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

Running title: Riley et al.; Lack of uniform scar progression in ARVD/C

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Abstract

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

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

**Conclusions:** In patients with ARVD/C and VT: 1) progressive RV dilatation is the rule; 2) rapid progression of significant macroscopic endocardial scar occurs in only a subset of patients. These results have important management implications and suggest efforts to prevent RV dilatation in this set of ARVD/C patients are needed and that an aggressive substrate based ablation strategy offers the potential to provide long term VT control.

**Key words:** cardiomyopathy, catheter ablation, mapping, remodeling, tachyarrhythmias
Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a complex disorder leading to structural abnormalities of the right ventricle characterized by fibrofatty infiltration, ventricular dilatation and segmental wall motion abnormalities. These structural changes coupled with extensive perivalvular fibrosis create the substrate for left bundle branch morphology ventricular tachycardias. Left ventricular involvement may occur. The exact etiology of ARVD/C has not been fully defined. At least five genes have been implicated in ARVD/C highlighting that there likely is a considerable level of variability in the pathogenesis of this disorder. It is unclear whether the disease represents a continuously progressive degenerative process or one with extended periods of anatomic stability followed by a step like deteriorations with a possible triggering event. The complex inter-relationship 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 ARVD/C patients suggests that environmental or acquired factors may play an important role in ARVD/C. As patients typically present at a young age with sustained ventricular tachycardia or syncope, 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 (ICDs), anti-arrhythmic drugs, lifestyle modification and catheter ablative therapy. A critical aspect of long-term management is designing treatment plans that will remain effective over time. The belief that ARVD/C is a progressive 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. The purpose of this study was to
evaluate for 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 LBBB ventricular tachycardia 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 ICDs implanted either prior to or immediately following their first ablation.

Electrophysiologic evaluation

All procedures were performed following the institutional guidelines of the University of Pennsylvania Health System after obtaining informed consent. All patients underwent EP guided 3D electroanatomic mapping and ablation for sustained ventricular tachycardia as defined by ECG and/or ICD shocks. Sinus rhythm 3D bipolar electroanatomic voltage maps of the entire
right ventricular endocardium were created in all patients at each procedure using either a 3.5 or 4mm bipolar mapping catheter (Biosense-Webster Inc, both with a 2mm ring. The bipolar signals were filtered at 30 to 400Hz and displayed at 200mm/sec speed on the CARTO (Biosense Webster Inc., Diamond Bar, CA) system. The peak to peak signal amplitude was measured automatically. A three-dimensional anatomical 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. For display purposes dense low voltage areas were arbitrarily defined as <0.5mV for display purposes, and the border zone defined as a transition between dense low voltage and normal tissue (0.5 to 1.5mV).

**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 recently employed Windows platform provided by Biosense Webster. 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 the chamber volume was measured and the area of confluent low voltage “scar” measured accurately utilizing planimetry to calculate a defined surface area (Figure 1). All repeat measurements were performed with the operator blinded to the results of the initial study. In two patients whose first ablation was performed early in our series and prior to epicardial ablation, aggressive ablation in normal voltage endomyocardium was performed with a cooled tip catheter targeting an epicardial VT. The resultant area of bipolar low voltage
observed on the subsequent procedure was excluded from the analysis as it was felt to be due to ablation. As evidence for this, one of these two patients underwent a repeat endocardial 3D electroanatomic map one month following the first procedure that showed extensive low voltage in the previously normal voltage region targeted with extensive cooled tip ablation. This region of low voltage was stably present on the subsequent and final 3D electroanatomic map analysed. In order to account for differences in scar area attributable to measurement variability, the scar area of all 22 maps was independently measured on two separate occasions separated by one to four weeks. The data presented was obtained on the first assessment. The difference in scar area attributable to measurement variability was less than or equal to 5 cm$^2$ in all cases. Based on this finding, a significant difference in scar area between voltage maps was defined as greater than two times this maximum measurement variability or 10 cm$^2$.

**Sinus rhythm 12 lead ECG progression**

The sinus rhythm 12 lead ECG was also assessed to determine if 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 value ≤ 0.05 was considered statistically significant.
Results

Patient Population

Eleven patients: nine men and two women met criteria to be included in this analysis (Table 1).

All eleven patients met Task Force diagnostic criteria for ARVD/C (Table 1) and presented at an average age of 34 ± 16 years (range 14-60 years)\(^3\). All patients had sustained ventricular tachycardia and underwent initial and then repeat catheter ablation procedures for VT episodes. The time between the initial and repeat ablation procedure averaged 57 +/- 31 months (range 9 – 96 months)

Electroanatomic Mapping and Scar Area

Detailed sinus rhythm electroanatomic voltage mapping of the right ventricle was performed in all patients at each procedure prior to induction of ventricular tachycardia and ablation. An average of 291 +/-122 points (range 114 - 558 points) was obtained to generate each voltage map. As described above, 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 more than 10 cm\(^2\) which was twice the maximum estimated measurement error. Of note, 10 cm\(^2\) represents a very small area (~4%) compared to the overall average RV area of 226 +/- 35 cm\(^2\) at initial and 267 +/- 38 cm\(^2\) at repeat study.

Using the specified criteria, only two of the eleven patients had an increase in scar area between the two studies (Figures 2 and 3). Patient #6 had an increase in total scar area (+47 cm\(^2\)) involving the inferior peri-tricuspid valve region. Patient #9 had an increase in scar area (+ 32 cm\(^2\)) involving the free wall of the RV. In contrast, the other nine patients did not show an
increase in scar area between the two studies (Figures 3 and 4). When all eleven patients are compared together, the scar area increases from an average of 46.8cm² on the first procedure to an average of 54.8cm² on the second procedure. This increase is not significant with a p-value of 0.28. Excluding patients #6 and #9 from the comparison yields an average scar area of 56.1cm² on the first procedure and 55.1cm² 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 show 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.

**Right Ventricular Volume**

The maps were also 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 more than 20 cc. Ten of the eleven patients had an increase in RV volume of more than 20 cc (Figure 5). The average increase in RV volume was 24%, from 212 +/- 67 cc to 263 +/- 52 cc (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 ventricular tachycardia. Interestingly, the one patient who did not exhibit an increase in RV chamber volume was the patient who had the most extreme chamber dilatation.

**Ventricular Tachycardia Morphologies**
For each procedure, we reviewed the ventricular tachycardia 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 eight of the patients, the VT deemed clinical on the second procedure was different than the clinical VT targeted during the first procedure. For two patients, the morphology appeared to be very similar. For one 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 prior to the first ablation procedure and at either their second procedure or 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 two patients who manifested an increase in endocardial scar area over time (Figure 6).

**Discussion**

This is the first study 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 eleven patients, only two showed evidence of progressive endocardial scarring as measured by detailed bipolar voltage mapping. Importantly, if recurrent ventricular arrhythmias are due to progressive scarring and fibro-fatty infiltration of
the RV, then our patient population would have been expected to be enriched for those patients 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 ventricular tachycardia 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 upon 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 in many patients sufficiently modify the substrate so as to make future ventricular tachycardia unlikely. Rather than uniform progression of abnormal substrate, this group of patients developed recurrent VT necessitating additional ablation for one of two reasons. The first is that early in our experience we likely delivered inadequate endocardial substrate modification with extensive ablation due in part to concerns about a thin walled ventricle. With the use of intracardiac echo we now know that the abnormal substrate in these patients is often quite thick, permitting aggressive high power ablation. The second reason for a failed endocardial ablation is the need for epicardial ablation.

**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 one 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, over time, will experience worsening RV function and develop signs and symptoms of right heart failure as a result of progressive RV dilatation. Whether this extent of RV dilatation also occurs in ARVD/C patients 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 (MI). In the case of post-MI remodeling, complex and progressive changes to LV size and function occur in the setting of stable scar. In the case of patients with ARVD/C, maladaptive changes to chamber size and function may be caused by neurohormonal influences, local factors including that caused by wall stress (tethering to scar) and tricuspid regurgitation. The tricuspid regurgitation present in these patients is both a cause and effect of RV dysfunction and dilation. ICD 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 LV dysfunction, ACE-Inhibitors, beta-blockers and, when appropriate, mitral valve surgery play a role in attenuating adverse remodeling. Whether these medications or others could play a role in the attenuation of the RV dilatation in patients with ARVD/C remains to be further 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. This 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/modification may offer the possibility of preventing new VT morphologies. We think this remains an open question 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 two 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 and thus we are confident that differences related to sampling should be small.

Second, it is our experience, as with others, that aggressive ablation in normal voltage myocardium (no longer our practice for ARVD/C patients), 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 two patients who 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\textsuperscript{18}. As 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 patients have undergone serial epicardial mapping. It is possible that while the endocardial substrate shows very limited progression the majority of patients, that there is progression along the epicardial and/or intramyocardial regions.

**Conflict of Interest Disclosures:** Francis E. Marchlinski, MD has a research grant and has been on the advisory board of Biosense Webster, Inc. Edward P. Gerstenfeld, MD has a research grant from Biosense Webster, Inc. David J. Callans has been on the advisory board of Biosense Webster, Inc.

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catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular

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with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular

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**Table 1.** Clinical characteristics of study patients. Time interval between first and last ablations, Task Force criteria for ARVD/C and age of presentation for the eleven patients included in this study.
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**Table 2.** Ventricular tachycardia morphology and lesion location. Column 1 lists each patient. Columns 2 through 5 show information regarding procedure #1. Column 2 lists the # and superior/inferior axis of induced VTs (all VTs were left bundle). Column 3 lists the axis for the clinical VT. Column 4 lists the location of ablation lesions and column 5 lists the number of radiofrequency lesions delivered. Columns 6 and 7 pertain to procedure #2. Column 6 lists the # and superior/inferior axis of induced VTs. Column 7 lists the axis for the clinical VT and whether it was similar or different compared to the clinical VT observed during procedure #1.
Figure Legends

Figure 1. Example of area and volume measurement. Panel A shows an RAO projection of a 3D electroanatomic sinus rhythm bipolar voltage map from a patient with ARVD/C (patient 11). Areas with bipolar voltage < 0.5 mV are represented in red. Areas with bipolar voltage > 1.5 mV are represented in purple. Border zone regions (0.5 mV to 1.5 mV) are shown in the rainbow colors. Panel B shows the same map with the region of low voltage demarcated using an area measurement tool. In this particular case, the area of this region of scar was 48 cm² out of a total surface area of the RV of 282 cm². Non-contiguous regions of scar are measured separately and added together. The volume of the chamber was calculated using software provide. In this example, the chamber volume is 283 cc.

Figure 2. Endocardial sinus rhythm bipolar voltage maps for the two patients who did manifest increases in scar area over time. Shown for each patient are complementary views of right ventricle voltage maps obtained during initial and subsequent ablations. Normal voltage regions are shown in purple, very low voltage areas are shown in red with border zones shown in rainbow colors.

Figure 3. Endocardial scar area changes. The scar area for each of the eleven patients is shown as measured at their two procedures. In gray is the scar area at ablation 1. In black is the scar area at ablation 2. Two patients (starred) had a greater than 10 cm² increase in scar area. The remaining nine patients did not demonstrate a significant increase or decrease in scar area.
Figure 4. Endocardial sinus rhythm bipolar voltage maps for four patients who did not manifest increases in scar area over time. Shown for each patient are complementary views of right ventricle voltage maps obtained during initial and subsequent ablations. Normal voltage regions are shown in purple, very low voltage areas are shown in red with border zones shown in rainbow colors.

Figure 5. Right ventricle volume changes. The right ventricular volume for each of the eleven patients is shown as measured at their two procedures. In gray is the volume at ablation 1. In black is the volume at ablation 2. Ten of the eleven patients (starred) had a greater than 20 cc increase in volume as measured at the second ablation. One patient did not show an increase in volume at the second ablation.

Figure 6. 12 lead ECG recordings from Patient #6 and Patient #9. Standard 12 lead electrocardiograms were obtained prior to initial ablation and at most recent outpatient follow-up visit. ECG parameters: paper speed 25 mm/sec, scale 10 mm/mV.
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Circ Arrhythm Electrophysiol. published online June 17, 2010;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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