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# Cooling or warming the esophagus to reduce esophageal injury during left atrial ablation in the treatment of atrial fibrillation --Manuscript Draft--

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1 TITLE: 2 Cooling or Warming the Esophagus to Reduce Esophageal Injury During Left Atrial Ablation in the 3 Treatment of Atrial Fibrillation 4 5 **AUTHORS AND AFFILIATIONS:** Jason Zagrodzky<sup>1</sup>, Mark Gallagher<sup>2</sup>, Lisa Leung<sup>2</sup>, Tiffany Sharkoski<sup>3</sup>, Pasquale Santangeli<sup>4</sup>, Cory 6 7 Tschabrunn<sup>4</sup>, Jose M Guerra<sup>5</sup>, Bieito Campos<sup>5</sup>, John MacGregor<sup>6</sup>, Jamal Hayat<sup>2</sup>, Brad Clark<sup>7</sup>, Alex Mazur<sup>8</sup>, Marcel Feher<sup>9</sup>, Martin Arnold<sup>9</sup>, Mark Metzl<sup>10</sup>, Jose Nazari<sup>10</sup>, Erik Kulstad<sup>11</sup> 8 9 <sup>1</sup> St. David's South Austin Medical Center, Austin, TX 10 <sup>2</sup> St George's University Hospitals NHS Foundation Trust, St. George's, University of London, 11 12 London, UK 13 <sup>3</sup> Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, 14 Philadelphia, PA <sup>4</sup> University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 15 16 <sup>5</sup> Hospital de la Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, CIBERCV, Carrer de 17 Sant Quintí, Barcelona, Spain <sup>6</sup> PeaceHealth Medical Group, St. Joseph Medical Center, Bellingham, WA 18 19 <sup>7</sup> St. Vincent Hospital, Indianapolis, IN <sup>8</sup> University of Iowa, Iowa City, IA 20 21 <sup>9</sup> University Hospital Erlangen, Erlangen, Germany 22 <sup>10</sup> NorthShore University Health System, Evanston, IL 23 <sup>11</sup> Department of Emergency Medicine, University of Texas, Southwestern Medical Center, 24 Dallas, TX 25 26 **Email Addresses of Co-Authors:** 27 Mark Gallagher (Mark.Gallagher@stgeorges.nhs.uk) 28 Lisa Leung (Lisa.Leung@stgeorges.nhs.uk) 29 John MacGregor (JMacGregor@peacehealth.org) 30 Tiffany Sharkoski (Tiffany.Sharkoski@uphs.upenn.edu) 31 Pasquale Santangeli (pasquale.santangeli@uphs.upenn.edu) 32 Cory Tschabrunn (cory.tschabrunn@uphs.upenn.edu) 33 Jose M Guerra (jguerra@secardiologia.es) 34 Bieito Campos (bcamposg@santpau.cat) 35 Jamal Hayat (jamal.Hayat@stgeorges.nhs.uk) Brad Clark (bradley.clark@ascension.org) 36 37 Alex Mazur (alexander-mazur@uiowa.edu) 38 Marcel Feher (Marcel.Feher@uk-erlangen.de) 39 Martin Arnold (martin.arnold@uk-erlangen.de) 40 Mark Metzl (MMetzl@northshore.org) Jose Nazari (JNazari@northshore.org) 41

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#### **KEYWORDS:**

Atrial fibrillation; radiofrequency ablation; cryoablation; esophageal injury; esophageal cooling; esophageal warming, atrioesophageal fistula

#### **SUMMARY:**

The goal of this protocol is to describe the use of esophageal temperature modulation to counteract esophageal thermal injury from left atrial ablation for the treatment of atrial fibrillation.

#### **ABSTRACT:**

Ablation of the left atrium using either radiofrequency (RF) or cryothermal energy is an effective treatment for atrial fibrillation (AF) and is the most frequent type of cardiac ablation procedure performed. Although generally safe, collateral injury to surrounding structures, particularly the esophagus, remains a concern. Cooling or warming the esophagus to counteract the heat from RF ablation, or the cold from cryoablation, is a method that is used to reduce thermal esophageal injury, and there are increasing data to support this approach. This protocol describes the use of a commercially available esophageal temperature management device to cool or warm the esophagus to reduce esophageal injury during left atrial ablation. The temperature management device is powered by standard water-blanket heat exchangers, and is shaped like a standard orogastric tube placed for gastric suctioning and decompression. Water circulates through the device in a closed-loop circuit, transferring heat across the silicone walls of the device, through the esophageal wall. Placement of the device is analogous to the placement of a typical orogastric tube, and temperature is adjusted via the external heat-exchanger console.

#### **INTRODUCTION:**

Left atrial ablation to perform pulmonary vein isolation (PVI) is increasingly utilized for the treatment of atrial fibrillation<sup>1</sup>. The attainment of PVI can be achieved with radiofrequency (RF) energy to burn atrial tissue or with direct application of cryothermal energy; however, collateral damage to surrounding structures remains a risk with either method, with esophageal injury being one of the most serious<sup>2-4</sup>. The most extreme esophageal injury, atrioesophageal fistula (AEF), remains challenging to prevent and diagnose, and carries a very high mortality<sup>5,6</sup>.

A number of techniques have been utilized to reduce the risk of AEF, including reducing power applied to vulnerable regions, monitoring luminal esophageal temperature (LET), deviating the esophagus during ablation, and cooling or warming the esophagus<sup>7</sup>. Directly countering the thermal energy delivered to the esophagus, primarily by cooling against the RF heating, has been used in a variety of formats<sup>8-16</sup>. An advantage to cooling during RF ablation or warming during cryoablation is that a preventive approach to injury is taken, in contrast to temperature monitoring, which involves a reactive approach (stopping ablation when temperature rises). The reactive approach, although often used, may be of limited efficacy<sup>17</sup>, with a recent review noting that currently available discrete sensor probes, whether single or multiple, do not appear to significantly reduce injury rates<sup>7</sup>. Cooling or warming also avoids the need for procedural pauses

and device manipulation required with esophageal deviation techniques, which have been reported to cause esophageal trauma and involve difficulties in use<sup>18,19</sup>. A recent meta-analysis of esophageal cooling for the purpose of protecting the esophagus during RF ablation found a 61% reduction in high-grade lesion formation in a total of 494 patients<sup>20</sup>. A recent randomized-controlled trial found a statistically significant 74% reduction in endoscopically identified lesions when using a dedicated cooling device compared to standard LET monitoring<sup>21</sup>.

The goal of this protocol is to demonstrate the use of esophageal cooling or warming during left atrial radiofrequency or cryo-ablation using an esophageal temperature management device (**Figure 1**).

#### PROTOCOL:

This protocol follows the guidelines of local institution's human research ethics committee where applicable.

#### 1. Assessment prior to placement

NOTE: Under current U.S. labeling, there are no formal contraindications listed. In the case of esophageal pathology, such as deformity, trauma, or recent ingestion of caustics or acidic material, caution is advised.

1.1 Ensure that necessary equipment, such as the heat exchanger, the esophageal temperature management device, and water-based lubrication, is available.

1.2 Attach the esophageal temperature management device to the heat exchanger via the device connectors, and power on the unit, placing it in manual mode. Ensure that the water is flowing through the esophageal temperature management device and confirm the absence of leaks.

#### 2. Placement

2.1 Determine the appropriate insertion depth for the esophageal temperature management device in similar manner to standard orogastric tube. Measure from the patient's lips to the earlobe and from the earlobe to xiphoid process and note this depth on the device (**Figure 2**).

2.2 Use water-soluble lubricant to lubricate the esophageal temperature management device generously, at least 15 cm, and up to 25 cm of the distal end (**Figure 3**).

NOTE: Patients are typically under general inhalational anesthesia (for example, using sevoflurane), but may also be under intravenous anesthesia (for example, using propofol), or in some cases under conscious sedation (for example, using meperidine or midazolam).

2.3 If possible, extend the patient's head to further facilitate insertion of the esophageal temperature management device using gentle pressure applied posteriorly and downwards, past

the oropharynx and into the esophagus. Lifting the mandible anteriorly may assist passage of the device, as might a reduction of pressure in the ETT cuff if overinflated. Apply light pressure on the device as needed to reach the desired depth of placement. (Figure 4).

2.4 If needed, determine placement location by fluoroscopy to check if the tip of the device is below the diaphragm (Figure 5).

2.5 Secure the water hoses and device to avoid accidental dislodgement; a common method is to place the connecting hose under the patient's left foam armrest.

2.6 If stomach decompression is desired, connect the central lumen to low-intermittent suction using standard suction tubing.

3. Temperature modulation – RF ablation

3.1 Ensure that the heat exchanger is set to manual mode and the appropriate water temperature is set. For example, on one typical heat exchanger, press the **Temp Control** button, then use the up/down arrows to select the target water temperature. Once the digital display shows the target temperature desired, initiate water flow by pressing the **Manual Control** button. A typical target is 4 °C water temperature when performing radiofrequency ablation at the posterior left atrial wall.

3.3 In order to anticipate the time needed for the heat exchanger to reduce temperature, use a water temperature setpoint of roughly 14 °C for initial insertion in RF cases while awaiting transseptal puncture. After transseptal puncture, and approximately 7-10 minutes before application of RF energy to the posterior atrial wall, change the water temperature setpoint to 4 °C (in manual mode).

NOTE: For additional anti-inflammatory effects of cooling which may reduce gastroparesis or chest pain post-procedure, operators may maintain the water temperature setpoint at 4 °C for 20 minutes after the completion of posterior wall ablation, at which point the machine can be turned off.

4. Temperature modulation – cryoablation

168 4.1 For cryoablation, use a water temperature setpoint of 42 °C (typical).

4.2 Set this water temperature shortly after placement (placing while cold is generally easier due to increased device stiffness), and continue throughout the case, providing additional patient warming to counter the systemic cooling effect of the cryoablation.

5. Patient temperature monitoring

NOTE: Because the temperature in the esophagus is modulated by the presence of an esophageal

heat transfer device, a different location is necessary for patient temperature measurement.

Options for patient temperature measurement include nasopharyngeal thermometer (ensure that the depth is less than 10 cm), Foley temperature sensor, rectal temperature sensor, tympanic membrane thermometer, or forehead thermometer (including zero-flux thermometry).

5.3 To maintain patient temperature when using esophageal cooling, use supplemental warming modalities, such as warming blankets or head covers if needed. During esophageal warming when performing cryoablation, the patient temperature will usually stay in a normothermic range.

#### 6. Troubleshooting

6.1. Ensure that no blockage of water flow occurs, and that the water paddle wheel, if present, is continuously spinning, or the low-flow alarm is not activated.

6.2. Blockage of water flow in the system will cause the paddle wheel to stop spinning and an occlusion alert on the external heat exchanger Stop treatment and determine the location and cause of obstruction. If necessary, remove and replace the esophageal temperature management device.

6.3. Confirm water flow at correct temperature by checking setpoint and touching device to ensure adequate pressure (device will be firm) and appropriate temperature.

#### 7. Removal of device

7.1 Press the appropriate button to pause water flow; this may be labelled "Monitor" or "Temp Set", but may vary by model.

7.2 If present, close clamps on the hose set and/or device tubing, and withdraw the device from the patient by gently pulling anteriorly in a similar manner to standard orogastric tube removal.

7.2 Power down the heat exchange unit via the power switch prior to unplugging from wall power.

7.3 Disconnect the water hose connectors from the device and dispose as per institutional policy (typically via contaminated waste container).

#### REPRESENTATIVE RESULTS:

A large number of patients have been studied using esophageal cooling via direct instillation of cold liquid into the esophagus during RF ablation (for example, by injecting a 20 mL bolus of ice-cold saline via orogastric tube into the upper esophagus when the LET increased by 0.5 °C above baseline). The findings of a meta-analysis of existing studies using this technique is summarized in **Figure 6**<sup>20</sup>.

Data from a randomized-controlled clinical trial evaluating a dedicated cooling device were recently presented, and are summarized in **Table 1**<sup>21</sup>. Ablation parameters for the control and treatment arms, respectively, were as follows: RF duration, 14.1 versus 14.5 minutes; average force, 19.1 versus 17.8 grams, maximum RF power, 33.9 versus 34.1 W, and average ablation index, 394 versus 384, with all differences non-significant. All patients had PVI with additional lesion sets when required. At the time of presentation, no difference in recurrence rate of atrial fibrillation at 6 months was found between the two groups (3/22 in control group, 2/17 in treatment group).

#### Example RF ablation result:

A 59-year-old female with a past medical history of hyperlipidemia, diabetes, and recurrent paroxysmal atrial fibrillation presented for an RF ablation procedure. An esophageal heat transfer device circulating 14 °C water was placed in the esophagus, with the setpoint reduced to 4 °C after transseptal puncture, approximately 8 minutes before the start of ablation. The ablation was performed using a three-dimensional mapping system and a 3.5 mm irrigated ablation catheter for segmental pulmonary vein isolation. A setting of 30 W on the posterior aspect of the pulmonary veins, with up to 40 W on the anterior was used, with duration of up to 20 seconds. PVI as well as linear posterior wall isolation (Box lesion) was performed. Patient temperature was measured via nasopharyngeal probe placed less than 10 cm into the nares, with patient start temperature of 36.4 °C, and end temperature of 36.1 °C. Approximately 20 minutes after completion of ablation on the posterior wall, the esophageal heat transfer device setpoint was raised to 40 °C to provide patient warming while access sheaths were removed and vascular closure was completed. Endoscopy performed the following day as part of a research protocol demonstrated no esophageal lesions.

#### Example cryoablation result:

A 68-year-old male with past medical history of hypertension and increasing episodes of paroxysmal atrial fibrillation presented for cryoballoon ablation. An esophageal heat transfer device circulating room temperature (22 °C) water was placed in the esophagus. Once placed, the setpoint temperature was raised to 42 °C. Ablations were performed with a cryoballoon system. Initial patient core temperature was measured at 36.3 °C via Foley catheter temperature sensor. Temperatures in the esophagus were measured with a single-sensor temperature probe (routine use of a temperature probe device co-located with the heat transfer device is not recommended, as the optimal benefit is obtained with full contact between heat transfer device and esophageal mucosa, but is described here to show the effect on preventing excessive temperature decreases). Beginning with cryoablation at the left superior pulmonary vein, the initial esophageal temperature measured was 38.6 °C and reached a nadir of 36.4 °C during the cryoablation. Nadir balloon temperature was -51 °C. Block was obtained in under 30 seconds, with a single 180 second freeze performed. At the left inferior pulmonary vein, the beginning temperature was 38.5 °C and reached a low of 38.0 °C after two cycles of treatment (a bonus freeze of 120 seconds was performed because of delay in obtaining block on initial freeze until 70 seconds in). Nadir balloon temperature was -48 °C. In the right superior pulmonary vein, initial esophageal temperature was 38.4 °C, remained unchanged through two cycles, and ended at

38.5 °C. Nadir balloon temperature was -47 °C. Finally, in the right inferior pulmonary vein, initial esophageal temperature was 38.9 °C and reached a nadir of 38.8 °C throughout two cycles of treatment. Nadir balloon temperature was -39 °C. Patient temperature at the end of the procedure was 36.0 °C, and all cryoballoon treatments maintained esophageal temperature well above common stopping thresholds (15 °C to 25 °C).

#### **FIGURE AND TABLE LEGENDS:**

**Figure 1. Image of esophageal temperature management device in-situ** (with permission from Attune Medical).

**Figure 2.** Measurement of the appropriate insertion depth for the esophageal temperature management device. This is performed by extending the device from the patient's lips to the earlobe and then from the earlobe to the tip of the xiphoid process, and then marking the insertion depth on the device.

**Figure 3. Lubrication of the device.** Lubrication of the esophageal temperature management device, generously applying approximately lubricant to 25 cm of the distal end with water-soluble lubricant.

Figure 4. Advancement of the device with light pressure, until the required length of tube has been inserted.

Figure 5. Fluoroscopic image demonstrating the tip of the device below the diaphragm.

Figure 6. Summary of data from meta-analysis of studies on esophageal cooling utilizing direct liquid instillation.

Table 1. Summary of primary outcome of randomized-controlled study of dedicated esophageal cooling device.

#### **DISCUSSION:**

Modification of the placement procedure may be necessary by crimping the water outflow tube, increasing the stiffness of the heat exchange device during placement. The identification of which connecting tube is water outflow can be performed by crimping either tube and examining to see which causes the device to stiffen, and which causes the device to soften. Crimping the inlet tube will decrease water inlet flow and soften the device, crimping the outlet will increase water backpressure and stiffen it.

Limitations of this method of esophageal temperature modulation to counteract thermal injury from left atrial ablation include the inherent heat-transfer limitation of any technology. Although whole-body temperature modulation can be achieved with esophageal heat exchange, there is still the potential to overcome this heat transfer capacity if sufficient energy is utilized in ablation. As such, changes from standard ablation parameters are not recommended, and usual ablation

technique should be maintained. In general, the device is utilized in patients that are endotracheally intubated; however, a number of sites utilize this protocol in patients under conscious sedation without difficulty<sup>22</sup>. Finally, there remains some uncertainty as to the factors necessary for fistula formation, and aspects beyond energy exchange may be involved.

The use of direct esophageal temperature modulation to prevent esophageal injury during atrial ablation has been used in various forms over the last several years. The most common use has been in cooling during RF ablation, using either balloon devices or direct instillation of cold fluid<sup>8-15</sup>. More recent use has focused on warming to counteract cryothermal injury during cryoablation<sup>23-26</sup>. Use of a dedicated esophageal heat transfer device such as described in this protocol offers the advantage of targeting specific temperatures in the esophagus while avoiding the significant risks and logistical workload of direct instillation of free liquid into the GI tract.

Future applications of this method include the leverage of the known protean effects of patient temperature modulation, in particular temperature reduction<sup>27,28</sup>. Given the well-described protective effects of hypothermia on injured neurons, an additional application may involve the reduction of post-operative cognitive dysfunction<sup>29-32</sup>. Recent data in the burn literature reviewing 2,495 patients highlight the importance of cooling thermal injury in reducing burn depth, grafting, and operative requirements, noting that the mechanisms involve more than just dissipation of heat, but also the alteration of cellular behavior through decreasing release of lactate and histamine, stabilizing thromboxane and prostaglandin levels, and inhibiting kallikrein activity<sup>33</sup>. If similar mechanisms of action are involved in the esophagus, additional benefits to surrounding structures might be anticipated. Preliminary findings and anecdotal data suggest that the anti-inflammatory effects of cooling may reduce infarct size after certain subsets of myocardial injury, renal dysfunction after transplantation, the occurrence of post-operative pericarditis, and the rate of post-procedure gastroparesis<sup>34-37</sup>.

Critical steps include ensuring (a) proper placement of the heat transfer device (b) proper water temperature setpoint, and (c) continual water circulation through the heat transfer device. Proper placement of the device is readily confirmed with fluoroscopy, with particular attention towards the epigastric region near where the tip of the heat exchange device is expected to terminate. Water temperature is easily adjusted on the heat exchanger console, keeping in mind that up to 7-10 minutes may be needed for the circulating water to attain the setpoint temperature from the starting temperature. Continual water circulation is necessary for the device to properly transfer heat. Water circulation can be confirmed by visualization of the spinning water-flow paddle wheel present on some heat exchanger models. On heat exchanger models that lack a water-flow paddle wheel, an alarm will trigger when flow is obstructed. A potential cause of water flow obstruction is improper placement of the heat exchange device (if placed too deep, causing bending/kinking of the tube in the distal stomach, or in rarer cases, if allowed to coil up and bend in the oropharynx or proximal esophagus during placement). Troubleshooting in this case involves a simple visualization under fluoroscopy to determine placement level and adjusting as needed.

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353 None

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#### **DISCLOSURES:**

- 356 EK is an equity owner of Attune Medical, manufacturer of esophageal heat transfer technology.
- 357 MG, PS, CT, JG, and BC serve as Principal Investigators for studies of esophageal cooling with
- 358 funding to their hospital institutions, but receive no direct corporate compensation. MM has
- 359 provided consulting services for Attune Medical. All other authors declare no conflicts of interest
- 360 with this work.

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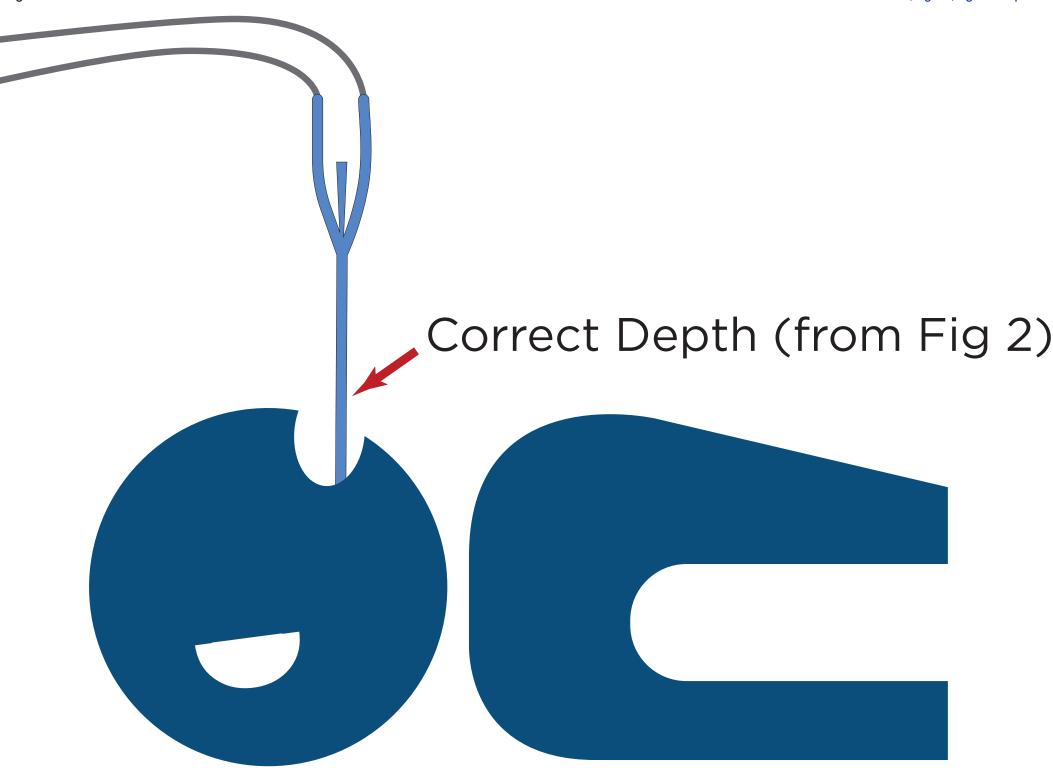
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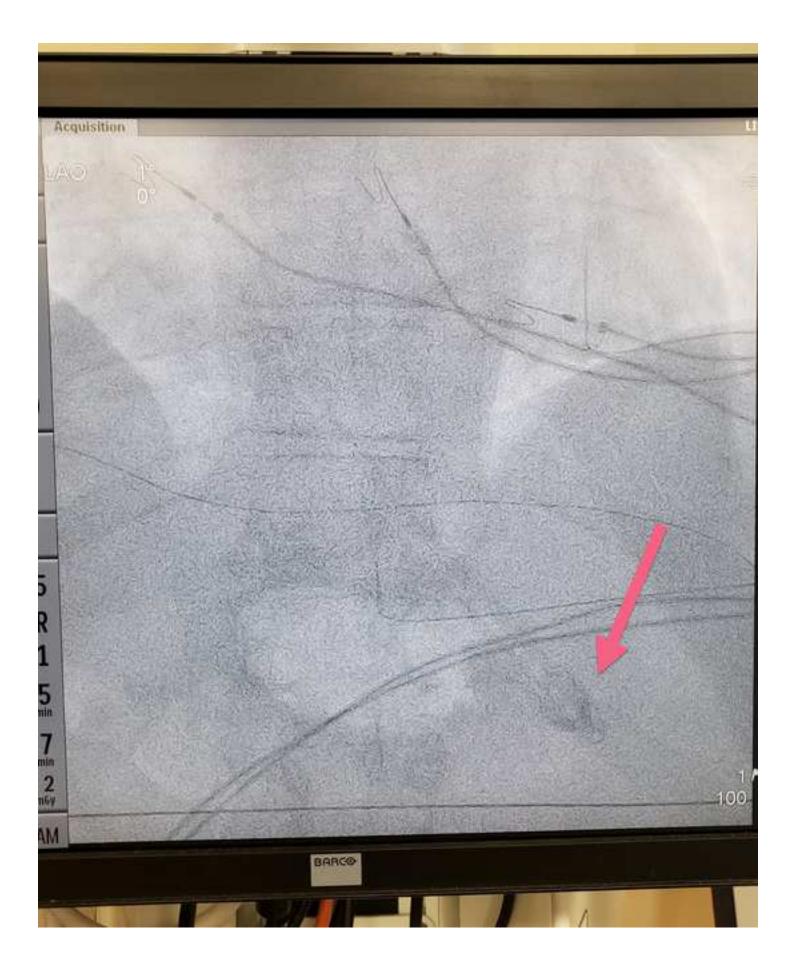
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- 459 37 Horiguchi, A. et al. Abstract 11134: Esophagus Temperature Monitoring Predicts Gastric
- 460 Hypoperistalsis After Catheter Ablation for Atrial Fibrillation. Circulation. 140 (Suppl\_1), A11134-
- 461 A11134 (2019).

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Figure 2





<u>\*</u>

ENDOSCOPY RESULTS (n=78)	PROTECTED (n=40)	CONTROL (n=38)	P value
ANY ENDOSCOPIC ABNORMALITY	3	11	0.018
SEVERE ENDOSCOPIC ABNORMALITY OR PLEXUS INJURY	1	8	0.013

Name of Material/ Equipment	Company	<b>Catalog Number</b>	Comments/Description
Cincinnati SubZero Blanketrol II	Gentherm	n/a	Compatible heat-exchanger with the ECD02
Cincinnati SubZero Blanketrol III	Gentherm	n/a	Compatible heat-exchanger with the ECD02
EnsoETM	Attune	ECD01	Device compatible with Gaymar/Stryker Medi-
	Medical		Therm III and Stryker Altrix Precision
			Temperature Management System
EnsoETM	Attune	ECD02	Device compatible with Cincinnati SubZero
	Medical		Blanketrol II and Cincinnati SubZero
			Blanketrol III
Gaymar/Stryker Medi-Therm III	Stryker	n/a	Compatible heat-exchanger with the ECD01
Stryker Altrix Precision Temperature			
Management System	Stryker	n/a	Compatible heat-exchanger with the ECD01
			Standard water-soluble lubricant used to ease
Water-soluble lubricant	Various	n/a	insertion of tubes, catheters, and digits

#### **Editorial Comments:**

• Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.

We have thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.

• **Textual Overlap:** Significant portions show significant overlap with previously published work. Please re-write lines 123-151, 212-224 avoid this overlap.

We have re-written lines 123-151, and lines 212-224, to avoid overlap with previously published work.

• **Introduction:** Please expand your Introduction to include the following: The advantages over alternative techniques with applicable references to previous studies; Description of the context of the technique in the wider body of literature; Information that can help readers to determine if the method is appropriate for their application.

We have now expanded the Introduction to include advantages over alternative techniques with applicable references to relevant studies, which puts the technique in context in the body of literature around esophageal protection. We have additionally included recent studies and reports showing the protective effects of the described technique to further allow readers to determine if the method is appropriate for their application.

• Protocol Detail: Please note that your protocol will be used to generate the script for the video, and must contain everything that you would like shown in the video. Please add more specific details (e.g. button clicks for software actions, numerical values for settings, etc) to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

We have added more specific details to the protocol steps accordingly.

1) 2.3: Is the patient sedated? If so, mention drugs used.

We have included additional details on sedation, general anesthesia, and drugs typically used.

2) 6.1: how?

We have removed this sentence, as it was redundant to section 2.3, and not as relevant in troubleshooting for this application.

• Results: Please present some of your results in graphical format, e.g., figure or table.

We have now included results from published or presented studies on esophageal cooling or warming in the Results section, with the addition of one Figure and one Table.

• **Discussion:** JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form (3-6 paragraphs): 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.

We have reorganized the Discussion accordingly.

• References: Please spell out journal names.

We have revised the References to spell out full journal names.

- **Commercial Language:**JoVE is unable to publish manuscripts containing commercial sounding language, including trademark or registered trademark symbols (TM/R) and the mention of company brand names before an instrument or reagent. Examples of commercial sounding language in your manuscript are ensoETM,
- 1) Please use MS Word's find function (Ctrl+F), to locate and replace all commercial sounding language in your manuscript with generic names that are not company-specific. All commercial products should be sufficiently referenced in the table of materials/reagents. You may use the generic term followed by "(see table of materials)" to draw the readers' attention to specific commercial names.

We have removed all instances of ensoETM, including from Figures.

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We have obtained figure permissions, but note that variations of some figures have also appeared in print in an earlier work published by JoVE.

#### **Comments from Peer-Reviewers:**

#### **Reviewers' comments:**

Reviewer #1:

Manuscript Summary:

Esophageal injury during either radiofrequency or cryo thermal ablation to achieve pulmonary vein isolation in the treatment of atrial fibrillation is a rare complication but carries extremely high morbidity and mortality. A proposed method for reducing the risk of esophageal injury is to counteract eating or cooling of the esophagus during ablation in the posterior left atrium this manual script describes a novel intra esophageal device to control local esophageal temperature during ablation. It also describes how the use of this device would look in practice with either radiofrequency or cryo thermal ablation. I feel this article does a excellent job explaining the thinking behind esophageal temperature modulation during ablation as well as the practical considerations surrounding the use of the device during a procedure.

#### Major Concerns:

I have no major concerns regarding this manuscript

#### Minor Concerns:

Most of my concerns may or may not be germane to this particular manuscript which principally discusses the function and design of this device as well as the practical considerations of its use. However, I feel it will be challenging to prove that techniques to prevent esophageal injury during atrial fibrillation ablation are effective given that severe esophageal injury is a high consequence but low incidence complication of ablation. As such it would be almost impossible to adequately power study to prove that any technique prevents esophageal atrial fistula per se and surrogate end-points such as post procedure endoscopy to evaluate for esophageal lesions will need to be used. I appreciate that the authors include the caution that standard ablation technique should be employed so that operators do not deliver excessively aggressive ablation energy to tissue adjacent to the esophagus .

Thank you for your review of our manuscript, and the supportive comments above. We agree that indeed, powering a study for fistula development as an end-point will require tens of thousands of patients. Fortunately, the general consensus that high-grade lesions are the precursor to fistula formation allows us to rely more heavily on surrogate end points of esophageal injury, with particular attention to high-grade lesions. We have now included

additional background and newer data on this aspect in the manuscript.

#### Reviewer #2:

Manuscript Summary: Esophageal warming and cooling devices have utility in temperature maintenance during catheter ablation of left atrial arrhythmia (both heat and cold). This manuscript attempts to describe the utility and usage of one of these devices. The authors have written a well-described manuscript.

#### Major Concerns:

As these are two case studies, please describe the catheter ablation parameters in more detail. RF parameters should include power (W), duration of ablation, and a description of the ablation strategy (PVI only?). The cryo parameter should include nadir balloon temp, duration of ablation, and number of ablations at each PV. This will help to better understand the conditions for temp change/control of the esophageal device.

We have now included more data from a recently presented study to provide further details on a larger number of patients in addition to the two example cases, and have added further details on the two example cases as suggested.

#### Minor Concerns:

Please review for small typing errors. Anesthesia does not need to be capitalized. "One may also need to have Anesthesia remove air from ETT cuff if overinflated and causing obstruction. Advance the device with light pressure until the required length of tube has been inserted. (Figure 4)."

We have reviewed for typos, and made corrections as identified.

In the limitations or discussion, the authors need to discuss (briefly) that AE fistula formation is not solely an energy exchange complication but that there are other factors involved (e.g., mis-match repair).

We have now included mention in the Limitations that other factors may be involved in fistula formation.

#### Reviewer #3:

#### Manuscript Summary:

This is a description of a new predicted to reduce thermal injury during LA ablation. The article appears to have been prepared in part by the manufacturers with in-depth

knowledge of the product. Only 2 cases are reported, thus any comments regarding clinical benefit are extremely premature.

#### Major Concerns:

As is the case in most techniques used to help prevent esophageal injury during LA ablation, the limitation is the lack of a very large cohort with a minimum follow-up of 60 days. None-the-less, the product is intriguing and worthy of further evaluation.

Thank you for your review and supportive comments. To better address this concern, we have now included more data in the Representative Results, including a recently published meta-analysis of almost 500 patients, and data from a randomized-controlled clinical study recently presented, both of which include longer-term follow up.

Minor Concerns:

None



To: Jove Publishing

Attune Medical hereby grants permission for Jove Publishing to reprint all figures in the article "Cooling or warming the esophagus to reduce esophageal injury during left atrial ablation in the treatment of atrial fibrillation" submitted by Zagrodzky et al., including Figures 1-5.

\_\_\_\_\_\_

Maria Gray

Vice President, Clinical and Field Operations

**Attune Medical** 



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	Jason Zagrodzky, Mark Gallagher, Lisa Leung, John MacGregor, Tiffany Sharkoski, Pasquale Santangeli, Cory Tschabrunn, Jose M. Guerra, et al.		
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