Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits

Running title: Haqqani et al.; Substrate for confined epicardial VT in ARVD

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Abstract:

**Background** - Ventricular tachycardia (VT) ablation in arrhythmogenic right ventricular dysplasia (ARVD) is more successful when including epicardial ablation. Scarring may cause independent, layered epicardial activation and promote epicardially-confined VT circuits. We aimed to characterize transmural right ventricular (RV) activation in ARVD patients and compare this to reference patients without structural heart disease.

**Methods and Results** - Eighteen ARVD patients underwent detailed endocardial and epicardial sinus rhythm electroanatomic mapping. Bipolar activation was annotated at the sharpest intrinsic deflection including late potentials and compared to 6 patients with normal hearts. Total scar area was larger on the epicardium (97±78 cm²) than the endocardium (57±44cm²; p=0.04) with significantly more isolated potentials. Total epicardial activation time was longer than endocardial (172±54 vs 99±27ms, p<0.01) and both were longer than in reference patients. Earliest endocardial site was the RV anteroseptum in 17/18 ARVD patients vs 5/6 controls (p=0.446) and latest endocardial site was in the outflow tract in 13/18 vs 4/6 and tricuspid annulus in 5/18 vs 2/6 (p=1.00). In reference patients epicardial activation directly opposite endocardial sites occurred in 5.2±1.9ms suggesting direct transmural activation. In contrast, ARVD patients had major activation delay to the epicardium with laminar central scar activation from the scar border, not by direct transmural spread from the endocardium.

**Conclusions** - Transmural RV activation is modified by ARVD scarring with a delayed epicardial activation sequence suggestive of independent rather than direct transmural activation. This may predispose to VT circuits contained entirely within the epicardium in ARVD and explains observations on the need for direct epicardial ablation to eliminate VT.

**Key words:** ablation; cardiomyopathy; catheter ablation; electrophysiology; tachycardia

**Abbreviations and Acronyms:** ARVD - arrhythmogenic right ventricular dysplasia; CMR - cardiac magnetic resonance; EAM - electroanatomic mapping; FP - fractionated potential; ILP - isolated late potential; RV - right ventricle; LV - left ventricle; VT - ventricular tachycardia
Introduction

Arrhythmogenic right ventricular dysplasia (ARVD) is a genetically-determined cardiomyopathy characterized by cardiomyocyte loss with replacement of the myocardium by fibrofatty tissue. The altered myocardial architecture resulting from this process causes delayed and disordered electrical propagation, and predisposes to the development of reentrant ventricular tachycardia (VT). Although the left ventricle (LV) can be involved, the disease process predominantly affects the right ventricle (RV), and both pathological and electroanatomic studies show a disproportionate burden of disease on the epicardium compared to the endocardium. This is likely to have implications for the nature and location of the reentrant VT circuits seen in ARVD. In particular, confluent epicardial or intramural scarring may prevent transmural endocardial-to-epicardial activation during VT, precluding endocardial involvement and establish the potential for all or major components of VT circuits to be confined entirely to the epicardium. We postulated that the compartmentalized activation of the epicardium induced by such confluent scarring would also alter the sinus rhythm right ventricular endocardial-to-epicardial activation sequence.

The purpose of this study was to define the pattern of activation of the RV endocardium and epicardium in patients without structural heart disease, and compare this to patients with anticipated extensive RV scarring caused by ARVD.

Methods

The study population (Group 1) consisted of 18 consecutive patients with ARVD (13 male, mean age 43±15 years) who had detailed endocardial and epicardial electroanatomic mapping (EAM) performed. Patients were studied between 2007 and 2010 and met Revised Task Force Criteria...
for ARVD as listed in Table 1. They had recurrent VT and multiple implantable cardioverter-defibrillator (ICD) therapies despite antiarrhythmic drugs, and were undergoing catheter ablation. Thirteen of the 18 patients (72%) had undergone a prior ablation procedure. Patients had recurrent monomorphic VT documented by either 12-lead electrocardiograph (ECG) or by stored ICD electrograms. The reference group (Group 2) consisted of 6 consecutive patients (3 male, mean age 44±16 years) with no structural heart disease who had endocardial and epicardial EAM performed during catheter ablation of idiopathic ventricular arrhythmias. All patients provided written informed consent for electrophysiologic study and catheter ablation in accordance with the University of Pennsylvania Health System’s institutional guidelines.

**Preprocedural imaging**

All patients underwent transthoracic echocardiography to exclude intracardiac thrombus. Cardiac magnetic resonance (CMR) imaging was performed to further define the arrhythmogenic ventricular substrate in some of the patients. Contrast-enhanced CMR was performed on a clinical 1.5T scanner (Avanto™, Siemens, Erlangen, Germany) using a standard protocol that included assessment of delayed gadolinium enhancement (DGE). To reduce the risk of radiofrequency-related heating of the intracardiac lead in patients with ICDs, the specific absorption rate was limited to 2W/kg using a TGRAPPA cine sequence with TR 14-43ms, TE 1-2ms, 1.9x1.9mm resolution and 8mm slice thickness. All devices were interrogated pre- and post-scanning with no change in pacing threshold, lead or battery data observed.

**Endocardial electroanatomic mapping**

Patients were studied in the post-absorptive state under conscious sedation or general anesthesia after pre-operative echocardiography excluded intracardiac thrombus. Anti-arrhythmic drugs were stopped >5 half-lives preoperatively. An intracardiac echocardiography (ICE) catheter
(ACUSON Acunav™, Siemens, Mountain View, CA) was deployed in the RV where it was used to assess ventricular function and scarring, confirm catheter contact and monitor lesion formation during ablation. The CARTO (XP and 3)™ system (Biosense Webster, Diamond Bar, CA) was used for EAM in conjunction with a standard open-irrigated catheter (Navistar Thermocool™, Biosense Webster) which has a 3.5mm tip electrode, a 2mm ring electrode and a 1mm inter-electrode spacing. Bipolar electrograms were filtered at 30 to 400Hz, displayed at 200mm/s sweep speed, and stored for offline annotation and analysis. Unipolar electrograms were filtered at 1 to 240Hz. Annular points were tagged and mapping density was sufficient to allow for complete surface geometry reconstruction with a fill threshold of <15mm. Normal bipolar endocardial RV electrogram voltage was defined as ≥1.5mV while ‘dense scar’ was taken to be <0.5mV. When endocardial bipolar voltage was unremarkable, we examined the unipolar electrograms with their wider ‘field of view’ for evidence of deeper subjacent substrate. Normal RV free wall unipolar electrograms were defined as having peak-to-peak amplitude ≥5.5mV.

Fractionated potentials (FP) were defined in the standard fashion as electrograms with multiple deflections from baseline, amplitude ≤0.5mV, duration ≥133ms, and/or amplitude:duration <0.005. Standard criteria were also used to define isolated late potentials (ILP) as those electrograms displaying an additional signal separated from the initial ventricular electrogram by a >20ms isoelectric interval, with the second component usually (but not invariably) occurring after the end of the surface QRS complex had been inscribed.

**Epicardial electroanatomic mapping**

Percutaneous pericardial access was obtained using a Tuohy needle via a subxiphoid approach as described by Sosa et. al. An open-irrigated EAM catheter was used to perform high-density mapping of the epicardium, particularly concentrating on the RV epicardium. As previously
described,\textsuperscript{4,11} to optimize the distinction between epicardial fat and fibrosis, we defined epicardial scar zones to be those areas with bipolar signal amplitude <1.0mV \textit{and} containing prolonged (>80ms) electrograms or isolated late potentials.

\textbf{Activation mapping}

Local sinus rhythm activation was annotated at the onset of the highest frequency deflection of the bipolar electrogram by two independent investigators. The latest, split component of isolated late potentials was taken to represent local activation and this was annotated (\textbf{Figure 1}). For fractionated signals, reference was also made to the steepest negative components of the tip and ring unipolar electrograms, as well as to the activation times of the immediately adjacent regions. Endocardial and epicardial virtual geometries were superimposed to determine the site of epicardial breakout relative to the underlying endocardium.

\textbf{Statistical analysis}

Continuous data are presented as mean ± 1 standard deviation after being assessed for a normal distribution by inspection of histograms, Q-Q plots and a one-sided Kolmogorov-Smirnov test. Baseline and mapping data were analyzed by the Fisher’s exact test and paired and unpaired Student’s t-test as appropriate. A two-tailed p<0.05 was considered to be statistically significant.

\textbf{Results}

\textbf{Baseline characteristics}

The baseline characteristics of the two groups are compared in \textbf{Table 2}. There were no significant differences between the two groups in terms of age, gender, LV size and systolic function, anti-arrhythmic drug use or sinus rhythm mean QRS complex duration. ICDs were present in 15/18 (83\%) ARVD patients and in none of the 6 control patients. Contrast-enhanced...
CMR was performed in 10/18 ARVD patients and showed regional RV wall motion abnormalities in 9 and delayed RV enhancement in 7. No CMR abnormalities were seen in the control patients. No adverse events related to CMR scanning occurred in patients with an ICD. The mean RV ejection fraction was 33±8% in the ARVD patients compared to 42±2% in the control group (p=0.02).

**Electroanatomic substrate mapping**

Endocardial RV point sampling was greater in the ARVD patients (294±110 points) than the control patients (113±33 points; p<0.01). Likewise, epicardial point sampling was also greater in the ARVD group (506±126 points vs. 258±50 points; p<0.01). The results of electroanatomic voltage mapping are presented in Table 3. The commonest sites of endocardial scarring in Group 1 patients were the infundibulum (15/18) and the basal peri-tricuspid region (15/18). No significant endocardial or epicardial scarring was seen in the control patients. In the ARVD patients, total scar area was greater on the epicardium than the endocardium (98±79cm² vs. 57±44cm²; p=0.048) and was often arranged in confluent sheets. The basal lateral free wall and peri-tricuspid region were involved with epicardial scarring in all ARVD patients, and the infundibulum was involved in 16/18.

In the ARVD group, a similar proportion of endocardial and epicardial electrograms were fractionated (3.6±3.1% vs.3.1±4.4%; p=0.727), however isolated potentials were significantly more prevalent on the epicardium than the endocardium (16±8.1% vs. 9.2±7.6%, p=0.017). A periannular, patchy distribution of endocardial ILPs was the commonest pattern seen (in 14/18 patients) while a minority had isolated anterior or inferior RV ILPs. In contrast, on the epicardium, large networks and clusters of ILPs across all regions were seen in all ARVD patients (Figure 2). The epicardium overlying the inferior RV displayed ILPs in 9/18 patients,
while the same was seen in 7/18 anterior walls. The epicardium overlying the infundibulum, the lateral RV free-wall and the lateral tricuspid annulus harbored ILPs in 16/18, 15/18 and 12/18 patients respectively. Both isolated and fractionated electrograms were rare in the control patients (0.3 and 0.1% of signals respectively).

**Endocardial RV activation**

Total endocardial RV activation was longer in the ARVD group compared to the control patients and accounted for a greater proportion of QRS duration (Figure 3). Earliest endocardial breakout occurred on the anteroseptal RV wall in 17/18 (94%) ARVD patients and 5/6 (83%) of control patients (p=0.446). Endocardial RV breakthrough occurred 5±13ms before QRS onset in the ARVD patients and 1±7ms in Group 2 (p=0.148). The latest endocardial activation occurred in the infundibulum in 13/18 (72%) ARVD patients and in 4/6 (67%) of control patients. The inferior tricuspid annulus was activated last in the remaining 28% of ARVD patients and 33% of control patients (p=1.00).

**Epicardial RV activation**

Similar to the endocardium, ARVD patients had longer total epicardial activation time than the control patients (Figure 3). A substantial portion of epicardial activation occurred after the end of the surface QRS due to the very late timing of most epicardial ILPs (Figures 1-3). Epicardial activation breakout occurred over the anteroseptal RV in all Group 2 patients, however one patient also had a simultaneous second breakout overlying the inferoseptal RV. The ARVD patients had epicardial breakout over the anteroseptal RV in 14/18 patients while the anterior LV was the earliest epicardial site in the remaining four. Of these 4 patients, 3 had a complete RBBB and one had a partial RBBB. Epicardial breakout time was not significantly different between the groups (6.3±12ms after QRS onset for Group 1 vs. 3.2±8.2ms for Group 2, p=0.493).
The latest epicardial RV activation was seen overlying the inferior tricuspid annulus in 5/6 and the infundibulum in 1/6 control patients. In the ARVD group, when annotating the second component of ILPs, the latest activation site was determined by the location of the dense scar sheets containing the longest coupled ILPs. This was overlying the inferior TA in 9/18, the infundibulum in 7/18 and the mid-RV free wall in 2/18. These regions usually contained networks or clusters of ILPs that were activated in one of three patterns. In 2 patients, broad sweeping wavefronts propagated from one end of the cluster to another. In 3 patients, a branching pattern of activation activated the scar from one end. In the remaining 13 patients, a collision of wavefronts was observed that activated epicardial scar from its periphery and progressed inward to its center (Figure 4).

**Relationship between endocardial and epicardial RV activation**

Activation at directly opposite endocardial and epicardial points was compared at the infundibulum, the lateral free RV wall, the anterior wall, the inferior wall, the apex and the inferolateral tricuspid annulus. In control patients, mean activation at the respective opposite epicardial site occurred with significantly shorter delay than in the ARVD patients (Figure 3D).

Latest epicardial RV activation occurred within 20ms after latest RV endocardial activation in all control patients. By comparison, in the ARVD patients a more than four-fold greater delay elapsed between the last recorded endocardial activation and the latest epicardial RV sites which were generally located within a cluster of late-coupled epicardial isolated potentials (Figure 3D).

**VT characteristics**

During these combined endocardial and epicardial procedure, 28 VTs were induced and targeted for ablation in these 18 patients, 1.6 VTs per patient. Of these, only 9 (32%) were mappable,
mainly due to short cycle length causing hemodynamic instability. Using a combination of limited entrainment data as well as activation and pacemapping, it was found that 22 of these 28 VTs (79%) had significant putative components of their circuits on the epicardium. Extensive epicardial ablation rendered 20 of these putative epicardial VTs (91%) non-inducible by the end of the procedure.

**Discussion**

This is the first study to examine the transmural right ventricular activation pattern both in a group of control patients without structural heart disease, as well as in patients with ARVD. The main findings are:

1. Sinus rhythm endocardial RV activation in the absence of structural heart disease progresses smoothly from earliest breakthrough in the apical anteroseptal endocardium towards the basal regions.

2. Reference patients without structural heart disease also show evidence of epicardial RV activation in a similar sequence to the endocardium with relative activation timing suggestive of direct transmural endocardial-to-epicardial depolarization.

3. Endocardial RV activation in ARVD is altered by the extensive fibrosis that characterizes this disease such that it takes proportionately longer but occurs in an overall similar sequence due to the largely periannular endocardial substrate distribution.

4. Epicardial RV activation is altered and activated in a delayed fashion, with a pattern that often appears independent of subjacent endocardial activation suggesting that the dense confluent fibrosis characteristic of ARVD may potentially compartmentalize the endocardium from the epicardium.
While some data exist on the normal sequence of ventricular activation in patients with and without structural and conduction system disease, these data are generally focused on the LV and concentrate on the endocardium using contact or non-contact mapping, and on the epicardium using electrocardiographic imaging. No studies have performed simultaneous contact mapping of the ventricular endocardium and epicardium to examine the sequence and relationship of activation of the two surfaces, and there have not been any data describing the effect of structural disease on this relationship. While existing studies have largely examined ventricular activation from the perspective of dyssynchrony resulting from intraventricular conduction delay (and its potential treatment with biventricular pacing), this activation sequence is also important in understanding the mechanism and location of ventricular tachycardias in various nonischemic cardiomyopathies (NICM). Compared to the post-infarct context, these are generally characterized by a typical basal, periannular substrate distribution, with a disproportionate burden of epicardial to endocardial scar. This epicardial substrate preponderance would be expected to increase the prevalence of VT circuits exiting on the epicardium, but it may also predispose to the creation of VT circuits confined entirely to the epicardium with only passive endocardial activation. In the latter situation, the endocardium behaves as a separate chamber and this is in contrast to its role in transmural VT circuits that may have entrance, exit and central isthmus in either the endocardium, epicardium or the intramural ventricle. The sorts of VT circuits established are likely to depend on the location and degree of transmural scar, as well as on the thickness of the ventricle, and this is likely to be different in the right and left ventricle.

A unique opportunity to understand the three-dimensional substrate underlying VT in NICM is presented by patients with ARVD. Patients requiring ablation for VT in this context
generally have significantly more epicardial than endocardial scar, but may also have substantial intramural fibrosis which would increase the likelihood of conduction block to the endocardium and independent activation of the epicardium in VT by circuits unable to traverse the intramural RV. In sinus rhythm, the footprint of such a schema would be the independent, laminar activation of the endocardium and epicardium.

Control group data from this study suggests that normal human RV activation occurs in an apex-to-base fashion, from its initial breakout at the myocardial arborization of the distal right bundle branch back towards the infundibulum and basal annuli. A similar sequence occurs on the epicardium, and this is consistent with the results obtained by Wyndham et. al.18 with surgical mapping of intact hearts with coronary disease but without prior myocardial infarction. In that study, a constant anterior RV epicardial breakout was also seen and latest activation was again heterogeneous in precise location, but generally in the basal regions of the RV. We observed a near simultaneous activation (delayed by only 5.2±1.9ms) at sequential fiducial points along the course of activation of the endocardium and epicardium. This suggests that progressive transmural activation of the epicardium from subjacent endocardial points (rather than independent epicardial laminar activation) is occurring as the absence of a Purkinje network on human epicardium would be expected to slow conduction relative to the endocardium to a significantly greater extent than that observed. The finding that the very latest epicardial site is activated within a mean of only 16ms of the completion of endocardial activation further supports this hypothesis.

By comparison, the normal pattern of RV activation during sinus rhythm is greatly altered in ARVD by the location and extent of the scarring process, and significant uncoupling of the endocardial and epicardial activation timing and pattern suggests the presence of significant
intramural or transmural substrate. Although RV free wall DGE was seen on CMR, the resolution of this modality at present is insufficient to be certain about the exact transmural scar distribution. Of note, both the degree and nature of scarring was heterogeneous in these patients, as not only was there a larger epicardial scar area but it also contained a greater number of fractionated and isolated potentials, and ILPs here had longer coupling intervals of the isolated electrogram component compared to those on the endocardium. The isolated component of ILPs is very likely to represent local activation occurring beneath the catheter tip and annotating this component generated two main results. Firstly, local epicardial activation occurs significantly later than the subjacent endocardium in ARVD, and secondly, it occurs in stereotypical patterns that are likely to be related to scar geometry. In particular, the majority of patients exhibited a reverse-centripetal pattern of activation of a confluent epicardial scar region from the periphery progressing to collision in the center. Such a pattern essentially excludes the possibility of direct sinus rhythm transmural endocardial-to-epicardial RV activation in these patients. This independent layered activation of the epicardium in sinus rhythm is likely to predispose to the existence of VT circuits partly of even completely confined to the epicardium as the intramural fibrotic process provides a limited number of possible breakthrough sites to the endocardium that are insufficient to short-circuit the reentrant VTs seen.

Clinical implications

In the presence of the type of dense fibrosis seen in ARVD, successful endocardial ablation of such VT may be less likely given the poor transmural penetration of current ablation energy sources. This is particularly likely to be a limitation when burning in the thickened, densely scarred right ventricles seen in this condition. Though no randomized comparisons are available, the incorporation of epicardial mapping appears to be associated with better outcomes for
ARVD-related VT ablation\textsuperscript{4,20} than does endocardial ablation alone. This is likely to be related to the increased ability to directly ablate the substrate for confined epicardial VT circuits when approaching these with a transpericardial, rather than a transmural, strategy.

**Limitations**

In this study, the endocardial and epicardial activation sequence have been determined in only the RV in ARVD patients with advanced scarring undergoing VT ablation, many of whom had undergone prior ablation which could alter activation. These results cannot be extrapolated to the thicker walled LV, nor to other disease states. Greater mapping density in the ARVD patients may also have affected the comparison with reference patients. Inaccuracies in determining local activation may have affected the results, including those related to the size of the mapping bipolar, the orientation of the catheter shaft and the difficulty in absolutely distinguishing far-field from local activation in fractioned signals. We could not map the midmural substrate by either electroanatomic mapping or imaging and our conclusions about intramural activation are surmised from examining the endocardial and epicardial activation alone. Also, currently available technology does not allow for the ability to directly record simultaneous contact activation from opposite endocardial and epicardial points and this may introduce some error into our analysis. Likewise, we did not in the present study record epicardial activation times whilst pacing from directly subjacent endocardial points.

Finally, to date the detailed characterization of the entire VT circuit in this setting has not been performed and correlated with the observations noted in the present study. Unfortunately VTs are frequently poorly tolerated in this setting particularly after general anesthesia used during epicardial mapping thus making such complete circuit characterization not possible at this point. Importantly, we have previously reported on successful ablation on epicardial sites directly
opposite normal endocardium and or directly opposite sites of ineffective endocardial ablation consistent with our observations of the epicardium being likely to be effectively compartmentalized from the endocardium. ⁴

Conclusions

Normal human RV activation progresses smoothly from apex to base on both the endocardium and epicardium, with likely direct transmural epicardial activation. Right ventricular activation in ARVD is modified by the presence of confluent scar with a delayed epicardial activation sequence suggestive of possible independent rather than direct transmural activation. This may predispose to VT circuits contained entirely within the epicardium in ARVD and explains observations on the need for direct epicardial ablation to successfully eliminate VT.

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Conflict of Interest Disclosures: Dr. Marchlinski has received research funding from Biosense Webster unrelated to this study.

References:


4. Garcia FC, Bazan V, Zado ES, Ren JF, Marchlinski FE. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular


16


Table 1: Task force criteria

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Table 2: Baseline characteristics

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<tr>
<td>QRS duration (ms)</td>
<td>101±28</td>
<td>93±15</td>
<td>0.74</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>3</td>
<td>0</td>
<td>0.55</td>
</tr>
</tbody>
</table>

* ICD = implantable cardioverter-defibrillator

Table 3: RV endocardial and epicardial substrate characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 ARVD (n=18)</th>
<th>Group 2 Control (n=6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV endocardial mapping points</td>
<td>362±161</td>
<td>124±45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EAM* SA (cm²)</td>
<td>233±38</td>
<td>168±67</td>
<td>0.06</td>
</tr>
<tr>
<td>RV endocardial EAM volume (cm³)</td>
<td>222±50</td>
<td>138±71</td>
<td>0.03</td>
</tr>
<tr>
<td>RV bipolar scar (&lt;1.5mV) SA (cm²)</td>
<td>57±44</td>
<td>7.6±14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV scar % of RV SA</td>
<td>24±15</td>
<td>3.2±6.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV mean bipolar voltage (mV)</td>
<td>2.7±0.9</td>
<td>5.4±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV unipolar scar (&lt;5.5mV) SA (cm²)</td>
<td>122±57</td>
<td>28±29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV mean unipolar voltage (mV)</td>
<td>4.8±1.6</td>
<td>10±0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV epicardial scar (&lt;1.0mV) SA (cm²)</td>
<td>98±79</td>
<td>0.6±1.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* EAM = electroanatomic map
‡ SA = surface area

Figure Legends:

Figure 1. An epicardial activation map annotating only the isolated late potentials from a patient with ARVD. The isolated potential displayed records its late, and presumably local, component 107ms after the end of the QRS complex.
**Figure 2.** Electroanatomic maps depicting endocardial activation, epicardial activation and epicardial bipolar voltage of the right ventricle of a control patient are displayed in Panel A. From a breakout in the anteroseptal region, activation can be seen to smoothly progress back towards the infundibulum and inferior tricuspid annulus. No evidence of endocardial (not shown) or epicardial scarring was seen in the control patients, with low-voltage red areas on the epicardium displaying otherwise normal electrograms indicating epicardial fat. Panel B shows the same electroanatomic maps in a 27 year old man with ARVD. Confluent epicardial scarring is seen on the right with low-voltage and large clusters of isolated potentials (black dots) and there were much less frequent on the endocardium. Although activation breakouts were in a similar region to the control patient, wavefront propagation is significantly altered by the sheets of scarring, particularly on the epicardium, where very delayed activation into the scar is seen.

**Figure 3.** Panel A shows an endocardial activation map from a 44 year old man with ARVD demonstrating smooth endocardial wavefront propagation from the apical anteroseptum to the base within 86ms. The epicardial shell of the same patient has had isolated potentials annotated in Panel B and this shows progressive, late activation from the mid-inferior RV toward the epicardial infundibulum. This occurs much later than corresponding endocardial activation and with a discordant vector suggestive of independent epicardial activation rather than multisite transmural conduction breakthrough from the endocardium. Overall, both endocardial and epicardial total activation time (TAT) was significantly longer in the ARVD patients than the control patients despite similar QRS duration (Panel C). In ARVD patients however, epicardial TAT was almost twice as long as endocardial TAT. The mean activation delay between corresponding endocardial and opposite epicardial points, as well as the delay between latest
activating endocardial and epicardial points, were both significantly greater in the ARVD patients (Panel D).

**Figure 4.** Patterns of epicardial isolated potential activation. Epicardial activation maps displaying and annotating only the late component of isolated potentials are shown here. In **Panel A**, the epicardial RV free-wall scar is seen to be activated by a broad sweeping wavefront progressing cranio-caudally towards the inferior RV. **Panel B** shows a branching pattern of activation with an initially broad wavefront arborizing deeper in the scar. **Panel C** displays examples of the reverse centripetal pattern with peripheral activation progressing inward and colliding in the center of the scar.
Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits
Haris M. Haqqani, Cory M. Tschabrunn, Brian P. Betensky, Nimrod Lavi, Wendy S. Tzou, Erica S. Zado and Francis E. Marchlinski

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