Determinants of Postinfarction Ventricular Tachycardia

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Background—Structural factors contributing to the development of postinfarction ventricular tachycardia (VT) are unclear. The purpose of this study was to analyze infarct architecture and electrogram characteristics in patients with and without inducible VT and to identify correlates of postinfarction VT.

Methods and Results—Twenty-four postinfarction patients (median age, 64 [53, 70] years) were referred for radiofrequency catheter ablation of VT (n=12) or frequent symptomatic premature ventricular contractions (PVCs) (n=12). Delayed-enhanced (DE) MRI was obtained before ablation. Electroanatomical mapping was performed and scar area and electrogram characteristics of the scar tissue compared in patients with and without inducible VT. The median ejection fraction in patients with and without inducible VT was 27% (22%, 43%) and 43% (40%, 47%), respectively (P=0.085). Subendocardial infarct area determined by DE-MRI was larger in patients with inducible VT (43 [38, 62] cm²) than in those with noninducible VT (8 [4, 11] cm²; P=0.002), and unipolar and bipolar voltages on electroanatomical maps were significantly lower in patients with inducible VT than in those without (13.2% versus 1.1% of points within scar; P<0.001). The number of inducible VTs correlated with the number of distinct sites with IPs (R=0.87; P<0.0001).

Conclusions—Scar tissue in postinfarction patients with inducible VT shows quantitative and qualitative differences from scars in patients without inducible VT. Scar size and IPs are correlated with VT inducibility. (Circ Arrhythm Electrophysiol. 2010;3:624-631.)

Key Words: myocardial infarction ■ tachycardia ventricular ■ potentials ■ scar ■ magnetic resonance imaging

Prior studies have suggested that the severity of ventricular arrhythmias after myocardial infarction is related to the extent of myocardial injury.1–3 However, ventricular arrhythmias do not invariably occur in patients with large infarcts.4 It may be that survival of myocardial fibers explains why arrhythmias occur in some, but not other patients.4 The purpose of this study was to compare infarct architecture, as determined by delayed enhanced (DE) MRI, infarct size, and electrogram characteristics, between postinfarction patients with and without inducible ventricular tachycardia (VT).

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Methods

Patient Characteristics

The subjects of this study were a consecutive series of 24 patients with postinfarction ventricular arrhythmias who were referred for catheter ablation with no contraindications for myocardial MRI (Table 1). Based on the results of the electrophysiology study, they were stratified into 2 groups: those in whom VT was inducible and those in whom VT was not inducible. None of the patients had prior ablation procedures.

MRI

Before the electrophysiology procedure, all patients underwent DE-MRI. The studies were performed on a 1.5-T MRI scanner (Signa Excite CV/i; General Electric; Milwaukee, Wis) with a 4- or 8-element phased-array coil placed over the chest of patients in the supine position. Images were acquired with ECG gating during breath holds. Dynamic short- and long-axis images of the heart were acquired using a segmented k-space, steady-state, free-precession pulse sequence (repetition time, 4.2 ms; echo time, 1.8 ms; in-plane spatial resolution, 1.4×1.4 mm; slice thickness, 8 mm). Fifteen minutes after administration of 0.20 mmol/kg of intravenous gadolinium diethylenetriamine penta-acetic acid (Magnevist; Berlex Pharmaceuticals; Wayne, NJ), 2D DE imaging was performed using an inversion-recovery sequence3 (repetition time, 6.7 ms; echo time, 3.2 ms; in-plane spatial resolution, 1.4×2.2 mm; slice thickness, 8 mm) in the short- and long-axis of the left ventricle at matching cine image slice locations. The inversion time (250 to 350 ms) was optimized to null the normal myocardium. All DE-MRI images were analyzed off-line with specialized postprocessing software (Cinetool; General Electric). For each subject, manual tracing of the endocardial contour of DE images was...
**Table 1. Patients Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Inducible VT</th>
<th>Noninducible VT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>No. of inducible VTs</td>
<td>3 (1, 6)</td>
<td>0 (0, 0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient age, y</td>
<td>65 (59, 72)</td>
<td>58 (49, 69)</td>
<td>0.25</td>
</tr>
<tr>
<td>Infarct age, y</td>
<td>12 (1, 16)</td>
<td>3.5 (1.5, 8.5)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Female/male sex</td>
<td>3/8</td>
<td>2/11</td>
<td>0.63</td>
</tr>
<tr>
<td>Ejection fraction (MRI), %</td>
<td>27 (22, 43)</td>
<td>43 (40, 47)</td>
<td>0.09</td>
</tr>
<tr>
<td>Infarct location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>8</td>
<td>4</td>
<td>0.30</td>
</tr>
<tr>
<td>Inferolateral</td>
<td>2</td>
<td>5</td>
<td>0.67</td>
</tr>
<tr>
<td>Anterior</td>
<td>3</td>
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<td>1.00</td>
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<tr>
<td>Anterolateral</td>
<td>0</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Amiodarone use</td>
<td>3</td>
<td>2</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Data are presented as counts or median (25th, 75th percentile).

performed on a stack of 15 to 20 short-axis images from base to apex of the left and right ventricles. The area of DE was then automatically determined by a region-growing algorithm as the area encompassing pixels with values ≥M/2, using the traditional method of full width at half maximum. Then the percentage of periinfarct zone was computed analogous to prior reports. All contours were exported for further processing with customized software using Matlab (Mathworks; Natick, Mass) to generate polar views representing the circumferential extent of DE from base to apex of the left and right ventricles. Subendocardial infarct area and infarct burden were measured. The infarct percentage was defined as the proportion of scar volume divided by the total myocardial volume.

**Electrophysiology Procedure**

A quadripolar electrode catheter was positioned in the right ventricle. Programmed stimulation was performed at the right ventricular apex and outflow tract using up to 3 drive cycle lengths and up to 4 extrastimuli. Isoproterenol was not used during programmed stimulation. All sustained, monomorphic VT morphologies that were induced before ablation were recorded and classified by 2 independent observers as identical or distinct if multiple VTs were induced before ablation were recorded and classified by 2 independent observers as identical or distinct if multiple VTs were induced. Only VT that was sustained was included. Sustained VT was defined as lasting ≥30 seconds or requiring termination <30 seconds secondary to hemodynamic intolerance. The protocol was performed in a similar manner in both patient groups and was finished only when the entire protocol was concluded from 2 right ventricular sites. Systemic heparinization with a target-activated clotting time of approximately 300 seconds was maintained throughout the procedure.

**Mapping Procedure**

An electroanatomical mapping system (CARTO; Biosense Webster Inc; Diamond Bar, Calif) was used in all patients. The mapping/ablation catheter was a 3.5-mm irrigated tip catheter. A 2-mm ring electrode was separated from the distal electrode by 1 mm (ThermoCool; Biosense Webster). Intracardiac electrograms were filtered at 50 to 500 Hz. The intracardiac electrograms and leads V1, V2, and V3 were displayed on an oscilloscope and stored on optical discs (EP Med; West Berlin, NJ).

Left ventricular access was obtained using a retrograde aortic approach. A sinus rhythm voltage map was performed in all patients. Bipolar pace mapping at an output of 10 mA and a pulse width of 2 ms was performed to identify VT reentry circuit exit sites and the sites of origin of premature ventricular complexes (PVCs). In patients with frequent PVCs, activation mapping also was performed.

**Analysis of Mapping Data**

Scarc was defined by a voltage <1.0 mV. Scar size was measured with CARTO version 7.0 software (Biosense Webster) (Figure 1A and B).

Mapping sites were considered distinct if they were separated by ≥5 mm. Bipolar electrograms were classified by 2 independent observers. Differences were resolved by consensus according to the following criteria,13 which were modified and adapted to the catheter and recording system used in this study:13

1. Normal electrograms: sharp biphasic or triphasic spikes with amplitudes ≥3 mV, duration <70 ms, and amplitude:duration ratio >0.046.
2. Fractionated electrograms: amplitude ≤0.5 mV, duration ≥133 ms, and amplitude:duration ratio <0.005.
3. Isolated potential: a potential separated from the ventricular electrogram by an isoelectric segment or a segment with low amplitude noise (<0.05 mV) of >20 ms duration at a gain of 40 to 80 mm/mV.
4. Electrograms that did not fit the first 3 categories were defined as nonfractionated abnormal electrograms.

If a site with an isolated potential was identified, higher resolution mapping was performed to allow demarcation of an area where contiguous isolated potentials were identified. An area with isolated potentials was considered distinct if it was surrounded by sites devoid of isolated potentials (Figure 2A).14 For hemodynamically tolerated VTs, a site was considered an isthmus site if 1 or both of the following criteria were present: (1) concealed entrainment with VT termination during radiofrequency ablation and (2) mechanical termination of VT with the catheter located at a certain location and VT no longer inducible after radiofrequency ablation. For nontolerated VTs, a matching pace map and noninducibility of VT after ablation were the criteria for a critical isthmus. A prior study demonstrated that these criteria are present at critical isthmus sites.13

**Radiofrequency Ablation**

Radiofrequency catheter ablation was performed at the critical isthmus sites of VT or at the site of origin of PVCs. Radiofrequency energy was delivered at 30 to 50 W targeting an impedance drop of 10 Ω with a maximal temperature of 45°C. If VT or spontaneous PVCs terminated during radiofrequency ablation, another application of radiofrequency energy was delivered at the same site.

**Follow-Up**

Patients who received an implantable cardioverter-defibrillator (ICD) were seen every 3 to 6 months in the ICD clinic. Patients who underwent PVC ablation were seen 3, 12, and 24 months postablation and had repeat Holter monitoring 3 months postablation.

**Methodological Analysis**

To identify the correlates of postinfarction VT, the electrogram characteristics of the arrhythmogenic substrate, including voltage, electrogram width, and the prevalence of abnormal electrograms, fractionated electrograms, and isolated potentials within the infarct region, were compared between patients with and without inducible VT. MRI findings that could identify patients at risk of postinfarct arrhythmia, such as left ventricular ejection fraction, infarct percentage, endocardial infarct area, infarct volume, percent of endocardial scar area, periinfarct zone percentage of scar, and periinfarct zone percentage, also were compared between the 2 groups.

**Statistical Analysis**

Data analysis was conducted using SAS version 9.1 (SAS Inc; Cary, NC). Continuous data were evaluated for normality and then compared between patients with and without VT using either Student t test or Wilcoxon rank sum test for normal and nonnormal data, respectively, with values expressed as mean ± SE or median (25th, 75th percentile) as appropriate. Categorical data were compared with Fisher exact test.
Odds ratios (95% CI) for nonrepeated data were generated using logistic regression. For repeated measures (electrogram width and unipolar and bipolar voltage), the distribution of data points was evaluated for normality and then the mean or median of each repeated variable was taken for each patient as appropriate. These data were compared across groups using independent-sample *t* tests or Wilcoxon rank sum test, as appropriate.

A receiver operating characteristic (ROC) curve for DE-MRI scar percentage and VT inducibility was generated, and the area under the curve was calculated. Scar percentage threshold was selected as that displaying optimal sensitivity and specificity for VT discrimination.

Mixed-model linear regression for repeated measures (random intercept) was then used to compare the unipolar voltage, bipolar voltage, and electrogram widths between patients with and without VT. Voltages obtained on electroanatomical mapping were dichotomized at the previously published threshold of <1 mV, the number of points at this threshold were compared between groups with Wilcoxon testing, and logistic odds ratios for VT inducibility were generated.

For all analyses, a *P* < 0.05 was considered statistically significant. This study was approved by the University of Michigan Medical Institutional Review Board.

**Results**

Characteristics of the cohort are shown in Table 1. Of the 24 subjects, 12 had clinical VT, and 12 had symptomatic PVCs. All patients had a history of myocardial infarction predating the catheter ablation procedure by a median of 5 (1, 12) years. Three of the patients with VT were treated with amiodarone within 6 weeks before the procedure. Two of the patients with PVCs had been treated with amiodarone within 6 weeks before the procedure.
Inducibility of VT
A total of 37 VTs (mean cycle length, 296 ± 58 ms) were induced in 11 of 24 patients. Twenty-eight VTs had a right bundle branch block morphology, and 9 had a left bundle branch block morphology. The other 13 patients had no inducible, sustained, monomorphic VT. Ten with inducible VT had a clinical history of sustained VT, and 1 with inducible VT had no clinical history of VT. In this patient, 4 monomorphic VTs were induced. One patient had clinical VT and PVCs, but only PVCs were inducible.

Electrogram Characteristics of Patients With and Without Inducible VT
In patients with inducible VT, 124 ± 94 endocardial points (range, 56 to 255 points) were registered during sinus rhythm compared to 148 ± 117 points (range, 37 to 416 points) in patients without inducible VT (P = 0.0001) (Table 2). The number of distinct points sampled within scar tissue in patients with inducible VT was 30 [28, 43] points versus 9 [6, 19] points in patients with noninducible VT (P = 0.003). The resulting point density was 0.94 [0.79, 1.22] points/cm² in patients with inducible VT compared to 1.25 [1.12, 1.64] points/cm² in patients without inducible VT (P = 0.01).

Distinct sites with isolated potentials were found almost exclusively in patients who had inducible VT, comprising 13.2% of the endocardial electrograms sampled in the scar areas (Table 2). In patients with noninducible VT, <1.1% of the scar electrograms displayed isolated potentials (P < 0.0001). In patients with inducible VT, 47.4% of the sites within the scar displayed fractionated electrograms compared to 26.9% of sites within the scar in patients without inducible VT (P = 0.0001). Sixty-four percent of the critical isthmus sites of reentrant VT displayed isolated potentials; 18% had fractionated electrograms, and another 18% showed nonfractionated abnormal electrograms.

Patients with inducible VT had significantly lower unipolar and bipolar voltages and longer electrogram widths than those without VT (Table 2). Accounting for correlated intrapatient data on repeated-measures analysis, patients with VT had a 71 ± 18% lower unipolar voltage (P = 0.011) and 10 ± 5.0% lower bipolar voltage (P = 0.004) than those without VT.

Inducible VTs and Critical Isthmus Areas
In patients with inducible VT, there was an association between the number of distinct sites with isolated potentials
and the number of inducible VTs ($R=0.77$; $P=0.005$). If patients with noninducible VT are included in the analysis, this association is stronger ($R=0.87$; $P<0.0001$) (Figure 3). Across the cohort, the odds (95% CI) of having inducible VT increased by 2.7 times [1.2 to 6.4 times] for each distinct site at which an isolated potential was recorded during the mapping procedure ($P=0.0043$). Infarct size as assessed by electroanatomical mapping also correlated with the number of inducible VTs ($R=0.74$; $P<0.0001$). In every patient with inducible VT, at least 1 critical isthmus of the VT reentry circuit was identified.

### Inducibility of VT and Infarct Size on DE-MRI

Although MRI-derived ejection fraction was not statistically different between groups, there was a trend toward a lower ejection fraction in patients with VT (Table 1). All DE-MRI measures of infarct size (infarct volume, infarct percentage, and endocardial infarct area) were associated with VT inducibility (Table 3). The odds of VT inducibility increased 40% (odds ratio, 1.4; 95% CI, 1.1 to 1.7) for each percentage of endocardial scar measured on DE-MRI. By ROC analysis (Figure 4), a scar burden of ≥14% on DE-MRI offered 100% sensitivity and 92% specificity for differentiating patients with inducible VT from those with noninducible VT (area under the curve, 0.94; $P=0.007$). The perifarct zone in patients with inducible VT was larger than in patients without inducible VT. If, however, the proportion of perifarct zone within the scar was compared, there was no difference between patients with or without inducible VT.

### Impact of Infarct Age

Patients without inducible VT tended to have more recent infarcts than patients with inducible VT (Table 1). Among the 12 patients referred for catheter ablation of VT, there was a significant correlation between infarct age and the number of sites with isolated potentials per patient ($R=0.56$; $P<0.01$). The percentage of nonfractionated abnormal electrograms in the scar tissue was inversely related to infarct age ($R=-0.55$; $P=0.006$). The older the scar, the higher the percentage of isolated potentials within the infarct scar ($R=0.5$; $P=0.017$). The percentage of fractionated electrograms within the scar did not correlate with infarct age ($R=0.38$; $P=0.07$).
A total of 15 different PVCs were targeted in the patients with PVCs. All sites of origin of the PVCs were located within scar tissue. All were successfully ablated, reducing the PVC burden from 14±13% to 0.7±1.1% on Holter monitoring.

**Clinical Follow-Up**
All but 1 patient presenting with VT and all patients who had inducible VT received an ICD (12 of 24 patients). The mean duration of follow-up was 13±12 months (range, 1 to 43 months). Two of the patients with inducible VT received appropriate ICD therapies during follow-up. In patients with frequent PVCs, 1 with frequent PVCs had recurrence of frequent PVCs. These PVCs were similar in morphology to the initially targeted PVCs. None of the patients without inducible VT had documented episodes of sustained VT during follow-up.

**Discussion**

**Main Findings**
This study analyzed infarct architecture by MRI technology and electrogram characteristics in patients with and without inducible VT and identified the determinants of postinfarction VT. The results of this study demonstrate that the scars in postinfarction patients with and without inducible VT have different architectural and electrophysiological features. Infarct scars in patients with inducible VT are larger and harbor more sites with isolated and fractionated potentials. A cutoff value of 14% of scar by DE-MRI best separated patients with inducible VT from those with noninducible VT. The influence of the periinfarct zone paralleled the impact of the scar size on inducibility. A randomized prospective study using infarct burden based on MRI as the only risk stratifier (Defibrillators To Reduce Risk by Magnetic Resonance Imaging Evaluation) currently is under way (http://clinicaltrials.gov; Unique Identifier: NCT00487279). This study will clarify the value of this parameter in patients who are candidates for an ICD for primary prevention of sudden cardiac death.

However, infarct mass and volume are not the only determinants of VT inducibility. The likelihood of having inducible VT was nearly 3-fold higher in the presence of an isolated potential. Additionally, there was a significant relationship between the number of areas displaying isolated potentials and the number of inducible VTs. Inducibility correlating with the presence of isolated potentials was reported in a recent study by Haqqani et al. In contradistinction to our study, no MRIs were used; therefore, and assessment of impact of infarct size and infarct architecture remains speculative. Our study highlights the importance of infarct size determination by DE-MRI, which complements the assessment of electrophysiological data and helps to begin to answer the question of arrhythmogenesis. Critical areas for VT were not characterized by Haqqani et al. In the
present study, we demonstrated that in the majority of critical isthmus areas, isolated potentials were present, indicating a relationship between the arrhythmogenic substrate and inducibility of VT, which was further supported by the strong correlation between the number of areas with isolated potentials and the number of inducible VTs.

A prior study demonstrated that isolated potentials are a manifestation of a fixed barrier within a VT reentry circuit. The higher prevalence of isolated potentials in patients with inducible VT probably reflects the presence of surviving muscle bundles within scar that serve as the substrate for slow conduction and reentrant postinfarction VTs. Isolated potentials rarely were recorded in patients without inducible VT. These findings support the results of a prior study in which intraoperative mapping in patients with a history of spontaneous VT demonstrated a higher prevalence of double potentials or fractionated electrograms than in patients with frequent PVCs but no VT.

Electrogram Characteristics and Infarct Age

Electrogram characteristics in scar tissue have not yet been systematically compared in patients with and without inducible VT. Electrogram characteristics reflect the tissue composition within the scar. The predominance of nonfractionated abnormal electrograms in patients with noninducible VT compared to the predominance of fractionated electrograms in patients with inducible VT indicates a higher degree of complex anisotropy, which could contribute to the genesis of sustained VT. Infarct age, probably by means of scar remodeling, affects impulse propagation through scar tissue, potentially accounting for the higher prevalence of isolated potentials and inducible VT in patients with older infarcts. This is supported by morphometric analysis of tissue composition in postinfarction animal models.

In parallel with infarct age, tissue composition (as reflected by electrogram characteristics) changes over time. It is possible that scar remodeling influences the development of ventricular arrhythmias over time, which may explain the absence of isolated potentials in patients with noninducible VT who also had more recent infarcts. Additional studies are necessary to clarify the temporal changes in scar architecture and electrogram characteristics after a myocardial infarction.

Limitations

The sample size in this cross-sectional study was small, and the results need to be confirmed in larger studies. Longitudinal studies might help to better assess scar tissue evolution over time. A limitation of this study is that there was no control group without VT or PVCs.

Another limitation of this study was a difference in the number of sampling points between patients with and without inducible VT. Despite a larger number of sampling points in the scar of patients with inducible VT, the sampling density within the scar actually was higher in patients without inducible VT. Therefore, it is possible that isolated potentials were underdetected in patients with inducible VT.

We performed several univariable analyses, and unadjusted $P$ values should be viewed with caution given the risk of a type I error. However, if a more stringent $P$ value of 0.004 is used, the significance of the statistical analysis remains largely unchanged.

Clinical Implications

Cardiac MRIs may assist in risk stratification of patients postinfarction. Scar size and electrogram characteristics of patients with inducible and noninducible VT differ significantly. Whether assessing the infarct burden on the basis of MRI as a risk stratifier will translate in mortality benefit will be clarified by an ongoing randomized study.

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Disclosures

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References

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Differences in surviving myocardial fibers and infarct architecture may explain why sustained ventricular tachycardia (VT) occur in some, but not all patients who have had myocardial infarction. In this study, we compared infarct architecture by MRI and the endocardial electrogram characteristics during ventricular mapping in postinfarction patients with and without inducible VT. Although the median ejection fraction was not significantly different between groups, the subendocardial infarct area determined by MRI was larger in patients with inducible VT. Unipolar and bipolar voltages on electroanatomical maps were lower in patients with inducible VT. Distinct sites with isolated potentials were more prevalent in patients with inducible VT than in those with noninducible VT. An infarct volume >14% identified 11 of 12 patients with inducible VT. Thus, quantitative and qualitative differences exist between scars in patients with and without inducible VT. Scar size and the presence of isolated potentials correlate with VT inducibility. The findings suggest that methods to characterize scars may facilitate risk stratification and help to guide catheter ablation.


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