Electroanatomic Substrate and Outcome of Catheter Ablative Therapy for Ventricular Tachycardia in Setting of Right Ventricular Cardiomyopathy

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Background—To gain insight into the pathogenesis of right ventricular (RV) cardiomyopathy and ventricular tachycardia (VT), we determined the clinical and electroanatomic characteristics and outcome of ablative therapy in consecutive patients with (1) RV dilatation, (2) multiple left bundle-branch block (LBBB)–type VTs, and (3) an abnormal endocardial substrate defined by contiguous electrogram abnormalities.

Methods and Results—All 21 patients had detailed RV bipolar electrogram voltage mapping. Eighteen patients had simultaneous left ventricular (LV) mapping, including all 4 patients with right bundle-branch block (RBBB) VT. VT was ablated in 19 patients by use of focal and/or linear lesions with irrigated-tip catheters in 10 of 19 patients. Eighty patients were men, age 47 ± 18 years, and none had a family history of RV dysplasia. RV volume was 223 ± 89 cm³. Electrogram abnormalities extended from perivalvular tricuspid valves (5 patients), pulmonic valves (6 patients), or both valves (10 patients). Electrogram abnormalities always involved free wall, spared the apex, and included the septum in 15 patients (71%). The area of abnormality was 55 ± 37 cm² (range, 12 to 130 cm²) and represented 34 ± 19% of the RV. In 52 of 66 LBBB VTs, the origin was from the RV perivalvular region. LV perivalvular low-voltage areas noted in 5 patients were associated with a RBBB VT origin. No VT recurred after ablation in 17 patients (89%) during 27 ± 22 months.

Conclusions—In patients with RV cardiomyopathy and VT, (1) perivalvular electrogram abnormalities represent the commonly identified substrate and source of most VT, (2) LV perivalvular endocardial electrogram abnormalities and VT can occasionally be identified, and (3) aggressive ablative therapy provides long-term VT control. (Circulation. 2004;110:2293-2298.)

Key Words: tachycardia ■ cardiomyopathy ■ catheter ablation ■ mapping

The diagnosis of “arrhythmogenic right ventricular dysplasia/cardiomyopathy” (ARVD/CMD) has been used to describe the right ventricular (RV) myopathy associated with multiple left bundle-branch block (LBBB)–type ventricular tachycardia (VT).1-3 ARVD has been associated with an autosomal dominant inheritance pattern, with 30% to 50% of family members of index patients having manifestations of the disease, suggesting a dysontogenetic or genetically determined degenerative process.3-5 A possible infectious or immunologic cause resulting in postinflammatory RV fibrofatty cardiomyopathy has also been suggested with up to 80% of hearts at autopsy documenting inflammatory infiltrates.6-8

We have recently described perivalvular LV endocardial electrogram abnormalities consistent with fibrosis in 19 patients with idiopathic left ventricular (LV) cardiomyopathy and VT.9 Importantly, the distribution of RV and LV electrogram abnormalities in patients with the diagnosis of RV cardiomyopathy and VT has not been described in detail and may provide insight into the disease pathogenesis. The purpose of this study was to define the clinical characteristics, RV and LV electroanatomic substrates, and outcome with ablative therapy in a consecutive series of patients with (1) RV dilatation, (2) multiple morphologically distinct LBBB VTs, and (3) a contiguous area of bipolar RV endocardial voltage electrogram voltage abnormalities.

Methods

Study Inclusion Criteria

Sixty-five consecutive patients who presented with LBBB VT and underwent detailed RV endocardial voltage mapping during baseline rhythm were considered for entry into the study. Thirty-eight patients were excluded because they had typical RV outflow tract VT and normal RV voltage maps.10 Six patients with VT from non-RV outflow tract sites but normal endocardial RV voltage maps were also excluded.
The 21 patients included in the study had (1) RV enlargement as documented on echocardiography, (2) multiple (≥2) morphologies of LBBB VT, and (3) detailed electroanatomic maps with an area of discrete contiguous bipolar electrogram voltage abnormalities (amplitude, <1.5 mV).

Two patients with the diagnosis of idiopathic LV cardiomyopathy and LV VT are also included in this report. Although these 2 patients were included to provide additional information linking the pathogenetic mechanisms that occur on RV and LV electroanatomic maps. These patients were included to provide additional information linking the pathogenesis of idiopathic LV cardiomyopathy and VT and the RV cardiomyopathy and VT described in the study population.

Clinical Characterization of Patients
Detailed family histories, clinical and ECG characteristics, and echocardiographic RV and LV size and function were assessed. MRI was not performed routinely because of the presence of an implantable defibrillator in 14 patients at the time of index evaluation.

Electrophysiological Evaluation
The study patients underwent electrophysiological evaluation after informed consent had been obtained. All procedures were performed according to the institutional guidelines of the University of Pennsylvania Health System. All patients underwent programmed stimulation that included up to triple extrastimuli from multiple ventricular sites using at least 2 drive cycle lengths.

Endocardial Mapping
All patients underwent detailed magnetic electroanatomic voltage mapping as previously described.9,12 RV endocardial mapping was performed in all 21 patients, with LV endocardial mapping in 18 of the patients. The mapping catheter (Navistar) had a 4-mm distal tip and 2-mm ring electrode with an interelectrode distance of 1 mm. The bipolar signals were filtered at 10 to 400 Hz and were displayed at 100-mm/s speeds on the CARTO (Biosense, Inc) system. The peak-to-peak signal amplitude of the bipolar electrogram was measured automatically. Electroanatomic mapping was performed during sinus rhythm in 17 patients and during RV paced rhythm in 4 patients.

The electrogram signals were displayed as color gradients on a 3D bipolar voltage map.9,12 Tricuspid and mitral valvular sites were identified by the fluoroscopic catheter tip positions at the ventricular base with discrete bipolar recordings that demonstrated both atrial and ventricular signals of approximately equal amplitude. The pulmonic valve was carefully identified by passing the mapping catheter into the pulmonary artery and slowly withdrawing it until an RV electrogram was identified. Valvular sites were given a “location only” tag to preclude their influence on the voltage map color display. Careful attention was paid to record multiple endocardial electrograms around valvular structures. To ensure adequate sampling and representation of the entire endocardial surface area, the Fill Threshold of the CARTO system was set at 20 mm. Intracavitary points were identified as abrupt indentations on the endocardial shell contour with associated sudden reductions in signal slew rate and were appropriately edited from the voltage maps.

VT Localization and Catheter Ablation
The 12-lead ECG morphology of all induced and spontaneous VTs was assessed to approximate the site of origin (see Figure 6).12,13 The VT mapping techniques included activation, entrainment, and pace mapping using standard criteria.9,12,14 The “site of origin” for mappable VT was demonstrated preystolic activity and entrainment with concealed fusion and a return cycle length within 30 ms of VT cycle length. Termination with focal endocardial RF energy application was associated with these criteria. For VT that was not mappable, the site of origin was approximated by the site of pace mapping that generated QRS complexes similar to those of VT.9,12 Detailed activation mapping and entrainment mapping could not be performed, but limited activation and entrainment information was used to corroborate pace map information when available. For unmappable VT, radiofrequency ablation was performed as linear lesions based on the location of the best pace map, the location of valvular anatomic boundaries, and the substrate defined by the voltage mapping as previously described.9,12 Characteristically, linear lesions crossed through the site of the best pace map and extended from the most abnormal endocardium (<0.5 mV) to either the valve annulus or normal myocardium (>1.5 mV).9,12 The efficacy of ablation therapy was assessed on the basis of inducibility of VT and clinical follow-up using implantable defibrillator interrogation to document arrhythmia recurrences.

Reference Values for Bipolar Voltage Mapping
Reference values for identifying abnormal bipolar electrogram signal amplitude in the RV and LV have been established using the Navistar catheter and the CARTO mapping system.11 In an attempt to adjust for factors such as hypertrophy and aging in our patient population, the reference value for bipolar electrogram amplitude used to identify “normal” endocardium in this study was set at 1.8 to 2.0 mV whenever we assessed size of LV endocardial scar and/or displayed RV and LV endocardial voltage maps simultaneously. For the display of the RV endocardial bipolar voltage maps only, a signal amplitude of >1.5 mV was categorized as normal and was represented by the color purple.12 Thus, abnormal endocardium on the voltage map displays was always represented by the nonpurple range of colors, with the most abnormal signal amplitude, defined as “dense scar” (consistent with signal amplitude <0.5 mV), represented by the color red (Figures 1 to 7).

Estimation of Abnormal RV Endocardium Using Endocardial Voltage Map
Abnormal RV endocardium was defined as areas of contiguous recordings with electrogram amplitude of ≤1.5 mV. The extent of
abnormal endocardium was estimated by measuring contiguous areas of abnormal electrogram signals from computer-generated color images using previously described techniques.9,12 By using the same “area calculation” algorithms, the entire RV endocardial surface area can be estimated, and the percentage of abnormal endocardium can also be measured.9,12 A total segment of electrogram abnormalities of at least 10 cm² with multiple sample points was required for study inclusion because small areas of perivalvular low voltage can occasionally be identified in the absence of RV cardiomyopathy because of inadequate bipolar electrogram sampling. Of note, RV volume measurements were automatically calculated for all patients using the system’s software.

Statistics
All results were presented as mean±SD. A probability value of P<0.05 was considered statistically significant.

Results
Patient Population
There were 18 men and 3 women, with a mean age of 47±18 years (range, 18 to 79 years). All patients presented for evaluation of sustained VT. On echocardiographic imaging, all had evidence of RV enlargement, with 17 patients having moderately to severely decreased RV function. Average RV volume from voltage maps was 223±89 cm³. The baseline 12-lead ECG showed precordial T-wave inversion (V2 and V3) in 15 patients, epsilon waves in 14 patients, and RV paced rhythm in 4 patients. Only 1 patient had a normal baseline ECG. Patients had clinical diagnosis of ARVD/CM on the basis of their clinical arrhythmia, echocardiographic findings, and/or the marked resting 12-lead ECG abnormalities.3 In 19 of the 21 patients, catheter ablation was attempted because of recurrent VT episodes. All patients had implantable defibrillators (14 before and 7 after their index evaluation). LV function was normal in 11 patients and depressed in 10 patients, with an LV ejection fraction of 20% to 45%. Five patients had a history of LV heart failure.

No patient had a family history of ARVD/CM. In addition, none of the study patients had a family history of ventricular
arrhythmias. One patient’s father had known coronary disease and died suddenly as a result of acute myocardial infarction.

**Electroanatomic Mapping**

An average of 186±87 sites were mapped per RV and LV chamber. The electrogram abnormalities in the RV were always perivalvular and tended to extend toward the apex, often in a cone-like manner involving both the free wall and, to a lesser extent, the septum (Figures 1 to 3). Three distinct patterns of perivalvular involvement were identified. Pattern 1, seen in 5 patients, demonstrated a confluent area of abnormal electrograms extending from the tricuspid valve only. Pattern 2, seen in 6 patients, demonstrated a confluent area of abnormal electrograms extending from the pulmonic valve only. Pattern 3, seen in 10 patients, demonstrated abnormal electrograms extending from both the tricuspid and pulmonic valve regions (Figures 2 and 3). Of note, in 15 patients (71%), the voltage abnormality included the septal aspect of the perivalvular region (Figures 2 and 3). In all patients, including those with extensive perivalvular abnormalities, the RV apex always demonstrated normal voltage and was represented by the purple color on the voltage maps. The extension toward the apical segment was quite marked in most abnormal myocardium, with a signal amplitude <0.5 mV, through abnormal endocardium with a good pace map match to annular/valvular structures as previously described.9,12 In patients with less extensive perivalvular bipolar voltage abnormalities, the linear lesion extended across the entire segment of abnormal myocardium.9 More than 1 ablation procedure was required in 13 patients. In 10 patients, a cooled-tip catheter was used for making linear lesions in conjunction with simultaneous CARTO-guided catheter mapping to facilitate accurate cooled-tip catheter lesion localization.

All VTs were seen to originate from endocardium demonstrating abnormal bipolar electrograms, and 52 of the 66 LBBB VTs were localized within 2 to 3 cm of the valve orifice in the RV (Figure 6). Only when the abnormal endocardial electrograms extended for a considerable distance from the valve (10 of the 21 patients) was the LBBB VT site of origin identified. In 3 patients (16%), a VT site of origin was identified in proximity to the apical extent of the identified abnormal endocardium. All 5 VTs with an RBBB morphology had positive R waves from V1 to V6 on the 12-lead ECG and were localized to the very basal LV segment in proximity to the mitral valve (Figure 6) from areas demonstrating abnormal bipolar electrograms. At the end of the ablation procedure, 14 of the 19 patients had no inducible VT, and 5 of the patients had polymorphic VT or rapid VT, cycle length <300 ms, that were not targeted for additional ablation. No complications were observed related to the ablation procedure.

Seventeen of the 19 patients (84%) had no VT after ablation during a mean follow-up of 27±22 months (range, 2
to 67 months). Two remaining patients had infrequent arrhythmia recurrence (≤1 episode/3-month period) during follow-up periods of 16 and 69 months, respectively. There were no arrhythmic deaths.

**Patients With LV Cardiomyopathy With RV Involvement**

The 2 additional patients who presented with LV cardiomyopathy with manifest LV heart failure and recurrent RBBB VT also had RV dilatation on echocardiography and inducible LBBB VT.

The following observations were noted at electrophysiological and/or pathological evaluation that link the pathogenesis between idiopathic LV cardiomyopathy and VT and RV cardiomyopathy and VT.

1. Both patients demonstrated mitral and tricuspid perivalvular contiguous areas of bipolar low-voltage electrogram abnormalities.
2. RBBB VTs were localized to and ablated in the region of the mitral valve in both patients.
3. LBBB VTs were localized to and ablated in the region of the tricuspid valve in both patients.
4. Epicardial mapping was performed in 1 of the 2 patients and identified low-voltage signals over the basal RV and LV, with the most marked abnormalities seen in proximity to the region of the tricuspid and pulmonic valves (Figure 7).
5. Analysis of the explanted heart in the second of the 2 patients identified endocardial fibrosis that corresponded in distribution to the areas with endocardial bipolar voltage abnormalities identified during electroanatomic mapping (Figure 8).

**Comparison With Previous Reports Using Electroanatomic Mapping**

Boulos et al\(^{15}\) identified areas of low electrogram voltage involving primarily the RV free wall in 7 patients with ARVD. Two of the study patients were brothers, but no other family history was identified. In that report, the authors noted

antrolateral RV involvement in 6 patients, RV outflow tract involvement in 4 patients, and identified apical involvement in only 2 patients (28%). They suggested that electrogram voltage changes should be considered diagnostic for the disease and an important part of a patient’s evaluation. The bipolar voltage map abnormalities noted for our study group of 21 patients extends Boulos’ work and identifies perivalvular involvement as being uniformly observed. Although free wall involvement extending from these perivalvular abnormalities predominates, the septum is more frequently involved than previously noted. The very apical region of the RV was noted to be spared in our patients, suggesting that apical bipolar voltage changes are unusual unless as an extension of antrolateral involvement. Importantly, only in that setting was a VT site of origin noted that more closely approximated the apex.

**Pathological Considerations and Relationship to LV Cardiomyopathy**

The disease has been reported to begin epicardially and progress to the endocardium.\(^{6,7,16}\) Endocardial fibrosis as reflected by the voltage map findings might be a manifestation of more extensive disease involvement and might be anticipated to be the more common substrate for uniform sustained VT. Consistent with our observations, one report described diffuse or patchy RV endocardial fibrosis in 14 of 34 hearts (41%) evaluated in an autopsy series of patients who presented with sudden death.\(^{16}\) Additional study will be required to determine whether an extensive perivalvular fibrotic process is fairly specific for patients who present with sustained unimorphic ventricular tachycardia in the setting of RV cardiomyopathy.\(^{6,7,16}\) Importantly, previous pathological studies also documented (1) a high incidence of LV involvement in patients presenting with RV cardiomyopathy, with LV involvement characteristically basal and lateral in origin, and (2) a high prevalence (≈67%) of inflammatory infl-
The similarities of the RV and LV voltage maps in a significant subgroup of patients noted in our study are consistent with the previous pathological reports. These observations, coupled with the electroanatomic and pathological findings noted in the patients presenting with LV cardiomyopathy in this and our previous report, suggest a strong pathogenic link between RV and LV cardiomyopathy.

Ablation of VT and Clinical Outcome

Ellison et al studied 5 patients with VT in the setting of arrhythmogenic RV cardiomyopathy and documented that reentrant circuits and sites of successful ablation tended to cluster around the tricuspid valve and the pulmonic outflow tract. Their findings are consistent with our observations in a larger series of patients. Importantly, in our study population with frequent arrhythmia recurrences and unmappable VT with multiple VT morphologies, long-term arrhythmia control was achieved by using both focal and linear lesion techniques and the use of a cooled-tip catheter when appropriate. Linear lesions characteristic were deployed to interrupt abnormal endocardium guided by pace mapping and extended to the valve orifices. Of note, the common occurrence of VT that mimics the QRS morphology of classic idiopathic RV outflow tract tachycardia has been described previously and is highlighted again by our study results.

Clues suggesting the presence of an RV cardiomyopathy, such as the presence of RV dilation, multiple VT morphologies, and the well-defined anatomic substrate, facilitate distinction from the more benign disorder. Importantly, the present report provides a clear guide for identifying abnormal perivalvular endocardial substrate, the anticipated site of origin for most VT and an ablation strategy that results in long-term VT control.

Limitations

In the absence of pathological studies, an anatomic description based on the bipolar voltage maps must be considered speculative. For example, aneurysmal dilatation of the VT at the apex has been described in pathology reports in patients with ARVD/CM. The absence of low-voltage areas may suggest that significant fiber disruption and fibrosis is not present but does not exclude the presence of aneurysmal thinning. In addition, it is possible that several of the patients with normal endocardial voltage maps with multiple LBBB VT who were excluded from analysis actually had fiber disruption leading to VT that had not reached the endocardium, and by excluding them, we underrepresented the full spectrum of VT in the setting of RV cardiomyopathy. Finally, voltage characteristics for defining normal for the epicardial spectrum of VT in the setting of RV cardiomyopathy. Importantly, the presence of RV dilation, multiple VT morphologies, and the well-defined anatomic substrate, facilitate distinction from the more benign disorder. Importantly, the present report provides a clear guide for identifying abnormal perivalvular endocardial substrate, the anticipated site of origin for most VT and an ablation strategy that results in long-term VT control.

References

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