The Effects of Ventricular Fibrillation Duration and Site of Initiation on the Defibrillation Threshold During Early Ventricular Fibrillation

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Objectives. The purpose of this study was to determine if the defibrillation threshold (DFT) is lower during the first few cycles of ventricular fibrillation (VF) than after 10 s of VF and, if so, if the effect is caused by local or global factors.

Background. The DFT may be low very early during VF because: (1) for the first few cycles VF arises from a localized region close to a defibrillation electrode where the shock field is strong (local factors), or (2) during early VF the effects of ischemia and sympathetic discharge have not yet fully developed and the heart has not yet completely dilated (global factors).

Methods. Protocol 1 included seven pigs in which a defibrillation electrode and a pacing catheter were both placed in the right ventricular apex. VF was induced by delivering a high current premature stimulus from the pacing catheter that should have caused reentry confined to the right ventricular apex for the first few cycles of VF. A bipolar electrogram was recorded from the tip of the defibrillation catheter. Using a three reversal up–down protocol, the DFT was determined for biphasic shocks delivered of the defibrillation catheter. Defibrillation thresholds were determined after 1, 2, 3, 4 and 5 VF activations following VF induction from the right ventricle (RV) or the left ventricle (LV) and after 10 s (control).

Results. In protocol 1, the mean ± SD DFTs were lower during the first three cycles than after 10 s of VF (3.0 ± 4.1 J for the first VF cycle vs 15.8 ± 6.6 J after 10 s of VF, p < 0.05). In protocol 2, the DFT for the first few cycles of VF induced near the first VF cycle was significantly lower than that after 10 s of VF (16.0 ± 2.2 J), whereas the DFT for the first few cycles induced near the first VF cycle from the right ventricular apex was significantly lower (2.3 ± 2.7 J for the first VF cycle) than that induced from the LV.

Conclusions. This study demonstrates that the DFT is significantly lower during the first few VF cycles than after 10 s of VF and that this decrease may be caused by both local factors and global factors. These results provide an impetus for exploring earlier shock delivery in implantable devices.

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Ventricular fibrillation (VF) has been classified into four stages (1). The first tachysystolic phase lasts for 1 to 2 s and is characterized by rapid, undulatory contractions that involve relatively large portions of the myocardium but arise from a single, localized region. Cardiac mapping of VF induced by premature stimulation has demonstrated that during this same period, figure-eight reentry occurs and is localized to the region around the stimulation site for a mean of 10 cycles (2). Thus, for the first second, VF is more organized than later, consisting of only a few wavefronts that originate from a single reentrant circuit near the stimulation site from which they spread circumferentially to activate the remainder of the ventricles. If an electric shock stops this reentrant circuit before other reentrant circuits have formed elsewhere throughout the ventricles, then VF should be halted.

A minimum potential gradient shock field has been reported to be necessary for defibrillation (3). The shock potential gradient decreases with distance from the electrode, so that the shock field is strongest near the defibrillation electrode (4,5). Therefore, if a defibrillation shock is given from an electrode near the site of electrical induction of VF, the defibrillation threshold (DFT) should be lower during the first few cycles of VF when reentry is confined to the region where the shock field is strong than later during VF when reentry is present away from the defibrillation electrode where the shock field is weak. The purpose of part 1 of this study is to test this hypothesis by initiating VF and administering defibrillation shocks from adjacent electrodes in the right ventricular apex and determining DFT very early and later after the initiation of VF.

These same considerations suggest that if VF is induced...
away from the defibrillation electrode where the potential gradient is weakest, the DFT should not be decreased very early during VF, because the shock must be large enough to generate the minimal potential gradient required for defibrillation in this region. At this shock strength, all of the ventricles will be exposed to a potential gradient greater than that necessary to halt reentrant pathways located anywhere in the ventricles. Thus, the shock strength required to terminate the localized activations early during VF when initiated away from the defibrillation electrode should be the same as the shock strength required to terminate all VF activations later during VF. For this reason, DFT very early as well as later during VF should be the same.

Conversely, other factors may lower the minimal potential gradient needed for defibrillation very early during VF, however, so that the DFT during the first few cycles of VF may be lower than later during VF even when VF is initiated away from the shocking electrode. Factors such as ischemia and elevated sympathetic tone caused by the lack of perfusion associated with VF may elevate the potential gradient required for defibrillation; during the first few cycles of VF, these factors have not been active long enough to significantly influence the potential gradient needed for defibrillation. It is also possible that during very early VF, the ventricles have not yet dilated as much as they will dilate later, so that during early VF the same strength shock produces a larger potential gradient field throughout parts of the ventricles than during later VF. The purpose of protocol 2 of this study is to test the hypothesis that DFT is lower during early VF than during later VF, even when it is induced from a site distant from the defibrillation electrode.

Methods

Two protocols were performed.

Protocol 1: The Defibrillation Threshold During Early Ventricular Fibrillation

The purpose of protocol 1 was to determine if DFT is reduced during the first 25 cycles of VF compared with DFT after 10 s of VF when VF is initiated near a defibrillation electrode.

Animal preparation. Seven adolescent pigs weighing 35–45 kg were studied. Animal preparation was carried out using a previously described protocol (6).

Under fluoroscopic guidance a double-coil defibrillation catheter (Endotak model 0070, CPI, St. Paul, Minnesota) was positioned via the right external jugular vein with the distal end in the right ventricular apex. The distal coil, 3.4 cm in length, was positioned in the right ventricle (RV), whereas the proximal coil, 6.8 cm in length, was positioned in the right atrium or superior vena cava. A quadripolar pacing catheter with 2-mm electrodes and 5-mm interelectrode spacing (Elecath, Electrocathe ter Corp., Rahway, New Jersey) was positioned via the right internal jugular vein in the right ventricular apex near the tip of the defibrillation catheter.

At the end of the study the animal was euthanized with an injection of potassium chloride.

Determination of ventricular fibrillation threshold. Stimulation was performed using a custom-built stimulator that was controlled by software on a Macintosh computer (Apple Computer, Inc., Cupertino, California). A VF threshold was determined by delivering 10 S1 basic drive stimuli and a premature S2 stimulus from the two distal electrodes of the quadripolar catheter. The strength of the premature S2 stimulus was increased in 10-mA increments until VF was induced. Once VF was induced, the S2 strength was increased by 40 mA and VF was reinduced three times to confirm reliable VF induction. This increment in S2 strength was chosen because it has previously been shown to result in highly reliable VF induction (>98% efficacy) (7).

Ventricular fibrillation sensing and timing of shock delivery. A local electrogram of each VF episode was recorded from the integrated bipolar pacing tip of the defibrillation electrode. The signal was amplified by a MAP Preamplifier (EP Technologies, Sunnyvale, California) and recorded using Labview software (National Instruments, Austin, Texas) on a Macintosh Computer. The amplified signal was also fed to the separate Macintosh-based stimulator, which triggered the defibrillator for shock delivery. During VF, activations that exceeded a threshold slope (determined during the first few VF inductions) were counted by the sensor and after a predetermined number of activations a shock was delivered. Shocks were delivered after 1, 2, 3, 4, 5, 7, 10, 15, 20 and 25 VF cycles and after 10 s of VF (control). Figure 1 depicts an example of one of these episodes. The VF duration for each episode was measured from the onset of the S1 stimulus to the onset of shock delivery.

Shock delivery. Shocks were delivered using an external defibrillator (HVS-02, Ventritex, Inc., Sunnyvale, California). Shocks were biphasic, truncated exponential waveforms in which phase one was 6 ms and phase two was 4 ms. The leading edge voltage of phase two was set equal to the trailing edge voltage of phase one and the overall tilt varied with the system impedance. For the first phase of the waveform the distal electrode was connected as the cathode and the proximal electrode was connected as the anode. A waveform analyzer (Model 6100, Data Precision, Danvers, Massachusetts) recorded the voltage and the current waveforms of each shock at 20,000 samples/s. Shock parameters were then measured (leading edge voltage and leading edge current) or calculated (total energy and phase one impedance).
Determination of defibrillation threshold. The DFT was determined for each timing interval plus the control (a total of 11 DFTs) using a modified Purdue protocol (8). The initial shock strength delivered for each interval was 400 V. In the event of successful defibrillation, shock strength was decreased in 80-V steps per defibrillation attempt until a first reversal from successful defibrillation to failure was achieved. In the event of unsuccessful defibrillation, shock strength was increased in 80-V steps per defibrillation attempt until a first reversal from failed defibrillation to success was achieved. After the first reversal the algorithm was iterated in the opposite direction, but the voltage step size was diminished to 40 V until a second reversal occurred and to 20 V and iterated in the original direction until a third reversal occurred. The DFT was defined as the lowest delivered total energy that successfully defibrillated the heart. Each DFT was determined simultaneously and in a random order and shock strengths were independently tracked for each interval, i.e., the first DFT shock for each interval was given before proceeding to the second DFT shock. This was done to prevent the potential effects of time from affecting the DFT results.

Protocol 2: The Effect of Ventricular Fibrillation Initiation Site on Defibrillation Threshold

The purpose of protocol 2 was to determine if the site of VF initiation affected the DFT during early VF by initiating VF near and away from a defibrillation electrode. Animal preparation. A second group of seven pigs was studied. Animal preparation was identical to that in protocol 1 except that an additional pacing catheter was placed via the femoral artery against the posterolateral left ventricle (LV).

Determination of ventricular fibrillation threshold. A VF threshold was determined in the same manner as in protocol 1 for the RV and LV individually with a pacing electrode in each ventricle. An S2 stimulus strength 40 mA higher than this value was tested three times and then used to reliably induce VF.

Ventricular fibrillation sensing and timing of shock delivery. Ventricular fibrillation sensing was identical to that used in protocol 1 and occurred from the defibrillation electrode in the RV. Ventricular fibrillation was induced from either the right or left ventricular quadripolar pacing catheter and the shock was delivered from the right ventricular defibrillation electrode. Shocks were delivered after 1, 2, 3, 4 and 5 activation cycles for VF induced from the right and left ventricular pacing catheters and after 10 s of VF initiated from the right ventricular pacing catheter (control).

Determination of defibrillation threshold. A DFT was determined for each timing interval forVF induced from the RV and LV individually with a pacing electrode in each ventricle. An S2 stimulus strength 40 mA higher than this value was tested three times and then used to reliably induce VF.

Statistical analysis. The effects of timing interval and location of VF induction on DFT were determined by repeated measures analysis of variance. In protocol 1, the number of VF cycles was used as the only factor in the analysis of variance. In protocol 2, both the number of VF cycles and location of VF induction were used as repeated factors. Post hoc comparisons between individual levels were carried out using the Student-Newman-Keuls test. The VF duration was compared between RV and LV VF inductions using repeated measures analysis of variance. For all statistical tests, the critical level of the statistic for rejection of the null hypothesis was set at $p = 0.05$.

Results

Protocol 1: The Defibrillation Threshold During Early Ventricular Fibrillation

The DFT was markedly reduced very early during VF, rising rapidly for the first four successive VF cycles (Table 1 and Fig. 2). The DFTs then rose more gradually with an
increase in the number of VF cycles and reached a plateau similar to the control DFT after approximately 25 VF cycles. The mean DFTs were significantly lower for the first three cycles, but there was a large amount of variability in the DFTs among animals. For example, for shocks delivered after the first VF activation, the DFT was <2 J in three animals and >8 J in two animals. As expected, the duration of VF increased with the number of VF cycles (Table 1).

Protocol 2: The Effect of Ventricular Fibrillation Initiation Site on Defibrillation Threshold

As in protocol 1, early during VF DFTs were reduced when VF was initiated from the right ventricular apex in close proximity to the defibrillation electrode (Fig. 3). DFTs were also reduced for early VF initiated from the posterolateral LV. However, the DFTs for VF induced from the LV were higher than the comparable DFTs for VF induced from the RV. There were significant reductions in the DFTs for the first four VF cycles initiated from the right side and the first two cycles initiated from the left side compared with the control DFT given after 10 s of VF. The duration of VF for the LV versus VF induction for the RV was longer by an average of 42 ms, a difference that was significantly different (Table 2).

Discussion

The major finding of this study is that the DFT is markedly lower very early during VF compared with the DFT 10 s later. When the electrode used to induce VF and the defibrillation electrode were both in the RV, the DFT energy during the first cycle of VF was only about 20% of the DFT after 10 s of VF. Even when VF was induced from an electrode on the opposite side of the heart from the defibrillation electrode, the DFT energy during the first cycle of VF was less than half that after 10 s of VF. These findings, that the DFT is lower during very early VF whether it is initiated near or away from the defibrillation electrode but that the DFT is lower when it is initiated near the defibrillation electrode than when it is initiated far from the electrode, suggest that two types of factors are responsible for this decrease in DFT: local factors in the region from which VF originates for the first few cycles and global factors that involve all of the ventricular myocardium.

Local factors. The most marked decrease in the DFT during very early VF was observed when the defibrillation electrode was located in close proximity to the site from which VF was initiated. The reason for this effect may be understood by examining the mechanism by which an electrical stimulus can halt an arrhythmia. One mechanism is by the potential gradient field of the stimulus altering the transmembrane potential in the arrhythmogenic region sufficiently to excite tissue or cause refractory period prolongation that halts the arrhythmia (9,10). The magnitude of the potential gradient is one factor that is directly related with the amount of membrane polarization by the stimulus (11), although other factors such as tissue anisotropy and fiber curvature have also been shown to be important (12–15). Because the potential gradient field falls off rapidly away from the defibrillation electrode, (4,5) an electric stimulus will alter the transmembrane poten-
tial more in the region near the electrode than in the tissue farther away.

A second mechanism by which the electrical stimulus may halt the arrhythmia is by initiating an activation front near the stimulating electrode that propagates into the arrhythmogenic region to halt the arrhythmia (16–20). Whichever of these two mechanisms is operative, the finding from this study that the DFT during early VF is lower when the shock is delivered from the same region in which VF is induced is consistent with previous findings, that for the first few cycles of electrically induced VF the arrhythmia is maintained by activation fronts that arise from the localized region around the site of induction (2, 21).

The existence of the protective zone also suggests that VF arises from the localized region around the initiating electrode site for a short time after the induction of the arrhythmia (22). After a large, premature electrical stimulus that would otherwise initiate VF, a later stimulus, if given during a certain time interval, can prevent the induction of VF. This time interval is called the protective zone and is present only during a portion of each VF cycle. Stimuli given at other times will result in the continuation of VF, by having no effect on the reentrant circuit or changing the activation pattern without terminating the arrhythmia (23). It has been shown that the stimulus during the protective zone must be given from an electrode that is near the site from which the large, premature stimulus is given and must fall within this narrow interval (22, 24, 25), again suggesting that up to the time of the protective zone the arrhythmia arises just from the region around the initiating electrode. It has recently been shown that recurrent protective zones occur following a strong premature stimulus that, in the absence of later protective stimuli, will induce VF (25). Recurrent protective zones have been shown to be present for at least portions of three or four cycles following the initial strong stimulus, although the time within the VF cycle at which the protective zone occurred was different in different animals. This finding is consistent with the concept that VF originates from this localized region for at least three or four cycles and is consistent with our finding that the DFT is low for this number of cycles. It may also explain why in protocol 1 the DFT during the first cycle of VF was \(< 2 J\) in three animals but \(> 8 J\) in two animals; the shocks may have been more consistently delivered during the protective zone in the three animals with the very low DFT and not delivered during the protective zone in the two animals with the higher DFTs. It should be noted that in both protocols there was variability within and between animals in the coupling intervals between the last activation and the shock. For this reason, shock timing within the VF cycle was not constant. Similarly, rarely were shocks delivered synchronously with the last VF activation. On the other hand, variations in catheter placement and the distance between the pacing catheter and the defibrillation catheter may also have affected the variability in DFT measurements between animals.

In addition to electrically induced VF, there is evidence that spontaneously occurring VF also frequently arises from a localized region for a short time after its initiation. For example, multichannel computer-assisted mapping of VF initiation caused by acute ischemia or acute ischemia followed by reperfusion indicates that for several cycles activation fronts originate from a localized region and propagate across the remainder of the ventricles (26–28). Thus, if it were possible to predict the portion of the myocardium from which VF would spontaneously arise, then a defibrillation electrode placed in this region might also have a very low DFT early during VF.

Global factors. Although not as low as when VF is initiated near a defibrillation electrode, the DFT is lower during early VF even when the site of initiation is distant from the defibrillation electrode (Fig. 3). There are several factors that may be responsible for this effect. A number of changes occur rapidly after the loss of blood flow following the development of VF. These changes include ischemia, elevated extracellular potassium, elevated extracellular pH, and elevated sympathetic discharge (29–38). These changes may increase the DFT. Very early in VF, these changes have not had time to develop, so that the DFT may be lower. Dilation of the heart, which occurs rapidly after the onset of VF (39), may decrease the potential gradient in that part of the heart by increasing its distance from the defibrillation electrode and by increased current shunting through the blood in the enlarged ventricular cavities (40). In this case, a larger shock would be required to achieve the necessary potential gradient, which would increase the DFT.

As can be seen from Tables 1 and 2, the activation rate during VF is fast and becomes even more rapid over the first few VF cycles. Through accommodation, the refractory period should progressively shorten during these first few cycles, decreasing the wavelength (26), which may increase the DFT. Because all activation fronts arise from a single region and the refractory period is longer during very early VF, fewer activation fronts may be present over the entire ventricular myocardium during this time; and these activation fronts may be more organized and coherent. This may lead to a more homogeneous dispersion of refractoriness early during VF, which may decrease the likelihood that the shock field induces new reentrant activation fronts that reinitiate VF (41–43).

Clinical implications. This study emphasizes the importance of intervening with a shock early even if the defibrillation electrodes are not near the site of VF to terminate VF with a low shock strength and a high success rate. Current implantable cardioverter and/or defibrillator systems used in patients require the detection of VF and charging of the capacitors before the delivery of shock therapy. The results of this study are not applicable to these devices because many patients with nonsustained arrhythmias would receive inappropriate therapy. This may change as our ability to predict the onset of spontaneous VF improves. For instance, Pozzatti et al. (44) have demonstrated a decrease in heart rate variability before the onset of sudden death in patients who were wearing Holter monitors at the time of their event (44). If the onset of the event can be predicted, then the capacitors could be charged in anticipation of the event and therapy delivered within a few beats of the arrhythmia. In addition, capacitor technology may improve to allow faster charge times or constant charge...
storage. Some patients, especially those with frequent ectopy or nonsustained ventricular tachycardia, would not be candidates for this mode of therapy because many of their short-lived arrhythmias would receive unnecessary shocks. The potential for proarrhythmia or a worsening of the DFT by these shocks is also possible (23,25).

These concepts could also be applied to the delivery of shocks for atrial fibrillation. For this arrhythmia, the potential advantages may be even greater, because a major limitation of atrial defibrillation is the discomfort associated with shock delivery in a conscious patient. Most studies report an atrial DFT of 0.5 to 3.7 J using a right atrial appendage to coronary sinus electrode system (45–47), whereas the pain threshold ranges from 0.1 to 1.5 J (46,47). If the same decrease in the atrial DFT is seen for shocks delivered early during atrial fibrillation as for shocks delivered early during VF, then shocks well below the pain threshold of most patients could be delivered. Except for its effects on device longevity, the problem of inappropriate shocks for frequent atrial ectopy would be mitigated because little or no sensation would be associated with shock delivery. Another potential benefit is that shocks below the VF threshold might be delivered, decreasing the probability of VF induction and increasing the safety of the atrial implantable defibrillator. The characteristics of early atrial fibrillation and early VF may not be similar, however, so further studies are necessary to test these hypotheses.

**Study limitations.** The primary limitation of this study is the use of an animal model in which the hearts are structurally normal. In addition, the spontaneous VF observed clinically in humans may not have the same characteristics in its early phase as VF induced by stimulation during the ventricular vulnerable period. Studies in humans with spontaneously occurring VF would be required to confirm our results and justify their useful application in a clinical setting. The use of a sensor that relies on a minimum dV/dt to record VF activations may introduce some error in the timing of shock delivery if undersensing or oversensing occurs due to irregularity of the bipolar electrogram. The variability of the VF duration, however, was small for the first five VF activations, but progressively increased as the number of VF activations increased. This indicates that the timing of shock delivery was fairly constant for the first five VF activations, but became less as VF progressed, most likely as a result of increasingly disorganized activations and electrograms, as previously discussed. As already discussed, the protective zone phenomenon may have contributed to the results of our study. Because of the variability of the shock timing within the VF cycle and the variability of protective zones between animals, it is unlikely that shocks were consistently delivered within the protective zone. Finally, the VF duration was longer by an average of 42 ms when VF was induced from the LV in protocol 2. This difference was most likely related to the longer time needed for activation fronts arising from the left ventricular initiation site to propagate to the right ventricular sensing electrode compared with the RV initiation site. Although this could partly explain the difference in the DFTs between the two sites, it is unlikely because the DFTs for VF induced from the RV were still lower even when the VF duration was longer, i.e., the DFT after four activations for VF initiated from the RV was lower than the DFT after three activations for VF initiated from the LV, despite the former having a longer VF duration.

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**References**


