Myocardial Discontinuities
A Substrate for Producing Virtual Electrodes That Directly Excite the Myocardium by Shocks

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Background—Theoretical models suggest that an electrical stimulus causes regions of depolarization and hyperpolarization on either side of a myocardial discontinuity. This study determined experimentally whether an artificial discontinuity gives rise to an activation front in response to an electrical stimulus, consistent with the creation of such polarized regions.

Methods and Results—After a thoracotomy in six dogs, a 504-unipolar-electrode plaque was sutured to the right ventricular epicardium to map activations. From a line electrode parallel to one side of the plaque, 10 S1 stimuli were delivered, followed by S2 and S3 stimuli (S1-S1, S1-S2, S2-S3 interval = 300 ms). S1 and S3 stimuli were 25 mA; 5-ms S2 stimuli of both polarities were initially 25 mA and increased in 25 mA increments. The plaque was removed, and a transmural incision was made through the ventricular wall in the middle of the mapped region and sutured closed. The plaque was replaced and the stimulation protocol repeated. Before the incision, S2 stimuli directly activated tissue only near the stimulation site. An activation front arose at the border of the directly activated region and propagated across the plaque. As the S2 stimulus strength was increased, the size of the directly activated region increased. After the incision, sufficiently large S2 stimuli caused direct activation of tissue adjacent to the transmural incision as well as at the stimulation site. Activation fronts that arose adjacent to the transmural incision either propagated proximally toward the stimulation site and collided with the activation front originating from the stimulation wire or propagated distally away from the incision. Minimum S2 stimulus strengths activating areas adjacent to the incision were only 45 ± 14% (cathode) and 39 ± 18% (anode) of the strengths required to directly activate the same area before the incision was formed (P < .05).

Conclusions—Myocardial discontinuities can give rise to activation fronts after a stimulus, suggesting the presence of polarized regions adjacent to the discontinuity. (Circulation. 1998;97:1738-1745.)

Key Words: defibrillation ■ excitation ■ mapping ■ electrical stimulation

An electrical shock is thought to defibrillate by directly exciting tissue to cause new cardiac action potentials or extension of action potentials.1-5 One of several factors that may contribute to the mechanisms by which the shock directly excites myocardium to cause a new action potential in tissue distant from the defibrillation electrodes is discontinuities between myofibers or between bundles of myofibers.6,7 These discontinuities can be normal, such as interstitial connective tissue and blood vessels, or abnormal, such as myocardial infarct scars and surgical incisions. By interrupting the closely coupled syncytium of myocytes, these discontinuities interrupt the intracellular space, requiring current that crosses the discontinuity caused by the shock to exit the intracellular space on one side and reenter the intracellular space on the other side of the discontinuity (Figure 1). This transmembrane current should alter the transmembrane potential near the discontinuity, causing depolarization on one side and hyperpolarization on the other. Thus, secondary sources can be created with a virtual cathode in the depolarized region and a virtual anode in the hyperpolarized region.

This study determined whether the magnitude of these secondary sources can be sufficient to directly activate tissue adjacent to the discontinuity. This was done by use of a series of electrical stimuli of increasing strength given before and after a large discontinuity was created by a transmural incision made through the right ventricle of the canine heart. Activation sequence maps were examined to see whether activation fronts arose from either side of the surgical incision, which would indicate that the discontinuity formed by the incision created a virtual electrode.
Methods

Six dogs (18 to 22.5 kg) were anesthetized with pentobarbital (30 mg/kg), intubated and mechanically ventilated with supplemental oxygen, and given maintenance intravenous fluids. The ECG and arterial blood pressure were continuously monitored. Core body temperature, arterial blood gas levels, and electrolyte levels were maintained within normal limits. Succinylcholine (0.3 mg/kg) was administered as needed to minimize skeletal muscle stimulation by the shocks. The chest was opened through a right thoracotomy, and a pericardial cradle was created to expose the right ventricle. A plaque containing 504 unipolar epicardial recording electrodes arranged in a 24×21 pattern was sutured onto the right ventricle (Figure 2). The interelectrode distance was 2 mm, resulting in a mapped area of 18.4 cm². The return electrode was sutured to the aortic root. A silver wire 4 cm long was sutured along one side of the plaque (Figure 2) for application of a series of stimuli, called S₁, S₂, and S₃. A titanium mesh electrode sutured on the left ventricle was used as the return electrode for stimulation.

All stimuli were 5-ms, square, constant-current pulses of the same polarity, with the S₁S₂, S₂S₃, and S₃S₁ intervals equal to 300 ms. The S₁ and S₂ stimuli were 25 mA. After 10 S₁ stimuli, the S₂ stimulus initially was 25 mA and then was increased in 25-mA increments until all tissue under the plaque was directly excited as determined by analysis of results during the study. Cathodal pulses were delivered first, followed by anodal pulses.

After all stimuli were delivered, the plaque was removed, with the sutures left in place. With umbilical tape, the superior and inferior venae cavae were constricted, and a transmural incision averaging 3.6±0.3 cm in length was formed by a cut through the right ventricle in the middle of the mapped area (Figure 2). The incision was sutured closed, and venous inflow was reinstituted. After the animal stabilized, as determined from ECG, blood-pressure, and blood-gas measurements, the plaque was resutured to the same location, and the stimulation protocol as described above was then repeated. In addition to the six experimental animals, two sham-treated animals were also studied. These animals underwent the same protocol as described above minus the creation of the incision.

After the experiment, a lethal dose of KCl was given, and the heart was removed. The region under the plaque was excised, and the tissue was fixed in formalin and sectioned parallel to the epicardial surface at 0.5-mm increments. Fiber orientation was determined from the histological sections. All animals were treated and cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Data Acquisition

Simultaneous recordings were made from the plaque with a 528-channel mapping system with AC-coupled amplifiers with a 0.5-Hz high-pass filter and a 500-Hz low-pass filter. During the S₂ stimulus, the attenuators were switched on, amplifiers were DC-coupled, and the gain of each channel was decreased. The signals were digitized at 2000 samples per second per channel and stored on a Sun workstation (Sun Microsystems Inc) for analysis during and after the experiment.

Data Analysis

The direction of wave fronts and the presence of collision or block were observed on a computer screen showing animated maps of the first derivative of the electrograms (dV/dt) determined by a parabola fitted to five data points. Electrodes were displayed as recording an activation when dV/dt was more negative than −0.5 V/s. In some cases, activation times were manually assigned to the fastest downslope of the electrograms to construct isochronal maps by use of discrete smooth interpolation. Electrodes with signals that were saturated or too noisy to allow identification of activations were not analyzed.

For each polarity, the minimum current required to directly activate the areas adjacent to the transmural incision after the incision was compared with the current required to directly activate the same areas before the incision. Also, the current required to directly activate all columns of the mapped region both before and after the incision was determined for each polarity. Direct activation of the mapped area was determined by viewing of animation sequences and by electrogram analysis. Tissue under electrodes that did not record an activation after S₂ stimulation was considered to be directly excited by the stimulus as described previously. To quantify the effect of the incision on the activation sequence, the time interval was determined from the begin-

Figure 1. Effect of an intracellular discontinuity on current flow. Top, As current (indicated by arrows) crosses from extracellular compartment to intracellular, a change in transmembrane potential is observed. Near an extracellular anode, transmembrane potential (Vₘ) is hyperpolarized as shown below. Near cathode, current exits intracellular compartment and depolarizes transmembrane potential. Bottom, When an intracellular discontinuity is present, current is forced from intracellular to extracellular compartment to intracellular, a change in transmembrane potential (Vₘ) is hyperpolarized as shown below. Near cathode, current exits intracellular compartment and depolarizes transmembrane potential. Bottom, When an intracellular discontinuity is present, current is forced from extracellular compartment to intracellular, a change in transmembrane potential is observed. Near an extracellular anode, transmembrane potential (Vₘ) is hyperpolarized as shown below. Near cathode, current exits intracellular compartment and depolarizes transmembrane potential.

Figure 2. Mapped area and incision on right ventricle. Each small circle represents a recording site on mapping plaque. Location of electrode 254 is indicated.
ning of the S1 stimulus to activation at electrode 254 in the center of the plaque distal to the incision (Figure 2). The time interval from the beginning of the S2 stimulus at the minimum strength required to directly activate tissue adjacent to the incision until the activation time at electrode 254 was also determined. These times were recorded both before and after the incision was created. Activation after the S3 stimulus was examined to determine whether the large S2 stimulus altered the activation sequence in response to a 25-mA stimulus. To assess the presence of injury currents as a result of the incision, ST segments were measured in all six animals at electrode 254 and compared at three times: the beginning of the study, immediately after the incision, and the end of the study.

Data are expressed as mean±SD unless otherwise specified. ANOVA with repeated measures and Student’s t test for paired samples were used to determine statistical significance. A value of P<.05 was considered significant.

Results

Cathodal Stimuli

Before Incision Formation

Before the incision, activation after cathodal S1 stimuli originated near the stimulating electrode and propagated across the recorded area (Figures 3A and 4A). Activation times for the S3 stimuli were similar to those for the S1 stimuli. The isochronal activation contours for five of the six animals were approximately linear and parallel to the stimulating electrode.

Increasing S2 strength increased the area of tissue directly activated. Figures 3B and 4B show an example for a 75-mA S2 stimulus that was sufficient only to directly activate a few electrodes in the first two columns of the plaque. At the border of the directly activated area, a wave front arose and propagated across the mapped area. As the S2 stimulus strength was increased, more tissue was directly activated. For a 250-mA S2 stimulus (Figures 3C and 4C), almost the entire proximal half of the plaque was directly activated. In Figure 4C, the top seven traces appear to be directly activated by the S2 stimulus, which corresponds to the direct activation of the first seven columns of electrodes in this region shown in Figure 3C. Eventually, the S1 stimulus strength was increased enough (400 to 600 mA, Table 1) to directly activate all columns of the mapped region.

After Incision Formation

For cathodal S1 stimuli after the incision, wave fronts propagated away from the stimulating electrode, blocked near the proximal border of the incision, and wrapped around the ends of the incision to collide on the distal side of the incision (Figures 3D and 4D). The activation patterns after S3 stimuli were similar to those after S1 stimuli.

As the S2 stimulus strength increased, areas of direct activation were observed on both sides of the incision as well as at the stimulation site. Activations originating on the proximal side of the incision propagated toward the stimulating electrode, colliding with the wave front arising near the stimulating electrode (Figures 3E and 4E). Activations originating on the distal side of the incision propagated distally.

<table>
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<th>Animal</th>
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<th>After Incision</th>
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<tbody>
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*P<.05 vs cathode, before incision; †P<.05 vs anode, before incision.
off the mapped region. The minimum S2 strength required to directly activate areas adjacent to the incision averaged 104 ± 37 mA (Table 2). This strength differs significantly from the strength required to directly activate the same tissue before the incision (229 ± 49 mA). The area directly activated by a 75-mA S2 stimulus before the incision (Figure 3B) was smaller than that directly activated after the incision (Figure 3E). Before the incision was made, an S2 strength of 250 mA was necessary to directly activate the tissue at the site of the incision (Figure 3C). The S2 strength required to activate all of the mapped region after the incision was also significantly different from that required before the incision (Table 1).

**Activation Times**

The time interval from the S1 stimulus to activation at electrode 254 was significantly shorter before the incision than after (Table 3), consistent with the incision’s creating a barrier that increased the conduction path from the stimulus site to the electrode (Figure 3A versus 3D). At the minimum S1 stimulus strength that caused activations adjacent to the incision (104 ± 37 mA), the time from the S2 stimulus to activation at electrode 254 was longer than for this same S2 stimulus strength before the incision (Figure 3B versus 3E).

**Anodal Stimuli**

Before Incision Formation

As for cathodal S1 stimuli, activation after anodal S1 stimuli originated from the proximal portion of the plaque (Figures 5A and 6A). For anodal pulses, however, the line of propagation was approximately parallel with the stimulation wire in only two animals, although this was observed in five animals with cathodal S1 pulses. The S1 stimulus activation patterns were again similar to those of S1 stimuli. As for cathodal S2 stimuli, increasing anodal S2 strength increased the area of tissue directly activated (Figures 5B and 6B). The average anodal S2 stimulus strength required to activate all columns of the mapped region was 517 ± 75 mA (Table 1).

After Incision Formation

After the incision, wave fronts originated near the anodal S1 stimulation site, propagated until they blocked at the incision, and then wrapped around the ends of the incision to propagate and collide on the distal side of the incision (Figures 5B and 6B). The average anodal S2 stimulus strength required to activate all columns of the mapped region was 517 ± 75 mA (Table 1).

### Table 2. Minimum Current Required to Activate Area Adjacent to Transmural Incision, mA

<table>
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<td>129*</td>
<td>104*</td>
<td>50†‡</td>
<td>163§</td>
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**P** indicates proximal; **D**, distal. *P<.05 vs cathode, before incision; †P<.05 vs anode, before incision; ‡P<.05 vs cathode, after incision; §P<.05 vs anode, P.

### Table 3. Interval From Beginning of S1 Stimulus to Activation at Electrode 254, ms

<table>
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<tr>
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<td>58*</td>
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**P<.05 vs cathode, before incision; †P<.05 vs anode, before incision.

### Table 4. Interval From Beginning of S2 Stimulus to Activation at Electrode 254, ms

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<td>Average</td>
<td>23</td>
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<td>32†</td>
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**P<.05 vs cathode, before incision; †P<.05 vs anode, after incision.

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Figure 5. Isochronal activation maps after anodal stimuli for one animal. Isochrones are drawn at 5-ms intervals timed from onset of S1 or S2 stimulus. Arrows represent direction of activation. Darkened regions represent areas directly activated. Black vertical lines represent approximate location of transmural incision. A, S1 stimulus delivered before incision; B, 75-mA S2 stimulus delivered before incision; C, S1 stimulus delivered after incision; D, 75-mA S2 stimulus delivered after incision; E, 250-mA stimulus delivered after incision; F, orientation of long axis of myocardial fibers.
When the anodal $S_2$ strength was increased to 50 mA for all animals (Table 2), areas of direct activation were observed adjacent to the incision, as with cathodal $S_2$ stimulation. Unlike with cathodal $S_2$ stimuli, however, activation originated only on the proximal side of the incision at this anodal $S_2$ strength (Figures 5D and 6D). The wave fronts that arose from the proximal side of the incision wrapped around to collide on the distal side of the incision. The anodal $S_2$ strength that directly activated the area proximal to the incision was significantly smaller than that required to activate the same tissue before the incision was formed (Table 2). When the $S_1$ stimulus strength increased to 163±65 mA (Table 2), activation began to originate directly from the tissue on the distal side of the incision. This $S_2$ stimulus strength was so large that it directly activated all of the tissue proximal to the incision (Figures 5E and 6E).

**Activation Times**

As with the cathodal $S_1$ stimuli, the time from anodal $S_1$ stimulation to activation at electrode 254 was shorter before than after the incision (Table 3), consistent with creation of a conduction barrier by the incision. For the minimum anodal $S_1$ strength that caused direct activation at the incision (50 mA), no significant difference was observed for activation times at electrode 254 before and after the incision (Table 4), consistent with the observation that, at this minimum $S_1$ stimulus strength, direct activation occurred only on the proximal side of the incision.

**Cathodal Stimuli Versus Anodal Stimuli**

Before and after the incision, anodal stimuli directly activated tissue just proximal to the incision site at a significantly lower $S_1$ strength than did cathodal stimuli (Table 2). No significant differences were observed for the two polarities in the stimulus strength required to activate the entire mapped region both before and after the incision (Table 1). Activation times at electrode 254 (Table 3) were significantly shorter for anodal than cathodal $S_1$ stimuli before the incision, whereas no significant differences for the two polarities were observed after the incision. Conversely, the activation times at electrode 254 were significantly shorter for cathodal than anodal $S_2$ stimuli after but not before the incision (Table 4).

Visual analysis of the computer animation of activation as well as statistical comparison of the activation times after $S_1$ and $S_2$ stimuli in the two sham-treated animals in which no incision was sham-treated indicated no significant differences in the activation patterns observed before and after the sham procedure, suggesting that the changes in the other six animals were caused by the incision.

Comparison and statistical analysis of the ST segments measured from electrode 254 before and after the incision indicated a significant change from before (0.58±0.72 mV) to after (6.96±2.68 mV) the incision. As the study progressed, the degree of ST-segment change decreased from 6.96±2.68 to 3.82±3.51 mV ($P=.11$).

**Fiber Orientation**

Fiber orientation for five animals ranged from 48° to 103° with respect to the parallel stimulation wire and incision (Figures 3F and 5F). For the sixth animal, the average fiber angle was 8°, nearly parallel to the stimulation wire and incision. The five hearts with a similar fiber orientation ranged in weight from 155 to 183 g, whereas the sixth heart had a large interatrial defect and weighed 344 g.

**Discussion**

Our major finding is that surgical incisions can create secondary sources during electrical stimulation. Evidence for this finding is that an electrical stimulus given from an electrode >2 cm away from the incision causes activation fronts to arise and propagate away from the incision at a stimulus strength that does not give rise to activation fronts in this area before the incision. In addition to visual examination of the animation sequences and isochronal maps (Figure 3), this finding was verified by quantification of the changes in activation time at a recording electrode near the incision (electrode 254, Figure 2). Before the incision, the time for activation to reach this electrode after a cathodal $S_2$ stimulus of 104±37 mA was 23±7 ms, whereas after the incision, this electrode recorded activation significantly earlier, 8±4 ms, in response to the same $S_2$ stimulus (Table 4).

A likely reason that activation arose near the incision was that the incision altered the transmembrane potential response in the adjacent myocardium caused by the $S_1$ stimulus. Such transmembrane potential changes were observed in a simulation using the bidomain formulation by Street and Plonsey. The surgical incision is thought to interrupt the intracellular space but, because the myocardium is sutured back together, not to interrupt the extracellular space. Because the intracellular space is interrupted, any intracellular current that would normally flow during the $S_1$ stimulus is forced to exit the intracellular space, cross the incision in the extracellular space, and then reenter the intracellular space on the other side of the incision (Figure 1). As current crosses the cell membrane, it alters the transmembrane potential. In this way, the incision serves as a boundary to current flow, causing depolarization on one side of the incision and hyperpolarization on the other.6,7
Injury potentials caused by the incision may have influenced these findings. To explore this possibility, computer simulations were performed that are presented in the “Appendix.” These simulations suggest that changes in the transmembrane potential caused by the incision can lower the stimulus strength required to directly excite tissue at the incision (Figure 7D). Elevation of the resting membrane potential to just below the threshold for activation of the sodium channels can cause the electrical stimulus to activate the tissue in this region even in the absence of an incision (Figure 7C). However, the alteration to cause this effect is extreme (i.e., 17 mmol/L extracellular potassium concentration) and may not be present 30 minutes after the incision is created.

The S2 stimulus was delivered in diastole, when activation is thought to occur in tissue that is sufficiently depolarized, but not in regions of hyperpolarization. Depression should occur on the distal side of the incision when the stimulus electrode is a cathode and on the proximal side of the incision when the stimulus electrode is an anode (Figures 1 and 7). Activation propagated away from both sides of the incision, not just the side that was thought to be depolarized. For a cathodal S2 stimulus, activation propagated away from both sides of the incision with the smallest S2 stimulus strength that caused activation to originate near the incision (Figure 3E). For an anodal S2 stimulus, activation first appeared only at the proximal side of the incision as the S2 strength was increased (Figure 5D). As the anodal stimulus strength was increased still further, activation fronts also originated from the distal side of the incision (Figure 5E).

The reason for these observations is unclear, but it may be related to the “dog bone” phenomenon reported by Wikswo and others, who found that along myofibers only 1 to 2 mm away from an anode, the change in transmembrane potential reversed from hyperpolarization to depolarization. Conversely, a few millimeters along fibers away from a cathode, depolarization changed to hyperpolarization. Similar findings have recently been observed for a wire stimulating electrode as used in our study. These changes in transmembrane potential are not seen in the simulation discussed in the “Appendix,” because they are one-dimensional. If the same changes occur just outside the secondary sources formed by the incision, a depolarized region should exist just proximal to the hyperpolarized region on the proximal side of the incision during a cathodal stimulus. Similarly, a depolarized region should exist just distal to the hyperpolarized region on the distal side of the incision during an anodal S2 stimulus. The areas of depolarization may give rise to the activation fronts seen in these regions after the S2 stimulus. Because the field strength of the S2 stimulus decreases with distance away from the electrode, it is probably smaller on the distal side of the incision than on the proximal side. If so, the depolarized region on the distal side of the incision during an anodal S2 stimulus may be weaker than the depolarized region on the proximal side during a cathodal stimulus. This may explain why a larger S2 stimulus is necessary to create an activation front on the distal side of the incision for an anodal stimulus than on the proximal side for a cathodal stimulus.

Another possible reason for this poststimulus activation behavior is the injury currents created by the incision (see “Appendix”). Experimentally, injury currents were detected adjacent to the incision in all animals. As the stimulation protocol progressed, the ST-segment changes tended to decrease with time, although they never completely disappeared. This suggests that the tissue surrounding the incision never had ample time to heal and as such may have continually produced an elevation in the transmembrane potential, which in turn may have altered tissue excitability after the incision. A third possible explanation for these findings is that break excitation occurred in areas hyperpolarized during the stimulus. For cathodal stimuli, break excitation may occur in the hyperpolarized region on the proximal side of the incision, resulting in subsequent propagation toward the stimulation wire. For an anodal shock of the same strength, hyperpolarization distal to the incision may be smaller than on the proximal side of the incision for a cathodal shock as a result of the smaller electrical field on the distal side of the incision, because it is farther from the stimulating electrode than the proximal side. Consequently, a larger stimulus strength would be required to directly activate the distal side of the incision by means of break excitation for anodal stimuli. On the basis of the results generated from the
simulations, however, break excitation is not the likely means of stimulation observed in this set of experiments, even in the presence of injury currents (see "Appendix").

These results have several implications for defibrillation. It is likely that secondary sources are not specific for surgical incisions but rather can form at any site in which the intracellular space is interrupted. Such interruptions occur naturally between bundles of myocardial fibers and where blood vessels and nerves traverse the myocardium. Thus, these results support the findings of Gillis et al and suggest that secondary sources can be an important mechanism for defibrillation. The magnitude of the secondary source probably depends on many factors, including size of the discontinuity, strength of the shock field, fiber orientation, and degree of anisotropy. This study indicates that when the discontinuity is transmural and several centimeters long, the secondary source can significantly affect the response to a shock. Such an interruption directly activated the tissue on at least one side of the incision with a stimulus strength that was only 39% of that required to directly activate this tissue when the interruption was absent (Table 2). The interruption had a smaller but still significant effect on direct activation by the shock 1 to 2 cm distal to the incision; the mean shock strength needed to directly activate tissue beneath all columns of the plaque was reduced 34% by the incision (Table 1).

Scars caused by infarction, cardiomyopathy, or surgical incisions may also serve as secondary sources. This phenomenon may explain why defibrillation thresholds are typically not increased by infarction, even though current shunting may occur through the scar, because its conductivity is higher than that of myocardium. Current shunting may be offset by secondary sources at the infarct border.

Surgical or ablative lesions may alter the defibrillation threshold. If the incisions are not transmural and do not extend to a boundary, they may be arrhythmogenic by allowing reentry to form around the anatomic barrier formed by the incision. If they are transmural and reach a boundary, however, they may lower the defibrillation threshold by creating barriers to conduction that decrease the incidence of reentrant pathways immediately after the shock, just as the maze surgical procedure decreases the incidence of spontaneous reentry leading to atrial fibrillation. Our study raises the possibility that surgical or ablative lesions also may lower the defibrillation threshold by a second mechanism: creation of secondary sources. These secondary sources may lower the shock strength needed to directly activate tissue, thus lowering the defibrillation threshold.

Appendix

We performed computer simulations to examine the effects of elevated [K+]i, one factor responsible for injury potentials associated with acute injury near the incision. Electrical activity was modeled by use of a one-dimensional bidomain representation of tissue structure:27

\[ I_{m} = V_{m} (\sigma_{i} \nabla \phi_{i}) + \nabla \cdot (\sigma_{e} \nabla \phi_{e}) \]

where \( \sigma_{i} \) is intracellular conductivity, \( \sigma_{e} \) is interstitial conductivity, \( \phi_{i} \) is intracellular potential, \( \phi_{e} \) is interstitial potential, and \( I_{m} \) is transmembrane current density. \( I_{m} \) was further specified in terms of membrane sources:

\[ I_{m} = A_{m} \left( \frac{\partial V_{m}}{\partial t} - I_{m} \right) \]

TABLE 5. Modeling Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific membrane capacitance ( C_{m} )</td>
<td>1.0 ( \mu F/cm^{2} )</td>
</tr>
<tr>
<td>Membrane surface-to-intracellular volume ratio ( A_{v} )</td>
<td>500 ( \text{cm}^{-1} )</td>
</tr>
<tr>
<td>Spatial integration step size ( dx )</td>
<td>100 ( \mu m )</td>
</tr>
<tr>
<td>Spatial integration step size ( dy )</td>
<td>25 ( \mu m )</td>
</tr>
<tr>
<td>Temporal integration step size ( df_{\text{int}} )</td>
<td>4.0 ( \mu s )</td>
</tr>
<tr>
<td>Number of nodes in ( x ) direction ( N_{x} )</td>
<td>1001</td>
</tr>
<tr>
<td>Number of nodes in ( y ) direction ( N_{y} )</td>
<td>2</td>
</tr>
<tr>
<td>Longitudinal intracellular coupling coefficient ( G_{ix} )</td>
<td>0.001 mS</td>
</tr>
<tr>
<td>Transverse intracellular coupling coefficient ( G_{iy} )</td>
<td>0.0001 mS</td>
</tr>
<tr>
<td>Longitudinal interstitial coupling coefficient ( G_{ex} )</td>
<td>0.0001 mS</td>
</tr>
<tr>
<td>Transverse interstitial coupling coefficient ( G_{ey} )</td>
<td>0.0005 mS</td>
</tr>
</tbody>
</table>

where \( C_{m} \) is specific membrane capacitance, \( V_{m} = (\phi_{i} - \phi_{e}) \) is transmembrane potential, \( I_{m} \) is ionic current source density, and \( A_{v} \) is ratio of membrane surface to intracellular volume. Substituting \( \phi_{i} = V_{m} + \phi_{e} \) into Equation 1, Equation 2 is rewritten as

\[ G_{ix} \frac{\partial^{2} V_{m}}{\partial x^{2}} + G_{ex} \frac{\partial^{2} \phi_{e}}{\partial x^{2}} + G_{iy} \frac{\partial^{2} \phi_{e}}{\partial y^{2}} = C_{m} \frac{\partial V_{m}}{\partial t} + I_{m} \]

where \( G_{ix} = (g_{i}/A_{v}) \) is a coupling coefficient expressed in terms of the specific intracellular conductivity along the fiber axis (\( g_{i} \)) and \( G_{ex} = (g_{e}/A_{v}) \) is expressed in terms of the specific intracellular conductivity across the fiber axis (\( g_{e} \)). In solving Equation 3, we assumed sealed end boundary conditions at the edges of the tissue and the interstitium. The model was 10 cm long and 50 \( \mu m \) wide, resulting in 2002 nodes (Table 5). We determined the interstitial potential distributions from the transmembrane potential distribution using a rewritten form of Equation 2,

\[ G_{ix} \frac{\partial^{2} \phi_{e}}{\partial x^{2}} + G_{ex} \frac{\partial^{2} \phi_{e}}{\partial y^{2}} = -G_{iy} \frac{\partial^{2} V_{m}}{\partial y^{2}} - G_{iy} \frac{\partial^{2} \phi_{e}}{\partial y^{2}} \]

where \( G_{ex} = (g_{e}/A_{v}) \) is a coupling coefficient expressed in terms of the specific interstitial conductivity along the fiber axis (\( g_{e} \)) and \( G_{iy} = (g_{i}/A_{v}) \) is expressed in terms of the specific interstitial conductivity across the fiber axis (\( g_{i} \)).

The numerical solution scheme was similar to that reported previously. Ordinary differential equations defining the gating variables for the individual ionic currents of \( I_{m} \) in Equation 2 were integrated numerically in time by an analytic method with Luo-Rudy membrane equations at all tissue nodes. Equations 3 and 4 were discretized in space with a five-point finite-difference stencil. Discretization in time used a semi-implicit averaging scheme analogous to the Crank-Nicholson method in one space dimension. Because the matrix for the linear system was sparse, efficient solutions for \( V_{m} \) were achieved with a preconditioned conjugate gradient scheme (DITSOL_PCG from the Digital Equipment Corp Digital Extended Math Library, dxml). A 5-ms monophasic "shock" was applied by modification of the difference equations for nodes on the left and right edges of the model to fix the interstitial potentials on each edge. Calculations were then continued for 5 ms after the shock. The resulting sparse linear system for \( \phi_{e} \) was solved with the same preconditioned conjugate gradient method as in solutions for \( V_{m} \).

To represent configurations similar to the experiments, we performed simulations using models that included (1) no incision and nominal [K\(^{+}\)]; (2) an incision, represented as a complete interruption in intracellular coupling between adjacent nodes located 2.5 cm from the left edge, combined with nominal [K\(^{+}\)]; (3) no incision and elevated [K\(^{+}\)] at nodes 2 to 3 cm from the left edge; and (4) an incision combined with elevated [K\(^{+}\)]. In each simulation, the cathode was located on the left edge of the model and the anode on the right edge. In models 1 and 2, shock strengths were increased until the diastolic threshold for stimulation (DTS) current was found. In models 3 and 4, [K\(^{+}\)], current was...
increased until a shock of strength 0.96×DTS initiated a depolarization wave front from the elevated [K⁺]e region.

No Incision, Nominal [K⁺]e
At the end of the stimulus, depolarization occurred at the cathode at DTS and 0.96×DTS (Figure 7A). At 10 ms, an action potential arose from the site of depolarization for the DTS stimulus and propagated toward the anode (Figure 7, right). Because the 0.96×DTS stimulus did not reach threshold, no action potential occurred.

Incision, Nominal [K⁺]e
With the incision, an area of depolarization occurred with both stimulus strengths at the cathode (Figure 7A). For both stimulus strengths, areas of hyperpolarization and depolarization occurred adjacent to the proximal and distal sides of the incision, respectively (Figure 7B, left). At 10 ms after the stimulus (Figure 7B, right), a depolarization wave front arose at the stimulation site for the DTS stimulus. A wave front also arose from the distal side of the incision where depolarization was created by the stimulus. No wave front arose at either site after the 0.96×DTS stimulus.

No Incision, Elevated [K⁺]e
In the absence of an incision, when extracellular potassium was increased to 16 and 17 mmol/L, resting membrane potential was elevated to −55.1 and −53.6 mV, respectively (Figure 7C, left). At 10 ms after the stimulus, the 0.96×DTS stimulus elicited an action potential at a potassium concentration of 17 mmol/L but not 16 mmol/L. This action potential propagated in both directions away from the site of elevated potassium but not from the cathodal end of the tissue, because the stimulus was slightly less than the DTS (Figure 7C, right).

Incision, Elevated [K⁺]e
With the incision present, 5 ms after the onset of the 0.96×DTS stimulus, an area of depolarization occurred at the cathode for both concentrations of potassium (Figure 7B). At the incision, hyperpolarization and depolarization were observed on the proximal and distal sides of the incision, respectively (Figure 7D, left). The degree of polarization was slightly larger for 7 mmol/L [K⁺]e (RMP = −75.8 mV) than for 6 mmol/L [K⁺]e (RMP = −79.6 mV). At 10 ms after the onset of the 0.96×DTS stimulus, a wave front arose on the distal side of the incision for 7 mmol/L but not 6 mmol/L potassium concentration (Figure 7D, right).

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