Relation Between Upper Limit of Vulnerability and Defibrillation Threshold in Humans

Peng-Sheng Chen, MD; Gregory K. Feld, MD; Jolene M. Kriett, MD; Morton M. Mower, MD; Riyad Y. Tarazi, MD; R. Peter Fleck, MD; Charles D. Swerdlow, MD; Eli S. Gang, MD; and Robert M. Kass, MD

Background. In the canine model, an upper limit of shock strength exists that can induce ventricular fibrillation during the vulnerable period of the cardiac cycle. This shock strength (the upper limit of vulnerability) closely correlates with the defibrillation threshold and supports the “upper limit of vulnerability” hypothesis of defibrillation. It is not known whether an upper limit of vulnerability exists in humans or whether this limit correlates with the defibrillation threshold.

Methods and Results. In 13 patients undergoing implantable cardioverter-defibrillator implantation, the shock strengths associated with a 50% probability of reaching the upper limit of vulnerability (ULV90) and a 50% probability of reaching the defibrillation threshold (DFT90) were determined by the up-down algorithm. The ULV90 was determined only for the mid-upslope of the positive T waves and for the mid-downslope of the negative T waves. No major complications occurred during surgery. An upper limit of vulnerability was demonstrated in each patient. The ULV90 was 300±138 V or 6.8±5.8 J, which was significantly lower than the DFT90 of 347±167 V (p=0.038) or 9.1±7.3 J (p=0.013). The correlation between the ULV90 and the DFT90 was significant (r=0.90, p<0.001 for voltage; r=0.93, p<0.001 for energy).

Conclusions. An upper limit of vulnerability is present in humans. There is a significant correlation between the ULV90 and the DFT90, and the ULV90 is significantly lower than the DFT90. (Circulation 1993;88:186-192)

Key Words • ventricular tachycardia • ventricular fibrillation • sudden cardiac death • electrophysiology • implantable cardioverter-defibrillator

The “upper limit of vulnerability” hypothesis for defibrillation1-4 asserts that unsuccessful shocks slightly weaker than necessary to defibrillate halt all activation fronts during ventricular fibrillation. However, because the same shock also stimulates regions of the myocardium during their vulnerable period, it gives rise to new activation fronts that reinitiate ventricular fibrillation. To successfully defibrillate, the shock strength must reach or exceed the upper limit of vulnerability. This hypothesis has been supported in part by 1) the demonstration of an upper limit of vulnerability of shock strength above which a shock cannot induce fibrillation even during the vulnerable period of the cardiac cycle2,5-7 and 2) evidence that this upper limit of vulnerability correlated well with the defibrillation threshold both at baseline2,6,7 and during lidocaine infusion.8 Because the conventional method of determining the upper limit of vulnerability requires scanning the T wave with multiple high-energy shocks that can potentially result in myocardial damage and prolong the duration of surgery, the correlation between the upper limit of vulnerability and the defibrillation threshold has not been demonstrated in humans. In an earlier study we developed a method to determine the upper limit of vulnerability by giving shocks only at the mid-upslope of the T wave during ventricular paced rhythm in a canine model.9 This method significantly reduced the number of shocks required to approximate the defibrillation threshold, thus making it possible to test the upper limit of vulnerability hypothesis in humans by comparing the upper limit of vulnerability and the defibrillation threshold during implantation of the implantable cardioverter-defibrillator (ICD).
Methods

The protocol of this study was approved by the Human Subjects Committees of the University of California at San Diego, the San Diego Veterans Affairs Medical Centers, and the Cedars-Sinai Medical Center (Los Angeles). Patients undergoing surgery for the implantation of an ICD from January 1991 to November 1992 were asked to participate. All patients received routine medical care before, during, and after surgery. Ventricular pacing was performed with bipolar sensing electrodes or temporary pacing wires placed at the left ventricular apex or free wall. A multichannel programmable stimulator was used to drive constant-current isolation units (Bloom, Reading, Pa.) to give 5-msec stimuli at twice cathodal diastolic threshold as the baseline drive (S1). The S1 cycle length was either 400 msec or 500 msec to overdrive the underlying heart rate. A total of eight to 11 S1 stimuli were given. The ECG leads I, II, and III were recorded on a strip-chart recorder with a paper speed of 100 mm/sec.

In the first eight patients, the interval between the onset of the last stimulus artifact and the mid-upslope of the positive T wave or the mid-downslope of the negative T wave was determined on ECG lead II according to a previously described method. This interval was used to program the second channel of the programmable stimulator to deliver a premature stimulus (S2) to a high-voltage stimulator (HVS-02, Ventritex; Sunnyvale, Calif.). The S2 was used as an external signal to trigger the immediate delivery from the HVS-02 a high-voltage truncated exponential shock with a 6-msec pulse duration and variable tilt to the mid-upslope of a positive T wave (or the mid-downslope of a negative T wave) to induce ventricular fibrillation and then determine the upper limit of vulnerability. These shocks were delivered by the defibrillating electrodes. Once ventricular fibrillation was induced, attempted defibrillation shocks were delivered by the same electrodes to determine the defibrillation threshold.

The results of the first eight patients showed that the average S1S2 interval was approximately 300 msec. To investigate whether an S1S2 interval of 300 msec can be used to determine the ULV50 without the need to accurately determine the mid-upslope of the T wave, in patients 9, 10, and 11, we first determined the ULV50 with an S1S2 interval of 300 msec, then determined the ULV50 with an S1S2 interval that fell on the mid-upslope of the T wave. In patients 12 and 13, only an S1S2 interval of 300 msec was used because the clinical condition of these two patients limited the number of tests that could be done.

Delayed Up-Down Algorithm for Upper Limit of Vulnerability Determination

Recent studies have shown that the upper limit of vulnerability, like the defibrillation threshold, is a probability function. Thus, we used the “four-episode delayed up-down algorithm” to determine the shock strength associated with a 50% probability of reaching the upper limit of vulnerability (ULV50) and the shock strength associated with a 50% probability of successful defibrillation (DFT50). A detailed description of this algorithm has been reported. The first shock strength was approximately 15–20 J. If this initial shock failed to induce ventricular fibrillation, the shock strength was decreased by a certain δ value for the next shock. If a shock resulted in ventricular fibrillation, the shock strength was increased by the same δ value for the next shock. There was an interval of at least 1 minute between shocks that failed to induce ventricular fibrillation and 3 minutes between the ventricular fibrillation episodes. For this study, we used 5 J as the δ value for patients whose ULV50 appeared to be >5 J. For patients with an ULV50 of <5 J, we chose 2.5 J as the δ value. If a 2.5-J shock failed to induce ventricular fibrillation, we gave a small shock of ≤1 J to induce ventricular fibrillation. The next shock was again 2.5 J.

The algorithm started to count the four required observations only when the first reversal in response (from no ventricular fibrillation to ventricular fibrillation by decreasing shock strength or from ventricular fibrillation to no ventricular fibrillation by increasing shock strength) was observed. The shock strength before the reversal of response was the first data point, and the shock strength after the reversal of response was the second data point. After obtaining the third and the fourth data points by the same up-down algorithm, the fifth data point was predicted based on the results of the fourth data point. The average of these five shock strengths was considered to be the ULV50.

In patients whose clinical condition required fewer or a limited number of ventricular fibrillation episodes, we performed an abbreviated protocol. The shock strength before the reversal of response was the first data point, and the shock strength after the reversal of response was the second data point. The third data point was predicted based on the results of the second data point. The average of these three shock strengths was the ULV50.

We have demonstrated previously in the canine model that the DFT50 determined with ventricular fibrillation induced during the ULV50 testing did not differ significantly from the DFT50 determined by ventricular fibrillation induced with rapid ventricular pacing. Therefore, to decrease the number of ventricular fibrillation episodes, the ventricular fibrillation episode induced during the ULV50 testing was used to test the DFT50.

Delayed Up-Down Algorithm for Defibrillation Threshold Determination

The same delayed up-down algorithm was used for the DFT50 determination. The first shock strength was 5 J stronger than the shock strength that successfully induced ventricular fibrillation during the ULV50 testing. Although the first shock strength does not affect the results of the DFT50 testing based on the delayed up-down algorithm, selecting shock strengths near the DFT50 as the first shock can decrease the number of ventricular fibrillation episodes needed. If the shock successfully defibrillated, the shock strength was decreased by a certain δ value for the next shock. If the shock failed to defibrillate, the shock strength was increased by the same δ value for the next shock. All shocks were delivered within 15 seconds of the onset of ventricular fibrillation. For this study, we used 5 J as the δ value for patients whose DFT50 appeared to be >5 J. For patients with a DFT50 of <5 J, we chose 2.5 J as the δ value. If a 2.5-J shock successfully defibrillated, we
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Heart disease</th>
<th>Ejection fraction</th>
<th>Types of ventricular dysfunction</th>
<th>Indication for ICD</th>
<th>ICD electrodes</th>
<th>Concomitant surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>M</td>
<td>CAD</td>
<td>0.40</td>
<td>Regional VT</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>CAD</td>
<td>0.26</td>
<td>Global and regional VT</td>
<td>Patch/patch</td>
<td>CABG</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>M</td>
<td>CM</td>
<td>0.17</td>
<td>Global Sudden death</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>M</td>
<td>CAD</td>
<td>0.30</td>
<td>Global and regional Sudden death</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>M</td>
<td>CAD</td>
<td>0.39</td>
<td>Regional Sudden death</td>
<td>Patch/patch</td>
<td>CAGB</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>CAD</td>
<td>0.21</td>
<td>Global and regional VT</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>M</td>
<td>CAD</td>
<td>0.53</td>
<td>Regional VT</td>
<td>Spring/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>M</td>
<td>None</td>
<td>0.79</td>
<td>None Sudden death</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>M</td>
<td>CAD</td>
<td>0.40</td>
<td>Regional VT</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>M</td>
<td>CAD</td>
<td>0.58</td>
<td>Regional Sudden death</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>M</td>
<td>CAD</td>
<td>0.33</td>
<td>Global and regional VT</td>
<td>Patch/patch</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>59</td>
<td>M</td>
<td>CAD</td>
<td>0.25</td>
<td>Global and regional VT</td>
<td>Endocardial</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>M</td>
<td>CM</td>
<td>0.20</td>
<td>Global VT</td>
<td>Endocardial</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Mean±SD  
61±16  
0.37±0.18

ICD, implantable cardioverter-defibrillator; CAD, coronary artery disease; CM, cardiomyopathy; VT, sustained ventricular tachycardia; CABG, coronary artery bypass grafting.

assumed that the next shock was 0 J and failed to defibrillate. The subsequent shock was again 2.5 J. The shock strength before the reversal of response was the first data point, and the shock strength after the reversal of response was the second data point. After obtaining the third and the fourth data points by the same up-down algorithm, the fifth data point was predicted based on the results of the fourth data point. The average of these five shock strengths was the DFT_{50}.^{12}

In patients whose clinical condition required fewer or a limited number of ventricular fibrillation episodes, we performed an abbreviated protocol. The shock strength before the reversal of response was the first data point, and the shock strength after the reversal of response was the second data point. The third data point was predicted based on the results of the second data point. The average of these three shock strengths was the DFT_{50}.

All patients received ECG examinations after surgery. In each of the first eight patients, a serial creatinine kinase (CK) and a CK-MB isoenzyme determination was performed during the first 24 hours after surgery.

Statistical analyses were performed using SYSTAT.^{14} t Tests, Pearson correlation coefficient tests, and linear regression analysis were used to compare the ULV_{50} and the DFT_{50}. A probability value of ≤0.05 was considered significant.

Results

A total of 13 patients were included in this report. The clinical characteristics of these 13 patients are presented in Table 1. Antiarrhythmic medications of 10 of the 13 patients had been discontinued for more than five half-lives before the study (Table 2). No patient was receiving amiodarone. Patient 3 was receiving a β-blocking agent (propranolol) at the time of surgery. The serum potassium level before surgery was normal for each patient, with a mean of 4.6±0.3 mEq/L. The serum magnesium level was normal in patients 1, 2, 7, 10, and 13. Patient 11 had a magnesium level of 1.5 mg/dL. The preoperative serum magnesium levels on other patients were not available.

In patients 1–11, one or two patch electrodes were used. These electrodes were made by CPI, St. Paul, Minn. The patch electrodes were placed inside the pericardium in patient 7 and outside the pericardium in patients 1, 2, 4, 5, 6, 8, 10, and 11. The patch locations for patients 3 and 9 are unknown. Patients 3, 8, and 9 underwent surgery for ICD generator replacement. The chest was not opened in these three patients. In each patient, the left ventricular patch was used as the cathode and the right ventricular patch or the spring electrode was used as the anode for defibrillation shocks.

Patients 12 and 13 had endocardial electrodes implanted by nonthoracotomy techniques. These electrodes were made by Medtronic, Inc., Minneapolis, Minn. Patient 12 received shocks with an electrode in the superior vena cava as an anode and an electrode in the right ventricular apex as a cathode. Patient 13 received shocks with electrodes in the superior vena cava and the skin patch as anodes and an electrode in the right ventricular apex as the cathode.

The first 11 patients completed the delayed four-episode up-down algorithm for both the ULV_{50} and the DFT_{50} determination. In patients 12 and 13, after the first few episodes of fibrillation–defibrillation, it became apparent that these shock pathways were associated with a defibrillation threshold that was too high to allow implantation of the device. To limit the number of fibrillation episodes and to allow for the testing of other defibrillation shock pathways, an abbreviated protocol was used to determine the ULV_{50} and the DFT_{50} in these patients.

Upper Limit of Vulnerability and Defibrillation Threshold

In each patient, an upper limit of vulnerability was demonstrated. An example of ventricular fibrillation induction during the ULV_{50} testing is shown in Figure 1. The interval from the onset of ventricular fibrillation to
### Table 2. Upper Limit of Vulnerability and Defibrillation Threshold

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>(S_1S_2) interval (seconds)</th>
<th>ULV(_{50})</th>
<th>DFT(_{50})</th>
<th>Antiarrhythmic medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>302</td>
<td>113</td>
<td>96</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>235</td>
<td>253</td>
<td>306</td>
<td>5.4</td>
</tr>
<tr>
<td>3</td>
<td>325</td>
<td>245</td>
<td>302</td>
<td>4.4</td>
</tr>
<tr>
<td>4</td>
<td>305</td>
<td>184</td>
<td>408</td>
<td>11.1</td>
</tr>
<tr>
<td>5</td>
<td>270</td>
<td>310</td>
<td>368</td>
<td>8.7</td>
</tr>
<tr>
<td>6</td>
<td>330</td>
<td>254</td>
<td>180</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>310</td>
<td>520</td>
<td>566</td>
<td>20.8</td>
</tr>
<tr>
<td>8</td>
<td>300</td>
<td>368</td>
<td>414</td>
<td>10.3</td>
</tr>
<tr>
<td>9</td>
<td>300</td>
<td>370</td>
<td>366</td>
<td>8.1</td>
</tr>
<tr>
<td>10</td>
<td>300</td>
<td>187</td>
<td>170</td>
<td>2.9</td>
</tr>
<tr>
<td>11</td>
<td>300</td>
<td>133</td>
<td>168</td>
<td>2.8</td>
</tr>
<tr>
<td>12</td>
<td>300</td>
<td>422</td>
<td>546</td>
<td>17.3</td>
</tr>
<tr>
<td>13</td>
<td>300</td>
<td>543</td>
<td>627</td>
<td>23.4</td>
</tr>
</tbody>
</table>

\(S_1S_2\) interval, interval from the last \(S_1\) to the time of shock in ULV\(_{50}\) (shock strength associated with a 50% probability of reaching the upper limit of vulnerability) testing; DFT\(_{50}\), shock strength associated with a 50% probability of reaching the defibrillation threshold.

The first attempted defibrillation shock was \(10.5\pm2.1\) seconds (range, 6.5–15 seconds). The actual values of the shock strengths associated with ULV\(_{50}\) and shock strengths associated with DFT\(_{50}\) are presented in Table 2. The mean ULV\(_{50}\) (300±138 V or 6.8±5.8 J, mean±SD) was significantly lower than the mean DFT\(_{50}\) (347±167 V or 9.1±7.3 J) for all patients combined.

The correlation coefficient between the ULV\(_{50}\) and the DFT\(_{50}\) was 0.90 \((p<0.001)\) for voltage and 0.93 \((p<0.001)\) for energy (Figure 2).

**S\(_1\)S\(_2\) Intervals Selected for ULV\(_{50}\) Determination**

In six of the first eight patients, the ULV\(_{50}\) was determined with the first selected \(S_1S_2\) interval. In two

---

**Figure 1.** Tracings: Testing the upper limit of vulnerability (from patient 3). Recordings on ECG lead II during the ULV\(_{50}\) (50% probability of reaching the upper limit of variability) determination are shown. Baseline (S\(_1\)) pacing interval was 500 msec; \(S_1S_2\) interval was 325 msec. Shocks of 510 V (15.1 J) and 420 V (10.3 J) did not induce ventricular tachycardia or fibrillation. A 300-V (5.1-J) shock induced nonsustained ventricular tachycardia, which spontaneously converted to sinus rhythm. A 190-V (2.1-J) shock induced ventricular fibrillation.
FIGURE 2. Scatterplots show correlation between the shock strength associated with a 50% probability of successful defibrillation (DFT$_{50}$) and that associated with a 50% probability of reaching the upper limit of vulnerability (ULV$_{50}$). Panel A shows the correlation in V; panel B shows the correlation in J.

of the first eight patients, however, the onset of the T wave was incorrectly determined, which resulted in the miscalculation of the S$_3$S$_2$ interval. A second S$_3$S$_2$ interval was then tested before the ULV$_{50}$ was determined. Figure 3 shows an example from patient 8. The first S$_3$S$_2$ interval was incorrectly calculated because a retrograde P wave altered the morphology of the ST segment on the ECG. Ventricular fibrillation could not be induced with this miscalculated S$_3$S$_2$ interval. The retrograde P wave was then recognized, and the S$_3$S$_2$ interval was redetermined. With this new S$_3$S$_2$ interval, ventricular fibrillation was induced and the ULV$_{50}$ was successfully determined. The final S$_3$S$_2$ interval used for the ULV$_{50}$ testing in the first eight patients averaged 297 $\pm$ 31 msec.

Based on the results of the first eight patients, an S$_3$S$_2$ interval of 300 msec approximates the mid-upslope of the T waves in most patients. To test whether the selection of the S$_3$S$_2$ interval can be simplified, we determined the ULV$_{50}$ in patients 9, 10, and 11 with an S$_3$S$_2$ interval of 300 msec, then determined the ULV$_{50}$ in the same patients with an S$_3$S$_2$ interval that was calculated to be the mid-upslope of the T wave. The mid-upslope of the T wave was calculated to be 275 msec, 270 msec, and 312 msec from the last S$_3$ pacing artifact for patients 9, 10, and 11, respectively. With these S$_3$S$_2$ intervals, the ULV$_{50}$ determined for patient 10 was 133 V or 1.6 J and for patient 11 was 120 V or 1.4 J. These values were close to the ULV$_{50}$ determined at 300 msec S$_3$S$_2$ intervals and the DFT$_{50}$ (Table 2). Ventricular fibrillation could not be induced with shocks as low as 210 V or 2.5 J in patient 9 with the S$_3$S$_2$ interval of 275 msec, whereas the ULV$_{50}$ determined with an S$_3$S$_2$ interval of 300 msec in the same patient approximates that of the DFT$_{50}$ (Table 2). Because the clinical situa-

FIGURE 3. Tracing: Alteration of T wave morphology by retrograde P waves (from patient 8). The ventricles were paced by the sensing electrode at the left ventricular base with a cycle length of 500 msec. The stimulus (S) captured the ventricles and resulted in an upright QRS complex and a negative T wave in lead II. Retrograde Wenckebach block was observed. The peak of the T wave was easily identified and occurred 340 msec after the stimulus. However, because of the retrograde P waves (P), the onset of the T wave was initially misidentified to be 200 msec after the onset of the stimulus artifact (open arrow). Thus, the interval from stimulus to the mid-downslope of the T wave was calculated to be 270 msec. Shocks given 270 msec after the last S$_1$ stimulus failed to induce ventricular fibrillation. Subsequent review of the tracing led to the discovery of the retrograde P wave. The onset of the T wave actually occurred 260 msec after the stimulus artifact (filled arrow), and the mid-downslope of the T wave was calculated to be 300 msec after the stimulus. The ULV$_{50}$ (50% probability of reaching the upper limit of vulnerability) was then redetermined with good results.
tion of patients 12 and 13 did not allow repeated ULV\textsubscript{50} determination, the ULV\textsubscript{50} was only determined with an S\textsubscript{51} interval of 300 msec in these two patients. The correlations between the ULV\textsubscript{50} and the DFT\textsubscript{50} in the last five patients were 0.98 (\textit{p} < 0.05) for voltage and 0.97 (\textit{p} < 0.006) for energy. These preliminary data showed that a fixed S\textsubscript{51} interval of 300 msec may be as effective as the actual mid-upslope of the T wave in determining the ULV\textsubscript{50} and avoid uncertainty associated with determining the onset of the T wave in some patients.

Safety of ULV\textsubscript{50} and DFT\textsubscript{50} Determination

All 13 patients survived surgery and were discharged from the hospital in good condition. None had clinical or ECG evidence of perioperative infarction.

In the first eight patients, the total energy delivered per patient was 103,448 J (range, 57−204 J). During the first 24 hours after surgery, CK averaged 564,462 IU (range, 57−2,570 IU). The CK-MB averaged 9,411 IU (range, 0−39 IU). In two patients, the concentration of CK-MB exceeded 2.5% of the total CK. This circumstance includes patient 5, who had concomitant coronary bypass grafting; he had a peak CK-MB of 39 IU and a peak relative index of 3.0%. Patient 6 had over 10 spontaneous consecutive ICD discharges during the immediate postoperative period caused by ventricular tachycardia triggered by atrial fibrillation. His CK-MB peaked at 16.5 IU, with a maximal index of 2.6%.

Discussion

Correlation Between ULV\textsubscript{50} and DFT\textsubscript{50}

The development of the ICD\textsuperscript{15,16} has improved the treatment of patients at high risk of sudden cardiac death. However, the precise mechanism by which ventricular defibrillation occurs is unknown. Based on the results of our animal experiments,\textsuperscript{1−4} we proposed the upper limit of vulnerability hypothesis to explain the mechanism of defibrillation. Major evidence in support of this hypothesis includes the existence of an upper limit of vulnerability above which an electrical stimulus cannot induce ventricular fibrillation,\textsuperscript{5} and the fact that this upper limit of vulnerability correlates closely with the defibrillation threshold in the canine model.\textsuperscript{2,6,7} For a shock to be successful in defibrillation, the shock strength must be equal to or higher than the upper limit of vulnerability. In this study, we demonstrated that the DFT\textsubscript{50} was slightly higher than the ULV\textsubscript{50} and that the two values were closely correlated. These data are compatible with the upper limit of vulnerability hypothesis.

Preliminary human data obtained by other investigators\textsuperscript{17,18} have also shown the presence of an upper limit of vulnerability in humans. However, because different experimental protocols were used, comparisons between our study and that of others are difficult.

Clinical Application of ULV\textsubscript{50} Testing

To test the placement of the defibrillation electrodes, defibrillation threshold testing is routinely performed during ICD implantation.\textsuperscript{19} Because repeated induction of ventricular fibrillation may result in cerebral ischemia,\textsuperscript{20} most centers do not perform enough episodes of defibrillation testing to accurately determine the defibrillation threshold.\textsuperscript{19} Upper limit of vulnerability testing can potentially improve the defibrillation threshold testing because it may provide an accurate estimate of the defibrillation threshold without inducing ventricular fibrillation. The results of our study, however, showed that significant differences between the ULV\textsubscript{50} and the DFT\textsubscript{50} may be present in some patients.

The reason for the discrepancies between the ULV\textsubscript{50} and the DFT\textsubscript{50} in some patients is unclear. One of the most likely explanations is that the S\textsubscript{51} intervals selected in this study may not correspond with the most vulnerable phase of the cardiac cycle because of the following reasons: 1) the location of the pacing electrodes may affect the activation and hence the repolarization sequences,\textsuperscript{21,22} Thus, the most vulnerable period of the cardiac cycle may not be at the mid-upslope of the T wave. 2) Because the T waves peak at different times in different ECG leads, the timing of the mid-upslope of the T wave may differ, depending on the ECG leads used. 3) The onset of the T wave may be difficult to determine in some patients, especially when a retrograde P wave is present (Figure 3). In the last five patients of this study, we used a 300-msec S\textsubscript{51} interval to approximate the mid-upslope of the T wave and hence eliminated the need to accurately determine the onset of the T waves. Although the results in these five patients showed that the ULV\textsubscript{50} determined by this method still correlated with the DFT\textsubscript{50}, large differences existed in patients 12 and 13. More studies will be needed to design a better method to choose the S\textsubscript{51} intervals for individual patients and to determine whether the ULV\textsubscript{50} can predict the DFT\textsubscript{50} with sufficient accuracy to be applied clinically.

Limitations of the Study

In addition to the problems associated with the selection of the most appropriate S\textsubscript{51} intervals for ULV\textsubscript{50} testing, several additional limitations exist in this study. First, to protect the research subjects, we chose not to scan the entire ventricular vulnerable period with high-energy shocks as we often do in the animal laboratory.\textsuperscript{2,8} Thus, we can only conclude that an upper limit of vulnerability is present when the shocks were given to the mid-upslope of a positive T wave or the mid-downslope of negative T wave. The same conclusion does not necessarily apply to the other parts of the cardiac cycle.

A second limitation is that we did not test the effects of antiarrhythmic medications on the relation between the ULV\textsubscript{50} and the DFT\textsubscript{50} in humans. In the canine model, a high dose of lidocaine increased both the ULV\textsubscript{50} and the DFT\textsubscript{50}.\textsuperscript{8} However, the increment in the ULV\textsubscript{50} was greater than the increment in the DFT\textsubscript{50}. In addition, by altering the depolarization and the repolarization characteristics, antiarrhythmic medications may affect the timing of the most vulnerable phase of the cardiac cycle, making it difficult to determine the optimum timing of shocks for ULV\textsubscript{50} testing. In this series, one patient had a DFT\textsubscript{50} of 11.1 J and an ULV\textsubscript{50} of 2.5 J (Table 2). Because this patient was on procarbamide and mexiletine until the day before surgery, it is possible that the antiarrhythmic medications contributed to the large discrepancy of these values.

A third issue is the safety of giving repeated shocks to patients for ULV\textsubscript{50} testing. Avital et al\textsuperscript{22} reported that no myocardial injury could be detected even when
shocks totaling 330 J were given, provided that the shocks were delivered at a rate of less than one shock per minute. The results of our study are compatible with theirs and showed that the risk of myocardial injury by repeated shocks is small. On the other hand, there is a cumulative depressive effect of repeated ventricular fibrillation episodes on electroencephalographic activities.20 By decreasing the number of ventricular fibrillation episodes, the upper limit of vulnerability testing may actually improve the safety of ICD implantation. Further studies will be needed to test this hypothesis.

Acknowledgments

The authors wish to thank Constance M. Calisi, RN; Chun Hwang, MD; Jeffrey Goodman, MD; Barry B. Peters, MD; Andra Thomas, RN; and James Sparks, BS, for technical assistance and Kerry McElhaney and Elaine Lebowitz for secretarial assistance.

References


Relation between upper limit of vulnerability and defibrillation threshold in humans.


Circulation. 1993;88:186-192
doi: 10.1161/01.CIR.88.1.186

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/1/186

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/