Internal Cardiac Defibrillation: Histopathology and Temporal Stability of Defibrillation Energy Requirements

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The automatic implantable cardioverter/defibrillator is tested intraoperatively to ensure effectiveness by performing a number of induced fibrillation-defibrillation trials. The temporal stability of defibrillation energy requirements and the histopathologic effects of multiple defibrillating shocks were studied in 12 dogs chronically instrumented with an internal spring-patch lead system identical to that used in humans. Dogs were studied on days 1, 11, 18, 25 and 32. Data were analyzed by logistic regression and the energy required for 50% (E50) and 80% (E80) success was compared. On day 32 the dogs were killed and the heart was removed for gross and microscopic pathologic examination.

There was a significant decrease in energy requirements from day 1 to day 11, as the E50 decreased from 6.9 ± 4.5 to 4.9 ± 2.5 J (p < 0.02) and the E80 decreased from 8.5 ± 5.2 to 6.1 ± 3.4 J (p < 0.02). The energy requirements then remained stable over the remainder of the experiment. The dogs were administered 209 ± 18 shocks (range 1 to 24 J) for a total cumulative dose of 1,524 ± 571 J. In all cases, both grossly and microscopically, there was no evidence of pathologic changes in the myocardium or coronary vessels. In all cases there was a fibrous plaque beneath the patch electrodes, at times containing an area of patchy hemorrhage; in a single specimen a mixed inflammatory infiltrate accompanied the hemorrhage. Endothelialization of the spring electrode with mild right atrial endocardial fibrosis was also observed.

Therefore, the energy requirements for successful defibrillation decrease during the first 11 days after testing at implantation, and then remain stable. Also, multiple, closely spaced defibrillating shocks applied through the spring-patch electrode system do not cause myocardial damage or changes other than those associated with the implantation.

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ologic effects of multiple defibrillating shocks delivered directly to the myocardium in dogs chronically instrumented with an internal lead system identical to that used in patients with the automatic cardioverter-defibrillator; in addition, the temporal stability of defibrillation energy requirements was evaluated.

**Methods**

**Animal preparation and instrumentation.** The experiments were conducted using 12 mongrel dogs of either sex with a mean weight of 23.6 kg (range 19.5 to 28.6). These animals were used in a study (3) of the effects of amiodarone on defibrillation energy requirements which showed that chronic oral amiodarone did not affect defibrillation efficacy at any time during the study; therefore, all 12 animals (6 control, 6 given amiodarone) are considered as one group for the present analysis. The dogs were anesthetized with intravenous sodium pentobarbital (20 to 25 mg/kg body weight, followed by 2 to 3 mg/kg per h as necessary [4]). They were intubated and ventilated with humidified room air by a Harvard model 613 respirator with adjustment based on arterial blood gases (Corning 165 pH/blood gas analyzer) measured every 30 minutes to maintain oxygen tension greater than 85 mm Hg and pH between 7.35 and 7.45; sodium bicarbonate was administered when necessary. Normal saline solution was infused at 2 cc/kg per h throughout the experiment, and normothermia was maintained with a heating blanket.

On day 1 of the experiment, using sterile technique, the heart was exposed through a left thoracotomy and suspended in a pericardial cradle. The internal defibrillating lead system, identical to that used with the Intec Systems AID-B, was then implanted. A 13.5 cm² titanium mesh patch electrode (cathode) was sutured directly to the epicardial surface of the left ventricle, and the titanium spring lead (anode) with approximately 7 cm² of surface area was inserted into the right atrium by way of the right atrial appendage. The chest was then closed except for the skin and subcutaneous layers, leaving the ends of the leads accessible for fibrillation/defibrillation trials. On each study day catheters were placed in the femoral vessels by the Seldinger technique. A NAMIC Radia-cath arterial catheter was positioned in the femoral artery and connected to a Statham fluid-filled pressure transducer. A 7F USCI Hemaquet percutaneous introducer set was inserted into the femoral vein through which a 6F USCI quadripolar catheter was fed and positioned in the right ventricle. Surface electrocardiographic leads II and aVL, femoral arterial blood pressure and an endocardial right ventricular electrogram were continuously monitored on a Beckman model E108 oscilloscope and recorded on a Honeywell model 941 Visicorder at paper speeds of 2.5 to 250 mm/s. At the conclusion of each study day, all lines were removed and the animals allowed to recover; intramuscular cefazolin (Kefzol), 1 g, was administered for four doses after surgery and three doses after each of the subsequent studies.

**Fibrillation/defibrillation trials.** Ventricular fibrillation was induced by a 1 to 2 second train of 10 ms cycle length paced current at four to seven times late diastolic threshold intensity through the right ventricular quadripolar catheter. The internal lead system was connected to a battery-operated external cardioverter-defibrillator (Intec Systems, Inc.) that could be preset to deliver an amount of energy variable from 1 to 40 J in 1 to 2 J increments. The defibrillating pulse was in the form of a truncated exponential with 60% tilt and the initial voltage varied depending on the selected energy, but pulse duration was constant for a given impedance (7.5 ms in a 50 Ω test load for all energies). The pulse waveforms were recorded on a Tektronix model 7623A storage oscilloscope, and the initial and final current and pulse duration were recorded. If the shock was unsuccessful, a “rescue shock,” believed to be of sufficient energy to achieve 100% successful defibrillations, followed in less than 10 seconds. Only the initial shocks were used for analysis. Fibrillation/defibrillation trials were performed at 3 minute intervals during the study.

**Protocol.** The animals were studied on days 1, 11, 18, 25 and 32.

**Day 1.** After the chest wall was closed, four energy levels in 1 to 2 J increments were chosen based on the animals’ weight and our past experience. Each of these four energy levels was tested three times in balanced random order for a total of 12 trials by referring to a standard table of random numbers (5). At the conclusion of these trials the ends of the leads were placed in a Dacron Parsonnet Pulse Generator Pouch (C.R. Bard, Inc.) and tunneled subcutaneously to lie in the animals’ back, and the thoracotomy incision was sutured close.

**Day 11.** Animals were anesthetized and catheters placed as previously described. Through a small skin incision the subcutaneous pouch was exposed and opened; the leads were exteriorized and connected to the defibrillator. Five energy levels were each tested five times in balanced random order for a total of 25 trials performed over 75 minutes. After 30 minutes, during which either saline solution or amiodarone was infused, the five energy levels were restested five times each in balanced random order so that a total of 50 trials were performed during this study day. The effect of acute intravenous amiodarone on defibrillation energy requirements is reported separately (3).

**Days 18, 25 and 32.** The animals were prepared as previously described, and five energy levels were each tested five times in balanced random order for a total of 25 trials performed over 75 minutes on each day.

**Histopathology.** After completion of the fibrillation/defibrillation trials on day 32, the dogs were killed by again inducing fibrillation. The fibrillating hearts were re-
moved through a left thoracotomy with the defibrillation electrodes in situ. The ventricles were opened by a single incision, or a transverse cut parallel to the base of the heart through both ventricles and the patch electrode. Gross pathologic observations were recorded and the specimens photographed. The hearts were then immersed in a solution of 10% buffered formalin for fixation. After fixation for 1 week, blocks of tissue were taken from each heart for microscopic study. Multiple transmural sections were taken of the left ventricle which included the myocardium directly subjacent to the patch electrode as well as adjacent left ventricular free wall. Other sections were also taken from the right atrium adjacent to the spring electrode. The tissue blocks were embedded in paraffin, sectioned and stained with hematoxylin-eosin; selected sections were stained with Masson’s trichrome procedure. Histopathologic assessment was made using a light microscope.

**Statistical analysis.** A curve relating energy to percent successful defibrillation for each series of shocks in each dog on each study day was generated by computer using a logistic regression model to fit the raw data to a sigmoidal dose-response curve (6). The resultant defibrillation curve gave the predicted energy level associated with any probability of successful defibrillation from 0.01 to 0.99. Changes in the likelihood of successful defibrillation were analyzed by paired \( t \) tests comparing the mean predicted energies associated with 50% (\( E_{50} \)) and 80% (\( E_{80} \)) success. Changes in \( E_{50} \) and \( E_{80} \) over time were analyzed by multivariate analysis of variance for repeated measurements. Results are reported as mean ± 1 SD and a probability (\( p \)) value of <0.05 was considered statistically significant for all analyses.

**Results**

**Defibrillation shock profile.** The total number of shocks (including rescue shocks), the range of energy, the total cumulative delivered energy and the average shock energy for the individual animals over the course of the entire experiment are given in Table 1. The dogs were each administered a mean of 208.6 ± 18.2 shocks using energies ranging from 1 to 24 J. The mean total cumulative delivered energy was 1,524.4 ± 570.6 J and the average shock strength was 7.20 ± 2.26 J.

**Histopathology.** *Gross.* In all 12 cases there was a thickened bed of fibrous connective tissue adhering to the overlying pericardium.

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Table 1. Profile of Defibrillation Shocks Given to Individual Dogs (\( n = 12 \)) Over the Course of The Experiment

<table>
<thead>
<tr>
<th>Dog</th>
<th>No. of Shocks</th>
<th>Energy Range (J)</th>
<th>Total Cumulative Dose (J)</th>
<th>Average Shock Energy (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>188</td>
<td>2 to 12</td>
<td>1,233</td>
<td>6.56</td>
</tr>
<tr>
<td>2</td>
<td>205</td>
<td>1 to 10</td>
<td>1,015</td>
<td>4.95</td>
</tr>
<tr>
<td>3</td>
<td>232</td>
<td>3 to 12</td>
<td>1,807</td>
<td>7.79</td>
</tr>
<tr>
<td>4</td>
<td>237</td>
<td>3 to 12</td>
<td>1,931</td>
<td>8.15</td>
</tr>
<tr>
<td>5</td>
<td>184</td>
<td>2 to 10</td>
<td>978</td>
<td>5.32</td>
</tr>
<tr>
<td>6</td>
<td>189</td>
<td>2 to 8</td>
<td>988</td>
<td>5.23</td>
</tr>
<tr>
<td>7</td>
<td>229</td>
<td>4 to 14</td>
<td>2,198</td>
<td>9.60</td>
</tr>
<tr>
<td>8</td>
<td>195</td>
<td>2 to 8</td>
<td>1,046</td>
<td>5.36</td>
</tr>
<tr>
<td>9</td>
<td>215</td>
<td>2 to 16</td>
<td>1,752</td>
<td>8.15</td>
</tr>
<tr>
<td>10</td>
<td>218</td>
<td>4 to 24</td>
<td>2,768</td>
<td>12.70</td>
</tr>
<tr>
<td>11</td>
<td>213</td>
<td>2 to 12</td>
<td>1,369</td>
<td>6.43</td>
</tr>
<tr>
<td>12</td>
<td>198</td>
<td>2 to 10</td>
<td>1,208</td>
<td>6.10</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>208.6 ± 18.2</td>
<td>1 to 24*</td>
<td>1,524.4 ± 570.6</td>
<td>7.20 ± 2.26</td>
</tr>
</tbody>
</table>

*Range of energies used in all dogs.*

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*Figure 1.* Excised heart with patch and spring electrodes in situ; the patch electrode has been partially covered with fibrous connective tissue adhering it to the overlying pericardium.
evidence of compression, thrombosis or damage to the vessel wall. On transverse section (Fig. 3) the fibrous plaque was seen not to extend into the left ventricular wall and the underlying myocardium appeared quite normal without any regions of paleness and was not felt to be turgid on palpation. In all cases the right atrial spring electrode underwent endothelialization and was covered by a translucent, gray-white fibrous sheath extending from the proximal end distally to involve much, if not all, of the length of the electrode within the right atrium (Fig. 4). In 10 of the 12 hearts the spring lead was adherent to the adjacent endocardium of the right atrium, but in no cases did it evoke a thrombotic response. In one heart a 1 cm hematoma was found within the pericardium over the posterior atrioventricular groove, but was thought to be due to surgical trauma at the time of implantation.

Microscopic. In all 12 cases sections of the patch electrode bed showed focal thickening of the epicardium with an admixture of old hemorrhage and healed granulation tissue (Fig. 5). Apart from one specimen there was no inflammatory infiltrate; in the single case (Dog 12) a mixed infiltrate was seen around the area of hemorrhage only and did not involve the myocardium (Fig. 6). The underlying myocardium was without evidence of any pathologic processes in every case (Figs. 5 and 6). No myocarditis, necrosis, fibrosis, hemorrhage or interstitial edema was present. There was no evidence of myofibrillar degeneration or injury such as cell swelling, hypereosinophilia, loss of cross striations, hypercontraction bands or pyknotic nuclei. In addition, these sections invariably contained transverse sections of coronary vessel or their small branches, and in no case was there any damage to the vessels or intravascular thrombosis associated with the overlying patch (Fig. 5 and 6). The atrial sections were also without significant pathologic changes. The endocardium of the right atrium had only mild focal fibrosis at the site of attachment of the spring.

Figure 2. Excised heart transected parallel to the base through both ventricles; the patch electrode (left) has been peeled back from the surface of the left ventricle revealing a thickened bed of fibrous connective tissue and an area of patchy hemorrhage (arrow) within the fibrous plaque.

Figure 3. Transverse section through the patch electrode and left ventricle; a thickened fibrous plaque is seen beneath the patch electrode which does not extend into the left ventricular wall, and the underlying myocardium appears to be without damage.
Figure 4. Spring electrode in situ within the exposed right atrium. The electrode has undergone endothelialization, covered by a translucent gray-white sheath, and is adherent to the posterior right atrial wall just above the tricuspid valve (T).

Figure 6. Section through the thick fibrous plaque of the bed of the left ventricular patch electrode. A mixed inflammatory infiltrate is seen around an area of hemorrhage, but does not involve the underlying myocardium. Note the normal myocardium, coronary artery and paired veins below the implantation site.

electrode and was without an inflammatory component. The sheath covering the lead was composed of fibrous connective tissue covered by endothelial cells.

Temporal stability of defibrillation energy requirements (defibrillation curve). In all 12 cases for each set of fibrillation/defibrillation trial a range of increasing energies was associated with a gradually increasing percent of success, permitting the construction of a set of defibrillation curves, relating the percent of successful defibrillations to energy, for each dog. Figure 7 shows the raw data along with the fitted curve generated by logistic regression in a representative animal on one study day; the predicted energy associated with 50 and 80% success are also demonstrated.

The mean (± 1 SD) energy associated with 50 and 80% success for the 12 animals on each study day is shown in Figure 8: the values on day 11 represent the results of the first (preinfusion) series of shocks only. There was a significant decrease in energy requirements from implantation of the lead system on day 1 to retesting on day 11. The energy required for 50% successful defibrillation decreased from 6.90 ± 4.47 to 4.90 ± 2.54 J (p < 0.02) and the energy associated with 80% success decreased from 8.52 ±

Figure 5. Section through the fibrous plaque (F) of the bed of the implanted epicardial patch electrode showing two small areas of patchy hemorrhage (arrows) confined to the plaque itself above the left ventricular myocardium. Note unaffected myocardium and coronary artery below the plaque. Hematoxylin-eosin stain, original magnification x 20, reduced by 29%.

Figure 7. Percent successful defibrillation (DF) versus energy (J) of a representative animal on one study day. The raw data (solid circles) are shown along with the fitted curve generated by logistic regression analysis. The predicted energies associated with 50% (E50) and 80% (E80) success are also depicted.
5.19 to 6.05 ± 3.38 J (p < 0.02). Multivariate analysis of variance for repeated measurements demonstrated no significant change in these values between day 11 and day 32; the final mean energy associated with 50 and 80% successful defibrillation on day 32 was 5.30 ± 1.77 J and 6.26 ± 2.22 J, respectively.

Discussion

Temporal stability of defibrillation energy requirements (defibrillation curve). We have previously shown (7) that the energy requirements for defibrillation in individual animals are best described as a curve relating percent successful defibrillation to energy rather than as a distinct "defibrillation threshold," because a range of energies are associated with intermediate levels of success between 0 and 100%. We showed in this study that energy requirements for successful defibrillation significantly decrease from the time of implantation to 11 days after surgery, after which they remain stable through at least 32 days after implantation. Deeb et al. (8), using a similar lead system in dogs, found the defibrillation threshold to be stable from the initial time of implantation to 11 days after surgery, after which they remain stable up to 26 weeks. They concluded that, if used clinically, the catheter system should be retested 5 weeks after implantation because shocks that successfully defibrillated the heart at surgery may become ineffective with time. The opposite time-dependent changes in energy requirements observed with the spring-patch and catheter leads systems are most likely due to differences in electrode design. For example, the histologic alterations observed, namely fibrosis, are detrimental to the totally right-sided, intracavitory bipolar catheter, although they are beneficial to the cathodal patch electrode, whose large surface area becomes more closely applied to the left ventricular epicardium. It is not known if different results would have been observed if the intracavitory spring electrode had served as the cathode.

The >25% reduction in energy requirements seen during this study may be large enough to allow the defibrillator to be effective in these patients.

Spring-patch versus catheter electrode defibrillation systems. The results of this study using the spring-patch lead system are in contrast to those using different implanted electrode systems. Schuder et al. (9), using two submuscular disk electrodes or a unipolar catheter in the superior vena cava/right atrium paired with a submuscular disk electrode over the apex of the heart, found that the energy required to achieve 90% successful defibrillation was increased by 50% in both systems from the time of implantation to 33 weeks after surgery. Kallok et al. (10), using a completely transvenous catheter defibrillator with one electrode in the superior vena cava and the other at the right ventricular apex, also found that energy requirements increased significantly (55%) over the first 5 weeks after implantation and then remained stable up to 26 weeks. They concluded that, if used clinically, the catheter system should be retested 5 weeks after implantation because shocks that successfully defibrillated the heart at surgery may become ineffective with time. The opposite time-dependent changes in energy requirements observed with the spring-patch and catheter leads systems are most likely due to differences in electrode design. For example, the histologic alterations observed, namely fibrosis, are detrimental to the totally right-sided, intracavitory bipolar catheter, although they are beneficial to the cathodal patch electrode, whose large surface area becomes more closely applied to the left ventricular epicardium. It is not known if different results would have been observed if the intracavitory spring electrode had served as the cathode.

The decrease in energy requirements over time may represent a distinct advantage of the spring-patch electrode system over the catheter defibrillator; although implantation does require a thoracotomy, many patients are in need of concomitant cardiac surgery. Kallok et al. (10) concluded that the defibrillation catheter used in their study permitted lower energy defibrillation than the spring-patch lead system, by comparing their results with those presented by Deeb et al. (8) using unpaired t tests. However, when the results of our study on day 32 (Fig. 2, E90) are compared with the results of Kallok et al. for nondislodged catheters at 5 weeks (their Fig. 4, Group A) using unpaired t tests, the spring-patch system appears to have significantly lower energy requirements (p < 0.001).

Histopathologic changes induced by implantation of defibrillation electrodes and internal electric shock. There have been many reports describing the histopathologic alterations induced by internal electric shock using both direct current with damped sinusoidal or trapezoidal waveforms and alternating current discharges. These past defibrillation studies have used spoon-shaped small paddle electrodes like those used in cardiac surgery (1,11–13) and transvenous
catheter-mounted electrodes (2,14–18), but there have been no reports evaluating the cardiac histopathologic alterations induced by the spring-patch electrode system used in the present study and with the clinically available automatic implantable defibrillator.

The observation of minimal pathologic changes in this study was surprising. The histologic changes seen in the right atrium associated with the spring lead were mild; the endocardial fibrosis and endothelialization of the electrode that did occur were identical to changes observed with chronically implanted pacemaker leads (19), and with transvenous catheter defibrillators that have not delivered any shocks (2,17), and are thought to be induced by “mechanical” trauma. In all cases the myocardium beneath the left ventricular patch electrode was without abnormalities and showed none of the changes previously described in hearts subjected to internal electric shock. Grossly, these include areas of pallor and turgor (1,2,12) that can be seen almost immediately after shocks and persist up through 8 weeks. Microscopically, the characteristic histologic features, termed “myofibrillar degeneration” by Reichenbach and Benditt (13), are swollen myocardial cells with loss of cross striations, pyknotic nuclei, vacuolization and the presence of dense eosinophilic transverse contraction bands; the interstitial connective tissue is also distended with edema fluid (1.11–13). By 2 to 4 days there is calcification of necrotic muscle fibers, an infiltrate of predominantly macrophages and fibroblast proliferation. In 2 to 4 weeks there is atrophy and loss of myocardial cells, fibrosis and stromal collapse that allows contraction of the lesion. These changes, including myocardial necrosis, were evident in past studies using single shocks of as low as 20 J with the spoon-type internal paddles (1) and 2.7 J with a chronically implanted transvenous catheter defibrillator (15,16).

Past studies have shown that the degree of myocardial damage is affected by a number of factors. Increasing shock strength is strongly correlated with increasing myocardial injury (12,16). In addition, when the total electrical dose is the same, multiple low energy shocks have been shown to cause more myocardial damage than a single high-energy shock (12). Injuries were also more severe with multiple shocks when a time interval of less than 1 minute was allowed between successive discharges (12). Finally, smaller electrode surface area has been associated with more severe myocardial damage and is thought to be due to higher current densities (12,20). In the present study shocks of 1 to 24 J were administered on the average 209 times over the 32 day experiment for a mean total electrical dose of 1524 J. Routinely, “rescue shocks” were given within 10 seconds, and on a few occasions three such shocks were needed, and consequently four shocks were given over approximately 30 seconds. All of these factors should have predisposed the hearts to even greater injury. On the other hand, the spring and patch electrodes had a relatively large surface area (7 and 13.5 cm², respectively) compared with the catheter electrodes (125 mm²).

Conclusions. We have demonstrated that in dogs with an automatic implantable cardioverter/defibrillator, the energy requirements for successful cardiac defibrillation significantly decrease during the first 11 days after surgical implantation and then remain stable. If defibrillation in humans behaves similarly, energy levels that are successful at surgery should remain effective with time, whereas in patients with initially unsatisfactorily high energy requirements, energy demands may decrease sufficiently during the 2 weeks after implantation to allow the cardioverter/defibrillator to function effectively. In addition, we have shown that multiple, closely spaced defibrillating shocks of up to 24 J for a total electrical dose of up to 2,768 J through the spring-patch electrode system do not cause myocardial damage or changes other than those associated with the implantation itself. These findings suggest that intraoperative and postoperative testing of the automatic implantable cardioverter/defibrillator may be performed without inducing significant myocardial injury. Differences between this and past studies of internal defibrillation may be due to electrode design.

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