The effects of shock energy, propranolol, and verapamil on cardiac damage caused by transthoracic countershock


ABSTRACT Myocardial damage by transthoracic countershocks was assessed by observation for electrocardiographic loss of R waves and elevation of ST segments, creatine kinase depletion, and histologic evidence of necrosis in damaged areas, and by excision and examination, 3 days later, of all tissue macroscopically observed to be damaged. When 4000 J of stored energy was passed across the chest of dogs anesthetized with pentobarbital sodium (30 mg/kg), more damage was caused when the energy was divided among 10 shocks than when it was applied in 20 or 40 shocks (at intervals of 0.5 min). The prior intravenous administration of verapamil (1 mg/kg) reduced the weight of damaged myocardium, the extent of histologic change, and creatine kinase depletion caused by 10 × 400 J shocks. Propranolol (0.4 mg/kg) had no effect. These results give further evidence for the role of calcium accumulation in cardiac necrosis after direct current countershocks. Multiple low-energy shocks cause less cardiac damage than do a few high-energy shocks of similar total energy.


TRANSTHORACIC direct current countershock has been clinically used for the correction of cardiac arrhythmias since 1962 when the work of Lown et al.1,2 led to widespread adoption of the technique as an alternative to alternating current countershock. The upper limit of stored energy for use in defibrillation was set at 400 J. Since then there have been two major developments. First, the latest generation of 400 J defibrillators deliver to the patient a greater proportion of the stored energy than did Lown’s original design.2 Second, because of claims that shocks of greater than 400 J may be needed to defibrillate some patients,3 new defibrillators storing more than 400 J have been introduced.

Serious doubts have been raised about the need for higher energies in correcting ventricular fibrillation in the clinical setting.4–6 No evidence has been produced to show that higher energies (more than 400 J) are effective in the few cases in which lower ones fail. Furthermore, direct current countershocks can cause cardiac damage.7–9 We have investigated the relationship between shock energy and myocardial damage in anesthetized dogs given a similar total dose of electrical energy divided over 10, 20, or 40 shocks.

The histologic changes observed by both light and electron microscopy in myocardium damaged by direct current countershock bear some resemblance to those produced by the administration of large doses of isoproterenol.10,11 Accordingly, we investigated the possible protective effect of β-adrenoceptor blockade with propranolol on shock-induced damage. The effect of verapamil was also studied as it has been suggested that the influx of calcium into myocardial cells is important in the development of cardiac necrosis. Preliminary reports of these studies have been given.12,13

Methods

Greyhound dogs of both sexes weighing 20 to 37 kg were anesthetized with sodium pentobarbital (Sagatal, May & Baker; 30 mg/kg intravenously), intubated, and ventilated at 18 times/min with room air at a stroke volume of 14 ml/kg. The hair of each dog was clipped closely on both sides of the chest. Polyethylene cannulas (gauge 17, Venflon, Viggo AB) were inserted percutaneously in the left femoral artery to record arterial blood pressure (Statham P23AA) and in a hind-leg vein to administer drugs and to obtain samples of peripheral blood.

During the control period the six standard limb leads and 11

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precostial leads of the electrocardiogram (ECG) (V_{2R}, V_{3R} and V_{2-V_{6}}) were obtained from subcutaneous needle electrodes and recorded on a Devices M4 polygraph. The precordial recording sites in the right and left fourth intercostal spaces were marked with indelible ink for later use. Full recordings of the limb and precordial leads of the ECG were made before and at 15 min, 1 hr, and 3 days after application of the shocks. PR and QT intervals were determined from recordings of lead II of the ECG made at a paper speed of 100 mm/sec. In the precordial leads recorded at a paper speed of 25 mm/sec, ST-T segment elevation was measured as the deviation of ST-T from the isoelectric TP segment of the trace 60 msec after the nadir of the S wave. Continuous recordings of lead II of the ECG, heart rate (Devices Ltd.), and mean arterial blood pressure were made at a slow paper speed before and for 1 hr after application of the shocks.

A defibrillator (Hewlett Packard 720-2A) was modified so that the static voltage across the main capacitor was shown on a digital voltmeter (Data Precision 3500; figure 1). The synchronizing pulse of the defibrillator was used to trigger the time base of a storage oscilloscope with two dual-channel differential amplifiers (Tektronix R5441).

Energy stored in the defibrillator (E) was estimated from the formula: E = \frac{1}{2} CV^2, where C was the capacitance (15.7 \mu F) and V the voltage across the charged capacitor shown on the digital voltmeter.

Transcutaneous voltage was recorded differentially through a voltage divider network as the potential difference between the output paddle of the defibrillator (on the left chest) and the return paddle (on the right chest).

Transcutaneous current was determined from the voltage drop across a 1 \Omega resistor in the circuit from the return paddle to earth. Since this method could underestimate current, other electrical paths to ground were reduced by placing each dog on a polyethylene sheet and by removing the right-leg electrode of the ECG before application of the shocks.

Transcutaneous impedance was obtained by dynamic division of the transcutaneous voltage by the transcutaneous current with the use of an electronic divider circuit (Analog Devices AD533).

The last three variables were displayed on the oscilloscope and recorded on Polaroid film with a Tektronix C12 camera. By these means it was possible to determine the energy stored on the capacitor, the peak transcutaneous current and the voltage, and the minimum transcutaneous impedance for successive shocks. Later the traces for transcutaneous current and voltage were digitized visually at intervals of 1 msec. For each time interval the two measurements were multiplied together, and the resulting curve of delivered energy with time was integrated by the trapezoidal rule to derive the total delivered energy of a shock.

Lead III of the ECG was obtained in each dog from silver-silver chloride pads (American Optical, 5113) applied to small areas of shaved skin on the left shoulder and the left thigh, amplified by the monitor channel of the defibrillator, and displayed on the polygraph.

This ECG monitor channel was modified so that the synchronizing pulse that discharged the main capacitor also clamped the ECG amplifier to ground for 120 msec. This reduced saturation of the monitor amplifier by the defibrillator shocks and permitted recording of the ECG usually within 1 sec after the application of the shock. The arrhythmogenic effects of the shocks were determined by examination of this recording.

After the ECG had been recorded the treatment that each dog would receive was decided upon by the opening of the next of a series of envelopes, each of which contained a randomly allocated group number. There were six animals in each group and they received the following: group 1, 10 ml of sterile 0.9% NaCl solution intravenously over 5 min, followed 2 min later by 10 shocks, each of 400 J of stored energy; group 2, 10 ml of sterile 0.9% NaCl solution intravenously, followed by 20 shocks of 200 J each; group 3, 10 ml of sterile 0.9% NaCl solution intravenously, followed by 40 shocks of 100 J each; group 4, propranolol (0.4 mg/kg iv over 5 min; IC1 Pharmaceuticals), followed after 2 min by 10 shocks of 400 J each; group 5, verapamil (1.0 mg/kg iv over 5 min).

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** In this simplified circuit diagram the defibrillator is represented by the capacitor (across which the voltage was shown by the digital voltmeter), the relay triggered by the QRS complex of the ECG, and the inductor. The potential differences across the chest paddles (and also in some experiments recorded across the ventricular septum from electrode catheters at the apexes of both ventricles) were displayed on a storage oscilloscope together with the transcutaneous current.
mg/kg iv over 5 min; Cordiloex, Abbott Laboratories), followed after 2 min by 10 shocks of 400 J each.

The defibrillator paddles (8 cm diameter) were placed firmly on the clipped skin over the apex beats of the right and left ventricles. Electrode paste (Redux paste; Hewlett Packard) was used to ensure good electrical contact. At intervals of 30 sec, shocks from the defibrillator were applied synchronously with the R wave of the ECG until the series of shocks was completed. When the last shock of the series caused ventricular fibrillation, it was terminated with another shock of the same size as that given in the rest of the series.

The surviving dogs were allowed to recover consciousness. Three days after the shocks had been given the dogs were reanesthetized with 30 mg/kg pentobarbital. A full ECG was recorded with the dog in the same position and with the same amplifier as used previously, and the chest was opened and the beating heart excised.

Small portions of myocardium were taken from the areas macroscopically observed to be damaged and from the adjacent, apparently normal areas of the right and left ventricles. When damage was seen the main site was on the free wall of the right ventricle. The first sample was taken from the most severely damaged tissue in this area or, if the absence of damage, from the center of this area. The second sample was taken 2 to 4 cm anteriorly to this in an apparently normal area of the outflow tract. In the left ventricle the first sample was taken from the most damaged tissue, which was to the left of the lower half of the anterior descending branch of the left coronary artery, or from normal tissue in this area in the absence of damage. The second left ventricular sample was obtained from apparently normal tissue 2 to 3 cm posterior to this zone. Each sample was divided into four parts.

One part of each myocardial sample was prepared for light-microscopic examination. The tissue was fixed in formaldehyde, embedded in paraffin wax, and stained with hematoxylin and eosin. The degree of myocardial damage was graded on coded sections as follows: grade 0, no damage; grade 1, heterogeneous cytoplasm with transverse bands of dense staining; grade 2, evidence of necrosis in the outer third of the section only; grade 3, presence of necrotic areas in the outer two-thirds of the thickness of the ventricle; grade 4, extension of the damaged area to more than the outer two-thirds of the section.

The concentration of creatine kinase in the second part of each tissue sample was determined as another index of myocardial damage. Samples of tissue were trimmed to give 150 to 200 mg of apparently homogeneous damaged or normal tissue, weighed, minced with scissors, mixed with 25 vol/g of a solution containing 0.25M sucrose, 0.001M sodium ethylenediamine tetra-acetate, and 0.1 mM mercaptoethanol and homogenized in a ground-glass tube with three to four strokes of a tight-fitting, motor-driven Teflon pestle (Thomas). The resulting suspension was then centrifuged at 16,000 × g for 15 min at 0° C. The supernatant was removed and diluted in a buffer solution of serum albumin and Tris. The myocardial supernatant and the plasma from the venous blood samples were assayed for creatine kinase by the Rosalki method with a commercial kit (Worthington). The protein content of the myocardial supernatant was estimated by the biuret method.16

**Statistical methods.** Tables 1 through 4 list results of testing for differences between groups by analysis of variance and for differences within the groups by paired t test. The null hypotheses were first that there were no differences between the five groups, whether they received 4000 J of stored energy divided as 10, 20, or 40 shocks after an injection of saline or as 10 shocks after pretreatment with propranolol or verapamil, and second that the values obtained in a group of animals did not differ with time or with site on the myocardium from which the samples were obtained.

Because of heterogeneous variances the arterial pressure, heart rate, and ECG data were examined with both parametric and nonparametric tests (figures 2 through 6). The null hypothesis that in any one group there was no significant change in data with time was examined with the Wilcoxon signed-rank test. The further null hypothesis that at any one particular time there was no significant difference between the results observed in the five groups was tested with the Mann-Whitney U test.

A nonparametric test was also applied to the data in table 4, which showed heterogeneous variance, and in table 5, which lists grades rather than measurements. The null hypothesis that there were no significant differences between the results observed in the five groups at a particular site was examined with the Kruskal-Wallis ANOVA test. The correlations between the weight of macroscopically observed damaged tissue under each paddle (or in the heart as a whole) and the ECG changes on the same side of the chest (or on both sides) were determined with parametric (Pearson product-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Treatment (stored energy and drug)</th>
<th>Delivered energy (J)</th>
<th>Peak transthoracic voltage (V)</th>
<th>Transthoracic impedance (Ω)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock 1</td>
<td>Shock 10</td>
<td>Shock 1</td>
</tr>
<tr>
<td>400 J × 10</td>
<td>231.2 ± 6.0</td>
<td>193.4 ± 1.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1947 ± 116</td>
</tr>
<tr>
<td>200 J × 20</td>
<td>120.5 ± 3.2</td>
<td>106.4 ± 3.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1491 ± 85</td>
</tr>
<tr>
<td>100 J × 40</td>
<td>61.9 ± 1.5</td>
<td>58.3 ± 2.2 (NS)</td>
<td>1088 ± 36</td>
</tr>
<tr>
<td>Propranolol + 400 J × 10</td>
<td>234.8 ± 9.5</td>
<td>204.9 ± 10.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1936 ± 145</td>
</tr>
<tr>
<td>Verapamil + 400 J × 10</td>
<td>233.2 ± 3.8</td>
<td>196.8 ± 5.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1748 ± 44</td>
</tr>
</tbody>
</table>

Trans thoracic voltage, current, and impedance were recorded during the first and tenth of a series of shocks in five groups, each of six dogs, which received shocks 400, 200, or 100 J of stored energy or 400 J after pretreatment with either propranolol or verapamil (mean values ± SEM). For the instantaneous shock energy the time curve was produced by multiplication of digitized values from the current and voltage traces against time and the area under this curve was measured to give the delivered energy of the shock.

The statistical significance of the differences between values for shock 1 and shock 10 are as follows: NS (at p > .05); <sup>a</sup>p < .05; <sup>b</sup>p < .01.
TABLE 2
Peak transthoracic currents

<table>
<thead>
<tr>
<th>Treatment (stored energy and drug)</th>
<th>Amperes (Shock 1)</th>
<th>Amperes (Shock 10)</th>
<th>Amperes per kilogram (Shock 1)</th>
<th>Amperes per kilogram (Shock 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 J × 10</td>
<td>48.8 ± 1.2</td>
<td>54.4 ± 0.5</td>
<td>2.0 ± 0.2</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>200 J × 20</td>
<td>34.8 ± 1.2</td>
<td>37.7 ± 0.3</td>
<td>1.3 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>100 J × 40</td>
<td>23.9 ± 0.4</td>
<td>26.4 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 J × 10</td>
<td>50.4 ± 1.3</td>
<td>53.2 ± 1.7</td>
<td>2.1 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 J × 10</td>
<td>53.0 ± 0.8</td>
<td>56.0 ± 1.2</td>
<td>2.3 ± 0.1</td>
<td>2.4 ± 0.1</td>
</tr>
</tbody>
</table>

Mean values ± SEM for groups of six dogs.

The statistical significance of differences between shocks 1 and 10 are as follows: *p < .05; **p < .01. There was no significant difference between the transthoracic currents in the three groups of dogs given 10 shocks of 400 J (after saline, propranolol, or verapamil).

Results

The effects of a reduction in the energy given per shock were studied in three groups of dogs given similar total doses of energy divided as 10 shocks of 400 J, 20 shocks of 200 J, or 40 J for 100 J.

The high voltages applied to the paddles gave transiently high transthoracic currents and voltages. When a stored energy of 400 J was discharged across the chest the peak current was 44 to 57 A and the peak transthoracic voltage was 1400 to 2000 V (tables 1 and 2). The recorded waveforms showed that the minimum transthoracic impedance was initially on the order of 30 to 50 Ω, and fell slightly to a plateau value that was maintained throughout much of the positive phase of the shock. In all of the groups studied the transthoracic impedance fell with repeated shocks, and fell by 20% to 30% by the tenth shock (table 1). As transthoracic impedance fell the peak transthoracic current rose, but did so to a lesser extent than the fall in impedance. Hence, the energy delivered to the dogs fell with repeated shocks, so that the energy delivered from the tenth shock was 90% of that delivered by the first. The groups of dogs that were given 20 and 40 shocks showed little further change in transthoracic impedance after the tenth shock, and were exposed to lower peak transthoracic voltages and currents. However, these two groups received total amounts of delivered energy that were similar to those in the group given 10 shocks of 400 J.

Effects of different shock energies. Shocks of 400 J caused the development of ventricular arrhythmias, usually in the form of ventricular tachycardia or ventricular fibrillation. The duration of ventricular tachycardia fell as the shock energy was reduced from 400 J. Ventricular fibrillation appeared after one or more of the shocks in six of the dogs given 400 J shocks, in two of the dogs given 200 J shocks, and in one of the dogs given 100 J shocks. Atrophicventricular block with a slower idioventricular rhythm developed after some of the shocks in two of the dogs given 400 J, but not in any of the dogs given 200 or 100 J shocks.

However, these effects on atrioventricular conduction were transient, and 1 min after the last shock in each group the PR interval on the ECG was similar to that before or 1 hr after the shocks. The corrected QT interval did not change after the shocks. The mean arterial blood pressure was lower 1 min after the last of the 400 J shocks than after shocks of 200 or 100 J.

TABLE 3
Effects of shock energy, propranolol, and verapamil on the weight of gross myocardial damage

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight of dogs (kg)</th>
<th>Weight of hearts (g)</th>
<th>Weight of myocardial damage (g)</th>
<th>Damaged myocardium (%)</th>
<th>Heart weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 J</td>
<td>25.6 ± 2.6</td>
<td>279.6 ± 25.9</td>
<td>30.1 ± 10.6 (n = 5)</td>
<td>11.7 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>200 J</td>
<td>26.6 ± 1.4</td>
<td>287.0 ± 14.4</td>
<td>5.1 ± 1.3 (n = 6)</td>
<td>1.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>100 J</td>
<td>24.8 ± 2.0</td>
<td>253.3 ± 14.8</td>
<td>0.6 ± 0.3 (n = 6)</td>
<td>0.2 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>400 J after propranolol</td>
<td>23.9 ± 1.7</td>
<td>266.6 ± 8.4</td>
<td>21.9 ± 9.0 (n = 4)</td>
<td>8.2 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>400 J after verapamil</td>
<td>23.3 ± 0.7</td>
<td>257.4 ± 14.3</td>
<td>6.2 ± 2.9 (n = 5)</td>
<td>2.3 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

The weights of the dogs, hearts, and macroscopically damaged ventricular muscle in grams or as a fraction of total heart weight are shown for the three groups of dogs that survived for 3 days after being given an intravenous injection of saline and shocks of either 400, 200, or 100 J of stored energy (mean values ± SEM). The only significant differences were in the smaller weights of myocardium damaged after 20 shocks of 200 J (p < .05) or 40 shocks of 100 J (p < .01) than after 10 shocks of 400 J. All dogs received similar total amounts of electrical energy. The other two groups received an intravenous injection of propranolol (0.4 mg/kg) or verapamil (1 mg/kg) 5 min before receiving 10 shocks of 400 J. The administration of verapamil significantly reduced the amount of myocardial damage below that in the first group (p < .05), whereas propranolol did not (p > .05).
TABLE 4
Tissue creatine kinase (IU/mg protein)

<table>
<thead>
<tr>
<th></th>
<th>Right ventricle</th>
<th></th>
<th>Left ventricle</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal area</td>
<td>Damaged area</td>
<td>Normal area</td>
<td>Damaged area</td>
</tr>
<tr>
<td>400 J</td>
<td>14.7±2.10</td>
<td>3.3±2.6b</td>
<td>16.6±1.9</td>
<td>5.5±3.6b</td>
</tr>
<tr>
<td>200 J</td>
<td>21.9±2.4</td>
<td>12.1±2.0b</td>
<td>23.2±4.2</td>
<td>11.9±3.9 (NS)</td>
</tr>
<tr>
<td>100 J</td>
<td>13.2±4.1</td>
<td>11.2±2.9 (NS)</td>
<td>14.3±4.1</td>
<td>10.0±3.3b</td>
</tr>
<tr>
<td>Propranolol</td>
<td>13.6±3.5</td>
<td>2.9±1.0b</td>
<td>13.3±5.2</td>
<td>3.9±3.0 (NS)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>11.7±2.8</td>
<td>7.8±2.8 (NS)</td>
<td>19.2±4.9</td>
<td>9.6±3.9 (NS)</td>
</tr>
</tbody>
</table>

Mean values (± SEM) are shown for creatine kinase activity in biopsies from apparently normal areas in the right and left ventricle, and from macroscopically observed damaged areas in the right and left ventricle (or from similar anatomic sites in the absence of gross damage) in five groups of dogs that survived for 3 days after receiving shocks of 400 (n = 5), 200 (n = 6), or 100 J stored energy (n = 6), or 400 J shocks after pretreatment with propranolol (n = 4) or verapamil (n = 5). The statistical significance of differences from activity in the apparently normal area in the same ventricle are indicated for each group. There were no significant differences between the five groups at normal sites in either ventricle, or at the damaged site in the left ventricle. The right ventricles of the 400 J group (saline) differed significantly from those of both the 200 and 100 J groups (p < .05). The propranolol group differed significantly only from the 200 J group. The verapamil group did not differ significantly from any of the other four groups.

NS (at p > .05); a p < .05; b p < .01.

partly because of the longer duration of the ventricular arrhythmias (figure 2).

The main ECG finding was the development of ST segment elevation in the unipolar chest leads over the right and left ventricles. The most severely affected records were made from areas that had been immediately under the paddles (V₁R–V₅R on the right chest, V₂–V₅ on the left chest). The elevation was maximal 15 min after the application of the 400 J shocks and fell towards control values over 3 days. This ST segment elevation was accompanied by a temporary loss of voltage in the R waves (right and left chest) and in the S waves (left chest), with a later increase in S wave voltage (both chests) and T wave inversion on the recordings from the damaged areas.

ST segment elevation was summed over the right chest (leads V₁R–V₆R) and over the left chest (leads V₂–V₆, figure 3). While control values for summed ST segment elevation were similar in the three groups at the two sites, a much greater rise in summed ST elevation was seen 15 min and 1 hr after the 400 J shocks than in the dogs given shocks of 200 or 100 J.

Summed R wave voltages over both the right (V₃R–V₆R) and left chests (V₂–V₅) did not differ significantly in dogs in the three saline-treated groups before the shocks, but after the 400 J shocks the R wave voltages were significantly less than in the 100 J group (figure 4). Summed S wave voltages fell significantly over the left chest (at 15 min) and increased over the right chest (at 1 hr) after the 400 J shocks, but did not change significantly with either 200 or 100 J shocks (data not shown).

Macroscopic myocardial damage in relation to shock energy. Three days after administration of the shocks the hearts were removed and examined. The severity of the gross macroscopic damage varied greatly. The most severely damaged hearts showed pale or hemorrhagic indurated paddle-shaped areas of yellow-brown
myocardium, which in the right (but not the left) ventricle often extended to involve the endocardium. Some hearts had no macroscopically apparent damage. Others had only a few pale superficial white or yellow spots on the epicardium of the areas of the ventricles that had been under the paddles. These lesions were not seen in dogs that had not received shocks.

The three groups of dogs had similar total body and heart weights, but differed significantly in the weight of their macroscopically observed damaged ventricular muscle (table 3). The same doses of energy as 20 shocks of 200 J (p < .05) or as 40 shocks of 100 J (p < .01) caused less damage than did 10 shocks of 400 J.

Depletion of the enzyme creatine kinase from the macroscopically observed damaged tissue was assessed at the end of each experiment by comparing the enzyme activity in myocardial biopsies from the most severely damaged area with that in an apparently undamaged area in each ventricle (table 4). Three days after the shocks there was significant depletion of creatine kinase in both right and left ventricular lesions of the dogs given 400 J shocks. Significantly less severe enzyme depletion was noted in the right ventricular lesions of the dogs given 200 or 100 J shocks.

Validation of gross dissection. Are macroscopic changes 3 days after the shocks an accurate indication of the extent of myocardial damage? A commonly used method for assessing the amount of myocardium damaged by ischemia involves the incubation of slices of myocardium in nitro blue tetrazolium (NBT).19 Nine dogs were given 10 shocks of 400 J at 30 sec intervals. Three days later the hearts were removed and frozen. A few hours later the frozen hearts were cut, parallel to the atroventricular groove, in 4 mm sections. Alternate slices were incubated in 50 mg/ml prewarmed NBT in Sorensen's phosphate buffer for 30 min at 37° C. The unstained areas were dissected out of each of the stained slices and weighed; the grossly abnormal areas in the alternate unstained slices were also dissected out and weighed. There was a high correlation between the weights of damaged myocardium determined in the nine hearts by the two methods (r = .998

**FIGURE 3.** The sum of the elevations of the ST segments of the ECG over the right chest (V<sub>2</sub>-R, V<sub>5</sub>-R) and over the left chest (V<sub>3</sub>-V<sub>6</sub>) are shown before and at 15 min, 1 hr, and 3 days after transthoracic shocks of 400 J (10 shocks), 200 J (20 shocks), or 100 J (40 shocks); mean values ± SEM. The preshock and 3 day values were not significantly different between the groups. Over the right chest the increases seen in the 400 J group were significantly greater than the values in the 100 J group (at 15 min and 1 hr; p < .05) and in the 200 J group (1 hr; p < .05). At 1 hr the 200 J group value was significantly greater than the 100 J value (p < .05). Over the left chest the differences between the groups were not significant except at 15 min when the 200 J group showed a greater increase than did the 100 J group (p < .05).
FIGURE 4. R wave amplitudes were summed for the ECG over the right chest (V2R-V6R) and over the left chest (V2-V6) before and at 15 min, 1 hr, and 3 days after the same total dose of energy given as shocks of 400, 200, or 100 J. Preshock and 3 day values were similar in the three groups. The R wave amplitudes in the 400 J group fell to values less than the 100 J mean values over the right chest (at 15 min and 1 hr; p < .05), and over the left chest (at 1 hr; p < .05). There were no significant differences between the 200 J group and either of the other groups.

FIGURE 5. The mean arterial blood pressure (BP) and ventricular rate (VR) are shown before and after the intravenous administration of saline, propranolol, or verapamil, and at 1 and 15 min, 1 hr, and 3 days after the 10 transthoracic shocks of 400 J (as in figure 2). Preshock values for BP and VR were similar in the three groups. The infusion of verapamil caused a significant reduction in arterial pressure below that in the saline and propranolol groups (p < .05) and 15 min after the shocks the BP was still less than that in the other two groups (p < .05). At 1 hr BP did not differ significantly in the three groups. VR did not change significantly with time in the propranolol or verapamil groups, but in the saline-treated animals it rose at 15 min and 1 hr to values significantly greater than in the other two groups (p < .05).

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Time After Shocks

### Effects of propranolol

The intravenous administration
of propranolol (0.4 mg/kg) over 5 min produced a slight fall in heart rate, no significant alteration in PR or corrected QT interval, and no change in mean arterial blood pressure (figure 5). When the shocks were given the mean plasma propranolol concentration was $1.52 \pm 0.83 \mu g/ml$. The effects of 10 shocks of 400 J each after propranolol were compared with those after treatment with saline. Complete atroventricular block with slow idioventricular rhythm was seen in all six of the propranolol-treated dogs, and it lasted for a longer period of time. Mean arterial blood pressure 1 min after the last shock was similar in the two groups. The summed ST segment elevation and the summed R wave loss in the leads over the right and left chests were similar in the saline- and propranolol-treated groups (figure 6).

Three days after the shocks the damage to the hearts of propranolol- and saline-treated dogs did not differ with respect to the weight of necrotic tissue, in the depletion of creatine kinase, or in the histologic grade of damage from those of the dogs treated with saline (tables 3 through 5).

**Effects of verapamil.** The intravenous administration of verapamil (1.0 mg/kg over 5 min) caused a pronounced drop in mean arterial blood pressure and slowed atroventricular conduction (figure 5). The effect on atrioventricular conduction was most marked during the administration of the drug, with periods of Wenckebach or 2:1 atroventricular block. Two minutes later, when the shocks were given, sinus rhythm had generally returned with a prolonged PR interval and the ventricular rate was often slightly higher than before the drug was given (figure 5). The corrected QT interval was not altered significantly.

The early effects of 10 shocks of 400 J in these dogs were compared with those seen in the dogs given the same 10 shocks and saline. The duration of ventricular
tachycardia, the incidence of ventricular fibrillation, the mean arterial blood pressure, and the ventricular rate 1 min after the shocks did not differ significantly in the two groups. There was no significant difference in the sum of the R wave voltages or the ST segment elevations over the right or left chest of the verapamil-treated group and the sums in the saline-treated dogs (figure 6).

Three days after the shocks there was no significant depletion of creatine kinase, and significantly less damaged tissue was noted on macroscopic or histologic examination of the hearts of the dogs treated with verapamil than in the dogs that received 400 J shocks after saline (tables 3 through 5).

Effects of ventricular fibrillation. Ventricular fibrillation occurred on several occasions during the series of experiments in the dogs given different shock energies, propranolol, and verapamil, despite synchronization of the shocks with the R wave on the ECG. The possible contribution of a period of ventricular fibrillation to myocardial damage was assessed in another study in three dogs. All had three separate episodes of ventricular fibrillation, each of 1 min duration and separated by a period of 1 min. Fibrillation was induced by a train of square-wave stimuli (5 msec duration pulses at intervals of 10 msec, 1 to 3 V in amplitude) applied by a pacing catheter to the endocardium of the apex of the right ventricle. After the ventricles had fibrillated for a period of 1 min sinus rhythm was restored by a shock of 100 J. One dog required a further shock of 100 J to abolish one of its three periods of fibrillation. Two dogs therefore endured 3 min of ventricular fibrillation over a 5 min period, and the third dog 3½ min of fibrillation over a 5 min period. After 3 days the hearts were removed. The damage was assessed by gross examination before and after staining with NBT. In only one dog could damage be seen and it consisted of two superficial lesions weighing less than 0.1 g. Similar lesions had been seen in dogs that received 40 shocks of 100 J uncomplicated by ventricular fibrillation. Since this period of fibrillation was greater than the total period of fibrillation in any of the dogs in the experimental groups, our results suggest that ventricular fibrillation as an isolated factor contributed little to the cardiac damage.

ECG changes and macroscopic damage. Cardiac damage and ECG changes were noted for both ventricles. There was a close correlation between the weight of damaged tissue excised from the left ventricle and that from the right ventricle in the five groups (21 hearts; \( r = .786, p < .001 \)).

The relationship between the ECG changes and the amount of macroscopically observed damaged tissue was determined with parametric and nonparametric tests. The correlation coefficients we report were the highest determined by the Spearman rank-correlation test. The correlations obtained with the Pearson product-moment test were generally higher, but in this test a normal distribution of the data is assumed.

The increase in ST segment elevation 15 min after the shocks showed the largest differences between the saline-treated groups given shocks of different energies (figure 3) and the best correlation between ECG changes and extent of damage (\( r = .701 \)) for changes in the right chest and right ventricular damage, 14 hearts, \( p < .01 \); \( r = .616 \) for changes in the left chest and left ventricular damage; and \( r = .736 \) for changes over both chests and total damage, 17 hearts, \( p < .001 \)). These correlations were changed little when the data from the propranolol- and verapamil-treated groups were added.

The decrease in the sum of the R waves over the right chest (\( r = .510 \)) and decrease in the sum of the S waves over the left chest (\( r = .772 \)) 15 min after the shocks in the three saline-treated groups correlated fairly well with damage to the right ventricle, but the corresponding decreases in R waves over the left chest (\( r = .195 \)) and S waves over the right chest (\( r = -.409 \)) did not correlate significantly with damage to the left ventricle. Although the late loss of R waves and increase in S waves at 3 days should indicate the most permanent loss of electrical activity, the losses in amplitude of both waves at 15 min or even 1 hr after the shocks gave the only significant correlation coefficients with the macroscopic damage observed 3 days after the shocks both in the three saline-treated groups and in all five groups together.

Discussion

Early effects of the transthoracic direct current shocks in our study included cardiac arrhythmias and elevation of the ST segments of the ECG. Cardiac damage caused by the shocks was evident on sequential ECGs, macroscopic and microscopic examination of the hearts, and examination of myocardial creatine kinase levels in the lesions. The extent of cardiac damage was related to shock energy. The same total dose of electrical energy caused more necrosis if given as 10 shocks of 400 J than if given as 20 shocks of 200 J or as 40 shocks of 100 J with an interval of 30 sec between shocks in each case. Pretreatment of the animals with verapamil, but not propranolol, reduced the extent of cardiac necrosis after shocks of 400 J.

The cardiac damage we observed showed the essen-
tial features described by other investigators, with disruption of the orderly arrangement of myofibrils, cell death, and a predominantly mononuclear infiltrate. Metabolic abnormalities, as shown by estimation of levels of creatine kinase or NBT staining, correlated well with macroscopic delineation of the damage 3 days after the shocks. Although most of the damaged muscle lay in the thin-walled right ventricle, there was no obvious reason for this. Electrical measurements showed no lower resistance between the right ventricular cavity and the chest wall than between the left ventricular cavity and the left chest wall. Perhaps the arrangement of the lung tissue in the right thorax gives less protection to the underlying myocardium.

Shock energy was an important determinant of the severity of cardiac arrhythmias and of the extent of cardiac damage. Shocks of 100 J caused less ST segment elevation, less loss of R wave voltage over the right chest, less macroscopically damaged tissue, less depletion of creatine kinase, and less severe histologic changes than the same total energy given as shocks of 400 J. While the biggest differences were seen between the 100 J and the 400 J groups the data from the 200 J group showed changes that were generally intermediate between those in the 100 J and 400 J groups. There was significantly more macroscopic damage after 200 J than after 40 J of 100 J, and significantly less than after 10 shocks of 400 J. Precordial ST segment elevation was significantly less than in the 400 J group (at 1 hr) and significantly more than in the 100 J group (at 15 min). Compared with the 400 J group there was no statistically significant or persistent loss of R wave voltage over the precordium after the 200 J shocks. There were no significant differences with respect to depletion of creatine kinase and histologic assessment of biopsies from the lesions in the 200 J group compared with either the 400 J or 100 J groups. Biochemical and histologic examinations of the entire lesions should confirm the gross findings more precisely. However, the data from the 100 J, 200 J, and 400 J groups are consistent with the concept of increasing cardiac damage with increasing shock energy.

The increase in cardiac damage with increase in shock energy may be due to the larger currents through the chest, to the larger voltage drop across the chest and myocardial structures, or to more heating of myocardium by the larger shocks. High voltages cause breakdown of the nerve membrane and alter electrical activity in isolated myocardial cells. With myocardial cells cultured in vitro the severity of electrical and mechanical disturbance and the degree of cellular damage are related to the voltage drop across the cells. A voltage drop of 80 V/cm causes little ultrastructural change, while 200 V/cm produces marked damage to some 40% of exposed cells. In our study we observed a voltage drop across the ventricular septum of some 100 V/cm after 400 J shocks, without macroscopic damage. Larger voltage drops occurred from skin to ventricular cavity, but the proportion of these drops across the free ventricular wall was not determined.

Transthoracic high-voltage shocks could also damage cardiac nerves, causing the release of neurotransmitter. Indeed, many of the histologic changes are typical of cardiac injury by sympathomimetic drugs such as isoproterenol. However, treatment with a reasonable dose of the β-adrenoceptor blocker propranolol did not significantly reduce the loss of R waves, the extent of myocardial damage, or the creatine kinase depletion. It was of particular interest that ST segment elevation was not reduced by propranolol in view of the beneficial effects of this drug on the ST elevation of acute myocardial ischemia.

Verapamil, in a dose that transiently interfered with atrioventricular node function, reduced the extent of macroscopic damage, histologic changes, and creatine kinase depletion. However, the drug did not reduce the short-term effects on the ECG of 10 shocks of 400 J. Fifteen minutes after the shocks the ST segment elevation and loss of R waves were similar in the verapamil-treated group and in the other groups receiving 400 J shocks. Since β-adrenoceptor blockade with propranolol did not reduce the severity of damage, it may be that verapamil acts through a direct effect on the myocardium rather than by reducing secretion of norepinephrine from sympathetic nerve endings or by reducing the effects of this transmitter on the myocardial calcium flux.

There is considerable other evidence that verapamil acts to ameliorate the progress from acute damage to cell death, perhaps by reducing the influx of calcium in damaged cells. Accumulation of calcium occurs with cellular damage due to catecholamines, reperfusion after myocardial ischemia, or reperfusion with calcium-containing solutions after a period of calcium deprivation. The most convincing evidence of the adverse effects of calcium overload is seen in the last situation in which the reperfusion with calcium causes mitochondrial damage, contracture, and release of creatine kinase. Verapamil reduces the contracture after the readmission of calcium, but does not reduce enzyme release. The drug also reduces the severity of damage due to catecholamines or seen in the posterior or papillary muscle after ischemia and reperfusion.
contrast to our results, pretreatment with either verapamil or propranolol was similarly effective in reducing the accumulation of calcium and the decline in metabolic function of mitochondria in ischemic and reperfused hearts. 32 While verapamil decreased the extent of acute ST segment elevation on the ECG after coronary occlusion, 33 it did not reduce shock-induced changes in our study. Since such ST elevation tends to reflect injury currents at the margin of myocardial lesions, 34 our results suggest that the demarcation of shock-induced damage is sharp and relatively unaffected by the reduced myocardial oxygen consumption that follows administration of propranolol or verapamil. 35

When do the beneficial effects of verapamil occur? Verapamil was given before the shocks in this study. Is it acting to limit cardiac damage and perhaps calcium accumulation during the time of administration of the shocks, or is it a benefit after the shocks have been given, ameliorating a long-term change caused by the shocks? Further studies are needed to answer this question before consideration is given to a therapeutic role for verapamil in maintaining cardiac integrity after multiple defibrillations in patients.

Our results are not entirely consistent with the dose-response relationship for cardiac damage shown for single shocks by the Purdy group. 36 37 In those studies the duration of ventricular tachycardia and atrioventricular block and the extent of ST segment elevation and histologic damage increased with increasing transthoracic current from 3 to 20 A/kg. However, in our study with multiple shocks of 400 J, we found complete atrioventricular block and ECG, biochemical, and histologic evidence of cardiac damage with transthoracic currents of 2 to 2.3 A/kg. There was even some cardiac damage with currents of 1 A/kg, as with the 100 J shocks. Furthermore, the ECG changes observed in our study correlated fairly well with the extent of gross cardiac damage. While the time interval between multiple shocks is an important determinant of the extent of myocardial damage, 9 our results give further evidence of the need for the minimum effective shock energy to be used in clinical defibrillation.

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