Comparison of the defibrillation threshold and the upper limit of ventricular vulnerability

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ABSTRACT To examine the relationship between the defibrillation threshold and the strength of shocks that induce ventricular fibrillation during the vulnerable period, we determined the defibrillation threshold in 22 open-chest dogs using epicardial defibrillation electrodes with the cathode at the ventricular apex and the anode at the right atrium. We also determined whether there was an upper limit of shock strength that induces fibrillation in the vulnerable period by giving shocks of various energy through these same electrodes during the repolarization phase of paced rhythm. The above determinations were also made with the anode at the ventricular apex and the cathode at the right atrium in eight of the dogs and with the cathode at the ventricular apex and the anode at the left atrium in another eight of the dogs. In all dogs for all electrode configurations, there was an upper limit to the shock strength that induced ventricular fibrillation during the vulnerable period. Depending on the electrode combination, this upper limit of ventricular vulnerability either was not significantly different from or was slightly lower than the defibrillation threshold. The correlation coefficient between the two was highly significant for all three electrode configurations. These results support the hypothesis that successful defibrillation with epicardial electrodes requires a shock strength that reaches or exceeds the upper limit of ventricular vulnerability and that shocks slightly lower than the defibrillation threshold fail because they reinstantiate ventricular fibrillation by stimulating portions of the myocardium during their vulnerable period.

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UNTIL RECENTLY, the accepted hypothesis for the mechanism of ventricular defibrillation was based on studies indicating that a critical mass of myocardium is necessary for the maintenance of fibrillation. It was thought that a shock causes defibrillation when it extinguishes activation fronts within a critical mass of myocardium by depolarizing all nonrefractory tissue within the critical mass. We found that the critical mass requirement is not sufficient to ensure defibrillation; unsuccessful defibrillation shocks of at least 1 J applied to the epicardium extinguished all epicardial, septal, and endocardial activations for 64 ± 22 msec (mean ± SD) yet failed to defibrillate because ventricular fibrillation was reinitiated after the shock. Since activation occurs continuously during fibrillation, repolarization also should occur continuously. Thus a defibrillation stimulus will always occur when some portion of the myocardium is repolarizing. A stimulus can induce fibrillation if given during the vulnerable period of repolarization. These findings suggest the hypothesis that unsuccessful epicardial shocks of at least 1 J halt fibrillation and then reinitiate it by stimulating myocardium that is in the vulnerable period of repolarization. The hypothesis implies that there is an upper limit of strength above which a shock will not induce fibrillation during the vulnerable period and that this upper limit of ventricular vulnerability should correlate with the defibrillation threshold. The purpose of this study is to test these implications.

Methods

Twenty-two mongrel dogs (mean weight ± SD, 18.9 ± 3.4 kg) were anesthetized with pentobarbital (30 to 35 mg/kg) and succinylcholine (1 mg/kg). Each was intubated with a cuffed endotracheal tube and ventilated with 30% to 60% oxygen through a Harvard respirator. Ringer’s lactate was continuously infused and supplemented with potassium chloride, sodium bicarbonate, and calcium chloride when indicated. Via a separate intravenous line, pentobarbital was infused at a rate of roughly 1 mg/min throughout the experiment to achieve ade-
quate anesthesia. The dose of pentobarbital was adjusted according to the depth of anesthesia assessed by signs such as shivering, eyelid reflexes, and pedal reflexes. * Succinylcholine at a bolus dose of 0.25 to 0.5 mg/kg was given no more than once per hour to decrease muscle contraction induced by the electric shock. This dose is much less than that required to cause significant changes in cardiac excitability. An arterial line was inserted into the femoral artery, and the systemic blood pressure was continuously displayed on an oscilloscope. Blood was withdrawn to determine the pH, PO₂, PCO₂, base excess, CO₂ content, and bicarbonate, sodium, potassium, and calcium concentrations. Normal metabolic status was maintained throughout the study by taking blood samples every 30 to 60 min and correcting any abnormal value.

The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. The sinoatrial node was crushed and the heart was paced from the right ventricular epicardium at rate of 150 beats/min. A pair of sensing wires was inserted 1 to 2 cm away from the right ventricular pacing wires so that shocks could be given at a predetermined interval after the last sensed depolarization. Truncated exponential defibrillation shocks of 5 msec duration and 7% tilt were generated by a special device built by Intermedics, Inc. This device was used both to induce fibrillation and to defibrillate. Round titanium patch electrodes, 4.5 cm² in area, were secured to the epicardium to form different electrode combinations. To determine the impedance for each electrode combination, the defibrillator was charged to 100 V and a shock was given 300 msec after the last sensed depolarization. The actual voltage and current delivered during this shock were displayed simultaneously on a separate oscilloscope. The value at the leading and trailing edges of the voltage and current waveforms were averaged and the means were used to represent the voltage and current of that shock. The impedance from this shock was then calculated and used to predict the voltage needed for the next shock during the study. The actual voltage and current of each subsequent shock, including those used to induce fibrillation and to defibrillate, were measured by the same method, and the impedances were calculated for each shock.

In all 22 dogs, titanium patch electrodes were secured to the right atrium and ventricular apex. Defibrillation shocks were given with the right atrium as anode and the ventricular apex as cathode (RA.V combination). The first six dogs were used to examine the reproducibility of the technique for RA.V combination. All measurements were repeated, and the results of the first and second determinations were compared. To examine the relationship of defibrillation and vulnerability in a different electrode combination with a higher defibrillation threshold, a titanium patch electrode was secured to the left atrium in eight of the 22 dogs. Defibrillation shocks were given with the left atrium as anode and the ventricular apex as cathode (L.A.V combination) as well as through the RA.V combination. The sequence of testing the RA.V combination and the L.A.V combination was alternated in each subsequent study. In another eight of the 22 dogs, defibrillation shocks were also given with the ventricular apex as anode and the right atrium as cathode (V.R.A combination) to study the effect of reversed polarity. The sequence of testing the RA.V combination and the V.R.A combination was also alternated in each subsequent study.

The ventricular fibrillation threshold was determined by first scanning electrical diastole with a 0.01 J stimulus delivered through the defibrillation electrodes. The scanning was conducted in 5 msec increments, starting at the end of QRS wave and stopping past the initial part of TQ segment, with an interval of 10 sec between stimuli. In all experiments, the scanning at least covered the period between 50 to 220 msec after the last sensed R wave. If fibrillation was not induced by the 0.01 J stimulus, the stimulus intensity was increased to 0.02, 0.05, and 0.1 J and then increased in 0.1 J increments until fibrillation was induced. If the voltage of stimulation that induced fibrillation was more than 3 V greater than the next lower stimulus intensity that failed to induce fibrillation, scanning was repeated with the stimulus strength 3 V above the latter. The smallest stimulus that induced fibrillation was called the fibrillation threshold.

Stimulus strength was then increased to 2 J, and electrical diastole was scanned starting 30 msec earlier and ending 30 msec later than the interval that induced ventricular fibrillation at the fibrillation threshold. Until fibrillation was induced. There was a 30 to 60 sec pause between stimuli. The energy was increased 2 J at a time until fibrillation was no longer inducible. If the interval that last induced ventricular fibrillation was at the extremes of the intervals that were scanned, additional 30 msec was scanned beyond the extremes of the previous scanning interval to ensure that ventricular fibrillation was indeed not inducible at this energy level. If this energy was more than 10% higher than the energy that last induced fibrillation, the energy was decreased 10% at a time until fibrillation was again induced by scanning. The highest energy that induced fibrillation was defined as the upper limit of ventricular vulnerability. In the eight dogs in which both the RA.V and V.R.A combinations were tested, the highest energy that did not induce ventricular fibrillation was used to scan the whole interval in 5 msec steps from the late QRS wave to the initial TQ segment, including as a result the interval from 50 to 220 msec after the last sensed depolarization, to ensure that ventricular fibrillation was not inducible at other coupling intervals. If atrial arrhythmias were induced during the protocol, the study was interrupted until the rhythm was converted spontaneously or by cardioversion. The study was resumed when stable ventricular pacing was again achieved.

The protocol of Bourland et al. was followed for the determination of defibrillation threshold. Only the first shock of a defibrillation attempt was considered for measurement. Defibrillation shocks were given 20 sec after the onset of fibrillation induced by scanning the vulnerable period to determine the lower and upper limits of ventricular vulnerability. The voltage and current of the shock were recorded on an oscilloscope, and the delivered energy was calculated as their product multiplied by shock duration (0.005 sec). If the shock was unsuccessful, defibrillation was achieved within 30 sec with a higher energy shock delivered through the same electrode combination. There was a 5 to 10 min interval between fibrillation episodes to avoid altering ventricular vulnerability and excitability or defibrillation threshold. The first shock was given with a predicted energy of 4 J. Shock strength was then increased 20% during each successive episode of fibrillation until defibrillation was achieved. The energy level was then decreased 10% for each successive episode. The energy of the last successful shock was called the defibrillation threshold energy.

The fibrillation threshold, upper limit of vulnerability, and defibrillation threshold were expressed per gram of heart weight. In the first six dogs, the fibrillation threshold, the upper limit of vulnerability, and the defibrillation threshold were all determined twice and the two values were compared by the paired t test. For these six dogs, one of the two sets of data was randomly chosen to be included with the data from the other 16 dogs. Correlation coefficients were calculated between these three variables and between these variables and impedance. To compare different electrode combinations, paired t tests were used in the eight dogs with both RA.V and L.A.V combinations and in the eight dogs with both RA.V and V.R.A combinations. The paired t test was also used to compare the mean intervals that induced ventricular fibrillation after the last sensed ventricular depolarization at high and low energy levels.
Table 1: Upper and lower limits of vulnerability and defibrillation threshold for each electrode combination

<table>
<thead>
<tr>
<th>Electrode combination</th>
<th>RA.V</th>
<th>L.A.V</th>
<th>V.RA</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of experiments</td>
<td>22</td>
<td>8</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>Heart weight (g)^a</td>
<td>158±29</td>
<td>158±23</td>
<td>152±18</td>
<td>158±29</td>
</tr>
<tr>
<td>Lower limit of vulnerability^a</td>
<td>0.022±0.019</td>
<td>0.024±0.019</td>
<td>0.037±0.032</td>
<td>0.025±0.022</td>
</tr>
<tr>
<td>(fibrillation threshold, J)</td>
<td>1.2±1.0</td>
<td>1.6±1.4^c</td>
<td>2.4±2.0^c</td>
<td>1.7±1.5</td>
</tr>
<tr>
<td>(J × 10^-4 / heart weight, g)</td>
<td>6.1±3.7</td>
<td>8.1±3.9</td>
<td>6.7±3.8</td>
<td>6.6±3.7</td>
</tr>
<tr>
<td>Upper limit of vulnerability^a</td>
<td>0.042±0.030</td>
<td>0.054±0.031^b</td>
<td>0.046±0.032^c</td>
<td>0.045±0.030</td>
</tr>
<tr>
<td>(J / heart weight, g)</td>
<td>6.8±2.9</td>
<td>10.9±4.3</td>
<td>6.4±2.3</td>
<td>7.6±3.5</td>
</tr>
<tr>
<td>Defibrillation threshold (J)^a</td>
<td>0.046±0.025</td>
<td>0.071±0.028^b</td>
<td>0.043±0.021^c</td>
<td>0.051±0.026</td>
</tr>
<tr>
<td>p value^d</td>
<td>.20</td>
<td>.043</td>
<td>.57</td>
<td>.055</td>
</tr>
</tbody>
</table>

All statistical tests were done after correction for heart weight.

^aExpressed as means ± SDs.
^bSignificantly different from RA.V in the eight dogs in which both combinations were tested.
^cNot significantly different from RA.V in the eight dogs in which both combinations were tested.
^dBetween the upper limit of vulnerability and defibrillation threshold.

Results

Existence of an upper limit of vulnerability. For all electrode combinations in every dog, there was an upper limit of shock strength above which a shock did not induce ventricular fibrillation in the vulnerable period (Table 1). As a part of the protocol, a total of 1404 shocks (37 ± 15 per experiment) were delivered during the vulnerable period of these 22 dogs with shock strengths 10% to 20% above the upper limit of vulnerability, and ventricular fibrillation was not induced. No ventricular fibrillation was induced when shocks above the upper limit were given throughout the interval from before the end of the QRS to after the end of the T wave in the eight dogs (16 experiments) tested.

The vulnerable period of the cardiac cycle was different for high-energy shocks at the upper limit of vulnerability than for low-energy shocks at the lower limit of vulnerability, i.e., at the fibrillation threshold. The mean interval after the last sensed ventricular depolarization for shocks that induced ventricular fibrillation at the vulnerable fibrillation threshold was 188 ± 27 msec, which is significantly longer (p = .0002) than 168 ± 23 msec for shocks that induced ventricular fibrillation at the upper limit of vulnerability.

Comparison of the upper limit of vulnerability and the defibrillation threshold. A total of 38 (22 RA.V, 8 LA.V and 8 V.RA) experiments were performed (Table 1). Each electrode combination is discussed separately.

RA.V combination. The reproducibility of measurements in the first six dogs is shown in Table 2. There were no statistically significant differences between the first and second measurements, although the second determinations tended to be higher than the first. For the RA.V combination, the upper limit of vulnerability was not significantly different from the defibrillation threshold (Table 1). There was a good correlation between the two (Figure 1). The correlation was not significant, however, between the fibrillation threshold and either the upper limit of vulnerability (r = .00, p = 1.00) or the defibrillation threshold (r = -.07, p = .76) in joules.

The impedance decreased with increasing shock strength; it was lower at the fibrillation threshold (171 ± 47 Ω) than at the upper limit of vulnerability (113
± 16 Ω; \( p = .0000 \)) or at the defibrillation threshold (112 ± 15 Ω; \( p = .0000 \)). The impedance was not significantly correlated with the upper limit of vulnerability (\( r = -.33, p = .13 \)) or the defibrillation threshold (\( r = -.15, p = .52 \)) but was weakly correlated with the fibrillation threshold (\( r = -.59, p = .0036 \)) in joules.

**LA.V combination.** For the LA.V combination, the upper limit of vulnerability was significantly less than the defibrillation threshold (table 1). The correlation between these two values was significant (figure 2). In the eight dogs in which both LA.V and RA.V combinations were tested, the upper limit of vulnerability (\( p = .028 \)) and the defibrillation threshold (\( p = .006 \)) were higher for the LA.V than for the RA.V combinations (table 1). Fibrillation thresholds for the LA.V (table 1) and RA.V combinations were not statistically different (\( p = .36 \)).

**V.RA combination.** For the V.RA combination, the upper limit of vulnerability was not significantly different from the defibrillation threshold (table 1). The correlation between these two values was significant (figure 3). In the eight dogs in which both the V.RA and RA.V combinations were tested, the upper limit of vulnerability (\( p = .93 \)) and the defibrillation threshold (\( p = .10 \)) were not significantly different between these two electrode combinations (table 1). The fibrillation thresholds for the V.RA (table 1) and RA.V combinations were not statistically different (\( p = .14 \)).

**Discussion**

This study demonstrates the existence of an upper limit to the shock strength that can induce fibrillation during the vulnerable period of paced rhythm for three electrode combinations on the epicardium. This upper limit was observed for shocks delivered throughout the interval from before the end of the QRS complex to after the end of the T wave. On a graph of the shock strength vs. the time interval between the last paced beat and the shock, the area of vulnerability is closed rather than open at the top. This result was suggest-
ed by Winfree\textsuperscript{16} on theoretical grounds and is compatible with other experimental findings for transthoracic defibrillation\textsuperscript{18} and for direct cardiac stimulation with electrodes of different shapes and sizes.\textsuperscript{19-21} For shocks considerably stronger than the upper limit of vulnerability, it is possible that another energy range of shocks exists that also induces fibrillation, perhaps from direct damage to myofibers by the shock.\textsuperscript{22}

Instead of restoring normal rhythm, a cardioversion shock given by an automatic implantable cardioverter occasionally converts stable ventricular tachycardia into fibrillation.\textsuperscript{23} A shock inadvertently delivered during the T wave of sinus rhythm may also induce fibrillation.\textsuperscript{16} The demonstration of an upper limit of ventricular vulnerability suggests that if the cardioversion shock of these devices is made greater than that which induces fibrillation when delivered during the vulnerable period, the induction of fibrillation by misplaced shocks can be avoided. This shock strength is within the range delivered by a device with the capability to defibrillate. However, discomfort caused by the shock\textsuperscript{23} may limit the use of such high-energy shocks for cardioversion. Furthermore, it remains to be seen whether an upper limit of ventricular vulnerability exists during ventricular tachycardia or in the diseased hearts of candidates for an automatic implantable cardioverter/defibrillator.

We found a significant high correlation between the upper limit of ventricular vulnerability and the defibrillation threshold for all three defibrillation electrode combinations. There was no significant correlation between the upper limit of vulnerability and either the impedance or the fibrillation threshold nor between the fibrillation threshold and the defibrillation threshold. These insignificant correlations are evidence against the possibility that the high correlation between the upper limit of vulnerability and the defibrillation threshold occurs because these two threshold variables are independent but are both highly correlated with a third variable such as stimulus impedance or cardiac anatomy or with some constitutional variable such as autonomic tone that could have similar effects on all three threshold values for each dog.

We tested only one pulse duration (5 msec). Since the center of the vulnerable period and the fibrillation threshold vary with pulse duration,\textsuperscript{24} the correlation between the defibrillation threshold and the upper limit of vulnerability should be examined for other durations and types of waveforms. Because ventricular vulnerability is different for transthoracic defibrillation electrodes\textsuperscript{25} than for defibrillation electrodes placed directly on the heart,\textsuperscript{26} the relationship between vulnerability and defibrillation should also be determined for transthoracic defibrillation.

The upper limit of vulnerability and the defibrillation threshold were not significantly affected by electrode polarity (table 1). In contrast to the results with wire stimulation electrodes,\textsuperscript{26} the polarity of the defibrillation electrodes did not affect the fibrillation threshold. One possible explanation for this difference is that we used electrodes with a much larger surface area and hence less current density\textsuperscript{21, 27} than the wire electrodes. To induce ventricular fibrillation, much higher total current was required for the defibrillation electrodes in this study than that reported for stimulating wires.\textsuperscript{26} It is possible that with higher total current, the propensity for anodal stimulation to induce ventricular fibrillation is no longer present.

The protocol of Bourland et al.\textsuperscript{13} was used in this study to estimate the defibrillation threshold. Although there is evidence suggesting that defibrillation threshold is best demonstrated with percent success rate,\textsuperscript{28, 29} the Bourland protocol has the advantage of estimating the defibrillation threshold in a short period of time.
thus avoiding large amount of high-energy shocks that are required for determining the percent success curve. The reproducibility of the measurements, as shown in table 1, was good but not perfect. This variation of the defibrillation threshold values may have decreased the correlation coefficients between the upper limit of vulnerability and the defibrillation threshold, and the actual correlation may be better than reported in this article.

The existence of an upper limit of vulnerability and the high correlation between this upper limit and the defibrillation threshold are consistent with the hypothesis that successful defibrillation with epicardial electrodes requires a shock strength that reaches or exceeds the upper limit of ventricular vulnerability. This hypothesis occurred to us because of our previous study suggesting that after an unsuccessful defibrillation shock through RA.V combination, activation fronts were halted for 64 ± 22 msec after the shock before activation reappeared and led to the resumption of fibrillation. According to this hypothesis, an unsuccessful epicardial shock of at least 1 J annihilates activation fronts within a critical mass of myocardium yet fails because it falls into the vulnerable period of one or more myocardial regions. Since fibrillation is sufficiently complex so that there are always some portions of the ventricles in the vulnerable period, a successful defibrillation shock not only must be strong enough to depolarize fibers within a critical mass of myocardium, which requires less than 1 J with the RA.V electrode combination, but also must be stronger than the upper limit of vulnerability so as not to reinroduce fibrillation.

This hypothesis, like other hypotheses of defibrillation, suggests that a uniform field through the myocardium is better than an extremely uneven field for defibrillation. Defibrillation shocks via epicardial electrodes create a nonuniform field with high potential gradients near the electrodes and low potential gradients away from the electrodes. Consequently, a shock that creates a field that is just above the depolarization threshold away from the electrodes creates a stronger field near the electrodes that may be above the fibrillation threshold. Thus defibrillation requires a much stronger shock, one that exceeds the upper limit of vulnerability in all parts of the ventricles. This hypothesis raises the possibility that (1) if an electrode combination can be developed with a uniform field through the ventricles and (2) if the depolarization threshold is lower than the fibrillation threshold during ventricular fibrillation, then defibrillation can be achieved at much lower energy by depolarizing all nonrefractory tissue within a critical mass of myocardium without reinitiating fibrillation.

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