Lack of Uniform Progression of Endocardial Scar in Patients With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy and Ventricular Tachycardia

Michael P. Riley, MD, PhD; Erica Zado, PA-C; Rupa Bala, MD; David J. Callans, MD; Joshua Cooper, MD; Sanjay Dixit, MD; Fermin Garcia, MD; Edward P. Gerstenfeld, MD; Mathew D. Hutchinson, MD; David Lin, MD; Vickas Patel, MD, PhD; Ralph Verdino, MD; Francis E. Marchlinski, MD

Background—The endocardial substrate for ventricular arrhythmias in patients with arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) is thought to be caused by a progressive degenerative process. Many clinical decisions and treatment plans are guided by this pathophysiologic assumption, but the extent of progression of macroscopic endocardial scar and right ventricular (RV) dilatation have not been assessed.

Methods and Results—Eleven patients with ARVD/C and ventricular tachycardia had 2 detailed sinus rhythm electroanatomic endocardial voltage maps (average, 291±122 points per map; range, 114 to 558 points) performed a mean of 57 months apart (minimum, 9 months) as part of ventricular tachycardia ablation procedures. Voltage-defined scar (<1.5 mV) and RV volume were measured by area and volume measurement software and compared. Two of the 11 patients had a clear increase in scar area (47 cm²; 32 cm²) confirmed by visual inspection. The remaining 9 (81%; 95% CI, 48% to 98%) patients had no increase (<10-cm² difference) in scar area between studies. In contrast, 10 of the 11 patients had a significant increase in RV volume, with an average increase of 24% (212±67 mL to 263±52 mL; P<0.01).

Conclusions—In patients with ARVD/C and ventricular tachycardia, progressive RV dilatation is the rule, and rapid progression of significant macroscopic endocardial scar occurs in only a subset of patients. These results have important management implications, suggesting that efforts to prevent RV dilatation in this population are needed and that an aggressive substrate-based ablation strategy offers the potential to provide long-term ventricular tachycardia control. (Circ Arrhythm Electrophysiol. 2010;3:332-338.)

Key Words: cardiomyopathies ■ catheter ablation ■ endocardial mapping ■ ventricular remodeling ■ ventricular tachycardia

Arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) is a complex disorder that leads to structural abnormalities of the right ventricle (RV) characterized by fibrofatty infiltration, ventricular dilatation, and segmental wall motion abnormalities.1–3 These structural changes coupled with extensive perivalvular fibrosis create the substrate for left bundle branch morphology ventricular tachycardias (Vrs).4–6 Left ventricular involvement may occur.7

Clinical Perspective on p 338

The exact etiology of ARVD/C has not been fully defined. At least 5 genes have been implicated in ARVD/C, highlighting that there likely is a considerable level of variability in the pathogenesis of this disorder.8,9 It is unclear whether the disease represents a continuously progressive degenerative process or one with extended periods of anatomic stability followed by step-like deteriorations with a possible triggering event.10–12 The complex interrelationship between various genetic components and the possible role of acute inflammatory triggering events may favor the latter hypothesis. The relatively low incidence of a positive family history in ours and many series of patients with ARVD/C suggests that environmental or acquired factors may play an important role in ARVD/C. Because patients with sustained VT or syncope typically present at a young age, a great deal of effort has been devoted to finding the means to effectively treat VT in these patients. Included in this effort has been the use of implantable cardioverter defibrillators, antiarrhythmic drugs, lifestyle modification, and catheter ablation therapy.5,13–17 A critical aspect of long-term management is designing treatment plans that will remain effective over time. The belief that ARVD/C is a degenerative disorder has greatly influenced treatment plans, specifically leading some to propose
that catheter ablation is inherently limited as a long-term strategy. A detailed examination of the nature of ARVD/C progression has not been demonstrated; thus, this study evaluated the progressive nature of macroscopic endocardial scar and RV dilatation over time in a series of patients presenting for repeat electrophysiology study and VT ablation.

Methods

Study Inclusion Criteria
As part of our clinical routine, we perform detailed sinus rhythm activation maps in all patients undergoing VT ablation in the setting of structural heart disease. The study population included those patients presenting with left bundle branch block VT in the setting of ARVD/C. The diagnosis of ARVD/C was established based on task force criteria. Because the aim of the study was to assess longitudinal changes in endocardially defined macroscopic voltage abnormalities, patients with procedures separated by at least 9 months were included in the study.

Clinical Characterization of Patients
Detailed personal and family histories, clinical and ECG characteristics, and echocardiograms were obtained in all patients. All patients included in this study had cardioverter defibrillators implanted either before or immediately after their first ablation.

Electrophysiological Evaluation
All procedures were performed following the institutional guidelines of the University of Pennsylvania Health System (Philadelphia, Pa) after obtaining informed consent. All patients underwent electrophysiological guided 3D electroanatomic mapping and ablation for sustained VT as defined by ECG, implantable cardioverter defibrillator shocks, or both. Sinus rhythm 3D bipolar electroanatomic voltage maps of the entire RV endocardium were created in all patients at each procedure using either a 3.5- or 4-mm bipolar mapping catheter, both with a 2-mm ring. The bipolar signals were filtered at 30 to 400 Hz and displayed at 200 mm/s speed on the CARTO system. The peak-to-peak signal amplitude was measured automatically. A 3D anatomic shell of the RV endocardium was constructed, and the electrogram signals were coupled and displayed as color gradients on a bipolar voltage map. Those areas with contiguous low bipolar voltage (<1.5 mV) extending >1 cm from the valve plane defined by fluoroscopy and equal A and V electrogram were defined as being consistent with scar. Dense, low-voltage areas were arbitrarily defined as <0.5 mV for display purposes, and the border zone was defined as a transition between dense low-voltage and normal tissue (0.5 to 1.5 mV).

Scar Area and Chamber Volume Measurements
The 3D electroanatomic endocardial RV bipolar voltage maps from all patients were analyzed on either the older UNIX-based system or the more recent Windows platform provided by Biosense Webster (Diamond Bar, Calif). On both systems, the fill thresholds were adjusted to no greater than 20, and the bipolar voltage settings set to >1.5 mV for normal signal. Using these settings and incorporated software, we measured the chamber volume, and the area of confluent low-voltage scar was measured accurately with planimetry to calculate a defined surface area (Figure 1). All repeat measurements were performed with the operator blinded to the results of the
Eleven patients (9 men; 2 women) met the study inclusion criteria (Table 1). All 11 patients met task force diagnostic criteria for ARVD/C and age of presentation for the 11 patients included in this study. RBBB indicates right bundle branch block; . . ., no data.

Presented are the time interval between first and last ablations and task force criteria for ARVD/C and age of presentation for the 11 patients included in this study. RBBB indicates right bundle branch block; . . ., no data.

**Table 1. Clinical Characteristics of Study Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period Between Ablations, mo</th>
<th>Structural Depolarization</th>
<th>Repolarization</th>
<th>Arrhythmia</th>
<th>Tissue</th>
<th>Family History</th>
<th>Age at Diagnosis, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>Major</td>
<td>Major</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
<td>Major</td>
<td>Paced</td>
<td>Paced</td>
<td>Minor</td>
<td>No</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Major</td>
<td>Major</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Major</td>
<td>None</td>
<td>RBBB</td>
<td>Minor</td>
<td>+ fibrosis</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>Major</td>
<td>None</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>Major</td>
<td>Minor</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>Major</td>
<td>Minor</td>
<td>RBBB</td>
<td>Minor</td>
<td>No</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>Major</td>
<td>None</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>89</td>
<td>Major</td>
<td>Major</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>Minor</td>
<td>Minor</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>79</td>
<td>Major</td>
<td>Major</td>
<td>Minor</td>
<td>Minor</td>
<td>No</td>
<td>17</td>
</tr>
</tbody>
</table>

Presented are the time interval between first and last ablations and task force criteria for ARVD/C and age of presentation for the 11 patients included in this study. RBBB indicates right bundle branch block; . . ., no data.

**Sinus Rhythm 12-Lead ECG Progression**

The sinus rhythm 12-lead ECG also was assessed to determine whether any progressive changes in the ECG could be identified. Specifically, the QRS width, limb lead amplitude, the presence of delayed S wave in the precordial leads and the presence of epsilon waves were assessed at both initial and time of repeat study. This visual analysis was performed by an electrophysiologist blinded to the date of the ECG and any clinical history about the patient except the diagnosis of ARVD/C. Antiarrhythmic drug therapy was documented at both procedures.

**Statistical Analysis**

Continuous variables (expressed as mean±SD when normally distributed) were compared using paired Student t test. A P≤0.05 was considered statistically significant.

**Results**

**Patient Population**

Eleven patients (9 men; 2 women) met the study inclusion criteria (Table 1). All 11 patients met task force diagnostic criteria for ARVD/C (Table 1) and presented at an average age of 34±16 years (range, 14 to 60 years). All patients had sustained VT and underwent initial and then repeat catheter ablation procedures for VT episodes. The time between the initial and repeat ablation procedures averaged 57±31 months (range, 9 to 96 months).

**Electroanatomic Mapping and Scar Area**

Detailed sinus rhythm electroanatomic voltage mapping of the RV was performed in all patients at each procedure before induction of VT and ablation. An average of 291±122 points (range, 114 to 558 points) was obtained to generate each voltage map. As described earlier, to account for differences in sampling between studies and the effect of prior ablation lesions near scar border zones, an increase in scar area was considered significant if the area increased by >10 cm², which is twice the maximum estimated measurement error. Of note, 10 cm² represents a very small area (~4%) compared to the overall average RV area of 226±35 cm² at initial and 267±38 cm² at repeat study.

Using the specified criteria, only 2 of the 11 patients had an increase in scar area between the 2 studies (Figures 2 and 3). Patient 6 had an increase in total scar area of 47 cm² that involved the inferior pericristuspid valve region. Patient 9 had an increase in scar area of 32 cm² that involved the free wall of the RV. In contrast, the other 9 patients did not show an increase in scar area between the 2 studies (Figures 3 and 4). When all 11 patients were compared together, the scar area increased from an average of 46.8 cm² on the first procedure to an average of 54.8 cm² on the second procedure. This increase is not significant (P=0.28). Excluding patients 6 and 9 from the comparison yielded an average scar area of 56.1 cm² on the first procedure and 55.1 cm² on the second procedure.

Despite subtle visual differences between longitudinal studies reflecting inherent differences in sampling and display of mapping data, the bipolar voltage maps showed remarkable overall similarity in location and size of the area of low voltage over time. These findings appear inconsistent with a progressive process, at least as measured from the endocardium.

**RV Volume**

The maps also were analyzed using volume measurement software to assess for changes in RV chamber size over time.
To account for differences in sampling between studies, an increase in chamber volume was considered significant if the volume increased by >20 mL. Ten of the 11 patients had an increase in RV volume of >20 mL (Figure 5). The average increase in RV volume was 24% (212 ± 67 mL to 263 ± 52 mL; \( P = 0.01 \)). The nearly uniform finding of RV dilatation confirms that this is a very common feature of the disease process in patients with ARVD/C and recurrent VT. Interestingly, the 1 patient who did not exhibit an increase in RV chamber volume was the patient who had the most extreme chamber dilatation.

**VT Morphologies**

For each procedure, we reviewed the VT morphologies induced and the morphology deemed the clinical VT (Table 2). We also cataloged the number and location of ablation lesions delivered during procedure 1. For 8 patients, the VT deemed clinical on the second procedure was different than the clinical VT targeted during the first procedure. For 2 patients, the morphology appeared to be very similar. For 1 patient, no VT was induced on the second procedure.

**ECG Changes**

Baseline ECGs from all patients were evaluated for the following characteristics: QRS width, limb-lead amplitude, the presence of a delayed S wave in the precordial leads, and the presence of epsilon waves. This analysis was performed by visual inspection on ECGs obtained before the first ablation procedure and at either their second procedure or their most recent outpatient follow-up (when available). There were no changes in any of the ECG characteristics examined. Shown in Figure 6 are the ECGs from the 2 patients who manifested an increase in endocardial scar area over time.

**Discussion**

This study is the first to our knowledge that has examined the extent to which the endocardial scar as measured by bipolar voltage mapping in patients with ARVD/C is progressive. The results of this study question the widespread impression that ARVD/C is universally a progressive disease process. In our group of 11 patients, only 2 showed evidence of progressive endocardial scarring as measured by detailed bipolar voltage mapping. Importantly, if recurrent VFs are due to progressive scarring and fibrofatty infiltration of the RV, then our patient population would have been expected to be enriched with those with the most dramatically progressive changes, and in fact, this was not observed in our patients.

**Lack of Endocardial Scar Progression**

The findings observed in this group of patients draw attention to the most appropriate treatment strategy for dealing with recurrent VT in patients with ARVD/C. A recent publication suggested that a strategy of VT ablation has a poor long-term success rate, a claim attributed to a progressive process. Based on the results presented here, progression of RV
endocardial scar appears to be limited to a subset of patients who meet criteria for ARVD/C. To the extent that these patients are not suffering from a progressive process, control of ventricular arrhythmias should be attainable. In this view, a sufficiently aggressive approach using electroanatomic mapping to precisely define the abnormal substrate coupled with extensive ablation may sufficiently modify the substrate in many patients so as to make future VT unlikely. Rather than uniform progression of abnormal substrate, this group of patients developed recurrent VT, necessitating additional ablation for 1 of 2 reasons. The first is that early in our experience, we likely delivered inadequate endocardial substrate modification with extensive ablation partly due to concerns about a thin-walled ventricle. With the use of intracardiac echocardiography, we now know that the abnormal substrate in these patients often is quite thick, permitting aggressive high-power ablation.14,18 The second reason for a failed endocardial ablation is the need for epicardial ablation.18

Progressive RV Dilatation

The lack of uniform scar progression is in contrast to the nearly uniform evidence for progressive and statistically significant RV chamber dilatation in this patient population. Indeed, some of the patients experienced a very significant increase in chamber size. The 1 patient who did not appear to have further dilatation already had an extremely dilated RV at baseline. This finding is very important and draws attention to the fact that many of these patients will experience worsening RV function over time and develop signs and symptoms of right-sided heart failure as a result of progressive RV dilatation. Whether this extent of RV dilatation also occurs in patients with ARVD/C who do not have recurrent VT is not known. Precisely why RV dilatation occurs in these patients has not been defined but likely has some similarities to the changes observed in left ventricular size and function following myocardial infarction. In the case of postmyocardial infarction remodeling, complex and progressive changes to left ventricular size and function occur in the setting of stable scar.19 In the case of patients with ARVD/C, maladaptive changes to chamber size and function may be caused by neurohormonal influences; local factors, including those caused by wall stress (tethering to scar); and tricuspid regurgitation. The tricuspid regurgitation present in these patients is both a cause and an effect of RV dysfunction and dilatation. Implantable cardioverter defibrillator leads and pulmonary hypertension exacerbate the extent of tricuspid regurgitation. This progressive RV dilatation should direct increased attention to the development and implementation of therapeutic modalities to reduce or attenuate this progressive process. In the case of left ventricular dysfunction, angiotensin-converting enzyme inhibitors; β-blockers; and, when appropriate, mitral valve surgery play a role in attenuating adverse remodeling.19 Whether these medications or others could play a role in the attenuation of the RV dilatation in patients with ARVD/C remains to be investigated.
Changes in Clinical VT Morphologies

It is interesting that many of the clinical VTs targeted on the second procedure were different compared to the first procedure, which may suggest that the substrate, though not expanding, can change over time and lead to new viable circuits, much as the substrate of healed infarction can change over time. A sufficiently aggressive substrate ablation and modification may offer the possibility of preventing new VT morphologies. We believe that this question remains open and an area for further investigation.

Limitations

There are several limitations relevant to the results of this study. One of the most important is the inherent differences in sampling of points during 2 different electroanatomic mapping procedures. Point-by-point mapping by definition does not sample the entire endocardium, and extrapolation between points may influence the size and contour of the regions of low voltage. That said, it is our standard to survey the entire endocardium and then perform very detailed mapping of regions of abnormality; thus, we are confident that differences related to sampling are small.

Second, it is our experience that aggressive ablation in normal-voltage myocardium (no longer our practice for patients with ARVD/C), especially with cooled-tip catheters, results in sufficient tissue destruction to cause extensive scarring. To the extent that all patients underwent ablation for VT during their first procedure, this might be expected to increase the amount of scarring and may account for some of the increase in the 2 patients in whom we did observe an increase in scar area.

Third, our analysis was restricted to the endocardium of the RV. When we have accessed the epicardium for mapping and ablation, we have observed extensive regions of low voltage.18 Because the combined approach of endocardial and
epicardial mapping and ablation appears to have a high level of successfully controlling ventricular arrhythmias in our patients, very few have undergone serial epicardial mapping. It is possible that although the endocardial substrate shows very limited progression in the majority of patients, there is progression along the epicardial and intramyocardial regions.

Sources of Funding

None.

Disclosures

Dr Marchlinski has a research grant and has been on the advisory board of Biosense Webster, Inc. Dr Gerstenfeld has a research grant and has been on the advisory board of Biosense Webster, Inc. Dr Callans has been on the advisory board of Biosense Webster, Inc.

References


CLINICAL PERSPECTIVE

Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C) is a complex disorder with poorly understood pathophysiology. We sought to examine the extent to which the RV endocardial scar area and chamber dilatation associated with ARVD/C increased progressively over time. Eleven patients with ARVD/C had RV scar area and volume measured on 2 occasions a mean of 57 months apart as part of ablation procedures for ventricular tachycardia. We found that although RV volume nearly universally increased over time (10 of 11 patients), the low-voltage area increased in only a small minority (2 of 11 patients). These findings have important prognostic and management implications for patients with ARVD/C. They suggest that in the absence of scar enlargement, efforts to control scar-based ventricular tachycardia with ablation should be possible. In addition, future research is needed to define ways to prevent RV dilatation.
Lack of Uniform Progression of Endocardial Scar in Patients With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy and Ventricular Tachycardia

Michael P. Riley, Erica Zado, Rupa Bala, David J. Callans, Joshua Cooper, Sanjay Dixit, Fermin Garcia, Edward P. Gerstenfeld, Mathew D. Hutchinson, David Lin, Vickas Patel, Ralph Verdino and Francis E. Marchlinski

Circ Arrhythm Electrophysiol. 2010;3:332-338; originally published online June 17, 2010; doi: 10.1161/CIRCEP.109.919530

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/3/4/332

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org/subscriptions/