 8% of total surface vs 28% for unipolar recordings. **B** – a patient with negative T waves in V_1 through V_6 and inferior leads. The abnormal area for ENDO bipolar recordings was 20% of total surface vs 82% for unipolar recordings (reproduced from Kubala et al)[16]

in 2010 resulting in a more sensitive modified TFC.[12] In probands, these criteria are currently applied to establish a diagnosis and are particularly useful to differentiate ARVC from dilated cardiomyopathy and idiopathic RV outflow tract tachycardia. In first-degree relatives who have a 50% probability of inheriting the gene defect, an isolated ECG, arrhythmic or echocardiographic features may be diagnostic without a need to fulfill complete TFC.[13,14] Although the modified TFC represent the most commonly used diagnostic approach, the diagnosis in the early stages of ARVC remains challenging and additional information is available from the ECG, imaging, and direct catheter-based electroanatomic recordings that warrant review.

Additional information from 12-lead electrocardiography and local unipolar recordings

The TFC focus on depolarization and repolarization changes in the anterior precordial leads V_1–V_3. Other ECG leads are typically ignored when searching for diagnostic clues. Described diagnostic surface ECG depolarization abnormalities include epsilon waves, and terminal QRS activation delay longer than 55 ms, measured from the nadir of the S wave to the end of QRS in V_1, V_2, or V_3. Detection and proper localization of arrhythmogenic endocardial and epicardial electroanatomic substrate before the ablation procedure is of major importance and clues can be provided from 12-lead ECG. More recently, we described QRS fragmentation in patients with ARVC and noted that such fragmentation could identify the extent and distribution of endocardial and epicardial voltage abnormalities (FIGURE 1).[15] Surface ECG fragmentation in the inferior leads was associated with inferior RV peri-tricuspid scar and changes in lead aVR and lead 1 identified peri-pulmonic valve scar indicating the value of assessing all 12 ECG leads.

Multilead surface ECG repolarization changes are also associated with larger endocardial and epicardial electroanatomic substrate abnormalities (FIGURE 2).[16] Negative T waves, typically observed in leads V_1 and aVR, may involve other ECG leads and represent a marker of not only greater endocardial but also epicardial extent of disease. Moreover, down-sloping elevated ST-segment pattern in V_1 and V_2 occurs with more unipolar endocardial voltage abnormality and identifies an epicardial VT substrate in the right ventricular outflow tract or RV mid-free wall region and can mimic changes noted in Brugada syndrome.

The electroanatomic substrate can also be approximated with the analysis of ventricular repolarization using local catheter-based unipolar recordings.[17] Areas of local inverted T waves are closely associated with depolarization low-voltage abnormalities on the epicardium. Repolarization abnormalities observed in local unipolar recordings correlate and better define the complex scar architecture than that defined by the analysis of local electrogram depolarization abnormalities alone. Of note, repolarization changes are not always observed in parallel with depolarization abnormalities. Accordingly, depolarization and repolarization abnormalities beyond V_1 to V_3 on 12-lead ECG and local electrogram T wave inversion have a complementary diagnostic value and potential to provide added value to define the location and extent of anticipated substrate abnormalities. Of note, despite the enthusiasm regarding the added information available from all 12 ECG leads, lack of depolarization and repolarization abnormalities on surface ECG should be interpreted cautiously because significant local voltage abnormalities can be still observed without any ECG changes in a significant minority of patients. Other electrocardiographic markers like a wider premature ventricular contraction QRS width, RV paced QRS width, or longer total endocardial activation time may also identify cellular uncoupling particularly with stress and may also be useful to suggest the presence of structural abnormalities in ARVC and facilitate diagnosis.[18,19] Finally, despite losing favor with some clinicians and investigators,[20] the signal-averaged ECG is still used at our institution as a valuable diagnostic test particularly when combined with other diagnostic standard 12-lead ECG clues.[21]

Improving diagnostic imaging clues It can be difficult to properly quantify RV morphological and functional abnormalities. Echocardiography is a first-line diagnostic test and is systematically used to assess the RV size and global function. Although improved image quality

provided by recent ultrasound techniques facilitates accurate diagnosis of ARVC, the complex RV geometry makes the volumetric assessment by transthoracic echocardiography challenging. Quantitative evaluation of RV function using regional strain analyses can be useful in early stages of ARVC and also appears to identify arrhythmic risk.[22] Typically, decreased function of RV basal segments and an abnormal strain pattern have been observed in the presence of early RV involvement.[22] Subclinical localized abnormal substrate can also be identified using RV deformation imaging.[23] The detection of these regional localized morphological changes can improve the ability to differentiate true ARVC from adaptation changes observed in endurance athletes with physiological ventricular enlargement.[24] However, ultrasound diagnostic tools remain limited by visually undetectable mild functional abnormalities and localized scarring. Cardiac MR is currently used in most patients when serious concerns about the ARVC diagnosis are present to best identify regional fibrosis and diastolic dysfunction.[25-28] Use of standardized late gadolinium enhancement (LGE)-cardiac magnetic resonance imaging (MRI) to identify nonconductive areas in the RV and enable noninvasive localization of important VT substrate has been proposed.[27,29] It has been demonstrated that the presence of LGE in the RV was associated with histologic fibrosis when regions with LGE were targeted for biopsy.[27] The regions of the RV epicardium which exhibit increased gadolinium uptake or slow washout onslow washout on late gadolinium enhancement–cardiac magnetic resonance imaging are consistent with lower regional bipolar and unipolar voltage amplitude on epicardial electroanatomic mapping.[29] Despite the progress in image analysis, cardiac MRI is limited by its lower sensitivity in the presence of mild or thinly layered regional pathological involvement and direct electrical recording with endocardial, and in selected cases epicardial catheter-based electroanatomic mapping appears to be the best diagnostic tool when ARVC is suspected.

Use of electroanatomic mapping to help establish diagnosis and define arrhythmogenic substrate There is now more than 20-year experience with electroanatomic endocardial and 12-year experience with epicardial electroanatomic mapping in the setting of ARVC.[30-32] An electroanatomic (EAM) endocardial area is considered abnormal in the presence of contiguous low-voltage electrograms at an amplitude less than 1.5 mV for bipolar or less than 5.5 mV for unipolar signal.[33] To avoid overstating abnormalities, the immediate 1-cm region adjacent to the valve is typically not included in the voltage assessment although electrograms can be directly assessed for late, and split characteristics consistent with disrupted myocardium. The use of unipolar endocardial recordings from the endocardium reflect epicardial bipolar abnormalities and can be helpful to identify transmural or epicardial substrate without requiring access to the epicardium and direct mapping.[34] Epicardial areas of abnormal electrograms are consistently more extensive than endocardial electrogram abnormality.[31,35] The presence of fat and large-vessel coronary vasculature may impact analysis of epicardial bipolar signals and more rigorous methods are required for appropriate detection of areas affected by ARVC.[31] To be defined as abnormal and a potential arrhythmogenic substrate, epicardial electrograms have to demonstrate more rigid low voltage cut-off defined as less than 1.0 mV. They are additionally required to be 1) wide (≥80 ms duration); 2) split (≥2 distinct components with 20 ms isoelectric segment between peaks of individual components); 3) multicomponent or fragmented; or 4) late (distinct electrograms with onset after the end of the QRS complex).[31,36,37]

Catheter-based electroanatomic mapping can identify endocardial and epicardial abnormal areas even in the absence of classic surface ECG changes consistent with the ARVC diagnosis.[16] Moreover, electrophysiological changes have been confirmed to precede detectable morphological changes using conventional cardiac imaging in patients with mutations in desmoplakin.[38] Isolated EAM abnormalities recorded from multiple adjacent sites extending over a 2 cm^2 are consistent with a truly early-stage clinical disease and should be utilized as an important diagnostic tool.

In a recent guideline document, despite the acknowledgment that RV endocardial voltage mapping (EVM) may be of added value for the diagnosis of ARVC since it has the potential to identify and quantify RV regions of electroanatomic scar with low-amplitude electrical signals, typically showing fractionation, double potentials, or conduction delay, the use of right ventricular EAM was not recommended as an appropriate tool to facilitate diagnosis of ARVC.[20] A rationale was provided that indicated "RV EAM is invasive, expensive, and highly operator dependent with a significant risk of inaccurate interpretation of low-voltage recordings in areas of normal myocardium due to suboptimal catheter contact. Moreover, a complete EAM should be also obtained from the epicardial side of RV, which implies a pericardial puncture which is not justifiable solely for diagnostic purposes." Also, it was emphasized in the same document that endocardial voltage map-guided endomyocardial biopsy of the RV free wall is not performed in the majority of interventional labs and cannot be proposed for routine diagnosis. We found those arguments unfounded and equivalent to suggesting that MRI should not be used

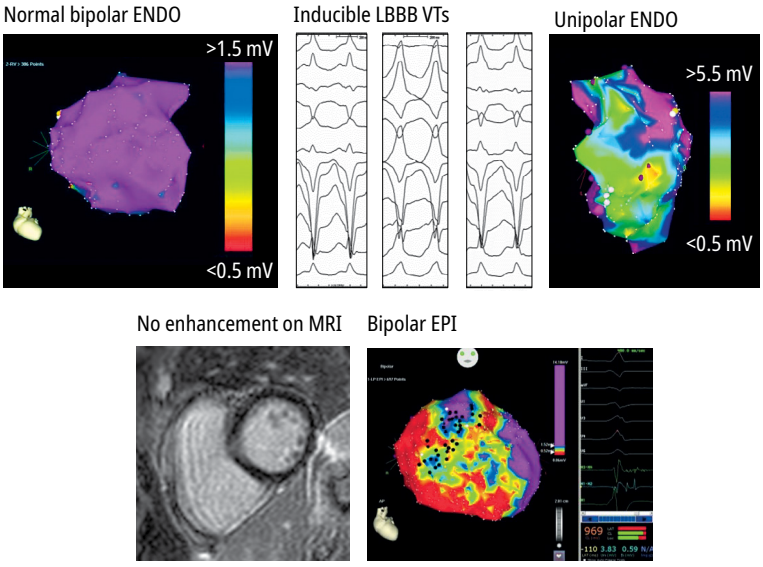

FIGURE 3 Unipolar endocardial electrograms appear to be more sensitive than magnetic resonance imaging for identifying layered epicardial scar. In the example shown, a normal bipolar endocardial voltage map (top left) is present in a patient with right ventricular dilatation but no gadolinium enhancement and no aneurysm formation. The patient had 3 inducible left bundle branch block (LBBB)-type ventricular tachycardias (VTs). The unipolar endocardial voltage map (top right) shows large areas of low voltage that predicted the presence of a layered epicardial scar with dramatic electrogram abnormalities that served as the substrate for all the VTs.

as an imaging standard in diagnosing ARVC simply because not everyone is skilled in accurately imaging and interpreting RV MR images. Electrogram information is, in fact, a very reliable reflection of tissue characteristics. It is incumbent on the electrophysiology community who routinely performs EAM to develop the skill to perform detailed and accurate RV maps. Recognition of the common perivalvular nature of the early or more limited forms of the disease is critical. Developing the ability to loop a catheter to best map the perivalvular region is essential. Contact force information and pacing to confirm contact can be part of the standard mapping technique particularly when technical skillsets are more limited. Attending to electrogram signal characteristics and not just amplitude can provide reassurance that abnormal electrograms are not just caused by poor contact.

It is also important to note that abnormal endocardial unipolar recordings (<5.5mV for the RV free wall), particularly in the setting of normal endocardial bipolar recording, accurately predict a high likelihood of epicardial bipolar electrogram abnormalities. Thus, definition of a high probability of an arrhythmia substrate can be provided by unipolar endocardial recordings without the need for direct epicardial recordings. In equivocal cases, the upper limit of the unipolar slider bar can be reduced to 4.5 mV to confirm an even higher probability that a confluent area of low endocardial unipolar voltage truly reflects an abnormality on the epicardium. In selected patients persistent inducible left bundle branch VT coupled with a unipolar voltage abnormality marks the presence of an epicardial substrate with a very high probability and appears more sensitive than MRI for identifying an epicardial layered scar (FIGURE 3).

Once the diagnosis is established, risk stratification can be performed at the time of voltage mapping to identify candidates with inducible monomorphic VT who would benefit from implantable cardioverter-defibrillator (ICD). Higher arrhythmic risk has been reported in patients with a greater number of inverted T waves, more extensive abnormalities on a signal-averaged ECG, and more extensive area of abnormal electrograms on electroanatomic mapping.[18,19,39,40]

Challenges in substrate localization and overcoming ablation challenges There are fundamental differences between ischemic scar typically spreading in an endocardial-to-epicardial direction and the fibrofatty tissue replacement that typically extends from the epicardium to the endocardium seen in ARVC.[41] In most ARVC patients, the endocardial bipolar voltage abnormalities are typically perivalvular and affect predominantly the RV free wall with minor extension to involve the septum.[30] Right ventricular apical scar and VT substrate is uncommonly (<2%) identified suggesting that there is not a true triangle of dysplasia but predominantly perivalvular scar extending toward but typically sparing the apex (27). Left ventricular (LV) involvement is observed in one-third of patients with ARVC but as indicated VT originating from the LV is uncommon.[42] Epicardial areas of abnormal electrograms are consistently more extensive than endocardial electrogram abnormality.[31,35] The presence of fat and large-vessel coronary vasculature may impact the analysis of epicardial bipolar signals and more rigorous signal analysis is required for appropriate detection of dysplastic areas.[31] Careful analysis of both surface ECG manifestations and cardiac MRI findings can provide preprocedural information about the extent and location of the RV substrate. Direct catheter-based voltage mapping and electrogram analysis helps define the substrate-based ablation targets when VT is not tolerated hemodynamically and cannot be mapped. Inducible VTs are frequently poorly tolerated and the majority of patients referred for CA present with unstable VTs preventing accurate definition of critical sites for ablation. The approximate site of origin of spontaneous and induced VTs is first determined by analyzing the 12-lead ECG VT morphology.[33,43] For unmappable VTs, the site of origin is also approximated by the site of pace mapping that generates QRS complexes similar to those of VTs.[30,33,44] In these cases, a limited activation and entrainment mapping information, when available, can

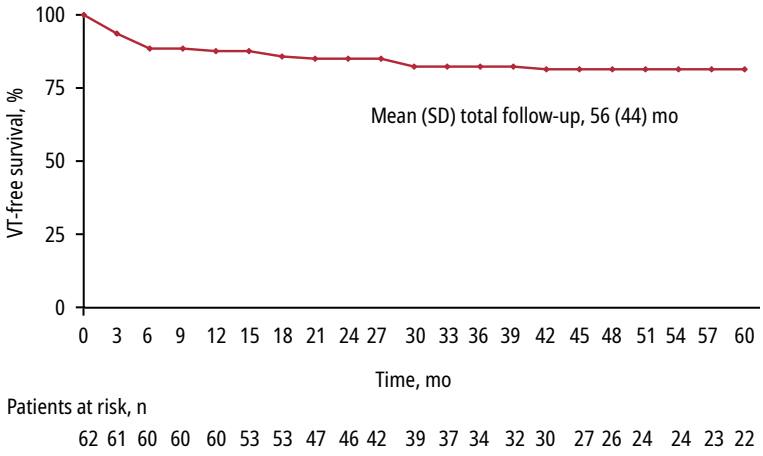

FIGURE 4 A Kaplan–Meier survival curve showing multiple procedure freedom from any sustained ventricular arrhythmia. Total number of patients followed from the last procedure is indicated at the bottom of the figure (modified from Santangeli et al)[54]

be complementary. Targets for CA will be identified on the basis of low voltage, the presence of late potentials and pace-mapping matches associated with a long stimulus to QRS interval. Lesions sets can be clustered around targets and extend as lines to the valve annuli and cross through abnormal substrate. Identification of critical sites for VT circuit can be further defined using the VT mapping techniques including activation, entrainment, and pace mapping using standard criteria.[33,44,45] Typically, the isthmus sites of mappable VT, which are appropriate ablation targets, demonstrate entrainment with concealed fusion (QRS during entrainment matches exactly that of the VT) with return cycle length within 30 ms of VT cycle length. Characteristically, VT circuits and successful ablation sites cluster around the tricuspid valve and the pulmonic outflow tract and are situated within abnormal voltage areas.[30,46] Therefore, an appropriate identification of abnormal myocardium (<1.5 mV) differentiated from the valve anulus is needed and detailed perivalvular voltage mapping is the first step to optimizing substrate definition and endocardial ablation success.

For many patients, the VT circuit appears to be compartmentalized to epicardial substrate and, despite a thin walled RV endocardial ablation, is ineffective. Even in experienced centers, the effectiveness of endocardial only ablation is 40% to 50%. This compartmentalized substrate includes a subepicardial scar which constitutes a barrier to radiofrequency energy delivery and conduction, resulting in delayed and independent epicardial activation and need for epicardial access and direct mapping and ablation.[32] Access to the epicardium is typically gained by a percutaneous subxiphoid route. A posterior approach to gain intrapericardial access is typically used because of the frequently encountered RV dilatation. Several unique features differentiating epicardial from endocardial ablation need to be considered. The presence of coronary vessels end epicardial fat measuring >5 mm can diminish the signal and pacing capture.[47,48] It has also been demonstrated that epicardial ablation over the sites with >10 mm of epicardial fat can be ineffective.[49] The integration of contrast-enhanced multidetector computed tomography allowing for imaging myocardial fat with 3 dimensional electroanatomic mapping provides valuable information on VT substrate localization and allows for direct visualization of the coronary arteries preventing coronary injury during ablation.[50] Moreover, epicardial ablation with different orientation of the catheter and lower contact force than on the endocardium can result in less effective lesions. Reduction of rates of irrigation flow and of the osmolarity of the irrigation solution during epicardial ablation may enhance ablation efficacy.[51,52] Of note, detailed analysis of endo and epicardial standard depolarization abnormalities display sampling density limitations. Recent mapping innovations, including ripple analysis, can be useful for better delineation of the arrhythmogenic substrate targeted with CA. Ripple mapping displays every deflection of a bipolar electrogram and enables the visualization of slow conduction channels. In patients with ARVC, ripple mapping conduction channels have been shown to be related to RV regions displaying LGE on preprocedural cardiac MRI and to the critical isthmus sites during entrainment.[53]

It has been demonstrated that a simultaneous epicardial and endocardial approach for VT mapping and extensive ablation was feasible and resulted in elimination of recurrent VT and improvement in long-term outcomes and the need for antiarrhythmic drug therapy (FIGURE 4).[31,35,54] Of note, in a multicenter study including patients treated with CA without ICD implantation, freedom from recurrent VT in a 46-month follow-up was 81%.[55] Hence, CA of VT in ARVC cannot be considered as only a palliative procedure to reduce the frequency of VT episodes but potentially a "curative" or at least long-term beneficial procedure in most patients. A combined endo / epi strategy significantly reduces the need for antiarrhythmic therapy.[54] In order to reduce VT recurrences, CA should be systematically preceded by a detailed electro-anatomic mapping and extensively target the endo and epicardial substrate using irrigated catheters to optimize success.[31,35,56-58]

By minimizing the risk of recurrent VT with CA, a question arises whether the indication for intravascular ICD implantation is still required and whether a subcutaneous ICD device can be used to minimize lead-related complications in young patients and further studies are warranted to determine the respective roles of device and ablative therapy. Current ablation guidelines recommend CA for sustained VT in ARVC

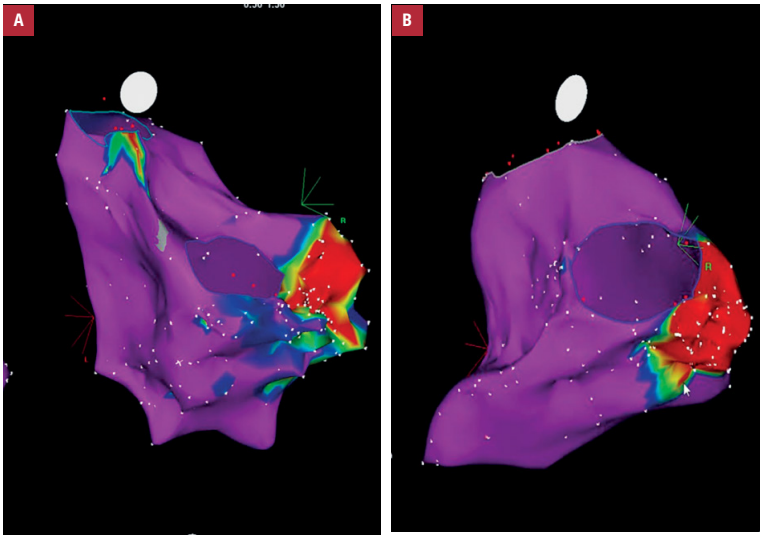

FIGURE 5 Comparison of bipolar voltage maps over time. Patient with arrhythmogenic right ventricular cardiomyopathy who underwent 2 detailed sinus rhythm electroanatomic endocardial voltage maps (31 months between maps; [**A**] baseline; [**B**] follow-up). Normal-voltage regions are shown in purple. Very low–voltage areas are shown in red. Border zones are multicolored. No significant progression of bipolar voltage scar was observed (bipolar: 25 vs 19 cm^2) (reproduced from Briceno et al)[61]

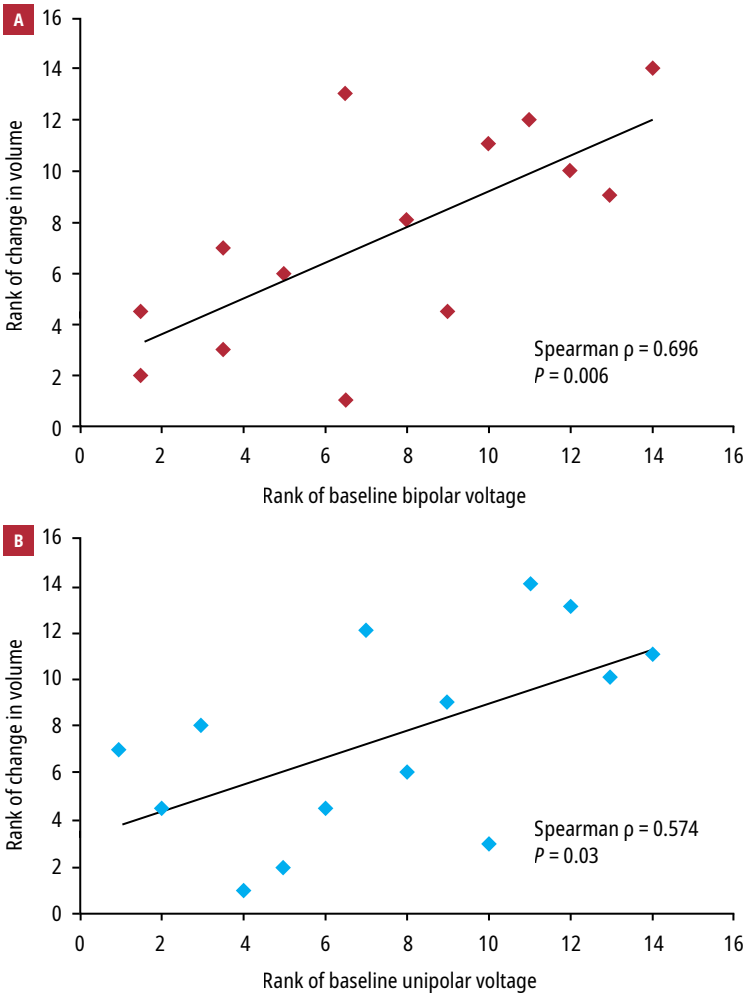

FIGURE 6 Spearman rank correlations between change in right ventricular (RV) volume and baseline scar. Larger bipolar and unipolar voltage indicated scars at baseline were associated with a significant increase in RV volume (Spearman correlation coefficient, 0.6965; $P = 0.006$; Spearman correlation coefficient, 0.5743; $P = 0.03$, respectively) (modified from Briceno et al)[61]

not only for patients in whom antiarrhythmic drug therapy is ineffective or not tolerated (class I recommendation) but also if not desired or preferred (class IIa recommendation).[59] In patients with ARVC who failed 1 or more attempts of endocardial VT CA, an epicardial approach added to the endocardial ablation is considered as a class I recommendation.

Scar progression in arrhythmogenic right ventricular cardiomyopathy It had been initially reported that VT recurrence after CA is common and is due to the progression of disease and fibrofatty replacement that should be manifest by a greater extent of bipolar and unipolar electrograms abnormalities.[60] Knowledge about the progression of the RV pathological process and the arrhythmogenic risk in ARVC are of major importance for optimal management and timing of interventional treatment. The growing available body of evidence shows lack of uniform progression of endocardial scar in patients with ARVC presenting for VT ablation and document that an increase in scar size greater than 10% defined by progression of low-voltage abnormalities over a 3 to 5 year period is uncommon (FIGURE 5).[61,62] Progression of abnormal endocardial voltage mapping is limited to a minority of patients meeting TFC at initial presentation. Furthermore, most of the recurrent VAs (72%) originate from regions of prior scar based on detailed mapping.[61-63] In addition, arrhythmogenic substrate responsible for recurrent VT remained confined to the originally defined area of bipolar voltage abnormality.[61] Hence, it should not be surprising that given the absence of rapid disease progression that extensive substrate-based electroanatomic guided and entrainment mapping guided VT CA produced long-term efficacy in the control of VAs.

Although scar progression is uncommon, progressive dilation of the RV is typically observed and has been demonstrated in several studies.[14,61,62,64] An increase greater than 20 ml in RV volume was seen in 77% of patients between initial and redo ablation procedures.[62] Voltage indexed scar area at baseline, but not changes in scar size over time, was associated with progressive increase in RV volume consistent with continuous adverse remodeling being associated with larger baseline scar area (FIGURES 5 and 6).[61] More research is needed to better understand and define measures to prevent adverse RV remodeling in ARVC.

Managing arrhythmogenic right ventricular cardiomyopathy after ventricular tachycardia is controlled Atrial arrhythmias are commonly observed in patients with ARVC with the frequency estimated at 34%.[65] Given an average observed age of 38 years, this represents an extremely high incidence. Cavotricuspid isthmus–dependent atrial flutter, rapid focal atrial tachycardias,

and atrial fibrillation with triggers from the right atrium are all commonly observed. Our threshold for creating a cavotricuspid line at the time of VT ablation is very low. Optimizing device programming to prevent VT therapy delivery for supraventricular tachycardia is also essential.

Tricuspid valve regurgitation due to severe annular dilation and perivalvular scaring is common in ARVC. In turn, moderate to severe tricuspid valve regurgitation will contribute to RV dilation and progression of RV failure. Tricuspid valve annuloplasty or replacement has not been systematically studied in ARVC. Further studies are needed to evaluate the role of tricuspid valve interventions and the timing of such procedures. The place of new percutaneous tricuspid repair techniques proposed in selected patients with severe tricuspid regurgitation also needs to be defined in ARVC.

Finally, although the need for cardiac transplantation due to uncontrolled VAs should be rare, progression of severe RV failure and the less common development of biventricular failure remains a significant risk. The most advanced late phase of ARVC is characterized by right ventricular failure due to loss of myocardium with severe dilation, systolic dysfunction, and an increase in right atrial and right ventricular thrombosis because of a low flow state. Evidence of severe RV failure including severe hepatic congestion and liver failure can ultimately result in the need for liver transplant, in addition to heart transplant (HT). Heart transplant before severe liver decompensation may be required to prevent the need for double organ transplant.

In patients with significant LV systolic impairment, manifest left sided heart failure, intracardiac thrombosis, and systemic thromboembolism can mimic dilated cardiomyopathy.[1,66] A significant decrease in biventricular function, although not uniformly noted, was observed in one-third of patients with ARVC in one report.[42] Genetic status affects the clinical course of patients with ARVC and observed LV involvement.[67,68] The degree of LV involvement depends on the genetic predisposition and is higher among phospholamban mutation carriers compared to desmosome ARVC mutations.[42,69] Also desmoglein-2 mutation carriers were found to be at higher risk of end-stage heart failure compared to the plakophilin-2 mutation, the most common ARVC-associated gene.[70] This data supports careful hemodynamic monitoring of ARVC patients coupled with detailed genetic analysis in all patients with the diagnosis. Further research is needed to determine whether novel pharmaceutic agents used in heart failure are of value in the treatment of patients with ARVC with predominant RV failure. Although specific recommendations on indications for listing ARVC patients for HT are lacking, refractory congestive heart failure will prompt the physician to discuss this therapeutic option.[71,72] In reported registries, patients with ARVC who underwent HT were younger and were predominantly referred for HT due to heart failure.[73] Survival in patients with ARVC after HT was similar to restrictive, hypertrophic, and dilated cardiomyopathies and significantly better than ischemic cardiomyopathy.[74] Accurate risk stratification and appropriate selection of patients with the most severe form of the disease for HT is challenging. Prognostic assessment of functional RV parameters showed that the dilation of right-sided cardiac chambers and tricuspid annulus plane systolic excursion were highly predictive of major adverse cardiovascular events including HT.[64] However, sufficient data on optimal timing of HT in advanced ARVC is still lacking.

Conclusions ARVC diagnostic and therapeutic challenges have been overcome particularly as it relates to the management of VAs. Rapid RV scar progression is uncommon. Combined and detailed endo- and epicardial catheter mapping and ablation produces good long-term outcomes and reduces the need for drug therapy.

Despite the progress, many questions remain regarding ARVC. What triggers the initial scar formation and uncommon progression? How to prevent and manage adverse RV remodeling? How to better predict and treat atrial arrhythmias and best prevent intracardiac and device lead thrombosis related to low flow states? How to manage progressive RV and LV dysfunction and delay or prevent the need for transplant? These are just a few of the questions indicating that although many challenges have been overcome, more remain to be addressed. Ongoing research will continue to allow for better understanding of this pathological condition and further improve outcome.

ARTICLE INFORMATION

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