Characterization of Refractory Period Extension by Transcardiac Shock

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Background. To better understand the refractory period extension (RPE) produced by transcardiac shocks and its possible role in defibrillation, we measured RPE under various experimental conditions.

Methods and Results. Using ventricular pacing in pentobarbital-anesthetized dogs, we characterized RPE in relation to the anatomic site of pacing, the local voltage gradient (LVG) produced by the shocks at the pacing site, and the pacing rate and pacing current used to make the measurements. We also determined if RPE persisted into the next refractory period after the shock and measured RPE at the end of 30-second episodes of acute ischemia to the pacing site, which were caused by occluding the left anterior descending artery. Each anatomic site tested showed RPE, which increased sharply with increasing LVG at lower levels but less sharply at higher LVG. The RPE versus LVG was approximated with an exponential curve that had an exponential constant of about 5–6 V/cm. At faster pacing rates, RPE occurred earlier in the refractory period but was unchanged when expressed as a percent increase of refractory period. RPE did not vary with the pacing current and was present only in the refractory period during which the shock was delivered. The RPE was not significantly altered by acute ischemia. These results show that transcardiac shocks selectively extend the refractory period of tissue proportional to the LVG and the timing of the shock in the refractory period. They are consistent with the concept that RPE prevents depolarization from tissue directly excited by a shock from propagating to tissue that was refractory to that same shock.

Conclusions. The insensitivity of RPE to short ischemic episodes and the presence of RPE at increased activation rates suggest that RPE might exist under conditions of fibrillation and be a major determinant of the success or failure of defibrillation. (Circulation 1991;83:2057–2066)

Using ventricular pacing in the experimental canine model, we have shown that timed transcardiac electrical shocks produce a nonlinear increase in the ventricular refractory period.1 This refractory period extension (RPE) becomes maximal when the shock is delivered shortly before the end of the absolute refractory period. We have postulated that this selective RPE may be an important part of the basic mechanism of defibrillation based on the following assumptions: 1) in a zone of tissue that is repolarizing after a depolarization wave front, the defibrillation shock directly depolarizes tissue that is nonrefractory; 2) in the absence of RPE, the first tissue to become nonrefractory after the shock would be the tissue that was closest to the end of its refractory period when the shock was delivered; 3) with RPE that tissue is delayed from becoming nonrefractory, producing a period of time just after the shock during which no tissue is nonrefractory; and 4) depolarization activity from the tissue directly depolarized by the shock may then fail to propagate to the tissue that was refractory to the shock because there is a sufficiently long time during which that tissue is incapable of supporting wave front propagation.

The present study was done to improve our understanding of RPE and examine it under conditions that may be operative during fibrillation and defibrillation. These experiments evaluated the RPE in terms of anatomic site, local voltage gradient (LVG), persistence into the next refractory period, altered tissue excitability after shock, dependency on basic pacing cycle length, and local ischemia. The results are consistent with the assumptions outlined above for the role of RPE in preventing depolarization from the shock from propagating to tissue that was refractory to the shock. In addition, the influence of short ischemic episodes and increased activation

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rates suggest that RPE might exist for shocks during ventricular fibrillation.

**Methods**

Each of six groups of animals was studied with a different experimental protocol. The surgical preparation was similar for all groups. The rationale for separate groups is included in the description of the protocol for each group along with any difference in experimental preparation. The basic technique to measure the RPE caused by shocks has been previously reported. A brief description of the measurement technique is given, and important changes in the technique are described in the protocol section as they are encountered. These experiments conform to the guiding principles of the American Physiological Society.

**Surgical Preparation**

Healthy adult mongrel dogs were anesthetized with sodium pentobarbital (35 mg/kg), intubated, and ventilated with room air. Arterial blood gases were monitored and adjusted throughout the experiment. The right femoral artery and vein were cannulated to measure arterial pressure and deliver fluids, respectively. The chest was opened, and a spring-patch defibrillation electrode configuration (models C10 and A67, Cardiac Pacemakers Inc., St. Paul, Minn.) was positioned, with the spring as the anode. Transcardiac shocks were delivered across these electrodes from an external cardioverter defibrillator (CPI) (model ECD, Cardiac Pacemakers Inc., St. Paul, Minn.), which was modified to provide variable leading-edge voltages and remote triggering. Shocks were monophasic truncated exponentials with a 63% tilt. Shock durations were typically 8–10 msec, but low-intensity shocks (2–4 J) were sometimes as long as 15 msec. A right atrial epicardial bipolar electrode was used for pacing at twice the diastolic threshold. An epicardial bipolar electrode on the midanterior left ventricle (except as noted) was used for ventricular pacing and measuring the ventricular refractory period (2-msec–duration pulses). The electrode was surrounded by six or eight unipolar plunge–recording electrodes (0.5–2.0 cm away) and four electrodes used to measure the LVG produced by the transcardiac shock. Unipolar electrograms were referenced to a subcutaneous stainless steel plate and filtered from 100 to 1,000 Hz, so that they recovered very quickly after a shock. After the surgical preparation, the ribs were reapproximated and the incision was covered. Lead II of the electrocardiogram, arterial pressure, and all electrograms were recorded on paper and FM tape.

**Local Voltage Gradient**

The LVG was measured from four electrodes (0.05-cm diameter) contained on the same button as the pacing electrode. These electrodes formed two bipolar pairs at 90-degree angles to each other. For groups 1 and 5, these pairs were spaced 0.3 cm apart.

For the other studies the spacing between poles was 0.425 cm, and the bipolar pairs formed an “X” across the pacing electrodes at the center of the button. An IBM PC-AT computer was used to measure the peak voltage difference across each pair during the shocks and determine the square root of the sum of the squares of the voltage difference. This value was then divided by the distance between poles to yield the magnitude of the LVG in volts per centimeter. The LVG was calibrated by a known voltage source of approximately 9 V.

**Refractory Period Extension**

The RPE was determined from refractory period measurements with and without transcardiac shocks introduced during the refractory period. The ventricular refractory period was measured with a series (usually 16) of S1 training stimuli (2 mA) delivered through the ventricular pacing electrode at a basic cycle length of 300 msec. Atrial pacing occurred simultaneously with the S1 training stimuli only. The last S1 training stimulus was followed by an S2 stimulus (2 mA) delivered through the ventricular pacing electrode. After a delay of 60–90 seconds, the stimulus train was repeated and the coupling interval of the S2 adjusted (2-msec resolution) until it did not elicit a propagated response, as determined from the electrograms of the recording electrodes surrounding the pacing site. This same measurement was made with a transcardiac shock delivered at various times after the last S1 stimulus but before the end of the refractory period. The increase in the refractory period with the shock was called the RPE. The 2-mA pacing currents (20–50-fold that of threshold) allowed pacing on the vertical portion of the strength interval curve, so that the measurement was less sensitive to changes in electrode contact or tissue excitability.

**Analysis**

All data are reported as mean±SD. All statistical data derived from paired t tests were for a difference from zero at the 0.05 level of significance.

**Group I: Refractory Period Extension Versus Anatomic Site**

In our earlier studies, the pacing electrode was always located on the midanterior left ventricle. To test if RPE was unique to this location, each of four animals (weight, 21.3±4.7 kg) was instrumented with sets of ventricular pacing and recording electrodes at four sites: the midanterior left ventricle, the left ventricular base, the right ventricular apex, and the right ventricular outflow tract. The defibrillator leading-edge voltage was set to achieve an LVG of approximately 10 V/cm at the left midanterior site. This same defibrillator energy setting was used throughout the day, and the LVG measurement was determined for each of the four sites. At each site, the refractory periods were measured without shocks with 2- and 5-mA S2 stimuli and 60-second delays between series of training stimuli. The refractory
period was then measured with a 2-mA S2 stimulus, with transcardiac shocks introduced at 10, 60, 110, and 120 msec after the last S1 stimulus. After a 15-minute recovery period, the measurements were repeated at a different site in random order.

**Group II: Refractory Period Extension Versus Local Voltage Gradient**

On the basis of our previous work, it was determined that the amount of RPE varied with shock energy. Others have found that tissue responses to electric stimulation and outcome after shock depend on the LVG. Thus, we examined the quantitative relation between RPE and LVG.

In four animals (weight, 23.5±2.4 kg) the defibrillator energy was adjusted to vary the LVG at the pacing site, and measurements of the refractory period were made. All measurements for an energy setting were completed before a new energy setting was selected. Control refractory period measurements and measurements of LVG, RPE, and the leading-edge shock voltage were repeated at an average of nine different energies (range, 1–30 J). Energies were selected starting near 10 J and then varied to cover a range of RPEs working toward lower energies. Energies of 15 and then 30 J were usually tested last for each animal. At each energy level, refractory periods were measured first with a 5-mA S2 and no shocks to determine the absolute refractory period (ARP). Refractory periods were then measured with a 2-mA S2, with shocks delivered 10 msec after the last S1 and 75 and 25 msec before the ARP.

**Group III: Strength Interval Curve After Shock**

In four animals (weight, 17.5±1.5 kg), we tested the possibility that the RPE resulted from a transient alteration in tissue excitability after the shock. With a transient reduction of excitability, the S2 pacing stimulus might require a longer coupling interval and/or higher current to evoke a response, thus appearing to be RPE. In this group, we measured the strength interval curve for the S2 stimulus with and without transcardiac shocks (LVG, 6 V/cm) delivered 25 msec before the ARP. Pacing (basic cycle length, 300 msec) was delivered through a unipolar (cathodal) electrode, with remote electrodes sutured to the myocardium 3–4 cm away. At the beginning of the experiment, the strength interval curve was measured with 12 strengths (0.2–7.5 mA) in random order. The curve was repeated, and at each strength the coupling interval was determined with and without transcardiac shocks (random order). The ARP was determined with a 5-mA S2 approximately six times during the experiment so that the shocks could be timed relative to it.

**Group IV: Duration of Refractory Period Extension Beyond S2 Stimulus**

The increased refractory period after the transcardiac shocks may represent a resetting of the tissue’s repolarization timing, or it may represent some alteration of tissue properties that caused the repolarization to proceed at a different rate. If the latter were the case, then recovery from the alteration in refractory period might continue for several beats after the shock. In this group of four animals (weight, 16.6±0.3 kg), we examined the refractory period after the S2 stimulus to see if it was also extended by a shock that caused RPE.

The stimulus timing for group 4 is presented diagrammatically in Figure 1. First, the refractory period after the last S1 stimulus (RP1) was measured with an S2 stimulus as shown in Figure 1A. The S2 was moved to a predetermined diastolic interval after RP1, and the refractory period after the S2 stimulus (RP2) was measured with an S3 stimulus (Figure 1B). Next, the refractory period after the last S1 was remeasured, with a 5 V/cm shock included 25 msec before RP1 to determine the extended refractory period (RP1e) as shown in Figure 1C. Then the S2 was delivered to allow the same diastolic interval after RP1e, and the refractory period after the S2 was remeasured (RP2e) as shown in Figure 1D. The measurements of RP1, RP2, RP1e, and RP2e were repeated with a 10-V/cm shock. All eight measurements were repeated with diastolic intervals of 5, 10, 15, 20, 30, 60, and 120 msec in increasing order. All ventricular pacing used 2-msec, 2-mA stimuli at a basic cycle length of 300 msec with a 60-second delay between series of training stimuli.

**Group V: Effect of Basic Cycle Length on Refractory Period Extension**

In the previous work, measurements of RPE were performed with ventricular pacing at 200 beats/min. During ventricular fibrillation, cellular activations are much more rapid in the range of 600–800 beats/min in dogs and 300–400 beats/min in humans. For RPE by transcardiac shocks to play an important role in the defibrillation, it must exist at these higher activation rates.
In this group of four animals (weight, 18.4±0.7 kg), the RPE was measured at basic cycle lengths of 500, 300, and 200 msec to determine if RPE was altered by basic cycle length. A median sternotomy was used and the sinus node crushed. When testing was not being performed, atrial pacing at a basic cycle length of approximately 350 msec was used to maintain blood pressure. At the beginning of the experiment, a strength interval curve was measured for the S2 stimulus with a basic cycle length of 300 msec and a 2-second delay between series of training stimuli. The refractory period after the last S1 was then measured at a basic cycle length of 500 msec with an S2 stimulus (2 mA) and a 2-second delay between series of training stimuli. It was then remeasured with a 60-second delay, with transcardiac shocks included at various times after the last S1. The shock leading-edge voltage was adjusted to provide an LVG of approximately 10 V/cm at the pacing site. Shocks were initially delivered 10 msec after the last S1. Other shock timings were 130, 140, 150, 160, 120, 110, 100, 90, and 60 msec in the order shown. After the measurements were completed for a 500-msec basic cycle length, they were repeated with basic cycle lengths of 300 and 200 msec.

**Group VI: Effect of Acute Ischemia**

Even if fibrillation were detected almost immediately, as with an automated implantable cardioverter/defibrillator (AICD®, CPI) (Cardiac Pacemakers Inc., St. Paul, Minn.), the heart would still have a brief period of ischemia for approximately 15–30 seconds before the shock. In this group of six animals (weight, 17.8±1.2 kg), we measured the influence of acute 30-second ischemic episodes on RPE to mimic the loss of blood flow during fibrillation. The left anterior descending coronary artery was isolated near its origin and occluded for 30 seconds. The area of reduced blood flow was noted by its surface discoloration, and the measurement electrodes were positioned in the center of the discolored area. At the end of the day, the location of the tissue perfused by the occluded artery was verified with a dye (methylene blue) injection into the occluded artery. Control (nonischemic) measurements of RPE were obtained on the right ventricle near the outflow tract.

Initially, three to six shocks were delivered 10 msec after the last S1 during pacing at the left ventricular site, while the shock intensity was adjusted to approximately 6 V/cm. This procedure was repeated at the right ventricular site. On both the left and right ventricles, the tissue refractory period was measured first without and then with transeardiac shocks. These measurements were then repeated with the training stimuli and shocks occurring at the end of 30-second occlusions. A delay of 60–90 seconds occurred between occlusions. The shock was introduced 25 msec before the end of the refractory period measured without the shock. If necessary, the shock intensity and timing were adjusted to produce a measurable RPE without occlusions. The same

<table>
<thead>
<tr>
<th>Site</th>
<th>LV midanterior</th>
<th>LV base</th>
<th>RV apex</th>
<th>RV outflow</th>
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<tr>
<td>No shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP at 5 mA</td>
<td>138±10</td>
<td>136±12</td>
<td>135±11</td>
<td>134±10</td>
</tr>
<tr>
<td>RP at 2 mA</td>
<td>143±15</td>
<td>138±12</td>
<td>135±11</td>
<td>135±11</td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVG (V/cm)</td>
<td>10±2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP with shock</td>
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<td></td>
<td></td>
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<tr>
<td>at (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>140±8</td>
<td>138±13</td>
<td>139±14</td>
<td>137±11</td>
</tr>
<tr>
<td>60</td>
<td>140±8</td>
<td>140±14</td>
<td>143±15</td>
<td>136±10</td>
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<td>150±14</td>
<td>167±19</td>
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<td>146±10</td>
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<tr>
<td>120</td>
<td>163±14</td>
<td>184±23</td>
<td>181±12</td>
<td>163±10</td>
</tr>
</tbody>
</table>

All values are mean±SD. Data are from four animals. LV, left ventricular; RV, right ventricular; LVG, local voltage gradient produced by shock at measurement site; RP, refractory period (msec) as measured with 2 or 5 mA S2 stimulus, with 60 seconds between series of S1 training stimuli at basic cycle length of 294±12 msec. Shocks were delivered 10 to 120 msec after last S1. *Paired difference from RP at 10 msec significantly (p<0.05) different from zero.

†Voltage field was too large to measure.

**Results**

**Group I Results: Refractory Period Extension Versus Anatomic Site**

The results from the group I animals are displayed in Table 1. The results show that RPE does occur at different sites on the heart and is not unique to the midanterior left ventricle. The refractory period extension was statistically significant at the right ventricular apex, right ventricular outflow, and left ventricular base sites. The 120-msec measurements at the left ventricular midanterior and base sites just failed to reach significance (p<0.05) because measurements in one animal could not be made due to the onset of fibrillation by the shocks.

These results confirm that the same shock produced different voltage gradients at different locations. The sites with higher LVGs showed more RPE. Also, at all sites the refractory periods are extended more if the shocks are given later after the last S1. These same characteristics were found in the earlier study.¹ Note that the refractory periods when shocks were delivered 10 msec after the last S1 are very similar (difference, 0±4 msec) to those measured with a 2-mA S2 stimulus without the shock but with a 60-second delay between series of S1 training stimuli.

**Group II Results: Refractory Period Extension Versus Local Voltage Gradient**

The results of group II are presented in Figures 2 and 3. Figure 2 shows the relation between the leading-edge voltage from the defibrillator and the LVG measured at the pacing site. Each curve shows...
FIGURE 2. Local voltage gradient produced at pacing site by transcardiac shocks versus shock’s leading edge voltage. Shocks are monophasic truncated exponentials with 63% tilt. Data are from four animals (weights shown).

the data from a different animal. Note that the curve for animal 1 (closed circles) is distinctly different from the other curves. The weight of animal 1 was larger than the other animals, but the placement of the defibrillation electrodes and the measurement site were the same. However, the local voltage intensity for the same leading-edge shock voltage was different for animal 1, indicating that the current was distributed differently over the heart such that the measurement site was in a relatively lower-intensity area. This variation demonstrates the importance of measuring an LVG because the leading-edge shock voltage cannot be relied on to control the intensity at the measurement site.

Figure 3 shows the RPE versus LVGs for each animal. Each of the four symbol types is for a different animal. Closed symbols represent transcardiac shocks given 25 msec before the ARP and open symbols shocks given 75 msec before the ARP. In each case, RPE is computed as the refractory period with the shock minus the refractory period with the same shock delivered 10 msec after the last S1. For the 25-msec timing before the ARP, the RPE was strongly related to the LVG. The RPE increased sharply with increasing LVG and then less sharply at higher LVGs. For the 75-msec timing before ARP, RPE was small at all LVGs. The average ARP was 139±6 msec, and average refractory period when shocks were introduced 10 msec after the last S1 was 139±7 msec (difference, 0±2 msec). All pacing was delivered at a 300-msec basic cycle length.

Group III Results: Strength Interval Curve After Shock

The strength interval curves for the S2 pacing stimuli given after shocks are shown in Figure 4. The pacing threshold current was 0.08±0.01 mA, and all S1 pacing stimuli were at 0.2 mA (basic cycle length, 298±5 msec). Figure 4 shows that RPE resulting from the shocks (6 V/cm, 25 msec before ARP) is about the same at all S2 pacing currents. The average paired difference of refractory periods with and without shocks was 24±7 msec (p<0.0005). Note that the “No Shocks” curve is consistently below (9±2 msec, p<0.005) the “Control” curve measured at the beginning of the experiment before the animal

FIGURE 3. Refractory period extension at pacing site versus local voltage gradient produced by shock. Shocks were introduced 25 msec (closed symbols) or 75 msec (open symbols) before tissue absolute refractory period (139±6 msec). Each symbol type represents one of four animals.

FIGURE 4. S1–S2 coupling interval required to evoke response versus S2 stimulus intensity. Control curve (•) was measured before animal received any shocks. Shocks (○) and No Shocks (□) curves were measured as pairs (random order) with and without transcardiac shocks (6 V/cm) delivered 25 msec before absolute refractory period. Mean±SD from four animals are shown. For Control curve, SD (not shown) was typically 10 msec.
TABLE 2. Effect of Transcardiac Shock on Refractory Periods After Last S1 Stimulus and S2 Stimuli

<table>
<thead>
<tr>
<th>LVG (V/cm)</th>
<th>5.2±0.2</th>
<th>10.1±0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 (msec)</td>
<td>RPE1</td>
<td>RPE2</td>
</tr>
<tr>
<td>5</td>
<td>19±11</td>
<td>7±14</td>
</tr>
<tr>
<td>10</td>
<td>18±9</td>
<td>3±4</td>
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<tr>
<td>15</td>
<td>19±6</td>
<td>4±6</td>
</tr>
<tr>
<td>20</td>
<td>15±8</td>
<td>1±2</td>
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<tr>
<td>30</td>
<td>16±6</td>
<td>−7±4</td>
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<td>60</td>
<td>14±8</td>
<td>−5±4</td>
</tr>
<tr>
<td>120</td>
<td>14±7</td>
<td>−1±2</td>
</tr>
</tbody>
</table>

All values are mean±SD. Data from four animals at 300-msec basic cycle length.

LVG, local voltage gradient produced by transcardiac shock at measurement site; D1, diastolic interval before S2 stimulus; RPE1, extension of refractory period after last S1 caused by shock delivered 25 msec before end of refractory period; RPE2, extension of refractory period after S2 stimulus caused by same shock. *Significantly (p<0.05) different from zero.

had received any shocks. The average of ARP measurements made during the experiment (133±9 msec) was similarly reduced from the 5-mA measurements on the control curve (140±10 msec).

Group IV Results: Duration of Refractory Period Extension Beyond S2 Stimuli

The group IV results are summarized in Table 2. The average across all diastolic interval trials shows that shocks given 25 msec before the ARP that produced 5.2±0.2 or 10.1±0.2 V/cm LVGs caused, respectively, 16±7 msec and 29±6 msec of RPE after the last S1 (RPE1, RP1e−RP1). The effect of these same shocks on the refractory period after the S2 (RPE2, RP2e−RP2) was 0±7 and 0±4 msec, respectively. However, RPE2 showed a dependence on the diastolic interval. When the S2 was delivered long after the shock (diastolic interval, 120 msec), that shock’s effect on the refractory period after the S2 (RPE2) approached zero. At intermediate times after the shock (diastolic interval, 20–60 msec), RPE2 seemed slightly negative, reaching statistical significance in several cases. At shorter times (diastolic interval, 5–15 msec), RPE2 seemed slightly positive.

Without shocks the refractory period after the S2 strongly depended on the diastolic interval, decreasing by 26 msec from 136±3 msec to 110±3 msec for diastolic intervals of 120 msec and 10 msec, respectively. When compared with the RPE caused by the shocks (RPE1) and to the amount of RP2 changes with the diastolic interval alone, the maximum RPE2 caused by the shocks (±7 msec) is small.

Group V Results: Basic Cycle Length

The results of the group V animals are shown in Figure 5, which plots the refractory periods after the last S1 stimulus against the time after the last S1 at which the shock was delivered. With longer basic cycle lengths, the refractory periods are greater. As the basic cycle length is decreased, the curves in

![Figure 5. Effect of basic cycle length on extension of refractory period after last S1 caused by transcardiac shock. Shocks were delivered at fixed times after last S1 and produced local voltage gradients of 10.6±0.9 V/cm. Measurements were repeated at basic cycle lengths of 500 (○), 300 (□), and 200 (△) msec. S1 and S2 pacing was 2 mA, with 60 seconds between series of S1 training stimuli. Symbols connected by lines show average of data contained in all four animals. Symbols without lines show average data in two or more animals.](http://circ.ahajournals.org/)

Figure 5 rise more sharply and break closer to the left. The strength interval curve measured at the beginning of the day was vertical for currents of 1 mA or greater. Thus, the 2-mA S2 stimulus used to measure refractory periods was well into the vertical portion of the curve. With a 2-second delay between series of training stimuli, the refractory periods were 146±4, 130±4, and 117±2 msec for basic cycle lengths of 500, 300, and 200 msec, respectively. With a 60-second delay, the refractory periods with shocks delivered 10 msec after the last S1 were 160±11, 149±8, and 134±6 msec, respectively.

Group VI Results: Effect of Acute Ischemia

Table 3 shows the influence of 30-second acute occlusions on the RPE produced by transcardiac shock. In the absence of occlusions, RPE occurred at both the left and right ventricular pacing sites. The LVGs and shock timing were similar for control and occlusion measurements on both sides.

On the right side the measurement site was not in the occluded zone, and the RPE was not significantly changed by the ischemic episodes (23±13 msec after occlusion versus 22±10 msec in control). On the left side the measurement site was in the occluded zone, and the RPE was also not significantly altered by the ischemic episode (19±12 msec after occlusion versus 23±17 msec in control).
TABLE 3. Effect of 30-Second Occlusion on Refractory Period Extension by Transcardiac Shock

<table>
<thead>
<tr>
<th></th>
<th>Left ventricle</th>
<th></th>
<th>Right ventricle</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Occlusion</td>
<td>Control</td>
<td>Occlusion</td>
</tr>
<tr>
<td>LVG (V/cm)</td>
<td>8.8±3.5</td>
<td>8.9±3.6</td>
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<tr>
<td>Timing (msec)</td>
<td>−28±3</td>
<td>−28±3</td>
<td>−28±5</td>
<td>−26±5</td>
</tr>
<tr>
<td>RP (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No shock</td>
<td>147±16</td>
<td>148±18</td>
<td>134±11</td>
<td>134±14</td>
</tr>
<tr>
<td>Shock</td>
<td>170±27</td>
<td>167±23</td>
<td>155±19</td>
<td>157±24</td>
</tr>
<tr>
<td>RPE (msec)</td>
<td>23±17</td>
<td>19±12</td>
<td>22±10</td>
<td>23±13</td>
</tr>
<tr>
<td>Change (msec)</td>
<td>−4±15</td>
<td>1±4</td>
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</tr>
</tbody>
</table>

All values are mean±SD. Data are from six animals. Left ventricular pacing site was in occluded area.

LVG, local voltage gradient produced by shock at pacing site. Timing, when shock was delivered before end of RP; RP, refractory periods after last S1s were measured with (Shock) and without (No shock) transcardiac shocks and with (Occlusion) and without (Control) 30-second acute occlusions of the left anterior descending coronary artery; RPE, difference between Shock and No-shock values; Change, RPE difference between occlusion and control.

Discussion

Collectively, the data from these six studies outline basic characteristics of RPE by transcardiac shocks. The results suggest that RPE is a very transient rescheduling of the tissue repolarization process, which is consistent with the idea that it may result from a local graded response\textsuperscript{10,11} of the cells to the shock stimulus. The results show that RPE is confined to the repolarization in which the shock is delivered; that RPE depends on the LVG produced by the shock and its timing in the repolarization process, and it is not caused by a transient change in tissue excitability. The variation of RPE with basic cycle length and its insensitivity to episodes of acute ischemia also suggest that it may exist in at least the early stages of ventricular fibrillation. These characteristics lend support to the concept that RPE may play a very important role in the mechanism of ventricular defibrillation. However, its existence during ventricular fibrillation and its role in defibrillation remain to be demonstrated.

Group I demonstrates that the phenomenon occurs at different locations in the heart. Because the choice of the sites to test was arbitrary, we may expect that all epicardial sites would show RPE. It remains to be shown that RPE occurs at sites other than on the epicardium. Group I also demonstrates that a single shock may produce different amounts of RPE at different locations. Because the LVG produced by the same shock showed a concomitant variation with location, this finding is consistent with the hypothesis that the RPE depends on the LVG produced by the shock.

The results of group II directly demonstrate a relation between RPE and LVG and confirm the earlier findings\textsuperscript{1} that the RPE increases with the shock’s proximity to the end of the refractory period. By general inspection of the data in Figure 3, it seems that the RPE in each animal starts near zero at zero LVG, rapidly increases with increasing LVG, and then increases less rapidly at larger LVGs. This observation suggests the following form to express RPE in terms of the LVG:

\[
RPE = RPE_{max} \times [1 - \exp(-LVG/K_v)]
\]  

where RPE is the refractory period extension, RPE\textsubscript{max} is a maximum RPE for shocks delivered with the 25-msec timing before the end of the refractory period, LVG is the local voltage gradient, and Kv is an exponential constant relating LVG and RPE. This relation was used to find the values of RPE\textsubscript{max} and Kv that best predicted the data obtained from group II, as determined by the minimum square error. The values RPE\textsubscript{max}=42.2 msec and Kv=5.65 V/cm produced the best least-squares fit against the data. This relation is plotted in Figure 6, along with the 25-msec data from group II. The RPEs for the 75-msec data were too small in comparison with their variation to perform a similar fit. But if the same constant (Kv=5.65 V/cm) is used, then the RPE\textsubscript{max} leading to a best fit for the 75-msec data is 6.8 msec. Although Equation 1 provides insight into the dependency of RPE on the LVG, it is based on a small number of animals. Furthermore, we do not know how the data are affected by other factors that might influence RPE. Thus, Equation 1 requires prospective verification.

Group III shows that the RPE does not depend on the intensity of the placing current used to make the measurement. If RPE resulted from a transient change in excitability, then changing the S2 currents would have affected the measurement. Transcardiac shocks have been reported to alter the electrophysiology of cardiac tissue, including its excitability.\textsuperscript{12–16} Much of the research on this topic concerns long-term or histological changes caused by the shock, but some studies have examined reversible changes occurring seconds to minutes after the shock. It may be that the measurement of RPE occurs so quickly after the shock that these changes in excitability are not important.

The results of group IV demonstrate that although the shocks may have some slight influence on the refractory period of the premature beat, the RPE is essentially restricted to the refractory period in which the shock is delivered. This finding is consistent with the results of group III in that the shock does not seem to alter the properties of the tissue (i.e., excitability or refractory period) for the next beat. This finding suggests that RPE relates to a rescheduling of the normal cellular repolarization process rather than some change in the tissue itself, which is consistent with the concept that RPE is a macroscopic manifestation of a graded depolarization response\textsuperscript{10,11} found in cellular recordings when stimuli are delivered early in repolarization.

From the group V results in Figure 5, it seems that at faster pacing rates (shorter cycle lengths) RPE
occurs earlier after the last S1 pacing stimuli. Because the refractory periods are shorter at the faster pacing rates, this observation is consistent with the concept that the timing of the shock in relation to the end of the tissue refractory period is more important than its timing after the last S1. In addition, we noted that the slope of RPE curves seemed sharper at faster pacing rates. This observation suggested that the RPE varied with the shock timing in the refractory period rather than with the absolute time before the end of the refractory period. Thus, to compare the RPE at the different basic cycle lengths, the shock timing was expressed as a percentage of the tissue refractory period measured when a shock was delivered 10 msec after the last S1 (RP10). Similarly, RPE was computed by subtracting RP10 from the refractory periods with a shock at other timings. In preliminary studies that used class III drugs to extend the tissue refractory period, the RPE seemed to change proportionally with the tissue refractory period. Thus, RPE is expressed as a similar percentage.

The results of these computations are plotted in Figure 7. The data in Figure 7 cluster along an exponential curve. Thus, the following equation expresses an empirical relation:

\[ \text{RPE/RP10} = \text{Km} \times \exp\left(-\text{Kt} \times (1 - \text{Time}/\text{RP10})\right) \]  (2)

where RPE/RP10 is the normalized RPE, Km and Kt are empirical constants describing the magnitude and time constant of the response, and Time/RP10 is the normalized shock timing. This relation was used to find the values for Km and Kt that led to the smallest least-squares error in predicting the data. They were Km=0.376 and Kt=5.68. This best-fit curve is plotted as the solid line in Figure 7. As with Equation 1, Equation 2 provides insight into the dependency of RPE on shock timing but is based on a small number of animals and without knowledge of the influence of other factors that might influence RPE. Thus, Equation 2 also requires prospective verification.

In Figure 7, the data measured at different basic cycle lengths collapsed on the same curve. Fibrillation has cycle lengths of 100 msec in dogs and 150–200 msec in humans. The finding that the data from cycle lengths of 500, 300, and 200 msec fall on the same curve suggests that the data at fibrillatory cycle lengths might also fall on that curve if those measurements were possible. Although this result is not evidence that RPE exists at higher activation rates, it shows that it changes with cycle length in a characteristic manner that would predict RPE at fibrillatory cycle lengths.

The results of group VI are also important with fibrillation, which show that the acute 30-second ischemic episodes have no significant effect on RPE. At the right ventricular pacing site, the measurement of RPE was unchanged by the 30-second ischemic episodes. Because the right ventricular site was not in the occluded area, it indicates that the whole-animal response to the ischemic episodes was not changing the RPE. The 30-second occlusions also had no significant effect at the left ventricular site that was in the ischemic zone. These data show that the short periods without blood flow do not prevent RPE by electric shock and support the hypothesis that RPE may exist during fibrillation.
Measurement of Refractory Period Extension

From the above results, we better understand the RPE phenomenon. Because RPE changes with both cycle length and local shock intensity, both of these factors must be controlled to make accurate measurements of RPE. As seen in Figure 6, the LVG is an adequate measure of the local shock intensity. To control the timing of the shock, an unambiguous measure of the end of the refractory period is necessary. The refractory period obtained with a shock delivered at 10 msec after the last S1 (RP10) seems suitable for this purpose. A tissue ARP measured at 2 or 5 mA is also suitable for this purpose, provided the time between series of training stimuli is sufficiently long. As seen in group III, the measure of tissue ARP might be different after shocks are given to an animal, so frequent measures are needed to ensure accurate shock timing. The choice of pacing current to make the measurement does not seem critical. Smaller currents lead to somewhat larger refractory period measurements (Figure 4), but the RPE was about the same at all currents.

The determination of RPE to within 2 msec could usually be made by delivering two to four shocks. For example, in group V the average number of shocks required to measure RPE was 3.6±1.4 (range, two to nine) shocks per measurement. In a preliminary study used for group V protocol development, the average number of shocks per measurement was 4.6±1.8, indicating that increased experience led to fewer shocks, probably because the range of timings to test could be better anticipated.

We did not explicitly test whether the shocks had a cumulative influence on the RPE measurements. As noted earlier, delivering shocks to the animals was associated with a decline in the tissue refractory period from its value before shocks were delivered. From the group IV results (Table 2), we note that RP1 and RPE1 measurements for the different diastolic intervals were repeated for each of the seven diastolic intervals. Because the values for RP1 and RPE1 do not directly depend on the diastolic interval, they could be viewed as repeated measurements over the course of the experiment. By a linear regression analysis and testing \((p<0.05)\) for a slope equal to zero, the data (averages of four animals) for RP1 and RPE1 showed slight but statistically significant trends toward smaller values over the course of...
the experiment. It is not known if this trend was caused by the cumulative effect of the shocks or some deterioration of the preparation over time.

An assessment of the repeatability of the RPE measurement might also be obtained from repeated RPE1 measurements made throughout the day in group IV animals. The SD of the seven repeated RPE1 measurements made in the same animal was typically 3 msec for the group IV animals.

The measurements of RPE require a long delay (60–90 seconds) between series of pacing stimuli to allow time for recovery from the shock. As seen in other studies, the refractory period measurement depends on the delay between series of training stimuli and may result from the difference between the animal’s natural rate and that of the pacing. This difference is very apparent in group V, as can be seen by comparing the refractory periods measured with a 2-second delay between series of training stimuli with the RP10s that were measured with a 60-second delay. The RP10s were approximately 16 msec longer. Thus, to compute RPE it is important to make the refractory period measurements with these longer delays even when no shocks are delivered.

In conclusion, this work demonstrated that the RPE caused by transcardiac shocks existed in all animals and at all epicardial sites tested. It also demonstrated that transcardiac shock did not substantially alter the refractory period of the next activation after the shock. The RPE was not caused by a transient alteration of the strength interval relation for tissue because the same extension was measured with a wide range of pacing strengths. The amount of RPE varied in a predictable manner with the LVG produced in the tissue by the transcardiac shock, with the tissue ARP, and with the timing of the shock before the ARP. When the RPE and the shock timing were expressed as percentages of the ARP, the resulting relation between them did not depend on the basic cycle length used to make the measurements over the range of basic cycle lengths tested (200–500 msec). In addition, the RPE measurement was not significantly altered by 30-second episodes of acute ischemia to the tissue produced by occlusion.

Although this study was performed with ventricular pacing, the variation of RPE with pacing rate and its insensitivity to brief ischemia would suggest that it may exist during defibrillation. In that regard the results provide an insight into defibrillation, providing a possible connection between defibrillation requirements and the electrophysiological state of the tissue during fibrillation.

References


KEY WORDS • refractoriness • ventricular defibrillation, mechanism of • ventricular fibrillation
Characterization of refractory period extension by transcardiac shock.
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