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Multistage Electrotherapy Delivered Through Chronically-Implanted Leads Terminates Atrial Fibrillation With Lower Energy Than a Single Biphasic Shock

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Objectives The goal of this study was to develop a low-energy, implantable device–based multistage electrotherapy (MSE) to terminate atrial fibrillation (AF).

Background Previous attempts to perform cardioversion of AF by using an implantable device were limited by the pain caused by use of a high-energy single biphasic shock (BPS).

Methods Transvenous leads were implanted into the right atrium (RA), coronary sinus, and left pulmonary artery of 14 dogs. Self-sustaining AF was induced by 6 ± 2 weeks of high-rate RA pacing. Atrial defibrillation thresholds of standard versus experimental electrotherapies were measured in vivo and studied by using optical imaging in vitro.

Results The mean AF cycle length (CL) in vivo was 112 ± 21 ms (534 beats/min). The impedances of the RA–left pulmonary artery and RA–coronary sinus shock vectors were similar (121 ± 11 Ω vs. 126 ± 9 Ω; $p = 0.27$). BPS required 1.48 ± 0.91 J (165 ± 34 V) to terminate AF. In contrast, MSE terminated AF with significantly less energy (0.16 ± 0.16 J; $p < 0.001$) and significantly lower peak voltage (31.1 ± 19.3 V; $p < 0.001$). In vitro optical imaging studies found that AF was maintained by localized foci originating from pulmonary vein–left atrium interfaces. MSE Stage 1 shocks temporarily disrupted localized foci; MSE Stage 2 entrainment shocks continued to silence the localized foci driving AF; and MSE Stage 3 pacing stimuli enabled consistent RA–left atrium activation until sinus rhythm was restored.

Conclusions Low-energy MSE significantly reduced the atrial defibrillation thresholds compared with BPS in a canine model of AF. MSE may enable painless, device-based AF therapy. (J Am Coll Cardiol 2014;63:40–8) © 2014 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common tachyarrhythmia worldwide, and the number of Americans afflicted with AF is projected to reach 12 million by 2050 (1). Although catheter ablation has become increasingly common for the treatment of AF, it imposes a significant risk of complications, and recurrence after a single catheter ablation procedure is relatively high (2). Cardioversion of AF by using high-voltage external biphasic shocks remains a mainstay of therapy. However, external cardioversion incurs costly anesthesia and hospitalization expenses; treatment fees associated with AF are estimated to cost Medicare more than $15.7 billion annually (3).

See page 49

Internal atrial cardioversion requires significantly less energy than external cardioversion (4). Thus, it may be possible to cardiovert AF internally below the pain threshold, which is variably reported to be between 0.1 J and 1 J (5,6). These considerations prompted efforts to design an implantable device that converts AF to sinus rhythm safely and painlessly, thereby ameliorating symptoms and potentially reducing the likelihood of atrial remodeling (7).

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Historically, these attempts failed largely due to the fact that the atrial defibrillation threshold (DFT) of a single biphasic shock (BPS) remains above the pain threshold (8–11).

We, therefore, developed an electrotherapy protocol arising from the demonstrated phase dependence of the tissue response to shocks (12). This therapy was developed from the initial discovery that there is a shock strength phase dependence for successful unpinning of atrial and ventricular tachyarrhythmias (13,14) and the notion that multiple pulses increase the probability of delivering a low-voltage shock during the optimal temporal window (12,15). From these initial studies, we hypothesized that a further decrease in peak voltage could be achieved if the multiple pulses were followed by antirepinning phases to prevent the reinitiation of AF. We previously tested several stages of multistage electrotherapy (MSE) and found that the 3-stage therapy resulted in the lowest atrial DFT (16). Therefore, our novel electrotherapy consists of 3 stages of successively decreasing energy levels, which we refer to as MSE (16,17). In the present study, we prospectively compared MSE with BPS to establish the defibrillation threshold in a canine in vivo model of tachypacing-induced AF, delivered through chronically-implanted transvenous leads. Subsequently, we investigated the mechanism by which MSE terminates AF by using optical mapping.

Methods

Surgical procedures. All animal procedures were performed in accordance with the position of the American Heart Association on the use of research animals (updated in 1985) and were approved by the Washington University Animal Studies Committee. Mongrel dogs (N = 14) weighing 20 to 25 kg were anesthetized, and pacing/defibrillation leads (Medtronic, Inc., Minneapolis, Minnesota) were introduced from the right internal jugular vein with fluoroscopic guidance. In all dogs, a pacing lead (model number 5096; Medtronic, Inc.) was implanted into the right atrial appendage (RAA), and defibrillation leads were implanted into the RAA (model number 6935; Medtronic, Inc.), left pulmonary artery (LPA), and coronary sinus (CS) (model number 6937A; Medtronic, Inc.). The CS of canine hearts often tapers abruptly, preventing implantation of a lead in the distal CS. The inferior branch of the LPA runs adjacent to the lateral CS and was therefore used to anatomically approximate the clinical distal CS implantation site (Fig. 1A).

The pacing lead was connected to an implanted high-rate pacing (HRP) device (Medtronic, Inc.) programmed with custom software. Defibrillation leads were connected to custom subcutaneous access ports (Evergreen Medical Technologies, Minneapolis, Minnesota). Figure 1 shows fluoroscopic and schematic images depicting subcutaneous access ports and lead positions.

Each animal underwent a complex experimental protocol, including the surgical implant and subsequent defibrillation studies. A timeline illustrating the experimental sequence of events is shown in Figure 1C.

During survival defibrillation studies, animals were reanesthetized, and the subcutaneous access ports were accessed transcutaneously by using needle electrodes (Evergreen Medical Technologies) under fluoroscopic guidance. Blood pressure, electrolyte levels, and arterial oxygen saturation were monitored continuously.

HRP-induced self-sustaining AF. The HRP at 400 beats/min began 1 week after implantation from the RAA pacing lead at twice the atrial capture threshold. Digoxin (Jerome Stevens Pharmaceuticals, Inc., Bohemia, New York) was administered orally once daily to limit the ventricular rate during HRP and AF. Device and rhythm checks were performed weekly to determine AF induction. AF was defined as an irregular fast atrial rhythm occurring at a cycle length (CL) of <150 ms (>400 beats/min). For this study, AF was defined as self-sustained AF lasting >30 min during interrogation. Once this arrhythmia was observed, the animal was rechecked 1 week later to determine if AF persisted for ≥1 week. If AF was present, survival defibrillation studies were performed. After the final in vivo defibrillation study, hearts were explanted for the in vitro mechanism investigations.

Atrial and ventricular shock excitation thresholds. Animals in AF at the start of the defibrillation study underwent cardioversion by using a 10- to 30-J external shock to enable accurate measurement of the atrial shock excitation threshold (ASET) and the ventricular shock excitation threshold (VSET) during sinus rhythm. ASET and VSET, defined as the minimum energy by which a 10-ms monophasic square wave shock excited the atrium or ventricle, respectively, were measured for each defibrillation vector (RA-CS and RA-LPA) at the start of each in vivo defibrillation study during the diastolic interval during sinus rhythm. Shock excitation thresholds were determined by evaluation of surface and endocardial electrograms.

Electrotherapies tested. The electrotherapies tested are shown in Figure 2A. BPS (Fig. 2A, left panel) triggered to the ventricular R-wave (6/4 ms duration and a 2:1 ratio of the leading-edge voltages of the 2 phases) was compared with MSE (Fig. 2A, right panel). Before each application of MSE, AF was analyzed using a fast Fourier transform algorithm to determine the dominant frequency, which was expressed as a CL. Once the AF CL was determined, the MSE was delivered in 3 stages. In Stage 1, 2 biphasic shocks

Abbreviations and Acronyms

ASET = atrial shock excitation threshold
BPS = single biphasic shock
CS = coronary sinus
DFT = defibrillation threshold
HRP = high-rate pacing
LA = left atrium
LPA = left pulmonary artery
MSE = multistage electrotherapy
OAP = optical action potential
PV = pulmonary vein
RA = right atrium
RAA = right atrial appendage
VSET = ventricular shock excitation threshold