Effects of Lidocaine on Relation Between Defibrillation Threshold and Upper Limit of Vulnerability in Open-Chest Dogs

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Background. The purpose of the present study was to test the effects of lidocaine on the relation between the defibrillation threshold and the upper limit of vulnerability.

Methods and Results. The shock strength associated with a 50% probability of successful defibrillation (DFT$_{50}$) and the shock strength associated with a 50% probability of reaching the upper limit of vulnerability (ULV$_{50}$) were determined in 11 open-chest dogs by using the delayed up-down method before and during lidocaine (seven dogs) or normal saline (four dogs) infusion. The ventricles were paced at a cycle length of 300 msec. Shocks of various strengths were then given via a patch-patch electrode configuration on the anterior and posterior surfaces of the ventricle to determine the ULV$_{50}$. Once ventricular fibrillation was induced, shocks were given 15–20 seconds later via the same electrode configuration to determine the DFT$_{50}$. Lidocaine infusion resulted in a serum level of 15±4 μg/ml. This was associated with a lengthening of the QT interval but not with the widening of the QRS complex. In all dogs, both the ULV$_{50}$ and the DFT$_{50}$ increased significantly when tested during lidocaine infusion. Mean ULV$_{50}$ during lidocaine infusion was 496±70 V or 13.1±4.3 J, which were significantly higher than the baseline values of 333±67 V or 5.3±2.2 J (p<0.001 for both voltage and energy). Mean DFT$_{50}$ during lidocaine infusion was 407±41 V or 8.7±1.7 J, which were significantly higher than the baseline values of 300±38 V and 4.4±1.1 J (p=0.004 for voltage and p=0.013 for energy). The $r$ values between the ULV$_{50}$ and the DFT$_{50}$ were 0.79 (p=0.037) for voltage and 0.80 (p=0.030) for energy at baseline and 0.85 (p=0.016) for voltage and 0.88 (p=0.009) for energy during the lidocaine infusion. However, the increments of the ULV$_{50}$ (163±88 V or 7.8±4.6 J) were significantly greater than the increments of the DFT$_{50}$ (107±51 V or 4.4±1.9 J, p=0.035 for voltage and p=0.023 for energy). Normal saline infusion did not alter DFT$_{50}$ or ULV$_{50}$.

Conclusions. Lidocaine infusion significantly increases both ULV$_{50}$ and DFT$_{50}$. These results are compatible with the upper limit of vulnerability hypothesis of defibrillation. However, the greater increase of the upper limit of vulnerability than the defibrillation threshold with lidocaine infusion indicates that other factors may also need to be considered to explain the results. (Circulation 1992;85:1146–1151)

KEY WORDS • electrophysiology • defibrillation • cardioversion

The upper limit of vulnerability hypothesis of defibrillation$^{1-4}$ states that unsuccessful shocks that are slightly weaker than is necessary for defibrillation halt all activation fronts during ventricular fibrillation (VF) but stimulate regions of the myocardium during their vulnerable period, giving rise to new activation fronts that reinitiate VF. To achieve successful defibrillation, a shock must reach the upper limit of vulnerability so that VF cannot be reinitiated. This hypothesis is supported by the significant correlation between the defibrillation threshold and the upper limit of vulnerability.$^{2,5,6}$ One study$^2$ tested the correlation between the upper limit of vulnerability and the defibrillation threshold when two different defibrillation patch electrode configurations were used. The results showed that when the defibrillation threshold increased, so did the upper limit of vulnerability. Significant correlations between the two values were found for both defibrillation electrode configurations. However, because electrical induction and termination of VF depend on not only the shock field strength distribution$^{7,8}$ but also the electrophysiological state of the myocardium,$^{1,3,4,9}$ it is important to test this correlation when the electrophysiological state is perturbed but the field strength remains constant. Lidocaine was recently shown to significantly increase the defibrillation threshold$^{10,11}$ and is therefore an ideal agent with which to perturb the electrophysiological state of the myocardium and to test the correlation between the upper limit
of vulnerability and the defibrillation threshold. The purpose of the present study was to compare the upper limit of vulnerability and the defibrillation threshold before and during lidocaine administration without changing the location of the defibrillation patch electrodes. The upper limit of vulnerability hypothesis of defibrillation will be supported if lidocaine infusion significantly increases both the upper limit of vulnerability and the defibrillation threshold, and there is a significant correlation between the two values both at baseline and during the administration of lidocaine. However, if the results show that lidocaine alters the upper limit of vulnerability and defibrillation threshold to a different degree, then other mechanisms have to be considered to explain these findings.

Methods

Surgical Preparation

Adult mongrel dogs were anesthetized with 25–35 mg/kg sodium pentobarbital,\textsuperscript{12,13} intubated, and ventilated with room air with a Harvard respirator (Harvard Apparatus, Millis, Mass.). An arterial line was inserted into the femoral artery to monitor blood pressure continuously. Blood was periodically drawn to determine pH, PO\textsubscript{2}, PCO\textsubscript{2}, base excess, and bicarbonate concentrations. Esophageal temperature was monitored and maintained at 36–37°C by heating the table with warm circulating water. The surface ECG leads I, II, III, aVR, aVL, aVF, and V\textsubscript{6} were recorded simultaneously with a computerized mapping system (BARD electrophysiology, Tewksbury, Mass.) and displayed on a multichannel oscilloscope throughout the study. The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. Two patch defibrillation electrodes with an active surface area of 13.5 cm\textsuperscript{2} (CPI, St. Paul, Minn.) were sutured to the anterior and posterior surfaces of the ventricles. A platinum pacing electrode was attached to the epicardium of the left ventricular apex for unipolar cathodal S\textsubscript{1} stimulation, with the anode on the chest wall. The same pacing site was used for all animals studied. The epicardium was kept moist with normal saline. After the study protocol (see below) was completed, the dogs were killed with an overdose of pentobarbital, and the heart was excised and weighed.

An SMP-300 multichannel stimulator (Biologic Instruments de Laboratories, Echirolles, France) was used to drive constant-current stimulation isolation units (Bloom, Reading, Pa.) to give 5-msec stimuli at twice cathodal diastolic threshold as the S\textsubscript{1}. Another channel of the SMP-300 stimulator was used to deliver a premature stimulus (S\textsubscript{2}) at predetermined S\textsubscript{1}S\textsubscript{2} coupling intervals. The S\textsubscript{2} was used as an external signal to trigger the delivery of high-voltage truncated exponential electric shocks with variable tilt via an HVS-02 defibrillator (Ventritex, Sunnyvale, Calif.) to the epicardial patch electrodes for the induction of VF. The leading edge voltage, delivered energy, and resistance of the shock were displayed on the defibrillator immediately after each shock was delivered. The current output was not measured. Once VF was induced, the defibrillator was switched to the asynchronous mode to attempt defibrillation in 15–20 seconds. The same defibrillation waveform was used throughout the study.

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

Delayed up-down algorithm. The delayed up-down algorithm\textsuperscript{14} was used to determine the shock strength associated with a 50% probability of reaching the upper limit of vulnerability (ULV\textsubscript{50}) and the shock strength associated with a 50% probability of successful defibrillation (DFT\textsubscript{50}). The up-down algorithm began by giving the first shock at a strength estimated to yield a 50% successful defibrillation. If this initial shock was unsuccessful, the shock strength was increased by a certain \( \delta \) value for the next shock. If a shock was successful, the shock strength was decreased by the same \( \delta \) value for the next shock. This process was continued until four shocks were delivered and one shock strength was projected but not delivered. The five shock strengths were then averaged for the threshold estimate.

This up-down algorithm is accurate only when the a priori estimates are good. The accuracy is significantly reduced for poor a priori estimates of the DFT\textsubscript{50}. This problem can be overcome by the delayed four-episode, up-down algorithm. This algorithm does not start counting the four required observations until the first reversal in response. With this procedure, the accuracy of determining the DFT\textsubscript{50} is greatly improved because it does not depend on the accuracy of an a priori estimate of the initial shock strength.

VF induction and ULV\textsubscript{50} determination. The ULV\textsubscript{50} was determined by the delayed up-down algorithm. The ventricles were paced at a 300-msec cycle length for 11 beats. The intervals between the last S\textsubscript{1} pacing artifact and the onset, peak, and end of the T waves on ECG lead II were determined by the mapping system. To induce VF and test the ULV\textsubscript{50}, a shock with a strength of 300 V was given at the onset of the T wave. The S\textsubscript{1}S\textsubscript{2} intervals were then progressively increased at 10-msec increments until a total of 15 shocks were given or VF was induced. With this method, the entire T wave was scanned. All shocks that did not induce VF were separated by 1 minute. Depending on whether VF was induced, subsequent shocks were given with a shock strength of 50 V higher or lower, respectively, than the previous shock energy until the opposite result was observed. The shock strength immediately preceding the opposite result was the first data point. The shock strength associated with the opposite result was the second data point. The up-down algorithm was then continued until a total of four data points were obtained and one was predicted.\textsuperscript{14} The ULV\textsubscript{50} was determined by averaging the five shock strengths. The shocks given before the first data point were excluded from analysis.

VF termination and DFT\textsubscript{50} determination. VF was induced as part of the upper limit of vulnerability testing described above. If the determination of DFT\textsubscript{50} had not been completed at the end of the ULV\textsubscript{50} testing, additional episodes of fibrillation–defibrillation were performed. The VF during these episodes was induced by giving a 100-V shock during the vulnerable period. Once VF was induced, the DFT\textsubscript{50} was determined with 6-msec monophasic shocks using the delayed up-down algorithm. The first defibrillation shock was 300 V for each dog studied. In subsequent episodes, the shock energy was increased by 50 V after failures or decreased by 50 V after successes until the opposite results were observed. The shock strength immediately preceding
the opposite result was the first data point. The shock strength associated with the opposite result was the second data point. The up-down algorithm was then continued until a total of four data points were obtained and one was predicted. The DFT$_{50}$ was determined by averaging the five shock strengths. The shocks given before the first data point were excluded from analysis. All fibrillation–defibrillation episodes were separated by at least 5 minutes. Salvage shocks were given immediately after an unsuccessful defibrillation shock. The shock strength of the salvage shock was not included in the data analysis.

**Protocol 1: ULV$_{50}$ and DFT$_{50}$ Before and During Lidocaine Infusion**

Seven dogs were used in this protocol. After baseline testing of the ULV$_{50}$ and the DFT$_{50}$, a high dose of lidocaine was administered (9.2-mg/kg load over 10 minutes followed by 285 μg/kg/min maintenance). This dosage of lidocaine was shown to result in a stable plasma concentration during the measurement (pseudo–steady state) and to increase the DFT$_{50}$. The ULV$_{50}$ and the DFT$_{50}$ were redetermined during the maintenance infusion 1 hour after the loading dose. The lidocaine concentration was sampled at the beginning and end of testing.

**Protocol 2: Control Studies**

Four dogs were used in this protocol. After baseline testing of the ULV$_{50}$ and the DFT$_{50}$, normal saline was administered (10-mL load over 10 minutes followed by 1 mL/min maintenance). The ULV$_{50}$ and the DFT$_{50}$ were redetermined during stable maintenance infusion 1 hour later. The DFT$_{50}$ was then determined for the third time when the VF was induced with rapid ventricular pacing.

**Data Analysis**

The QRS widths and the QT intervals of ECG lead II were measured during sinus rhythm. The QTc was calculated by dividing the QT interval by the square root of the preceding RR interval (seconds). The intervals between the stimulus and the onset, peak, and end of the T wave of the last S$_1$ beat were also measured. These data were compared with the S$_1$S$_2$ interval to determine where on the T wave a shock was given.

All statistical analyses were performed with SYSTAT. The Pearson correlation coefficient analysis, linear regression analysis, and Newman-Keuls test were used to compare the ULV$_{50}$ and the DFT$_{50}$ before and during lidocaine infusion. The t tests and Pearson correlation coefficient analyses were also used to compare the QRS widths, QTc intervals, and increments of the ULV$_{50}$ and the DFT$_{50}$ before and during lidocaine infusion. A value of $p \leq 0.05$ was considered significant.

**Results**

**Protocol 1**

The mean±SD body weight of the seven dogs studied was 21±3 kg, and the mean±SD heart weight was 162±25 g. The serum lidocaine concentration was 18±13 μg/ml 1 hour after the loading dose and 15±4 μg/ml at the end of the study ($p=NS$). The duration of the experimental protocol (from the time of the first shock to the end of the study) averaged 275±22 minutes. There was no difference between the QRS width before (67±15 msec) and during (73±16 msec) lidocaine infusion. However, the QTc intervals increased from 335±59 msec at baseline to 397±32 msec during the lidocaine infusion ($p=0.045$). Lidocaine infusion was also associated with a significantly decreased heart rate. The RR intervals at baseline (420±14 msec) were significantly less than those during lidocaine infusion (547±103 msec).

**ULV$_{50}$ and DFT$_{50}$ before and during lidocaine infusion.**

In all dogs, both the ULV$_{50}$ and the DFT$_{50}$ increased significantly when tested during lidocaine infusion. The mean ULV$_{50}$ during lidocaine infusion was 496±70 V or 13.1±4.3 J, which were significantly higher than the baseline values of 333±67 V or 5.3±2.2 J ($p<0.001$ for both voltage and energy). Mean DFT$_{50}$ during lidocaine infusion was 407±41 V or 8.7±1.7 J, which were significantly higher than the baseline values of 300±38 V and 4.4±1.1 J ($p=0.004$ for voltage and $p=0.013$ for energy). The correlation between the ULV$_{50}$ and the DFT$_{50}$ was significant both before and during the lidocaine infusion (Figure 1).

The increments of the ULV$_{50}$ and the DFT$_{50}$ were highly correlated (Figure 2), indicating that dogs with a greater increase of the ULV$_{50}$ also had a greater increase of the DFT$_{50}$. However, the increments of the ULV$_{50}$ (163±88 V or 7.8±4.6 J) were significantly greater than the increments of the DFT$_{50}$ (107±51 V or 4.4±1.9 J, $p=0.035$ for voltage and $p=0.023$ for energy).

As a result, although there was no difference between the ULV$_{50}$ and the DFT$_{50}$ at baseline, the ULV$_{50}$ became significantly greater than the DFT$_{50}$ during lidocaine infusion ($p=0.007$ for voltage and $p=0.004$ for energy).

**Timing of shock and induction of VF.** Lidocaine infusion significantly increased the intervals from the last S$_1$ stimulus to the beginning, peak, and end of the T waves on ECG lead II. The intervals from the last S$_1$ to the beginning, peak, and end of the T waves at baseline were 135±8, 244±24, and 291±20 msec, respectively. These intervals were significantly shorter than the 197±64 ($p=0.048$), 310±84 ($p=0.050$), and 383±85 msec ($p=0.019$) observed during lidocaine infusion.

For shocks that induced VF during the upper limit of vulnerability testing, the interval from the last S$_1$ to the time of the shock was 191±26 msec ($n=21$) at baseline and 225±80 msec ($n=26$) during lidocaine infusion ($p=0.05$). In all except one of the 47 episodes, VF was induced when the shock was given on the upslope of the T wave.

**Protocol 2**

The body weight of the four dogs in the study averaged 17.9±5.4 kg, and the heart weight averaged 157±36 g. There was no difference between the QRS width before (51±17 msec) and during (46±10 msec) normal saline infusion. The QTc intervals before (326±58 msec) and during (337±51 msec) normal saline infusion were also not statistically different. The infusion of normal saline did not change the heart rate. The RR intervals at baseline (431±86 msec) were not significantly different from those recorded during normal saline infusion (443±10 msec).

The ULV$_{50}$ determined at the baseline (350±127 V or 6.1±4.7 J) was not significantly different from that recorded during normal saline infusion (332±167 V).
Effects of Limit of Ventricular Rapid Pacing

The presence of an upper limit of vulnerability has been demonstrated since the discovery of a vulnerable period of the cardiac cycle. By definition, the upper limit of vulnerability is the stimulus strength above which VF cannot be induced even if the stimulus were given during the vulnerable period of the cardiac cycle. A similar phenomenon has also been observed in the atrium. Subsequently, investigators demonstrated that the upper limit of vulnerability correlated well with the defibrillation threshold. By changing the location of the anodal defibrillation patch electrode from the right to the left atrium, with the same cathodal electrode on the left ventricular apex, alterations of the electrical field distribution resulted in the increase of not only the defibrillation threshold but also the upper limit of vulnerability as well. The correlation between the two values was significant for either electrode combination.

FIGURE 1. Scatterplots of correlation between a 50% probability of successful defibrillation (DFT50) and a 50% probability of reaching the upper limit of vulnerability (ULV50) before and during lidocaine infusion. Panels A and B: Correlation between DFT50 and ULV50 before and during lidocaine infusion, respectively, measured in volts. Panels C and D: Same correlations measured in joules. Although values of ULV50 and DFT50 both increased significantly with lidocaine infusion, correlation between DFT50 and ULV50 remains significant. ○, Data obtained at baseline; ●, data obtained during lidocaine infusion.

FIGURE 2. Scatterplots of correlation between increments of a 50% probability of successful defibrillation (DFT50) and a 50% probability of reaching the upper limit of vulnerability (ULV50) of each dog during lidocaine infusion. Panel A: Correlation measured in volts. Panel B: Correlation measured in joules. Slopes of regression line indicate that increments of ULV50 are greater than increments of DFT50. ΔDFT50 is increment of DFT50 from baseline; ΔULV50 is increment of ULV50 from baseline.
Furthermore, more recent studies\textsuperscript{18} showed that like the defibrillation threshold,\textsuperscript{19} the upper limit of vulnerability is a probability function, and the probability curves of these two tests in the same animal parallel each other. In the present study, we demonstrated that the upper limit of vulnerability and the defibrillation threshold can both be increased by the administration of lidocaine without changing the location of the defibrillation patch electrodes. The two values were highly correlated, both at baseline and during the lidocaine infusion. The increments of these two values were also highly correlated. In contrast, normal saline infusion did not alter either the ULV\textsubscript{50} or the DFT\textsubscript{50}. These data showed that with the perturbation of either the field strength distribution\textsuperscript{2} or the electrophysiological state of the myocardium, the defibrillation threshold and the upper limit of vulnerability remain closely correlated. Although this close correlation supports the upper limit of vulnerability hypothesis of defibrillation,\textsuperscript{3,4} a greater increase of the upper limit of vulnerability than of the defibrillation threshold with the administration of lidocaine indicates that other factors may also need to be considered to explain these results.

It is well known that the sodium channel–blocking effect of lidocaine is dependent on the heart rate (use dependence) and the transmembrane potential.\textsuperscript{20–23} Ventricular fibrillation is associated with a cycle length of approximately 100 msec\textsuperscript{1} and transmembrane action potentials of extremely short duration and low amplitude.\textsuperscript{24,25} Although the short cycle length during VF may facilitate sodium channel block,\textsuperscript{20–23} the brief duration of the action potential is unfavorable for the blocking action of lidocaine.\textsuperscript{26,27} Because of the differences in cycle lengths and the transmembrane action potentials between the paced rhythm and VF, the sodium channel–blocking effects of lidocaine could also differ. This difference may account for the discrepancies between the increments of the upper limit of vulnerability and the defibrillation threshold during lidocaine infusion.

The second possibility is the different magnitude of action potential and refractory period extension produced by shocks during VF and during paced rhythm. The upper limit of vulnerability hypothesis proposed that after an unsuccessful defibrillation shock, new activation wave fronts arise as a result of a complex interaction between the shock’s electric field and tissue refractoriness.\textsuperscript{4} Two results of such an interaction are the time- and energy-dependent action potential\textsuperscript{28,29} and refractory period\textsuperscript{30–32} extension. The magnitude of the action potential and the refractory period extension may be important in determining vulnerability and defibrillation. Because of the faster excitation rate during VF, the action potential was much shorter during VF than it was during paced rhythm. It is highly probable that the extents of the action potential and the refractory period extension after a shock during VF differ significantly from that found during paced rhythm, even though the strength of the shock is the same. The effects of such a difference may be aggravated by lidocaine and account for the differences between the ULV\textsubscript{50} and the DFT\textsubscript{50} during lidocaine infusion.

The third possible explanation is that the upper limit of vulnerability hypothesis is incorrect. Shibata et al.\textsuperscript{9} demonstrated that with a few exceptions, VF initiated by shocks delivered during the vulnerable period was usually associated with large reentrant circuits. However, the new activation fronts observed at the early sites after an unsuccessful shock often arise from a focal (or perhaps microreentrant) pattern.\textsuperscript{3} Thus, different mechanisms may be responsible for vulnerability and defibrillation. Lidocaine infusion perturbed these two mechanisms to different degrees and therefore results in greater increase of the upper limit of vulnerability than the defibrillation threshold.

**Upper Limit of Vulnerability and Midupslope of T Wave**

We\textsuperscript{33} previously demonstrated that the upper limit of vulnerability determined at the midupslope of the T wave can be used to accurately predict the defibrillation threshold. In contrast, the upper limit of vulnerability determined at the peak and the middleslope of the T wave had a poorer correlation with, and was significantly lower than, the defibrillation threshold. We concluded that the defibrillation threshold could be estimated by shocks given only at the midupslope of the T wave. In the present study, we scanned the T wave starting with short S\textsubscript{S} intervals, and then progressively increased the S\textsubscript{S} coupling interval if the previous shock failed to induce VF. We found that both before and during lidocaine infusion, the shock that induced VF also occurred at the upslope of the T wave. Further studies will be needed to determine whether the midupslope is also the best time to test the upper limit of vulnerability during lidocaine infusion.

**Accuracy of DFT\textsubscript{50} Determination**

There is no consensus on which method best estimates the defibrillation efficacy. Two methods have been used the most. The first is the “defibrillation threshold” method,\textsuperscript{34} and the second is the “dose–response curve” method.\textsuperscript{19} Jones et al.\textsuperscript{35} recently compared these two methods using animal experiments. To determine the defibrillation threshold, they used an iterative increment-decrement protocol similar to the delayed up-down methods\textsuperscript{14} used in the present study. The results were compared with the DFT\textsubscript{50} determined by the dose–response curve method. The results showed that there was no statistical difference between the DFT\textsubscript{50} as estimated by either method. These experimental results are compatible with the results obtained by mathematical modeling study\textsuperscript{14} and showed that the DFT\textsubscript{50} can be accurately estimated with an up-down algorithm without constructing the entire dose–response curve of defibrillation. Based on the results of these studies,\textsuperscript{14,35} we believe that the methods used in the present study produce accurate estimates of the DFT\textsubscript{50}.

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