Low-Energy Multistage Atrial Defibrillation Therapy Terminates Atrial Fibrillation With Less Energy Than a Single Shock

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Background—Implantable device therapy of atrial fibrillation (AF) is limited by pain from high-energy shocks. We developed a low-energy multistage defibrillation therapy and tested it in a canine model of AF.

Methods and Results—AF was induced by burst pacing during vagus nerve stimulation. Our novel defibrillation therapy consisted of 3 stages: stage (ST) 1 (1–4 low-energy biphasic [BP] shocks), ST2 (6–10 ultralow-energy monophasic [MP] shocks), and ST3 (antitachycardia pacing). First, ST1 testing compared single or multiple MP and BP shocks. Second, several multistage therapies were tested: ST1 versus ST1/ST3 versus ST1+ST2+ST3. Third, 3 shock vectors were compared: superior vena cava to distal coronary sinus, proximal coronary sinus to left atrial appendage, and right atrial appendage to left atrial appendage. The atrial defibrillation threshold (DFT) of 1 BP shock was >1 MP shock (0.55±0.1 versus 1.38±0.31 J, P=0.003). Two to 3 BP shocks terminated AF with lower peak voltage than 1 BP or 1 MP shock and with lower atrial DFT than 4 BP shocks. Compared with ST1 therapy alone, ST1+ST3 lowered the atrial DFT moderately (0.51±0.46 versus 0.95±0.32 J, P=0.036), whereas 3-stage therapy (ST1+ST2+ST3) dramatically lowered the atrial DFT (0.19±0.12 versus 0.95±0.32 J for ST1 alone, P=0.0012). Finally, the 3-stage therapy was equally effective for all studied vectors.

Conclusions—Three-stage electrotherapy significantly reduces the AF DFT and opens the door to low-energy atrial defibrillation at or below the pain threshold. (Circ Arrhythm Electrophysiol. 2011;4:917-925.)

Key Words: atrial fibrillation • defibrillation • cardioversion • vagal nerve stimulation

Atrial fibrillation (AF) is the most common tachyarrhythmia worldwide. The number of Americans with AF will increase to >12 million by 2050, placing a significant additional burden on the healthcare system. Moreover, patients with AF experience serious consequences, including increased rates of thromboembolic stroke, congestive heart failure, cognitive dysfunction, and mortality.2–4

Clinical Perspective on p 925

Catheter ablation has become increasingly common for the treatment for AF, but its success rate varies widely, and it is beset by a significant rate of major and minor complications. Although success rates vary depending on operator and patient selection, arrhythmia-free survival rates after a single catheter ablation procedure are <29% at 5 years. Complication rates likely will improve over time, yet risks such as stroke, pulmonary vein stenosis, phrenic nerve injury, and the rare, but often fatal atrioesophageal fistula have made this a less-than-ideal treatment modality.6–9

For symptomatic patients, cardioversion of AF to sinus rhythm using high-voltage external shocks, with or without antiarrhythmic drugs, remains a mainstay of therapy. External cardioversion is painful and can lead to bradyarrhythmias and tachyarrhythmias, necessitating anesthesia and careful periprocedural patient monitoring. Hospitalization, anesthesia, personnel, and ancillary procedures associated with AF are estimated to cost Medicare more than $15.7 billion annually.10

These considerations have prompted efforts to design an implantable device that converts AF to sinus rhythm safely. Such a system would enable rapid cardioversion soon after the onset of AF, ameliorating symptoms and, importantly, reducing the likelihood of atrial remodeling.11 Moreover, because internal atrial cardioversion requires significantly less energy than external cardioversion,12 it may be possible to deliver this therapy below the pain threshold, which generally is considered to be between 0.1 to 1 J.13,14 Several internal atrial cardioverters have been developed in the
past\textsuperscript{15,16} but received limited acceptance primarily because of the discomfort associated with shocks.\textsuperscript{17–20}

Experimental and clinical studies have demonstrated that vagus nerve stimulation promotes sustained AF by decreasing the atrial effective refractory period (AERP) and AERP rate adaption in an anatomically heterogeneous manner, thus creating the substrate for maintenance of sustained AF.\textsuperscript{21,22} This acute model readily produces sustained AF and has been used extensively to study mechanisms of and therapies for AF.\textsuperscript{23} The AF generated by this model was shown to be of significantly longer duration and higher dominant frequency compared with that induced by chronic rapid pacing, making it a reasonable model to study the electrotherapy of AF.\textsuperscript{24}

Previously, we compared multiple monophasic (MP) shocks to a single shock for defibrillation of AF and atrial flutter in an ex vivo rabbit model\textsuperscript{25} and in a rabbit chronic infarction model of ventricular tachycardia (VT).\textsuperscript{26} In both models, multiple MP shocks significantly lowered the defibrillation threshold. The goal of the present study was to develop a low-energy therapy for defibrillation of AF in vivo.

**Methods**

**Surgical Procedures**

Mongrel dogs (n=16) weighing 20 to 25 kg were intubated and anesthetized with propofol (7.5 mg/kg IV) and 2% to 3% inhaled isoflurane in oxygen (Model 2000; Hallowell EMC; Pittsfield, MA). The right femoral artery was cannulated for continuous blood pressure monitoring and periodic measurements of arterial blood gas and electrolytes. After median sternotomy, the pericardium was incised to expose the heart. Bilateral carotid cut downs were performed to isolate the vagus nerves. Cuff electrodes (A0004–6; Evergreen Medical Technologies, LLC; St Paul, MN) were placed around each nerve for subsequent stimulation.

**Electrode Placement**

Bipolar electrodes were sutured to the right atrium for pacing and to the left atrium and ventricular apex for sensing. Atrial and ventricular epicardial electrograms (EGs) and surface ECGs were recorded continuously.

Custom defibrillation disc electrodes of 1.27- or 2.54-cm diameter were sutured to the right atrial appendage (RAA), left atrial appendage (LAA), and superior vena cava (SVC). A custom-made 4-F lead with 2 shock coils, each 2.54 cm in length separated by an intercoil distance of 1.27 cm, was placed into the coronary sinus (CS) (Evergreen Medical Technologies); the proximal and distal coils are referred to as CSp and CSt, respectively. A schematic of the defibrillation electrodes is shown in Figure 1.

**Determination of Atrial and Ventricular Shock Excitation Threshold**

After the placement of electrodes, atrial and ventricular shock excitation thresholds (SETs) were measured for each defibrillation electrode pair tested. Atrial SET was defined as the minimum voltage at which a 10-ms MP shock captured the atrium. Similarly, the ventricular SET was defined as the minimum voltage at which a 10-ms MP shock captured the ventricle. Shocks were delivered during the diastolic interval while the animal was in sinus rhythm. Atrial and ventricular capture was determined by evaluating the surface ECG and the bipolar atrial and ventricular sensing electrodes. In general, the atrial SET was lower in voltage than the ventricular SET. In the rare instances where there was no difference between the atrial and ventricular SETs for a given vector, leads were repositioned, and the atrial and ventricular SETs were remeasured.

**Vagus Nerve Stimulation and Induction of AF**

Bilateral vagus nerve stimulation was performed with 10- to 20-V pulses of 1-ms duration starting at 4 Hz through a stimulator (SD9; Grass Technologies; West Warwick, RI). Frequency of vagal stimulation was increased in 1-Hz steps until AF lasted 10 minutes or longer. AERP was measured immediately before and 30 s after vagus nerve stimulation. After 30 s of stimulation, AF was induced through right atrial burst pacing at 10 to 20 Hz at 4 times the atrial capture threshold through a stimulus isolator (A365R; World Precision Instruments; Sarasota, FL). AF was defined as a rapid, irregular atrial rhythm with varying atrial EG morphology, whereas atrial flutter was defined as a rapid, regular atrial rhythm with consistent atrial EG morphology. If atrial flutter was induced, antitachycardia pacing or multiple-shock therapy was applied to restore sinus rhythm. Antitachycardia pacing consisted of 6 to 10 bipolar pacing stimuli, each 5 ms in duration, delivered at an amplitude of 4 times the atrial pacing capture threshold and at a cycle length equal to 88% of the AF cycle length, with no decrement. Vagus nerve stimulation was then resumed with a higher frequency, and AERP was remeasured. After every successful termination of AF or atrial flutter, stimulation was withheld for 5 minutes to allow for recovery of the nerve.

**Individual Stages of Multistage Electrotherapies**

**Stage 1**

Initially, we tested the abilities of single or multiple MP or biphasic (BP; 6 ms duration of positive phase, 4 ms duration of negative
The following combinations of stages were tested: (1) ST1, (2) ST1 + ST2, and (3) ST1 + ST2 + ST3. Results from testing ST1 therapies determined that 2BP shocks were the optimal ST1 therapy in terms of peak voltage and total energy, so 2BP shocks were used as the ST1 waveform in all subsequent multistage testing. The delay between each stage was 100 to 400 ms. Pilot studies showed that ST2 alone or ST3 alone did not terminate AF (data not shown); therefore, these stages could not be tested individually. Instead, they were incorporated in the multistage electrotherapy in all cases after ST1 therapy had been applied. Because of limitations on the number of combinations that could be formally evaluated, ST1 + ST2 alone was not tested formally. Rather, the incremental advantage of ST1 + ST2 + ST3 was compared with ST1 + ST3 alone.

**Electrotherapy Protocol**

This study was carried out in 2 parts. First, the atrial defibrillation thresholds (DFTs) of single versus multiple MP or BP shocks were determined according to a randomized protocol. A random number generator was used to generate the specific therapy to be tested after each induction of sustained AF. From this first part, we concluded that 2BP shocks represented the optimal compromise between peak shock voltage and total energy. In the second part, we compared the atrial DFTs of ST1, ST1 + ST3, and ST1 + ST2 + ST3 electrotherapies, again according to a randomized protocol.

The atrial DFTs of each waveform tested for ST1 depicted in Figure 2A were determined using a step-up protocol with voltage increments. After induction of AF, electrotherapies were delivered according to a randomized protocol. The initial peak voltage of the ST1 waveform was 10 V. If the individual therapy failed to terminate AF within 10 s, the peak voltage of the ST1 waveform was increased in 5-V increments to a maximum of 100 V. After successful termination and a wait period to allow vagus nerve recovery, AF was reinduced, and the next ST1 electrotherapy was tested according to a randomized protocol.

The atrial DFTs of multistage therapies depicted in Figure 2B and 2C were measured according to an identical step-up protocol with voltage increments, in which the peak voltage of the ST1 waveform was increased until AF was terminated. All multistage electrotherapies used 2BP shocks as the ST1 waveform. The voltage of the ST2 component of multistage therapy, set at 60% of the ventricular SET, and the voltage of the ST3 component, set at 4 times the atrial pacing capture threshold during sinus rhythm, did not vary.

**Determination of Atrial DFTs**

Atrial DFT voltage was defined as the peak leading-edge voltage of the ST1 shock that terminated AF using the step-up protocol. Atrial DFT total energy was calculated as the sum of the ST1 and ST2 and electrotherapies delivered (ie, the square of the total voltage integrated over time divided by the shock impedance). ST3 energy was negligible and, therefore, not included in the calculation.

Finally, we determined the atrial DFTs of 3 defibrillation vectors: SVC to Csd, LAA to Csp, and RAA to LAA. For each vector, 3 combinations of therapy (as just described) were tested. All therapies were delivered by a custom-built LabVIEW software program (National Instruments; Austin, TX) and amplified by a computer-controlled, regulated power supply (BOP 100–4M; Kepco; Flush, NY). The impedance of each defibrillation vector was measured using a current probe (A622; Tektronix, Inc; Beaverton, OR).

**Statistical Analysis**

Student’s t test was used to compare the average vagus nerve stimulation frequencies that induced AF versus atrial flutter, the dominant frequency of AF versus atrial flutter, and AERF before versus after vagus nerve stimulation and atrial and ventricular SETs. Atrial and ventricular SET shock vector impedances were compared using 1-way ANOVA. The protocol randomized treatment sequence to prevent confounding effects of treatments with respect to time. Atrial DFT for each waveform and defibrillation vector tested were analyzed with linear mixed random-effects models, with animal ID and treatment as fixed effects; animal ID×vector and animal ID×therapy also were analyzed as random effects to test for interactions. Estimates were calculated with the MIXED procedure in SAS version 9.2 (SAS Institute Inc; Cary, NC). Results are reported as mean ± SD. A P ≤ 0.05 was considered significant.

**Results**

**AF Model**

Sustained AF was induced in 12 of 16 dogs. The average number of AF episodes induced per dog was 25±8. The
average duration of an experiment was 4±1.5 hours. Characteristics of the AF generated are shown in Figure 3. AERP decreased significantly during vagal stimulation (79.6±8.7 versus 117.1±14.7 ms without stimulation, \(P<0.001\)). In general, durations of AF increased with the frequency of vagus nerve stimulation, and the stimulation frequency that sustained AF was significantly shorter than that which sustained atrial flutter (6.7±2.1 versus 12.0±4.4 Hz, \(P=0.03\)). As expected, average dominant frequency of sustained AF was significantly higher than that of atrial flutter (7.7±0.4 versus 10.4±1.4 Hz, \(P=0.004\)).

**Shock Excitation Threshold**

Atrial and ventricular SETs were measured for each defibrillation vector and for both polarities during sinus rhythm before induction of AF. A representative example of SET measurement is shown in Figure 4. In this case, a 0.5-V, 10-ms shock failed to capture atrial or ventricular tissue (Figure 4A), whereas a 1-V shock captured the atria but not the ventricles (Figure 4B). Increasing the shock amplitude to 6.5 V captured both atria and ventricles (Figure 4C).

Changing shock polarity did not significantly alter atrial or ventricular SET (Figure 5A). The atrial SET was significantly less than the ventricular SET for each vector tested (Figure 5B). This finding enabled the application of ST2 shocks above the atrial SET and below the ventricular SET delivered outside the ventricular refractory window without inducing VT or VF.

**Electrotherapy Applications and AF Terminations**

An average of 287 electrotherapies per animal were applied using the voltage-regulated step-up protocol. An average of 22 AF episodes were terminated per animal by the electrotherapies applied.

**Testing MP Versus BP and Single Versus Multiple Shocks**

Atrial DFTs for ST1 shock waveforms are summarized in Figure 6, with peak shock voltage shown at the top and total energy shown at the bottom. Total energy was calculated as the sum of the energies of individual shocks. In all cases, atrial flutter was easily terminated by a single BP shock at 0.0003±0.0001 J or antitachycardia pacing, with a success rate of 100% for each therapy. For termination of AF, the atrial DFT of 1BP shock was significantly lower than that of 1MP shock (0.55±0.1 versus 1.38±0.31 J, \(P=0.003\)). Similarly, the atrial DFT of 2BP shocks was significantly lower than that of 2MP shocks (0.72±0.19 versus 1.92±0.56 J, \(P<0.0001\)). Interestingly, the atrial DFT of 4BP shocks was significantly higher than that of 2BP (1.50±0.50 versus 0.72±0.02 J, \(P=0.003\)) because the voltages required to terminate AF were similar for 2BP, 3BP, and 4BP shocks. Additionally, although the efficacy of 1BP shock was lower compared with 2BP shocks, the peak voltage was significantly higher. Therefore, we deemed 2BP shocks to be the optimal waveform and chose it as the ST1 of subsequent multiple-stage therapy.

**Development of a Low-Energy Multiple-Stage Defibrillation Therapy**

The 2BP shocks (ST1) proved an optimal compromise with respect to peak voltage and total energy for cardioversion of
AF in this model. Next, we asked whether additional stages, such as subventricular excitation shocks (ST2) and antitachycardia pacing (ST3) further lowered the atrial DFT. Figure 7 shows a representative example of AF termination by 1-, 2-, and 3-stage therapies and the corresponding atrial DFTs. The summarized results are shown in Figure 8. The 2BP shocks followed by antitachycardia pacing (S1/S3) reduced the atrial DFT to 0.51±0.06 J compared with 0.95±0.32 J for ST1 alone (shock vector RAA>LAA, \( P=0.036 \)). Significantly, atrial DFT was dramatically reduced further by the combination of 2BP shocks followed by subventricular SET shocks and then antitachycardia pacing (ST1+ST2+ST3). This 3-stage therapy reduced the atrial DFT by nearly 4-fold to 0.19±0.12 J (versus 0.95±0.32 J for ST1 alone, \( P=0.001 \)). The 3-stage therapy was then tested across multiple vectors.

The Relationship of Shock Vector to Atrial DFT

We applied the 3-stage therapy across 3 vectors: RAA to LAA, CSd to RAA, and LAA to CSp. Surprisingly, we detected no significant difference in atrial DFT (Figure 8D).

Safety Considerations

Two of 3444 AF termination attempts induced VF. One episode was caused by improperly triggered ST1 application (not delivered on the R wave) because of unexpected noise in the ventricular EG. Adding an R-wave recognition algorithm in the trigger function and using the surface ECG as the trigger input when the signal-to-noise ratio of the ventricular EG was poor overcame this problem. The second VF episode was induced by ST2 shocks when the applied shock amplitude was very close to the ventricular SET. This problem was avoided in subsequent trials by strictly limiting the amplitude of ST2 shocks to <50% of the ventricular SET.

Discussion

The main findings of the present study are as follows: (1) Single and multiple BP shocks in ST1 were significantly more effective at terminating AF than the same number of MP shocks, (2) increasing the number of BP shocks in ST1 to >2 did not decrease the atrial DFT in this model, (3) a 3-stage therapy (ST1+ST2+ST3) significantly reduced the atrial DFT compared with 1-stage (ST1) and 2-stage (ST1+ST3) therapies, and (4) 3 tested defibrillation vectors (RAA to LAA, RAA to CSd, and LAA to CSp) were equally effective for all tested combinations of stages of therapy (ST1, ST1+ST3, and ST1+ST2+ST3).

A prevailing theory is that AF is induced and maintained by a single or a small number of stable, self-sustained mother rotors that give rise to exceedingly high-frequency excitation, with resultant fibrillatory conduction in the atria.27 Rotors are organized around phase singularities, which tend to anchor to anatomic or functional syncytial heterogeneities.28 Attempts to optimize electrotherapy of fibrillation should be based on directly targeting the phase singularities.27,29,30 However, we have demonstrated in the present study that electrotherapy may fail to defibrillate despite successful termination of AF.
phase singularities that maintain the ongoing arrhythmia. This occurs because defibrillation simultaneously terminates existing phase singularities while inducing new phase singularities through the virtual electrode-induced phase singularity mechanism.\(^31\) BP shocks with appropriate energy ratios between the first and second phases can create homogeneous postshock transmembrane polarization and phase distribution, which reduces the probability of inducing new phase singularities.\(^32\) Therefore, an optimized BP shock therapy has been proven safe and reliable in treating AF.\(^15\)

The atrial DFT of a conventional single BP shock remains above the human pain threshold.\(^17\)–\(^20\) This fact greatly limits implantable device therapy for cardioversion of AF. High-voltage shocks also cause electroporation\(^33\) and impair efferent sympathetic neural function.\(^34\) The 3-stage AF therapy developed and tested in the present study is below the thresholds of electroporation and nerve damage.\(^33\)–\(^35\) Most importantly, the energies and voltages necessary to cardiovert AF using multistage therapy are well below the human pain threshold,\(^36\) making realistic the possibility of an implantable device for defibrillation of AF.

As early as 1945, Gurvich\(^37\) tested 2 to 4 discharges of a single capacitor with different intervals ranging from 250 ms to 2 s between each discharge for transthoracic defibrillation of VF in dogs. He found that 2 to 3 multiple shocks with an interval of 1.33 to 2 s were capable of terminating VF in dogs with a voltage \(\approx 50\%\) to 70\% of the DFT of a single shock. In addition, Gurvich discovered that this multiple-shock defibrillation technique could be improved by shortening the interval between pulses to a range of 333 to 250 ms.

We previously found that multiple MP shocks achieve lower defibrillation thresholds than BP shocks in an in vitro model of VT in chronically infarcted rabbit hearts.\(^26\) In contrast, this study shows that multiple BP shocks are superior for the defibrillation of AF, a finding that is consistent with the studies of traditional high-energy, single-shock defibrillation.\(^38\),\(^39\) The apparent discrepancy in findings among these studies may be explained by different mechanisms of low-energy defibrillation in these different tachyarrhythmias. VT in the rabbit model was maintained by a single rotor with phase singularity attached to a chronic infarction scar. Successful multiple-shock low-voltage defibrillation was achieved by maintaining a small region refractory in the reentry circuit through the virtual electrode polarization effect induced by MP shocks until the wavefront crashed into this refractory region and terminated. Accordingly, the second phase of BP shocks reverses the VEP effect of the first phase and is therefore disadvantageous.\(^26\) Hence, BP shocks have higher DFTs than MP shocks for termination of VT. In contrast, AF is sustained by multiple rotors with different frequencies, phases, and anatomic locations. Therefore, extinguishing all existing rotors is fundamental to the

![Figure 7. Representative atrial electrograms of atrial fibrillation terminations. Peak voltage in ST1 and total energy is denoted above the corresponding atrial electrogram in each part. The time that each individual therapy was delivered is indicated with an arrow. A, ST1 therapy of 2 100-V biphasic shocks (total energy, 1.14 J) terminated atrial fibrillation. B, ST1+ST3 lowered the peak voltage of ST1 to 70 V and the atrial defibrillation threshold to 0.56 J. C, Three-stage therapy (ST1+ST2+ST3) dramatically reduced the total energy to 0.05 J and the peak voltage of ST1 to 20 V. Abbreviations as in Figure 2.](image)

![Figure 8. Atrial DFTs for each shock vector tested. Atrial DFTs of ST1, ST1+ST3, and ST1+ST2+ST3 are shown for each vector tested in total energy. A, Shock vector SVC>CSd. B, Shock vector CSp>LAA. C, Shock vector RAA>LAA. D, Atrial DFT of 3-stage therapy (ST1+ST2+ST3) did not significantly differ with respect to shock vector tested. DFT indicates defibrillation threshold. Other abbreviations as in Figures 1, 2 and 5.](image)
defibrillation of AF. This is better achieved by BP shocks, which create a more homogenous VEP pattern than MP shocks and provides a mechanistic explanation of the present findings.

Another important difference between the defibrillation of VT versus AF is the optimal number of shocks. In a canine infarct model of VT, we found that 3 MP shocks had the highest DFT, whereas 10 MP shocks applied within 2 VT cycles had the lowest DFT compared with 1, 3, 5, and 7 MP shocks applied within 1 VT cycle. In the present study, we demonstrated that applying >2 BP shocks in STI did not lower the DFT. This difference suggests fundamental differences in the mechanisms of defibrillation of a relatively slow and more-organized VT wavefront versus a faster and more-disorganized collection of wavefronts seen in AF; a longer train of shocks in a short interval could lead to defibrillation failure not by failing to terminate the existing disorganized wavefronts per se but, rather, by inducing new wavefronts. Moreover, from a neurological point of view, a smaller number of shocks is advantageous in developing a painless AF cardioversion strategy because perceived pain increases with increasing number of shocks.

The present 3-stage therapy significantly lowers the energy for cardioversion of AF by application of 3 different stages of therapy, which we mechanistically relate to the (1) unpinning of wavefronts that maintain AF, (2) prevention of repinning of wavefronts to tissue heterogeneities such as scar, and (3) annihilation of remaining wavefronts. The unpinning stage uses multiple pulses aiming to unpin the reentry from the stabilizing resistive heterogeneity. The applied electric field creates stronger virtual electrode polarization at tissue heterogeneities, which causes excitation and then unpinning of the reentry. However, this stage leaves behind a number of unpinned phase singularities that could then repin to heterogeneities and perpetuate AF. Thus, the antirepinning stage likely prevents the meandering singularities from anchoring back to the tissue heterogeneities by applying an entrainment shock train. After the first 2 stages, the last stage adopts antitachycardia pacing to drive the remaining reentry circuits to the boundaries of the atria (ie, tricuspid or mitral annulus, vena cavae, or pulmonary veins), thereby annihilating the arrhythmia to restore sinus rhythm.

AF rarely is fatal, yet atrial defibrillation stimuli could lead to VF, as was found earlier and in the present study. Accordingly, the safety of any atrial defibrillation therapy must be considered the highest priority. The present study revealed several techniques to improve safety. Synchronization of the first stage shocks to the R wave to deliver it within the ventricular effective refractory period is critical to avoiding potentially lethal postshock ventricular arrhythmias. Similarly, the shock amplitude of the second stage has to be significantly below the ventricular SET. We found that delivering the second stage <50% of the ventricular SET provided an adequate safety margin and prevented unintended ventricular excitation.

Prior studies of atrial defibrillation delivered shocks from a CS coil to a right atrial coil positioned along the lateral wall to minimize damage to the sinoatrial and atrioventricular nodes. The present study indicates that a defibrillation vector involving the CS may enhance the probability of inducing VF because of the relative ease of exciting ventricular tissue from the canine CS. In contrast, the human CS is better insulated from the ventricular myocardium because of a thicker fatty and fibrotic tissue barrier that is more robust than that of canines (data not shown). Nevertheless, because of the larger size of human CS anatomy, the migration of such a lead after implantation could cause unintended ventricular capture during ST2 and ST3 of the 3-step therapy. Such migration may be prevented by cautious implantation to avoid placing the CS lead into subvessels from which the coil may easily migrate and by designing leads that more stably maintain their position after implantation.

Further reductions in atrial defibrillation energy may be achieved by thoughtful engineering. Larger impedances require higher-voltage shocks to deliver adequate defibrillation energy, yet large voltage shocks are more likely to be painful. Previous studies showed that increasing electrode surface area by using multiple cathode or anode electrodes can significantly reduce the overall impedance. Importantly, such a reduction also would decrease the peak voltage necessary for defibrillation, which is directly linked to pain sensation. Another strategy is to deliver sequential shocks across multiple vectors using several different pairs of electrodes. This strategy also could be used to lower DFTs by eliminating the region of low-field gradient created between 2 electrodes that are electrically tied together. In addition to multiple-stage therapy, the engineering techniques discussed here may be crucial to keeping the atrial DFT under the pain threshold and should be explored in future studies.

The present study demonstrates that multistage electrotherapy significantly reduces the atrial DFT compared with a single shock. It is important to point out that these findings are derived from an experimental animal model of AF and do not replicate the spectrum of disease leading to AF in humans. Also important is that extrapolation of these results to human AF requires formal testing.

**Conclusions**

We found that multiple BP shocks were significantly more effective for cardioversion of AF than MP shocks and that 2 sequential BP shocks were optimal in terms of atrial DFT and peak voltage. We also showed that a novel 3-stage therapy achieved the lowest atrial DFT. Importantly, the atrial DFT of 3-stage therapy was at or below the pain threshold (0.19±0.12 J). Finally, the study demonstrated that the defibrillation vector did not significantly alter atrial DFT. Based on this study, we conclude that 3-stage therapy may allow pain-free cardioversion of AF.

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**Disclosures**

Dr Sha is an employee of CardiaLen, Inc, and owns stock in CardiaLen. Dr Schuessler is a member of the scientific advisory board for and owns stock in CardiaLen. Dr Efimov is a chairman of the scientific advisory board and a member of the board of directors.
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CLINICAL PERSPECTIVE

Atrial fibrillation (AF) is the most common tachyarrhythmia worldwide, and the number of Americans with this condition is expected to grow as the population ages. Patients with AF experience increased rates of thromboembolic stroke, congestive heart failure, cognitive dysfunction, and mortality. For symptomatic patients, cardioversion of AF to sinus rhythm using a single high-voltage external shock remains a mainstay of therapy. External cardioversion is painful, necessitating costly anesthesia and careful periprocedural patient monitoring. Previous attempts to design an implantable device that converts AF to sinus rhythm safely have been hampered primarily because of the discomfort associated with shocks. Defibrillating AF with a conventional, single biphasic shock remains significantly above the human pain threshold. However, prior studies in rabbits and dogs showed that atrial defibrillation could be achieved with significantly lower energy if multiple shocks are used rather than a single biphasic shock. The goal of this study was to further reduce the atrial defibrillation threshold in vivo, using a more clinically relevant canine model of AF. Here we introduce a novel multiple-shock, multistage electrotherapy that significantly reduces the atrial defibrillation threshold below single biphasic and multiple-shock therapies. Importantly, the novel electrotherapy tested here cardioverts AF at an energy that is likely at or below the human pain threshold (0.19±0.12 J). The findings give clinicians hope that multiple-stage electrotherapy may eventually allow pain-free cardioversion of AF, and opens (or reopens) the door to the possibility of an implantable device that achieves pain-free defibrillation of AF in humans.
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