Ablation of Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Arrhythmia-Free Survival after Endo-Epicardial Substrate Based Mapping and Ablation

Running title: Bai et al.; Endo-epicardial ablation of VT in ARVD/C

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Journal Subject Code: [22] Ablation/ICD/surgery
Abstract:

Background - In patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), freedom from ventricular arrhythmias (VAs) after endocardial ablation is limited. We compared the long term freedom from recurrent VAs by using endocardial-alone ablation vs. endo-epicardial substrate based ablation.

Methods and Results - 49 patients with ARVD/C undergoing ablation of ventricular tachycardia (VT) were divided into 2 groups: endocardial-alone ablation (Group 1, n=23) and endo-epicardial ablation (Group 2, n=26). All patients had an implantable cardioverter defibrillator (ICD). Conventional and 3D mappings were utilized to determine the mechanism of induced VTs and to identify area of "scar" or "abnormal" myocardium. All critical sites responsible for VTs and points with “abnormal” potential were targeted for ablation from endocardium (Group 1) or from both endocardium and epicardium (Group 2). Procedural endpoint was noninducibility of sustained, monomorphic VT with isoproterenol. The presence of frequent premature ventricular contractions (PVCs) at the end of ablation was recorded. Patients were followed-up by ECGs, Holter and ICD interrogation. After a follow up of at least 3 years, freedom from VAs or ICD therapy was 52.2% (12/23) in Group 1 and 84.6% (22/26) in Group 2 (p=0.029) with 21.7% (5/23) and 69.2% (18/26) patients off AAD (p<0.001), respectively. Compared to patients with no PVC after ablation, patients with frequent PVCs after ablation were more likely to have VA recurrence/ICD therapy [3/33, (9%) vs. 12/16 (75%), Log rank p<0.001].

Conclusions - An endo-epicardial based ablation strategy achieves higher long-term freedom from recurrent VAs off anti-arrhythmic therapy in patients with ARVD/C when compared to endocardial-alone ablation. The presence of ≥10 PVCs per minute after ablation is associated with more VA recurrence.

Key words: arrhythmogenic right ventricular dysplasia; cardiomyopathy; ventricular tachycardia; ablation; epicardial; premature ventricular contraction
Introduction

Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C) is characterized by ventricular arrhythmias (VAs) or even sudden cardiac death (SCD) secondary to fibro-fatty replacement of the right ventricular (RV) myocardium. It is a genetically determined myocardial disease where the pathological lesions are believed to progress over time from the epicardium to the endocardium and with diffuse involvement of the RV and the left ventricle (LV) in rare cases [1,2]. Patients having recurrent sustained VT while on optimal pharmacological therapy are candidates for catheter ablation. Even though the recent technological advances with electroanatomic and voltage mapping systems have significantly improved the outcomes, catheter ablation of ventricular tachycardia (VT) in ARVD/C patients is not considered curative and has not been supported by the guideline as a first-line therapy [3-5]. However, only an endocardial approach was used in most of the cases previously reported [3, 6-8]. We hypothesized that the epicardial substrate may play an important role in the development of VT in patients with ARVD/C and an ablation strategy including both endocardial and epicardial substrate modification may be necessary to achieve better outcome. This multicenter study compared the long-term freedom from VA in ARVD/C patients undergoing VT ablation by using either an endocardial-alone or an endo-epicardial based approach. We also sought to identify the predictor to ablation failure and recurrence of VA.

Methods

1. Study population

This is a prospective study including forty-nine (49) consecutive patients with ARVD/C undergoing ablation of VTs at 7 centers in USA, Italy, Colombia and Canada. They were
diagnosed with ARVD/C according to the Task Force Criteria $^{[9,10]}$. All patients had at least one episode of symptomatic, sustained, monomorphic VT with left bundle branch block pattern documented by ECG or Holter, with or without syncope. They all had received an implantable cardioverter defibrillator (ICD) prior to the ablation but still suffered from recurrent VTs or multiple ICD therapies despite anti-arrhythmic drugs (AAD) including sotalol, amiodarone, dofetilide and beta-blockers. The study population was divided into 2 groups based on the ablation strategy chosen by the ablating physician: in 23 patients (Group 1) ablation was performed by an endocardial-alone approach; while 26 patients (Group 2) underwent an endo-epicardial based ablation. Prior to the index procedure, 14 patients from Group 2 had one failed endocardial ablation which had been performed at other centers using only standard activation map of induced VT. They were referred to participating centers of the present study and did not overlap with the patients in Group 1. The rest of the patients from Group 2 (N=12) underwent endo-epicardial ablation as their primary procedures. All patients signed an informed consent for catheter ablation of their VTs.

2. Electrophysiology Study and mapping

Patients were studied in the electrophysiology laboratory in the fasting state under conscious sedation. Venous access was obtained from the groin veins. One quadripolar catheter and one duo-decapolar catheter (St. Jude Medical Inc., Minneapolis, MI) were placed in the RV and coronary sinus-right atrium, respectively. In patients in Group 2, subxiphoid epicardial access was obtained by using fluoroscopic guidance as previously described $^{[11]}$. Programmed stimulation including burst ventricular pacing and ramp pacing with up to 3 ventricular extrastimuli were delivered from 2 different RV sites in order to induce VA.
Intravenous isoproterenol was also used (maximum dose 10μg/min) when necessary. Induced VTs were compared with 12-lead ECGs of the clinical VT.

Endocardial mapping was performed in all patients while epicardial mapping was performed once the epicardial space was accessed in Group 2 patients. Conventional mapping techniques included pace mapping, activation mapping and entrainment mapping which helped understanding the mechanism of the arrhythmias and identifying potential critical sites. The 3D electroanatomic CARTO maps (Biosense Webster, Diamond Bar, CA), including the activation and voltage map, were obtained in sinus rhythm and/or during hemodynamically-stable VT using a 3.5mm open irrigated tip catheter (Biosense Webster, Diamond Bar, CA). Bipolar electrogram signals were filtered at 30 to 400 Hz and were displayed on a real-time recording system. A fill threshold < 15mm was used when CARTO map points were collected. Bipolar voltage definitions of abnormal and normal myocardium were based on values validated previously in both right and left ventricles [12, 13]. Endocardial regions with a bipolar electrogram amplitude >1.5 mV were defined as “normal,” and “scar” is defined as those area with an amplitude <0.5 mV. “Abnormal” myocardium was defined as a region with a bipolar electrogram amplitude between 0.5 and 1.5 mV. However, considering that overlying fat may result in voltage attenuation of epicardial electrogram, the cut-off to define “normal” area of epicardium was set as a bipolar electrogram amplitude > 1.0 mV while the “scar” myocardium was defined as a bipolar electrogram amplitude < 0.5 mV. In addition to voltage criteria, “abnormal” electrogram both in the endocardium and the epicardium included the delayed, split and fragmental recordings [14]. The area of scar was measured by using the “area calculation” software included in the CARTO system.
3. Ablation strategy

In the index procedure, we intended to ablate not only the clinical VTs but all inducible, sustained, monomorphic VTs at the time of electrophysiology study. Ablation was typically performed with the 3.5mm open irrigated tip catheter. At each ablation point, radiofrequency energy was applied for 60 to 120 seconds with a power output starting at 30 W and titrating up to 45 W with a maximum temperature limit of 41°C. In regions close to the phrenic nerve, high output pacing (20 mA) was performed via the ablation catheter, and these locations were marked on the electroanatomic map.

In general, our targets for ablation were:

(1) All points with “abnormal”, fractionated or delayed electrograms regardless of the location within or around the scar area. In the epicardium, the endpoint was the elimination of these potentials. In the endocardium, when we targeted low voltage potentials (bipolar voltage amplitude 0.5-1.5mV) the endpoint was signal attenuation (bipolar voltage amplitude decreased to <0.5mv); while when we targeted fragmented or delayed potentials with bipolar voltage amplitude 0.5-1.5mV, the endpoint was the complete elimination of these potentials.

(2) Points those were critical in the initiation or maintenance of a VA (e.g. isthmus of a circuit or a focal firing). If no specific foci/isthmus could be determined as the mechanism of the target VTs or if the patients became hemodynamically unstable during the induced VTs, only substrate ablation was performed to abolish all “abnormal” potentials. The specific ablation techniques used in different groups were described below.

Group 1: Endocardial-alone ablation. Radiofrequency energy was delivered at specific sites demonstrating “abnormal” voltage, isthmus of a circuit or arrhythmogenic foci. Under CARTO
guidance, linear ablation lines were created to modify the endocardial substrate and were designed to (1) connect scar/abnormal myocardium to valve continuity; (2) connect scar/abnormal myocardium to another scar, or (3) encircle the scar/abnormal region, depending on the scar location and size (Figure 1A-1B).

Group 2: Endo-epicardial ablation. An epicardial mapping and ablation was planned at the beginning of the procedure rather than as a complimentary approach to an unsuccessful endocardial ablation. Coronary angiogram was performed to confirm the absence of a coronary artery at the ablation site based on the operator preference. At those specific sites suggestive of “abnormal” myocardium on both endocardial and epicardial mapping, radiofrequency energy was delivered from the endocardium and the opposite epicardial position to created transmural lesions. At target sites demonstrating “abnormal” electrogram solely on the epicardial surface but not on the endocardial mapping, ablation was delivered only in the epicardial space. In certain cases, epicardial linear ablation was designed to encircle the entire scar/abnormal region and composed with sequential point lesions along the boundary and within the scar area, with a goal to eliminate/isolate all the “abnormal” recordings (Figure 1C-1D).

Programmed RV stimulation was repeated after completion of ablation. As before, up to 3 extrastimuli at 2 different RV sites were used to attempt to induce VT. If VT was still inducible, additional ablation was performed following the strategy described previously. If the ablated VTs or other sustained monomorphic VT could not be induced even with intravenous isoproterenol infusion (up to 10μg/min), the procedure was considered successful. No further ablation was performed when the only inducible arrhythmias were polymorphic VT/ventricular fibrillation. After removing all the catheters from the ventricle, frequent spontaneous premature ventricular contractions (PVCs) ≥ 10 beats/minute with/without isoproterenol provocation were
recorded, but not targeted for additional ablation. All patients received screening for pericardial effusion at the end of the procedure with echocardiography and fluoroscopy.

4. Follow-up

The patients were followed-up by their treating electrophysiologist. AADs were either discontinued after ablation or maintained for 3 additional months and subsequently stopped. Patients were routinely followed up in the outpatient clinic at 3, 6, and 12 months and then every 6 months thereafter when an ICD interrogation was performed to assess arrhythmia recurrence at each office visit. AAD was resumed at physician’s discretion if recurrent VA was documented by ECG, Holter or EGM retrieved from an ICD. Long term success was defined as a lack of recurrence of sustained VT and/or appropriate ICD therapy.

5. Statistics

The data were prospectively collected. All continuous data are presented as mean +/- standard deviation and were compared using student t-test or Wilcoxon rank-sum test where appropriate. Categorical variables are described as count and percent and compared by using the Fisher’s exact test. Since the ablation method was determined by the physicians at the participating centers, it was necessary to test if difference in procedure assignment was not more frequent than as predicted by chance alone. The Fleiss’s Kappa, an extension of Cohen's Kappa to evaluate concordance between multiple raters, was utilized to assess the agreement in the choice of ablation strategy among participating centers. Kaplan-Meier event-free survival analysis was conducted to assess the cumulative freedom from VA recurrence/ICD therapy and log-rank test
was used to compare recurrence between groups. A p value < 0.05 was considered statistically significant. SAS 9.2 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

Results

1. Patients.

Baseline clinical characteristics of the patients are summarized in Table 1. The demographics were comparable between the two groups. All the patients had recurrent VT refractory to AADs (Median 2, range 1-4) and underwent an ICD implant prior to the index ablation procedure. No statistically significant bias was noted in the choice of procedure by physicians at the participating centers (Fleiss’s Kappa=0.667; 95% CI 0.48-0.87, p= 0.001).

2. Electrophysiology study, mapping and ablation.

During the electrophysiology study, a median of 2 VTs (range from 1 to 4 in Group 1 and from 1 to 5 in Group 2) were induced and targeted for ablation. The procedure, fluoroscopy and radiofrequency times were longer in Group 2 (Table 2).

CARTO map was successfully performed in all patients. Scar was identified in all patients with predominant locations at the lateral tricuspid annulus, RV outflow tract, anterior or apical RV wall and inferior RV wall. In Group 2 patients, the area of scar was larger in epicardium (17.6±14.8 cm²) than that in endocardium (9.8±7.0cm²; Table 2, p=0.04; Figure 1C-1D). All patients achieved the procedural endpoint at the end of ablation. Polymorphic VT/VF was induced in 1 patient from Group 1 and 2 patients from Group 2, these tachycardias were not targeted for further ablation. However, the presence of frequent PVCs after ablation was noted in 12 (52.1%) patients from Group 1 and 4 patients (15.4%) from Group 2 (p=0.006 vs. Group 1),
respectively (Table 3). No tachycardia could be induced in these patients and the PVCs were not subject to ablation in the index procedure.

3. Complications.

There were no major complications associated with the procedure in all patients. A groin hematoma was noted in 2 patients in Group 1 and 1 patient in Group 2. No patient in Group 2 had symptomatic pericardial effusion/tamponade post ablation or at the time of discharge.

4. Follow-up.

No patient died or underwent heart transplantation during the follow-up period. After a follow-up of at least 3 years (1224±310 days for Group 1 and 1175±112 days for Group 2), freedom from VA or appropriate ICD therapy was 52.2% (12/23) in Group 1 and 84.6% (22/26) in Group 2, respectively (Table 3). Among these patients, 5 from Group 1 (5/23, 21.7%) and 18 from Group 2 (18/26, 69.2%) were off AAD (p<0.001). Out of the 4 patients who had recurrence of VA in Group 2, one patient had an ICD shock 2 weeks after the procedure, one had a VT treated with anti-tachycardia pacing at 6 months follow up, and two had an ICD shock after one year when discontinuing AADs. The Kaplan-Meier curve showed significant difference of arrhythmia/ICD therapy-free survival between two groups (Log rank p=0.029, Figure 2).

Out of the 26 patients in Group 2, 14 (54%) had prior VT ablation at other centers from endocardium before the index procedure. We performed a sub-analysis to examine if patients with prior endocardial ablation had significantly different success rate compared to those undergoing their first procedure. The event-free survival at the end of follow-up was 86% among
patients with previous endocardial ablation and was 83% for those undergoing endo-epicardial ablation as the first procedure (Log rank p=0.884).

At the end of the procedure, more patients in Group 1 presented with frequent PVCs than Group 2 (12/23 vs. 4/26, p=0.006; Table 3). More VA recurrence/ICD therapy were seen in patients who had frequent PVCs after ablation (12/16, 75%) compared to patients in whom PVC was absent (3/33, 9%; Log rank p<0.001; Table 3). In the overall study population (Figure 3A) or in each separate group (Figure 3B-3C), patients who had no PVC after isoproterenol challenge at the end of the procedure had higher VA/ICD therapy-free survival.

**Discussions**

The main findings of this study are: (1) compared to an endocardial-alone ablation strategy, an endo-epicardial based approach increases long-term arrhythmia-free survival in patient with ARVD/C; (2) the endo-epicardial ablation is more likely to result in discontinuation of AAD; (3) at the end of the VT ablation procedure, the presence of frequent PVCs was associated with more VA recurrence at follow up.

Arrhythmogenic right ventricular dysplasia cardiomyopathy is a genetic, heterogeneous disorder characterized by an autosomal dominant pattern of inheritance; and by histopathologic changes of the myocardium which are believed to keep progressing. The disease process usually begins in the subepicardium and progresses to the subendocardium, and rarely from RV to LV [15,16]. The clinical presentation of ARVD/C is variable and is thought to be related to the temporal progression of the pathologic lesions. Accordingly, ARVD/C patients are classified into four clinico-pathologic stages: “Concealed Phase or Silent Phase”, “overt arrhythmic phase”, “global right ventricular dysfunctional phase” and “bi-ventricular pump failure phase” [17]. However,
mostly commonly, patients with ARVD/C come to clinical attention owing to the development of symptomatic VA with RV origin, usually at the age of 30-40 years and precipitated by exercise. This subgroup of ARVD/C patients mostly remained in the second stage of the disease and constituted the majority who seek treatment for their arrhythmias rather than heart failure. At this time, the disease is characterized by segmental or global RV pathological changes with residual normal myocardium located in the endocardium, rarely associated with histological evidence of LV involvement [15-19]. The regional (between “normal’ and “scar/abnormal” areas) and transmural (between epicardium, mid-layer myocardium and endocardium) electrophysiological heterogeneities provide the arrhythmogenic substrate which are the targets of ablation in ARVD/C patients [20]. In light of this, one would expect that a combined endo-epicardial ablation approach would achieve higher freedom from recurrent arrhythmias.

Radiofrequency ablation of VA has traditionally only been used in medically refractory ARVD/C cases due to fear of perforation of the thin right ventricular wall and the progressive nature of the disease [5]. With the currently available techniques, catheter ablation has become a therapeutic option in ARVD/C patients with recurrent VA, as AAD have not clearly proven to be effective and ICD implantation itself is not curative. However, most of procedures in the published series were performed using an endocardial approach and the ablation success rate was not satisfactory [3-8, 21-23]. Epicardial ablation has been recently applied in ARVD/C patients and associated with better arrhythmia control, but under most circumstance, this technique was used as a complimentary approach to previous single or multiple failed endocardial-alone ablations [14, 24, 25]. Of note, the initial experience on non-pharmacologic therapy of refractory VT in ARVD/C came from surgeons who either made epicardial incision or placed surgical ablation at the site of origin of VT, which successfully prevented the recurrence of arrhythmias [26, 27]. Several
mechanisms may explain the uniform outcome of endocardial-alone ablation and the necessity of performing endo-epicardial based ablation in ARVD/C patients. First, parts of the RV wall may have become thickened in some ARVD/C patients and RF energy delivered from the endocardium alone is unable to achieve transmural lesions \cite{14}. To this aspect, the endo-epicardial ablation is more likely to create full-thickness permanent myocardial necrosis and eliminate the arrhythmogenic sources including intramural phase 2 reentry. Second, the specific target of ablation based on endocardial mapping (i.e. exit of a reentry circuit or a focal pattern activation) could be just the breakout site of a reentry circuit that is located in the epicardium. Therefore, the tachycardia can only be abolished by RF ablation in the epicardial space. Furthermore, it has been noted that the epicardial scar/abnormal region identified by 3D voltage mapping many times extends beyond the site of the endocardial scar/abnormal areas \cite{14, 28}, suggesting that parts of the epicardial arrhythmogenic substrate would never be targeted and modified by extensive endocardial-alone ablation. Our approach used in Group 2 patients included linear ablation encircling the epicardial scar/abnormal area and abolition of any delayed, split, and fragmented “abnormal” electrograms. By this way, potential arrhythmogenic sources localized within this zone were isolated or abolished and possible reentrant circuits located in the scar border zone were also eliminated. Similar technique was recently reported by Bakir I. et al \cite{29} who used cryo energy in a surgical ablation procedure in an ARVD/C patient with incessant VT despite 3 endocardial ablations; and by Garcia FC. et al \cite{14} who reported their experience on epicardial ablation in patients with previously failed endocardial procedures.

It has been recognized that the fat tissue in the pericardial space may influence the human epicardial bipolar electrogram recordings by which an ablation target is determined \cite{30, 31}. However, the fat pad will only decrease the amplitude of the electrogram if it is overlying an area
of normal myocardial, but will not make the electrogram becoming delayed, split or fragmental which are characteristics of diseased myocardium. Looking at the amplitude, timing and morphology of the epicardial electrogram we were able to accurately detect the boundary of “abnormal/scar” region and distinguish it from normal myocardium. This is consistent with the findings during LV epicardial mapping [28].

Even though reentry is the main mechanism of VT in ARVD/C, enhanced automaticity occurring during exercise and trigged activity from inflammatory myocytes may also contribute to the development of VA. When reentrant circuit was present, PVCs associated with trigger activity could initiate sustained reentry tachycardia. In addition, after all existing reentrant circuits are ablated, enhanced automaticity could initiate focal tachycardia [20]. On the other hand, due to the progressive nature of ARVD/C, new reentrant circuit may become manifested. This could explain why the presence of frequent PVCs after VT ablation was associated with higher recurrence of arrhythmia in ARVD/C patients. Whether these PVCs should be targeted for ablation in order to further improve procedure success remained unclear and warrant additional studies.

**Study limitations**

This was not a randomized study but consecutive patients were enrolled in different centers. There could have been potential biases in selecting the ablation strategy for the patients. However, our subgroup analysis showed no inter-center difference in choice of procedure and no outcome difference between patients with and without previous endocardial ablation within Group 2. This made it less likely that non-randomization bias had significant influence on our results. Given the small number of events, we could not perform multivariable Cox analysis with
the current population, which might not have sufficient power to show independent predictor(s).

Biopsy and genetic testing were not available in all patients, but ARVD/C was diagnosed according to the consensus document criteria.

**Conclusion**

Epicardial scar and abnormality play an important role in the development of VAs in ARVD/C. An ablation strategy based on substrate modification with simultaneous endocardial and epicardial RF energy delivery is associated with improved arrhythmia-free survival and higher probability of AAD discontinuation. This approach should be considered as the initial strategy of VT ablation in patients with ARVD/C. The presence of ≥10 PVCs per minute after ablation is associated with more VA recurrence.

**Funding Sources:** Dr. Bai was supported from China by the Program for New Century Excellent Talents in University (NCET-09-0376); the National Natural Science Foundation (NSFC-30700297 and 30973601) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars (SFR ROCS 2008-101).

**Conflict of Interest Disclosures:** Preliminary results of this study were presented as an abstract at the European Cardiology Society Scientific Session 2010 and the American Heart Association Scientific Session 2010. Dr. Di Biase is a consultant for Hansen Medical and Biosense Webster. Dr. Natale received speaker honorariums from Boston Scientific, Biosense Webster, St. Jude Medical, Biotronik and Life Watch.

**References:**


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**Table 1.** Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N=23)</th>
<th>Group 2 (N=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong>†</td>
<td>34±14</td>
<td>37±11</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>15 (65%)</td>
<td>18 (69%)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)†</strong></td>
<td>57±7</td>
<td>53±10</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Failed AAD prior to index ablation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sotalol</em></td>
<td>11 (47.8%)</td>
<td>13 (50%)</td>
<td>1.00</td>
</tr>
<tr>
<td><em>Amiodarone</em></td>
<td>17 (73.9%)</td>
<td>18 (73.1%)</td>
<td>0.72</td>
</tr>
<tr>
<td><em>Dofetilide</em></td>
<td>1 (4.3%)</td>
<td>2 (7.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td><em>Beta blocker</em></td>
<td>4 (17.4%)</td>
<td>5 (19.2%)</td>
<td>0.97</td>
</tr>
<tr>
<td><em>Class I and other AADs</em></td>
<td>7 (30.4%)</td>
<td>6 (23.1%)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

AAD: anti-arrhythmic drug; LV: left ventricular

†: The numbers represent mean +/- standard deviation.
Table 2. Comparison of Procedural Parameters between Two Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N=23)</th>
<th>Group 2 (N=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT targeted for ablation‡</td>
<td>2 (1-4)</td>
<td>2 (1-5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Cycle length of VTs (ms)</td>
<td>262±62</td>
<td>287±57</td>
<td>0.85</td>
</tr>
<tr>
<td>Endocardial CARTO map points</td>
<td>316±127</td>
<td>356±143</td>
<td>0.87</td>
</tr>
<tr>
<td>Epicardial CARTO map points</td>
<td>N/A</td>
<td>334±123</td>
<td>N/A</td>
</tr>
<tr>
<td>Endocardial scar area (cm²)</td>
<td>10.9±6.4</td>
<td>9.8±7.0</td>
<td>0.51</td>
</tr>
<tr>
<td>Epicardial scar area (cm²)</td>
<td>N/A</td>
<td>17.6±14.8*</td>
<td>N/A</td>
</tr>
<tr>
<td>Procedure time (hour)</td>
<td>3.9±1.1</td>
<td>5.3±1.2</td>
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<tr>
<td>Fluoroscopy time (minute)</td>
<td>51.3±20.2</td>
<td>65.9±13.1</td>
<td>0.015</td>
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<tr>
<td>Radiofrequency time (minute)</td>
<td>20.2±15.3</td>
<td>25.8±13.7</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*: p=0.04 compared to endocardial scar area in Group 2 patients. VT: ventricular tachycardia
‡ The numbers represent median (range). The rest of numbers provided in the table represent mean +/- standard deviation.

Table 3. Prevalence of PVC and Recurrence of VA in Two Groups

<table>
<thead>
<tr>
<th></th>
<th>Presence of frequent PVC with/without Isoproterenol</th>
<th>Absence of PVC with Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No VA Recurrence/IC D Therapy</td>
<td>VA Recurrence/IC D Therapy</td>
</tr>
<tr>
<td>Group</td>
<td>Total</td>
<td>Recurrence/IC</td>
</tr>
<tr>
<td>Group 1 (N=23)</td>
<td>12</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Group 2 (N=26)</td>
<td>4</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Total (N=49)</td>
<td>16</td>
<td>4 (25%)</td>
</tr>
</tbody>
</table>

PVC: premature ventricular contraction; VA: ventricular arrhythmia; ICD: implantable cardioverter-defibrillator
Figure Legends:

**Figure 1 A-B.** Bipolar voltage map of the RV endocardium in a patient with ARVD/C from Group 1 (A: LAO view; B: AP view). Regions in red represent scar (bipolar voltage <0.5 mV), and purple regions represent normal myocardium (bipolar voltage >1.5 mV). Other colored regions represent abnormal myocardial regions (bipolar voltage between 0.5 and 1.0 mV). The scar is located in superior anterior RV and proximal RV outflow tract. In this case, serial ablations were applied (red dots) inside scar region and to surround region of abnormal voltage. RV: right ventricular; ARVD/C: arrhythmogenic right ventricular dysplasia/cardiomyopathy.

**Figure 1 C-D.** Endocardial (C: AP view) and epicardial (D: AP view) bipolar voltage map of the RV in a patient with ARVD/C from Group 2. Definitions of endocardial scar or normal myocardium remained the same as in Figure 1A and 1B. Epicardially, “normal” area was set as a bipolar electrogram amplitude > 1.0 mV while the “scar” myocardium was defined as a bipolar electrogram amplitude < 0.5 mV. EGMs of representative endocardial/epicardial mapping site were shown in the middle panel. In each EGM recording, in addition to ECG leads II, V3 and aVL, electrograms on proximal (M3-M4) and distal (M1-M2) ablation catheter were shown. The scar region was larger in the epicardium, and it was located in anterior and lateral RV extending to the basal RV and tricuspid valve area. In addition to lesions (red dots) placed at opposite endocardial and epicardial sites with abnormal voltage, more RF applications were applied in the epicardium at sites demonstrating abnormal recordings. EGM: electrogram.

**Figure 2.** Ventricular arrhythmia/ICD therapy-free survival by the ablation approach. The Kaplan-Meier curve showed significant difference of ventricular arrhythmia/ICD therapy-free survival between Group 1 (Endocardial-alone ablation) and Group 2 (Endo-epicardial ablation). ICD: implantable cardioverter defibrillator; VA: ventricular arrhythmia.

**Figure 3.** Ventricular arrhythmia/ICD therapy-free survival by the presence of frequent PVCs in the entire study population (A) and in Group 1 (B) or Group 2 (C). Regardless of the ablation approach, the presence of frequent PVCs at the end of ablation was associated with more VA recurrence. PVC: premature ventricular contraction; VA: ventricular arrhythmia.
Endocardial map

Epicardial map
Ablation of Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Arrhythmia-Free Survival after Endo-Epicardial Substrate Based Mapping and Ablation

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Circ Arrhythm Electrophysiol. published online June 10, 2011;
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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