Relation of Atrial Refractoriness to Upper and Lower Limits of Vulnerability for Atrial Fibrillation/Flutter Following Implantable Ventricular Defibrillator Shocks

Amos Katz, MD; Robert J. Sweeney, PhD; Robert M. Gill, BS; Philip R. Reid, MD; Eric N. Prystowsky, MD

Background—Implantable ventricular cardioverter defibrillator (ICD) shocks can cause atrial fibrillation/flutter (AF). This study investigated the pathogenesis of AF after ICD shocks in a canine model.

Methods and Results—The study was conducted in 8 dogs. In 5 dogs (group 1), truncated exponential (8 ms, 78% tilt) monophasic and biphasic shocks were delivered through a bipolar epicardial (patch) or endocardial lead. After the last S1 of atrial pacing at a cycle length of 350 ms, shocks of 0.1 to 7.6 A (0.005 to 27.7 J) were delivered, timed to the atrial effective refractory period (AERP). Ventricular defibrillation thresholds were also determined. In 3 dogs (group 2), the effect of the open versus closed chest technique on AF induction was tested in the endocardial biphasic shock configuration. AF was induced in all 8 dogs and in all waveforms and configurations. Mean AF duration was 11.5±6 s, with a mean ventricular rate of 184±37 bpm. Ventricular shocks could induce AF only if they were timed between an AERP of −60 to 40 ms, −40 to 60 ms, −40 to 60 ms, and −20 to 60 ms in the epicardial monophasic, epicardial biphasic, endocardial monophasic, and endocardial biphasic configurations, respectively. The mean±SD of the upper limit of vulnerability (ULV) for AF induction (in J) was 5.2±0.6, 3.5±0.4, 5.2±1.2, and 2.5±0.1 for the epicardial monophasic, epicardial biphasic, endocardial monophasic, and endocardial biphasic configurations, respectively (P<0.05). The lower limit of vulnerability (LLV) was 0.8±0.1, 0.8±0.1, 0.9±0.0, and 0.6±0 for the epicardial monophasic, epicardial biphasic, endocardial monophasic, and endocardial biphasic configurations, respectively (P=NS). The ventricular defibrillation threshold (in J) for all wave forms and configurations was higher than the ULV (P<0.05).

Conclusions—(1) An atrial LLV and ULV exist for ventricular ICD shock–induced AF; (2) the shock-induced AF is independent of atrial sensing capability. Thus, an improved understanding of the relationship between atrial electrical activity and ventricular shock may lead to overall improvement in defibrillation therapy. Although in clinical practice, the induction of atrial fibrillation with ventricular defibrillation shock is infrequent, ventricular cardioversion using lower energy is not a rare event. The growing number of dual-chamber defibrillators implanted and the capability to synchronize ventricular shocks for stable ventricular arrhythmia to atrial electrical activity have major implications for the application of atrially and ventricularly triggered shocks. The purpose of this study was to determine the mechanism of AF induction by ICD shocks and its relationship to atrial refractoriness and ventricular shock current.

Key Words: atrium • defibrillation • electrophysiology • fibrillation

Atrial fibrillation or atrial flutter (AF) may occur after successful high-energy transthoracic or low-energy epicardial or endocardial cardioversion and defibrillation for ventricular tachyarrhythmias. The mechanism postulated for AF induction by ventricular cardioversion or defibrillation is energy delivery during the atrial vulnerable period. An upper limit of vulnerability (ULV) was postulated for AF induction after endocardial defibrillation. The incidence of AF after implantable ventricular defibrillator (ICD) shocks may be up to 23%, and its occurrence may result in hemodynamic compromise, repeated and/or unnecessary shocks, waste of energy, and patient discomfort.

The latest generations of dual-chamber ICDs have atrial sensing and pacing capabilities. The application of a test or therapeutic shock synchronized to the ventricle, with a regular sinus rhythm in the atria, may fall into the atrial refractory period independent of atrial sensing capability. Thus, an improved surgical preparation

Surgical Preparation

Eight healthy adult mongrel dogs (24.8±3.1 kg) were anesthetized with sodium pentobarbital (35 mg/kg induction; 4 mg · kg⁻¹ · h⁻¹ induction).
After the closed-chest part of the experiment, the atrial and the proximal 2 electrodes were used for recording the right atrial electrogram under fluoroscopic guidance to the right ventricular apex. A 7-F electrode was introduced through the right jugular vein and advanced into the right atrium. Two bipolar plunge electrodes were placed in the right and left atrial appendices, respectively, and used to record the right and left atrial electrograms. In the epicardial configuration, a bipolar plunge electrode was placed in the right ventricular outflow tract and the 2 small patch electrodes at the lateral left ventricular apex (cathode) and lateral right ventricular apex (anode). In the endocardial configuration, the right ventricular outflow tract bipolar plunge electrode and the 2 small patch electrodes were removed, and an Endotak lead was left in the right ventricular apex. The Endotak lead was left in the right ventricular apex.

Maintenance, intubated, and ventilated with room air. The right femoral artery and vein were cannulated to measure arterial pressure and deliver fluids. In the first 5 dogs (group 1; Figure 1), both epicardial and endocardial lead configurations were tested, as were monophasic and biphasic shocks in all dogs. The order of testing was randomized for epicardial and endocardial configurations and for the monophasic and biphasic waveforms. After a left thoracotomy was performed in these dogs, a bipolar plunge electrode was placed in the right atrial lateral wall near the sinus node and used to pace the right atrium. Two bipolar plunge electrodes were placed in the right and left atrial appendages, respectively, and used to record the right and left atrial electrograms. In the epicardial configuration, a bipolar plunge electrode was placed in the right ventricular outflow tract and used to record the right ventricular electrogram and the induction of ventricular fibrillation. Shocks were delivered via 2 small patch electrodes (A67, Cardiac Pacemakers, Inc) that were sutured to the lateral left ventricular apex (cathode) and lateral right ventricular apex (anode). In the epicardial configuration, the right ventricular outflow tract bipolar plunge electrode and the 2 small patch electrodes were removed, and an Endotak defibrillation lead system (C0052, Cardiac Pacemakers, Inc) was positioned manually through the right jugular vein so that the distal electrode was in the right ventricular apex and the proximal electrode was in the superior vena cava. The tip electrode was used to record the right ventricular electrogram and the induction of ventricular fibrillation. If the epicardial configuration was used first, the Endotak electrode was removed and the epicardial configuration was installed. After electrode placement, the pericardium was closed, the ribs were approximated, and the skin was closed.

In 3 other animals (group 2; Figure 1), only the endocardial biphasic configuration was used, in an open or closed chest preparation, to test the effect of thoracotomy and pericardiotomy on AF induction. Beginning with a closed chest animal, an Endotak electrode was introduced through the right jugular vein and advanced under fluoroscopic guidance to the right ventricular apex. A 7-F quadripolar deflectable tip electrode was introduced through the left jugular vein and advanced under fluoroscopic guidance to the high lateral right atrial wall. The distal 2 electrodes were used for pacing, and the proximal 2 electrodes were used for recording the right atrial electrogram. After the closed-chest part of the experiment, the atrial electrode was taken out, a left thoracotomy was performed, and a bipolar plunge electrode was placed in the right atrial lateral wall near the sinus node and used to pace the right atrium. A plunge electrode was placed in the right atrial appendage for electrogram recording. The Endotak lead was left in the right ventricular apex. ECG lead II, arterial pressure, and right ventricle and right atrial electrograms were continuously monitored and recorded (ES-1000, Gould Inc).

Our institution is accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). These experiments conformed to this group’s guidelines for the use of animals in research and were approved by the institution’s animal use committee.

Pacing and Atrial Effective Refractory Period

The right atrial pacing threshold was determined at a pacing cycle length of 350 ms using a 2.0-ms rectangular pulse, and it was set at twice diastolic threshold for the remainder of the experiment. Right atrial effective refractory period (AERP) was determined using a drive train of 15 beats and premature intervals of 5 ms. The AERP was defined as the longest S1 to S2 interval without an A2. The AERP was retested before every shock timing, and the new AERP was used for the next run.

Shocks

Shocks were delivered using a custom arbitrary waveform defibrillator that produced a controlled current output. The defibrillator was triggered by the pacing stimulator to deliver shocks at selected times after the last S1 of the atrial drive train, and it delivered an 8-ms monophasic or 5 ms/3 ms biphasic truncated exponential (78% tilt) shock to the epicardial patches or the Endotak lead. Because the shocks were delivered by a defibrillator that produced a controlled current output (in amps), the potential was measured in volts for each shock, and the energy was calculated in joules.

Experimental Protocol

At the start of testing for each lead configuration, the current required for 50% success at ventricular defibrillation (I50) was measured for both waveforms using a previously reported,31 three-reversal up/down method. The protocol (Figure 1) consisted of determining the AERP, delivering ventricular shocks of different currents at various timings before and after AERP, and observing the presence or absence of AF after each shock. All measurements (see below) for a selected shock timing (80 ms before to 80 ms after AERP in 20-ms steps or 10-ms steps if no AF was induced in the last timing) were made before the next shock timing was used (Figure 2). Shock timings were selected in random order in each animal. At each

**Figure 1.** Study design. AERP was determined at pacing cycle length of 350 ms. Ventricular shocks of different energies were delivered at various timings before and after AERP and observed for presence or absence of AF after each shock. In group 1, 5 dogs with open chest preparation were all tested in epicardial and endocardial configurations with monophasic and biphasic waveforms. In group 2, 3 dogs were tested only in endocardial biphasic configuration in closed-chest versus open-chest preparations. Ep indicates epicardial; En, endocardial; M, monophasic; B, biphasic; and LS1, last S1.

**Figure 2.** Relationship of ventricular shock to atrial and ventricular activation during shock delivery at 60 ms before AERP (AERP–60), AERP, and 60 ms after AERP (AERP+60). II indicates ECG lead II; BP, blood pressure; RA, right atrial electrogram; and RV, right ventricular electrogram. Arrows indicate ventricular shock; atrial stimulus spike is shown.
timing, the set of measurements was made using either a randomly selected monophasic or biphasic waveform and then repeated for the other waveform.

Upper and Lower Limits of Vulnerability

The lower limit of vulnerability (LLV) of the atrium was defined as the highest intensity threshold below which the ventricular shock would not induce AF. The ULV of the atrium was defined as the lowest intensity threshold above which the ventricular shock would not induce AF (Figure 3).

Electrogram Analysis

Atrial fibrillation was defined as irregular atrial activity seen on the atrial electrogram (Figures 3B and 3C) with a mean cycle length of \(150\) ms. Atrial flutter was defined as regular atrial activity seen on the atrial electrogram with a mean cycle length of \(250\) ms. Both atrial fibrillation and/or flutter episodes were accepted for calculation if they lasted \(>1\) s, and they were cardioverted if they lasted \(>60\) s.

Statistical Analysis

All data are reported as mean±SD. Statistical comparisons were performed using a commercially available software package (JMP, version 3.1, SAS Institute Inc); 0.05 was the level of significance. ANOVA was used to compare trends, and a paired \(t\)-test was used for pooled differences.

Results

We were able to complete the experimental protocol in all animals, and no data were excluded from analysis. The mean AERP over the course of the experiment was \(150±24\) ms, and it did not differ during monophasic or biphasic waveform testing or when using epicardial or endocardial lead configurations. However, AERP increased over the course of the experiment (\(P=0.005\)), from \(136±18\) ms at the start to \(178±21\) ms at the end of the experiment. No significant difference existed between mean AERP measured for epicardial shocks (\(155±12\) ms) versus endocardial shocks (\(148±26\) ms) or monophasic shocks (\(150±16\) ms) versus biphasic shocks (\(147±21\) ms). The mean arterial blood pressure (\(101±7\) mm Hg) and the sinus cycle length (\(437±12\) ms) did not change over the course of the experiment.

Upper and Lower Limits of Vulnerability

Shocks (monophasic or biphasic) in either lead configuration (epicardial or endocardial) at various times with respect to the AERP either did or did not induce AF depending on shock intensity and timing. Figure 4 presents the results of shock intensity as a function of the shock timing relative to right AERP in group 1 experiments. Data are shown for monophasic and biphasic shocks in both lead configurations. In all animals and all configurations, both waveforms had a LLV below which the shock would not induce AF and an ULV above which the shock would not induce AF. Between these thresholds, the shocks consistently induced AF.

In the epicardial configuration, the mean ULV for monophasic shocks was \(5.2±0.6\) J (\(3.3±1.1\) A) and the biphasic mean ULV was \(3.5±0.4\) J (\(2.7±0.9\) A; \(P=NS\)). This pattern of difference was demonstrated in all timings, but it was not statistically significant. In the endocardial configuration, mean ULV for monophasic shocks was \(5.2±1.2\) J (\(3.3±1.6\) A), and the biphasic mean ULV was \(2.5±0.04\) J (\(2.3±0.3\) A; \(P=0.02\)). In the endocardial configuration at

![Figure 3](http://circ.ahajournals.org/)

Figure 3. LLV and ULV determined 20 ms after AERP (AERP+20) in 1 of the dogs using endocardial configuration, biphasic waveform. A, Shock energy of 0.9 J (1.4 A) did not induce AF; B, shock energy of 1.0 J (1.5 A) induced AF; C, shock energy of 4.3 J (3.0 A) induced AF; and D, shock energy of 4.6 J (3.1 A) did not induce AF. LLV is 1.0 J (1.5 A) and ULV is 4.3 J (3.0 A). Abbreviations as in Figure 2.

![Figure 4](http://circ.ahajournals.org/)

Figure 4. Shock intensity as a function of the shock timing relative to AERP in epicardial and endocardial configurations using monophasic (M) or biphasic (B) waveforms in group 1 (dogs 1 to 5). LLV and ULV are shown. Striation areas are time and intensity windows for AF induction for biphasic waveforms. Dotted areas are time and intensity windows for AF induction for monophasic waveforms. *\(P<0.05\) versus monophasic waveform; \#\(P<0.05\) versus monophasic endocardial waveform.
each timing, the difference between the monophasic and biphasic ULV was significant. The mean biphasic endocardial ULV was significantly lower than the monophasic epicardial mean ULV ($P=0.005$), but it was not significantly lower than the biphasic epicardial ULV. The LLV curves for monophasic and biphasic shocks in the epicardial or endocardial configuration were similar ($P=NS$).

**Open Versus Closed-Chest**
A comparison of LLV and ULV values between open and closed chest configurations showed no significant differences (Figure 5) using the endocardial biphasic shock configuration (group 2). The LLV and ULV values for group 2 were similar to the those determined in group 1 experiments (in the endocardial configuration, biphasic waveform). The closed chest model in this group had a wider window of vulnerability, but this difference was not statistically significant.

**Relation of Shock Timing on ULV and LLV**
In group 1 experiments (Figure 4) in the epicardial configuration, monophasic shocks delivered up to 60 ms before AERP could induce AF, whereas biphasic shocks could induce AF only up to 40 ms before AERP ($P=0.08$). In the endocardial configuration, monophasic shocks delivered up to 40 ms before AERP could induce AF, whereas biphasic shocks could induce AF only up to 20 ms before AERP ($P=0.03$). In group 2 experiments, biphasic shocks could induce AF up to 20 ms before AERP. In both configurations, monophasic and biphasic shocks could induce AF up to 60 ms after AERP.

**AF Duration**
Of the 491 episodes of AF induced in the study, the mean duration was 11.5±6 s (range, 1.1 to 60 s), with a mean ventricular cycle length of 326±55 ms during the AF episodes.

**AF During Ventricular Defibrillation**

**Threshold Testing**
During measurement of the ventricular defibrillation threshold ($I_{50}$), 184 episodes of ventricular fibrillation (VF) were induced and terminated by the same waveform and the configuration was tested for LLV and ULV for AF induction. In 9 episodes (4.8%), VF was terminated and AF was induced. This corresponds to 3.0% (3 of 65) of the endocardial shocks and 5% (6 of 119) of the epicardial shocks ($P=NS$) or to 5.0% (7 of 138) of the biphasic shocks and 4.3% (2 of 46) of the monophasic shocks ($P=NS$). During the VF episodes, the ventricular and atrial electrograms were recorded, and the time relationship between the ventricular shocks and the atrial electrical activity was analyzed. AF was induced only when the ventricular shock was delivered within a time window of 100 to 320 ms after right atrial activation (Figure 6A). No AF was induced with a current $<7.7$ J (4 A) or $>37$ J (10 A) (Figure 6B). Of note, the 2 shocks with energy $>21$ J that induced AF were rescue shocks using a rectangular waveform.

**Relationship Between ULV for AF and VF Defibrillation Thresholds**
The mean ULV for AF induction (in J) was lower than the defibrillation threshold (in J) using endocardial biphasic (2.5±0.04 versus 28.0±0.1; $P=0.04$), endocardial monophasic (5.2±0.6 versus 30.0±0.1; $P=0.007$), epicardial biphasic (3.5±0.4 versus 13.0±1.2; $P=0.04$), and epicardial monophasic shocks (5.2±0.6 versus 22.2±0.6; $P<0.01$).

**Discussion**
In this study, we presented new observations on the mechanism of AF induction by ventricular shocks. We demonstrated that in AF initiation, a clear relationship exists...
between the timing of the shock and the atrial refractoriness and shock intensity. No AF could be induced if the shock was delivered 60 ms after AERP or 60 ms earlier than AERP. Biphasic endocardial shocks could induce AF during a smaller time window relative to AERP than monophasic endocardial shocks or monophasic and biphasic waveforms delivered through an epicardial lead system. We demonstrated upper and lower shock intensity thresholds—the ULV and LLV. Shocks with an intensity above the ULV or below the LLV could not induce AF. The mean ULV for biphasic endocardial shocks was lower than the mean ULV for monophasic endocardial, monophasic epicardial, or biphasic epicardial shocks by 43%, 43%, and 15%, respectively.

These findings demonstrate that ventricular shock-induced AF is time and energy dependent. A time-current window exists, wherein a ventricular shock may induce AF if the shock current is between the LLV and ULV. This time-current window and the range between LLV and ULV are smallest for endocardial biphasic shocks.

Upper and Lower Limits of Vulnerability
Previous studies have described a ULV for electrical shock field strength for the induction of ventricular fibrillation. Our study demonstrated that such a phenomenon also exists for the induction of AF in a paced atrium model. Atrial fibrillation is induced and maintained by the atrial disparity of refractoriness and conduction, which allows multiple, simultaneous reentrant wavelets. Defibrillation shocks in the ventricle create a nonuniform field in the atria, with a high potential gradient near the electrodes and a low potential gradient away from the electrodes. The different atrial tissue field stimulation imposed by the ventricular shocks delivered during certain timings of the atrial refractory period can induce changes in atrial refractoriness with unidirectional block and subsequent AF. Using higher current, this nonuniformity will vanish and no AF will be induced (this occurs at the ULV of ventricular shock to induce AF). The capability of low-energy shocks to induce AF was demonstrated in a recent study of implantable atrial defibrillators used to treat atrial fibrillation by Wellence et al, who used low-energy shocks to induce atrial fibrillation.

Relation to Atrial Refractoriness
AF could be induced only if the shock in the ventricle was induced during the vulnerable period of the atrium. This time window is related to atrial refractoriness, which is AERP±60 ms in this pacing model. This linkage of shock-induced AF to AERP is consistent with the previously proposed mechanism of a nonuniform field created in the atria leading to AF.

Monophasic versus Biphasic Shocks
Data from several studies demonstrated that biphasic waveforms do not stimulate tissue or prolong its recovery timing as effectively as a similar monophasic waveform. The biphasic shock is less capable of inducing nonuniform dispersion of refractoriness in atrial tissue; therefore, the time window for AF induction is smaller for biphasic shocks. The lower ULV with the biphasic shocks may also be related to the limited effect on tissue refractoriness and stimulation by biphasic shocks. This finding is consistent with the reported lower clinical incidence of AF after endocardial biphasic shocks.

Epicardial versus Endocardial Shocks
Defibrillation shocks from epicardial electrodes create a nonuniform field in the atria, with a high-potential gradient near the electrodes and a low-potential gradient away from the electrodes. This nonuniform field may initiate AF. Using a higher current, this nonuniformity will vanish. Because the field stimulation is weaker during endocardial shocks, the ULV is lower during endocardial shocks; this is why biphasic waveforms are less capable of tissue stimulation. The presumed differences in field strength in the atrium during epicardial and endocardial shock delivery to the ventricles in the present study may explain the narrow time window and smaller current range for AF induction by endocardial energy delivery.

Thoracotomy and Pericardiotomy
Thoracotomy and pericardiotomy increase the risk of postoperative AF, even after the implantation of an epicardial, ventricular ICD. However, in this study, shock-induced AF was not altered by the surgical procedure. It is not clear whether differences in vulnerability to postoperative AF exist between canine and human atria.

Spontaneous AF During Ventricular Defibrillation Threshold Testing
There were 9 episodes of AF induced by ICD shocks during ventricular-defibrillation threshold testing. By recording the timing between the atrial activation and the ventricular shocks and the ventricular shock intensity, we could demonstrate an atrial time-current window of LLV and ULV that was postulated by our study in the atrial-pacing model. Thus is consistent with our previous observations in humans.

Clinical Implications
Newer generation implantable defibrillators have atrial sensing and pacing capabilities. Thus, timing the ventricular shock to the atrial electrical activation might be feasible. The ULV data and previous clinical data suggest it might be important to time only low-energy shocks to the atrial refractory period to prevent AF induction. Often, low-energy shocks are used in slower, more stable ventricular tachycardias, and a slight delay in shock delivery may be acceptable. In such a case, the atria could be paced at the ventricular tachycardia rate with the atrial activation before the ventricular activation, thus possibly increasing cardiac output and minimizing the chances of AF. Higher energy shocks are above the ULV and should not induce AF. Prevention of shock-induced AF might be very important in patients with decreased left ventricular function in whom the atrial hemodynamic contribution is critical. Atrial activation and refractoriness can also be synchronized in sinus. Recently, one of the newest commercially available versions of the dual-chamber ICD incorporated a feature called atrial vulnerable period operation during synchronization into the ventricular cardioversion algorithm. This device follows
atrial activity, and the shock is synchronized to the ventricle but avoids the atrial vulnerable period to prevent induction of AF by ventricular shocks in these patients. This feature is activated automatically for ventricular tachycardia therapy (usually using low-energy shocks) and with relatively stable ventricular tachyarrhythmias.

Although in clinical practice, the induction of AF with a ventricular defibrillation shock is a very rare event, the discovery of upper and lower vulnerability thresholds has major implications for the applications of ventricular-triggered test shocks.

Study Limitations

Shock Protocol
This study used an atrial pacing situation instead of ventricular fibrillation to assess the timing of shock and AERP. The AERP was determined using pacing of twice the diastolic threshold. Thus, the absolute AERP was not evaluated, although it will affect the time window for AF induction.

Shock Waveform
The present study used a particular waveform. The time window, LLV, and ULV may change with different waveforms.

Voltage Field
The voltage fields produced in the atrium during ventricular defibrillation shock are a very rare event, the discovery of upper and lower vulnerability thresholds has major implications for the applications of ventricular-triggered test shocks.

Voltage Field

The present study used a particular waveform. The time window, LLV, and ULV may change with different waveforms.

Atrial Fibrillation/Flutter

We consider AF as one entity because of the effect on the defibrillator-sensing capability (rate cutoff). The different cycle length of AF beyond a rate cutoff was not analyzed.

Conclusions

Lower and upper limits of vulnerability exist for shock-induced AF, and the occurrence of shock-induced AF is related to AERP. AF may occur after low-energy ventricular shocks used to cardiovert ventricular tachycardia or during test shocks. AF may be avoided by delivering shocks at currents above the ULV for ICD shocks to induce AF. Future efforts should explore the delivery of ventricular shocks during AERP to avoid AF.

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