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Novel Balloon Catheter Device with Pacing, Ablating, Electroporation, and Drug Eluting Capabilities for Atrial Fibrillation Treatment – Preliminary Efficacy and Safety Studies in a Canine Model

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Abstract

Pulmonary vein isolation is an established therapeutic procedure for symptomatic atrial fibrillation (AF). This approach involves ablation of atrial tissue just outside of the pulmonary veins. However, patient outcomes are limited by a high rate of arrhythmia recurrence. Ablation of electrically active tissue inside the pulmonary vein may improve procedural success, but is currently avoided due to the complication of post-ablation stenosis. An innovative device that can ablate inside pulmonary veins and prevent stenosis is a viable strategy to increase long-term efficacy. We have developed a prototypical balloon catheter device and have demonstrated its functionality in four acute canine experiments. Further optimization of this device may provide an innovative means to simultaneously ablate and prevent pulmonary vein stenosis for improved AF treatment in humans.

Introduction

Catheter ablation via pulmonary vein isolation is an established treatment for symptomatic atrial fibrillation (AF).¹ Pulmonary veins harbor the triggers for AF from atrial muscle sleeve extensions.² Electrical isolation of these muscle sleeves is a common means to treat AF by radiofrequency (RF) energy application to atrial tissue surrounding the pulmonary vein ostia.^{3, 4} However, this approach is fraught with AF recurrence because of incomplete ablation lesions and/or electrical reconnections of the pulmonary vein muscle to the atrium.⁵

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A method to enhance efficacy of ablation would involve direct ablation of the myocardial sleeves within the pulmonary veins. This strategy is usually avoided intentionally because of the well-established, life-threatening complication of pulmonary vein stenosis that can occur post-ablation.⁶⁻⁸

Though not completely understood, the mechanism for pulmonary vein stenosis has been suggested to involve smooth muscle activation with medial thickening and intimal hyperplasia, as well as scar retraction,⁹⁻¹¹ all leading to pulmonary vein narrowing. In an effort to combat this, investigators have placed drug eluting stents inside pulmonary veins, and were able to show a decrease in scarring response and prevention of post-ablation stenosis.¹² Therefore, an innovative approach to improve AF catheter ablation success would be a combination of RF energy ablation inside the pulmonary vein, along with delivery of an anti-proliferative agent to halt this cascade.

We propose a novel strategy that offers the ability to 1) pace inside the pulmonary vein to detect the desired site for ablation, 2) ablate inside the pulmonary vein with R For direct current (DC) energy, 3) elute an anti-proliferative agent at the site of ablation to prevent tissue hyper-proliferation and vein stenosis, 4) deliver DC energy at electroporative doses to enhance drug uptake at the site of ablation. We have conducted preliminary efficacy and safety studies to test and optimize our prototype device.

Methods

Four mongrel dogs, weighing 30 to 40 kg, were anesthetized with ketamine (10 mg/kg IV) and diazepam (0.5 mg/kg IV) for induction and isoflurane (1% to 5% continuous inhalation) for maintenance of anesthesia. Positive pressure ventilation was given through an endotracheal tube and core body temperature was maintained at 37 °C using a heating pad placed underneath dog. Standard 9-12 French sheaths were placed percutaneously in the femoral artery, femoral veins, and external jugular vein for catheter access to the heart. Heart rate and femoral arterial blood pressure were continuously monitored.

Standard electrocardiographic leads and intracardiac electrograms filtered at 30 – 500 Hz were electronically recorded using a Prucka CardioLab® recording system (GE Healthcare, Wauwatosa, WI). Bi-plane fluoroscopy and intra-cardiac ultrasound (Acuson Sequoia, Siemens) were used to navigate the cardiac chambers and to guide catheter manipulation. For RF ablation, a Boston Scientific EPT 1000XP Ablation generator (EP Technologies, Boston Scientific Corp., Natick, MA) was used (power 5-50 Watts, duration 60-120 seconds). During ablation energy delivery, saline irrigation was delivered using a Biosense Webster Cool-Flow irrigation pump system (5-17 cc/min)(Diamond Bar, CA). A Grass S48 stimulator (Astro-Med Inc., Warwick, RI) was used for DC electroporation (current 7500 μ A, frequency 7 kHz, duration 60-300 seconds). A Bloom stimulator (Fischer Medical Technologies LCC, Broomfield, CO) was used for pacing. Heparinized saline was used to prevent intraprocedural clotting.

At the end of each study, animals were sacrificed with electrical induction of ventricular fibrillation with DC current. Post-mortem gross anatomic examination was performed to

evaluate for complications and efficacy of ablation. Histologic samples were obtained after embedding hearts in paraffin for 1-2 weeks post-procedure. After sectioning the heart, histologic staining was performed with hematoxylin and eosin to assess for tissue ablation changes.

Results

Prototype Design

We designed a novel, balloon ablation catheter device with the capability to sense, pace, deliver ablation lesions with either RF or DC energy, and deliver drug to tissue at the site of ablation. The electrodes on the surface of the balloon device are used for RF or DC energy lesion application. The device electrodes are 1 mm in diameter and are on the surface of the outer balloon.

The constructed device involves an elongated catheter shaft imbedded in a double balloon with a lumen to facilitate liquid drug delivery (Figure 1). There are two lumens in the inner shaft that are in communication with one lumen open to each of the balloons for air inflation or liquid delivery that are delivered from the end of the device through separate ports. The inner balloon was inflated with 10-15 cc of air, and the outer balloon was inflated by the elution of heparinized saline at 5-17cc/min from the cool flow through the inner shaft to provide both an expandable fit inside the thoracic vein it was expanded in, as well as cooling of the electrodes during ablation. The micropore size for the outer balloon is .008 inch, allowing for elution to the local tissue in contact with the balloon device.

The double balloon construction allows for the inner balloon to provide a secure and stable position of ablation catheter inside cardiac structures, such as a thoracic or pulmonary vein. Once location is secured through inner balloon inflation, subsequent inflation of the outer balloon to abut the surface of cardiac tissue, allows for exact electrode-tissue contact, which is ideal for ablation and liquid elution to tissue (Figure 2). Refinement of the initial prototype to smaller sized inner and outer balloons allowed for better accommodation of the pulmonary and thoracic veins, as well as easier access and navigation throughout the cardiac chambers (initial design had an outer balloon with dimensions of 20mm × 55mm, and a 30mm round inner balloon. The re-iteration device had a smaller in diameter and had dimensions of 15 mm × 25 mm, and a 25 mm triangular inner balloon).

Prototype Functionality

Demonstration of the novel balloon ablation catheter to sense, pace, ablate, and elute liquid were demonstrated in all four experiments (Figure 3). In these acute studies, we have successfully shown functionality and reliability of our novel device to 1) sense electrical activity and accurately capture local atrial and ventricular tissue; 2) pace and capture desired tissue location prior to delivery of energy; 3) apply RF or DC ablation energy to the superior vena cava, inferior vena cava, right atrial appendage, left atrial appendage, and pulmonary veins; 4) elution of saline through internal shaft side ports to mimic liquid drug elution, 5) expand the balloon to achieve a secure fit in various cardiac structures, and 6) cooling of the electrodes during ablation energy delivery (Table 1). During ablation, no steam “pops” were

heard. At gross anatomic inspection, no damage to cardiac or extracardiac structures was seen. Efficacy of delivering superficial ablative lesions to the endocardial surface of these structures was visible on gross anatomic inspection in all four canine experiments (Figure 4). In addition, histological analysis using hematoxylin and eosin staining showed evidence of ablation of the endocardial surface (Figure 5).

Prototype Safety

During the entire electrophysiologic study and at necropsy, there was no evidence of acute hemorrhage, perforation, or edema in any of the four canine experiments.

Discussion and Clinical Implications

We report the preliminary efficacy and safety of a novel balloon catheter based system that can directly ablate cardiac tissue using RF or DC energy. The double balloon design provides easy navigation throughout the cardiac chambers and into the thoracic and pulmonary veins. The inner shaft ports and porous configuration of the outer balloon provide an avenue for liquid delivery to the surrounding ablated tissue, cooling of the electrodes during ablation, and pressure to expand the balloon to achieve a secure fit. In addition, the balloon surface electrodes are able to deliver DC electroporation energy, and may enhance anti-proliferative agent uptake into tissues. This novel optimized device has set the stage for future experiments involving both ablation inside the pulmonary vein and a mechanism to potentially prevent pulmonary vein stenosis. This innovative approach may provide improved AF ablation outcomes in future human studies.

Future Directions

The next phase of this study will involve evaluation of this device in a chronic canine model. Ablative lesions followed by elution of an anti-proliferative drug inside the pulmonary veins will be performed, and the animals will be followed chronically to assess for extent of pulmonary vein stenosis, as well as evaluating for bi-directional electrical block between vein and atrium. If efficacy and safety are adequately displayed, we will move towards applying our novel prototype and method to conduct the first-in-human trials for refractory AF patients. Furthermore, our novel ablation catheter and method for ablation may be applied to other difficult to treat diseases. For example, it may find utility in ablation and autonomic manipulation of the renal vasculature, and/or pulmonary artery ablation for pulmonary hypertension. This technology will also be used to gain increased understanding of how to manipulate DC energy to create non-thermal ablation of tissue and may be able to be applied to many diseases involving and extending beyond the field of cardiac electrophysiology.

Acknowledgments

Dr. Asirvatham and Dr. Holmes are named inventors on a patent application covering the technology in this manuscript. Neither Mayo Foundation nor Drs. Asirvatham and Holmes have received any compensation for the patent application to date but may do so in the future. All other authors have nothing to disclose

All authors have read and agree with the journal's authorship agreement

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Abbreviations

AF	Atrial fibrillation
RF	Radiofrequency
DC	Direct current

Figure 1. Novel Balloon Catheter Ablation Device

A. Catheter device with external balloon surface electrodes and inner shaft with liquid drug elution capabilities – both balloons deflated. **B.** Inner balloon inflated (arrow) for catheter stabilization. **C.** Inner and outer balloon inflated (arrows) to create an interface between electrodes on surface of balloon with internal face of tissue for ablation and elution of liquid drug to the surrounding tissue.

Figure 2. Fluoroscopic view of balloon ablation catheter in superior vena cavae

A. Antero-posterior fluoroscopic view of the balloon catheter in superior vena cava – both inner and outer balloons deflated (arrow). **B.** Antero-posterior fluoroscopic view of the balloon catheter in superior vena cava – both inner and outer balloons inflated (arrow).

Figure 3. Electrophysiologic display of electrical sensing and pacing from electrodes on balloon surface

ECG, sensed electrograms (red star = sensed atrial electrogram; yellow star = sensed ventricular electrogram) by prototype electrodes and from coronary sinus electrodes. **B.** Pacing from the prototype electrodes (arrow = pacing spike; green star = simultaneous atrial and ventricular capture). *III, I, II, V1 = surface ECG recordings; EI 1-2, 3-4, 5-6, 7-8 = bipolar recordings from ablation balloon; CS 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-1 = bipolar recordings from coronary sinus catheter; PAo = arterial blood pressure.

Figure 4. Gross lesions of cardiac and venous structures post ablation

A. Superior vena cava ablation lesion at necropsy. **B.** Inferior vena cava ablation lesion at necropsy. **C.** Right atrial appendage ablation lesion at necropsy. **D.** Left superior pulmonary vein ablation lesion at necropsy.

Figure 5. Endocardial ablation of myocardial tissue with RF energy

A. Histologic section stained with hematoxylin and eosin at $1.25 \times$ magnification. Ablation lesion is seen extending from the endocardial towards the epicardial tissue layer. **B.** $4 \times$ magnification showing tissue ablation from the endocardial surface.

Table 1

Ablation characteristics

	Location	Energy	Power	Irrigation	Impedance	Time
Dog #1	LSPV	RF	30 W	17 ml/min	78 – 80 Ω	120 s $\times$ 2
	IVC	DC	7500 μ A	17 ml/min	-	240 s
	SVC	RF	30 – 40 W	17 ml/min	52 – 55 Ω	180 s
	RAA	RF	30 – 50 W	17 ml/min	54 – 56 Ω	120 s $\times$ 3
	SVC	DC	7500 μ A	17 ml/min	-	300 s $\times$ 4
Dog #2	SVC	RF	50 W	17 ml/min	58 Ω	120 s
	LAA	DC	7500 μ A	17 ml/min	-	300 s
	LAA	RF	50 W	17 ml/min	65 Ω	120 s
	RAA	DC	7500 μ A	17 ml/min	-	300 s $\times$ 2
	RAA	RF	50 W	17 ml/min	63 Ω	120 s
Dog #3	SVC	DC	7500 μ A	17 ml/min	-	300 s $\times$ 3
	SVC	RF	50 W	17 ml/min	52 – 61 Ω	120 s $\times$ 3
	IVC	DC	7500 μ A	17 ml/min	-	300 s
	IVC	RF	50 W	17 ml/min	58 Ω	120 s
	RAA	DC	7500 μ A	17 ml/min	-	300 s
Dog #4	RAA	RF	50 W	17 ml/min	51 Ω	120 s
	SVC	DC	7500 μ A	17 ml/min	-	300 s $\times$ 2
	SVC	RF	50 W	17 ml/min	60 – 75 Ω	120 s $\times$ 2
	RAA	DC	7500 μ A	5 ml/min	-	300 s
	RAA	RF	50 W	5 ml/min	58 – 68 Ω	120 s $\times$ 2
	IVC	DC	7500 μ A	5 ml/min	-	300 s $\times$ 3

LSPV = left superior pulmonary vein; IVC = inferior vena cava; SVC = superior vena cava; RAA = right atrial appendage; LAA = left atrial appendage; RF = radiofrequency; DC = direct current