

The Influence of Ventricular Fibrillation Duration on Defibrillation Efficacy Using Biphasic Waveforms in Humans

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Objectives. The purpose of this study was to prospectively investigate the influence of ventricular fibrillation (VF) durations of 5, 10 and 20 s on the defibrillation threshold (DFT) during implantable cardioverter-defibrillator (ICD) implantation.

Background. Although the DFT using monophasic waveforms has been shown to increase with VF duration in humans, the effect of VF duration on defibrillation efficacy using biphasic waveforms in humans is not known.

Methods. Thirty patients undergoing primary ICD implantation or pulse generator replacement were randomly assigned to have the DFT determined using biphasic shocks at two durations of VF each (5 and 10 s, 10 and 20 s or 5 and 20 s).

Results. There was no statistically significant difference in the

mean DFT comparing VF durations of 5 s (9.5 ± 6.0 J) and 10 s (10.8 ± 7.0 J) ($p = 0.4$). The mean DFT significantly increased from 10.9 ± 6.1 J at 10 s of VF to 12.6 ± 5.6 J ($p = 0.03$) at 20 s of VF, and from 7.0 ± 3.5 J at 5 s of VF to 10.5 ± 6.3 J ($p = 0.04$) at 20 s of VF. An increase in the DFT was observed in 14 patients as VF duration increased. There were no clinical characteristics that differentiated patients with and without an increase in the DFT.

Conclusions. Defibrillation efficacy decreases with increasing VF duration using biphasic waveforms in humans. Ventricular fibrillation durations greater than 10 s may negatively affect the effectiveness of ICD therapy.

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Defibrillation efficacy is defined by a sigmoidal-shaped probability function with a gradual transition from unsuccessful to successful shocks as the shock strength is increased rather than by a discretely defined value (1–3). Although the mechanism for the probabilistic nature of defibrillation remains unclear, several factors have been identified that influence defibrillation efficacy, including shock waveform and polarity (4–7), chronicity of lead implantation (8,9), electrode size (10–12), location (12–16), material (17) and geometry (18), drug therapy (15,19–22) and heart and body weight (23–25).

The effect of ventricular fibrillation (VF) duration on defibrillation efficacy is, however, not well established. Using monophasic waveforms, Echt et al. reported an increase of the defibrillation threshold (DFT) comparing VF durations of 5 and 30 s (26). In contrast, although Bardy et al. found no change in defibrillation efficacy using monophasic waveforms with VF duration of 10 and 20 s in humans during implantable cardioverter-defibrillator (ICD) implantation (27), the same group of investigators found an increase in the DFT after unsuccessful monophasic first shocks (28).

Biphasic waveforms defibrillate with greater efficacy than monophasic waveforms (29–32), and have largely replaced other waveforms in contemporary devices. In isolated rabbit hearts, biphasic waveforms provide lower energy and voltage defibrillation thresholds than monophasic shocks at VF durations to 30 s, and the relative efficacy of biphasic shocks improves with increasing VF duration (33). Furthermore, a recent study examining the influence of VF duration using biphasic waveforms in pigs reported a paradoxical decrease in defibrillation energy with VF duration up to 20 s using biphasic waveforms (34). However, the effect of VF duration on defibrillation efficacy using biphasic waveforms has not been studied in humans.

The effect of VF duration on defibrillation efficacy is of particular importance, since current generation ICDs have options for programming low energy cardioversion and anti-tachycardia pacing that can lead to prolonged arrhythmia duration before defibrillation. Thus, this study was designed to investigate the influence of VF durations on defibrillation efficacy using biphasic waveforms in humans.

Methods

Patient population. In accordance with institutional guidelines, written, informed consent was obtained from all patients within a protocol approved by the Institutional Review Board of the University of Alabama at Birmingham. Thirty patients

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Abbreviations and Acronyms

DFT = defibrillation threshold
 ICD = implantable cardioverter–defibrillator
 VF = ventricular fibrillation

undergoing primary ICD implantation or pulse generator replacement were enrolled. Their demographic data are described in Table 1. All patients who were thought able to give consent and complete the protocol were approached. None refused participation. There was one patient enrolled who did not complete the protocol because his lead dislodged after the first set of DFT tests. The protocol was not repeated after the lead was repositioned.

According to a computer-generated random number sequence, patients were assigned to one of three groups with 10 patients in each. The DFT was determined twice in each patient: at VF durations of 5 and 10 s in Group 1, 10 and 20 s in Group 2 and 5 and 20 s in Group 3 (Fig. 1). Since the primary aim of the operations was safe and successful ICD implantation, VF durations of 5–10 s were tested first (in accordance with usual practice) to assure a satisfactory DFT for implantation. Thus, DFTs in Groups 1 and 2 were determined first at 10 s of VF, followed by a second determination at 5 or 20 s of VF, respectively. In Group 3, DFTs were determined first at 5 s of VF followed by a second determination at 20 s of VF.

Defibrillator implantation and defibrillation threshold testing. All procedures were performed in the electrophysiology laboratory of the University of Alabama at Birmingham. General anesthesia with isoflurane was used in five patients and intravenous sedation with midazolam and fentanyl in the 25 others. Electrocardiograms and electrograms were displayed online and recorded (Cardiolab, Prucka Engineering,

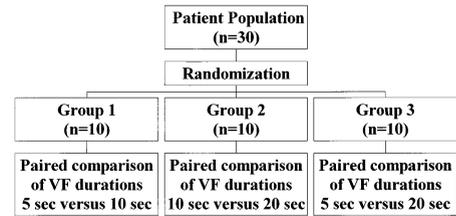


Figure 1. Description of the patient groups. VF = ventricular fibrillation.

Houston, TX). Details of the implantation procedures are summarized in Table 2.

Defibrillation threshold testing commenced after the defibrillation electrodes were appropriately positioned or, in the case of previously implanted leads, after removal of the old pulse generator. All testing was performed using an external programmable defibrillator (HVS-02, Ventritex, Inc., Sunnyvale, CA). All shocks were biphasic with equal first and second phase durations, first and second phase capacitances of 150 and 300 μF respectively and leading edge voltages of the second phase equal to 50% of the trailing edge voltage of the first phase. After a low energy test shock was delivered to measure the defibrillation system impedance, the pulse width was optimized for the test shock impedance for further testing. For each subsequent shock, the external defibrillator automatically calculated the delivered energy in joules based on the measured defibrillation system impedance.

Ventricular fibrillation was induced with burst pacing, and diagnosed when the surface electrocardiogram was grossly disorganized without clearly defined QRS complexes. Other arrhythmias were not included in the analysis. Ventricular fibrillation duration was defined as the time from the onset of burst pacing to the delivery of the test shock, measured using electronic calipers. The time of pacing was included in the VF duration, since it allowed for easy timing of shock delivery, and hemodynamic collapse always occurred during the pacing train.

The first shock was given at a leading edge voltage of 400 V. If unsuccessful, a high energy rescue shock was delivered. In the case of successful defibrillation, the shock strength was decremented by 100 V, and in the case of an unsuccessful

Table 1. Demographics

Clinical Characteristic	Number (%)
Number	30 (100)
Age (years)	61 \pm 12
Gender (male/female)	22/8 (73/27)
Left ventricular ejection fraction	0.32 \pm 0.12
Cardiac disease	
Coronary artery disease	20 (67)
Dilated cardiomyopathy	5 (17)
Valvular heart disease	2 (6)
Arrhythmogenic right ventricular dysplasia	1 (3)
Idiopathic ventricular fibrillation	2 (6)
Presenting arrhythmia	
Sustained ventricular tachycardia	17 (57)
Ventricular fibrillation	13 (43)
Antiarrhythmic drug therapy	
Amiodarone	6 (20)
Sotalol	1 (3)

Table 2. Implantation Procedures

Procedure	Patients
Primary ICD implantation	21
ICD generator replacement	9
Endocardial leads	21
Endocardial leads and subcutaneous patch electrode	2
Epicardial leads	7
Pectoral pocket	20
Abdominal pocket	10
General anesthesia	5
Conscious sedation	25

ICD = implantable cardioverter–defibrillator.

Table 3. Defibrillation Threshold Data

	Group 1			Group 2			Group 3		
	5-s VF	10-s VF	p Value	10-s VF	20-s VF	p Value	5-s VF	20-s VF	p Value
Energy (J)	9.5 ± 6.0	10.8 ± 7.0	0.40	10.9 ± 6.1	12.6 ± 5.6	0.03	7.0 ± 3.5	10.5 ± 6.3	0.04
Voltage (V)	365 ± 108	385 ± 131	0.34	390 ± 113	425 ± 107	0.07	320 ± 86	385 ± 118	0.05
Impedance (ohms)	49.7 ± 8.7	50.4 ± 9.4	0.25	49.1 ± 7.6	48.7 ± 9.1	0.58	57.8 ± 16.0	55.7 ± 16.4	0.07
VF duration (s)	5.6 ± 0.4	9.9 ± 0.5	—	10.2 ± 0.7	20.0 ± 0.5	—	5.5 ± 0.3	19.8 ± 0.4	—

VF = ventricular fibrillation.

shock increased by 100 V until an outcome reversal was observed. After the first outcome reversal, the shock strength was increased by 50 V if the prior shock had failed to defibrillate, or decreased by 50 V if the prior shock was successful. The DFT was defined as the lowest shock energy resulting in successful defibrillation. Each VF induction and defibrillation sequence was separated by a minimum of 5 min. After the DFT was determined for one VF duration, the procedure was repeated in identical fashion for the second VF duration.

Statistical analysis. Continuous variables were expressed as mean ± 1 SD. Nominal variables were compared by chi-square analysis. Paired data were compared using the Wilcoxon Signed Rank Test. Unpaired data were compared using simple regression analysis. Statistical significance was defined as $p < 0.05$.

Results

Paired comparison of DFT at VF durations of 5, 10 and 20 s. The defibrillation threshold data for voltage, energy and impedance are summarized in Table 3. For patients in Group 1, the DFT of 9.5 ± 6.0 J (365 ± 108 V) at 5 s of VF was not different from the DFT of 10.8 ± 7.0 J (385 ± 131 V) at 10 s of VF ($p = 0.4$, Fig. 2). For patients in Group 2, the DFT increased by 16% from 10.9 ± 6.1 J (390 ± 113 V) at 10 s of VF to 12.6 ± 5.6 J (425 ± 107 V) at 20 s of VF ($p = 0.03$, Fig. 3). Similarly, for patients in Group 3, the DFT increased by 50% from 7.0 ± 3.5 J (320 ± 86 V) after 5 s of VF to 10.5 ± 6.3 J (385 ± 118 V) after 20 s of VF ($p = 0.04$, Fig. 4). Thus, although there was no difference in the DFT at 5 and 10 s of

VF, energy requirements significantly increased at 20 s compared with both 5 and 10 s of VF.

Unpaired comparison of DFT at VF durations of 5, 10 and 20 s. The mean DFT increased from 8.3 ± 4.9 J at 5 s of VF to 10.8 ± 6.4 J and 11.5 ± 6.0 J at 10 and 20 s of VF, respectively ($p = 0.08$, Fig. 5). The mean number of DFT tests/VF inductions done for the 5-, 10- and 20-s groups (20 tests for each) were 4.3 ± 1.3 (range 3 to 9), 5.0 ± 1.9 (range 3 to 10) and 5.1 ± 1.6 (range 3 to 10), respectively.

With increasing VF duration, the DFT increased by at least 1 J in 14 patients (47%), remained unchanged in 14 patients and decreased in 2 patients. Clinical characteristics did not predict DFT changes (Table 4). In Group 1, the DFT increased in four patients from 8.3 ± 3.1 J (350 ± 71 V) to 12.4 ± 6.1 J (425 ± 104 V) ($p = 0.07$), remained unchanged in five patients at 11.2 ± 8.0 J (390 ± 143 V), and decreased in one patient from 6 J (300 V) to 2.6 J (200 V). In Group 2, the DFT increased in four patients from 7.6 ± 2.2 J (338 ± 48 V) to 12.0 ± 3.6 J (425 ± 65 V) ($p = 0.07$) and remained unchanged in six patients (13.0 ± 7.0 J, 425 ± 135 V). In Group 3 the DFT increased in six patients from 7.5 ± 4.5 J (325 ± 113 V) to 14.0 ± 5.8 J (450 ± 110 V) ($p = 0.03$), remained unchanged in three patients (6.4 ± 1.2 J, 317 ± 29 V) and decreased in one patient from 7.8 J (350 V) to 5.7 J (300 V).

Discussion

This study demonstrates that defibrillation efficacy using biphasic waveforms decreases with increasing VF duration in humans. Although there was no difference in the DFT at 5 and 10 s of VF, the DFT increased significantly at 20 s compared

Figure 2. Change in the defibrillation threshold energy at ventricular fibrillation (VF) durations of 5 and 10 s.

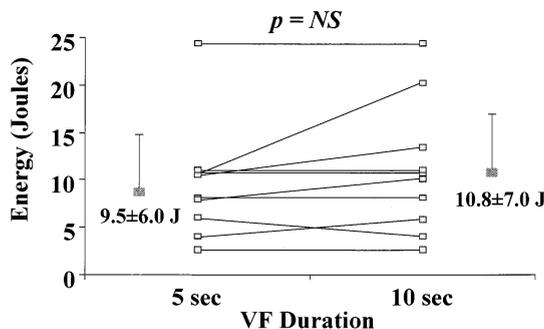
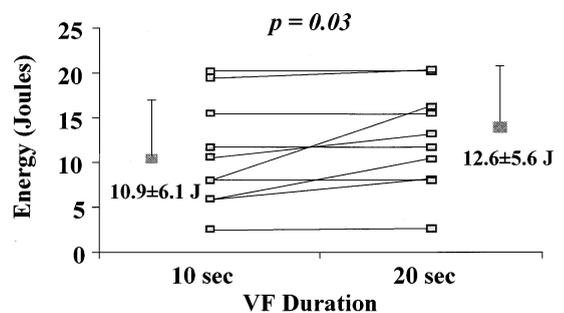


Figure 3. Change in the defibrillation threshold energy at ventricular fibrillation (VF) durations of 10 and 20 s.



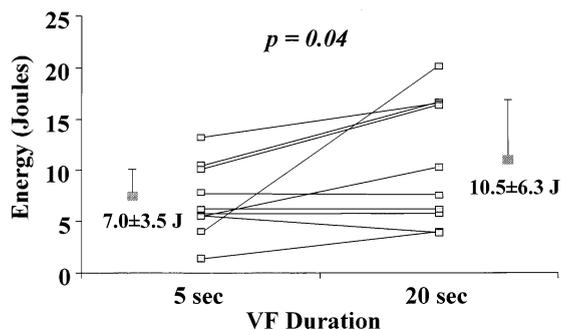


Figure 4. Change in the defibrillation threshold energy at ventricular fibrillation (VF) durations of 5 and 20 s.

with both 5 and 10 s of VF. The increase of the mean DFT was a modest 16% comparing VF durations of 10 and 20 s, but increased by 50% comparing VF durations of 5 and 20 s. Despite these VF duration–dependent changes in DFT, an appropriate safety margin to allow implantation of the device was demonstrated in all patients.

Although the VF duration–dependent increase in DFT was observed in 14 of 30 patients, it remained unchanged in 14 and decreased in 2. Thus, rather than a gradual VF duration–dependent increase in DFT in all patients, the DFT did not change in about half of the patients and increased substantially in the other half. In those patients with an increased DFT, the changes were large, with a mean increase of 49% (8.3 J vs. 12.4 J) comparing 5 and 10 s, 58% (7.6 J vs. 12.0 J) comparing 10 and 20 s and 87% (7.5 J vs. 14.0 J) comparing 5 and 20 s. Clinical variables did not predict which patient would exhibit a VF duration–dependent increase in DFT.

Previous studies. The effect of VF duration on defibrillation efficacy has been previously investigated in various species at several VF durations using different waveforms and experimental designs that may have resulted in discordant findings. Thus, for monophasic waveforms, as VF duration increases, the DFT has been reported to increase in dogs (26) and humans (35,36), and to remain unchanged in pigs (37), dogs (38) and humans (27). Bardy et al. compared the efficacy of monophasic waveforms during ICD implantation via thoracotomy or pulse generator replacement in 10 patients and found

Figure 5. Grouped data for the defibrillation threshold energy for all patients (20 each tested at 5, 10 and 20 s of ventricular fibrillation [VF], respectively).

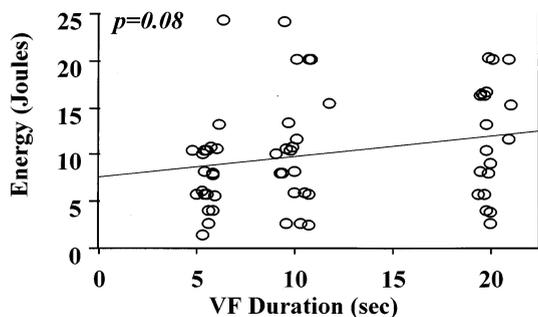


Table 4. Influence of Clinical Characteristics of Defibrillation Threshold

	Increase in DFT	No Change in DFT	p
Patients (n)	14	16	NS
Age (yr)	58 ± 14	63 ± 10	NS
Gender (male/female)	9/5	13/3	NS
Left ventricular ejection fraction	0.36 ± 0.15	0.29 ± 0.09	NS
Cardiac disease			
Coronary artery disease	8	12	NS
Dilated cardiomyopathy	2	3	NS
Presenting arrhythmia			
Sustained ventricular tachycardia	7	10	NS
Ventricular fibrillation	7	6	NS
Amiodarone therapy	3	3	NS

DFT = defibrillation threshold.

no difference in DFT at 10 and 20 s of VF (27). The same investigators have also shown that an unsuccessful monophasic first shock was associated with a 61% increase in the DFT for the second shock (28). It was hypothesized that the time difference between VF termination with (28 ± 6.2 s) and without (12.4 ± 3.5 s) a first unsuccessful shock may have been responsible for this difference. Winkle et al. reported higher defibrillation efficacy at 5 than 15 s of VF using monophasic waveforms (35). Platia et al. found that for monophasic shocks, prolonging VF duration from 5 to 15 and to 25 s increased the DFT from 7 ± 4 to 13 ± 4 and 23 ± 8 J, respectively (36).

Biphasic waveforms have replaced monophasic waveforms in contemporary ICDs due to their superior defibrillation efficacy (4,10,29,33,39) and less traumatic effects on cardiac tissue (31,32,40). The mechanism responsible for the increased efficacy is not known. It has been hypothesized that biphasic waveforms require a lower potential gradient field for successful defibrillation (41), are less (42) or more (43) able to excite refractory myocardium and are less likely to cause conduction block and reentry in high potential gradient areas (44).

The effect of VF duration on defibrillation efficacy using biphasic waveforms was first reported by Jones et al. using an isolated rabbit heart model (33). Although defibrillation energy requirements increased for monophasic waveforms in this study, the mean DFT remained unchanged for biphasic waveforms at 5, 15 and 30 s of VF. The investigators speculated that the stabilizing effect of biphasic waveforms on defibrillation requirements was a result of the first phase of the waveform causing recovery of excitation channels in depolarized, partially refractory ventricular cells. In a recent study examining the effect of VF duration in pigs using biphasic waveforms, a paradoxical decrease of defibrillation requirements was observed at 20 s compared with 10 s of VF (34).

The present study is the first to investigate defibrillation efficacy of biphasic waveforms at different VF durations in humans. In contrast to the experimental data in animals, defibrillation requirements increased significantly beyond 10 s of VF. This difference may be the result of interspecies differences, or because of differences in the arrhythmia sub-

strate and experimental design. Furthermore, a stabilizing effect of biphasic waveforms on DFT in humans at VF durations beyond 20 s cannot be excluded, since they were not investigated in this study. However, our data are in concert with the VF duration–dependent increase in the DFT using monophasic waveforms in humans reported by Winkle et al. (35) and Platia et al. (36), and with their observations of high defibrillation efficacy at particularly short (5-s) VF durations.

Limitations. There are several limitations to the present study. First, there was considerable variation in lead configuration, chronicity of the implanted leads and pulse generator location. However, since each patient served as his own control, the potential for error was minimized. Second, the influences of general anesthesia and intravenous sedation on autonomic tone and the DFT are unknown. However, the use of anesthesia and sedation conforms to standard practice. Third, only biphasic waveforms were used in this study. The influence of VF duration on the DFT when other waveforms are used is unknown.

Fourth, VF was induced in this study by burst pacing. There are various methods to induce VF, including alternating current, T wave shocks and burst pacing, and their impact on the DFT is not known. However, it is conceivable that each method results in a different form of VF with various numbers of activation fronts and cycle lengths that may change with time, and therefore, have influence on defibrillation efficacy.

Fifth, defibrillation at 20 s always followed testing after determination of the DFT at 5 or 10 s, which might have biased the results against the 20-s tests. However, this approach was chosen because the primary purpose of the procedure was to implant an ICD, and testing more traditional VF durations to establish defibrillation efficacy allowed this determination to be made before the investigation portion of the study was undertaken. It is impossible to know just how much of an effect the performance of this order of testing had on the study results.

Sixth, the present study does not provide evidence for the mechanism responsible for the increased defibrillation energy requirement when VF duration is prolonged. Possible explanations include increased ischemia that results in extra- and intracellular metabolic derangements, changes in the myocardial cell membrane, an increase in heart size due to diastolic filling that decreases defibrillation efficacy (45) and evolutionary changes of VF characteristics, such as VF cycle length and number and size of activation fronts at the time of shock delivery. Finally, no longitudinal follow-up was performed to assess the reproducibility of the findings.

Clinical implications. The observations made in the present study have several theoretical and practical implications related to DFT testing and programming of contemporary ICD devices. First, VF duration during DFT determination should be standardized, at least in research protocols, to insure comparability of results between studies and individual patients. If both the energy and VF duration change during testing, the results will reflect not only the change in energy but also the change in VF duration.

Second, although device-based DFT testing is a practical

method to assess defibrillation efficacy, the defibrillation energy requirement determined by this method will depend on not only shock strength but also the arrhythmia detection time and charge time of the device being tested. For example, very high shock strengths that require long charging times (such as 20 s as tested in this study) will shift the probability of success curve toward higher values, whereas low shock strengths having short charging times (<5 s) will shift the probability of success curve toward lower values. Although this may mimic the real-life situation at the beginning of ICD battery life, the term “DFT” in the context of device-based testing is a relative, and potentially misleading term, since as ICD batteries age and charge times prolong, more energy may be needed to defibrillate. Although this may be less relevant to most patients in this era of declining DFTs, the occasional patient with a high DFT at the time of implantation may not have a sufficient safety margin to ensure reliable defibrillation during long-term follow-up (46). Furthermore, for patients with a high DFT and narrow margin of safety for defibrillation, interventions that prolong arrhythmia duration before shock therapy, such as antitachycardia pacing and/or low energy cardioversion, probably should be avoided in the interest of reliable defibrillation.

Finally, the upper limit of vulnerability has been shown to correlate with the DFT in both animals and humans (47–50). An advantage of using the upper limit of vulnerability to determine defibrillation efficacy at ICD implantation is the need for fewer episodes of VF to be tested. Another potential advantage of the upper limit of vulnerability is its independence of VF duration. However, if clinical efficacy in the field depends in part on VF duration, the upper limit of vulnerability may not be as useful as the DFT to establish adequate margins of safety for defibrillation. Furthermore, since comparison of the upper limit of vulnerability with the DFT has usually been done at predetermined VF durations, the correlation between the DFT and the upper limit of vulnerability may be less if different durations were studied.

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