



Atrial fibrillation and flutter conversion with pulsed electric field delivery: preclinical proof of concept

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Abstract

Introduction Device-based therapies for treating atrial fibrillation (AF) episodes are limited. Using pulsed electric fields (PEF) to induce reversible electroporation of cardiac tissue may effectively terminate AF. Thus, we aimed to assess the feasibility of PEF delivery for converting atrial arrhythmias via reversible electroporation.

Methods and results Four swine models were used in this acute study. Custom-made decapolar catheters for PEF delivery were deployed with the following configurations: (1) Endocardial right atrium (RA) and coronary sinus (CS), $n=2$; and (2) Endocardial RA and epicardial left atrium (epiLA), $n=2$. AF and atrial flutter (AFL) were induced with programmed stimulation. PEF delivery was performed using the BTX 830 generator. For each attempt, a single monophasic pulse at 10 or 20 μ s pulse width was administered, with voltage varied across attempts (range 750–3000 V). Successful (type 1 and 2 breaks) and unsuccessful conversion attempts were recorded. Post-PEF signal changes and arrhythmias were identified. A total of 58 AF/AFL (28 and 30 respectively) episodes were induced. Of the 37 successful conversion attempts, 33 (89.1%) were type 1 breaks. Conversion success probabilities generally increased with higher voltages for both configurations. Greater than 70% conversion success was seen with ≥ 1500 V for the RA/CS configuration and ≥ 2000 V for the RA/epiLA configuration. Arrhythmias including intra-atrial delay and high-grade atrioventricular block were seen, usually following successive PEF deliveries. Significant muscle stimulation was provoked with the current experimental setup.

Conclusion Termination of atrial arrhythmias with PEF delivery is feasible, although further work is required to optimize its efficacy and safety.

Keywords Atrial fibrillation · Atrial arrhythmias · Electroporation · Defibrillation · Cardioversion · Rhythm control

Abbreviations

AF Atrial fibrillation
AFL Atrial flutter
CS Coronary sinus

ECG Electrocardiogram
ECMO Extracorporeal membrane oxygenation
IRE Irreversible electroporation
EpiLA Epicardial left atrium
LA Left atrium
LV Left ventricle
PEF Pulsed electric field
PFA Pulsed field ablation
RA Right atrium

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1 Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder in the United States (US), with an estimated prevalence of 2% in the general population [1]. Although not an imminently life-threatening arrhythmia, AF is strongly

associated with stroke and heart failure [1, 2]. Furthermore, many patients experience significant symptoms from AF, resulting in negative impacts on quality of life. There have been numerous exciting developments in the management of AF, not least being pulsed field ablation (PFA) [3–5]. Unfortunately, despite these advances, a significant number of patients still suffer from symptomatic recurrences. From a device therapy perspective, atrial anti-tachycardia pacing algorithms have been used for treating paroxysms of atrial arrhythmias; however, while it can terminate organized rhythms such as atrial flutter (AFL), it has no meaningful utility in converting patients out of AF [6, 7]. Although an atrial defibrillator system was previously developed [8], this fell out of favor due to technical complexity and patient discomfort during defibrillation. Thus, additional tools are needed to bridge this gap in the management of paroxysmal AF.

When cells such as cardiomyocytes are exposed to pulsed electric fields (PEF), membrane permeability is transiently increased—a phenomenon known as electroporation [3, 9]. With the appropriate PEF delivery configuration and parameter set, irreversible electroporation (IRE) occurs leading to cell death, thereby forming the premise for PFA [3, 5]. Yet, while IRE/PFA has rapidly transformed the landscape of cardiac catheter ablation, reversible electroporation may also harbor enormous potential for treating heart disease. In fact, prior fundamental research into cardiac defibrillation suggested that electroporation may play a key mechanistic role in disrupting the drivers of fibrillatory rhythms and thereby lead to arrhythmia termination [10, 11]. With this in mind, we hypothesized that PEF delivery could consistently convert atrial arrhythmias—both fibrillation and flutter—to sinus rhythm. In this preclinical study, we explored the feasibility of applying PEF to terminate atrial arrhythmias using swine models.

2 Methods

2.1 In vivo model and experiment set-up

Four swine (species *Sus domesticus*) were used in this study; median weight was 55.0 kg (range 53.5–56.9 kg). They were fasted the night prior to the experiment. For each procedure, they were placed under general anesthesia, intubated, and mechanically ventilated. Vascular access to the femoral, internal jugular, and/or carotid vessels was obtained percutaneously. Subxiphoid epicardial access was obtained using a long micropuncture needle housed within an 18-gauge guiding needle (“needle-in-needle”) technique. Mechanical circulatory support with

veno-arterial extracorporeal membrane oxygenation (ECMO) and/or percutaneous left ventricular assist device was used. For the former, 25 French venous and 17 French arterial cannulas were connected to the Cardiohelp System (Getinge, Sweden), which then circulated blood through a membrane oxygenator; for the latter, an Abiomed Impella 5.5® (Danvers, MA) was introduced into the left ventricle (LV) from a left carotid arterial 14 French sheath. Mechanical circulatory support was titrated to maintain a mean arterial pressure of above 65 mmHg. This allowed for adequate hemodynamic support when hypotension was encountered during the experiments and/or when concomitant studies involving ventricular arrhythmias were being undertaken (not reported here). Intravenous heparin was administered and titrated to an activated clotting time of above 400 s. Intracardiac signals were recorded using the General Electric Healthcare CardioLab™ (Chicago, IL) system. The study was approved by the Mayo Clinic Institutional Animal Care and Use Committee.

2.2 Pulsed electric field parameters and configurations

The BTX® ECM 830 Electroporation Generator (Holliston, MA) was used for PEF delivery in this study. Briefly, the generator can deliver square-wave, monophasic pulses with voltages of 505–3000 V and pulse widths of 10–600 μ s (high-voltage mode). There was no electrocardiogram (ECG) gating capability.

Custom-made 6 French decapolar catheters from Access Point Technologies (St. Louis, MO) were utilized for intracardiac PEF delivery. Each electrode was 4 mm long with an interelectrode distance of 2 mm. The catheter was steerable in one direction. Two main catheter configurations were implemented: (1) one catheter in the right atrium (RA) and another in the coronary sinus (CS); (2) one catheter in the RA and another along the epicardial surface of the left atrium (epiLA). In all studies, the RA catheter was kept as the cathode.

2.3 Atrial fibrillation/flutter induction and pulsed electric field delivery

After access, mechanical circulatory support, and catheter placement were established, AF/AFL was induced with rapid atrial burst pacing. AF was defined as a rapid and irregular atrial rhythm with corresponding disorganized/irregular intracardiac atrial electrograms, whereas AFL was defined as an organized atrial rhythm with distinct flutter waves on surface electrocardiogram and consistent/regular intracardiac atrial electrograms. Following induction, each

episode was monitored to ensure persistence for ≥ 30 s. Subsequently, the catheters were disconnected from the recording system and connected to the PEF generator. Voltage was varied throughout the study (tested range 750–3000 V), with pulse number ($n=1$) and pulse width (10 μ s for RA/CS configuration, 20 μ s for RA/epiLA configuration) held constant. Successful and unsuccessful attempts at termination of AF/AFL were recorded. Immediate termination of AF/AFL was considered a type 1 break, whereas persistence of AF/AFL for several beats post-PEF was classified as a type 2 break. When PEF delivery failed to convert AF/AFL to sinus rhythm, the sequence was repeated with the same voltage at least once; with a subsequent failure, the applied voltage was increased (step-up approach). To optimize animal use efficiency, multiple attempts at AF/AFL induction and conversion were made in each study. Pre-PEF (sinus and AF/AFL), immediate post-PEF, and 5-min post-PEF signals were recorded.

2.4 Gross pathology

After completion of each experiment, the animal was sacrificed using intravenous pentobarbital sodium (FATAL-PLUS). The heart was excised and gross examination was performed. There was no histopathology analysis for this preliminary study.

2.5 Statistical analysis

Descriptive statistics were used in this study. Continuous variables were expressed as mean (standard deviation [SD]) or median (25th–75th quartile). Categorical variables were expressed as number (%).

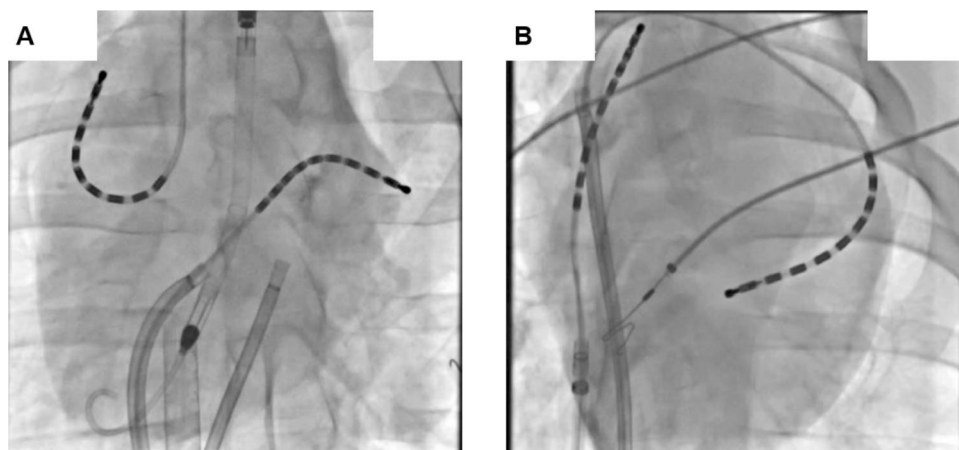
3 Results

3.1 Pulsed electric field delivery for atrial arrhythmias

The RA/CS and RA/epiLA catheter configurations were tested in two swine experiments each. Representative fluoroscopic images of the experiment and catheter set-up are shown in Fig. 1.

A total of 58 AF/AFL PEF delivery attempts (28 AF, 30 AFL) took place across the four experiments—24 with the RA/CS configuration and 34 with the RA/epiLA configuration. The mean tachycardia cycle length of the AFL episodes was 146.7 (± 16.9) ms. Representative tracings of successful and unsuccessful conversion attempts are highlighted in Fig. 2. For the former, both immediate (type 1 break; Fig. 2A) and delayed termination of AF/AFL (type 2 break; Fig. 2B) were observed. Type 1 breaks accounted for 33/37 (89.1%) total successful conversion attempts. A graphical summary of PEF delivery attempts across a range of voltages applied for each catheter configuration is shown in Fig. 3. In general, AF/AFL conversion attempts were likely to succeed with higher voltages, with 8/11 (72.7%) success using 1500 V in the RA/CS configuration and 9/11 (81.8%) success using 2000 V in the RA/epiLA configuration. Figure S1 shows PEF delivery attempts in both configurations stratified by AF and AFL. Qualitatively, conversion of AFL was more likely to succeed with lower voltage applications compared to AF. With PEF delivery, significant muscle stimulation was noted; this was more apparent with higher voltages.

Fig. 1 Experiment and catheter set-up. **A** Endocardial RA and CS decapolar catheter placement. Note that venous ECMO cannula, Impella®, and epicardial access sheath are in view. **B** Endocardial RA and epicardial LA decapolar catheter placement



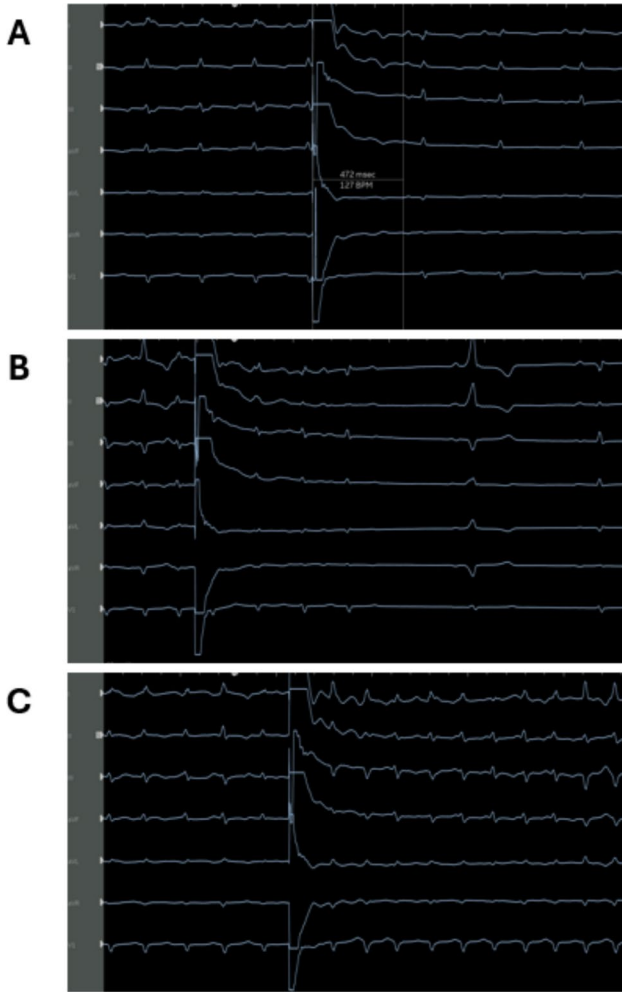


Fig. 2 AF/AFL conversion attempts with PEF delivery. **A** Successful conversion (type 1 break). **B** Successful conversion (type 2 break). **C** Unsuccessful conversion

3.2 Signal changes and arrhythmias following pulsed electric field delivery

Immediately following PEF delivery, transient decreases in near-field electrogram voltages on the decapolar catheter channels were seen compared to pre-PEF; these often recovered to some extent within 5 min. However, subtle but persistent changes in electrogram voltages emerged following successive deliveries (Fig. 4). In addition, other rhythm abnormalities were observed, usually after multiple PEF deliveries (Fig. 5). These included the following: intra-atrial delay and sinus node exit block; junctional rhythm; and high-grade atrioventricular block with RA/LA dissociation. The noted arrhythmias resolved within a few minutes.

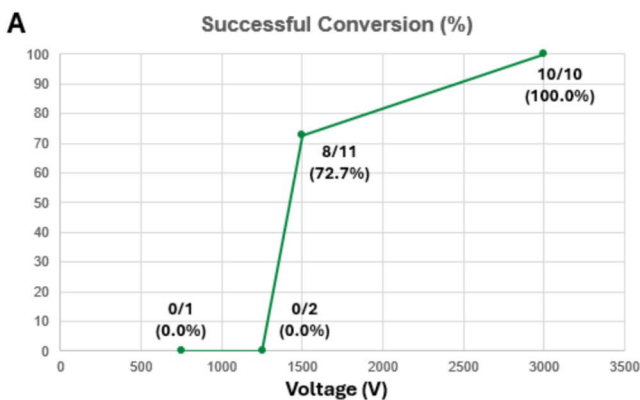
3.3 Gross pathology

On examination, hemorrhagic lesions were noted in the locality of catheter placement; representative pictures are shown in Fig. 6.

4 Discussion

In this preclinical study, we investigated the utility of PEF delivery for terminating AF/AFL via percutaneously positioned catheters. Salient findings were as follows: (1) AF/AFL episodes were reproducibly terminated with single microsecond range pulses delivered from both RA/CS and RA/epiLA configurations; (2) conversion success rates generally increased with increased voltage application; and (3) local atrial electrogram changes and rhythm disturbances

Right Atrial / Coronary Sinus



Right Atrial / Epicardial Left Atrial

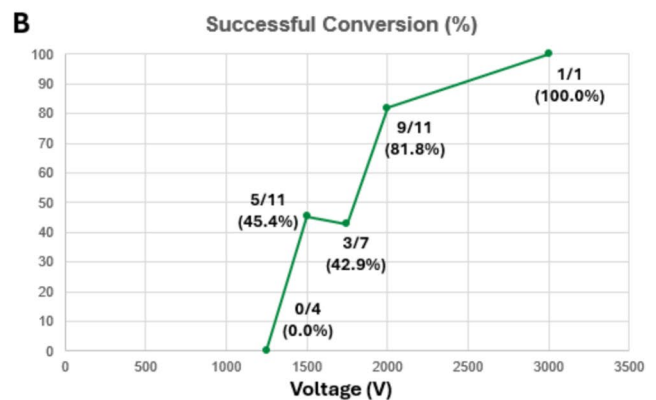


Fig. 3 Summary of conversion success probabilities. **A** RA/CS configuration. **B** RA/epiLA configuration

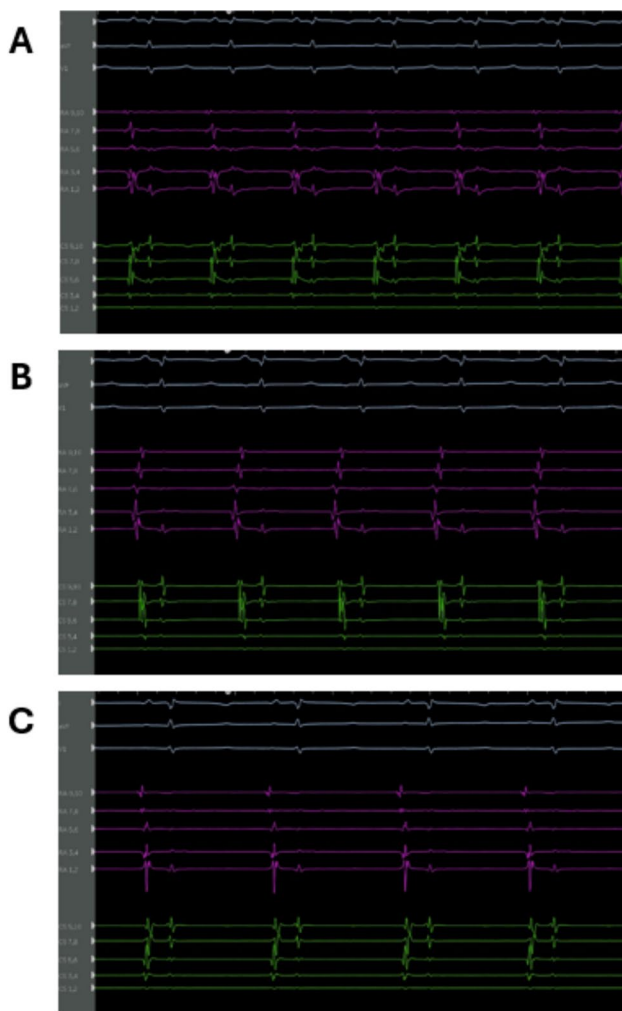


Fig. 4 Transient and persistent electrogram changes post-PEF. Attenuation of atrial electrograms immediately post-PEF (A) that returns to baseline after 5 min (B). Blunting of atrial electrograms after five successive PEF deliveries (C), most apparent in CS channels compared to B, that persists despite several minutes of observation

(sinus pauses, heart block etc.) were observed post-PEF, which were more evident following successive PEF deliveries. These data provide preliminary proof-of-concept that microsecond range PEF may be a feasible means for converting atrial arrhythmias.

Despite decades of research, the mechanisms of AF remain incompletely elucidated. In brief, the main determinants are abnormal ectopic firing (e.g., from pulmonary veins) [12] and re-entry facilitated by structural as well as functional heterogeneity [2, 13]. Medical and percutaneous/surgical rhythm control measures therefore aim to eliminate the major triggers of AF and modify the underlying milieu that maintains it [1]. While we have made remarkable strides in this endeavor, many patients remain at risk of experiencing AF episodes in the outpatient setting.

The concept of an implantable atrial defibrillator system had been previously explored. This involved delivering 6 ms biphasic direct current shocks between RA and CS defibrillation leads, synchronized to the R wave. While effective in terminating AF episodes, patients experienced significant discomfort with such shocks, leading to the device's eventual discontinuation from the market [8]. Atrial ATP algorithms have demonstrated utility for pace terminating AFL and potentially reducing overall atrial arrhythmia recurrences [6, 7]; however, AF is not directly susceptible to overdrive pacing approaches. Recently, multipulse therapy (MPT), which incorporates three stages of low-voltage shocks/pulses to terminate AF without potentially incurring pain, has shown some promise in animal and human studies but is not ready for clinical use [14, 15]. The search for an ideal device-based solution to treating AF episodes therefore remains underway, but if achieved, it would have a tremendous impact in managing the growing number of patients who suffer from AF.

The advent of PFA has catalyzed enormous excitement and growth in the field of electroporation. Although cardiac ablation via irreversible electroporation remains a key focus of clinicians and industry alike, there is burgeoning interest in the biophysics and applications of reversible electroporation. For example, deliberate non-lethal PEF delivery (at “reversible electroporation” doses)—coined pulsed field mapping—may be used to delineate regions critical for fostering arrhythmias before fully committing to ablation [16]. Similarly, reversible electroporation may render a critical mass/area of cardiac tissue temporarily inexcitable, impeding fibrillatory wavefronts and thereby leading to arrhythmia cessation [10]. Other groups have assessed the potential of PEF-based defibrillation in small animal models [17, 18]; our work adds to the body of evidence that “pulsed field defibrillation” may be an eventuality in clinical practice. PEF involves a complex interweaving of delivery parameters (voltage, pulse width, pulse number, pulse shape, inter-pulse interval, etc.), form factor configuration, and biological surroundings [3, 5]. Although we are only scratching the surface in terms of our current understanding, the extraordinary customizability of PEF delivery along with cardiomyocytes' relative sensitivity to its effects offers a theoretical unique opportunity to effectively defibrillate without causing overt smooth muscle and nerve stimulation, thereby overcoming a major shortcoming to current cardioverter-defibrillator systems.

We highlight several limitations to the current study. First, although swine hearts share many similarities to that of humans, there are some differences in terms of atrial size/shape, pulmonary veins, and CS; these may affect thresholds for AF/AFL termination. Second, we

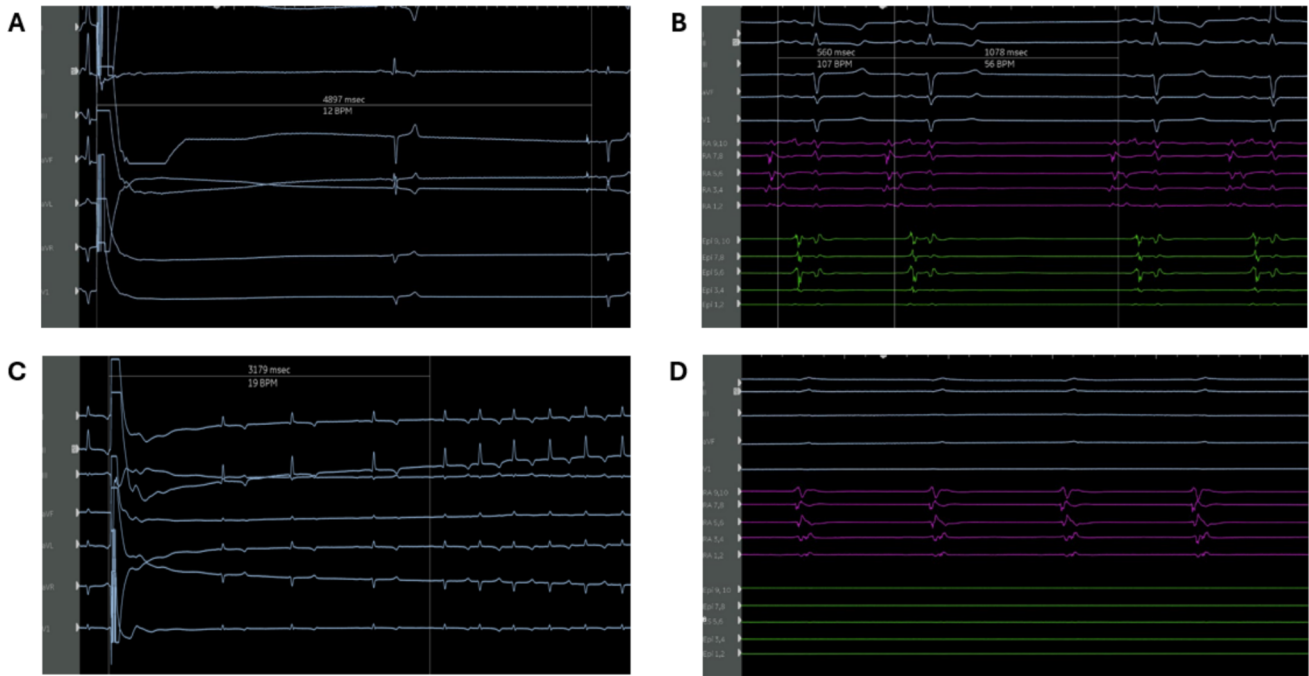
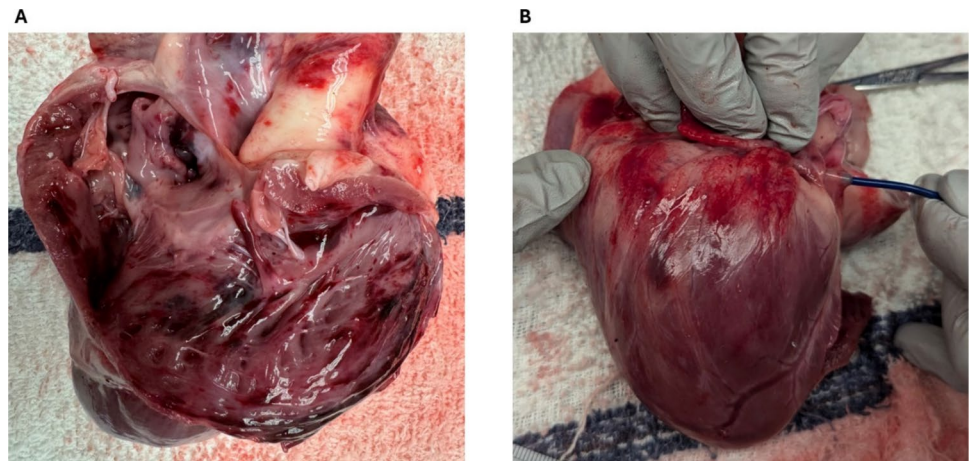


Fig. 5 Observed arrhythmias following PEF delivery. **A** Sinus pause. **B** Sinus node exit block; also note marked intra-atrial delay between RA and CS signals. **C** Junctional rhythm. **D** Sinus tachycardia with atrioventricular block and RA/LA dissociation

Fig. 6 Gross pathology of excised hearts. **A** Endocardial RA surface. **B** CS with catheter placed for demonstrative purposes



held catheter shape/location as well as pulse width/number constant to better understand the effect of voltage on conversion success in this study. However, determining the optimal parameter set and configuration for achieving effective arrhythmia termination will require more comprehensive and iterative finetuning. Third, both AF and AFL episodes were induced with atrial programmed stimulation. Although these were combined to assess conversion success probabilities, significant differences in conversion thresholds may exist between them. Fourth, prominent muscle stimulation was invoked with

the tested PEF parameter set and catheter configuration. Pertinently, we were limited to monophasic pulses with the BTX generator. Subsequent investigation with more customizable electroporation generators will be helpful in overcoming this [19, 20]. Fifth, significant arrhythmias including conduction abnormalities were seen with PEF delivery. This may be related to the electric field vector and its effects on exposed structures such as Bachmann's bundle and the atrioventricular node. Sixth, each attempt was treated as independent when constructing the voltage-probability curves; however, despite the 5-min

wait time between attempts, preceding PEF deliveries might still have “stacking” effects on subsequent deliveries. Seventh, signals could not be recorded during PEF delivery with the current experiment setup. Finally, the etiology of the hemorrhagic lesions on gross pathology is unclear. This may be related to cumulative PEF deliveries leading to inadvertent myocardial injury versus mechanical trauma. Again, this will need to be elucidated further to ensure long-term safety.

5 Conclusion

We demonstrate early feasibility of using PEF delivery from intracardiac catheters to terminate AF/AFL episodes in swine models. Although considerable refinement is required, the study provides evidence that pulsed field defibrillation may be an effective and realistic option for terminating cardiac arrhythmias.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10840-025-02115-7>.

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Declarations

Conflict of interest The authors declare no competing interests.

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