**Low-Energy Multi-Stage Electrotherapy Cardioverts AF With Lower Energy Than a Single Biphasic Shock: *In Vivo* Results and Mechanism Revealed by Optical Mapping *In Vitro*.**

## Introduction:

Previous attempts to develop an implantable device to cardiovert AF were limited by painful, high-energy (3-6 J) biphasic (BP) shocks. Here, we show that Multi-Stage Electrotherapy (MSE) significantly reduces the atrial defibrillation threshold (DFT) compared to a single BP shock in a canine chronic pacing model of persistent AF, and describe the mechanism of MSE using optical mapping.

## Methods:

Right atrial appendage (RAA) pacing lead and defibrillation coils were implanted into the RAA, coronary sinus (CS) and left pulmonary artery (LPA) in N=14 canines. Persistent AF was induced by 6±2 weeks of RAA tachypacing. The atrial DFT *in vivo* of a BP shock was compared to MSE. Following *in vivo* studies, hearts (N=7) were excised and atria were isolated. AF was induced by burst pacing alone. Defibrillation by a single biphasic shock or MSE was optically mapped. MSE consists of 3 sequential stages. *Stage 1*: 2 BP shocks delivered within 1 AF cycle length (CL); *Stage 2*: 6 monophasic atrial entrainment shocks delivered at a rate of 88% of the AF CL, at 60% of the ventricular capture voltage; *Stage 3*: 8 pacing stimuli at a rate of 88% of the AF CL delivered from the RAA.

## Results:

*In vivo*, the atrial DFT of MSE was 18.5 ± 14.9 V (0.10 ± 0.14 J) versus 154.1±22.9 V (1.02 ± 0.44 J) for a single BP shock ($p<0.001$). During *in vitro testing*, activation maps showed that AF was maintained by 2-5 ectopic foci/micro-reentrant circuits (EF/MR) adjacent to the pulmonary veins. Crowded isochrones were seen around pulmonary veins. MSE Stage 1 shocks caused nearly simultaneous atrial activation. Post-shock, re-emergent EF/MR were gradually eliminated by the train of Stage 2 entrainment shocks, resulting in an increasingly homogeneous activation pattern. Stage 3 pacing resulted in a consistent RA-LA activation pattern until sinus rhythm was restored. *In vitro*, the atrial DFT of MSE was 38.8 ± 9.9 V (1.2 ± 0.2 J) versus 94.0 ± 13.4 V/cm (3.4 ± 0.4 J) for a single BP shock ($p<0.05$).

## Conclusions:

Low-energy MSE terminates persistent AF by eliminating EF/MR over several stages, and may enable painless, device-based cardioversion of AF.