Upper Limit of Vulnerability Reliably Predicts the Defibrillation Threshold in Humans

Chun Hwang, MD; Charles D. Swerdlow, MD; Robert M. Kass, MD; Eli S. Gang, MD; William J. Mandel, MD; C. Thomas Peter, MD; Peng-Sheng Chen, MD

Background The upper limit of vulnerability is the stimulus strength above which electrical stimulation cannot induce ventricular fibrillation even when the stimulus occurs during the vulnerable period of the cardiac cycle. The purpose of this study was to test the hypothesis that the upper limit of vulnerability can accurately predict the defibrillation threshold in patients undergoing implantable cardioverter-defibrillator (ICD) implantation using nonthoracotomy lead systems.

Methods and Results We studied 77 patients at the time of ICD implantation. Multiple endocardial-endocardial and endocardial-subcutaneous shock pathways were used. Two different protocols were used to test the upper limit of vulnerability. In protocol 1 (n=17), the upper limit of vulnerability was tested with two shocks on the peak or the up-slope of the T wave of paced rhythm. The shocks were given randomly either at the peak and 20 milliseconds before the peak of T wave (n=7) or at 20 and 40 milliseconds before the peak of T wave (n=10). In protocol 2 (n=60), the upper limit of vulnerability was tested with three shocks delivered at 0, 20, and 40 milliseconds before the peak of the T wave. The weakest shock that failed to induce ventricular fibrillation by a 5-J step-down procedure was defined as the upper limit of vulnerability. The defibrillation threshold was also determined by a 5-J step-down or step-up method. In protocol 1, the upper limit of vulnerability (9±6 J) was significantly lower than the defibrillation threshold (13±7 J) with a correlation coefficient of .87 and P<.001. In protocol 2, the upper limit of vulnerability (13±6 J) was not significantly different from the defibrillation threshold (12±6 J) with a correlation coefficient of .85 and P<.001. In 45 of the 60 patients, the upper limit of vulnerability was ≤15 J; all had a defibrillation threshold of ≤20 J. In 51 of the 60 patients, the upper limit of vulnerability was within 5 J of the defibrillation threshold. The upper limit of vulnerability overestimated the defibrillation threshold by >10 J in 8 patients and underestimated the defibrillation threshold by >10 J in only 1 patient. The overestimation and underestimation occurred only in patients with the upper limit of vulnerability >15 J.

Conclusions When tested with three shocks on and before the peak of the T wave, the upper limit of vulnerability accurately predicted the defibrillation threshold in patients undergoing ICD implantation using nonthoracotomy lead systems. This method required either one or no episodes of ventricular fibrillation in most patients. (Circulation. 1994;90:2308-2314.)

Key Words • cardioverter-defibrillators • defibrillation

Implantable cardioverter-defibrillators (ICDs) have achieved widespread acceptance for the treatment of patients with life-threatening ventricular tachyarrhythmias. Nonthoracotomy implantation techniques using transvenous leads and subcutaneous patches have diminished the morbidity and mortality associated with open-chest implantation. However, measurement of a defibrillation safety margin is still necessary. This requires initiation of multiple episodes of ventricular fibrillation with the attendant risks of circulatory arrest, particularly if testing of multiple lead systems is required. Determination of the defibrillation threshold, the accepted measure of the efficacy of a defibrillation system, requires additional episodes of ventricular fibrillation. It is therefore highly desirable to develop a method that can accurately predict defibrillation threshold without subjecting the patients to repeated episodes of circulatory arrest. One method that can potentially be useful in achieving this goal is to use the “upper limit of vulnerability” determined in paced rhythm as a surrogate for the defibrillation threshold.

The upper limit of vulnerability is a shock strength above which ventricular fibrillation cannot be induced even when shocks occur during the vulnerable period of the cardiac cycle. The existence of a stimulus strength above which ventricular fibrillation cannot be induced in experimental animals was first observed in 1889 by Frederic Battelli. Since then, many investigators have reported the presence of an upper limit of vulnerability during normal and paced rhythms in animals and humans. Furthermore, it has been demonstrated that the upper limit of vulnerability correlated closely with the ventricular defibrillation threshold. A preliminary study in humans reported a good correlation between the upper limit of vulnerability and the defibrillation threshold. However, the study protocol was complex, and more than one episode of ventricular fibrillation was needed before the upper limit of vulnerability could be determined.

The purpose of the present study was to develop a method of upper limit of vulnerability testing that can (1) accurately predict the defibrillation threshold for patients undergoing nonthoracotomy ICD implantation, (2) require delivery of only a limited number of shocks in paced rhythm, and (3) require the induction of only one or no episodes of ventricular fibrillation.
Shock Strength Calculations

When the HVS-02 external defibrillator was used, the delivered energy, peak voltage, and peak impedance were calculated automatically by the defibrillator. For the Medtronic model 2394 external defibrillator, the delivered voltage, current, and pulse duration of the waveforms were measured by oscilloscopes. The stored and delivered energies were then calculated manually by the following formulas:

\[ \text{Stored energy (J)} = 0.5 \cdot CV_0^2 \]

\[ \text{Delivered energy (J)} = 0.5 \cdot CV_0^2 \left[ 1 - (1 - \text{tilt})^2 \right] \]

where C is the capacitance \((1.2 \cdot 10^{-4} \, \text{F})\), \(V_0\) is the stored (peak) voltage in volts, and tilt is 65%. The actual delivered energy and the peak voltage were used for analysis of the upper limit of vulnerability and the defibrillation threshold.

In clinical practice, however, the shock strength usually refers to the programmed (stored) energy, not the actually delivered energy. To be compatible with this practice, in the following sections, the terms “5 J” and “steps of 5-J shock strengths” refer to the programmed energy, not to the actual delivered energy. The same is true when shock strengths of 10, 15, 20, and 25 J were used. However, only actual delivered energy and voltage units were used for statistical analysis.

Upper Limit of Vulnerability Testing

Protocol 1

In this protocol, we delivered two shocks of the same strength on the up-slope or the peak of the T wave before changing the shock strength. Patients were assigned randomly to either group A or group B to test the effects of the timing of the shock on the correlation between the upper limit of vulnerability and the defibrillation threshold.

Patients randomized to group A received shocks on the peak and 20 milliseconds before the peak of the T wave. The sequence of the \(S_S\) intervals was also randomized. The first shock strength was either 10 or 15 J (programmed). If the first shock failed to induce ventricular fibrillation, the next shock with the same strength but with a different interval was delivered. If both shocks failed to induce ventricular fibrillation, the strength for the next shock was decreased by 5 J. If one of the two shocks induced ventricular fibrillation, the strength for the next shock was increased by 5 J. This process continued until a reversal of response was observed. For the purpose of upper limit of vulnerability testing, an induction of nonsustained polymorphic ventricular tachycardia of greater than 3 seconds’ duration was treated as the induction of ventricular fibrillation, even though the arrhythmia spontaneously terminated before a defibrillation shock was given. An interval of 30 seconds to 1 minute was allowed between the shocks that failed to induce sustained ventricular arrhythmias. The weakest shock strength with which neither shock induced ventricular fibrillation was the upper limit of vulnerability. If two shocks at 5 J failed to induce ventricular fibrillation, then the upper limit of vulnerability was considered to be 5 J.

In patients randomized to group B, the shocks were delivered at 20 and 40 milliseconds before the peak of the T wave. The remaining part of the protocol was the same as that for patients in group A.

Protocol 2

After we studied 17 patients according to protocol 1, we found that in 1 patient in each group (A and B), the upper limit of vulnerability underestimated the defibrillation threshold by \(>10\) J. We hypothesized that two shocks might not be enough to cover the entire vulnerable period. Furthermore, a parallel study in our animal laboratory\(^{15}\) showed that when determined with three shocks at each energy level, the upper limit of vulnerability closely predicted the defibrillation
threshold of a transvenous lead system. Therefore, we modified the protocol to deliver shocks at 0, 20, and 40 milliseconds before the peak of the T wave. The first shock interval was chosen randomly in the first 14 patients. Based on the results of these 14 patients, the protocol was modified to give the first shock on the peak of the T wave, the second shock at 20 milliseconds before the peak of the T wave, and the third shock at 40 milliseconds before the peak of the T wave in all subsequent patients. As in protocol 1, the strength of the next shock was decreased by 5 J if neither shock induced ventricular fibrillation, and the strength of the next shock was increased by 5 J if any one of these shocks induced ventricular fibrillation. The weakest shock strength with which none of the three shocks induced ventricular fibrillation was the upper limit of vulnerability. If three shocks at 5 J failed to induce ventricular fibrillation, then the upper limit of vulnerability was considered to be 5 J.

Defibrillation Threshold Testing

The defibrillation threshold was measured according to a step-up or step-down protocol, with the first shock strength being 15 or 20 J after 10 seconds of induced ventricular fibrillation. Ventricular fibrillation was induced by 60 cycle current, rapid ventricular pacing (cycle length <100 milliseconds), or shocks on the T wave. The lowest energy that successfully defibrillated the ventricles was the defibrillation threshold. There was a minimum 3-minute interval between the fibrillation-defibrillation episodes. During their first 24 hours after surgery, all patients were closely monitored, and 12-lead ECGs were obtained.

Statistical Analysis

All statistical analyses used the actual delivered energy, not the programmed energy. t tests and Pearson correlation coefficient tests were used to compare the upper limit of vulnerability and the defibrillation thresholds of all patients. To determine the effects of amiodarone and shock waveforms, subgroup analyses were also performed. Because the same data set was used three times for statistical analyses, a value of P<.05 divided by 3, or .017, was considered significant (Bonferroni procedure).

Results

During the study period, 83 patients underwent ICD implantation using nonthoracotomy lead systems. Of these, 2 patients did not consent to participate in the study. In 4 patients, the study was not performed due to technical or clinical considerations. The data from the remaining 77 patients were included in this report. The clinical characteristics of the patient population are presented in Table 1. Antiarrhythmic medications were discontinued for more than five half-lives before the study in 66 of the 77 patients. In the remaining 11 patients, 1 patient was receiving sotalol, and 10 patients were receiving long-term amiodarone therapy. There was no overlap between the patients in this study and the patients reported in our previous study.

In each patient, an upper limit of vulnerability was demonstrated. In 50 patients, sustained ventricular fibrillation was induced. In 5 patients, the upper limit of vulnerability was determined when self-terminating polymorphic ventricular tachycardia or fibrillation of >3 seconds’ duration was induced. In the remaining 22 patients, the upper limit of vulnerability was 5 J (programmed), and determination of the upper limit of vulnerability did not require induction of ventricular fibrillation. The interval from the onset of ventricular fibrillation to the first attempted defibrillation shock was 9.6±1.4 seconds (range, 8.5 to 13.5 seconds). The total energy delivered during upper limit of vulnerability testing per patient was 77±27 J (range, 30 to 158 J).

The average impedance and pulse width were 67±12 Ω and 9.8±1.7 milliseconds, respectively, when the Ventritex HVS-02 defibrillator was used (n=20) and were 51±11 Ω and 11.3±5.8 milliseconds, respectively, when the Medtronic 2394 defibrillator was used (n=57).

Protocol 1

Results of protocol 1 are summarized in Table 2. The correlation between the upper limit of vulnerability and the defibrillation threshold (Fig 2) was significant. However, in 1 patient in each group, the upper limit of vulnerability was 10 J less than the defibrillation threshold, resulting in a significant underestimation of the defibrillation threshold in >10% of the patients.

In patients randomized to group A, ventricular fibrillation was induced by shocks at the peak of the T wave in 4 patients and 20 milliseconds before the peak of the T wave in 3 patients. In patients randomized to group B, ventricular fibrillation was induced by shocks given 20

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### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>17 60</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>12/5 45/15</td>
</tr>
<tr>
<td>Age, mean±SD (yr)</td>
<td>63±8 65±13</td>
</tr>
<tr>
<td>Underlying heart diseases, n</td>
<td>14 51</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 9</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1 1</td>
</tr>
<tr>
<td>Electrodes used, n</td>
<td>12 51</td>
</tr>
<tr>
<td>Medtronic Transvene</td>
<td>5 9</td>
</tr>
<tr>
<td>CPI-Endotak</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic medications, n</td>
<td>2 8</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>0 1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.33±0.12 0.34±0.11</td>
</tr>
<tr>
<td>Indications for ICD, n</td>
<td>10 32</td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>7 28</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator.

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### Table 2. Relation Between Upper Limit of Vulnerability and Defibrillation Threshold

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limit of vulnerability</td>
<td>9±6 J 13±6 J</td>
</tr>
<tr>
<td>(382±109 V) (424±127 V)</td>
<td></td>
</tr>
<tr>
<td>Defibrillation threshold</td>
<td>13±7 J 13±6 J</td>
</tr>
<tr>
<td>(488±147 V) (465±129 V)</td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>.87 (P&lt;.001) .85 (P&lt;.001)</td>
</tr>
<tr>
<td>S, to peak to T-wave interval, ms</td>
<td>378±48 361±35</td>
</tr>
<tr>
<td>(330-530) (310-500)</td>
<td></td>
</tr>
</tbody>
</table>

*P<.001 compared with the upper limit of vulnerability.
1P=NS compared with the upper limit of vulnerability.
milliseconds before the peak of the T wave in 7 patients and 40 milliseconds before the peak of the T wave in 3 patients. These data suggested that if the three shocks were to be given at all three of the S1S2 intervals, the accuracy of using the upper limit of vulnerability to predict the defibrillation threshold might improve.

Protocol 2

The results of protocol 2 are also presented in Table 2. Analysis of the initial 14 patients (whose first shock interval was randomly chosen) showed that ventricular fibrillation was induced by the shock at the peak of the T wave in 8 patients, the shock at 20 milliseconds before the peak of the T wave in 4 patients, and 40 milliseconds before the peak of the T wave in 2 patients. Therefore, in the subsequent 46 patients, the first shock was always given on the peak of the T wave. In these 46 patients, ventricular fibrillation was induced with shocks at the peak of the T wave in 31 patients (67%), at 20 milliseconds before the peak of the T wave in 10 patients (22%), and at 40 milliseconds before the peak of the T wave in 5 patients (11%). By using this protocol, the upper limit of vulnerability and the defibrillation threshold differed by 10 J (upper limit of vulnerability > defibrillation threshold) in 8 patients. In these 8 patients, despite the high upper limit of vulnerability (~20 J), the defibrillation threshold was ≤15 J (Fig 2). In an additional patient, the defibrillation threshold was >10 J higher than the upper limit of vulnerability. The ventricular fibrillation was induced by a shock at 20 milliseconds before the peak of the T wave in this patient. In the remaining 51 patients, the upper limit of vulnerability and the defibrillation threshold were within one 5-J step.

In 45 of the 60 patients (75%), the upper limit of vulnerability was ≤15 J (programmed). All 45 patients had defibrillation thresholds ≤20 J (programmed) and met the minimum device implant criteria. In 35 of the 60 patients (58%), the upper limit of vulnerability was ≤10 J (programmed); all had a defibrillation threshold of ≤15 J (programmed). In 13 of 60 patients (22%), the upper limit of vulnerability was 5 J (programmed); all had a defibrillation threshold of ≤10 J (programmed).

Fig 2 shows the linear regression analyses between the defibrillation threshold and the upper limit of vulnerability. The upper limit of vulnerability tested with protocol 2 closely predicted the defibrillation threshold in most patients.

ECG Leads Used to Find Peak of T Wave

The correlation between the upper limit of vulnerability and the defibrillation threshold was not determined by the ECG lead used to find the peak of the T wave. The peak of the T wave was determined with ECG lead I in 11 patients, with ECG lead II in 31 patients, with ECG lead III in 27 patients, and with reversed lead V1 in 4 patients. The correlation coefficients between the upper limit of vulnerability and the defibrillation threshold were .89, .80, .83, and .87, respectively (P<.001 for each correlation). The differences were not statistically significant among these four groups. In the remaining 4 patients, the ECG lead used to determine the peak of T wave could not be identified.

Changes in Interval Between S1 and Peak of T Wave During Upper Limit of Vulnerability Testing

Prolongation of the interval between the last S1 and the peak of the T wave was observed in 4 patients during the course of the study. All 4 patients required one adjustment of the S1 to the shock interval during the upper limit of vulnerability testing. The average lengthening of the interval between the S1 and the peak of the T wave in these 4 patients was 25 milliseconds (range, 20 to 30 milliseconds). All 4 patients had an upper limit of vulnerability ≤15 J (programmed) and defibrillation thresholds ≤20 J (programmed).

Effects of Amiodarone and Shock Waveforms

A total of 10 patients were receiving long-term amiodarone therapy. The mean upper limit of vulnerability was 10±7 J (402±132 V), and the mean defibrillation threshold was 13±8 J (471±153 V, P<.001). The correlation coefficient (r value) between the upper limit of vulnerability and the defibrillation threshold in J was .96 (P<.001) and in V was .87 (P<.001). The mean interval between the last S1 to the peak of the T wave was 410±61 milliseconds, which was significantly (P<.001) longer than the mean interval between the last S1 to the peak of the T wave from the patients not receiving amiodarone therapy (372±54 milliseconds).

Asymmetric biphasic waveform shocks were used in 5 patients in protocol 1 and in 28 patients in protocol 2. The remaining patients received monophasic truncated waveform shocks. Table 3 shows that with either waveform there was a good correlation between the upper limit of vulnerability and the defibrillation threshold.

Discussion

Upper Limit of Vulnerability Reliably Predicts Defibrillation Threshold

In the present study, we developed a method of upper limit of vulnerability testing that can reliably predict
TABLE 3. Effects of Waveforms

<table>
<thead>
<tr>
<th>Waveform</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Upper limit of vulnerability</td>
<td>8±6 J (374±98 V)</td>
<td>12±7 J (432±110 V)</td>
</tr>
<tr>
<td>Defibrillation threshold</td>
<td>13±8 J* (482±137 V)*</td>
<td>14±7 J† (483±131 V)†</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>.85 (P&lt;.001)</td>
<td>.87 (P&lt;.001)</td>
</tr>
<tr>
<td>Biphasic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Upper limit of vulnerability</td>
<td>9±5 J (388±114 V)</td>
<td>13±6 J (414±145 V)</td>
</tr>
<tr>
<td>Defibrillation threshold</td>
<td>14±6 J* (492±157 V)*</td>
<td>13±5 J† (424±125 V)†</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>.87 (P&lt;.001)</td>
<td>.84 (P&lt;.001)</td>
</tr>
</tbody>
</table>

*P=.002 compared with the upper limit of vulnerability. †P=NS compared with the upper limit of vulnerability.

defibrillation threshold with sufficient accuracy to be clinically useful. This method, which is described in “Methods” protocol 2, requires shocks to be given at 0, 20, and 40 milliseconds before the peak of T wave for each energy level. The upper limit of vulnerability determined by this method is within 5 J of the defibrillation threshold in approximately 85% of patients. In only 1 patient did the upper limit of vulnerability underestimate the defibrillation threshold by >10 J.

This simplified method of upper limit of vulnerability testing is easily applicable clinically because of the following features: (1) the peak of the T wave during ventricular pacing is easy to identify, allowing reproducible determination to time the shocks; (2) because shocks can be given within 1 minute of each other until ventricular fibrillation is induced, the entire upper limit of vulnerability testing takes no more than 10 minutes to perform; and (3) no more than one episode of ventricular fibrillation is needed in most cases, and therefore we propose that this method of upper limit of vulnerability testing (protocol 2) can be substituted for defibrillation threshold testing during ICD implantation in most patients.

Clinical Application of Upper Limit of Vulnerability Testing

There are at least three ways to apply the upper limit of vulnerability testing during ICD implantation. The first application is to determine the safety margin of the ICD being implanted. For example, if a 15-J defibrillation threshold were considered to have an acceptable safety margin for an ICD that has >30 J maximum shock strength, then an upper limit of vulnerability of 10 J should be considered as sufficient evidence for an acceptable safety margin. In these patients, which accounted for 58% of the patients in the present study, the induction of ventricular fibrillation would not be needed for defibrillation threshold testing. One episode of ventricular fibrillation may still be needed to test the device itself. If a 20-J defibrillation threshold were considered to have an acceptable safety margin for ICD implantation, then an upper limit of vulnerability of 15 J should be considered sufficient for implantation. In the present study, 75% of the patients met this criteria.

The second application of the upper limit of vulnerability testing is to use it as a surrogate for the defibrillation threshold testing in research protocols. For this application, the shock strength of the upper limit of vulnerability testing should be progressively decreased until ventricular fibrillation is induced. The upper limit of vulnerability determined by this step-down method accurately predicts the defibrillation threshold to be within 5 J in the vast majority of patients. Repeated episodes of ventricular fibrillation are therefore not necessary.

If a step-down or a step-up defibrillation threshold is considered necessary, the upper limit of vulnerability testing can still be helpful. Based on the results of the protocol 2 of the present study, the first shock strength programmed to be 5 J higher than the upper limit of vulnerability successfully defibrillated 98% of patients tested. To minimize the fibrillation-defibrillation episodes required for a step-down defibrillation threshold testing, the shock strength of first defibrillation attempt should be programmed to be no more than 5 J higher than the upper limit of vulnerability.

Definition of Upper Limit of Vulnerability

The definition of the upper limit of vulnerability in the present study is different from that of a previous report,6 which defined the upper limit of vulnerability as the highest energy that induced ventricular fibrillation. Because the upper limit of vulnerability hypothesis6,17-20 states that successful defibrillation occurs when the shock fails to reinitiate ventricular fibrillation, the lowest energy that cannot induce ventricular fibrillation in paced rhythm should be equal to the defibrillation threshold. Therefore, we defined the upper limit of vulnerability as the lowest shock strength that cannot induce ventricular fibrillation in the vulnerable period. In a significant number of patients, ventricular fibrillation could not be induced even with a 5-J shock. In these patients, the upper limit of vulnerability was 5 J according to the current definition. Our data also showed that with the current definition, there were no significant differences between the upper limit of vulnerability and the defibrillation threshold. It may be more convenient for the clinicians to estimate defibrillation threshold by upper limit of vulnerability, not by upper limit of vulnerability plus 5 J.

Comparison of Protocols

In addition to protocols 1 and 2 of the present study, we tested another protocol11 that gave shocks only at the mid-upstroke of the T wave. This latter protocol and the protocol 1 of the present study resulted in >10-J underestimation of the defibrillation thresholds in more than 10% of the patients. In comparison, giving three shocks on the T wave (protocol 2 of the present study) resulted in better correlation between the upper limit of vulnerability and the defibrillation threshold and only a 2% probability of underestimating defibrillation threshold by >10 J.

Because the upper limit of vulnerability testing is a probability function,21 it is possible that by giving more
shocks at each energy level, regardless of the timing of the shocks, would have improved the accuracy of the upper limit of vulnerability testing. Although we did not specifically test this hypothesis, we propose that the timing of the shocks was also important. (1) In our previous study,6 we used an up-down algorithm to test the upper limit of vulnerability, which required multiple shocks at the same S3S4 interval. The results were not as good as the results of the present study. (2) In 11% of the patients studied with protocol 2, a shock induced ventricular fibrillation when it fell at 40 milliseconds before the peak of the T wave, whereas shocks of the same strength at the peak or at 20 milliseconds before the peak of the T wave failed to induce ventricular fibrillation. Therefore, the best time for upper limit of vulnerability testing may vary from patient to patient, and three shocks at different times on the T wave were needed to cover the most vulnerable phase of the cardiac cycle.

Implications for Mechanisms of Ventricular Defibrillation

In the present study, we enrolled consecutive patients undergoing nonthoracotomy ICD implantation. Despite the wide variation in underlying heart diseases, presenting arrhythmias, ejection fractions, lead systems, shock waveforms, and the use of antiarrhythmic medications such as amiodarone, a close correlation between the upper limit of vulnerability and the defibrillation threshold was consistently present. These data are compatible with the upper limit of vulnerability hypothesis of defibrillation,17-19 which asserts that the mechanisms by which an electric shock induces ventricular fibrillation from normal rhythm (ventricular vulnerability) are closely related to the mechanisms by which an electric shock terminates ventricular fibrillation (ventricular defibrillation). Studies on the exact mechanisms by which a strong electrical stimulus can induce ventricular fibrillation during the vulnerable period of the cardiac cycle22-25 may have relevance to the mechanisms of ventricular defibrillation as well.

Study Limitations

One limitation of the present study is that the location of the pacing electrodes may affect activation and therefore the repolarization sequences.26,27 Therefore, the results of this study are only pertinent to the ICD systems that were used in this study, with the S1 pacing site located at the right ventricular apex.

A second limitation is that we did not test the effects of antiarrhythmic medications on the relation between the upper limit of vulnerability and the defibrillation threshold. A previous study28 showed that high doses of lidocaine increased the upper limit of vulnerability to a greater extent than it increased the defibrillation threshold. Therefore, for patients receiving antiarrhythmic medications other than amiodarone, it is unknown whether the upper limit of vulnerability accurately estimates the defibrillation threshold. Further studies in this area are needed.

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