Defibrillating Shocks Delivered to the Heart Impair Efferent Sympathetic Responsiveness

Makoto Ito, MD; Harald P. Pride, BS; Douglas P. Zipes, MD

Background. Functional studies indicate that sympathetic efferents are located in the superficial subepicardium and vagal efferents are located in the subendocardium. It is possible that electrical shocks applied directly to the heart might affect the function of these autonomic nerves.

Methods and Results. Low- (≤1 J), medium- (6 to 16 J), or high- (30 to 35 J) energy truncated monophasic exponential shocks, synchronized to the R wave during sinus rhythm, were delivered over implantable patches sutured inside the pericardium in anesthetized open-chest dogs. Shortening of ventricular effective refractory period (ERP), produced by bilateral ansae subclaviae stimulation (SS), was measured before and after shock delivery. High-energy shocks shifted the SS frequency–ERP response curves downward and to the right (P<.001) for sites beneath and apical to the patches; ERP shortening at basal sites remained unchanged. Such sympathetic attenuation occurred with shocks >10 J but not with shocks ≤10 J, was noted 15 minutes after the shock, and showed incomplete return to control values at 3 hours. Neither low- nor high-energy shocks affected norepinephrine dose–ERP response curves, indicating normal myocardial responsiveness. Low- and high-energy shocks did not attenuate bilateral cervical vagal stimulation-induced ERP prolongation. High-energy shocks delivered over patches sutured outside of the pericardium showed no effects on sympathetic response, suggesting a protective effect of the pericardium against shock-induced sympathetic attenuation.

Conclusions. DC shocks >10 J delivered directly to the epicardium attenuated efferent sympathetic neural function. Such changes may affect electrophysiological, as well as hemodynamic, responses to sympathetic neural stimulation after cardioversion-defibrillation. (Circulation. 1993;88:2661-2673.)

KEY WORDS • DC shock • electrodes • effective refractory period • autonomic neural function

Implantable cardioverter-defibrillators using epicardial patch systems effectively cardiovert ventricular tachycardia and defibrillate ventricular fibrillation.1,2 Antiarrhythmia devices undergoing clinical investigation deliver discharges that can be set from 0.1 to 34 J.3 Excessive voltages cause myocardial damage,4,8 the extent of which correlates with shock strength and shock intervals in experimental animals.5,7,8 Repeated electrical shocks over implantable patches induce pathological changes in humans.9 Electrical shocks affect central and peripheral nerves, altering neural function transiently, permanently, or progressively.10-12

We have shown that sympathetic efferent fibers are located within the superficial subepicardium, while efferent vagal nerves en route to the ventricle cross superficially at the atrioventricular groove and are then concentrated in the subendocardium.13,14 Electrical shocks over epicardial patch electrodes could influence the function of these autonomic nerves and alter the response that sympathetic and vagal stimulation produces in the myocardium. However, little is known about the effects of DC shocks on efferent sympathetic or vagal function to the heart. The purpose of this study was to determine if the electrical shocks delivered through an epicardial patch system modulated efferent sympathetic and vagal function to the myocardium.

Methods

Surgical Preparation

Fifty-nine mongrel dogs of either sex weighing 20 to 36 kg were anesthetized with pentobarbital (30 mg/kg IV). Additional amounts of pentobarbital were given as necessary to maintain anesthesia during the study. The dogs were ventilated by means of a cuffed endotracheal tube and volume-cycled respirator (model 607, Harvard Apparatus, South Natick, Mass). The chest was opened through a median sternotomy. A fluid-filled catheter was placed in the left femoral artery and connected to a transducer (Statham P-23 Db, Gould, Cleveland, Ohio) to monitor arterial blood pressure. The left femoral vein was cannulated to infuse normal saline at 100 to 200 mL/h to replace spontaneous fluid losses. Dogs were placed on a heating pad, and the thoracotomy was covered by a plastic sheet. A thermistor (model 400, Yellow Springs Instrument, Yellow Springs, Ohio) was used to monitor epicardial temperature. An operating room table lamp was used to maintain epicardial temperature at 36 to 38°C. Arterial blood gases and pH were monitored and maintained within the physiological range.

Patch Electrode Placement

The small size oval epicardial patch electrode (model 6871, the surface area of electrode=17 cm², Medtronic Inc, Minneapolis, Minn) was sutured to the inside of the...
pericardium overlying the left anterolateral ventricular epicardium and served as the cathode. A second patch electrode was sutured to the inside of the pericardium and positioned over the right lateral ventricular wall and served as the cathode (Fig 1). In groups 1 through 10, the patches were positioned inside the pericardial sac. In group 11, the patches were positioned on the outside of the pericardium. When shocks were applied to the heart, patches were fixed firmly over the heart surface to create an even contact between patches and heart.

**Electrode Placement for Measurement of Effective Refractory Period**

Using a 25-gauge needle, two hook electrodes made from Teflon-coated wires, insulated except for their tips, were placed in the left ventricular midmyocardium basal to the left epicardial patch. Two electrodes were inserted in the left ventricular midmyocardium beneath the patch, and three additional electrodes were inserted in the left ventricular midmyocardium apical to the patch (Fig 1). The electrodes served as the cathode for unipolar stimulation to determine effective refractory periods (ERPs). An anodal electrode consisting of a 33-mm-diameter metal disk was placed in the abdominal wall. A bipolar plunge electrode was inserted in the myocardium of the right ventricular outflow tract to record the ventricular responses. Another bipolar plunge electrode was inserted in the myocardium of the right ventricular apex and connected to the external defibrillator unit. Data collection began 30 minutes after the placement of the plunge electrodes.

**Measurement of Effective Refractory Period**

The ERP was determined at each electrode site by the extrastimulus technique employing a programmable stimulator (Krannert Medical Engineering, Indianapolis, Ind) and a constant current isolator. Each ventricular test site was driven with a 2-msec rectangular stimulus twice diastolic threshold, which was measured during each intervention. A train of eight stimuli (S1) was followed by a late premature stimulus (S2) that produced a propagated ventricular response. The S1-S1 interval was 230 to 240 msec and was kept constant throughout the experiment. The ventricular responses to S1 and S2 were recorded from lead II ECG and from a right ventricular

![Fig 1. Diagram of heart. Solid circles indicate sites of plunge electrode placement; shaded areas, placement of patch electrodes; AO, aorta; LA, left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; and RV, right ventricle.](image)

**Table 1. Delivered Energy, Leading-Edge Voltage, Leading-Edge Current, Duration, Tilt, and Impedance of Truncated Exponential Monophasic Shock Waves**

<table>
<thead>
<tr>
<th>Group</th>
<th>N=6</th>
<th>Delivered Shock Energy, J (range)</th>
<th>Leading-Edge Voltage, V</th>
<th>Leading-Edge Current, A</th>
<th>Duration, ms</th>
<th>Tilt, %</th>
<th>Impedance, Ω</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>6</td>
<td>Low: 0.90±0.01 (0.88-0.92)</td>
<td>138±1.5</td>
<td>1.92±0.08</td>
<td>7.8±0.2</td>
<td>57±2</td>
<td>76±2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 30.8±1.4 (25.0-33.7)</td>
<td>771±12</td>
<td>12.0±0.5</td>
<td>7.4±0.4</td>
<td>59±1</td>
<td>63±2</td>
</tr>
<tr>
<td>Group 3</td>
<td>6</td>
<td>Low: 0.86±0.07 (0.54-1.00)</td>
<td>137±0.4</td>
<td>2.16±0.1</td>
<td>7.0±0.5</td>
<td>64±2</td>
<td>68±3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 31.6±3.1 (16.4-35.8)</td>
<td>773±11</td>
<td>13.5±0.8</td>
<td>6.9±0.6</td>
<td>62±1</td>
<td>58±4</td>
</tr>
<tr>
<td>Group 4</td>
<td>7</td>
<td>Low: 0.88±0.05 (0.76-1.15)</td>
<td>141±0.7</td>
<td>1.98±0.05</td>
<td>8.2±0.6</td>
<td>66±1</td>
<td>76±3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 32.3±1.6 (23.3-35.8)</td>
<td>767±6.5</td>
<td>12.0±0.4</td>
<td>8.0±0.4</td>
<td>62±0.4</td>
<td>63±2</td>
</tr>
<tr>
<td>Group 5</td>
<td>7</td>
<td>Low: 35.0±0.9 (31.8-38.4)</td>
<td>765±4</td>
<td>12.2±0.4</td>
<td>8.5±0.3</td>
<td>62±0.4</td>
<td>61±2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 6.3±0.4 (5.8-7.4)</td>
<td>339±14</td>
<td>5.5±0.6</td>
<td>8.1±0.5</td>
<td>63±0.2</td>
<td>64±5</td>
</tr>
<tr>
<td>Group 7</td>
<td>3</td>
<td>Low: 9.8±0.04 (9.7-9.8)</td>
<td>419±3</td>
<td>6.8±0.2</td>
<td>8.1±0.3</td>
<td>63±1</td>
<td>63±2</td>
</tr>
<tr>
<td>Group 8</td>
<td>6</td>
<td>Low: 0.49±0.02 (0.43-0.52)</td>
<td>133±1.7</td>
<td>1.96±0.09</td>
<td>4.9±0.1</td>
<td>66±0.4</td>
<td>73±2</td>
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<tr>
<td></td>
<td></td>
<td>Medium: 15.7±0.5 (13.7-17.3)</td>
<td>745±9</td>
<td>11.9±0.4</td>
<td>4.0±0.1</td>
<td>62±0.2</td>
<td>62±2</td>
</tr>
<tr>
<td>Group 9</td>
<td>3</td>
<td>Low: 15.9±2.5 (12.4-20.9)</td>
<td>527±43</td>
<td>8.5±0.8</td>
<td>7.9±0.1</td>
<td>62±1</td>
<td>62±1</td>
</tr>
<tr>
<td>Group 10</td>
<td>3</td>
<td>Low: 16.3±0.4 (15.7-17.0)</td>
<td>764±8</td>
<td>11.7±0.4</td>
<td>4.1±0.1</td>
<td>62±1</td>
<td>64±1</td>
</tr>
<tr>
<td>Group 11</td>
<td>6</td>
<td>Low: 30.1±1.3 (25.8-33.6)</td>
<td>788±9</td>
<td>10.3±0.4</td>
<td>8.4±0.8</td>
<td>61±2</td>
<td>77±3</td>
</tr>
</tbody>
</table>

Values are mean±SEM. N indicates number of test dogs.
bipolar electrogram and displayed on a storage oscilloscope. The S1-S2 interval was shortened in steps of 2 msec until S2 failed to produce a propagated ventricular response. The S1-S2 interval was then increased by 5 msec and was shortened by 1-msec decrements until S2 failed to produce a propagated ventricular response. The ERP was defined as the longest S1-S2 interval at which S2 failed to produce a propagated response. The ERPs were determined twice, and values were within 1 msec of each other or the data were discarded and the determination was repeated.

Neural Stimulation

The ansae subclaviae were isolated bilaterally as they exited from the stellate ganglia, doubly ligated, and cut. The cervical vagi also were isolated bilaterally, doubly ligated, and transected. Shielded bipolar electrodes were placed on the right and left anterior and posterior ansae subclaviae to stimulate the efferent cardiac sympathetic nerves with a stimulator (model SD-88, Grass Instrument Co, Quincy, Mass). Stimuli were rectangular 4-msec pulses delivered at a frequency of 1 to 4 Hz and at 1.0 to 4.0 mA. Determination of the ERP was started 2 minutes after the onset of ansae subclavia stimulation. The cervical vagi were stimulated through two Teflon-coated wire electrodes embedded in the cardiac end of the cut nerve. Rectangular pulses of 4-msec duration were delivered at a frequency of 20 Hz. The current strength was 0.05 mA greater than that required to produce asystole (>2 seconds) for the right vagus and asystole or complete atrioventricular block during spontaneous rhythm for the left vagus. The effects of efferent vagal stimulation on ventricular ERP were determined during intravenous infusion of norepinephrine at a rate of 0.25 μg·kg⁻¹·min⁻¹ to achieve a constant background of sympathetic effect. The conditions of neural stimulation were kept constant in each experiment.

DC Shocks

DC shocks were delivered by using an external cardioverter/defibrillator (model 2394, Medtronic Inc, Minneapolis, Minn). The amount of voltage charged to the output circuit for delivery to the lead system was set at 130 to 800 V, and capacitance was 50 to 120 μF. Shocks were synchronized to the R wave of the local electrogram recorded from the right ventricular apex during sinus rhythm. Delivered voltage and current waveforms from the defibrillator unit were displayed on a storage oscilloscope (model 5223 Digitizing Oscilloscope, Tektronix, Beaverton, Ore) and photographed. Shocks were monophasic truncated exponential waveforms. Durations were defined by the tilt setting of 65% (dial setting) in 55 dogs. In another 4 dogs (2 dogs in group 1 and 2 dogs in group 11), durations were set at 8.0 msec.

Protocols

Effects of low- and high-energy shocks on ansae subclaviae frequency- and norepinephrine dose-refractory period response relations. Group 1. To analyze the effects of low-energy and high-energy shocks on the efferent sympathetic response, we obtained the ansae subclaviae stimulation–ERP response (frequency–ERP response) curves in 6 dogs. In each dog, the ERP was determined in the baseline state and then during bilateral ansae subclaviae stimulation at frequencies of 1, 2, and 4 Hz. The order of stimulation frequencies was chosen randomly and given at 10-minute intervals. Ten minutes after the final frequency–ERP response curve was obtained during the control state, a low-energy shock was delivered. Fifteen minutes later, ERPs were determined, and frequency–ERP response curves were again obtained. Then, 10 minutes later, a high-energy shock was delivered, and frequency–ERP response relationships were determined 15 minutes after the high-energy shock. In 4 of 6 dogs, baseline ERP and ERP response to norepinephrine infusion (0.5 μg·kg⁻¹·min⁻¹) were determined before low-energy shock (control state) and after high-energy shock. ERPs were determined 5 minutes after initiation of norepinephrine infusion to allow equilibration. Time interval between low- and high-energy shocks was 60 to 70 minutes.

Table 2. Baseline Heart Rate and Mean Arterial Blood Pressure Before and After Shocks

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate, bpm</th>
<th>Mean Arterial Blood Pressure, mm Hg</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>After Shock</td>
</tr>
<tr>
<td></td>
<td>Low energy</td>
<td>High energy</td>
</tr>
<tr>
<td>Group 1 (N=6)</td>
<td>114±2</td>
<td>117±1</td>
</tr>
<tr>
<td></td>
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<td>117±2</td>
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<tr>
<td>Group 2 (N=7)</td>
<td>132±9</td>
<td>134±10</td>
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<td></td>
<td></td>
<td>135±8</td>
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<tr>
<td>Group 3 (N=6)</td>
<td>117±2</td>
<td>122±2</td>
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<tr>
<td></td>
<td></td>
<td>131±3</td>
</tr>
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<td>Group 4 (N=3)</td>
<td>118±2</td>
<td>121±2</td>
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<tr>
<td></td>
<td></td>
<td>98±11</td>
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<tr>
<td>Group 5 (N=3)</td>
<td>130±8</td>
<td>132±6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>109±2</td>
</tr>
<tr>
<td>Group 6 (N=6)</td>
<td>125±3</td>
<td>123±3</td>
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<tr>
<td></td>
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<td>124±3</td>
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<tr>
<td>Group 7 (N=3)</td>
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<td>102±5</td>
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<td></td>
<td></td>
<td>101±8</td>
</tr>
<tr>
<td>Group 8 (N=6)</td>
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<td>96±7</td>
</tr>
<tr>
<td>Group 9 (N=3)</td>
<td>111±4</td>
<td>113±7</td>
</tr>
<tr>
<td></td>
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<td>104±3</td>
</tr>
<tr>
<td>Group 10 (N=3)</td>
<td>116±3</td>
<td>116±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85±5</td>
</tr>
<tr>
<td>Group 11 (N=6)</td>
<td>121±4</td>
<td>118±2</td>
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<tr>
<td></td>
<td></td>
<td>108±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>111±4</td>
</tr>
</tbody>
</table>

Values are mean±SEM and were obtained during control period and 15 minutes after delivery of each shock. bpm indicates beats per minute; and N, number of test dogs.
TABLE 3. Baseline Ventricular Effective Refractory Period Before and After Shocks

<table>
<thead>
<tr>
<th>Ventricular Effective Refractory Period</th>
<th>Control</th>
<th>Low energy</th>
<th>High energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N=6)</td>
<td>Basal sites (n=12)</td>
<td>165±3</td>
<td>169±4</td>
</tr>
<tr>
<td></td>
<td>Patch sites (n=12)</td>
<td>169±3</td>
<td>171±4</td>
</tr>
<tr>
<td></td>
<td>Apical sites (n=18)</td>
<td>171±2</td>
<td>174±2</td>
</tr>
<tr>
<td></td>
<td>Sham (first)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sham (second)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2 (N=7)</td>
<td>Basal sites (n=14)</td>
<td>152±3</td>
<td>152±3</td>
</tr>
<tr>
<td></td>
<td>Patch sites (n=14)</td>
<td>156±3</td>
<td>155±2</td>
</tr>
<tr>
<td></td>
<td>Apical sites (n=20)</td>
<td>155±2</td>
<td>155±2</td>
</tr>
<tr>
<td></td>
<td>Low energy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>High energy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3 (N=6)</td>
<td>Basal sites (n=12)</td>
<td>154±2</td>
<td>153±2</td>
</tr>
<tr>
<td></td>
<td>Patch sites (n=12)</td>
<td>159±2</td>
<td>159±1</td>
</tr>
<tr>
<td></td>
<td>Apical sites (n=18)</td>
<td>159±1</td>
<td>160±1</td>
</tr>
<tr>
<td>Group 6 (N=3)</td>
<td>Basal sites (n=6)</td>
<td>159±2</td>
<td>159±3</td>
</tr>
<tr>
<td></td>
<td>Patch sites (n=6)</td>
<td>161±2</td>
<td>160±3</td>
</tr>
<tr>
<td></td>
<td>Apical sites (n=12)</td>
<td>160±1</td>
<td>159±2</td>
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<td>Group 7 (N=3)</td>
<td>Basal sites (n=6)</td>
<td>162±4</td>
<td>162±4</td>
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<tr>
<td></td>
<td>Patch sites (n=6)</td>
<td>161±2</td>
<td>162±2</td>
</tr>
<tr>
<td></td>
<td>Apical sites (n=12)</td>
<td>162±2</td>
<td>162±2</td>
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<tr>
<td>Group 8 (N=6)</td>
<td>Basal sites (n=12)</td>
<td>155±1</td>
<td>158±1</td>
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<tr>
<td></td>
<td>Patch sites (n=12)</td>
<td>159±1</td>
<td>162±1</td>
</tr>
<tr>
<td></td>
<td>Apical sites (n=18)</td>
<td>158±2</td>
<td>160±1</td>
</tr>
<tr>
<td>Group 9 (N=3)</td>
<td>Basal sites (n=6)</td>
<td>161±2</td>
<td>161±2</td>
</tr>
<tr>
<td></td>
<td>Patch sites (n=6)</td>
<td>161±3</td>
<td>157±3</td>
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<tr>
<td></td>
<td>Apical sites (n=12)</td>
<td>160±2</td>
<td>158±2*</td>
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<td>Group 10 (N=3)</td>
<td>Basal sites (n=6)</td>
<td>153±5</td>
<td>156±6</td>
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<td>Patch sites (n=6)</td>
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<td></td>
<td>Apical sites (n=12)</td>
<td>154±4</td>
<td>157±3</td>
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<tr>
<td>Group 11 (N=6)</td>
<td>Basal sites (n=12)</td>
<td>157±1</td>
<td>160±1*</td>
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<td>Patch sites (n=12)</td>
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</tr>
<tr>
<td></td>
<td>Apical sites (n=18)</td>
<td>160±1</td>
<td>165±1*</td>
</tr>
</tbody>
</table>

Values are mean±SEM and were obtained during control period and 15 minutes after each shock. N indicates number of test dogs; and n, number of ventricular test sites.

*P<.05 vs control value.

Group 2. Seven dogs just received patch implantation, as in group 1 dogs, but no discharge of shocks. Ansae subclaviae stimulation–ERP response curves were determined three times, using the same time intervals of ERP determination as in group 1.

Group 3. The effects of low- and high-energy shocks on myocardial response to norepinephrine infusion were studied in 7 dogs. ERP was determined in the baseline state and during intravenous infusion of norepinephrine at doses of 0.1, 0.25, and 0.5 µg·kg⁻¹·min⁻¹. ERPs were determined 5 minutes after initiation of each infusion. The order of doses was chosen randomly and given at 10-minute intervals. Ten minutes after determination of the last norepinephrine dose–ERP response curve during the control period, a low-energy shock was discharged. Fifteen minutes after the low-energy shock, norepinephrine dose–ERP response curves were obtained. Then, 10 minutes later, a high-energy shock was delivered, and norepinephrine dose–ERP response curves were determined 15 minutes later. Time interval between the two shocks was 70 to 80 minutes.

Effects of Low- and High-Energy Shocks on Refractory Period Response to Vagal Stimulation

Group 4. Effects of DC shocks on efferent vagal responses were studied in 7 dogs. Baseline ERP and ERP during bilateral vagal stimulation were determined during control state, 15 minutes after a low-energy shock, and 15 minutes after a high-energy shock. Time interval between the two shocks was 30 to 40 minutes.
Time Effect of High-Energy Shocks on Refractory Period Response to Ansae Subclaviae Stimulation

Group 5. The time course of alterations in sympathetic responsiveness after a shock was evaluated in 7 dogs. Baseline ERP and ERP during bilateral ansae subclaviae stimulation were determined before and 15, 60, 120, and 180 minutes after a single high-energy shock. The frequency of ansae subclaviae stimulation was constant at 4 Hz. The ERP response to norepinephrine infusion (0.5 μg · kg⁻¹ · min⁻¹) was obtained at the end of the study in 6 dogs.

Effects of Shock Energy Level on Refractory Period Response to Ansae Subclaviae Stimulation

Groups 6, 7, and 8. Twelve dogs in three groups were studied to determine the threshold energy level that attenuated sympathetic responsiveness. Group 6 consisted of 3 dogs receiving a single shock of 6 J; group 7 consisted of 3 dogs receiving a single shock of 10 J; and group 8 consisted of 6 dogs receiving shocks of 0.5 and 16 J. Bilateral ansae subclaviae stimulation–ERP response curves were determined before and 15 minutes after each shock. Methods and time intervals were the same as in group 1.

Effects of Leading-Edge Voltage and Current on Refractory Period Response to Ansae Subclaviae Stimulation for Medium-Energy Shocks

Groups 9 and 10. Effects of leading-edge voltage or current on efferent sympathetic responsiveness were studied in 6 dogs receiving shocks of 16 J, which is an energy just exceeding the threshold that attenuated sympathetic responsiveness. Group 9 consisted of 3 dogs that received a 16-J shock with a low leading-edge voltage and current, while group 10 consisted of 3 dogs that received a 16-J shock with a high leading-edge voltage and current. Capacitance was 100 μF in group 9 and 50 μF in group 10. Stimulus frequency of ansae subclaviae stimulation–ERP response curves was determined before and 15 minutes after the shock.

Fig 2. Plots show ansae subclaviae stimulation–effective refractory period (ERP) response curves at basal, patch, and apical test sites. ERP shortening (ordinate) in response to various stimulation frequencies of bilateral ansae subclaviae stimulation (abscissa) obtained during control, 15 minutes after low-energy shock, and 15 minutes after high-energy shock from 6 dogs (A). B, Similar frequency-response curves during control and 15 minutes after first and second sham shocks from 7 dogs. High-energy shocks shifted frequency-response curves down and rightward. Values are mean±SEM. n indicates number of test sites. *P<.001 vs control.

Fig 3. Plots of norepinephrine dose–effective refractory period (ERP) response curves. Shortening of ERP (ordinate) during intravenous infusion of norepinephrine (abscissa) at basal, patch, and apical test sites obtained during control, 15 minutes after low-energy shock, and 15 minutes after high-energy shock from 6 dogs. Values are mean±SEM. n indicates number of test sites.
Effects of High-Energy Shock Delivered Through the Pericardium on Refractory Period Response to Ansa Subclaviae Stimulation

Group 11. Effect of the patch electrodes positioned outside the pericardium was tested in 7 dogs. Each dog received a single high-energy shock over patches sutured to the outside of the pericardium. Ansa subclaviae stimulation–ERP response curves were determined before and 15 minutes after high-energy shocks.

Analysis of Data

As reported in the previous studies,\textsuperscript{15,16} data from ventricular test sites with less than 9-msec shortening of the ERP elicited by bilateral ansa subclaviae stimulation at 4 Hz or less than 3-msec lengthening of ERP induced by bilateral vagal stimulation during the first control determination were excluded because of insufficient effects of neural stimulation at those particular sites. Two dogs (one in group 1 and the other in group 11) were excluded from the analysis because ventricular fibrillation occurred after shocks.

Data were expressed as mean±SEM. Two-way repeated-measures ANOVA was used to compare the ansa subclaviae stimulation frequency–ERP response curves or norepinephrine dose–ERP response curves. One-way repeated-measures ANOVA was used to compare effects of energy levels on vagal stimulation–induced ERP prolongation and time course of baseline ERPs, hemodynamic data, or ansa subclaviae stimulation–induced ERP shortening after the shocks. A statistical significance was set at \( P<.05 \).

Results

Effects of Low- and High-Energy Shocks on Ansa Subclaviae Frequency- and Norepinephrine Dose–Refractory Period Response Relations

Calculated values for the various shock waveforms are shown in Table 1. Blood pressure, heart rate, and baseline ERP during control states and after shocks of various energies are shown in Tables 2 and 3.

In group 1, low-energy shocks did not affect the ansa subclaviae stimulation–ERP response curves at sites basal to, beneath, or apical to the patches (Fig 2A). However, high-energy shocks shifted the frequency–response curves downward and to the right at sites apical to and beneath the patches but not at sites basal to the patches (Fig 2A). Frequency–response curves were unchanged in sham dogs (group 2, Fig 2B).

ERP shortening in response to norepinephrine infusion was 17.3±1.3 versus 16.8±1.3 msec at basal sites, 19.6±2.0 versus 19.1±1.8 msec at patch sites, and 20.3±1.6 versus 20.5±1.1 msec at apical sites during control versus after high-energy shock \( (P<.05) \).

Norepinephrine dose–ERP response curves in group 3 are shown in Fig 3. Neither low- nor high-energy shocks affected dose–ERP response curves at basal, patch, and apical test sites.

Effects of Low- and High-Energy Shocks on Refractory Period Response to Vagal Stimulation

Table 4 shows the baseline ERP values of test sites during norepinephrine infusion. Both low- and high-energy shocks did not affect the ERP prolongation induced by bilateral vagal stimulation at sites basal to, beneath, or apical to the patches in group 4 (Fig 4).

Time Effect of High-Energy Shocks on Refractory Period Response to Ansa Subclaviae Stimulation

Heart rate, mean arterial pressure, and baseline ERPs in group 5 are shown in Table 5. Baseline ERPs at patch or apical test sites were unchanged \( (P>.1) \) over time, while baseline ERPs at basal sites showed slight prolongation \( (P<.01) \) after the shock. Fig 5 shows that 15 minutes after high-energy shocks, ERP shortening induced by bilateral ansa subclaviae stimulation was unchanged at sites basal to the patches but was attenuated at sites beneath and apical to the patches. ERP shortening at patch and apical test sites in response to ansa subclaviae stimulation was attenuated during a 3-hour period after delivery of the high-energy shock.

ERP shortening during norepinephrine infusion was 21.8±1.2 msec for basal sites, 21.5±0.8 msec for patch sites, and 20.4±1.2 msec for apical sites \( (P>.7) \) 3 hours after the shock.

We compared the time course of ERP response with ansa subclaviae stimulation after a single high-energy shock at individual test sites and dogs. After the shock, no basal test sites showed ERP shortening in response to ansa subclaviae stimulation that was <80% of control values. ERP shortening at patch and apical sites was attenuated 15 minutes after the shock in each dog (Fig 6A), but the reduction of ERP shortening was different among dogs (ERP shortening was 35±2% to 85±4% of control values 15 minutes after the shock). ERP response returned to control value 180 minutes after the shock in the dog that received a 33-J shock (ERP shortening 15, 120, and 180 minutes after the shock was 85±4%, 64±5%, and 104±7% of control values, respectively; Fig 6A*). The dog that received a 36-J shock showed sustained attenuation of ERP response during a 3-hour period after the shock (ERP shortening 15 and 180 minutes after the shock was 54±2% and 41±4% of control values, respectively; Fig 6A†). In the other dogs, ERP response showed incomplete return to control values at 180 minutes (ERP
shortening 15 and 180 minutes after the shock was 35±2% to 76±7% and 73±8% to 86±8% of control values, respectively, but the restoration curves were different among dogs.

Attenuation and restoration of ERP response after the shock were different among test sites in each dog (Figs 6B and 6C). In the dog that received a 33-J shock (Fig 6B), ERP response in two patch sites and in two of three apical sites was attenuated 15 minutes after the shock but returned toward control values 30 minutes after the shock (ERP shortening 15 and 30 minutes after the shock was 29% to 41% and 71% to 75% of control values, respectively). ERP response in one apical site showed delayed recovery (ERP shortening 15, 60, 120, and 180 minutes after the shock was 36%, 27%, 32%, and 50% of control value, respectively). In the dog that received a 32-J shock (Fig 6C), ERP response in one of two patch sites was almost unchanged (ERP shortening 15 and 180 minutes after the shock was 100% and 94% of control values, respectively). ERP response in the other patch site and in one of three apical sites was attenuated 15 minutes after the shock but recovered toward control values (ERP shortening 15 and 180 minutes after the shock was 74% to 83% and 83% to 84% of control values, respectively). ERP response in two of three apical sites showed sustained attenuation (ERP shortening 15 and 180 minutes after the shock was 54% to 67% and 53% to 63% of control values).

Effects of Shock Energy Level on Refractory Period Response to Ansae Subclaviae Stimulation

Medium-energy shocks of 16 J (group 8) shifted the ansae subclaviae stimulation–ERP response curves at patch (P<.022) and apical test sites (P=.003), while shocks of 0.5 J (group 8), 6 J (group 6), or 10 J (group 7) did not (Fig 7). Ansae subclaviae stimulation–ERP response curves were unchanged at basal test sites in these three groups (not shown).

Fig 8 shows the relationship between energy level and attenuation of ERP shortening in response to ansae subclaviae stimulation after a single shock. Basal sites showed no attenuation of ERP shortening at any energy levels. ERP shortening in response to ansae subclaviae stimulation was unchanged after single shocks of 0.5 to 10 J but was attenuated after single shocks of >10 J at patch and apical test sites. Attenuation of ERP shortening after 16-J shock was similar to 35-J shock.

Effects of Leading-Edge Voltage and Current on Refractory Period Response to Ansae Subclaviae Stimulation for Medium-Energy Shocks

Parameters of shocks in groups 9 and 10 are shown in Table 1. Delivered energy level was similar among shocks that had low (group 9) and high (group 10) leading edges of current (P>.05). Attenuation of sympathetically induced ERP shortening at patch and apical sites in response to ansae subclaviae stimulation was

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**TABLE 5.** Time Course of Baseline Heart Rate, Mean Arterial Blood Pressure, and Ventricular Effective Refractory Period Before and After DC Shock in Dogs That Received Single High-Energy Shock in Group 5

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate, bpm (N=7)</strong></td>
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<td>119±4</td>
<td>120±5</td>
<td>119±5</td>
<td>119±6</td>
</tr>
<tr>
<td><strong>Mean arterial blood pressure, mm Hg (N=7)</strong></td>
<td>103±5</td>
<td>104±6</td>
<td>102±5</td>
<td>102±7</td>
<td>100±5</td>
</tr>
<tr>
<td><strong>Ventricular ERP, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal sites (n=14)</td>
<td>153±2</td>
<td>156±2*</td>
<td>157±2*</td>
<td>157±2*</td>
<td>157±2*</td>
</tr>
<tr>
<td>Patch sites (n=14)</td>
<td>157±1</td>
<td>157±1</td>
<td>159±1</td>
<td>158±1</td>
<td>159±2</td>
</tr>
<tr>
<td>Apical sites (n=21)</td>
<td>157±1</td>
<td>157±1</td>
<td>158±1</td>
<td>158±1</td>
<td>158±1</td>
</tr>
</tbody>
</table>

Values are mean±SEM; N indicates number of test dogs; n, number of ventricular test sites; and bpm, beats per minute.

*P<.01 vs control.
Major Effects

response pericardium (P<.05).

High-energy shocks do not shift norepinephrine dose-
 Ezra response curves at basal, patch, and apical test sites; low- and high-energy shocks do not attenuate the
 ERP prolongation produced by efferent vagal stimulation; a single high-energy shock attenuates ERP shortening in response to ansae subclaviae stimulation at patch and apical test sites for as long as 3 hours; threshold energy level that attenuated ERP shortening induced by ansae subclaviae stimulation is 10 to 16 J; both high and low leading-edge current shocks of 16 J attenuate the ERP shortening in response to ansae subclaviae stimulation; and pericardial placement of patch electrodes seemed to protect against shock-induced attenuation of ERP shortening in response to ansae subclaviae stimulation.

Effects of DC Shocks on the Response to Efferent Sympathetic and Vagal Stimulation

Effects of countershock on the myocardium have been evaluated, using histology, 4-6,8 ECG mapping, 5 enzymatic analysis, 17 and scintigraphic methods. 18,19 In the present study, we demonstrated for the first time that defibrillating shocks delivered over implantable patches impair the refractory period response to efferent sympathetic stimulation but not efferent vagal stimulation in dogs. Sympathetic responsiveness was attenuated at patch and apical test sites but not at basal test sites. Norepinephrine dose–ERP response curves did not shift after high-energy shocks at any sites, indicating that the responsiveness of the myocardium was normal and unchanged.

We have shown previously that efferent sympathetic nerves are located in the superficial subepicardium. 13 It is likely that electrical shocks impaired efferent sympathetic nerves at the position of patch electrodes because attenuation of sympathetic response occurred only at sites beneath and apical to the patch electrodes. The ERP response was not attenuated at sites basal to the patch electrodes. In contrast, high-energy shocks did not alter ERP prolongation produced by vagal stimulation because vagal fibers are concentrated in the subendocardium 15,14 and thus removed from contact with the patch. Morphological studies indicate that damage by transthoracic or epicardial shocks tends to be concentrated in the epicardial and subepicardial regions at the site of electrode application. 6,20 If the upper edge of the patch had reached the atrioventricular groove before vagal fibers dive to the endocardium, 14 it is possible that the shock might have affected vagal nerves as well.

Patients with implantable cardioverter-defibrillators show shock-related pathological changes in myocytes subjacent to the patch electrode. 9 Morphological alterations after shocks are different between subepicardium and subendocardium. 6,20 Electrical countershocks cause contraction abnormalities in subepicardial zones when shocks are given directly to the epicardium but not in the subendocardial zone. 21 In a scintigraphic study, the major component of technetium-99m uptake occurs in the epicardial layers when shocks ≤50 J are applied directly to the heart. A single shock ≥50 J induces technetium-99m uptake in the subendocardial layers. 22

delivered directly to the epicardial surface attenuate ERP shortening in response to ansae subclaviae stimulation at sites beneath and apical to the patch electrodes but not at sites basal to the patch electrodes; low- and high-energy shocks do not shift norepinephrine dose–ERP response curves at basal, patch, and apical test sites; low- and high-energy shocks do not attenuate the ERP prolongation produced by efferent vagal stimulation; a single high-energy shock attenuates ERP shortening in response to ansae subclaviae stimulation at patch and apical test sites for as long as 3 hours; threshold energy level that attenuated ERP shortening induced by ansae subclaviae stimulation is 10 to 16 J; both high and low leading-edge current shocks of 16 J attenuate the ERP shortening in response to ansae subclaviae stimulation; and pericardial placement of patch electrodes seemed to protect against shock-induced attenuation of ERP shortening in response to ansae subclaviae stimulation.

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similar among low and high leading-edge current shocks (Fig 9).

Effects of High-Energy Shock Delivered Through the Pericardium on Refractory Period Response to Ansae Subclaviae Stimulation

Delivered energy, leading-edge voltage, duration, and tilt in group 11 were similar (P>.05) to the high-energy shocks of group 1 dogs with patches sutured inside the pericardium (Table 1). Leading-edge current was lower and impedance was greater in group 11 than in group 1 (P<.05). High-energy shocks delivered over patches sutured outside of the pericardium did not affect ERP response to ansae subclaviae stimulation (Fig 10).

Discussion

Major Findings

The major findings from this study are that single high-energy truncated monophasic exponential shocks
Thus, single shocks <50 J mainly damage the subepicardial myocardial tissue, which is consistent with our observation that a single shock ≤35 J affected the epicardial and/or subepicardial region and attenuated the sympathetic response. Subendocardial layers were not affected by this energy level, as judged by the preserved vagal response. Higher-energy shocks applied to the heart are probably necessary to produce transmural damage and attenuate the vagal response.

Mechanisms of Shock-Induced Attenuation of Efferent Sympathetic Response

Although transthoracic defibrillator shocks induce the local release of acetylcholine and catecholamines, the DC shocks have no sustained effects on such neurotransmitter release. For DC shocks to exert sustained effects on sympathetic responsiveness, as in the present study, several mechanisms, alone or in combination, can be postulated. Electric shocks can damage the subepicardial myocardium and cause diffusion of metabolites from the injured tissue to affect the autonomic function; electric shocks can damage the blood vessels supplying the nerve axons; or electric shocks can directly injure the sympathetic nerve axons.

Although we did not perform a histological examination of the heart, multiple shocks from 1 to 24 J delivered directly to the heart using implantable patches show only minimal pathological changes in dogs. Single defibrillation shocks with a cardioverter/defibrillator showed no pathological cardiac changes, and multiple shocks exhibited only superficial myocardial injury under the patch electrodes in humans.

Electrical shocks impair myocardial anaerobic metabolism and increase myocardial potassium efflux without reduction of myocardial blood flow. However, such metabolic changes are short, lasting only several minutes. It is not likely that accumulation of these metabolites affected sympathetic response for longer time periods. Further, it is unlikely that metabolites diffusing from such a small area of injured myocardium caused sympathetic attenuation at much larger areas located apically and beneath the patch electrodes.

Myocardial blood flow or coronary blood flow is unchanged after transthoracic (200 to 460 J) or epicardial shocks.
Fig 8. Plot shows relationship between shock energy level (abscissa) and effective refractory period (ERP) shortening in response to ansae subclaviae stimulation at 4 Hz after a single shock compared with control values in percentage (ordinate). Data were obtained from control values and after first shock in groups 1, 5, 6, 7, 8, 9, and 10. ERP data after a second shock were not included in this figure. Shocks >10 J attenuated ERP response, while shocks ≤10 J showed no significant effects on ERP response to ansae subclaviae stimulation.

dial (5 to 75 J) DC shocks.19,21,30 However, myocardial ischemia might occur after high-energy shocks because shocks >30 J but not shocks ≤30 J applied directly to the heart reduce both thallium-201 uptake and myocar- dial blood flow to shock sites.22 These regional blood flow changes could modulate autonomic neural func-
tion. Although we did not measure myocardial blood flow, reduction of regional myocardial blood flow probably does not play a major role in shock-induced sympathetic attenuation because 16-J shocks also attenuated sympathetic responsiveness in our study but do not reduce myocardial blood flow.22

Vascular disorders are observed in dogs receiving electrical defibrillation.4 DC shocks might damage vessels supplying the nerves and alter sympathetic function. However, the arterial supply to the sympathetic and vagal nerves of the heart is not well established, and we cannot entirely exclude this as a possibility.

In our study, some test sites beneath or apical to the shock area showed marked sympathetic attenuation 15 minutes after shock delivery but recovered toward control values over time after a single high-energy shock. These results indicate that shock-induced sympathetic attenuation can be a transient event, probably functional in origin at some sites. Electrical shocks to peripheral nerves cause functional changes in nerve impulse conduction.11 Excessive amounts of electric current injure the nerves and produce morphological damage due to the high electric energy10 and may have been the responsible mechanism in our study.

Sustained Sympathetic Attenuation After High-Energy Shocks

Restoration of nerve action potential after DC shocks depends on the shock voltage and capacity of the condenser.11 Shocks <200 V produce transient disturbances of nerve action potential, while discharges of 1000 V cause total block of nerve conduction followed by action potential abnormalities lasting >60 minutes. High-voltage shocks from small-capacity condensers create greater disturbances than low-voltage shocks from larger capacitors. The restoration kinetics following the high-voltage pulses are slower than for the low-voltage pulses of the same energy.

In the present study, restoration of sympathetic responsiveness after high-energy shocks was observed at some test sites exhibiting marked sympathetic attenuation but not at others. Some patch and apical test sites showed no recovery during a 3-hour period. These results might reflect excessively high energy delivery to some sympathetic nerves because of local “hot spots” around the edges of the patches that can occur following the shock. Conceivably, the lack of recovery could also reflect progressive neural damage following the initial shock.

The current density at the edges and corners of the electrodes is more dense than that within the body of the electrodes.31 This so-called edge effect creates zones of high current density limited to the edges of the patches31,32 and could injure sympathetic nerves that lie in the superficial subepicardium (depth ≤0.5 mm) when the patch electrodes are applied directly to the epicar-
dium. Because local current density beneath the shock electrode is uneven,31,33 it might cause attenuation of sympathetic responses at some sites beneath and apical to the patch electrode but not at others. The fact that vagal nerves are concentrated in the subendocardium, far from such high current density areas, might be a reason that shocks did not affect efferent vagal function. If the patches were placed over the vagal nerves prior to
their intramural course,\textsuperscript{14} vagal dysfunction likely would have resulted as well.

**Patches Outside the Pericardium Protect Against DC Shock–Induced Attenuation of Efferent Sympathetic Response**

High-energy shocks applied to patches outside the pericardium did not attenuate the ERP response to sympathetic stimulation. These shocks had higher impedance and lower leading-edge current than did high-energy shocks over patches inside the pericardium. Such high impedance reflects the electrical character of the pericardium, which contains collagenous and elastic fibers. Although the high impedance provided by the pericardium might slightly reduce the energy reaching the epicardium,\textsuperscript{36} the pericardium is too thin to affect the total shock energy very much. However, pericardium interposed between the patch electrodes and epicardium might blunt the high current density zones at the edges of the electrodes\textsuperscript{31,32} and reduce damage to sympathetic nerves.

**Methodological Consideration**

We used only the small patch electrodes to replicate the approximate patch-myocardium relationship found in human defibrillator implants. The surface area of implantable patches used in humans is 10 to 27 cm\textsuperscript{2},\textsuperscript{35,36} while the surface area of the patch electrodes in our experiment was 17 cm\textsuperscript{2}. Larger electrodes reduce both the defibrillation threshold and average current density and could decrease the myocardial injury\textsuperscript{22,37-39} and perhaps the attenuation of sympathetic responsiveness as well. Larger electrodes would not necessarily eliminate edge effects, however. Regardless, given the size of the canine heart, it was very difficult to obtain both even contact with epicardium and sufficient distance between the borders of the two patches when using the medium size patch. Delivered energy level (0.5 to 35 J) in the present study was comparable with that of implantable cardioverter-defibrillators in humans.

Modeling studies of current distributions of defibrillating shocks show uneven current density near the defibrillation electrode.\textsuperscript{27,33} Electrode configuration also affects such current distribution,\textsuperscript{31,40} and electrodes of different contours might have modified our results.

We sutured the patch electrodes to the pericardium to avoid injury to the epicardium. We tried to maintain firm and even patch electrode contact with the ventricular epicardium, but we were not able to exclude poor contact at some points of the patch electrode. Elevated ventricular wall temperature and myocardial burns can occur at such sites after defibrillator shocks\textsuperscript{41} and could account for irreversible sympathetic nerve injury. Overall patch contact was good since our results showed impedance values similar to those reported using conventional patch electrodes (58 to 64 Ω for medium- and high-energy shocks over patches inside the pericardium).\textsuperscript{38}

Higher currents delivered by smaller capacitors at identical energy levels are arrhythmogenic,\textsuperscript{42,43} since peak current rather than energy level determines the extent of myocardial damage.\textsuperscript{43,44} In our study, high or low leading-edge voltage and current shocks showed similar effects on sympathetic attenuation at the same energy level of 16 J. Leading-edge voltages between 527 and 764 V and currents between 8.5 and 11.7 A had no significantly different effects on neural function. However, we cannot exclude more sustained sympathetic attenuation with high leading-edge voltage shock because we measured the ERP response to sympathetic stimulation only once.

Shock waveforms affect both defibrillation energy and myocardial damage.\textsuperscript{45-47} Forty-joule damped sine wave shocks attenuated efferent sympathetic response, but 1-J shocks did not (authors’ unpublished data). Effects of other waveforms on sympathetic neural function need to be tested in the future.

**Study Implications**

Although arrhythmia induction was not tested in the present study, regional sympathetic attenuation after DC shock creates uneven efferent sympathetic actions on the heart that could produce ventricular tachyarrhythmias.\textsuperscript{46} One of the causes of postoperative inhospital death after cardioverter-defibrillator implant is incessant ventricular tachycardia/fibrillation.\textsuperscript{49} The mechanism of this exacerbation of ventricular arrhythmia, so-called "VT storm," is unknown but could be related to shock-induced heterogeneous sympathetic attenuation. Furthermore, hemodynamic depression, another known complication following cardioverter-defibrillator implantation, could be related to sympathetic neural depression. It is important to stress that our data showed sympathetic neural attenuation after only one high-energy shock. Initial energy levels to
cardiovert-defibrillate the heart sometimes exceed 15 J in humans.\textsuperscript{2,50,51} Generally, a minimum of three such shocks is necessary during cardioverter-defibrillator implantation. The incidence of high defibrillation thresholds is low, but such patients may need multiple high-energy shocks.\textsuperscript{52} It is possible that nonthoracotomy cardioverter-defibrillator implantation may protect against shock-induced sympathetic attenuation and may reduce arrhythmia and hemodynamic problems after cardioverter-defibrillator implant.

It is tempting to recommend that patches should be implanted in patients on the outside of the pericardium, based on the results from this study. However, as always, caution must be exercised in applying observations from animals to patients. Placement of a patch electrode outside the pericardium may result in phrenic nerve damage and may increase the defibrillation energy.\textsuperscript{54} Also, it is possible that repeated shocks, even with the pericardium interposed, might still attenuate sympathetic neural function.

**Acknowledgments**

Supported in part by the Herman C. Krannert Fund; by grants HL-42370 and HL-07182 from the National Heart, Lung, and Blood Institute of the National Institutes of Health; US Public Health Service; and the American Heart Association Indiana Affiliate, Inc. We thank Naomi S. Fineberg, PhD, for statistical analysis and Jacob Rohleder, BS, for technical assistance.

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Defibrillating shocks delivered to the heart impair efferent sympathetic responsiveness.
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Circulation. 1993;88:2661-2673
doi: 10.1161/01.CIR.88.6.2661

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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