Determination of the Upper Limit of Vulnerability Using Implantable Cardioverter-Defibrillator Electrograms

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Background—The upper limit of vulnerability (ULV) correlates with the defibrillation threshold and can be determined with 1 episode of ventricular fibrillation (VF). To automate the ULV in an implantable cardioverter-defibrillator (ICD), the most vulnerable intervals must be identified from an ICD electrogram rather than the latest-peaking surface T wave (T_peak). We hypothesized that the recovery time (T_R), defined as the maximum derivative (dV/dt) of the T wave of the shock electrogram, correlates with the most vulnerable intervals.

Methods and Results—We determined ULV, defibrillation threshold, and the most vulnerable intervals in 25 patients at ICD implantation. The ULV was the weakest T-wave shock that did not induce VF. The most vulnerable intervals were the ones associated with the strongest shocks that induced VF. Telemetered shock electrograms were stored on digital tape and differentiated offline to measure T_R. T_peak and T_R were highly correlated (T_peak-T_R=-2±11 ms; r=0.80, P<0.001). At least 1 most vulnerable interval timed between -20 ms and +20 ms relative to T_peak in all patients and between -40 ms and +20 ms relative to T_R in 96% of patients.

Conclusions—The recovery time of shock electrograms provides accurate information about global repolarization. T_R closely approximates T_peak. The ULV method may be automated in an ICD by timing T-wave shocks relative to T_R.

Key Words: defibrillation ▪ fibrillation ▪ shock

The upper limit of vulnerability (ULV) is the weakest shock that does not induce ventricular fibrillation (VF) when delivered during the vulnerable period. It correlates closely with the minimum shock energy that defibrillates reliably.1-3 Studies have validated the ULV as a basis for closely approximating the peak of the vulnerable zone.6 This interval is identified relative to the ones associated with the strongest shocks that induced VF. Because ICD electrograms typically have biphasic T waves, their peaks are difficult to measure. The ULV method may be automated in an ICD by timing T-wave shocks relative to T_R. Determination of the ULV requires that T-wave shocks be timed at the most vulnerable intervals, corresponding to peak of the vulnerable zone.6 This interval is identified relative to an easily determined and reliable measure of repolarization, usually the peak of the latest peaking T-wave recorded from multiple surface ECG leads.2-5 ULV testing would be more efficient if the most vulnerable intervals could be identified from ICD electrograms, permitting ICDs to select timing intervals automatically for T-wave shocks.

Methods

Patients

Patients were candidates for this study if they had left pectoral implants of an ICD with a lead implanted at or near the right ventricular apex. All gave written, informed consent according to a protocol approved by the Human Subjects Committee. Patient characteristics are shown in Table 1.

Study Procedure

The implant procedure has been described.3-5 We measured ULV and defibrillation threshold (DFT) by an interleaved protocol.3 Testing was performed using the implanted pulse generator (Medtronic models 7274 or 7276), which delivered biphasic shocks from right ventricular coil to left pectoral ICD case (CAN) plus superior vena cava (SVC) electrode using a true-bipolar, dual-coil electrode (Medtronic model 6947).

Right ventricular apical pacing was performed at a baseline (S1) cycle length of 500 ms. All 12 surface ECG leads were recorded simultaneously on a computer screen and displayed at a 200 mm/s. The T waves were inspected to select the lead with the latest-peaking monophasic T wave that had opposite polarity to the QRS complex.3-5 The interval from S1 to the peak of this T wave (S1-T_peak) was measured initially and after every fourth T-wave shock. Because the timing of T-wave shocks was programmable in increments of 10 ms, S1-T_peak was rounded to the nearest 10 ms to select shock coupling intervals. T-wave shocks were delivered after 8 S1s. The sequence of shock energies used for both ULV and DFT testing is shown in Figure 1A.
T-Wave Shock Protocol

This protocol identified both the ULV and the most vulnerable intervals, corresponding with the peak of the vulnerable zone, defined as those intervals associated with the strongest shocks that induced VF. The protocol delivered T-wave shocks until the most vulnerable intervals were bounded on 3 sides by intervals and shock energies at which VF was not induced (shorter and longer intervals at the same energy and higher energy at the same and adjacent intervals). There were 3 main steps. In step A, the intervals at 0 and 20 ms relative to Tpeak were tested using decreasing energies until VF was induced. This strategy was chosen to limit the number of shocks based on a report that 1 of these intervals identified the peak of the vulnerable zone in ~90% of patients. In step B, to establish the ULV, shock energy was increased by 1 step and shocks were delivered at any untested intervals in the range −20 to +20 ms relative to the interval that induced VF. If VF was induced at this higher energy, this step was iterated. If VF was not induced, step C was performed. In step C, to establish the inner and outer boundaries of the peak of the vulnerable zone, shorter and longer intervals were tested at the greatest energy that induced VF. If VF was induced, this step was iterated. If VF was not induced, shocks were delivered. Steps B and C were interleaved until the most vulnerable intervals were bounded on 3 sides.

Figure 1B shows an example. In step A, neither shock 1 at Tpeak or shock 2 at −20 ms relative to Tpeak induce VF. Shock energy is then decremented, and these intervals are retested (shocks 3 through 5) until VF is induced (shock 5). In step B, shock energy is increased by 1 step, and shocks are delivered to any untested intervals in the range of −20 ms to +20 ms relative to the interval of shock 5. The first 2 intervals (−20 and 0 ms) already have been tested (shocks 3 and 4), so shock 6 is delivered at the last interval (+20 ms) and does not induce VF. In step C, shock 7 is delivered 20 ms before the interval at which shock 5 induced VF and at the same energy. Because shock 7 induces VF, step B is performed to cover the range −20 ms to +20 ms relative to the interval of shock 7 by delivering shock 8 at the next higher energy. Because shock 8 did not induce VF, step C is performed relative to the interval of shock 7 by delivering shock 9 at an interval 20 ms earlier. Then shock 10 is delivered 20 ms after the longest interval that induced VF. In this example, the ULV is 6 J and the peak of the vulnerable zone includes the intervals at −20 and 0 ms relative to Tpeak.

If either of the 2 initial shocks at 9 J induced VF, the shock energy was increased as shown in Figure 1A and a corresponding protocol was followed until both the ULV and the width of the peak of the vulnerable zone were identified.

Determination of the DFT

VF was induced by T-wave shocks. If the T-wave shock protocol was completed before the DFT was determined, VF was induced by 2 J monophasic T-wave shocks at Tpeak. The sequence of shock energies for DFT testing was identical to that for ULV testing. The DFT was defined as the lowest measured shock energy that terminated VF.

Pacing at Different Cycle Lengths

In the last 15 patients, we performed additional pacing for 10 seconds at cycle lengths 400, 500, 600, 800, and 1000 ms if hemodynamically tolerated (400 ms) and if pacing was maintained without sinus capture beats (800 and 1000 ms).

Recording and Analysis of Electrograms

Surface ECG lead II and 2 telemetered ICD electrograms (filtered 3 to 100 Hz) were recorded using a digital tape recorder (Tecac Model RD-145T). Electrograms were telemetered at 256 Hz and digitized on an 8-bit scale with a range of −4 to +4 mV. Signals were transferred to a personal computer and differentiated using Origin 5.0 (Microcal Software).

Depending on the programmable options for each ICD model, we recorded the electrogram from either right ventricular coil to CAN (Coil-CAN, model 7276) or from right ventricular coil to a common
electrode of CAN and SVC coil (Coil-CAN+SVC, model 7274). These were the principal electrograms used for data analysis, and T_R refers to the recovery time measured from them. In the first 15 patients, we recorded electrograms from the right ventricular tip to right ventricular coil (Tip-Coil) electrodes in addition to the principal electrogram.

Data Analysis
When measurements were made from 8-beat pacing trains, S1-T_peak was the average value for the last 2 beats. When pacing was performed for 10 seconds, S1-T_peak was the average value for the last 5 beats. T_R was measured on a computer screen using digital calipers at the maximum of the time derivative of the T wave of each electrogram. S1-T_peak was measured on the same beats used for measuring S1-T_peak, and average values were calculated in the same way. The width of the peak of the vulnerable zone was the difference between minimum and maximum intervals at the peak. If this peak included more than 1 interval, the timing of the peak was the average of these intervals. A P<0.05 using the 2-tailed, t test, χ² test, or ANOVA was used to reject the null hypothesis. The Lin concordance coefficient (r) was computed between T_peak and T_R. This coefficient is similar to the Pearson correlation coefficient but measures closeness of points to the line of identity rather than the line of regression.

In the first 15 patients, repeated-measures ANOVA was used to compare T_peak, T_R, and the recovery time recorded from the Tip-Coil electrogram (T_R[Tip-Coil]). Post-hoc analysis was performed using Fisher’s protected least significant difference test.

Results
ULV Versus DFT
The ULV and DFT were highly correlated (ULV: 9.4±5.5 J; DFT: 7.8±6.0 J; r=0.92, P<0.0001). Shock lead impedance was 39±8 Ω. Patients received 8.7±2.2 T-wave shocks. There were no perioperative complications.

Measurement of T_R
Figure 2 shows surface ECG lead II, intracardiac electrogram, and the derivative of the electrogram from 1 patient. There was close agreement between T_peak on the surface ECG and T_R on the differentiated electrogram. In all patients, electrograms had biphasic T waves similar to those in Figure 2. Thus, the method of identifying the most vulnerable intervals used for surface ECG leads, based on the peak of a monophasic T wave, could not be applied to electrograms. The slew rate at T_R was 1.4±0.5 V/s.

T_peak Versus T_R
In all patients, S1-T_peak and S1-T_R were highly correlated at cycle length 500 ms (S1-T_peak: 345±18 ms; S1-T_R: 347±18 ms; r=0.80, P<0.001). The difference in T_peak and T_R was −2±11 ms (median, −4 ms; range, −23 to +22 ms). The absolute value of this difference was 9±7 ms. T_peak−T_R was not significantly different for the 2 electrode configurations of the principal electrogram (Coil-CAN: 1±11 ms; Coil-CAN+SVC: −5±11 ms; P=0.18). Table 2 shows that there was no significant effect on T_peak−T_R of clinical variables.

<table>
<thead>
<tr>
<th>TABLE 2. Effect of Clinical Variables</th>
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<tr>
<td>Cardiac disease</td>
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<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy*</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>LV ejection fraction†</td>
</tr>
<tr>
<td>QRS duration‡</td>
</tr>
<tr>
<td>&gt;120 ms</td>
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<tr>
<td>≤120 ms</td>
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<tr>
<td>Class III antiarrhythmic drug</td>
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Mi indicates myocardial infarction; LV, left ventricular.
*Includes hypertensive and primary hypertrophic cardiomyopathy.
†Dichotomized by median value of 0.39.
‡Two patients were pacemaker dependent.
such as cardiac disease, left ventricular ejection fraction, QRS duration, or class III antiarrhythmic drugs.

**Recovery Time for Tip-Coil Electrogram**

Tip-Coil electrograms could be analyzed for 10 of the first 15 patients. In the remaining 5 patients, the amplitude of the T wave was so low that quantization noise made interpretation of the derivatives unreliable. In 10 analyzed patients, mean values for $S_1-T_{peak}$, $S_1-T_R$, and $S_1-T_{R[Tip-Coil]}$ were $343\pm16$, $345\pm23$, and $314\pm27$ ms, respectively. Repeated-measures ANOVA identified significant differences among these variables: $F(2,18)=11.7$, $P<0.001$. Post hoc analysis identified significant differences ($P<0.001$) for $S_1-T_{peak}$ versus $S_1-T_R$[Tip-Coil] and for $S_1-T_R$ versus $S_1-T_{R[Tip-Coil]}$ but not for $S_1-T_{peak}$ versus $S_1-T_R$ ($P=0.79$).

**$T_{peak}$ Versus $T_R$ at Multiple Cycle Lengths**

Figure 3 shows the ECG and the derivative of the electrogram at multiple paced cycle lengths from a single patient. $T_{peak}$ and $T_R$ increase in parallel as cycle length increases. Figure 4 shows the strong correlation between $T_{peak}$ and $T_R$ at multiple paced cycle lengths in the last 15 patients; $\rho=0.90$, $P<0.001$.

**Most Vulnerable Intervals**

Figure 5 shows the timing of the most vulnerable intervals and $T_R$ relative to $T_{peak}$ in all patients. The peak of the vulnerable zone included 1 tested interval in 8 patients (32%), 2 intervals in 12 patients (48%), 3 intervals in 4 patients (16%), and 4 intervals in 1 patient (4%). The difference between the longest and shortest most vulnerable interval was $20\pm17$ ms (median, 20 ms; range, 0 to 60 ms).

The peak of the vulnerable zone was $6\pm15$ ms after $T_{peak}$ versus $4\pm21$ ms after $T_R$. $T_{peak}$ identified the peak of the vulnerable zone in 19 patients (76%), and the 2 intervals at 0 and $+20$ ms relative to $T_{peak}$ identified the peak of the vulnerable zone in 24 patients (96%). In all patients, at least 1 most vulnerable interval was timed from $-20$ to $+20$ ms relative to $T_{peak}$.

In 22 of 25 patients (88%), at least 1 most vulnerable interval timed from $-20$ to $+20$ ms relative to $T_R$. In the remaining 3 patients, the most vulnerable interval timed at $T_R$ $-29$ ms for a Coi-CAN electrogram and at $T_R+36$ ms and $T_R+40$ ms for 2 Coi-CAN+SVC electrograms.

**Discussion**

Our principal finding is that $T_R$ on the shock electrogram closely approximates $T_{peak}$. The clinical implication is that the ULV method may be automated in an ICD by timing T-wave shocks relative to $T_R$.

**Clinical Application of the ULV**

Vulnerability testing provides either a patient-specific measure of defibrillation efficacy (the ULV)$^2$ with 1 episode of VF or a reliable defibrillation safety margin without VF. In comparison with ICD implant testing using the fibrillation-defibrillation method, the vulnerability method minimizes those risks that are related to VF or circulatory arrest rather than to shocks, such as intractable VF, cerebral hypoperfusion, and myocardial ischemia.

The ULV corresponds to the peak of the vulnerable zone, a bounded region in a 2-dimensional space defined by coupling interval (time) on the abscissa and shock strength on the ordinate.$^6$ To measure the ULV, T-wave shocks must be timed to coincide with this peak. During right ventricular apical pacing, the peak of the vulnerable zone times closely with the latest-peaking monophasic T wave in any ECG lead.$^3$ The peak of the T wave corresponds with epicardial repolarization during endocardial pacing.$^{10}$ This suggests that the timing of the latest-peaking T-wave ($T_{peak}$) may correspond...
with the timing of latest epicardial repolarization and that the timing of the peak of the vulnerable zone approximates that of latest epicardial repolarization.

The present clinical method for identifying the most vulnerable intervals has practical limitations. It requires inspecting multiple (preferably all 12) ECG leads, identifying those with monophasic T waves, and measuring their S1–Tpeak intervals. This is impractical in catheterization laboratories or operating rooms if only 1 to 3 ECG leads are recorded or if measurements can be made only at 25 to 50 mm/s. Because the S1-Tpeak interval may vary, S1-Tpeak should be remeasured during the testing procedure. Operator error may occur if biphasic T-waves are measured or retrograde P waves are not identified. ULV testing would be more efficient if ICDs selected timing intervals for T-wave shocks automatically based on measurements made from electrograms.

Recovery Time
T_R on a unipolar electrogram has been validated as a measure of local repolarization in basic physiological studies. The activation-recovery interval has been used to assess local repolarization in canines and humans. Activation-recovery intervals recorded from point electrodes act as a spatial average and are thus dominated by the action potentials of cells closest to the recording site.

Present Study
This study demonstrates that Tpeak can be estimated accurately by a recovery time recorded from a global electrogram between large, widely spaced intracardiac and extracardiac electrodes. The recovery time recorded from 2 electrodes in the right ventricle (Tip-Coil) did not correlate closely with Tpeak. To the best of our knowledge, this is the first application of the recovery time method to global repolarization. However, T_R does not identify the most vulnerable intervals as accurately as Tpeak. A 3-shock T-wave scan relative to Tpeak identified the most vulnerable intervals in all patients. But a 4-shock T-wave scan relative to T_R was required to identify the most vulnerable intervals in 24 of 25 patients (96%).

Timing of the Peak of the Vulnerable Zone
The present study confirms that the peak of the human vulnerable zone is narrow, including a median of only 2 20-ms intervals. Accurate, a priori knowledge of the timing of this peak is required to minimize the number of shocks required for a clinical T-wave scan.

In previous studies using a 2-electrode Coil-CAN shock pathway, the ULV could be determined accurately by a 3-shock T-wave scan at −40, −20, and 0 ms relative to Tpeak. In the present study, which used a 3-electrode Coil-
CAN+SVC shock pathway, the optimal timing of a 3-shock T-wave scan differed at −20, 0, and +20 ms relative to $T_{\text{peak}}$. This small difference is important clinically. The peak of the vulnerable zone was identified only $\geq +20$ ms relative to $T_{\text{peak}}$ in 5 of the 25 patients in the present study versus none of the 14 patients in a previous study. A 20-ms difference in the coupling interval of T-wave shocks can result in significant underestimation of the ULV.

Induction of VF by a T-wave shock depends on a critical relationship between the sequence of repolarization and the region of weakest shock field. In swine, the timing of the peak of the vulnerable zone differs for different pacing configurations, providing the shocking configuration is kept constant. Comparison of the present study with our previous clinical study suggests that the timing of the peak of the vulnerable zone differs for different shocking configurations, providing the pacing configuration is kept constant.

**Limitations**

The ICD pulse generators in the present study applied a 3-Hz high-pass filter to telemetered electrograms. We do not know how our results would be affected by different filtering. Our results apply specifically to right ventricular apical pacing. Pacing from other locations might affect the relationship between $T_{\text{peak}}$ and $T_R$. This study was performed using true-bipolar defibrillation leads. Use of integrated-bipolar leads, which pace through the distal coil, might cause pacing artifact that affects measurement of $T_R$. Although the study was performed using ICDs from one manufacturer, the results should be applicable to other ICDs if similar sampling rates, filtering, and electrodes are used. This study did not determine which conditions, if any, alter the close relationship between $T_{\text{peak}}$ and $T_R$. Although we did not identify any such conditions, it is possible that specific antiarrhythmic drugs, repolarization abnormalities, cardiac pathology, or other conditions might alter this relationship. We cannot exclude a small effect on $T_{\text{peak}}-T_R$ between the 2 electrode configurations used for the principal electrogram.

**Conclusion**

Application of the recovery time method to widely spaced defibrillation electrodes provides accurate information about global repolarization. $T_R$ on the Coil-CAN or Coil-CAN+SVC electrogram closely approximates $T_{\text{peak}}$ on the latest-peaking monophasic T wave. The ULV method may be automated in an ICD by timing T-wave shocks relative to $T_R$.

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**References**

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