Assessment of Global Atrial Fibrillation Organization to Optimize Timing of Atrial Defibrillation

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Background—We hypothesized that frequency domain analysis of a wide bipolar interatrial electrogram describes the global organization of atrial fibrillation (AF) and should vary over time. By timing shocks to periods of high organization of AF, cardioversion efficacy should improve.

Methods and Results—A total of 15 dogs (weight, 28.2±3.4 kg) were rapidly paced for 48 to 72 hours to induce AF. Coils electrodes with a surface area of 1.80 cm² were then placed in the left and right atria to form a wide bipole. Wide bipolar electrograms were digitally filtered, and a fast Fourier transform was performed over a sliding 2-s window every 0.5 s. The organization index (OI) was calculated as the ratio of the area of the dominant peak and its harmonics to the total area of the magnitude spectrum. The atrial defibrillation threshold (ADFT₅₀) was determined using a 3-ms/3-ms biphasic shock and an up-down-up protocol. Additional shocks with higher and lower energies were delivered in a random sequence to develop a distribution curve. The OI varied over time, with a mean of 0.42±0.03, a maximum of 0.65±0.07, and a minimum of 0.20±0.06. The OI changed rapidly, with durations of high organization (OI>0.5) ranging from 1 to 5 s. The ADFT₅₀ for QRS complex–synchronized shocks was 183±56 V, versus 142±49 V for shocks synchronized to an OI>0.5 (P<0.001). The distribution curve shifted leftward when shocks were synchronized to an OI>0.5.

Conclusions—AF signals show a high degree of variability. Shock efficacy is increased when shocks are delivered during periods of high AF organization as determined by the OI method. (Circulation. 2001;103:2857-2861.)

Key Words: arrhythmia ■ fibrillation ■ defibrillation ■ Fourier analysis

Atrial fibrillation (AF) is a common disease that is associated with an increased risk of stroke and mortality, impaired exercise tolerance, fatigue, and heart failure.1–5 The atrial implantable defibrillator is being developed as a possible therapy for AF.6–13 Although initial clinical trials have shown that the atrial implantable defibrillator has a high specificity and sensitivity to AF and delivers safe and effective shocks, it has not gained patient acceptance because the energy level needed for successful cardioversion exceeds the pain threshold.14–16

It has been theorized that the most common mechanism of AF is reentry with multiple simultaneous wavelets circulating in the atria.17 It has also been shown that 4 to 6 wavelets are needed in order to sustain continuous propagation of AF.18 The number of wavelets circulating in the atria probably varies over time, changing with changing global and regional atrial refractoriness.19 A decrease in wavelength likely will decrease the prevalence of anatomic (as opposed to functional) reentrant waves, thereby decreasing the regions of excitatory gap.17,20

We hypothesized that decreasing numbers of wavelets and increasing regions of excitable gaps might increase atrial defibrillation efficacy, and visa versa. A method that could quantify these periods of high and low AF organization, respectively, might improve the likelihood of atrial defibrillation. We sought to accomplish this with frequency domain analysis of a filtered wide bipolar atrial electrogram, analogous to an interatrial defibrillation lead system. We conjectured that discrete harmonic wavelet activity would predict higher defibrillation efficacy and lower defibrillation energy requirements.

Methods

Animal Preparation

A total of 15 mongrel dogs weighing 28.2±3.4 kg were induced with sodium pentothal (0.25 mg/kg), intubated, and isoflurane (0.5% to 1.5%) and fentanyl were used for maintenance anesthesia. The right neck and interscapular regions were sterilely prepped and draped. An active fixation atrial J permanent pacemaker lead (Medtronic Inc) was introduced into the right jugular vein through a cutdown incision and was advanced into the right atrial appendage under fluoroscopic guidance. Pacing parameters were tested, and the lead position was fixed at the venous entry point. The lead was tunneled to a pacemaker pocket that had been created between the scapulae, and it was connected to a specially modified Teletronics unipolar implantable pulse generator. Appropriate atrial pacing was confirmed. After the wounds were repaired, the animals were returned to the vivarium.

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The pacemakers were programmed to a rate of 640 bpm and an output of 2 to 3 times the atrial diastolic threshold. After 48 to 72 hours of rapid atrial pacing, the animals were anesthetized and the femoral vessels were accessed via cutdown incision. Two transseptal catheterizations were performed using a Brockenbrough needle and two 9.5F 60-cm sheaths. Decapolar catheters with 10-mm spacing between each bipole were placed in the right and left atrium for electrogram recording. Defibrillation catheters were placed contiguous to the right and left atrial free walls, and from them, an interatrial bipole electrogram was acquired. A 6F quadripolar sensing catheter was placed retrogradely into the left ventricle for atrial shock synchronization. At the completion of the protocol, the dogs were euthanized with a barbiturate overdose.

Signal Processing
The wide bipole signal obtained from the defibrillation catheters (Figure 1A) was digitized at 1000 Hz using a 66-MHz computer with a 486 processor and an AT-DSP2200 data acquisition card (National Instruments Corp) programmed in Turbo C++. An ideal QRS was determined by averaging 100 QRS complexes. This ideal QRS was then subtracted from each individual QRS complex in the signal. After QRS subtraction, the resulting AF wave form (Figure 1B) was band-pass filtered using a 40- to 250-Hz second-order digital Butterworth filter. The absolute value of the filtered wave form was low-pass filtered using a 20-Hz second-order digital Butterworth filter (Figure 1C). This filtering process extracts a time-varying wave form proportional to the amplitude of the high-frequency components in the original atrial electrogram, enhancing the periodicity or nonperiodicity of the signal. This algorithm was used to transform a complex wave form into a series of atrial activations while diminishing the effects of changing electrogram morphology or amplitude.21,22

Frequency Domain Analysis
A fast Fourier transform (FFT) was calculated on the digitally filtered wave form over a sliding 2-s window of 2048 points every 0.5 s (Figure 2). The data were tapered using a split-cosine bell window. The largest peak of the resulting magnitude spectrum was identified, and on the basis of its position, the positions of the harmonic peaks were determined. The areas under the largest peak and 3 of its harmonic peaks were calculated over a 1-Hz window, producing an area under 4 peaks. The total area of the spectrum was

Figure 1. A, Four-second acquisition of an unfiltered, unmodified wide bipolar electrogram between coil electrodes in the left and right atria is displayed. High-amplitude, far-field ventricular complexes are the dominant feature of this tracing and preclude accurate analysis of the AF signal. B, Ideal template for the ventricular electrogram is generated, then digitally subtracted from the electrogram signal. Remaining signal represents composite of left and right atrial wavelet activity. C, Resulting signal after filtering (see text for more detail).

Figure 2. Results from an FFT performed on 2 separate sections of a digitally filtered wave form. A, Dominant peak can be seen at 4 Hz with discrete harmonics at 8, 12, 16, and 20 Hz. OI was calculated as the ratio of the sum of areas under the peaks at 4, 8, 12, and 16 Hz to the total area from 2.5 to 19.5 Hz. Between harmonic peaks, there is little spectral energy. This resulted in a high (organized) OI number. B, No discrete dominant peak or harmonics can be seen. Between peaks, there is high magnitude of spectral power. This resulted in a low (disorganized) OI.
calculated from 2.5 Hz up to, but not including, the fifth harmonic peak. Higher frequencies were excluded because they were assumed to exceed the physiological range of frequencies for AF wavelets. The ratio of the power under the harmonic peaks to the total power in this range was calculated, and the resulting number was termed the organization index (OI). We theorized that the OI represents the organization of AF during the 2-s time window. A spectrum with a dominant peak and discrete harmonics would represent fewer wavelets circulating within the atria and thus a higher OI. With a higher number of wavelets, more frequency components are added to the atrial signal, which would appear in the spectrum and result in a lower OI. An OI threshold $>0.5$ was selected to represent periods with relatively organized AF signals.

**Defibrillation Protocol**

In all cases, atrial defibrillation was performed after spontaneous or induced AF of $\geq30$ s sustained duration. After each cardioversion, AF was reinitiated with 10-s bursts of rapid atrial pacing at a 50-ms cycle length, an output of 10 mA, and a 9.9-ms pulse width. The defibrillation catheters were specially constructed 7F catheters with stainless steel defibrillation coils (Boston Scientific Corp) with a surface area of 1.80 cm$^2$. These coils were connected to a Ventritex HVS-02 programmable defibrillator (Ventritex, St. Jude Corp) with a capacitance of 150 $\mu$F. Each shock was a truncated biphasic, exponential wave form with a pulse width of 3 ms/3 ms synchronized to the left ventricular apical electrogram. Each phase of the wave form had a 35% tilt with a 100-$\mu$s gap between the positive and negative phases. The leading-edge voltage was adjustable over a range of 50 to 990 V in 10-V steps. All shocks were synchronized either to the left ventricular apical electrogram alone or to the ventricular signal found in the signal collected from the defibrillation catheters and to periods of high measured AF organization.

The atrial defibrillation threshold (ADFT$_{50}$) was determined using an up-down-up protocol starting at 50 V and (1) increased in 20-V increments until a successful conversion to sinus rhythm was accomplished; then (2) decreased in 20-V decrements until 2 consecutive shocks failed to convert the rhythm; and (3) increased in 20-V increments until 2 consecutive shocks converted the rhythm to sinus. AF was reinitiated as needed during the protocol and allowed to persist for at least 30 s before each shock. The defibrillation threshold was defined as the mean voltage of the 2 consecutive unsuccessful shocks from step 2 and the 2 consecutive successful shocks from step 3. A successful cardioversion was defined as restoration of sinus rhythm within 1 s of energy delivery. In 8 dogs, the ADFT$_{50}$ was first determined using QRS-synchronized shocks. In 7 dogs, the ADFT$_{50}$ was first determined using shocks synchronized both to the QRS and to an OI $>0.5$. Before the first shock was delivered in each dog, 60 s of an AF electrogram was acquired. With a sliding 2-s window, significant variability of the OI over time was observed (Figure 3).

In these 15 animals, the OIIs were normally distributed with a mean of 0.42 $\pm$ 0.03, a maximum of 0.65 $\pm$ 0.07, and a minimum of 0.20 $\pm$ 0.06. The OI changed rapidly with a maximum duration of high organization (OI $>0.5$) of 2.5 $\pm$ 1.8 s (range, 1.0 to 5.0 s).

ADFT$_{50}$ results for random shocks and for shocks synchronized to an OI $>0.5$ for each of the dogs are shown in Figure 4. The mean ADFT$_{50}$ for QRS-synchronized shocks was 183 $\pm$ 56 V, versus 142 $\pm$ 49 V for shocks synchronized both to the QRS and to the point when the OI exceeded 0.5 ($P=0.00064$). Of the 15 animals, 13 showed a decrease in the ADFT$_{50}$ when shocks were synchronized to an OI $>0.5$. Of note is the fact that the 2 animals that did not show a change in the ADFT$_{50}$ had the lowest mean OI overall and a higher OI variance (0.38 $\pm$ 0.07 versus 0.43 $\pm$ 0.024; $P<0.03$). A probability distribution curve was generated for each animal, and the average of these curves is shown in Figure 5. The curve for shocks synchronized both to the QRS and to an OI $>0.5$ is shifted leftward toward lower energy levels ($P<0.001$).

**Results**

**Defibrillation Thresholds**

A total of 1805 shocks were delivered to 15 animals. Of these, 952 shocks were synchronized to the QRS, and 853 shocks were synchronized both to the QRS and to an OI $>0.5$. Before the first shock was delivered in each dog, 60 s of an AF electrogram was acquired. With a sliding 2-s window, significant variability of the OI over time was observed (Figure 3). In these 15 animals, the OIIs were normally distributed with a mean of 0.42 $\pm$ 0.03, a maximum of 0.65 $\pm$ 0.07, and a minimum of 0.20 $\pm$ 0.06. The OI changed rapidly with a maximum duration of high organization (OI $>0.5$) of 2.5 $\pm$ 1.8 s (range, 1.0 to 5.0 s).

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Mechanisms of Atrial Defibrillation

The mechanism of atrial defibrillation is not fully understood. Several studies have been performed analyzing the mechanism of ventricular fibrillation and experimenting with different techniques to improve ventricular defibrillation efficacy. From these studies, several theories have been developed about the requirements for successful ventricular defibrillation, among them: (1) A critical mass of myocardium must be depolarized; (2) a sufficient amount of current density must travel through the myocardium; and (3) there must be a prolongation of refractoriness in the myocardium after the shock. Whether or not these theories can be applied to atrial defibrillation is unknown. As in ventricular defibrillation, however, it has been theorized that in order to achieve a successful atrial defibrillation, a critical mass of atrial tissue needs to be depolarized, thereby terminating the wavelets. To depolarize the atrial tissue, a dominating electrical current is needed to overcome the varying states of activation of the atria caused by the circulating wavelets associated with AF. A higher number of wavelets might result in an increased mass of atrial myocardium that is not fully excitable and might translate into higher energy requirements for a successful defibrillation.

Discussion

In this study, a new method was introduced for quantifying AF organization using AF signal filtering and FFT analysis. A wide intratral bipolar electrode array was used to emulate the shocking coil electrodes used in implantable atrial defibrillators and to record global activation of both atria with a single bipolar signal. The signal was highly filtered, using methodology analogous to that described by Botteron and Smith. Recent studies have been performed showing that the AF wave form can be effectively analyzed in the frequency domain. The spectrum of the AF wave form often showed a single dominant peak with other multiple peaks within the frequency range of 0 to 20 Hz. Filtered AF signals in these experiments were analyzed with FFT in semi-real time (0.5-s delay, 2-s sliding time window). A mathematical calculation of the organization or disorganization of the FFT analysis was then defined as the OI and was hypothesized to represent the degree of AF wavelet organization during that 2-s time window.

We then applied this methodology to intra-atrial defibrillation. The OI algorithm proved very sensitive to the changes in the appearance of the raw and filtered AF signals and changed dynamically with each 0.5-s interval calculation. Shocks delivered during periods of high OI (hypothesized to correlate with fewer wavelets and increased excitable gap) had a higher efficacy than randomly delivered shocks. When the algorithm was used to select the timing of shock delivery during intra-atrial defibrillation, the leading-edge voltage needed for a successful conversion to normal sinus rhythm 50% of the time (the ADFT<sub>50</sub>) was reduced by ~30%. Application of the OI algorithm also shifted the probability of successful defibrillation toward lower energy levels over a wide range of leading-edge voltages.

Clinical Implications

A limitation for the use of the atrial implantable defibrillator as a possible therapy for AF is shock-related discomfort. Clinical studies have shown that the energy needed for successful cardioversion in humans is much higher than the energy needed for cardioversion in animals. Clinical studies have also shown that shocks >2 J resulted in patient discomfort and can be painful and that a 2-J defibrillation energy level may be inadequate for a successful cardioversion. If cardioversion efficacy could be increased at lower energy levels, patient acceptance of this therapy may grow. In the present study, there was a marked increase in cardioversion.
sion efficacy when the shocks were timed to high levels of AF organization.

Limitations
This study was performed in canine hearts; it is not known if human hearts would respond in the same fashion. It is also not known if the observations reported would be the same for chronic AF. Because of the difficulty in accessing the coronary sinus in a closed-chest procedure in canine, a right atrium–left atrium defibrillation vector was chosen instead of the right atrium–coronary sinus vector used in human patients. QRS detection and subtraction may become invalid during intermittent bundle-branch block. Finally, we acknowledge that multiple factors, known and unknown, probably contribute to the success or failure of atrial defibrillation. An OI >0.5 measured in the present study is associated with defibrillation efficacy, but causality has not been established.

Conclusions
The frequency domain analysis of an intra-atrial AF electrogram is an indicator of AF organization. From this analysis, a novel, high–temporal resolution algorithm termed the organization index was developed to quantify AF organization. AF organization is highly variable over time. Time periods with high OIs may correlate with increased AF organization. Time periods with high OIs may correlate with increased AF organization.

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References
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