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Esophageal cooling in radiofrequency cardiac ablation: Pilot study

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Site(s) where study will be performed: Riverside Medical Center
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List of Acronyms

Activated Clotting Time	ACT
Advanced Cardiovascular Life Support	ACLS
Adverse Event	AE
Atrioventricular	AV
Esophageal Cooling Device	ECD
Food and Drug Administration	FDA
Luminal Esophageal Temperature	LET
Principal Investigator	PI
Pulmonary Vein Isolation	PVI
Radiofrequency (Ablation)	RF
Serious Adverse Event	SAE
Transesophageal Echocardiography	TEE
Unanticipated Problem	UP

1. Study Summary

Title	Esophageal cooling in radiofrequency cardiac ablation: Pilot study
Protocol Number	RMC IRB # 187
Study Design	Randomized, Single-Blind, Interventional, Post-Market pilot study
Study Duration	1 Year
Sample Size	6
Primary Objective	To assess the reduction in the occurrence and severity of esophageal injury in patients who have the EnsoETM inserted into the esophagus during Radiofrequency (RF) ablation.
Secondary Objectives	To assess the safety of the EnsoETM and efficacy of ablation when the EnsoETM is used to regulate temperature
Exploratory Objectives	To assess the EnsoETM's ease of use during ablation

2. Introduction

2.1. Background Information

2.1.1. Atrial and Ventricular Arrhythmias

Atrial and ventricular arrhythmias include a broad range of atypical myocardial conduction which are named based on their site of origin. Intervention for these arrhythmias include medications and/or ablation strategies. Of primary interest is the atrial arrhythmia termed atrial fibrillation. This type of arrhythmia involves multiple points of origin typically in the left atrium and the base of the pulmonary veins at the junction of the left atrium. The most common ablative strategy includes pulmonary vein isolation which involves heating (RF ablation) or cooling of the posterior aspect of the left atrium which lies near the esophagus.

2.1.2. EnsoETM Device Description

The EnsoETM is a silicone tube with three lumens that is placed in the esophagus. Distilled water is circulated through the two cooling lumens, while the third lumen connects to wall suction and is used for standard gastric decompression. The EnsoETM is composed of standard medical-grade silicone, and it is a single-use, disposable, non-implantable device with an intended duration of use of 36 hours or less. In 2015, Attune Medical, LLC received approval from the FDA on their *de novo* request for classification of the Esophageal Cooling Devices (ECD) named EnsoETM. This class II device is used to apply a specified temperature to the endoluminal surface of the esophagus via an external controller. This study will be utilizing the EnsoETM, because it is designed to fit the Gaymar Medi-Therm III Conductive Hyper/Hypothermia System[Naiman]. There are three contraindications for this device: (1) patients with known esophageal deformity or evidence of esophageal trauma, (2) patients with known ingestion of acidic or caustic poisons within the prior 24 hours, and (3) patients with less than 40 kg of body mass.[Naiman, Shanley]

2.1.2.1. Regulatory Status

The Food and Drug Administration (FDA) identifies the EnsoETM as:

Esophageal thermal regulation device. An esophageal thermal regulation device is a prescription device used to apply a specified temperature to the endoluminal surface of the esophagus via an external controller. This device may incorporate a mechanism for gastric decompression and suctioning. The device is used to regulate patient temperature.

Indications for Use:

The EnsoETM is a thermal regulating device, intending to:

- Connect to a Gaymar Medi-Therm III Conductive Hyper/Hypothermia System to control patient temperature, and
- Provide gastric decompression and suctioning

Limitations:

Prescription use only: Federal (USA) law restricts this device to sale by or on the order of a physician.

The EnsoETM may cause or exacerbate esophageal tissue damage in patients with esophageal deformity or evidence of esophageal trauma, or in patients who have ingested acidic or caustic poisons within the prior 24 hours.

The safety and effectiveness of the EnsoETM have not been evaluated in patients with less than 40 kg of body mass

The EnsoETM should only be used by healthcare professionals with training in the use of orogastric tubes and the use of the Gaymar Medi-Therm III Conductive Hyper/Hypothermia System.

The EnsoETM is intended for esophageal placement. Inserting the EnsoETM in the trachea, bronchi, or lungs can result in serious harm.

Attachment of the EnsoETM to unapproved or unintended connections can result in serious patient harm

The presence of the EnsoETM may interfere with other devices in the esophagus or mouth. Dual placement of other devices in the esophagus with the EnsoETM in place, such as an enteral feeding tube, may result in patient harm.

Large patients with body mass greater than 120 kg may exhibit slower responses to intended temperature changes. Small patients with a body mass less than 60 kg may exhibit faster cooling than anticipated, and may exhibit slower rewarming than anticipated.

2.1.3. Prior Clinical Studies

The first case of esophageal trauma associated with left atrial posterior wall ablation for atrial fibrillation was reported in 2003 (Lequerica JL B. E., 2008). Since then there have been a myriad of interventions in hopes of preventing such damage. This ranges from mechanical manipulation of the esophagus to esophageal cooling with various mechanisms including ice water lavage. This also includes the development of a cooled intraesophageal balloon with mixed results (Berjano EJ, 2005) (Lequerica JL B. E., 2008) (Lequerica JL B. E., 2008) (Tsuchiya T, 2007)]. Further in-vitro evaluation of animals has been performed using a controlled saline circulating system (EPSac) which spares the esophagus from collateral thermal injury (Arruda MS, 2009). The novel idea of cooling the esophagus to prevent transmural damage has been documented as overwhelmingly positive. The most notable clinical evaluation of an esophageal cooling mechanism was performed by Tsuchiya et. which included a cooled water-irrigated intraesophageal balloon. (Tsuchiya T, 2007) A limitation of this study included the inability to assess the deeper muscular layer of the esophagus for evidence of injury. Several limitations to the above mentioned approaches include cost, physician availability, displacement of the esophagus, and ability to monitor the luminal esophageal temperature (LET).

2.2. Rationale

Left atrial ablation is a standard therapy in the management of atrial fibrillation; however esophageal injury is a known potential consequence of this procedure.[1-4] Delivery of the radiofrequency energy necessary to perform left it real ablation has the potential to cause injury to the nearby esophagus and its associated vagal innervation, with injuries including ulceration, hematoma, spasm, disorders of esophageal motility, and atrial-esophageal fistula (the latter representing the extreme consequence of esophageal thermal injury due to posterior left atrial ablation).[1, 2] Esophageal mucosal lesions are commonly reported with an incidence ranging widely from 3%to 60%, and recent observations suggest a potential contribution of the transesophageal echocardiogram probe to esophageal injury seen after catheter ablation.[5] Although ablation of the left atrium poses the greatest risk, right atrial ablation also has the potential to allow esophageal damage to occur.

Although luminal esophageal temperature monitoring is one proposed measure to reduce the incidence of esophageal injury during atrial fibrillation ablation, the success of temperature monitoring has varied widely.[6, 7] It is fairly well established that effective measuring of the esophageal temperature depends on the position of the temperature probe relative to the heated cardiac tissue and also on good contact with the esophageal mucosa.[8] However, the esophagus often is mobile and shifts sideways by >2 cm in a patients undergoing catheter ablation for atrial fibrillation under conscious sedation.[9] Using fairly sophisticated approaches (e.g., deploying an ablation catheter with thermistor tip into the esophagus [as both a measurement device and a deflection tool], along with position confirmation using intracardiac echo) appears to be the only measurement technique that offers adequate protection.[6] This approach does not seem to be a technique that is routinely feasible (due to both the cost of equipment and the need for additional operators during the procedure).[6]

Moreover, there is the suggestion that the temperature probe used for esophageal temperature monitoring may contribute to a thermal effect and enhance direct tissue heating.[10]

Data from animal models show that the muscular layer is disrupted and necrotic myocytes are seen at the border of lesions in the esophagus even when no lesions on the epithelial layer were found, suggesting that cooling the deep muscular layer of the esophagus may be needed to prevent esophageal injury.[11] Prevention of esophageal injury via cooling of the esophagus has been investigated with mathematical modeling, preclinical models, and in the clinical arena. A finite element model in three dimensions investigating the effects of a cooled intra-esophageal balloon suggested that this approach could be a viable method to prevent thermal injury to the esophagus during intraoperative ablation of the left atrium.[12] Specifically, the authors found that (i) chilling the esophagus by means of a cooled balloon placed in the lumen minimizes the lesion in the esophageal wall compared to the cases in which no balloon is used (a collapsed esophagus) and with a non-cooled balloon; (ii) the temperature of the cooling fluid has a more significant effect on the minimization of the lesion than the rate of cooling (the thermal transfer coefficient for forced convection); and (iii) pre-cooling periods previous to RF ablation do not represent a significant improvement. Finally, the authors also suggest that the use of a cooled balloon could affect the transmurality of the atrial lesion, especially in the cases where the atrium is of considerable thickness (or in other words, in the presence of an atrium of considerable thickness, when a short duration and a low target temperature are programmed, the use of a cooled balloon could reduce the possibilities of achieving a transmural lesion in the atrium.

Subsequent study using an agar phantom-based model that was built to provide temperature readings at points between the esophageal lumen and the myocardium found that this method was able to provide effective thermal protection, although it was noted that the method could fail under certain unfavorable topical and procedural conditions.[13] In this study, a balloon utilizing water temperature of 5° C flowing at a rate of 25 mL per minute was used, which likely significantly limits the capability of this device to extract heat effectively.

Further study by this same group utilized varying coolant temperatures between 5°C and 37°C but maintained the coolant flow rate at 25 mL per minute.[14] The authors conclude that their results suggest that it is possible to thermally protect the esophagus (including the transmural region 2 mm away from the mucosal surface) during radiofrequency cardiac ablation by means of a cooling balloon placed in the esophageal lumen utilizing coolant temperature of 5°C or less and involving a precooling period of two minutes.

A custom developed system utilizing temperature controlled saline or water circulating at a flow rate tween 50 to 300 mL per minute and a temperature of 5 to 25°C was evaluated using an in vitro Lamb heart – esophagus preparation, followed by an in vivo model with six dogs.[15] This custom system consisted of a 12 French probe with a distal expandable compliant latex sack with a diameter of up to 3 cm fully expanded. The authors found that a circulating water temperature of 25° C failed to spare the esophagus from thermal injury. However lowering the circulating temperature to 10° C or 5°C spared thermal injury (although expanding the balloon diameter by increasing circulating volume substantially to

intentionally displace the esophagus towards the left atrium allowed the development of shallow esophageal injury to the external layers of the muscularis).

A clinical study [16] of eight patients used a closed loop system with low flow rates (25 mL/min) and a water temperature of 4.5±3.1◦C to build upon computer modelling demonstrating that a cooled balloon catheter (with a diameter of 10 mm) could transmurally cool the esophagus. They found that without cooling, esophageal temperature increased from a baseline of 36.4°C up to 40.5°C in under 30 seconds during ablation, whereas with the esophageal cooling balloon, esophageal temperature decreased down to 30.2°C with the balloon in place, and allowed an increase in temperature to only 33.5°C. The authors conclude that luminal esophageal temperature during the left atrial ablation was lowered by esophageal cooling using their catheter to a level where no thermal damage to the esophagus would likely be induced.

A study presented in 2007 in abstract form described the use of a saline filled esophageal balloon to attempt esophageal protection in an animal model, and found that in four dogs, a saline solution of 10°C was not sufficient to prevent thermal injury.[17] However, details of balloon configuration and, more importantly, coolant flow rate, were not provided, and a formal manuscript further describing these findings appears not to have yet been submitted.

Free water instillation into the esophagus has been tried with varying success. A study of 100 patients used very small volumes (5 mL) of ice water as the instilled volume, which was injected prior to RF energy delivery, and subsequently when esophageal temperatures reached 42°C.[18] The authors found that this approach alleviated the severity of esophageal lesions, but did not reduce the incidence: lesions occurred in 20% of the experimental group, and 22% of the controls, with three moderate and seven mild in the cooled group and three severe, one moderate, and seven mild in the control.

Another study utilized infusion of cooled saline mixed with Gastrografin or Iopamidol, with slightly higher, but still limited volumes (10 – 20 mL in repeated injected aliquots with a temperature of approximately 10°C).[19] A total of 318 patients were randomized between groups receiving only temperature monitoring without cooling, temperature monitoring with cooling when temperature exceeded 43°C, and temperature monitoring with cooling received when temperatures exceeded 39°C. The percentage of patients free from any ulceration or erosion in each group was found to be 63.6%, 87.5%, and 95.2%, respectively, and the authors conclude that these findings suggest that esophageal damage can be reduced by reducing cooling solution into the esophagus via a gastric tube when luminal temperature exceeds 39°C during ablation.

In summary, although abundant data suggest that cooling of the esophagus during ablation procedures can protect against esophageal injury, no commercially available device has yet been shown to perform this task.
Our intention is to evaluate the use of an esophageal cooling catheter to protect the esophagus during atrial fibrillation RF ablation. This will theoretically eliminate esophageal tissue damage. As noted above, this is not a novel idea, however, there are several advantages that this device offers. The most significant of which includes a large area of

distribution of cooling effect throughout the length of the catheter as well as a large lumen. The lumen size provides more rapid thermal energy exchange thus limiting the extent of esophageal damage. There are no metal parts included in this catheter, therefore, eliminating the concern for the device acting as a wick for energy transfer and enhanced direct tissue heating. (Deneke T, 2011) The cooling catheter does not require advanced training for placement or monitoring and also acts as an oral-gastric tube during the procedure. This device is also cost effective as the cooling source is used by hospitals (nearly ubiquitously) for standard cooling blankets.

2.3. Potential Risks and Benefits

2.3.1. Known Potential Risks

The following potential risks are associated with the use of esophageal thermal regulation devices:

- Adverse tissue reaction
- Gastric distension
- Injury to the esophagus
- Harmful hypo/hyperthermia
- Injury to the trachea
- Interference with other device in the esophagus or mouth leading to esophageal trauma

The following potential risks are associated with RF ablation:

- Bleeding or infection at the puncture site(s)
- Vascular damage from mechanical shear stress on the vessel wall from the catheters
- Myocardial rupture with tamponade
- Valvular heart damage which might cause regurgitation
- Arrhythmia possibly requiring pacemaker implantation
- Venous thromboembolism
- Stroke or heart attack
- Pulmonary vein stenosis
- Acute kidney injury related to dye use during the procedure
- Atrio-esophageal fistula formation
- Death in rare cases

The following potential risks are associated with general surgery:

- Adverse reaction to anesthesia
- Hematoma or seroma at the operative site
- Failure to improve
- Persistent or worsened pain
- Infection of the wound

- Radiation exposure
- Wound dehiscence
- Vascular disorders, including thrombus
- Bronchopulmonary disorders, including emboli
- Genitourinary disorders
- Pneumonia
- Hemorrhage
- Myocardial infarction
- Death

3. Objectives and Purpose

3.1. Primary Objective

The primary objective of this study is to evaluate the reduction in the occurrence and severity of esophageal injury in subjects who had a cooling tube inserted into the esophagus during radiofrequency ablation.

3.2. Secondary Objectives

The secondary objective of this study is to assess the safety of the EnsoETM and efficacy of ablation when the EnsoETM is used to regulate temperature.

3.3. Exploratory Objectives

This study will assess the EnsoETM's ease of use during RF ablation.

4. Study Design and Endpoints

4.1. Description of Study Design

Single-center, randomized pilot study of esophageal temperature management using Attune Medical's EnsoETM during RF ablation vs. RF ablation without the EnsoETM.

4.2. Study Endpoints

4.2.1. Primary Endpoint

- Esophageal mucosal damage as assessed by endoscopic evaluation and graded using Zagar's modified endoscopic classification scheme.

Table 1
Zargar's grading classification of mucosal injury caused by ingestion of caustic substances

Grade 0	Normal examination
Grade 1	edema and hypermia of the mucosa
Grade 2a	Superficial ulceration, erosions, friability, blisters, exudates, hemorrhages, whitish membranes
Grade 2b	Grade 2a plus deep discrete or circumferential ulcerations
Grade 3a	Small scattered areas of multiple ulceration and areas of necrosis with brown-black or greyish discoloration
Grade 3b	Extensive necrosis

- Radiofrequency ablation of the posterior aspect of the left atrium has been shown to cause esophageal mucosal irritation which may be exacerbated by LET monitoring and/or TEE. We believe that cooling of the esophagus will lead to a reduction of esophageal damage. To date there are bench models that suggests such an esophageal sub-mucosal protection but this has not been proven in human studies.
- Providing evidence that a reduction in sub-mucosal esophageal damage using the ECD may be a precursor to reduction in atrial-esophageal fistula formation.

4.2.2. Secondary Endpoints

- 1) Safety of the EnsoETM placement as measured by the number of adverse events recorded
- We believe that cooling of the esophagus will lead to a reduction of esophageal damage. The use of an EnsoETM would replace LET monitoring during ablation of the posterior aspect of the left atrium. This endpoint was chosen to prove that replacing the LET monitor with a cooling catheter is a safe alternative.
- This is of primary importance as any evidence of esophageal damage or adverse events related to the use of the EnsoETM would deter any further use of this approach to Pulmonary Vein Isolation (PVI).
- 2) Altered submucosal tissue architecture as assessed by endoscopic ultrasound (EUS)
- While mucosal injury may suggest significant thermal injury to related to RF ablation there is also concern that this injury may be more of a mechanical process from TEE and LET monitoring. We aim to assess the submucosa using EUS for differentiation between superficial and deep injury which may provide further insight into the risk of atrio-esophageal fistula formation. A grading scheme has not been developed for this type of evaluation so we will assess for individual changes with pre-procedure to post-procedure comparison.

4.2.3. Exploratory Endpoints

- Efficacy of PVI by evaluation of rhythm at 3 months following the procedure.
  - This endpoint was chosen as a precursor to future larger studies that may focus on efficacy to ensure that PVI with EnsoETM is non-inferior to PVI with LET.
- Does the use of an EnsoETM prolong or shorten the overall ablation time?

5. Study Enrollment and Withdrawal

5.1. Inclusion Criteria

Patients must meet all of the inclusion criteria to be enrolled as subjects in this study.

- Subject is between ages 18 – 90 years
- Subject has an atrial or ventricular arrhythmia requiring radiofrequency ablation on the posterior aspect of the heart
- Subject is willing and able to provide informed consent
- Subject is capable of adhering to the expectations of the study protocol (e.g., attending follow-up visit)

5.2. Exclusion Criteria

- Subject has known esophageal deformity, or evidence of esophageal trauma, prior radiation therapy involving the esophagus, or previous esophageal disease (for example, known esophageal varices, cirrhosis, history of esophagectomy, previous swallowing disorders or dysphagia, achalasia, known ingestion of acidic or caustic poisons within the prior 24 hours etc.).
- Subject is incarcerated
- Subject is pregnant or plans to become pregnant
- Subject has a silicone allergy
- Subject has esophageal bleeding prior to EnsoETM insertion

5.3. Recruitment Strategy

Patients will be recruited from the Principal Investigator's clinic when the decision to perform RF ablation in order to treat the patient's condition is made. The Principal Investigator (PI) or designee will provide a brief explanation of the study by describing the study objectives. If the patient is interested in learning more about the study, the PI will initiate the informed consent process.

5.4. Participant Withdrawal

5.4.1. Reasons for Withdrawing

- Subject's refusal to participate

5.5. Participant Removal from Study

- Subject has esophageal stricture or ulceration

- Subject death
- Physician scheduling conflict

6. Study Device

6.1. Acquisition

Study device is currently undergoing evaluation on-site and supply is already available on-site, with additional available upon request via standard shipping.

6.2. Formulation, Appearance, Packaging, and Labeling

Study device, the EnsoETM, is a non-sterile multi-lumen silicone tube placed in the esophagus for the purpose of cooling or warming a patient while simultaneously allowing gastric decompression and drainage. Modulation and control of the patient's temperature is achieved by connecting the EnsoETM to an external heat exchanger. Two lumens connect to the external heat exchanger, while a third central lumen provides stomach access for connection to a fluid collection device with low intermittent suction for gastric decompression. The EnsoETM is made of standard medical-grade silicone. It is a single-use, disposable, non-implantable device with an intended duration of use of 36 hours or less.

Additional details can be found in the attached Instructions for Use which are packaged along with the device as a package insert.

6.3. Products Storage and Stability

Describe the study device's storage needs. Include:

- Storage requirements: Store in a dry and clean place
- Stability requirements: 5C to 32C, with no humidity requirement.
- Expiration date: 3-year shelf life

6.4. Preparation

The Manual of Procedures details the preparation of the study device and is attached to this protocol as an appendix.

6.5. Administration

Placement of the EnsoETM

The external heat exchanger must be in proper operating condition and must have received all the required maintenance. Failure to ensure that the heat exchanger is in proper condition may result in suboptimal performance. Ensure that no contaminants are present in the heat exchanger water.

Measure the patient for EnsoETM placement carefully before use. Insertion of an excessive length of the EnsoETM into the stomach may lead to coiling, kinking, knotting, or breakage of the EnsoETM. To measure the patient for EnsoETM placement, extend the EnsoETM from the patient's lips to the earlobe and then from the earlobe to the tip of the xiphoid process (xiphisternum). Mark the location on the EnsoETM.

Follow the Instructions for Use for the external heat exchanger for all device operations, including connections to electric wall power, patient probes, and tube set connections. Connect the EnsoETM (Figure 1) to the external heat exchanger in place of a blanket or pad, using a Cincinnati Sub-Zero connector hose (CSZ P/N 286) with the connectors as shown in Figure 1. Turn on the external heat exchanger.

Ensure that the patient has a temperature probe with a monitor in use (for example, a Foley catheter temperature probe or a rectal temperature probe). The temperature probe must be connected to the external heat exchanger, as directed in the external heat exchanger‘s Instructions for Use. Ensure that the temperature monitor is functioning correctly and that the temperature probe is not damaged, expired, or compromised in any other way.

Select the control mode and target patient temperature on the external heat exchanger. Ensure that water is flowing through the EnsoETM, and that no leaks are present. Failure to initiate water flow prior to insertion may hinder placement of the EnsoETM.

Lubricate the EnsoETM generously with water soluble lubricant prior to insertion. Do NOT use petroleum-based products, because these may be harmful to the respiratory tract.

Insert the EnsoETM using gentle pressure posteriorly and downwards through the mouth, past the oropharynx and into the esophagus. Gently assist the passage of the EnsoETM with light pressure until the required length of tube has been inserted.

Do not use force during insertion of the EnsoETM, because this may cause bleeding and/or damage to the oropharynx or other structures. If resistance is encountered during insertion of the EnsoETM, immediately stop the procedure.

Confirm placement of the EnsoETM by the following:

- injecting 5 to 20 mL of air (with a 50 or 60 ml syringe) through the central lumen while auscultating over the stomach for a “swoosh” or a “burp” indicating gastric placement,
- aspirating gastric contents with a syringe (using a 50 or 60 ml syringe) through the central lumen, and
- confirming the location and placement of the EnsoETM with an x-ray.

Secure the EnsoETM with a securement device or tape in accordance with hospital protocol. Ensure the EnsoETM and tube set connections are not in contact with the patient’s skin. Direct contact between the EnsoETM and exposed skin may cause shivering.

For stomach decompression, connect the central lumen of the EnsoETM (Figure 1) to low-intermittent suction using standard suction tubing (not supplied) and adaptor (not supplied). Always use the lowest suction setting that will effectively decompress the stomach.

The central lumen of the EnsoETM is not intended for enteral feeding or for administration of oral medication. If the central lumen of the EnsoETM becomes blocked or clogged,

standard approaches for clearing blocked gastric tubes are recommended. For example, disconnect the EnsoETM from wall suction and use a saline flush. If the standard approaches are unsuccessful, it may be necessary to remove and then replace the EnsoETM.

Monitor patient temperature using both monitors during use. Ensure that the temperature monitors are reporting temperatures that are in agreement; if the discrepancy between the two monitors is greater than 0.5°C, discontinue treatment and investigate the cause of the discrepancy. Replace the temperature probes or secondary monitor if necessary. Ensure both temperature probes remain in place without accidental dislodgement during the entire course of patient treatment. Monitor circulating coolant temperature and ensure that it does not fall below 4°C or exceed 42°C.

6.6. Device Specific Considerations

- Device size: The device has outside diameter less than or equal to 13.3mm, with a wall thickness of 0.65mm±0.1mm.
- Device model: *EnsoETM Model: ECD02*
- Duration of exposure: less than 36 hours
- Frequency of exposure: Single-use

7. Study Procedures and Schedule

7.1. Study Procedures/Evaluations

7.1.1. Study Specific Procedures

- Study specific imaging with include endoscopic evaluation of the esophagus one day before surgery at the time of the pre-op Transesophageal Echocardiography (TEE) and again 1-day post-op. This will include endoscopic esophageal intubation with visual assessment of the entire esophagus and grading of lesions. Coupled with this procedure will include endoscopic ultrasound assessment of the esophagus at the level of the left atrium with specific attention to the sub-mucosal layer that separates esophagus from the cardiac tissue. The patient will undergo moderate sedation during this procedure, which will accompany the TEE.
- The ECD will be placed by trained study staff following endotracheal intubation. Proper positioning will be verified. A temperature probe will be placed to verify the patients core temperature. The target temperature will be set to the core temperature at the beginning of the procedure. Two minutes prior to ablation on the posterior wall the target temperature will be changed to the minimum temperature setting which will allow for maximal cooling. Cooling will take place throughout the duration of posterior wall ablation. After ablation in this territory is complete the target temperature will return to the patients core temperature. The device will be removed at the completion of the procedure by anesthesiology when there is no further need for an orogastric tube.
- LET monitoring will not be performed in the patients of the intervention group as the ECD is prohibitive. Therefore, ice lavage of the esophagus, as detailed below, will not be performed in this group.

7.1.2. Standard Care Procedures

- Medical History will be obtained by interview and will involve identification of contraindications to the use of the ECD. This includes a history of esophageal perforation or varices. An allergy to silicone will be assessed.
- The patient's active medication list will be reviewed as is standard protocol for atrial fibrillation ablation, but this is not specific to the study as there are no medications that would impact the use of the ECD.
- All subjects will be on Protonix (40mg; twice daily) immediately following surgery for 30 days and anticoagulation for 3 months following surgery.
- The physical exam will be performed as is customary for the procedure. Study specific exam is included as part of the airway assessment which is performed on a regular basis by anesthesiology. The oropharynx will be assessed prior to placement of the ECD.
- The patient will be administered general anesthesia by the anesthesia department with hemodynamic monitoring. Two 8-French sheaths placed in the right femoral vein. A 7- and a long 9-French sheath will then be placed in the left femoral vein and a 7-French sheath placed in the right subclavian vein. Under fluoroscopic guidance, a quadripolar catheter is then placed through the left femoral venous sheath to the His bundle region. His-bundle electrocardiography is performed with measurement of intervals. A decapolar catheter with 2-5-2 spacing is then placed through the right subclavian venous sheath and utilized to intubate the coronary sinus for left atrial recordings. Ventricular pacing is used to demonstrate VA 1:1 conduction. Next, trans-septal puncture is performed with the use of a SL-1 sheath from Daig, a Baylis needle, and intracardiac echocardiography. Then, a separate slightly higher puncture of the atrial septum is performed with intracardiac echo guidance into the left atrium also using a Baylis needle and SL-1 sheath. The participant will be given 5000 units of heparin bolus after the first transseptal puncture and again after the second transseptal puncture. The participant will then be maintained on heparin infusion with intermittent boluses to maintain ACT between 300 and 350 seconds. At this point, a multi-pole loop catheter will be placed through the sheath into the left atrium. Three-dimensional geometry will be obtained of all four pulmonary veins, left atrial appendage, and left atrium. Then, the loop catheter will be placed in the left superior vein and ablation will be carried out utilizing an 8 mm distal tip large curve ablation catheter from Boston Scientific. Ablation will be carried out with 35 watts of energy at 55 degree temperature on the posterior wall and 50 watts of energy and 55 degree temperature on the anterior wall. The participants with LET monitoring may require intermittent boluses of iced lavaged saline through the nasogastric tube when the temperature rises above 1 degree centigrade. Next, ablation will be carried out of the left superior pulmonary vein until completely isolated as well as the carina. The loop catheter will then be placed in the left inferior pulmonary vein and isolation of the left inferior pulmonary vein is obtained as well. The loop catheter will then be placed in the right superior pulmonary vein with isolation of that catheter and then brought down into the right inferior pulmonary vein with entrance block demonstrated from that catheter. All veins then demonstrate exit block with additional consolidating ablations as required. All four veins will be checked at that point. Next, Isuprel provocation will be initiated. Pacing will be

performed to the atrioventricular (AV) nodal Wenckebach block rate and to the AV nodal effective refractory period. Then the patient is placed on 10-20 mcg of Isuprel and repeat burst pacing from the coronary sinus as well as the high right atrium is performed. Should atrial fibrillation recur then further ablation is carried out from the roof anteriorly from the right superior pulmonary vein to the left superior pulmonary vein with bidirectional conduction block detected. A complex atrial fractionated electrogram map may be performed to determine fractionated areas for further ablation lines. Should atrial fibrillation persist then anterior septal ablation will be carried out for complex atrial fractionated electrograms as well as spot ablation within the atrial appendage or atrial appendage isolation if required. Should the patient develop mitral isthmus atrial flutter then an ablation line will be performed from the left inferior pulmonary vein to the mitral annulus posteriorly. Should the patient develop typical atrial flutter, a cavo-tricuspid isthmus (CTI) right atrial flutter line may be performed. Other right atrial lesions will be targeted as required, including superior vena cava isolation if needed. Organized atrial tachycardias will be mapped and ablated as needed. At the conclusion of the ablation, heparin is discontinued and catheters removed. Sheaths are removed once the (activated clotting time) ACT is below 180 seconds or following administration of protamine. At the conclusion of the procedure the intracardiac echocardiogram is used to demonstrate no evidence for pericardial effusion or fluid.

7.2. Radiographic Procedures/Evaluations

7.2.1. Esophagoscopy

The patient will present for endoscopic evaluation the day prior to surgery. During this time **t**he patient will undergo moderate sedation with continual monitoring of vital signs. Following adequate sedation the proceduralist will proceed with esophageal intubation with visual assessment of the entire esophagus and grading of lesions (Zargar classification). Furthermore, the submucosal tissue will be assessed with EUS at the level of the left atrium. This procedure will be preceded by TEE with moderate sedation maintained.

The day following the PVI the patient will undergo repeat endoscopic evaluation of the esophagus in the same manner as detailed above. The proceduralist will document their findings including the condition of the sub-mucosal esophageal tissue as noted by EUS.

7.3. Study Schedule

7.3.1. Screening/Enrollment/Baseline (Visit 1, Day 0)

Screening/Enrollment/Baseline Visit (Visit 1)

- Obtain informed consent of potential participant verified by signature on written informed consent form
- Review medical history to determine history based on inclusion/exclusion criteria
- Review medications history to determine eligibility based on inclusion/exclusion criteria
- Obtain demographic information and tobacco use history

- Record vital signs, results of examinations, other assessments
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria
- Schedule EGD 1 day prior to surgery.
- Schedule follow-up visits for patients who are eligible and available for the duration of the study
- Provide patients with instructions needed to prepare for the first study visit/procedure

7.3.2. Endoscopic evaluation and TEE (Visit 2)

The patient will present to the hospital on the day prior to their RF ablation procedure as is standard of care for transesophageal echocardiography (TEE). The patient will be prepped for moderate conscious sedation with appropriate monitoring of vital signs under the care of a nurse and as directed by the physician. For this study we will add the patient will undergo direct visualization of the esophageal mucosa as well as ultrasound assessment of the sub-mucosal tissue in the area of the left atrium. The patient will be sedated to a level of moderate conscious sedation as is typical for endoscopic evaluation and TEE. The endoscopic probe will be passed into the esophagus with appropriate imaging obtained throught the length of the esophagus. Then EUS will be used to assess the submucosal tissue

7.3.3. Surgical Procedure Visit (Visit 3)

Subjects will undergo the RF ablation procedure within 30 days of randomization unless there is a medically valid reason to the delay the procedure. The procedure is describe below. Details of the procedure are referenced in section 7.1.2 of this study protocol. The investigator's procedure note will be included in the study files to gather endpoint and exploratory data.

The following day the patient will undergo repeat endoscopic evaluation in the same fashion as the prior study with moderate sedation. This will include visual assessment of the esophagus with video imaging as well as EUS at the area of interest near the left atrium at the level of the pulmonary veins.

7.3.4. Follow-up Visit (Visit 3)

The first follow-up visit will occur 12 days (+4/-4) days after the surgery procedure.

- Review medical history and medications history
- Record vital signs
- Adverse event assessment
- Assess study eligibility

7.3.5. Final Study Visit (Visit 4)

The final study visit will occur 3 months (+30/-30 days) after the surgery procedure.

- Review medical history and medications history
- Record vital signs
- Adverse event assessment
- PVI Efficacy as assessed through placement of an event monitor
- Assess study eligibility

7.3.6. Unscheduled Visit

In addition to standard care provided during unscheduled visits, an adverse event assessment will be performed to determine whether an adverse event is present. Any adverse events will be recorded on the AE case report form.

7.4. Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.5. Rescue Medications, Treatments, and Procedures

- If evidence of bleeding with placement of the ECD then the device will be removed.
- Surgical exploration and repair of esophageal fistula.
- Hemodynamic support including (Advanced Cardiovascular Life Support (ACLS) protocol will be implemented as needed.

8. Safety Assessment

8.1. Specification of Safety Parameters

8.1.1. Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2. Definition of Serious Adverse Events (SAE)

An AE is considered *serious* if, in the view of the PI, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not fall under one of these categories may be considered serious when, based on upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3. Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in protocol-related documents, such as the IRB-approved research protocol and informed consent; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possible related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2. Reporting Procedures

8.2.1. Adverse Event Reporting

If a subject presents with an adverse effect, the PI will evaluate whether or not the event is related to the use of the study device by completing an adverse event report. If the PI determines the adverse event to be related with the study device, or if the adverse event is unexpected, he must:

- Complete and submit the adverse event report to the IRB in a timely manner (10 working days after the investigator determines the adverse event is related to the study device).

8.2.2. Serious Adverse Event Reporting

All unanticipated adverse device effects are considered Serious Adverse Events (SAEs). The PI will submit to the RMC IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

8.2.3. Unanticipated Problem Reporting

The study investigator shall complete an *Adverse Event Report* and submit it to the RMC IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

8.3. Classification of an Adverse Event

8.3.1. Severity of Event

On the *Adverse Event Report*, the investigator will characterize the severity of each AE as mild, moderate, or severe. The investigator will use medical judgment to compare the report AE to similar types observed in normal clinical practice. To assess the severity of an AE, the following guidelines are to be followed:

- **Mild:** The AE is transient and easily tolerated by the subject
- **Moderate:** The AE causes the subject discomfort and interrupts the subject's daily activities
- **Severe:** The AE causes considerable interference with the subject's usual activities; may be incapacitating and may require hospitalization

8.3.2. Relationship with Study Device

On the *Adverse Event Report*, the PI will characterize the AE's relationship with the study device by indicating one of the following:

- **Definitely Related:** clearly related to the research
- **Probably Related:** likely related to the research
- **Possibly Related:** may be related to the research but information not yet available to assess the likelihood of this
- **Probably Not Related:** doubtfully related to the research
- **Definitely Not Related:** clearly not related to the research

8.3.3. Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described for the study device. This assessment

8.4. Time Period and Frequency for Event Assessment and Follow-Up

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within **7 calendar days** of initial receipt of information	Investigator	• Local/Internal IRB • NHLBI and/or Data Coordinating Center (DCC)
		Sponsor or Designee	• FDA (if IND study)
Non-fatal, non-life-threatening unexpected,	Within **15 calendar days** of initial receipt of information	Investigator	• Local/Internal IRBs/Institutional Officials

suspected serious adverse reactions			• NHLBI and/or DCC
		Sponsor or Designee	• FDA (IND/Marketed Products) • All participating investigators
Unanticipated adverse device effects	Within **10 working days** of investigator first learning of effect	Investigator	• Local/internal IRBs • NHLBI and/or DC
		Sponsor or Designee	• FDA (if IDE study)
Unanticipated Problem that is not an SAE	Within **14 days** of the investigator becoming aware of the problem	Investigator	• Local/internal IRBs/Institutional Officials • NHLBI and/or DCC
All Unanticipated Problems	Within **30 days** of the IRB's receipt of the report of the UP from the investigator	IRB	• OHRP
		Investigator	• IRB

8.5. Safety Monitoring

If necessary, the PI will collaborate with the Riverside Medical Center IRB to develop a safety monitoring plan to ensure the proper conduct of monitoring study data and activities.

9. Statistical Considerations

9.1. Statistical and Analytical Plans

A detailed statistical analysis plan will be developed and added to the study protocol on a later date.

9.2. Measures to Minimize Bias

9.2.1. Enrollment / Randomization / Masking Procedures

Patients will be randomly assigned on a 1:1 ratio (ECD during RF ablation:No ECD device during RF ablation) one of two study groups. A random permuted block will be generated to decide the randomization assignments. The rationale for the use of random permuted block assignment is to ensure a 1:1 group assignment ratio.

To minimize bias, the individual who evaluates the radiographic imaging will be blinded to the study hypotheses and subject's group assignment, so as not to influence his/her evaluation of the condition of the subjects' esophagus. It is not possible to blind the PI, as he will be performing the procedure. Further, the patient will be blinded to the study group to which he or she was assigned. Study subjects will be debriefed regarding his or her study assignment at the final study visit. The informed consent form will explain this process to subjects. The rationale for blinding subjects to their study group assignment is to minimize the influence of the Placebo Effect.

10. Source Documents

As part of conducting an IRB-approved study, the PI will permit authorized representatives of the Riverside Medical Center IRB and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluations of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. This may include, but is not limited to, hospital records, clinical and office charts, lab notes, memoranda, evaluation checklists, pharmacy dispensing records, radiographic imaging, and other study-related documents. A case report form will be used to organize all the study data.

11. Ethics/Protection of Human Subjects

11.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for Protection of Human Subjects of Research.

11.2. Institutional Review Board

The protocol, informed consent form, and all participant materials will be submitted to the Riverside Medical Center IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before any changes are implemented to the study. All changes to the consent form will be IRB approved and a determination will be made regarding whether previously consented participants need to be re-consented.

11.3. Informed Consent Process

Subject participation in this research is voluntary. Subjects must give informed consent before they can be enrolled in this study, and the Principal Investigator is responsible for obtaining informed consent before any study-related activities are performed (this includes any screening procedures that are not considered conventional care).

The PI will obtain and document the subject's informed consent in accordance with State and Federal regulations and Riverside Medical Center's Institutional Review Board policies. The informed consent form must be approved by the Riverside IRB.

The informed consent process will include the following steps:

- Be conducted by the PI or designated study team member with appropriate training
- Avoid any undue influence or coercion of subjects to participate in the study
- Make it clear to the subject that participation in the study is voluntary and that refusing to participate in the study will not result in any loss of benefits
- Make no statement that the subject's legal rights are waived by participating

- Use plain language that is understandable to the subject to describe all aspects of the study that subjects need to make an informed decision to participant
- Provide sufficient time for the subject to consider his/her participation
- Answer all of the subject's questions to ensure he/she fully understands the study
- Provide subjects with new information throughout the study, if applicable
- Ensure the informed consent form is signed and dated by the subject

Any changes to the informed consent form will be approved by Riverside Medical Center's IRB before use in the informed consent process.

11.3.1. Consent and Other Informational Documents Provided to Subjects

Consent forms describing in detail the study device, study procedures, and risks are given to the subject and written documentation of informed consent is required before starting intervention. The informed consent form is submitted with this protocol.

11.4. Subject and Data Confidentiality

Study data will be recorded on an encrypted Excel spreadsheet, and all copies of source documents will be locked in a cabinet only accessible to the study investigators. Study ID numbers will be assigned to subjects, and the Study ID will be used in lieu of the subject's name on the Case Report Form.

Any publications or presentations resulting from this study will not contain any identifying information of subjects enrolled in this study.

Study data may be audited or monitored by the Riverside Medical Center IRB and State and Federal agencies that have the right to access the data in order to ensure the study is being conducted in accordance with applicable regulations and policies.

12. Data Handling and Record Keeping

12.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial the date on which the change was made.

Clinical data (including Adverse Events, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into an Excel spreadsheet. The spreadsheet will include a password and will only be accessible to authorized study personnel.

12.2. Study Records Retention

Study documents must be retained for a minimum of 3 years after the study has been formally closed (e.g., submission of a study closure report to the IRB).

12.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may either be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the study team, or required by the IRB, and implemented promptly to minimize the occurrence of future deviations.

It is the responsibility of the PI to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation. All deviations must be address in study source documents and reported to the Riverside Medical Center IRB.

13. Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and reviewed. A conflict of interest statement will be submitted to the Riverside Medical Center IRB to review.

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