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. Coil 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 excitable 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 Telecortrons 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.2122

**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
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 ≥30 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 cm². These coils were connected to a Ventritex HVS-02 programmable defibrillator (Ventritex, St. Jude Corp) with a capacitance of 150 μF. 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-μs 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 (ADFT₅₀) 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 successive 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 ADFT₅₀ was first determined using QRS-synchronized shocks in 7 dogs, the ADFT₅₀ was first determined using shocks synchronized both to the QRS and to the point when the OI exceeded 0.5. Of the 15 animals, 13 showed a decrease in 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).

Statistical Analysis
Data were expressed as the mean±SD. A 2-tailed, paired Student’s t test was used to compare ADFT₅₀ values. Energy levels closest to ±10% and ±20% of the ADFT₅₀ were pooled in order to generate a distribution function for the 2 groups (random OI and OI>0.5). The actual energies representing the ADFT₅₀ and the ±10% and ±20% values were presented in the distribution function graphs as mean±SD. Differences between the curves were determined with a 2-factor ANOVA. Data were tested for normality using the Kolmogorov-Smirnov test. Statistical significance was defined as P<0.05.

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 OIs were normally distributed 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 a maximum duration of high organization (OI>0.5) of 2.5±1.8 s (range, 1.0 to 5.0 s). ADFT₅₀ 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 ADFT₅₀ for QRS-synchronized shocks was 183±56 V, versus 142±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 ADFT₅₀ 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 ADFT₅₀ had the lowest mean OI overall and a higher OI variance (0.38±0.07 versus 0.43±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).
Filtered AF showed a single dominant peak with other multiple peaks in the AF waveform can be effectively analyzed in the frequency range of 0 to 20 Hz.

Several studies have been performed analyzing the mechanism of atrial defibrillation is not fully understood. Recent studies have been performed showing that a sufficient amount of current must be depolarized;27 a critical mass of myocardium28 and (3) there must be a prolongation of refractoriness in the myocardium after the shock.29 Whether or not these theories can be applied to atrial defibrillation is unknown. In atrial 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.6

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.

Previous Studies

High-density mapping frequently has been used as a method to measure AF organization. It has been shown that there are multiple wavelets circulating in the atria during AF27 and that there are time periods during which AF seems more organized.32 Algorithms have been developed in an attempt to quantify AF organization. Botteron et al21,22 developed an algorithm that measured the correlation of atrial activation from 5 equally spaced electrodes. The correlation-versus-electrode distance was a decaying exponential function from which a spatial organization constant was calculated. In this method, calculations were made over AF recorded longer than 30 s that averaged out any temporal variability in the AF organization. Sih et al33 developed an algorithm that measured AF organization by calculating the mean-squared error in the linear prediction between AF signals from 2 electrodes. This calculation was performed over a sliding 300-ms window every 10 ms. Smaller mean-squared error values would indicate a more organized signal. Although both of these algorithms measure AF organization, they do so in a relatively small region of the atria, thus providing a measurement of only local AF organization. These prior algorithms have not been reported to improved likelihood of successful atrial defibrillation. The algorithm presented in this study provides a high temporal resolution of AF organization over a wide bipole across both atria, giving a global measurement of organization, and was demonstrated to improve shock delivery timing during AF in order to optimize defibrillation efficacy.

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.14–16,34 Clinical studies have also shown that shocks >2 J resulted in patient discomfort and can be painful14,15,34 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 energy level may be inadequate for a successful 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 contribute to the success or failure of atrial defibrillation. The frequency domain analysis of an intra-atrial AF electrogram is a promising approach. OIs during periods with high OIs may correlate with increased AF organization. Time periods with high OIs may contribute to the success or failure of atrial defibrillation.

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References
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