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## First Description of a Novel Method that Allows for an Efficient & Fast Ablation of Atrial Arrhythmia While Using an 8 mm Focal Cryoablation Catheter --Manuscript Draft--

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<b>Abstract:</b>	Cryothermal ablation of atrial arrhythmias is now becoming more popular as an effective alternative to radiofrequency (RF) ablation with perhaps some advantageous with regards towards patient safety and acute post-procedural patient discomfort. In general, cryofocal catheters for point ablations have been widely used in the treatment of atrioventricular nodal reentry tachycardia ablations and Wolff-Parkinson-White syndrome termination. Additionally, purpose-built anatomical cryoablation catheters (e.g., cryoballoon) have made pulmonary vein isolation (during atrial fibrillation (AF) ablation) effective, safe, and efficient. However, cryofocal ablation of typical right atrial flutter (AFL) during an AF ablation has been challenging with regard to procedure time efficiency. Since each cryofocal application can encompass up to five minutes in duration (or longer), the combined total time of connecting nine-to-ten lesion sets can be time consuming in comparison to current RF ablation catheter usage for typical right AFL termination. This study examined AFL ablations with the 8 mm focal cryoablation catheter that occurred during an AF ablation with the cryoballoon system. The cryofocal ablation method uses the advantage of connecting lesion sets by freeze propagation of hypothermic temperatures in cardiac tissue. Spatial monitoring is performed with the usage of intracardiac echocardiography, and complete bi-direction block at the inferior vena cava-tricuspid valve isthmus is achieved with typically four-to-five cryofocal applications lasting 4-5 minutes in duration. Consequently, usage of this cryofocal method in AFL/AF ablation can obtain durable long-term results in AFL/AF ablation with total procedure times that are similar to RF catheter usage while still maintaining the beneficial cryoablation safety profile.
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Dear JoVE editorial staff,

We are happy to submit this manuscript for review. The methods described are an enhancement on the usage of the cryofocal catheter. This line of study in atrial flutter has had minimal previous publications, and I am sure that this new idea will draw attention to the method, procedure, and JOVE. These types of methods manuscripts will be extremely beneficial and well read.

Best regards,

Hae Lim

**TITLE:**

First Description of a Novel Method that Allows for an Efficient and Fast Ablation of Atrial Arrhythmia While Using an 8 mm Focal Cryoablation Catheter

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**KEY WORDS:**

Atrial fibrillation, atrial flutter, catheter ablation, cardiovascular, cryoballoon, cryofocal, electrophysiology, heart

**SHORT ABSTRACT:**

This goal of this study is to demonstrate a method by which an 8 mm cryofocal ablation catheter can be used efficiently (with regard to procedure time) during a cryoballoon procedure for the treatment of atrial arrhythmia.

**LONG ABSTRACT:**

Cryothermal ablation of atrial arrhythmias is now becoming more popular as an effective alternative to radiofrequency (RF) ablation with perhaps some advantageous with regards to patient safety and acute post-procedural patient discomfort. In general, cryofocal catheters for point ablations have been widely used in the treatment of atrioventricular nodal reentry tachycardia and Wolff-Parkinson-White syndrome. Also, purpose-built anatomical cryoablation catheters (e.g., cryoballoon) have made pulmonary vein isolation during atrial fibrillation (AF)

ablation effective, safe, and efficient. However, cryofocal ablation of typical right atrial flutter (AFL) during an AF ablation has been challenging with regard to procedure time efficiency. Since each cryofocal application can encompass up to five minutes in duration (or longer), the combined total time of connecting fifteen to twenty lesion sets can be time consuming in comparison to the current RF ablation catheter usage for typical right AFL termination. This study examined AFL ablations with the 8 mm cryofocal ablation catheter that occurred during an AF ablation with the cryoballoon system. The cryofocal ablation method employed in this study uses the advantage of connecting lesion sets by freeze propagation of hypothermic temperatures in cardiac tissue. Spatial monitoring is performed with the usage of intracardiac echocardiography (ICE), and complete bi-direction block at the inferior vena cava-tricuspid valve isthmus is achieved with typically five to ten cryofocal applications lasting approximately three minutes (each) in duration. Consequently, usage of this cryofocal method during AFL/AF cryoballoon ablation can obtain durable long-term results in AFL/AF ablation with total procedure times that are similar to RF catheter usage.

## **INTRODUCTION:**

Traditionally, radiofrequency (RF) catheter ablation is the typical method for termination of typical right atrial flutter (AFL) when a catheter-based electrophysiological intervention is medically necessary.<sup>1-3</sup> As with most atrial arrhythmia ablation, long-term efficacy is primarily dependent on the ability to create a transmural lesion that is continuous for the length of electrical blockade,<sup>4</sup> and thus, establishing a bi-directional conduction block for aberrant electrical signal propagation.<sup>5</sup> However, the problems associated with RF catheter ablation of the atria are well documented (e.g., steam pop, thrombus formation, and errant collateral tissue damage).<sup>6,7</sup> When using a RF ablation catheter, lesion size and transmurality are heavily dependent on the energy delivery to the tissue, the temperatures achieved on the target location, and the contact-force utilized during the ablation.<sup>7</sup>

More recently, clinical studies have determined that cryoablation catheters can be used for the ablation of atrial fibrillation (AF) and the accompanying AFL with long-term efficacy and a favorable safety profile.<sup>7-9</sup> Yet, a potential hurdle to more wide-spread adoption and usage of the cryofocal catheter during AF/AFL ablation could be the duration of procedure times. When examining cryofocal AFL ablation, mean procedure-, fluoroscopy-, and cryoapplication-times for the Montenero *et al.* study were 88, 24, and 45 min, respectively.<sup>8</sup> In another cryofocal AFL ablation study (Kuniss *et al.*), these same procedural measurements were 120, 18, and 40 min, respectively.<sup>9</sup>

Consequently, the aim of this current study was to demonstrate a method that uses typically five to ten cryofocal applications of the 8 mm focal ablation catheter during an AFL ablation, when the cryofocal catheter was used with the cryoballoon system for a primary AF indication. In this study, most cryofocal AFL ablations were three minutes in duration, and the ablations are spread through the isthmus between the tricuspid valve (TV) annulus and the inferior vena cava (IVC) which is also known as the cavotricuspid isthmus (CTI) or the IVC-TV isthmus. By using this novel protocol, the typical total cryofocal application time is reduced, and it is more representative of RF catheter ablation times when treating patients with typical right AFL.

This study examined 13 patients that had an ablation termination of typical right AFL while using the 8 mm focal cryoablation catheter during an AF ablation with the cryoballoon catheter for pulmonary vein isolation (PVI). All 13 patients had an AF/AFL patterned arrhythmia, and additionally follow-up on efficiency, safety, and efficacy was conducted on these patients.

## **PROTOCOL:**

Informed consent was obtained from all patients. All methods used in this study were considered as standard-of-care during the time of patient treatment.

### **1. Patient Preparation**

1.1 Maintain patient on an oral anticoagulation drug (warfarin, dabigatran, rivaroxaban, or apixaban) according to manufacturer's prescribing information for at least one month prior to the AF/AFL ablation procedure.

1.2 Discontinue the anticoagulation drug for at least one pharmacokinetic half-life before the day of procedure.

1.2.1 If a patient is taking warfarin, discontinue patient usage for one full day before the AF/AFL ablation procedure.

1.2.2 If a patient is taking a novel oral anticoagulation drug (dabigatran, rivaroxaban, or apixaban), discontinue the patient usage for one dosage before the ablation procedure which is typically the evening dose.

1.3 Achieve an international normalized ratio (INR) between 1.8 and 2.0 on the morning of the ablation procedure, which will confirm that the patient is in a proper state of blood anticoagulation.

1.3.1 Obtain a blood sample (~5 to 10 mL) drawn from a venous route captured into a clinical standard sodium citrate test tube.

1.3.2 Separate blood cells from plasma by centrifugation of the blood sample (10 to 15 minute spin at ~3000 rpm or ~1500 X g), and test plasma for the prothrombin time ratio on a certified clinical diagnostic instrument (according to manufacturer's protocol) at 37°C.

1.4 Re-schedule an ablation date for any patient that cannot maintain a therapeutic INR on the day of the ablation procedure (INR below 1.7).

1.5 If a patient reports a deviation in the pre-ablation anticoagulation protocol, administer a transesophageal echocardiogram (up to 48 hours before the ablation) to exclude the presence of atrial thrombus.<sup>10,11</sup>

1.6 If the pre-procedure INR needs to be elevated, administer a heparin bolus according to the patient weight (50 IU/kg) delivered via right femoral vein access.

## **2. Procedure Setup**

2.1 Prescribe a fasting protocol for the patient for at least 12 hours before the ablation procedure.

2.2 Establish patient sedation with the usage of a general anesthesia protocol using intravenous propofol according to prescribing information, and do not use a paralytic agent so that phrenic nerve monitoring can be used during the cryoballoon ablation procedure.

2.2.1 Calculate general anesthesia dose based on ASA score, patient medical history, and patient physical demographics.

2.2.2 Ensure that a proper level sedation plane has been achieved while using the least possible amount of anesthesia.

2.3 Establish cardiac atrial access through femoral vein cannulation with a trocar and cannula using the modified Seldinger technique.<sup>12</sup>

2.4 Establish left atria (LA) access via transseptal puncture using a Mullins-type sheath in combination with a Brockenbrough-styled (BRK) transseptal needle, which is introduced via femoral vein access.

2.4.1 Flush the dialator sheath and insert a J-tip guidewire into the dialator.

2.4.2 Advance the dialator through the right femoral vein to the level of the junction with the superior vena cava and the right atrium (RA).

2.4.3 Remove the guidewire and insert the BRK transseptal needle into the dialator just inside the distal tip.

2.4.4 Using fluoroscopy<sup>13</sup>, pull the dialator down the septal wall until the fossa ovalis is reached.

2.4.5 Confirm the fossa ovalis position by pushing the dialator towards the LA and examining the septum under ICE imaging. When the dialator is in the correct position, the thin fossa ovalis will “tent” in shape because of the leftward pressure from the dialator.

2.4.6 Advance the BRK transseptal needle past the dialator and puncture the fossa ovalis, and then advance the dialator across the interatrial septum and into the LA using ICE guidance.

2.4.7 Remove the BRK transseptal needle, and confirm LA access by flushing the dialator with saline. Use Doppler mode ICE imaging during the saline flush to demonstrate saline flow in the LA and confirm that transseptal access is achieved.

2.4.8 Advance the guidewire through the dialator and into the LA chamber, and then exchange the dialator with a Mullins-type sheath while leaving the guidewire in the LA.

2.5 Administer an intravenous heparin bolus when transseptal puncture is first achieved using a patient weight-based protocol. A typical first bolus dose of heparin can be between 5,000 and 10,000 units.

2.6 Give supplemental doses of heparin throughout the entire ablation procedure with the goal of maintaining an active clotting time (ACT) range between 350 and 400 seconds.<sup>7</sup>

2.6.1 At the time of transseptal puncture, draw an intravenous blood sample and place a drop of blood onto an ACT cartridge.

2.6.2 Insert the ACT cartridge into a Hemochron-styled micro-coagulation reader to measure ACT.

2.6.3 Adjust ACT as needed throughout the procedure using multiple non-continuous doses of heparin (as needed).

2.6.4 Re-check ACT levels every 10 to 15 minutes until a therapeutic anticoagulation level is achieved (350 to 400 seconds), and thereafter, re-check ACT levels at 15 to 30 minute intervals.<sup>7</sup>

### **3. AF ablation with the cryoballoon catheter**

3.1 Using the Mullins-type sheath, introduce a guide wire into the LA and place the guide wire distally into the left superior pulmonary vein (LSPV).

3.2 Exchange the Mullins-type sheath, for the cryoballoon steerable sheath while maintaining the guidewire position in the LSPV.

3.2.1 Specifically, with the guidewire in the LSPV, remove the Mullins sheath over the guidewire.

3.2.2 Backload the cryoballoon steerable sheath onto the wire, and insert the steerable sheath into the LA.

3.3 Introduce the cryoballoon catheter over the guidewire, through the steerable sheath, and into the LA chamber.



3.4 Inflate the cryoballoon catheter by pushing the inflation button on the cryoconsole.

3.5 Obtain pulmonary vein (PV)-to-balloon occlusion by pushing the balloon towards the PV antrum while using fluoroscopy guidance.<sup>13</sup>

3.6 Confirm PV-to-balloon occlusion by using radiopaque contrast agent and imaging with fluoroscopy<sup>13</sup>.

3.6.1. Inject a 50% saline to 50% radiopaque contrast agent mix through the dedicated central lumen of the cryoballoon catheter (~3 mL total volume of injection).

3.6.2 Use fluoroscopy and assess the retention of contrast agent at the distal cryoballoon tip.<sup>13</sup>

3.6.3 Detect a non-occlusive balloon position by observing the presence of contrast agent leakage into the LA chamber.<sup>13</sup>

3.6.4. Alternatively or additionally, use the ICE catheter to assess PV-to-balloon occlusion.

3.6.4.1 Use the Color Flow Doppler mode to visualize movement across the balloon surface which is indicative of a leak and lack of balloon occlusion.

3.6.4.2 Ensure that imaging with the ICE catheter is completed by sweeping the entire balloon surface during visualization.

3.6.5 Reposition the balloon if a leak is detected, or start the cryoballoon freeze if occlusion is confirmed.

3.6.6 Start a cryoballoon ablation by pushing the “CryoAblation” square on the touch-sensitive screen of the cryoconsole.

3.7 Establish each subsequent PV-to-balloon occlusion at the antral surface of the LA using fluoroscopy.<sup>13</sup> Start and stop the fluoroscopy imaging using the foot pedals attached to the fluoroscope unit.

3.7.1 When PV-to-balloon occlusion is established, freeze each PV for a minimum of two applications (freeze-thaw-freeze) with each lasting at least 180 seconds.

3.7.2 Ensure that cryoballoon nadir temperatures are no colder than -55° C, and immediately terminate freezes that are colder.<sup>13</sup>

3.7.3 After each freeze, do not move the cryoballoon catheter until the catheter achieves a temperature reading of above 35° C.<sup>13</sup>

3.7.3.1 View the cryoconsole screen to monitor the return gas temperature to ensure that the balloon temperature is above 35° C.

3.7.3.2 Use fluoroscopy during the first initial balloon movements after a freeze to ensure that the surround ice has melted. Under fluoroscopy imaging, slowly move the catheter and ensure that the surround cardiac tissue is not also moving which is indicative of tissue-to-balloon attachment by cryoadhesion.

3.8 Pace the phrenic nerve near the RA and superior vena cava junction with a diagnostic catheter at 20 mA amplitude and 2.0 ms pulse width during right-sided PV ablations.

3.8.1 Monitor phrenic nerve function by manual detection of diaphragmatic contractions, and immediately terminate any ablation if phrenic nerve function is reduced. Detect phrenic nerve function loss by a reduction in diaphragmatic movement which is palpable with a physician's hand on the patient's abdomen.

3.8.2 Alternatively, use an additional phrenic nerve monitoring technique (as an adjunctive method) to determine nerve function, such as diaphragmatic electromyogram monitoring.<sup>14</sup>

3.9 Confirm PVI by testing electrical entrance and exit blockage at each PV while using two diagnostic cardiac catheters in a "pace-and-capture" protocol.

3.9.1 In the pace-and-capture protocol, place one circular conventional duo-decapolar diagnostic mapping catheter (variable loop diameter) within the PV and place the second linear decapolar diagnostic mapping catheter in the proximal coronary sinus.

3.9.2 Alternatively, use the dedicated cryoballoon intraluminal octapolar circular mapping catheter in replacement of the duo-decapolar circular diagnostic mapping catheter.

3.9.3 Confirm both entrance and exit block at each PV using the pace-and-capture protocol.

3.9.3.1 To confirm exit block, pace (stimulate) from the circular mapping catheter inside the PV and capture the signal (or lack of signal) from the linear diagnostic catheter inside the CS. To confirm entrance block, pace (stimulate) from the linear diagnostic catheter inside the CS and capture the signal (or lack of signal) from the circular mapping catheter inside the PV.

3.9.3.2 During the pace-and-capture protocol, start the pacing stimulation at 20 mA and use a 2.0 ms pulse width. If signal contamination is suspected, adjust the pacing stimulation to 10 mA or 5 mA to obtain a robust signal quality during pacing.

Note: Entrance and exit block is confirmed when there is no signal capture in both directions.

3.9.4 Exchange electrical pacing by switching the pacing output to one catheter at a time through the pacing stimulator and capture between the two diagnostic catheters to confirm PV electrical isolation by the absence of electrical capture at each PV location.

3.10 Use differential, site-specific, and/or decremental pacing techniques when signal interpretation is complex with far-field signal contamination.<sup>15</sup>

3.11 Withdraw the cryoballoon catheter from the patient when AF ablation is completed, and move the steerable sheath into the RA for AFL ablation.

#### **4. AFL ablation with the cryofocal catheter**

4.1 Introduce the 8 mm (9 Fr) cryofocal ablation catheter through the cryoballoon steerable sheath in the RA.

4.2 Using separate delivery sheaths, introduce a 7 Fr diagnostic duo-decapolar catheter to assess right AFL and to confirm bi-directional block during the cryofocal ablation procedure, and introduce an ICE catheter into the RA to visualize cardiac structures and ablation equipment.

4.3 Place the duo-decapolar diagnostic catheter at the IVC-TV isthmus to access clockwise and counter-clockwise electrical activation around the TV annulus and CTI (Figure 1).

4.4 Deliver five to ten cryofocal lesions with the 8 mm ablation catheter with each ablation session lasting three minutes in duration with a target nadir temperature of about -80°C.

4.5 Use ICE imaging of the cryofocal catheter and the IVC-TV isthmus to space the ablation lesion sets at an equidistant location between focal lesion sets (Figure 2).

4.5.1 Place the ICE probe in a superior and lateral position near the IVC-TV isthmus.

4.5.2 Sweep the ICE probe across the intended ablation area to determine cryofocal catheter position and cardiac anatomy in the area of ablation.

4.5.3 Utilize the higher frequency settings available on the ICE system to maximize visual image clarity and contrast.

4.6 Use the freeze time duration (of 180 seconds), to allow for the growth of the cryolesion by freeze temperature propagation, which will allow continuous lesions to be formed without the usage of an overlapping focal “point-to-point” method (Figure 3).

4.7 Employ the 3-dimensional electroanatomical mapping (3-D EAM) system to record previous cryofocal ablation locations, which will also facilitate placing ablation lesions at equidistant locations (Figure 4).

4.7.1 Construct a RA 3-D EAM using a conventional circular diagnostic catheter to map the area near the ICV-TV isthmus using approximately 30 points of anatomical reference that are near the ICV-TV isthmus. Gather the points of reference by making contact with the diagnostic catheter and the RA. Use the 3-D EAM mapping system tool software to collect the data which is then automatically integrated in the software tool.

4.7.2 Use the circular mapping catheter to gather electrical and anatomical data while the catheter is making contact with the inferior margins of the RA chamber.

4.7.3 Integrate this information on the 3-D EAM software that is provided with the mapping system. During data point collections, use the voltage collection mode and also use the software module that will allow the user to freeze between beats.

4.7.4 Guide the cryofocal ablation catheter tip to the desired ablation location by visualizing the catheter tip on the 3-D EAM system.

4.7.5 Record the ablation position by saving the location on the 3-D EAM system, and continuously record all subsequent ablation positions.

4.7.6 Use the 3-D EAM system to guide the cryofocal ablation catheter to the next target location while measuring distances between ablations on the 3-D EAM system software.

4.8 When all freeze lesions are complete, assess the ablation procedure by activation mapping with the duo-decapolar diagnostic catheter to demonstrate a complete bi-directional electrical block (Figure 5).

4.8.1 Use electrical stimulation through the pacing stimulator and delivery pacing to the catheters on either side of the line of lesions to demonstrate block at the line from both directions (bi-directional block).

4.8.2 Conduct stimulation and activation mapping (at both the inferior septal and inferior lateral sites) to assess bi-directional block through the CTI, which is confirmed by an activation in the contralateral atrial wall at sites adjacent to the line of block during electrical pacing.<sup>16,17</sup>

4.9 Remove all catheters and sheaths from the patient and use standard medical care to stop bleeding at the vascular entry points (groin), which can include manual pressure application at the site of vascular entry and intravenous protamine delivery after femoral sheath removal to reverse the biological effects of the heparin given during the LA ablation.<sup>18,19</sup>

4.10 When protamine is used, administer a 0.5 to 1.0 mg dose of protamine per 100 units of heparin received, and delivery it slowly over the course of five minutes.<sup>18,19</sup>

## **5. Post-ablation Care**

5.1 On morning post-ablation, re-start the patient's anticoagulation drug at the previous dosage and schedule, and if necessary, administer a heparin bolus to maintain an INR  $\geq$  2.0 at the time of hospital discharge.

5.2 Before hospital discharge, administer the patient's antiarrhythmic drug (AAD) at the previous dosage and schedule.

5.3 Maintain AAD(s) usage for the next three months post-ablation to allow for proper healing and cardiac scar formation at the areas of catheter ablation.

5.4 After three months post-ablation, eliminate or reduce the AAD(s) usage based on patients AFL/AF symptomology.

5.5 Schedule patient follow-up visits at 1, 3, 6, 9, and 12 months to assess current cardiac rhythm status via review of electrocardiography.

#### **REPRESENTATIVE RESULTS:**

The 13 patients in this study had AAD-refractory recurrent symptomatic paroxysmal AF and typical right AFL. All 13 patients were treated at a single-center by one physician operator during the 2014 calendar year. At the time of their catheter-based ablation treatment, the cryoballoon catheter was used to create a PVI during the AF ablation, and the 8 mm cryofocal catheter was used to create bi-direction block at the IVC-TV/CTI isthmus during the AFL ablation. Acute success was achieved in all patients as tested and recorded by complete PVI and bi-directional block at the IVC-TV/CTI isthmus before the end of the ablation procedures. In both AF and AFL post-ablation testing, diagnostic catheters were used to assess electrical blockade. After the ablation procedure, patients had undergone electrophysiological examination at 1, 3, 6, 9, and 12 months using a 14-day cardiac Holter monitor. At six months post-ablation, all 13 patients were free of AFL (100% success), and 10 of the 13 patients were free of AF (77% success). The group mean follow-up period was 8.1 months ( $\pm$  1.9 SD; median = 7.5). Additionally, there were no recorded acute- or longer-term complications for these 13 patients, and all patients were discharged normally (post-ablation procedure) within one day of the initial procedure admission to the hospital.

Figure 1 (panel A) illustrates the entire tool set that is necessary to achieve termination of AFL by this method during a cryoablation procedure. Correspondingly, Figure 1 (panel B) demonstrates the same placement of equipment as it is actually viewed by fluoroscopy during the AFL ablation procedure. ICE images (Figure 2) are used to visualize the lesion set, to track ablation catheter movement, and to assess distance between the lesion sets. When visualized by 3-D EAM (Figure 4), it is clear that these sets of lesions are not in direct "point-by-point" connection; however, electrical bi-directional blockage confirms that tissue isolation has occurred and that the patient has terminated AFL (Figure 5). Additionally, the complete elimination of AFL at six months (post-ablation) for this 13 patient cohort also substantiates the longer-term durability of this technical approach.

By using ICE and 3-D EAM, this study demonstrated that the cryofocal lesion set does not need to be in direct point-by-point contact to be effective and durable (Figure 3). As a direct result, procedure times were minimized and less radiation was administered to the patient during fluoroscopy. Table 1 summarizes the procedural measurements that were recorded during this study of 13 patients. The average procedure time (including both AF and AFL ablation) was four hours which was measured as first skin entry by trocar and last catheter exit from the body. Mean fluoroscopy time was 22 minutes for the group. An average of 30 minutes was spent on cryofocal ablations of AFL. The mean number of cryofocal applications per patient was nine (median = 7) during AFL ablations, and each application was typically 180 seconds in duration and achieved a mean nadir temperature of -86° C during the cryofocal freeze application.

**Table 1. Procedure summary of 13 patients with AFL/AF.**

**Figure 1. Schematic of tools used in AFL ablation.** The blue catheter is the 8 mm focal cryoablation catheter, and the black catheter is the diagnostic duo-decapolar. Intracardiac echocardiography (grey catheter) is used to visualize catheter movement and placement. Four point ablations (blue circles) have been applied with continuous bi-directional block established with the freeze propagation protocol.

**Figure 2. Imaging during cryofocal ablation.** ICE imaging is used to guide the 8 mm focal cryoablation catheter. Using ultrasound image guidance, the focal catheter can establish an anatomical position and then move to the next ablation location with equidistant ablation placement.

**Figure 3. Freeze propagation diagram.** Four cryofocal ablations are completed with the 8 mm focal cryoablation catheter (panel A). A traditional 3-D anatomical mapping system would depict these ablations as non-continuous; however, freeze propagation of hypothermic temperatures in cardiac tissue will damage the adjacent cardiac tissue and create one continuous bi-directional block. Cryofocal ablation along the same distance can take as much as double the amount of lesions (and procedural time) when using 3-D electroanatomical mapping system guidance for catheter placement (panel B) in a point-to-point configuration.

**Figure 4. 3-D EAM of cryofocal ablation.** 3-D electroanatomical mapping of the focal locations will not show the continuous “point-by-point” lesion depiction that is necessary in a traditional RF ablation. However, by marking the cryofocal ablations on the mapping system the equidistant ablation locations are recordable during the procedure.

**Figure 5. Bi-directional block confirmed.** Activation mapping with the diagnostic duo-decapolar catheter demonstrates that bi-directional conductance has been blocked, and this patient did acutely terminate AFL symptomatology. Note the reversal in conduction direction after a line of block is created.

## **DISCUSSION:**

The main findings of this clinical study are that the 8 mm cryofocal ablation catheter can be used in a manner that minimizes the ablation procedure times while still maintaining the favorable long-term efficacy and safety profiles associated with cryoablation. Central to this method is the usage of an ICE ultrasound catheter, and the correct interpretation of the spatial information that is reported on the 3-D EAM system. The cryofocal lesion sets as viewed on the 3-D EAM system do not necessitate overlapping lesion sets because of the hypothermic energy propagation that occurs in tissue (beyond the focal point of contact). By using the ICE catheter effectively the physician user has greater control on the focal placement of each ablation, and by using 3-D EAM in the RA, the spatial separation between lesions is roughly equidistant. The end result is this novel lesion set of cryofocal applications that are connected through cold propagation in the cardiac tissue, and the 3-D EAM system is important in creating this equal distance relationship. Consequently, this protocol/method allows the cryofocal user to achieve AFL ablation times that are comparable to RF catheter usage while still maintaining the cryoablation benefits with regards to patient efficacy, safety, and comfort which were demonstrated in the long-term follow up of this study.

In particular, cryoablation is associated with an enhanced safety profile compared to RF ablation. Cryoadherence of the cryoablation catheters can reduce the risk of atrioventricular (AV) block compared to RF ablation catheters,<sup>20</sup> and it also reduces the risk of systemic embolization.<sup>20</sup> Maintenance of direct tissue contact during a cryocatheter ablation allows for a predictable energy transfer that is primarily time-dependent, when a cooling gas (nitrous oxide) nadir temperature is reached. By comparison, RF catheters can move, chatter, and bounce during a beating-heart ablation, and the heat energy transfer of a RF catheter is dependent on several factors, including: contact-force, current density, electrode size, edge effects, tip temperature, ablation duration, and active versus passive tissue cooling (with irrigated versus non-irrigated systems). Also, cryoablation is known to not disrupt the endothelial layer during ablation which lowers the risk of thrombus formation compared to RF ablation.<sup>21-24</sup> This preservation of cardiac tissue architecture (during cryoablation) also reduces the risk of myocardial perforation compared to RF catheters during AF and AFL ablation.<sup>23</sup>

With regard to patient pain, a cryoablation can have less patient perceivable pain during an AF/AFL ablation compared to a RF catheter procedure.<sup>22,24-27</sup> Particularly, RF catheter ablation (in the area of the inferior isthmus and the IVC) is a well-known source of patient discomfort during an AFL ablation procedure.<sup>24,28</sup> In fact, procedural general anesthesia followed-up with post-procedural analgesia usage is a common course of action during a typical RF catheter ablation of AFL. By comparison, the cryofocal ablation of AFL can be done easily while the patient is under conscious sedation during the procedure without the need of post-procedural analgesia usage. This can be (potentially) safer for patients with known anesthesia reactions, allergies, and/or side effects. Also, post-procedural care and discharge can be made easier with patients that have undergone a conscious sedation procedure compared to general anesthesia.

Importantly, while the safety advantages of cryoablation have been well described, it remains critical to not generalize these features across the entire category of newer/novel catheters. In fact, AV block and tamponade have been observed in evaluations of novel cryocatheters,

including the CryoCor study.<sup>29</sup> These novel cryoablation catheters typically use different gases to achieve even lower nadir temperatures compared to the 8 mm cryofocal ablation catheter that is used in this study. The catheter that was used in the CryoCor study is not currently market available, and any novel cryoablation catheter will need to establish a new safety and efficacy profile (especially if a different gas is used).

The design of this study and publication was to present a technical discussion on a method/protocol that may enhance procedure time reduction while still allowing for a safe and effective cryofocal ablation of typical right AFL during a cryoballoon AF ablation procedure. By this smaller study design, no attempt was made to measure or present a mean procedural time reduction in this methodology nor were direct comparisons to RF catheter ablation times made. Further investigation(s) with a larger patient population and randomized patient design are necessary before such statements can be made. However, to date, this study records the shortest mean ablation time used for cryofocal ablation of AFL (30 minutes), and the total fluoroscopy time used during both AF and AFL ablations (22 minutes total) were similar to those published during single AFL cryoablation procedures.<sup>8,9</sup>

By utilizing ICE imaging, the 8 mm focal cryoablation catheter can be directed to precise anatomical locations. Using the advantage of thermal propagation of cold, the focal cryoablation lesions do not have to be in “point-by-point” connection, as viewed on a 3-D EAM system. Acute bi-directional block and longer-term freedom from AF/AFL demonstrates that this method is effective, and mean ablation times indicate that this method can enhance efficiency. A key to establishing this protocol is the alignment between the visual information guidance given from the ICE catheter, fluoroscopy, and the 3-D EAM system. ICE imaging modifications can be made by varying the sweep angle, depth of view, and location of the ICE catheter. In this article no specific directions were given to these modifications because of the large variety of ICE catheter systems in the market. Lastly, the lack of clinical complications in this abbreviated study coincides with the favorable safety profile that has been previously studied in cryoablation procedures.<sup>8,9</sup>

In summary of the study and novel method, the critical steps needed to utilize this protocol were the imaging modalities (ICE and 3-D EAM) being used to minimize the total number of cryofocal applications during an AFL cryoablation which resulted in short procedure times, and the equidistant placement of cryoablations which resulted in long-term durable efficacy while still maintaining a favorable safety profile throughout the procedure. However, the main limitation to this protocol/study was that it was conducted at a single-center by a well-practiced physician. Protocol mastery of this technique may involve a steep learning curve, and short procedure times may not be immediately noticeable with a new user. With mastery of the technique, most protocol adopters should maintain a good efficacy and safety profile as the primary modification is simply a reduction in total cryoapplications during ablation of AFL.

Finally, it is important to acknowledge that this protocol uses adjunctive imaging modalities to decrease the typical procedure time during AFL ablation by maximizing the spatial placement of each focal lesion. Cost constraints at different healthcare systems may make the usage of ICE



and/or 3-D EAM imaging challenging. Importantly, the cryoballoon and cryofocal ablations can be completed safely without ICE and/or 3-D EAM usage.

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Dr Stuart Adler has been a paid consultant for Medtronic, and he has been involved with physician training programs that were sponsored by Medtronic. Troy Bertram and Hae Lim are employees of Medtronic.

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Figure1

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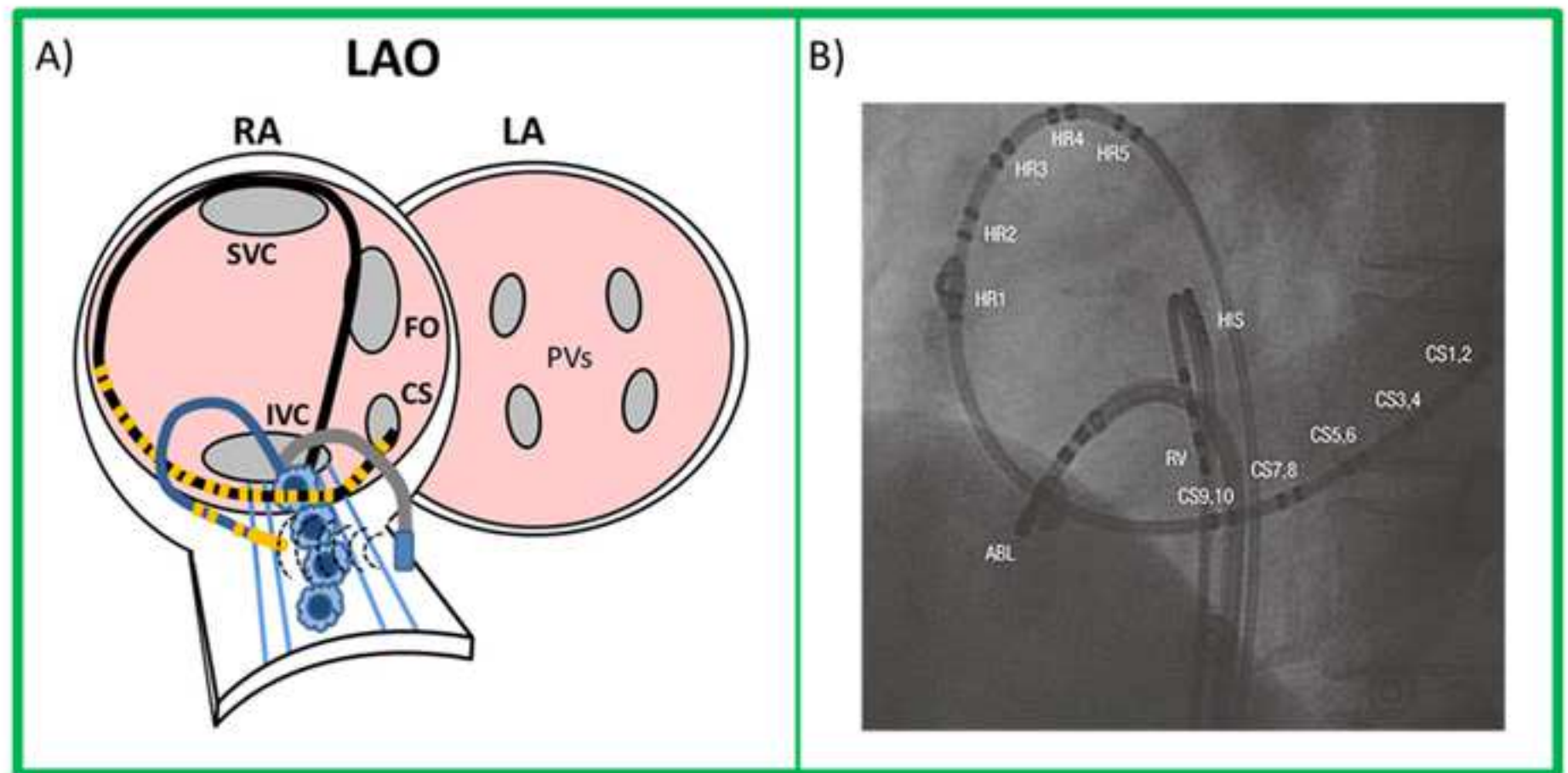


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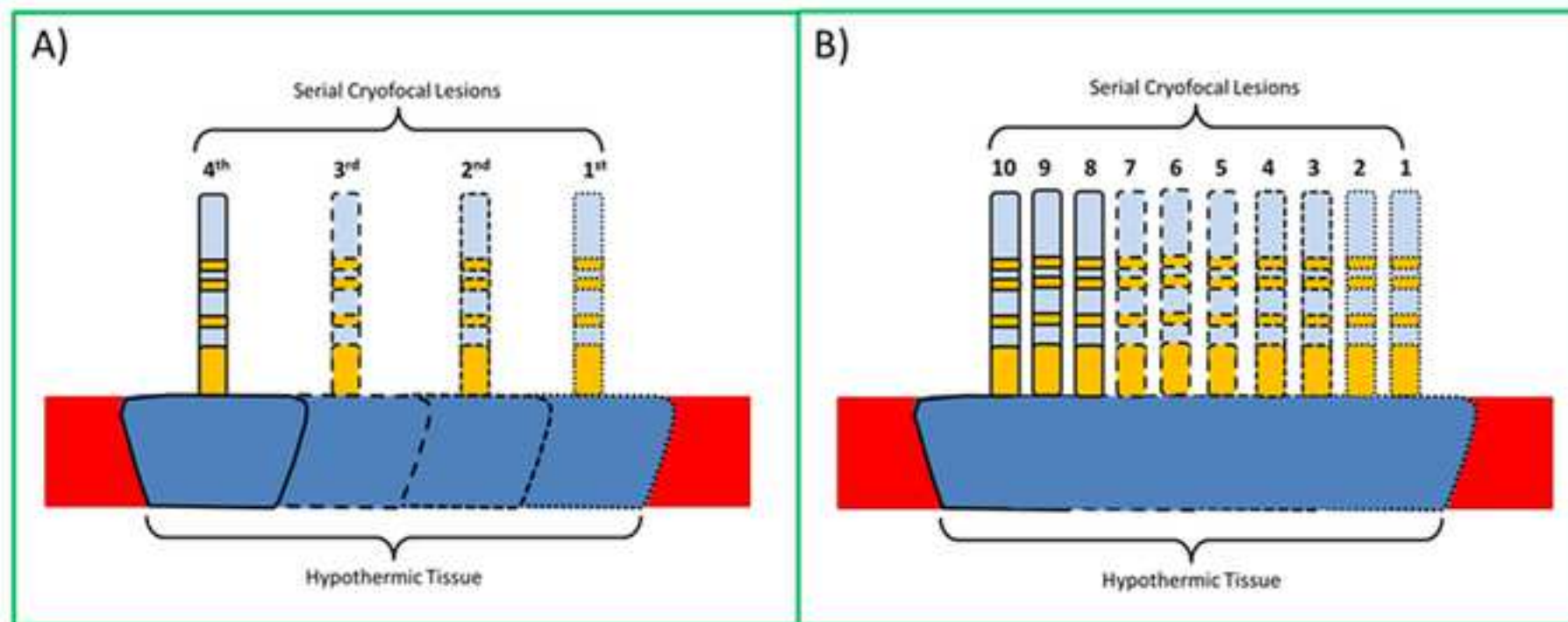
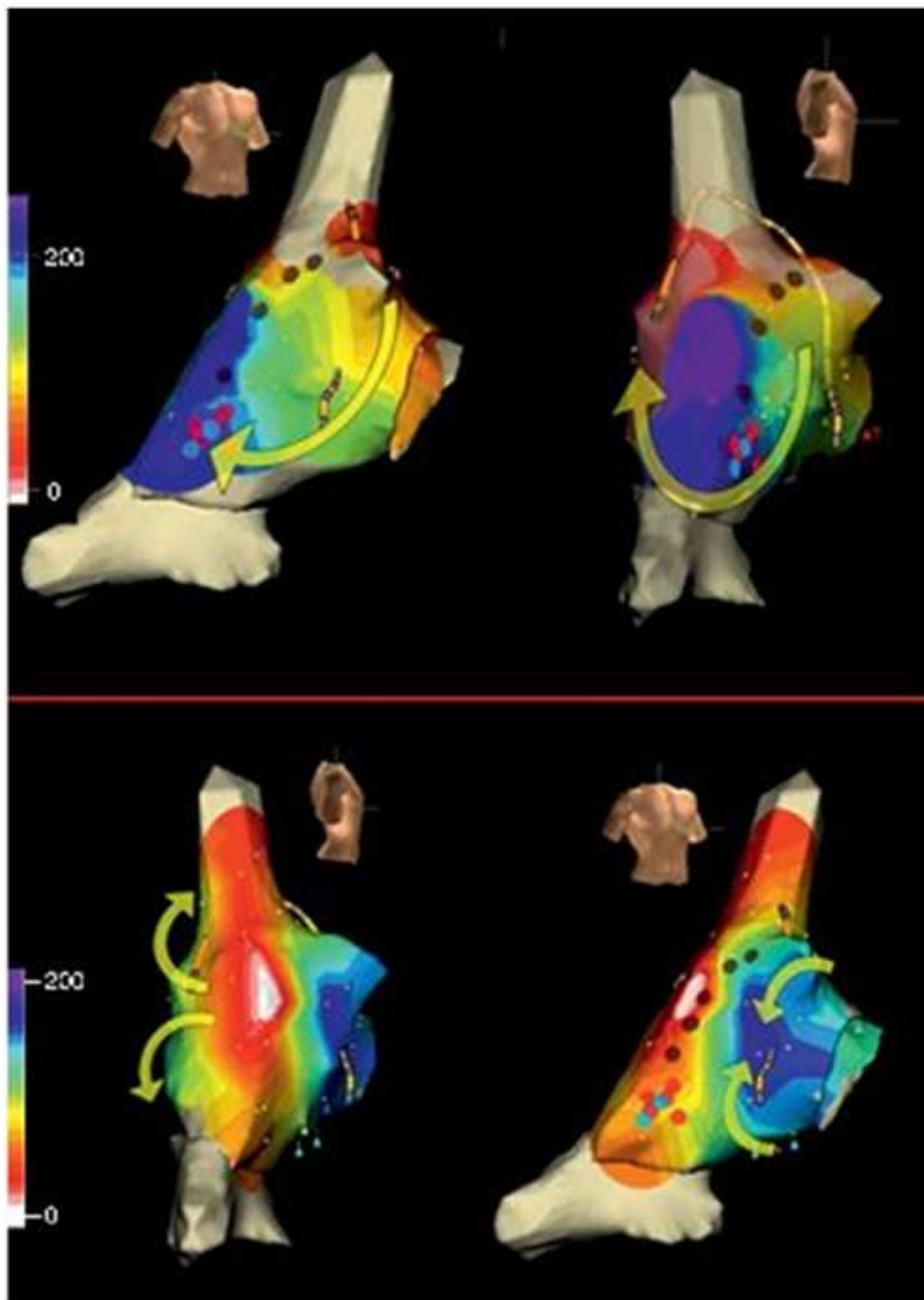
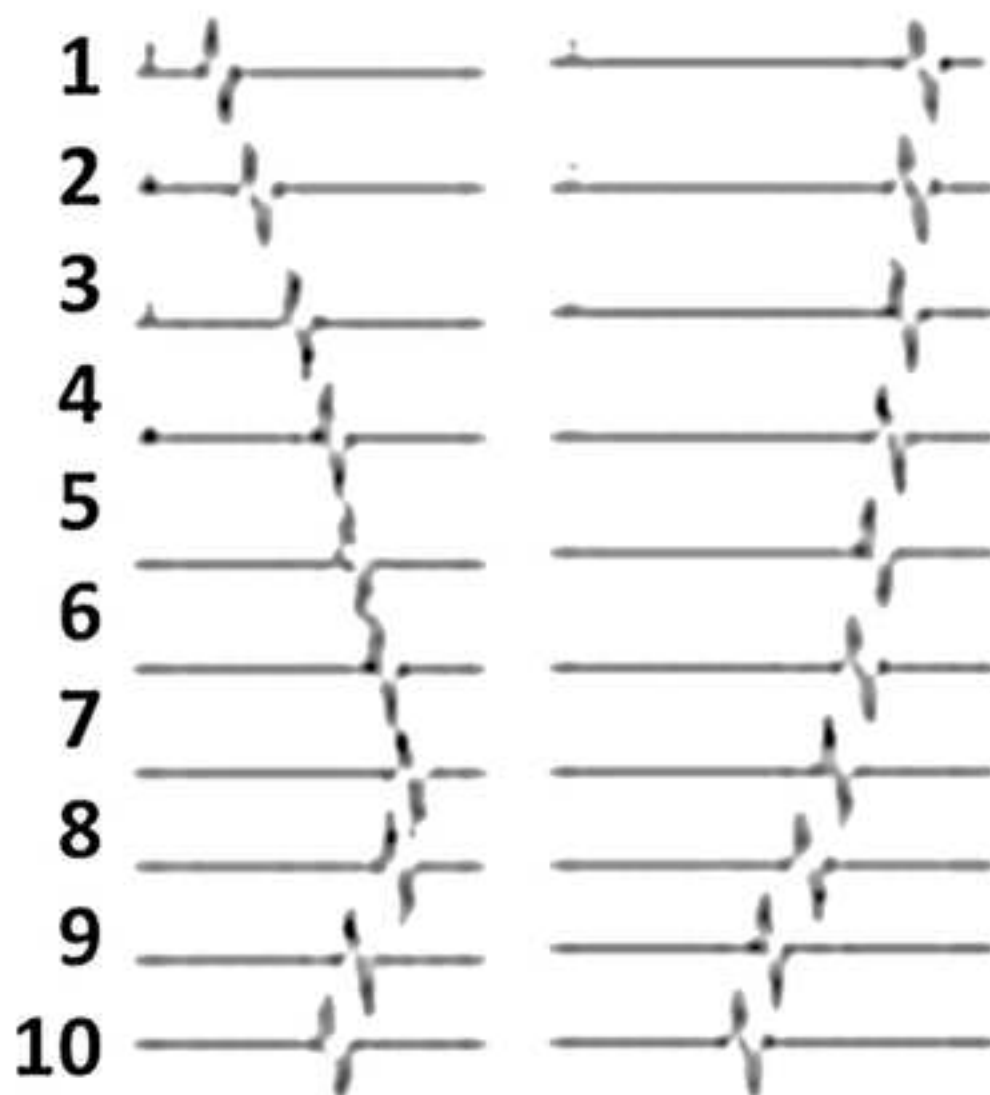


Figure4  
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## Duo-Deca Catheter



Pre-                  Post-  
AFL ablation



	Mean	SEM	STD	Median
Total procedure time (skin to skin) including cryofocal & cryoballoon ablations (Min.)	240.6	15.4	55.6	223.0
Total fluoroscopy time including cryofocal & cryoballoon ablations (Min.)	22.4	1.9	6.9	20.0
AFL cryoablation time (Min.)	29.7	4.3	15.3	22.6
Number of cryofocal ablation applications	9.4	1.3	4.8	7.0
Cryofocal ablation time/application (Sec.)	178.7	1.0	10.6	180.0
Cryofocal catheter freeze nadir temp (°C)	-86.1	0.2	2.4	-86.0

Name of Reagent/ Equipment	Company	Catalog Number	Comments/Description
Freezor MAX CryoAblation Device	Medtronic , Inc.	229F3	8 mm cryofocal catheter
Arctic Front Advance Cardiac CryoAblation Catheter	Medtronic , Inc.	2AF284	28mm Cryoballoon catheter



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Dear Nam Nguyen and two peer reviewers,

Thank you for the thoughtful comments. We have elected to accept all comments and have made revisions to the manuscript accordingly. Reviewer #1 is especially well versed in the cryoablation literature, and we thank this reviewer for the insightful comments. Below are our descriptions of the changes that can be found in the new manuscript version. We believe that comment #7 was important, but we simply did not collect the data in this manner. Our hope is that we have addressed this comment #7 to the satisfaction of the reviewer.

Best regards,

Hae Lim and Dr S. Adler

From Nam:

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues. The JoVE editor will not copy-edit your manuscript and any errors in the submitted revision may be present in the published version.

- Thank you. We have proof read the manuscript.

2. 1.3.2: Please express the centrifugation speed in terms of x g. file.

- We have now expressed this measurement as Xg and RPM.

3. Visualization: Please provide an SW file for all highlighted material in the protocol to orient the scriptwriter regarding any images/screenshots to be included in the video in addition to videographer footage.

- The SW file is now attached.

4. Formatting:

-3.7 should be reorganized to include timing and cycles in the appropriate position in the substeps.

- The steps have been reorganized in order.

-Figure 5 legend – Please describe what is shown the figure rather than describing the outcome. (What is shown in 1-10?)

- The legend has been corrected.

5. Discussion: What troubleshooting/modifications could be performed?

- The 2<sup>nd</sup> to last paragraph of the discussion now contains some troubleshooting guidance.

6. Continuity: Are steps 3.1, 3.2, 3.6, and 4.2 nonessential? There is room to incorporate more steps into the protocol if the authors wish to film them.

- Thank you. With the room available, these steps have been selected for incorporation.

From reviewer #1:

1) On page 2 in the introduction section it is stated, that radiofrequency catheter ablation is the

typical method when a surgical intervention is necessary.

A catheter ablation is an electrophysiological interventional catheter based treatment, not a surgical one.

- Thank you for this catch. The sentence has been rewritten.

2) The number of enrolled patients is low, what is significant limitation stated in the manuscript. It is mentioned, that in all patients a 3D EAM system was used to guide the cryofocal catheter. Please describe in detail, which system was used and how the anatomical reconstruction of the RA model was performed, and which catheter was used. The use of a 3D EAM system in Cryoballoon ablation procedures for pulmonary vein isolation is not standard of care, however, it is exceptional to use it in the described setting. Please comment also on the economic aspects of using the described setting, especially in combination with the use of ICE.

- Thank you for this suggestion. Section 4.7 now includes more details of the RA mapping using 3D EAM.
- Also, the last paragraph of the discussion now including careful thoughts about the economic aspect.
- Specifically, the 3D EAM system used here is an Ensite Velocity system with the Precision mapping module and NavX guidance system. However, the journal format rules do not allow the usage of specific products names within the text of the manuscript.

3) On page 5 it is described how to introduce the transseptal sheath. Rather introducing a guide wire into the LA I would recommend to introduce the guide wire into the left superior pulmonary vein.

- Thank you, we agree and have made this change.

For the introduction of the cryoballoon catheter this guidewire was used. An intraluminal circular mapping catheter, which can be used instead of a guide wire, is available. Why was that catheter not used?

- The Achieve mapping catheter can be used here in replacement of the guidewire. Although this is not Dr Adler's usage protocol, this has now been noted in the manuscript as an alternative or option.

What specific circular mapping catheter was used to confirm isolation of the pulmonary veins? Please describe the "pace and capture" protocol used in detail.

- Thank you, we have described the mapping catheters used by their generic description based on journal rules. Additionally, we have further described the entrance and exit block testing (pace and capture protocol). Lastly, we have given a reference for more extensive testing techniques as described by Andrade et al 2015.

4) On page 6 (3.9) it is described how the monitoring of the phrenic nerve function was monitored during the freeze. Why has the technique of CMAP not been used for more intensive monitoring of the nerve function?

- Thank you. While we did not CMAP monitor phrenic nerve function during this protocol, we do agree that this method is important and have put it into the protocol as an additional usage.

5) In 3.6.4 it is described how PV occlusion with the cryoballoon was assessed. Because ICE has been used in each of the patients, it would have been elegant to demonstrate possible leaks during cryoballoon positioning at the PV using ICE imaging. Please comment.

- Yes, we agree. The usage of ICE is now included with directions.

6) On page 11 it is mentioned that the catheter used in the CryoCor study is a novel cryoablation catheter. As far as I am informed the CryoCor catheter is not available any more since years. The study was published in 2008, however, further safety and efficacy aspects will not be available in the future. Please comment.

- Thank you. We have edited this paragraph more carefully and in agreement with your comment.

7) It is stated by the authors, that this study records the shortest mean procedure time of 30 minutes. In table one the total procedure time including cryofocal and cryoballoon ablation is 240.6 min, so approximately 4 hours. In recent publications reporting of PVI using the Cryoballoon system procedure times for PVI were approximately 100-120 minutes. Please provide detailed data of exact procedure times for PVI using Cryoballoon and for the Isthmus ablation using cryofocal ablation. A procedure time of 30 minutes is not plausible due to the fact, that total cryofocal ablation time for atrial flutter was 29.7 minutes. This needs to be clarified. In table 1 total procedure times in total, for PVI only and for AFL only should be stated, also cryoablation times in the same manner.

- We feel that there is some data confusion here, due to our terminology usage. So we have tightened the language throughout the manuscript.
  - We absolutely agree that upon retrospective examination of the data that we should have separately collected a PVI procedure time and an AFL procedure time during the collection of data. However, we did not collect this data.
- Consequently, below are our clarifying statements.
- The ~30 minute cryoapplication time (29.7 min) to complete an AFL ablation is amongst the shortest reported thus far with Montenero and Kuniss reporting 45 and 40 min, respectively.
- The ~240 minute is the total procedure time (skin to skin; femoral puncture to last catheter exit).
  - We agree that there have been more recent balloon protocols with AFAdv that use shorter application times to achieve 120 minute procedures, but we were not using these shorter protocols during this study.
  - And we are not sure (or convinced) that everyone is reporting skin to skin time which is more akin to total physician time.
- We did not record our PVI time in this study, as it was not our original design intent of the study. Admittedly, our table will be missing a PVI procedure time and an AFL procedure time.



- This study is not trying to report a short cryoballoon usage time, and it does not give protocol advice that would promote short cryoballoon times.
  - As an example, we did not use Achieve and instead used a conventional circular mapping catheter which did add time (during PVI) due to exchange between balloon and circular catheter to confirm block at each PV.
- Instead, some physicians feel that usage of cryofocal ablation for AFL is not possible because of the lengthy procedure and we wanted to offer a protocol that may shorten the procedure (a bit).
  - By reducing the AFL ablation time by ~15 minutes, this protocol achieves the original study goal of finding a protocol that is closer to an RF ablation time of AFL while still maintaining safety and efficacy.

8) Please describe the new methodology how to place the cryofocal lesion sets more in detail. Is the use of a 3D EAM system possibly of greater advantage compared to the novel lesion set? Please comment on that in the discussion section.

- Yes, the 3-D EAM is critically important, and the first discussion paragraph now reflects this comment.

**Reviewer #2:**

*Manuscript Summary:*

It is a nice paper even though it describes an old technique.

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