Electrophysiological and Anatomic Differences Between Canine Hearts With Inducible Ventricular Tachycardia and Fibrillation Associated With Chronic Myocardial Infarction

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This study examined electrophysiological and anatomic differences between dogs with ventricular tachycardia (VT) and fibrillation (VF) inducible by programmed ventricular stimulation 7-21 days after left anterior descending coronary artery ligation. Of 106 dogs studied, 40 had inducible VT, 19 had inducible VF, and 47 had no inducible arrhythmias. Differences between these three groups of animals were examined with cardiac mapping (to determine ventricular activation time in sinus rhythm) and post-mortem pathology (to measure infarct size and to reconstruct the anatomy at the infarct edge). Animals with inducible VT had longer maximal epicardial activation time (127±8 msec) than did animals with inducible VF (91±8 msec, p<0.05) or animals with no inducible arrhythmias (75±2 msec, p<0.001). Delayed epicardial activation occurred in 90% of animals with VT, 42% of animals with VF, and in only 6% of animals with no inducible arrhythmias. Endocardial and myocardial activation times were similar for the VT and VF groups. Infarct size was 18±2% of the ventricles for the VT group, much higher than for the VF group (11±2%, p<0.001) or for the group with no inducible arrhythmias (9±1%, p<0.001). The maximum diameter of viable muscle bundles interdigitating with scar tissue at the infarct edge was much larger in animals with VT (2.4±0.2 mm) than in animals with VF (1.8±0.2 mm, p<0.05) or animals with no inducible arrhythmias (1.7±0.1 mm, p<0.01). Thus, when compared with animals with inducible VF, animals with inducible VT had longer epicardial activation time, larger infarct size and viable muscle bundles of larger diameter at the infarct edge. (Circulation Research 1989;64:155-166)
Harvard respirator (400 ml/min; South Natick, Massachusetts). Oxygen was added at a rate of 300 ml/min, and anesthesia was maintained with nitrous oxide (200 ml/min), halothane (2%), and methoxyfluorane (1%). Throughout the subsequent surgery, the ECG was monitored and a defibrillator and programmable stimulator were available if required for cardioversion or ventricular pacing.

The heart was approached with sterile technique via a left lateral thoracotomy through the fourth intercostal space. Pairs of stimulating and recording electrodes (silicone-coated copper wire, interelectrode distance 0.5–1 cm) were sewn onto the right ventricular outflow tract and left ventricular apex and were passed subcutaneously to the back of the neck, where they were secured in a pouch.

To create an anterior infarct, braided silk was used to ligate the left anterior descending coronary artery between the first and second diagonal branches. The first diagonal and intermediate vessels were often ligated as well to obtain a larger infarct. For control operations, no coronary artery ligatures were placed. The pericardium was then closed, and air was excluded from the left pleural cavity before chest closure. Dogs were extubated on regaining consciousness. Prophylactic lidocaine (300 mg i.m.) was given at the conclusion of each operation.

Programmed Ventricular Stimulation

Programmed ventricular stimulation was performed 7–21 days (mean 11 days) after the initial thoracotomy. The dogs were postabsorptive but not sedated. A 12-lead ECG (six limb leads, six chest leads) was performed prior to study, and one to three ECG leads were monitored throughout stimulation.

A Medtronic 5325 programmable stimulator (Minneapolis, Minnesota) was used to stimulate the right and/or left ventricles with the wires that had been implanted at the primary thoracotomy. Pacing threshold was usually 4–5 mA with these chronically implanted electrodes, which were sewn onto the epicardial surface. They were not screwed into the myocardium.

The protocol for programmed stimulation was similar to that described by Richards et al. Drive trains of eight stimuli (2 msec rectangular pulses) were applied and were followed by single and paired extrastimuli. The basic cycle length was set as long as possible (350–400 msec). Single extrastimuli (S2) were introduced during diastole beginning at 300 msec and using 10 msec decrements until the ventricular effective refractory period was reached. With paired extrastimuli, S2S2 was set at the effective refractory period plus 10 msec, and the second extrastimulus (S3) was introduced during diastole from 300 msec to the effective refractory period. Pacing was performed at the right ventricular (RV) outflow tract and/or the left ventricular (LV) apex, first at twice diastolic threshold current intensity, then at 20 mA. There was a 3-second delay between each pacing sequence.

For each dog, the maximum number of nonstimulated ventricular beats was noted for each pacing site, as were the morphologies of sustained arrhythmias. As in our studies in which a similar protocol was used in patients with previous myocardial infarction, an inducible arrhythmia was defined as VT or VF lasting more than 10 seconds at programmed stimulation. VT was said to be present if there was a well-organized rhythm from the outset, with constant or nearly constant (±5%) cycle length and stable ECG morphology for at least 5 seconds. The classification of an arrhythmia as VT was not altered if VF subsequently supervened. VF was said to be present if, from the outset, there was a disorganized rhythm with irregularly timed electrograms and either no clearly defined QRS complexes on the ECG or QRS complexes of continuously varying configuration. After 10 seconds, attempts were made to terminate VT or VF by pacing or by cardioversion. Preliminary studies showed that the resuscitation rate in these conscious dogs was much lower if attempts to terminate the arrhythmias were postponed to 30 seconds.

The reproducibility of VF induction was not tested in this study. Reproducibility of VT induction was tested in seven consecutive dogs with VT not requiring cardioversion at conscious stimulation. Fifteen minutes was allowed to elapse between induction of VT at the first stimulation and commencement of repeat stimulation.

Animals resuscitated from VT or VF and animals without inducible arrhythmias underwent myocardial mapping within 48 hours under general anesthesia. The hearts of dogs not resuscitated were excised and preserved in 10% formalin for pathological examination.

Cardiac Mapping

Anesthesia was induced with thiopentone sodium (20 mg/kg i.v.), a cuffed endotracheal tube was inserted, and ventilation and anesthesia were maintained as described for the primary operation.

We exposed the heart for mapping either by reopening the original thoracotomy or by performing a median sternotomy. In animals undergoing endocardial mapping on cardiopulmonary bypass, the aorta and right atrium were cannulated, and normothermic cardiopulmonary bypass was instituted with a modulator roller pump to maintain a flow rate of 1–1.5 l/min and a mean femoral arterial pressure of 60–80 mm Hg. For the bypass studies, muscle paralysis was maintained with incremental doses of pancuronium (up to 4 mg).

Amplified electrograms recorded either from the body surface or directly from the heart were transmitted via a delay circuit for display on a storage oscilloscope. The oscilloscope was triggered from a ventricular reference electrogram recorded from the RV or LV epicardial electrodes implanted at the
intravenous pentobarbitone sodium (approximately with delayed potentials in sinus rhythm were ringed wires with the same protocol used before anesthesia. If VT was induced, the epicardial activation sequence in VT was mapped.

The duration of activation at each site was determined for each animal from a mean of the durations of activation at individual sites. The standard sites from which these recordings were made were spread evenly over the right and left ventricular epicardial and endocardial surfaces. Recordings from the myocardium, the needle electrode was inserted to a depth of 2 mm from the RV free wall epicardium and 5–6 mm from the LV and septal epicardium. For endocardial recordings, the depths were 4 mm from the RV free wall epicardium and 10–12 mm from the LV free wall epicardium.

During sinus rhythm mapping, the probe electrode signals were amplified 1,000 times to facilitate identification of fractionated, low amplitude signals in the ST segment (delayed potentials). The total duration of ventricular activation was measured in milliseconds from QRS onset to the end of the local ventricular electrogram for each free-wall site (16 LV and eight RV epicardial, 16 LV and eight RV myocardial, and 16 LV and eight RV endocardial) as well as each septal site (eight epicardial, eight myocardial, six LV endocardial, and six RV endocardial). The duration of activation at each site was measured, and the maximum duration for each animal was noted. In addition, the mean value was determined for each animal from a mean of the durations of activation at individual sites. The standard sites from which these recordings were made were spread evenly over the right and left ventricular epicardial and endocardial surfaces. Recordings were made on paper at 100 or 250 mm/sec paper speed with an ink-jet recorder (Mingograf 804, Siemens Elema, Stockholm, Sweden).

After mapping in sinus rhythm (and before any proposed ventriculotomy), programmed stimulation was performed through the RV or LV epicardial wires with the same protocol used before anesthesia. If VT was induced, the epicardial activation sequence in VT was mapped. At the conclusion of cardiac mapping, the sites with delayed potentials in sinus rhythm were ringed with proline sutures, the animals were killed with intravenous pentobarbitone sodium (approximately 1 g), and the hearts were excised and preserved in 10% formalin.

Pathology

The atria were cut from the excised hearts, the ventricles were weighed, and the coronary arteries and ligature sites were inspected. The hearts were then sliced in breadloaf fashion from apex to base in 1-cm thick slices, and infarct size was estimated by measurement of the maximum extent of the infarction in three dimensions in each slice and then addition of the infarct size for each slice to achieve the value for each heart. The infarct size (cm³) was expressed as a percentage of the volume of the ventricular myocardium (cm³), which was derived from the ventricular weight (g), assuming the density of ventricular myocardium to be 1 g/cm³.

From preliminary studies we found that by considering the maximum dimensions of the infarct in each slice, infarct size was overestimated for each animal by about 25% (compared with results obtained by planimetry of each slice), but the detailed histology at the infarct edge was preserved for three-dimensional tissue reconstruction. Preservation of the microanatomy at the infarct edge would not have been possible had tetrazolium staining with incubation at 37° C¹² or "cut-and-weigh" techniques been used to determine infarct size.¹³ Slides for light microscopy were prepared from sections taken from standard blocks cut from the center of the infarct and from each edge (superior, inferior, and both lateral edges). Additional sections were taken from areas found at cardiac mapping to have delayed potentials if the standard blocks had not already encompassed such areas. In control animals, sections were taken from macroscopically normal myocardium in the distribution of the left anterior descending coronary artery and also from any areas of macroscopic discoloration of the myocardium. All slides were stained with hematoxylin and eosin. The maximum diameter of viable bundles of myocardium interdigitating with scar tissue in the subepicardium was quantitated with a microscope graticule after each block was sectioned at 100-µm intervals. Only those viable muscle bundles running perpendicular to the plane of section were measured.

In 24 animals, more detailed histological examination was performed with serial sectioning from epicardium to endocardium at sites with and without delayed potentials in sinus rhythm. Reconstruction was performed at sites along the edge of macroscopic infarction where no delayed potentials were detectable (20 sites in 10 dogs) and at sites where delayed potentials were detectable (14 sites in 14 dogs). The tissue of interest was embedded from the ventricular weight (g), assuming the density of ventricular myocardium to be 1 g/cm³.
dial plane, as was the percentage of the infarct that was patchy at each site.

In addition, three dimensional models were constructed to enable pictorial display of infarct anatomy at sites with and without delayed potentials in six dogs where epicardial, intramural, and endocardial recordings were made in sinus rhythm. To make these models, the stained thin sections were projected onto transparencies, and the outlines of surviving myocardium were first drawn on to the transparencies and were then traced on to sheets of dental modeling wax. Sections of wax representing viable myocardium were cut out and removed, so that a wax mold of the surviving myocardium was made. Casting resin (Araldite LC 177, CIBA-GEIGY) was poured into the mold. When it had set, the wax was melted away, leaving behind a three-dimensional reconstruction of the surviving myocardium at the edge of the infarct. The horizontal and vertical proportions of the original tissue were preserved at either ×20 or ×40 magnification.

Statistical Analysis

For continuous variables, paired and unpaired t tests were used where appropriate, with the Bonferroni procedure applied for multiple simultaneous comparisons. For discrete variables, either a Yates’ corrected χ-square test or Fisher’s exact test was used. Statistical significance was defined as p<0.05.

Results

One hundred twenty dogs (106 infarcted dogs, 14 controls) survived for at least 1 week after the initial thoracotomy and form the basis of this report. Seven of the infarcted dogs had at least one episode of spontaneous VT (lasting more than 30 seconds) documented on ECG 3–9 days after coronary artery ligation.

Programmed Stimulation

Dogs underwent programmed stimulation while conscious 7–21 days (mean 11 days) after implantation of epicardial electrodes with or without coronary artery ligation. No control animal had inducible VT or VF. The maximum number of nonstimulated ventricular beats in control animals was eight.

Of the 106 infarcted animals, 47 (44%) had no inducible VT or VF. VF was inducible in 19 animals (18%), and monomorphic VT was inducible in 40 animals (38%). Mean cycle length of inducible VT was 182 msec (range 100–290 msec). Twelve dogs with inducible VF and 30 dogs with inducible VT were resuscitated from the inculable arrhythmias. In each of the seven dogs in which reproducibility of VT induction was tested, reinduction of VT was achieved at repeat stimulation. The cycle length of VT induced at each of the studies was highly significantly correlated (r=0.96, p<0.005).

Of the seven animals with spontaneous VT, six (86%) had inducible VT at programmed stimulation, and one had inducible VF.

<table>
<thead>
<tr>
<th>Site</th>
<th>VAT (msec)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardium</td>
<td>73±2</td>
<td>14</td>
</tr>
<tr>
<td>Myocardium</td>
<td>71±2</td>
<td>8</td>
</tr>
<tr>
<td>Endocardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free wall</td>
<td>67±2</td>
<td>8</td>
</tr>
<tr>
<td>Septum</td>
<td>60±3</td>
<td>5</td>
</tr>
</tbody>
</table>

VAT, ventricular activation time (mean±SEM).

Cycle length of inducible VT was much longer (197±8 msec) in the animals in which VT was able to be pace-terminated than in the animals in which VT degenerated into VF (148±10 msec, p<0.001).

PREAMPTUREITY OF VENTRICULAR EXTRASTIMULI

In the control animals without infarction (no inducible arrhythmias), the minimum coupling intervals used during programmed stimulation were 107±5 msec for S1S1 and 69±4 msec for S2S3. For the infarcted animals with no inducible VT or VF, the minimum coupling intervals (117±2 msec for S1S1 and 84±3 msec for S2S3) tended to be slightly higher than for control animals, but the trends did not reach statistical significance.

The mean S1S1 coupling intervals at which VF and VT were induced in infarcted animals were 111±2 msec and 122±3 msec, respectively, not significantly different from the minimum S1S1 (117±2 msec) for infarcted animals with no inducible arrhythmias. However, mean S2S3 coupling interval for induction of VT was higher at 132±7 msec than either the S1S1 interval for induction of VT (95±3 msec, p<0.005), or the minimum S1S1 coupling interval achieved in infarcted animals with no inducible VT or VF (84±3 msec, p<0.001). Four animals with inducible VT required only a single extrastimulus for VT induction.

Cardiac Mapping

Cardiac mapping was performed in 14 control dogs and in 89 infarcted dogs, including all 47 animals with no inducible arrhythmias and the 42 dogs that were successfully resuscitated from inducible VT or VF.

Ventricular activation times for epicardium, myocardium, and endocardium are shown in Table 1. Maximum epicardial activation time for each animal averaged 73 msec, with a 95% confidence limit of ±17 msec. Delayed epicardial activation was henceforth defined as epicardial activation time exceeding 90 msec and was invariably a result of fractionated low amplitude signals extending into the ST segment (delayed potentials, Figure 1). Delayed myocardial, endocardial free wall, and endocardial septal activation times were similarly defined as activation times exceeding 90 msec, 80 msec, and 75 msec, respectively.

The corresponding results for infarcted animals are shown in Table 2 and in Figure 2. The three
FIGURE 1. Delayed potentials detectable in chronic canine infarction. X and Y surface electrocardiogram leads are shown, together with electrograms recorded at the same gain from left ventricular epicardial (EPI) and myocardial (MYO) sites with delayed potentials (DP). The MYO site was 2 mm deep to the EPI site.

groups of infarcted animals differed significantly with respect to maximum epicardial activation time, so that maximum epicardial activation time was longest (127 msec) in animals with inducible VT and shortest in animals with no inducible arrhythmias (75 msec, $p<0.001$). Animals with inducible VT tended to have longer maximum myocardial and endocardial activation times than did animals with no inducible arrhythmias, but these trends did not reach statistical significance.

Mean epicardial activation time (averaged over the 32 sites mapped) was higher (64±2 msec) for animals with inducible VT than for animals with no inducible arrhythmias (55±1 msec, $p<0.001$). The mean activation time on the epicardium was intermediate in value at 60±3 msec in the animals with inducible VF.

As shown in Table 3, delayed epicardial activation was present in 90% of animals with inducible VT, in 42% of animals with inducible VF, and in only 6% of animals with no inducible arrhythmias. Epicardial delayed potentials were usually located at the edge of the area of macroscopic infarction or at sites of patchy infarction. Delayed myocardial and endocardial activation were present more frequently in animals with inducible arrhythmias than in animals with no inducible arrhythmias, but the incidence was similar for the VT and VF groups (Table 3).

Although markedly prolonged epicardial activation time was associated with inducible VT, the cycle length of inducible VT was not significantly related to epicardial activation time ($r=0.32$, $p=0.13$), and maximal epicardial activation time did not predict the animals in which inducible VT degenerated into VF.

Figure 3 shows the number of epicardial sites per animal at which delayed potentials were detectable in infarcted animals with and without inducible arrhythmias. In animals with no inducible arrhyth-

<p>| TABLE 2. Maximum Ventricular Activation Times in Infarct Animals |
|------------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>VT or VF</th>
<th>Inducible VT</th>
<th>Inducible VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>VAT (msec)</td>
<td>75±2</td>
<td>91±8</td>
</tr>
<tr>
<td>Myocardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>VAT (msec)</td>
<td>70±5</td>
<td>88±6</td>
</tr>
<tr>
<td>Endocardium (free wall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>VAT (msec)</td>
<td>75±4</td>
<td>89±2</td>
</tr>
<tr>
<td>Endocardium (septum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>VAT (msec)</td>
<td>69±6</td>
<td>74±5</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia; VF, ventricular fibrillation; VAT, ventricular activation time (mean±SEM). Unless otherwise indicated, differences between groups were not significantly different. *$p<0.05$; **$p<0.01$; ***$p<0.001$. 

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mias, delayed potentials were an infrequent finding and were present at a maximum of two epicardial sites (32 mapped). Delayed potentials were present at an average of 1.1±0.5 epicardial sites (maximum 4) in animals with inducible VF and 1.8±0.3 sites (maximum 6) in animals with inducible VT. This difference in extent of delayed potentials between these two groups was not significantly different.

For dogs with inducible VT as well as spontaneous VT, maximum epicardial activation time averaged 120±11 msec, not significantly different from 128±28 msec for dogs with inducible VT but no spontaneous arrhythmias.

The epicardial activation sequence during monomorphic VT was determined at cardiac mapping in 14 dogs. Fifteen morphologies of VT were mapped, and in 10 (67%) earliest epicardial activation during VT occurred at, or immediately adjacent to, an epicardial site with delayed potentials in sinus rhythm. Mean VT cycle length in this group was 246±27 msec. The cycle length of VT was not

<table>
<thead>
<tr>
<th>Site</th>
<th>No inducible VT or VF</th>
<th>Inducible VT</th>
<th>Inducible VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardium</td>
<td>3/47 (6%)</td>
<td>5/12 (42%)</td>
<td>27/30 (90%)</td>
</tr>
<tr>
<td>Myocardium</td>
<td>2/15 (13%)</td>
<td>4/8 (50%)</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>Endocardium (free wall)</td>
<td>5/15 (33%)</td>
<td>6/8 (75%)</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td>Endocardium (septum)</td>
<td>1/5 (20%)</td>
<td>***</td>
<td>2/5 (40%)</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia; VF, ventricular fibrillation. Unless otherwise indicated, differences between groups were not significantly different. *p<0.01; **p<0.001.
Pathology of Infarction

The hearts of all dogs studied by programmed stimulation were examined histologically. Absence of infarction was confirmed in all control animals. All animals with infarcts had predominantly subendocardial infarction. As shown in Table 4, the incidence of transmural infarction, extending from epicardium to endocardium, was highest in dogs with inducible VT, but in all the dogs with transmural infarction, there was lateral subendocardial extension of the infarction, with the overlying subepicardium being spared.

Infarct size was similar in dogs with inducible VF and in dogs with no inducible arrhythmias. In dogs with inducible VT, mean infarct size was larger (by a factor of two). Infarct size was not, however, significantly correlated with the cycle length of inducible VT ($r=0.12$, $p=0.52$), and did not predict the animals in which inducible VT degenerated into VF.

Table 4 shows the maximum diameter of viable muscle bundles at standard sites. The diameter of the muscle bundles was larger in animals with inducible arrhythmias. In animals with inducible VT, at least one of the standard blocks was usually also a site with delayed potentials in sinus rhythm. The maximum diameter of viable muscle bundles interdigitating with scar tissue at the infarct edge was 20 and 30 msec ahead of earliest endocardial activation.

Tissue with transmural infarction was electrically inert, both during sinus rhythm and during VT.

Table 4. Pathology of Canine Infarction: Relation to Inducibility of Ventricular Tachyarrhythmias

<table>
<thead>
<tr>
<th></th>
<th>No VT/VF inducible</th>
<th>VF inducible</th>
<th>VT inducible</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>47</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Ventricular weight (g)</td>
<td>157±5</td>
<td>162±14</td>
<td>162±5</td>
</tr>
<tr>
<td>Infarct depth (1.0=transmural)</td>
<td>0.83±0.03</td>
<td>0.81±0.05</td>
<td>0.95±0.02</td>
</tr>
<tr>
<td>Transmural infarction</td>
<td>47%</td>
<td>42%</td>
<td>83%</td>
</tr>
<tr>
<td>Infarct size (% of ventricles)</td>
<td>9±1</td>
<td>11±2</td>
<td>18±2</td>
</tr>
<tr>
<td>Maximum diameter of VMB (mm)</td>
<td>1.7±0.1</td>
<td>1.8±0.2</td>
<td>2.4±0.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Unless otherwise stated, differences were not statistically significant (NS). *$p<0.05$; **$p<0.01$; ***$p<0.001$.

The significantly different (257±33 msec) in the five morphologies of VT in which earliest epicardial activation was distant from sites with delayed potentials. In the two dogs in which both intramyocardial and endocardial mapping were performed in addition to epicardial mapping during VT, earliest epicardial activation was 20 and 30 msec ahead of earliest endocardial activation.

FIGURE 4. Histology of a site with epicardial delayed potentials. The epicardium is shown at the top of the illustration. Bundles of viable myocardium (arrowed) are seen in the subepicardial region and are surrounded by organizing scar tissue. The scale bar represents 0.1 mm.
FIGURE 5. Diagrammatic representation of the histology at a site with delayed potentials. The tortuous interconnections between viable bundles of myocardium interdigitating with scar tissue in the subepicardial region are shown at a site with delayed potentials in sinus rhythm. The necrotic and degenerative myocardium to the left of the site of coronary artery ligation was electrically inert. In the right half of the diagram, where viable myocardium is interdigitating with necrotic myocardium, delayed potentials were recorded in sinus rhythm from the epicardium and also from intramural recordings to a depth of 2 mm from the epicardium.

(Figure 4) was larger at sites with delayed potentials in sinus rhythm (2.4±0.3 mm) than at sites with no delayed potentials (1.7±0.1 mm, p<0.05).

The muscle bundles at sites with delayed potentials had numerous tortuous interconnections, as shown in two dimensions in Figure 5 and three dimensions in Figure 6. These interconnections gave the infarct-normal muscle border zone a very ragged appearance. At sites with no delayed potentials in sinus rhythm, the smaller muscle bundles at the infarct-normal muscle border zone had few interconnections, and the edge of the infarct was much less ragged (Figure 7). Although infarct depth was similar at sites with and without delayed potentials (10.1±0.7 mm and 9.6±0.7 mm, respectively), the proportion of the infarct that was patchy was higher at sites with delayed potentials (30±4%) than at sites with no delayed potentials (20±4%, p<0.05). Of the 10 animals studied with delayed potentials, the majority of the raggedness was located at the subepicardial border in eight, at the subendocardial border in one, and at both the subepicardial and lateral intramyocardial borders in the remaining animal.

Discussion

This study suggests that there are different electrophysiological and anatomic abnormalities responsible for VT and VF inducible in conscious dogs with 1–3-week-old experimental myocardial infarction. We have shown that animals with the two arrhythmias differ with respect to duration of ventricular activation in sinus rhythm, infarct size, and the anatomy of the infarct edge.

Ventricular Activation in Sinus Rhythm

Several groups have noted that VT (either spontaneous or inducible) is usually associated with longer activation time in sinus rhythm than is VF (either spontaneous or inducible). Evidence for this comes from studies of patients with previous myocardial infarction or chronic canine infarct models. In the present study, conduction delay was sought not only on the epicardium, as in the previous studies, but also in the myocardium and endocardium. Although endocardial and myocardial activation tended to be longer in animals with inducible arrhythmias than in animals with no inducible arrhythmias, there were no differences in activation times between animals with VT and VF in either the endocardium or in the myocardium. The clear difference in activation time between animals with VT and VF was confined to the epicardium. Within the limitations of mapping only 32 epicardial sites, the present study showed that conduction
FIGURE 6. Three-dimensional reconstruction of the edge of the infarct at a site with delayed potentials. Three-dimensional tissue reconstruction from epicardium to endocardium is shown at a site at the edge of macroscopic scar tissue from which delayed potentials were recorded at epicardial and intramyocardial mapping in sinus rhythm. For both illustrations (of the same model), the outline of scar tissue is shown in white, and the three-dimensional relief depicts surviving myocardium. On the left of the section, the infarct is transmural, while on the right it is subendocardial. The horizontal and vertical scales are identical, with the scale at the left of each illustration representing 4 mm (subdivided into 1 mm divisions). The edge of the infarct is very ragged, with numerous tortuous interconnections between peninsulas of viable myocardium interdigitating with scar tissue. White tubing has been passed under some of the interconnecting myocardial bridges in the top illustration.
delay in sinus rhythm was much more marked on the epicardium in animals with inducible VT than in animals with inducible VF. The degree of epicardial conduction delay in sinus rhythm was similar in animals with inducible VT that had exhibited spontaneous VT and in animals with inducible VT that had not had spontaneous arrhythmias documented during the comparatively short follow-up period.

The present study also found that while the degree of conduction delay in sinus rhythm was related to whether VT or VF was induced, the degree of conduction delay was not closely related to the cycle length of inducible VT. This is consistent with the results of a previous study, which used endocardial catheter mapping to measure conduction delay in sinus rhythm in patients with previous myocardial infarction. This finding implies that while localized conduction delay may be important in determining arrhythmia morphology, it may have little influence on cycle length of VT, which is presumably dependent on other factors such as the anatomy of the reentrant circuit.

A critical factor in induction of VT or VF appears to be the relation between conduction delay and refractory periods at short extrastimulus coupling intervals in the infarct and the adjacent normal myocardium. Premature ventricular extrastimuli and spontaneous premature ventricular contractions can promote induction of VT or VF by increasing the conduction delay already present in sinus rhythm. As noted in the present study, inducible VF was associated with less marked conduction delay in sinus rhythm than was inducible VT, and shorter extrastimulus coupling intervals were required for induction of VF than for induction of VT, as we have found previously in patients with inducible arrhythmias after myocardial infarction.

Infarct Size and Histopathology

While animal studies and studies involving patients with myocardial infarction have indicated that VT is associated with large infarct size, few studies have drawn attention to the differences in infarct size (or left ventricular ejection fraction) associated with inducible VT and inducible VF. A large infarct is presumably also associated with a larger number of potential reentrant circuits at the infarct border.

In addition to infarct size, the histology at the infarct edge was found to be particularly important.
in determination of the morphology of the inducible arrhythmia. The present study showed from two- and three-dimensional display of the histology at the infarct edge that an irregular infarct-normal muscle border predisposed to both inducible VT and to delayed conduction in sinus rhythm. Delayed ventricular activation was most notable at the epicardium and corresponded with tortuously interconnected subepicardial viable muscle bundles and a more ‘patchy’ edge of the infarct. When no delayed activation was present, the border zone was much less irregular, and the viable muscle bundles interdigitating with scar tissue were smaller and had fewer interconnections. These tortuous interconnections between bundles of viable myocardium seen “trapped” in scar tissue in single histological slides may be at least part of the explanation for the conduction delay, which is a factor in the genesis of reentrant arrhythmias.

It has previously been noted\textsuperscript{22,23} that the action potentials recorded from the surviving myocardial cells interdigitating with scar tissue at the infarct edge are almost always normal. However, within a relatively small area of tissue, there is heterogeneity of conduction which is reflected in asynchrony of action potentials as adjacent regions are activated. The different components of the fractionated and delayed electrograms coincide with the asynchronous, but normal action potentials,\textsuperscript{22} implying that the cause of the asynchrony is normal impulse conduction through multiple anatomic pathways of different lengths. The present study suggests that the numerous tortuous interconnections between peninsulas of viable myocardium at the infarct edge may be one of the anatomic correlates for these electrophysiological findings.

Sites with marked conduction delay in sinus rhythm may facilitate activation of adjacent excitable tissue, thus initiating one or more reentrant beats or sustained VT. Thus, an area of early activation in VT may represent the site closest to the exit path from the area of conduction delay in sinus rhythm.\textsuperscript{24} While the reentrant circuits involved in VT were not defined in the present study, sites with earliest epicardial activation were usually coincident with or adjacent to sites with delayed epicardial activation in sinus rhythm.

The finding that the most marked conduction delay is on the epicardium is probably related to the anatomy of canine infarction, where subepicardial tissue is characteristically spared.\textsuperscript{23,25,26} The situation is usually different in patients with VT after infarction, who characteristically have subendocardial sparing.\textsuperscript{21}

The dog infarct models may differ from the human infarct situation because of the sequence of events in the coronary arteries. Thus, in canine infarction there were one or two ligations occurring at the same time in an otherwise normal arterial tree. By contrast, many patients with infarction have repeated occlusions of multiple arteries at different times leading to cumulative damage.

Possible Implications

This study indicates that in canine myocardial infarction, inducible VF is associated with fewer electrophysiological abnormalities in sinus rhythm, smaller infarct size, and a less ragged infarct edge than is inducible VT. VT and VF should not be grouped together when evaluating the electrophysiology and significance of inducible arrhythmias after myocardial infarction.

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References


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