Relationship of Slow Conduction Detected by Pace-Mapping to Ventricular Tachycardia Re-Entry Circuit Sites After Infarction

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OBJECTIVES
This study sought to characterize the relationship of conduction delays detected by pace-mapping, evident as a stimulus to QRS interval (S-QRS) delay ≥40 ms, to ventricular tachycardia (VT) re-entry circuit isthmuses defined by entrainment and ablation.

BACKGROUND
Areas of slow conduction and block in old infarcts cause re-entrant VT. In 12 patients with VT after infarction, pace-mapping was performed at 890 sites. Stimulus to QRS intervals were measured and plotted in three-dimensional reconstructions of the left ventricle. Conduction delay was defined as ≥40 ms and marked delay as >80 ms. The locations of conduction delays were compared to the locations of 14 target areas, defined as the region within a radius of 2 cm of a re-entry circuit isthmus.

METHODS
Pacing captured at 829 sites; 465 (56%) had no S-QRS delay, 364 (44%) had a delay ≥40 ms, and 127 (15%) had a delay >80 ms. Sites with delays were clustered in 14 discrete regions, 13 of which overlapped target regions. Only 1 of the 14 target regions was not related to an area of S-QRS delay. Sites with marked delays >80 ms were more often in the target (52%) than sites with delays 40 to 80 ms (29%) (p < 0.0001).

RESULTS
Identification of abnormal conduction during pace-mapping can be used to focus mapping during induced VT to a discrete region of the infarct. Further study is warranted to determine if targeting regions of conduction delay may allow ablation of VT during stable sinus rhythm without mapping during VT. (J Am Coll Cardiol 2003;41:802–9) © 2003 by the American College of Cardiology Foundation

CONCLUSIONS
In many patients with sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction, catheter ablation is complicated by VTs that are unstable for mapping due to hemodynamic instability, poor reproducibility for initiation, or spontaneous changes from one VT to another. Feasibility of ablation of unstable VTs largely during stable sinus rhythm has been demonstrated (1–3). Extensive radiofrequency (RF) ablation lines were placed over low voltage areas, or limited lines were placed through a target region based on limited assessment of sites during VT. The infarct regions are typically large. New methods to guide placement of RF ablation lines during sinus rhythm are of interest.

Abnormal, slowed conduction through regions of surviving myocardial bundles is an important substrate causing VT (4), often associated with critical isthmuses that are desirable targets for ablation (5). The isthmus consists of an exit from which the re-entrant wavefront propagates to the surrounding more normal myocardium producing the QRS complex, and a segment that is proximal to the exit.

During sinus rhythm, when pacing is performed from the mapping catheter located at the exit from the isthmus, the resulting QRS morphology should theoretically resemble that of the tachycardia. Analysis of the QRS complex produced by ventricular pacing during sinus rhythm, known as “pace-mapping,” is useful for targeting focal VTs, but of limited utility and potentially misleading for mapping scar-related VT (6–8) (Fig. 1). However, pace-mapping also provides a means of identifying areas of abnormal conduction from analysis of the interval between the stimulus and QRS onset. A stimulus to QRS interval (S-QRS) ≥40 ms is associated with abnormal electrograms and consistent with slow conduction away from the pacing site (8–11). The aim of our study was to define the extent of regions of S-QRS delays and to assess their proximity to defined VT re-entry circuit isthmuses. For this purpose, we defined a potential “target area” as the region within a radius of 2 cm of a defined re-entry circuit isthmus. Ablation over such an area has been shown to be feasible (1–3).

METHODS
Patient population. The study included 12 consecutive patients (Table 1) who were referred for ablation (all males, mean age 68 ± 8 years), and who underwent catheter mapping with an electroanatomic mapping system (Biosense, TIRAT Hacarmel, Israel; Cordis Webster, Diamond Bar, California) with custom software that allowed construction of three-dimensional anatomic maps with plots of the S-QRS interval during pace-mapping. All patients had a remote (>2 months) myocardial infarction, the location of
which was inferior or posterior in eight patients, anterior in two patients, and in two discrete regions in two patients (posterobasal and inferoseptal in one patient, and anteroapical and inferoseptal in the other patient). The mean left ventricular ejection fraction was 24 ± 8%. Each patient had ≥2 episodes of sustained monomorphic VT within the preceding six months (mean 17.0 ± 14.3, range 2 to 46). The number of inducible VTs was 4.3 ± 2.4 (range 2 to 10). All but one patient had a previously implanted cardioverter-defibrillator. All patients had failed antiarrhythmic drug therapy (Table 2).

Electrophysiology study and ablation. Patients underwent catheter mapping and ablation according to a protocol approved by the Human Research Committee of Brigham and Women’s Hospital. After written informed consent was obtained, 6-F multi-electrode catheters were inserted percutaneously into the left femoral vein and positioned in the high right atrium, at the His position, and in the right ventricular apex. Left ventricular mapping used either a retrograde aortic or trans-septal approach. Systemic anticoagulation with heparin was adjusted to an activated clotting time >250 s. Conscious sedation was achieved with intermittent administration of fentanyl and midazolam.

Catheter position was monitored and three-dimensional ventricular reconstructions of ventricular voltage maps were constructed with the non-fluoroscopic mapping system CARTO (Biosense; Cordis Webster) (12). Custom software allowed acquisition of data during different rhythms (atrial pacing, right ventricular pacing, pace-mapping, and VT) at left ventricular sites. The 7-F 4 mm tip quadrupolar mapping and ablation catheter has spacings of 1, 7, and 4 mm between electrodes. Bipolar electrograms from the distal electrodes of the mapping catheter were filtered at 10 to 400 Hz. The surface electrocardiogram (ECG) leads and intracardiac electrograms, filtered at 30 to 500 Hz were also stored on optical disc on a separate system (Prucka Engineering, Houston, Texas).

The first part of the procedure, included mapping and pace-mapping (as follows) during stable sinus rhythm. The geometry of the left ventricle was defined, local electrograms were acquired during atrial pacing and right ventricular pacing, and pace-mapping was performed at each site. A VT was then induced by programmed stimulation. At selected sites endocardial electrograms were acquired and entrainment performed and analyzed for participation in the re-entry circuit (13).

For analysis, any of the following criteria defined an isthmus site (5):

1. Pacing at the site entrains VT with concealed fusion with an S-QRS <70% of the VT cycle length and either an S-QRS that matched the electrogram-QRS (±20 ms) or post-pacing interval tachycardia cycle length difference ≤30 ms;
2. RF current application terminates VT without inducing ventricular ectopy;
3. Repeated VT termination occurs with catheter manipulation or pacing at the site (which prevents assessment of ablation during VT) and RF ablation abolishes that inducible VT.

For the purpose of correlating pace-mapping findings with re-entry circuit locations we defined the target area as all sites within a radius of 2 cm of an isthmus.

Acute success of the procedure was defined by programmed stimulation with up to three extra-stimuli from two right ventricular sites using drive trains of 600 and 400 ms. A VT that was no longer inducible was successfully ablated. If other VTs remained inducible, the VT substrate was defined as modified. If the targeted VT was still inducible the procedure was defined as failed.

Pace-mapping. At each stable catheter location pace-mapping was attempted using unipolar stimuli from the distal electrode of the mapping catheter (cathode) and an electrode in the inferior vena cava (anode). Stimuli had an amplitude of 10 mA and pulse width of 2 ms. The resulting 12-lead ECG morphology was stored from all sites with capture. Locations where pacing did not capture were marked with gray tags indicating dense scar. The S-QRS interval was measured to the onset of the QRS in the ECG lead with the shortest S-QRS by a custom, automated program, and subsequently confirmed by manual review. Electroanatomic maps of color-coded S-QRS intervals were created. Based on previous studies, S-QRS delays indicating abnormal conduction were defined as ≥40 ms (Fig. 1), and marked delays were defined as >80 ms (8,10).

For sites where the S-QRS delay was >80 ms, the paced QRS morphology was compared to the QRS morphologies of spontaneous or induced VTs. A pace-map QRS morphology that matched VT in 10 or 11 out of 12 ECG leads was defined as a close match. A match in all 12 leads was defined as an exact match.

Statistical analysis. All values are expressed as mean value ± standard deviation. Continuous variables are compared using the two-tail paired and unpaired t test as appropriate. Discrete variables were compared using the Fisher exact test. Generalized estimating equations were used to adjust for multiple observations in individual patients (14). A two-sided p value of <0.05 was considered statistically significant (SAS Statistical Software, Version 6.12, Cary, North Carolina).

RESULTS

In the 12 patients a total of 51 different monomorphic VTs were inducible, of which 42 were found to have an isthmus
Figure 1. The 12-lead electrocardiogram of ventricular tachycardia (VT) (left panel), pace-mapping at site 5 (inferoseptal left ventricle) (middle panel), and pace-mapping at site 6-8 (basal lateral left ventricle (LV)) (right panel) in Patient 3 are shown. The pace-map at site 5 is a much closer match of VT with stimulus to QRS interval (S-QRS) <40 ms (no conduction delay) than the pace-map at site 6-8, which does not resemble VT but has a S-QRS delay of 65 ms. Entrainment mapping indicated that site 5 was an outer loop site and site 6-8 was an isthmus site in the re-entry circuit. Patient 3 in Figure 2 shows the S-QRS map and voltage map of this patient.
The geometry of the left ventricle was defined with a mean of 132 ± 39 acquired left ventricular sites. Maps of maximal electrogram voltage during atrial pacing identified large regions of low amplitude (<1.5 mV) signals in a distribution consistent with an infarction in all patients (Figs. 1 and 2). The target areas were confined to the low voltage areas, consistent with the infarct or its border zone.

Pace-mapping was performed at 890 sites (mean per patient 74 ± 23) of which 224 (25%) were in a target region and 666 (75%) were outside a target. Capture was present at 829 sites and capture was absent at 61 sites. Of the 829 captured sites, 209 (25%) were in the target and 620 (75%) were outside a target. Capture was present at 1,279 sites and capture was absent at 61 sites. Of the 1,279 capture sites, 209 (25%) were in a target region and 1,070 (80%) were outside a target. The mean S-QRS of sites in the target area was longer than that for sites outside the target region (69 ± 49 vs. 45 ± 29; p < 0.0001; unpaired t test). Only 17% of sites without delays (S-QRS < 40 ms) were in the target region compared to 27% of sites with delays 40 to 80 ms (p < 0.0001; Fisher exact test) and 52% of sites with marked delays > 80 ms (p < 0.0001; Fisher exact test). Sites with S-QRS delays of 40 to 80 ms were significantly closer to the center of the target than sites with delays between 40 to 80 ms (21.4 ± 12 mm vs. 38.4 ± 23 mm; p < 0.0001; unpaired t test).

One area of abnormal conduction was identified as the QRS morphology did not improve the ability of pace-mapping to identify target regions. Of the 127 sites with a delay > 80 ms, the paced QRS was a close match for a VT at 52 (41%) sites and an exact match at only 12 (9%) sites. Of the sites with a close match, 54% were in the target whereas 46% were outside the target. For sites with an exact match, 7 (58%) were in the target and 5 (42%) were outside the target. Marked mismatches between the paced QRS morphology compared with that of VT were common in target regions, as has been previously reported (8).

At the end of the procedure no VT was inducible in 7 (58%) patients; in the remaining 5 (42%) patients at least one inducible VT had been abolished, but another VT remained inducible (Table 2). The mean duration of the procedure was 5.8 ± 0.9 h. Radiofrequency ablation was applied at a mean of 10 ± 3 sites in the target area. A second ablation procedure was performed within the following two weeks in six patients (50%) due to spontaneous or inducible VT at programmed stimulation before planned discharge interpreted as due to partial healing of the initial RF lesions. The second procedure generally focused on the same target areas. Previously ineffective anti-arrhythmic drugs were continued in 10 patients (Table 2). All patients had complete follow-up for the six months after ablation during which time three patients died of sepsis or heart failure not felt to be related to the ablation procedure (Table 2); two patients had episodes of VT prior to death. The remaining nine patients were alive and free of VT, despite incessant VT prior to ablation in one patient and a mean of 18 ± 16 episodes of VT during the six months prior to ablation detected by a previously implanted ICD in the remaining eight patients.

**DISCUSSION**

Pace-mapping in sinus rhythm provides two types of data that could potentially assist in finding re-entry circuits: the
QRS morphology and the delay between the stimulus and the QRS complex. Previous studies found that a S-QRS interval >40 ms during pace-mapping occurred only at sites with abnormal electrograms (8,10). Those observations and the association with re-entry circuit sites are consistent with abnormal conduction away from the pacing site as the likely mechanism of the delay. The long delays (up to 318 ms in the present study) despite pacing at rates of only 86 to 120 beats/min also suggest abnormal, slow conduction rather than stimulus latency, as the mechanism (8,10,11,15). A previous report found long S-QRS delays during pace-mapping at some re-entry circuit sites identified by entrainment, particularly at central and proximal regions in the circuit (9). In contrast, the re-entry circuit exit, which is more likely to be at the border of the infarct and close to the normal myocardium, often has no delay during pace-mapping even though it is a desirable target for ablation (15).

In contrast to previous studies this study employed electroanatomic mapping with exact anatomic localization of the region with long S-QRS delays that allowed the size of these areas to be related to the infarct region and to determine the distance to the target area. Our data showed that sites with an S-QRS delay were always in the infarct region (as identified by electrogram voltage) (Fig. 2) and 13 of 14 areas of conduction delay were associated with a re-entry circuit isthmus.

Conduction away from the pacing site can potentially be influenced by the pacing, rate, and antiarrhythmic drugs. To minimize the impact of rate-related changes in conduction, we paced at a relatively slow rate for each patient. Pacing slower than the rate of the VT may have further reduced the relationship of the paced QRS morphology to that of VT target area. During bipolar pacing, capture at the proximal electrode rather than the distal electrode can also modify the QRS morphology (16). The sequence of ventricular activation can vary during pacing at different stimulus strengths. This phenomenon is more pronounced with bipolar than unipolar pacing, likely due to anodal capture at higher stimulus strengths (17). We avoided this potential problem by using unipolar pacing (18) and by limiting the current output to 10 mA and 2 ms, which is within the range of routine programmed stimulation.

The area of tissue depolarized directly by the pacing current can be thought of as the “virtual electrode” created during pacing (19). The size of the virtual electrode produced during pacing with mapping catheters in humans is unknown. Pacing was performed from a large surface electrode of the type used for ablation, which would reduce the current density at the electrode tip in comparison to that

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*p = 0.002; †Follow-up shorter than 6 months (see Comment column).

ICD = implantable cardioverter-defibrillator; RF = radiofrequency.
of a standard size ablation electrode (19). A recent observation suggested that increasing stimulus strengths from threshold to 20 mA at 2 ms pulse width increases the radius of the virtual electrode in one dimension by approximately 8 mm (20). The unipolar pacing threshold approximately doubles after RF ablation (Delacretaz E, personal communication, 2000). It is likely that bipolar pacing and pacing at different stimulus strengths than were used in this study would alter the size of the area with conduction delays.

The limitations of the QRS morphology for pace-mapping of scar-related re-entry have been previously discussed (7,16). Although the pace-mapping QRS morphology may resemble that of VT when pacing near the re-entry circuit exit, pacing over an area of 4 cm² can produce a similar QRS pattern (16). At other re-entry circuit sites, the pace-mapping QRS morphology is markedly different from that of VT, as was again observed in this study (7). During VT regions of functional block and wavefront collision may produce a different activation sequence of wavefront emerging from the circuit as compared to the activation sequence that occurs during pace-mapping at a circuit site (8). Because these limitations are well recognized we analyzed only the QRS morphology produced by pace-mapping at sites of conduction delay, finding that analysis of the QRS morphology was not helpful in further refining the relationship of these sites to the re-entry circuit in this small series.

Study limitations. The patients were consecutive in our laboratory, but referred for ablation and, therefore, were selected. This is a relatively small series of patients. However, the relationship of S-QRS delays to target areas in all but one of our patients was striking. The pace-mapping findings were related to the location of a defined target region, having an arbitrarily defined radius of 2 cm surrounding a defined VT circuit isthmus site. Identification of all re-entry circuit sites would have been ideal, but is rarely achieved and generally not practical during catheter map-
Figure 3. Plots for each of the 14 targets in the 12 patients (abscissa) showing the distance to the center of the target for all pace-mapping sites (y-axis). Sites are coded according to stimulus to QRS interval (S-QRS) during pace-mapping as <40 ms (open circles), 40 to 80 ms (gray circles), and >80 ms (black circles).
ping. It is possible that the areas of slow conduction that extended outside the defined target area also contained portions of the re-entry circuit, as well as bystanders. The defined target size used in this study relates reasonably well to the constraints of catheter mapping and is also a feasible area for anatomically guided catheter ablation during sinus rhythm (1–3).

Due to clinical limitations of catheter mapping, sampling of sites was not homogeneous throughout the ventricle, with much higher density of acquired sites in the infarct region. Therefore, we also described the relationship of the individual region of abnormal conduction to the target in each patient. In addition, it is possible to ablate some circuits at the exit, where minimal or no delay is often present (10). Thus, identification of sites with conduction delays is unlikely to be required for successful ablation of all tachycardias. This study was not designed to test the efficacy of ablation guided only by pace-mapping for preventing recurrent VT.

Clinical implications. Areas with abnormal conduction in infarct regions are detectable with pace-mapping and are often within 2 cm of a re-entry circuit isthmus. This may facilitate detection of re-entry circuit isthms during sinus rhythm. Ablation of VT during sinus rhythm, by targeting these areas of conduction delay may be feasible when VT is unstable for mapping.

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REFERENCES