Relation of Cardiac Surface QRST Distributions to Ventricular Fibrillation Threshold in Dogs

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The relation between ventricular fibrillation threshold (VFT) and cardiac surface QRST area distributions was studied in eight pentobarbital-anesthetized dogs. Unipolar epicardial electrograms were recorded from 64 sites evenly distributed on the right and left ventricles. Localized areas of short repolarization properties were produced by directing five intensities of light onto the surface of the anterior right ventricle through apertures of three sizes. VFT, measured at the center of the lesion, decreased during warming and had a high negative correlation to the change (warming-control) in QRST area (ΔQRST) in the electrogram recorded from the center of the lesion. This correlation was independent of lesion size. For the six experiments, the correlation coefficients for 400-, 800-, and 1,600-mm² lesions averaged -0.95, -0.94, and -0.96, respectively. The correlation between VFT and ΔQRST, without regard to lesion size averaged -0.88. VFT also had a negative correlation to root mean square (RMS)ΔQRST because of warming. RMSΔQRST was calculated from the change in QRST areas (warming-control) in all 64 electrograms. The correlation between VFT and RMSΔQRST was dependent on lesion size. For all experiments, the correlation between VFT and RMSΔQRST averaged -0.97, -0.93, and -0.93 for 400-, 800-, and 1,600-mm² lesions, respectively. The correlation between VFT and RMSΔQRST without regard to lesion size, however, was considerably lower, -0.59. The results of this study provide the first direct evidence that VFT is correlated with cardiac surface QRST area distributions. (Circulation, 1988;78:171-177)

Several studies have been reported in which the relation of QRST area distributions of body surface maps to arrhythmia vulnerability was evaluated.1-4 The rationale for these studies was the role of disparity of ventricular repolarization properties in vulnerability to arrhythmias5-10 and the ventricular gradient concept.11-17 Wilson et al11 developed a theoretical analysis supporting their insight that the QRST area should be a measure of inhomogeneity of ventricular repolarization properties. The theoretical basis of this hypothesis was developed further by Burger12 and more recently by Plonsey,13 Geselowitz,14 and Cohn et al.15 Direct evidence that QRST areas of cardiac surface electrograms are related to inhomogeneity of repolarization properties has been obtained from animal experiments.16,17

Although there are theoretical reasons why QRST area distributions should be related to arrhythmia vulnerability18 and although clinical1-3 and experimental studies support this relation, there have been no studies in which arrhythmia vulnerability was directly measured and related to QRST area distributions. The purpose of this investigation was to obtain direct evidence that changes in cardiac surface QRST area distributions are related to fibrillation threshold.

Materials and Methods

Experimental Preparation

Experiments were performed on eight dogs that were anesthetized with intravenous sodium pentobarbital 30 mg/kg. Before recording cardiac surface electrograms and measuring ventricular fibrillation threshold (VFT), an additional dose of intravenous sodium pentobarbital, 15 mg/kg, was given. An intravenous infusion of 500 ml 0.9% NaCl containing 240 mg pentobarbital was also given slowly over the 3-4 hour duration of each experiment. Large doses of this anesthetic have been shown previ-
ously to reduce spontaneous variations of ventricular repolarization properties, probably by reducing fluctuations of autonomic nervous tone.16,17

Under artificial ventilation, the heart was exposed through a midline thoracotomy and supported in a pericardial cradle. The sinus node was crushed, and bipolar stimulating electrodes used for delivering basic driving stimuli were attached to the right atrium and right ventricle near the pulmonary conus. Two additional bipolar electrodes were placed on the anterior right ventricle for delivering VFT test stimuli. The heart was paced at a cycle length of 400 msec with 2-msec duration square-wave stimuli at twice diastolic threshold intensity. The driving stimuli were applied to both the right atrium and right ventricle simultaneously. An array of 64 fine silver wire unipolar electrodes, insulated, except at their points of attachment, was mounted with uniform electrode spacing on a nylon sock that was stretched over the heart and anchored near the pericardial reflection. These 64 electrodes were used to record unipolar electrograms. Each cardiac surface electrode was referenced to a Wilson central terminal. All 64 electrodes were sampled once every msec, with a multiplexed data recording system.19 Recordings were taken with amplifiers set at a 0.03–500-Hz bandwidth. A 12-bit A to D converter that provided a resolution of approximately 50 μV was used. Continuous records were sampled for 3 seconds. To minimize beat-to-beat variations in the electrograms, all recordings were obtained with the respirator held in full expiration. At least 58 electrograms from each experiment were technically adequate for interpretation. One to six electrograms were excluded from analysis because of noise or mechanical artifacts. The animals were kept on a heated table, and right ventricular subepicardial temperature was monitored with a thermocouple. The heart was kept moist with saline.

Ventricular recovery properties were altered by localized myocardial warming. A light source from a tungsten-halogen lamp was directed through a condenser lens assembly and directed onto the anterior right ventricle through a circular aperture. The aperture diameter was variable from 50 to 2,400 mm². This technique has been used previously to evaluate the relation of localized alterations of ventricular recovery properties to changes in cardiac surface electrograms.16,17,20 In two of the eight experiments, the aperture size was fixed at 800 mm², and measurements of electrograms and VFT were repeated alternately during control periods and periods of local warming. In these two experiments, only one intensity of warming was used. In the other six experiments, localized alterations of recovery properties were produced by directing the light through aperture sizes of 400, 800, and 1,600 mm². Areas of alteration of recovery properties will be referred to as “lesions.” The order in which the effects of lesion size were evaluated was varied in different experiments to minimize any bias that might be introduced because of time. Electrograms were recorded, and VFT was measured during five intensities of warming of the three lesion sizes. The heart was warmed for 5 minutes before electrograms were recorded and VFT measured. The animal was allowed to recover for 5 minutes between each intervention. Control measurements were obtained before each series of measurements. A diagram of the experimental preparation is shown in Figure 1. The anterior wall of the right ventricle was warmed by a light spot centered at VFT test electrode 1, which was in close proximity to the unipolar recording electrode at the center of the warmed area. The approximate areas warmed by light spots with 400-, 800-, and 1,600-mm² apertures are indicated in the figure. VFT test electrode 2 was in close proximity to a unipolar recording electrode at the boundary of the 1,600-mm² warmed area. The epicardial temperatures at the center of warmed areas were measured by a thermocouple, and with different intensities of light, these ranged from 36° to 42° C.

VFT was measured with gated trains of pulses delivered to bipolar VFT test electrode 1 or 2. The VFT test electrodes had interelectrode distances of 2–3 mm. The pulses were 4 msec in duration and were delivered at 10-msec intervals (100 Hz) after every 10th driving stimulus. The train was set to start 80 msec after the driving stimulus and had a duration of 200 msec. With these settings, the train started just after the QRS complex and continued until approximately the end of the T wave in a vertical-lead electrocardiogram. The strength of the pulse train was increased in 1-mA increments, and trains of stimuli at each strength were delivered

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**FIGURE 1.** Diagram of the experimental preparation. Dots distributed over the heart indicate the 64 unipolar electrogram recording sites. Arrows that are labeled electrode 1 and electrode 2 indicate locations of bipolar electrodes (not shown) used to measure ventricular fibrillation threshold. Concentric circles on right ventricle indicate the 400-, 800-, and 1,600-mm² regions warmed. AO, aorta; RA, right atrium; LA, left atrium; POST, posterior; RV, right ventricle; ANT, anterior; LAD, left anterior descending coronary artery; LV, left ventricle.
twice before the intensity was increased. The least amount of current required to induce ventricular fibrillation was taken as the VFT. After fibrillation was induced, defibrillation was accomplished by direct-current shock (10−15 W/sec) delivered through catheter electrodes inserted into the cavities of the left atrium and left ventricle through the left atrial appendage and apex of the left ventricle. With this electrode arrangement, defibrillation was accomplished rapidly, and QRST area distributions during control periods were stable after as many as 30 episodes of ventricular fibrillation and defibrillation.

The simultaneously recorded electrograms of single complexes were processed with an interactive computer program. The complexes were digitized; gain and baseline were adjusted and stored on digital magnetic tape as previously described.\textsuperscript{20} QRST deflection areas were calculated by integrating each electrogram over the QRST interval. The root mean square (RMS) voltage of all 64 leads was plotted against time, and onset of QR and end of T-wave deflections were manually selected from the RMS curve. The RMS curve is calculated from deflections in all electrograms and has a more abrupt onset and termination than the QRST in individual electrograms. The RMS curve was used to select onset and termination of the QRST interval to decrease the likelihood of missing low-amplitude deflections at the beginning and end of individual electrograms. Even if there were small errors in selecting the interval for integration, they would have negligible effects on the results because excluded areas would be extremely small in comparison with the changes in QRST area induced by warming. The right atrium was paced simula-
taneously with the ventricle, and the P waves were a small constant value included in QRST areas recorded during both control and test conditions.

Data Analysis

Data from the six experiments in which multiple temperatures and three aperture sizes were used were analyzed with respect to changes in QRST areas (QRST during warming−control QRST). In each experiment, change in QRST area in the electrogram at the center of the lesion (ΔQRST\textsubscript{1}) and the RMS value of change in QRST area in all 64 electrograms (RMSΔQRST) were determined. A total of eight correlation coefficients between VFT and QRST changes was calculated for each experiment by means of the least-squares method of linear regression analysis:

1. VFT versus ΔQRST\textsubscript{1} for all intensities of warming of all lesion sizes.
2. VFT versus ΔQRST\textsubscript{1} for all intensities of warming of 400-mm\textsuperscript{2} lesions.
3. VFT versus ΔQRST\textsubscript{1} for all intensities of warming of 800-mm\textsuperscript{2} lesions.
4. VFT versus ΔQRST\textsubscript{1} for all intensities of warming of 1,600-mm\textsuperscript{2} lesions.

5. VFT versus RMSΔQRST for all intensities of warming of all lesion sizes.
6. VFT versus RMSΔQRST for all intensities of warming of 400-mm\textsuperscript{2} lesions.
7. VFT versus RMSΔQRST for all intensities of warming of 800-mm\textsuperscript{2} lesions.
8. VFT versus RMSΔQRST for all intensities of warming of 1,600-mm\textsuperscript{2} lesions.

Results

Two dogs were studied to document that myocardial warming lowers VFT and to demonstrate the stability of VFT and QRST area after multiple episodes of warming and fibrillation and defibrillation. In these experiments, VFT measurements during control periods and during myocardial warming of an 800-mm\textsuperscript{2} area were alternated. VFT was measured at two sites. Site 1 was at the center of the 800-mm\textsuperscript{2} lesion, and site 2 was approximately 5 mm outside of it (see Figure 1). The intensity of light was adjusted to raise myocardial temperature to 40−42° C.

The results of one of these experiments are shown in Figures 2−4. Fibrillation threshold measured at site 1 averaged 44.1±3.9 mA (mean ± SD) during control periods and decreased to 4.7±1.6 mA during myocardial warming (p<0.01). VFT measured at site 2 averaged 45±4.2 mA during control periods and was not significantly different during warming, 46.7±3.2 mA. The results of the other experiment were comparable. The findings confirm previous reports that warming decreases VFT\textsuperscript{10} and that VFT is dependent on the site used to make the measurement.\textsuperscript{10,21} Figure 2 clearly illustrates that the differences between VFT during control periods and VFT during warming greatly exceeded the differences in measurements during a given state. As illustrated in Figure 3, the QRST area recorded near VFT test site 1 changed more during warming than the QRST area recorded near
VFT test site 2. The figure also shows that QRST areas at site 1 were less variable during repeated recordings in a given state than QRST areas during control recordings compared with QRST areas during warming. Warming had little effect on activation sequence, see Figure 4.

In the other six experiments, observations were made during control periods and during five intensities that warmed the three lesion sizes. Mean control values of VFT ranged from 15.7 mA to 41.3 mA in the six experiments. However, in individual experiments, the variability of the control measurements was relatively small, and the maximum difference between measurements ranged from 1 mA to 9 mA. The differences in repeated control measurements were small with respect to the difference between VFT during control and warming periods.

The relation of changes in QRST area at site 1 (ΔQRST1) to VFT of one dog is shown in Figure 5. The correlation coefficients between VFT and ΔQRST, for lesions of five intensities in 400-, 800-, and 1,600-mm² areas were -0.95, -0.99, and -0.96, respectively. The correlation coefficient between VFT and ΔQRST1, calculated without regard to lesion size was -0.94. The results of all six experiments were comparable and are summarized in Table 1. Correlation coefficients between VFT and ΔQRST1 for lesions of all sizes ranged from -0.80 to -0.95, mean -0.88. The averages of correlation coefficients for all six experiments, between VFT and ΔQRST1 for 400-, 800-, and 1,600-mm² lesions, were -0.95, -0.94, and -0.96, respectively. In a previous study,20 we showed that QRST area at the center of a lesion is highly correlated with lesion severity and is independent of lesion size. The results of the present study show there is also a high correlation between VFT and ΔQRST1, that is, lesion severity, which is independent of lesion size. As shown in Figure 3, there was

**Table 1. Correlation Coefficient Between Ventricular Fibrillation Threshold and ΔQRST**

<table>
<thead>
<tr>
<th>Dog</th>
<th>All</th>
<th>400 mm²</th>
<th>800 mm²</th>
<th>1,600 mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.95</td>
<td>-0.97</td>
<td>-0.92</td>
<td>-0.98</td>
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<tr>
<td>2</td>
<td>-0.86</td>
<td>-0.97</td>
<td>-0.97</td>
<td>-0.95</td>
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<tr>
<td>3</td>
<td>-0.80</td>
<td>-0.90</td>
<td>-0.91</td>
<td>-0.93</td>
</tr>
<tr>
<td>4</td>
<td>-0.85</td>
<td>-0.99</td>
<td>-0.95</td>
<td>-0.94</td>
</tr>
<tr>
<td>5</td>
<td>-0.94</td>
<td>-0.95</td>
<td>-0.99</td>
<td>-0.96</td>
</tr>
<tr>
<td>6</td>
<td>-0.88</td>
<td>-0.94</td>
<td>-0.88</td>
<td>-0.99</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.88</td>
<td>-0.95</td>
<td>-0.94</td>
<td>-0.96</td>
</tr>
</tbody>
</table>
little difference in QRST area recorded at the periphery of the warmed area during control and warming periods. Therefore, VFT measured at site 1 was not correlated with QRST area recorded at the periphery of the warmed area.

Unlike the relation of VFT to ΔQRST₁, which was relatively independent of lesion size, the relation of VFT to RMSQRST was dependent on lesion size. As shown in Figure 6, there was a linear relation between VFT and RMSQRST for each lesion size. Also shown in the figure, for a given RMSQRST, VFT was lower for smaller lesions than for larger lesions. These data are from the same experiment illustrated in Figure 5. Data from all six experiments are summarized in Table 2. Correlation coefficients between VFT and RMSQRST for lesions of a given size were between −0.75 and −0.99 and averaged −0.97, −0.93, and −0.93 for 400-, 800-, and 1,600-mm<sup>2</sup> lesions, respectively. The correlation coefficients calculated without regard to lesion size ranged from −0.35 to −0.84 and averaged −0.59. RMSQRST, which was calculated from all 64 electrograms, reflects lesion size as well as lesion severity. In all six experiments, the regression line for VFT versus RMSQRST for 400-mm<sup>2</sup> lesions was shifted to the left of the regression line for VFT versus RMSQRST for 1,600-mm<sup>2</sup> lesions. We have previously shown that gradients of QRST area between warmed and surrounding areas increase as the intensity of myocardial warming increases but that the locations where QRST area changes occur are relatively unaffected by the intensity of myocardial warming. The results therefore suggest that lesion severity plays a major role in arrhythmia vulnerability.

**Discussion**

A relation between QRST area distribution and VFT is suggested by previous studies<sup>5–8</sup> that documented that agents known to increase arrhythmia vulnerability increased disparity of ventricular repolarization and by the ventricular gradient hypothesis proposed by Wilson et al.<sup>11</sup> Their hypothesis stated that the QRST area was a measure of inhomogeneity of ventricular repolarization. Later studies on experimental animals provided direct evidence that the QRST deflection areas of cardiac surface electrograms do in fact reflect disparity of repolarization.<sup>16,17</sup> Methods of analyzing QRST area distributions and relating these distributions to arrhythmia vulnerability have been evaluated in both an animal study<sup>4</sup> and in clinical studies.<sup>1–3</sup> In the animal study, interventions known to enhance arrhythmia vulnerability such as digitalis intoxica-

**TABLE 2. Correlation Coefficient Between Ventricular Fibrillation Threshold and RMSQRST**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Total</th>
<th>400 mm&lt;sup&gt;2&lt;/sup&gt;</th>
<th>800 mm&lt;sup&gt;2&lt;/sup&gt;</th>
<th>1,600 mm&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−0.77</td>
<td>−0.97</td>
<td>−0.94</td>
<td>−0.95</td>
</tr>
<tr>
<td>2</td>
<td>−0.38</td>
<td>−0.97</td>
<td>−0.98</td>
<td>−0.96</td>
</tr>
<tr>
<td>3</td>
<td>−0.35</td>
<td>−0.97</td>
<td>−0.78</td>
<td>−0.94</td>
</tr>
<tr>
<td>4</td>
<td>−0.56</td>
<td>−0.97</td>
<td>−0.93</td>
<td>−0.75</td>
</tr>
<tr>
<td>5</td>
<td>−0.66</td>
<td>−0.95</td>
<td>−0.96</td>
<td>−0.97</td>
</tr>
<tr>
<td>6</td>
<td>−0.84</td>
<td>−0.99</td>
<td>−0.96</td>
<td>−0.99</td>
</tr>
<tr>
<td>Mean</td>
<td>−0.59</td>
<td>−0.97</td>
<td>−0.93</td>
<td>−0.93</td>
</tr>
</tbody>
</table>

RMS, root mean square.
tion and hypothermia were used, but vulnerability to arrhythmias was not directly measured. In the clinical studies, body surface QRST area distributions of patients at risk of ventricular tachyarrhythmias were analyzed. As in the animal study, there was no direct measure of arrhythmia vulnerability. The results of both the animal and clinical studies suggested that analysis of QRST area distributions provides prognostic information regarding arrhythmia vulnerability. The present study, however, provides direct evidence that VFT is correlated with QRST distributions of cardiac surface electrograms. VFT is a commonly used method of quantifying arrhythmia vulnerability in animal experiments. Although the exact physiological basis for the measurement has not been defined, VFT decreases in conditions associated with spontaneous fibrillation such as coronary occlusion. A relation between VFT and occurrence of spontaneous arrhythmias in the clinical setting seems reasonable but remains speculative.

In these experiments, the lesions were localized areas of abnormally short repolarization properties induced by warming the anterior surface of the right ventricle. Localized warming has previously been reported to lower fibrillation threshold and enhance reentrant activity. Kuo et al. however, were unable to induce ventricular tachyarrhythmias by programmed stimulation in dogs during regional coronary artery perfusion with warm blood unless the animals were systemically hypothermic. The reason for the differences between their findings and our findings is uncertain. Our method of warming the myocardium produces relatively sharp borders between warmed areas with short repolarization properties and surrounding areas with normal repolarization properties. On the other hand, it is likely that regional perfusion of warm blood results in more gradual transitions in repolarization properties transmurally and at the boundaries of the perfusion field than our model and that the gradient of properties may be inadequate to increase ventricular vulnerability. In addition, the methods for evaluating vulnerability were different in our study and in the study by Kuo et al.

Increased disparity of ventricular repolarization properties was the likely mechanism for the decrease in VFT during myocardial warming. Warming shortens ventricular repolarization properties, and localized shortening of repolarization properties would be expected to increase T-wave amplitude in regionally sensitive electrocardiographic leads and alter QRST area distributions. In our experiments, VFT had a high inverse correlation with the alterations in QRST areas because of lesions with short repolarization properties. Although we did not assess the correlation between VFT and QRST alterations due to localized lesions with prolonged repolarization properties, it seems likely there would also be a high correlation between VFT and QRST alterations in this state. However, the correlation would be a positive one rather than a negative one because localized prolongation of repolarization properties due to cooling would decrease both T-wave amplitude and VFT.

Local disparity of repolarization properties, however, is not the only factor that plays a role in arrhythmia vulnerability, and other factors affecting arrhythmogenesis may not be detectable in QRST area distributions. It seems unlikely that arrhythmia vulnerability due to enhanced automaticity would be detected in maps of QRST area distribution. Slow conduction, which also plays a role in arrhythmia vulnerability, may have small effects on QRST waveform. Recent studies from our laboratory have shown that conduction delays electrotonically modulate repolarization properties. Whether or not the modulation of repolarization properties due to conduction delays is sufficient to alter QRST area distributions remains to be investigated.

Despite these limitations, the results of the present study document an excellent inverse correlation between VFT and change in QRST area in the electrogram at the center of a localized lesion with short repolarization properties. QRST area progressively increased and VFT progressively decreased as the severity of the lesion was increased. The correlation between VFT and change in QRST at the center of the lesion was relatively independent of lesion size (see Figure 5 and Table 1). For a given change in QRST area at the center of the lesion, fibrillation threshold was the same regardless of whether the lesion was large or small. This is in keeping with findings of a previous study from our laboratory that showed a high correlation between change in QRST area and lesion severity that was independent of lesion size. Increased severity of lesions increased the magnitude of QRST change recorded from sites within the light spot but did not increase the number of sites affected.

The correlation between VFT and RMSAQRST, however, was dependent on lesion size (see Figure 6 and Table 2). For lesions of a given size and different severities, the correlation coefficient was between −0.75 and −0.99. Correlation coefficients calculated for VFT and RMSAQRST for lesions of all sizes and all severities were between −0.35 and −0.84. For a given RMSAQRST, fibrillation threshold was lower for small lesions than for large lesions. A small lesion would have to have greater abnormalities in repolarization properties than a large lesion to result in the same RMSAQRST. Therefore, the dependence of the relation of VFT to RMSAQRST on lesion size suggests that lesion severity plays a major role in arrhythmia vulnerability. Abildskov and Steinhaus’s findings from computer simulations also support this conclusion. They found that small severe lesions resulted in striking decreases in fibrillation threshold. Fibrillation threshold, however, did not decrease further when lesion size was increased and when lesion severity was kept the same. With less severe lesions,
lesion size had only a small effect on VFT, and a 10-fold increase in lesion size decreased VFT by only 13%.

The results of our study provide direct evidence that decreased VFT due to local disparity of repolarization properties is correlated with cardiac surface QRS area distributions. Additional studies are needed to establish the correlation between VFT and QRS area distribution alterations induced by other abnormalities. We did not examine the relation of VFT to body surface QRS area distributions. However, analysis of regionally sensitive electrocardiographic leads provides reasonably accurate estimates of localized cardiac abnormalities. Previous work from our laboratory has shown that activation and recovery times estimated from the minimum derivative of the QRS and maximum derivative of the T wave of cardiac surface electrograms are highly correlated with the times estimated from distant electrocardiographic leads.25 We have also shown previously that localized repolarization abnormalities associated with acute coronary occlusion are clearly evident in body surface as well as cardiac surface QRS distributions in the presence of simulated left bundle branch block.26 Additional experimental and clinical studies to evaluate the relation of cardiac and body surface QRS area distributions to arrhythmia vulnerability therefore seem warranted.

References


Key Words • arrhythmia vulnerability • isoarea maps • cardiac surface maps
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