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DESIGN PAPER

Hybrid epicardial and endocardial sinus node–sparing ablation therapy for inappropriate sinus tachycardia: Rationale and design of the multicenter HEAL-IST IDE trial

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BACKGROUND Inappropriate sinus tachycardia (IST) is defined as resting heart rate >100 beats/min and average 24-hour heart rate >90 beats/min. It is associated with distressing symptoms and significant loss of quality of life. Drugs are not effective in symptom control of IST in up to 30% of patients. Catheter ablation of the sinus node has a high recurrence rate, and the complications are significant. Recently, a novel hybrid sinus node–sparing ablation approach for IST was described.

OBJECTIVE The objective of the Hybrid Epicardial and Endocardial Sinus Node Sparing Ablation Therapy for Inappropriate Sinus Tachycardia (HEAL-IST) investigational device exemption trial (NCT05280093) is to evaluate safety and effectiveness of the hybrid sinus node–sparing ablation procedure for the treatment of symptomatic, drug-refractory or drug-intolerant IST.

METHODS The HEAL-IST trial is a prospective, multicenter, pivotal, single-arm trial. Up to 142 subjects in up to 40 centers will be treated in the trial with a Bayesian adaptive design.

RESULTS Subjects will be assessed for primary safety through 30 days post–hybrid ablation procedure. The primary effectiveness endpoint will be freedom from IST at 12 months. Freedom from IST will be defined as mean heart rate of ≤90 beats/min or at least a 15% reduction in mean heart rate as compared with baseline, in the absence of new or higher dosage of previously failed medications at a 24-month follow-up assessment.

CONCLUSION The HEAL-IST trial is the first multicenter trial evaluating hybrid IST ablation in patients with symptomatic IST and refractory or intolerant to drugs. The results of this study will help guide decision making regarding the best management in this population.

KEYWORDS Inappropriate sinus node tachycardia; Electrophysiological mechanism; Sinoatrial node; Catheter ablation; Hybrid sinoatrial node sparing ablation

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Introduction

Inappropriate sinus tachycardia (IST) is defined as a resting daytime heart rate >100 beats/min and an average 24-hour heart rate >90 beats/min (tachycardia), with sinus P-wave morphology and axis on standard 12-lead electrocardiogram and without a known cause, thus excluding physiological or other pathological conditions known to increase heart rate.[1,2] The estimates of IST prevalence vary from 1% to 1.2% of the

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KEY FINDINGS

- Inappropriate sinus tachycardia (IST) is a prevalent, debilitating condition that significantly impacts quality of life in otherwise healthy younger patients and lacks effective treatment options.
- The Hybrid Epicardial and Endocardial Sinus Node Sparing Ablation Therapy for Inappropriate Sinus Tachycardia (HEAL-IST) investigational device exemption trial is a prospective, international multicenter, single-arm trial to evaluate the safety and effectiveness of a hybrid epicardial-endocardial sinus node–sparing ablation procedure for the treatment of symptomatic, drug-refractory or drug-intolerant IST.
- The results of the HEAL-IST trial will help guide medical decision making for this challenging condition and provide long-term results of this novel approach to IST treatment.

general population.[2] Common complaints include the following: palpitations, lightheadedness, presyncope, syncope, orthostatic intolerance, chest pain or pressure, dyspnea, and exercise intolerance. Noncardiac symptoms are frequent, such as anxiety, depression, abdominal discomfort, myalgia, insomnia, and headaches.[3] Interestingly, up to 90% of IST patients are young females with an average age of approximately 30 years.[3–6] The electrophysiological mechanisms of IST remain elusive and the increased heart rate may be due to dysfunctional intrinsic mechanisms affecting sinoatrial node (SAN) pacemaker automaticity or intracardiac autonomic nerves activity impairment.[7,8]

Pharmacological treatment of IST aims to reduce heart rate and symptoms. Following current guidelines, drugs such as ivabradine and long-acting beta-blockers can be an effective first-line therapy.[9] Alternatively, nondihydropyridine calcium-channel blockers, including verapamil and diltiazem, are also useful to treat IST.[10] Ivabradine is not effective in symptom control of IST in up to 30% of patients.[11] Poor symptom control with drugs or drug intolerance are indications for IST catheter ablation.[9]

Two ablation strategies have been described: the endocardial SAN ablation and the hybrid epicardial-endocardial SAN-sparing ablation. The former aims at targeting directly the SAN anatomical region, to reduce heart rate >50% from the baseline or a minimum of 25% reduction under catecholamine infusion. However, this SAN modification approach is also associated with a pacemaker implantation rate as high as 50% patients.[12] More recently, a novel hybrid SAN-sparing ablation approach for IST has been described; epicardial lesions are applied to electrically isolate the SAN from the superior vena cava (SVC) and inferior vena cava (IVC), and an intercaval line is added.[12–14] In the multicenter SUSRUTA-IST (Sinus Node Sparing Hybrid Thoracoscopic Ablation Outcomes in Patients with Inappropriate Sinus Tachycardia) registry,[12] this hybrid ablation approach demonstrated a rate of pacemaker implantation as low as 4%, with a 100% acute success rate and 8% of recurrence.

Herein, the design and rationale of a prospective, international, multicenter, investigational device exempt (IDE) trial on hybrid epicardial and endocardial SAN-sparing ablation for the treatment of IST (Hybrid Epicardial and Endocardial Sinus Node Sparing Ablation Therapy for Inappropriate Sinus Tachycardia [HEAL-IST] trial) is presented.

Objectives

IST is a prevalent and debilitating condition in otherwise healthy younger patients, resulting in significant loss of quality of life (QoL), and lacking effective treatment options or systematic clinical evidence to support a therapy. The HEAL-IST IDE trial (NCT05280093) is proposed to gather clinical data on the safety and effectiveness of a hybrid sinus node–sparing ablation procedure utilizing the ISOLATOR Synergy Surgical Ablation System (AtriCure, Mason, OH).

Design

The HEAL-IST IDE trial is a prospective, multicenter, pivotal, single-arm IDE trial sponsored by AtriCure, Inc. This trial is conducted in the United States of America, United Kingdom, and European Union under a single protocol approved by an Institutional Review Board (IRB) or Ethics Committee (EC) for each site prior to implementation at the trial site. Up to 40 sites will participate in the trial. Up to 142 subjects will be treated as part of the trial. The first patient was enrolled May 31, 2022. The expected duration of enrollment will be 36 months from first subject enrollment. Subjects will be assessed for primary safety through 30 days post–hybrid sinus node–sparing ablation procedure. Primary effectiveness will be assessed at the 12-month postprocedure visit. Long-term effectiveness information will be obtained at a 24-month follow-up assessment. Independent core laboratories will be utilized for assessment of electrocardiogram and continuous rhythm monitoring (Table 1).

Primary effectiveness endpoint

The primary effectiveness endpoint is freedom from IST at 12 months. Freedom from IST is defined as mean heart rate of ≤90 beats/min or at least a 15% reduction in mean heart rate as compared with baseline, in the absence of new or higher dosage of previously failed medications (Table 2). The 15% reduction in mean heart rate was included for those with extreme mean heart rates (ie, above 110 beats/min) whose clinically relevant reduction in mean heart rate post–hybrid ablation might be below 100 beats/min but not below a mean of 90 beats/min.

In particular, the mean heart rate will be collected using 7-day continuous monitoring (baseline) and at 12 months postprocedure (follow-up) within the prespecified visit windows. Medications will include rate control drugs (beta-blockers/calcium-channel blockers, ivabradine) or antiarrhythmic drugs (AADs).

Secondary effectiveness endpoints are listed in Table 2.

Table 1 Schedule of events following SPIRIT guidelines

			Post–index procedure					
				Therapy consolidation period				
	Enrollment/baseline visit (within 30 d of procedure)	Procedure	Predischarge	1 mo	3 mo	6 mo	12 mo	24 mo
Enrollment	X							
Eligibility screen	X							
Informed consent	X							
Assessments								
Medication review	X			X	X	X	X	X
Symptom review	X			X	X	X	X	X
12-lead ECG	X		X	X	X	X	X	X
7-day heart rate monitoring	X					X	X	X
AEs (MAEs, AEs)		X	X	X	X	X	X	X
Exercise regimen*	X			X	X	X	X	X
TTE				X†		X		
6-min walk test	X					X	X	X
SAS assessment	X					X	X	X
SF-12	X					X	X	X

Unscheduled visits will include review of symptoms and medications, 12-lead ECG, MAE/AE assessment, and computed tomography/magnetic resonance imaging if clinical evidence of constrictive pericarditis and/or superior vena cava/inferior vena cava stenosis.

AE = adverse event; ECG = electrocardiogram, MAE = major adverse event; SAS = Self-Rating Anxiety Scale; SF-12 = 12-item Short Form Survey; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials; TTE = transthoracic echocardiogram.

*At physician's discretion or standard of care.

†If symptoms suggestive of delayed pericardial effusion or pericarditis are reported (eg, chest pain, shortness of breath).

Primary safety endpoint

The primary safety endpoint for the study will be defined as the incidence of device- or procedure-related major adverse events (MAEs) for subjects undergoing the hybrid sinus node–sparing ablation procedure from the index procedure through 30 days postprocedure. Permanent diaphragmatic paralysis occurring more than 30 days postprocedure and lasting for 12 months will also contribute toward the primary safety endpoint. MAEs are defined in Table 2. Phrenic nerve injury will be assessed fluoroscopically at the complete of postprocedural mapping to assure movement of the diaphragm. Additionally, chest radiographs will be obtained if the patient complaints of shortness of breath.

Study population

This clinical investigation will enroll subjects diagnosed with symptomatic IST who are refractory or intolerant to rate control drugs (eg, beta-blocker, calcium-channel blockers, ivabradine) and/or AADs. Subjects must meet all eligibility criteria and provide written informed consent to the treating physician. If any of the exclusion criteria are met, the subject will be excluded from the clinical investigation and cannot be enrolled. Full inclusion and exclusion criteria are shown in Table 3. The diagnostic criteria for IST are the following: (1) documentation of mean heart rate >90 beats/min with 7-day monitor at baseline; (2) documentation of a resting heart rate of >100 beats/min; (3) documentation of presence of IST for at least 6 months (intravenous) and documentation of absence of other tachycardias; and (4) documentation of absence of secondary causes such as hormonal issues or systemic illness that might contribute to increased heart rate.

Interventions

The ISOLATOR Synergy Surgical Ablation System delivers bipolar radiofrequency (RF) to ablate cardiac tissue (Figure 1). The goal of tissue ablation is to create scar tissue that cannot conduct electrical activity. In the case of treating IST, the tissue is ablated to isolate electrical activity in part of the heart to decrease the heart rate. The RF clamp and pen devices (EMR/EML, MAX5, MLP1) produce transmural linear ablations for targeted applications in cardiac anatomy.

Preablation investigation with transesophageal echocardiography and baseline electrophysiologic trial results are conducted to confirm that none of the following trial intraoperative exclusions are present: (1) presence of adhesions that would prevent epicardial access to the pericardial space, or the creation of the trial recommended complete lesion pattern; or (2) other mechanisms of supraventricular tachycardia discovered in the baseline electrophysiologic study during procedure.

Once the procedure intraoperative exclusion conditions have been evaluated, the procedure will proceed as follows. All procedures will be performed under general anesthesia and single lung ventilation. The right chest will be accessed via 5- to 12-mm ports, under direct visualization. The pericardium will be opened. Endocardial mapping will be performed to define structures of the right atrium (RA), SVC, and IVC and baseline electrophysiological study. The earliest SAN activation will be located and marked. Isoproterenol infusion

Table 2 Effectiveness and safety endpoints

Primary effectiveness endpoint	Freedom from IST defined as mean heart rate of ≤90 beats/min or at least a 15% reduction in mean heart rate as compared with baseline, in the absence of new or higher dosage of previously failed medications.
Secondary effectiveness endpoints	Change in 6-MWT from baseline compared with 6, 12, and 24 mo postprocedure.
	Change in Borg dyspnea severity of breathlessness and fatigue score from baseline compared with 6, 12, and 24 mo postprocedure. The Borg dyspnea score will be assessed at each of the 6-MWT.
	Change from baseline in psychological evaluation compared with 6, 12, and 24 mo postprocedure utilizing the SAS.
	IST symptom reduction at baseline and 6, 12, and 24 mo postprocedure.
	Change in QoL based on a SF-12 domain and component scores at baseline compared with 6, 12, and 24 mo postprocedure.
	Change in mean heart rate at 6, 12, and 24 mo postprocedure compared with baseline, using 7-d continuous monitoring.
	Freedom from IST or at least 15% reduction in mean heart rate at 12 and 24 mo compared with baseline, in the absence of rate control drugs (beta-blockers/calcium-channel blockers, ivabradine) and/or AADs.
	Freedom from IST or at least a 15% reduction in mean heart rate at 12 and 24 mo compared with baseline, regardless of rate control drugs (beta-blockers/calcium-channel blockers, ivabradine) and/or AADs.
	Device- or procedure-related SAEs through 12 mo.
	Improved heart rate variability for subjects using 7-d continuous monitoring.
	Improved heart rate variability and activity levels for subjects with ILRs.
	Health economics: emergency room visits and readmission.
Primary safety endpoint	Pericardial effusions with cardiac tamponade requiring surgical intervention.*
	Cardiovascular injury requiring surgical intervention.*
	Excessive bleeding requiring reoperation or 2 or more units of PBRC transfusion or results in ≥20% decrease in hematocrit within 30 d of the index procedure.*
	Pericarditis requiring surgical treatment (ie, pericardiotomy).*
	Permanent pacemaker implantation (eg, due to lack of sinus node recovery or bradycardia <40 beats/min).*
	New atrial arrhythmia as a result of the hybrid ablation procedure, requiring intervention.*
	Infection at the surgical site requiring reoperation.*
	Permanent diaphragmatic paralysis.†

6-MWT = 6-minute walk test; AAD = antiarrhythmic drug; ILR = implantable loop recorder; IST = inappropriate sinus tachycardia; MAE = major adverse event; PBRC = packed red blood cell; QoL = quality of life; SAE = serious adverse event; SAS = Self-Rating Anxiety Scale; SF-12 = 12-item Short Form Survey.
*These MAEs occurring within 30 days of the ablation procedure will contribute toward the primary safety endpoint.
†This MAE occurring after 30 days of the procedure and lasting for 12 months will also contribute toward the primary safety endpoint.

during mapping of the sinus node will be left at discretion of the treating physician. Epicardial bipolar RF ablation will be performed with minimum lesion sets at the following locations (Figure 2): (1) crista terminalis, (2) IVC (at the junction of RA, and (3) SVC (at the junction of RA). Endocardial remapping of areas for scar and electrical isolation confirmation will be performed. Endocardial and/or epicardial catheter ablation will be used to close gaps, if needed. At the end of procedure, thoracic drains will be placed, the lungs will be reinflated and pericardium and port site closed.

In particular, direct visualization in this context will require that the surgeon is able to see the heart directly, with assistance from a camera, endoscope, etc., or any other appropriate viewing technology. In certain anatomies, the physician may need to anchor the study device on the right pulmonary veins to ensure stability while completing the crista terminalis lesions.

Follow-up

Patients will be followed up in outpatient clinic at 1, 3, 6, 12, and 24 months post–index procedure. The following assessments will be completed at 1 or more visits, as outlined in Table 1: medications review; symptoms review; 12-lead electrocardiogram (subject rhythm evaluation); evaluation of any MAEs; exercise regimen, per physician discretion or per standard of care; prophylactic drugs for inflammation; and review for presence of inflammatory response or pericarditis. Furthermore, at the 6-, 12-, and 24-month visits, the following will be evaluated: 7-day heart rate monitoring, 6-minute walk test, psychological evaluation based on the Self-Rating Anxiety Scale assessment, and QoL assessment based on 12-item Short Form Survey (SF-12).

If symptoms suggestive of delayed pericardial effusion or pericarditis are reported (eg, chest pain, shortness of breath), additional testing (such as an echocardiogram) will be performed. Transthoracic echocardiogram will be performed routinely at the 6-month visit but may be performed 30 days post–index procedure if there are symptoms suggestive of delayed pericardial effusion or pericarditis.

The period from the index procedure to the 6-month postprocedure visit will be considered the therapy consolidation period. During this period, an increase in dose of rate control drugs, ivabradine, or any recurrence of episodes of IST will not be considered a treatment failure. Additionally, 1 repeat catheter ablation or intervention within the 6-month therapy

Table 3 Inclusion and exclusion criteria

Inclusion criteria	1. Age $\geq$18 y and $\leq$75 y at time of enrollment consent 2. Subject has a diagnosis of IST: a. Documentation of mean heart rate >90 beats/min with 7-d monitor at baseline and b. Documentation of a resting heart rate of >100 beats/min and c. Documentation of presence of IST for at least 6 mo d. Documentation of absence of other tachycardias e. Documentation of absence of secondary causes such as hormonal issues or systemic illness that might contribute to increased heart rate 3. Documentation of refractoriness (intolerance or failure) of a drug (eg, rate control drugs such as beta-blockers/calcium-channel blockers, ivabradine), and/or AADs 4. Subject is willing and able to provide written informed consent
Exclusion criteria	1. Subjects on whom cardiac surgery or single lung ventilation cannot be performed 2. Subjects with indication for or existing ICDs/pacemakers 3. Presence of channelopathies 4. Previous cardiothoracic surgery 5. LVEF <50% 6. BMI $\geq$35 kg/m^2 7. Presence of supraventricular or ventricular tachycardia 8. Presence of POTS 9. Presence of congenital heart disease 10. History suggestive of secondary cause of tachycardia such as pheochromocytoma, anemia, thyrotoxicosis, chronic fever of unknown origin, COPD, long-term bronchodilator use, severe asthma, or carcinoid syndrome 11. Subjects who have had a previous catheter ablation in the right atrium for IST or other disorders 12. Life expectancy <24 mo 13. Pregnant or planning to become pregnant during study 14. Subjects with substance abuse 15. Subjects with previous weight loss surgery 16. Subject is unwilling and/or unable to return for scheduled follow-up visits 17. Current participation in another clinical investigation of a medical device or a drug, or recent participation in such a study that may interfere with study results 18. Not competent to legally represent him or herself (eg, requires a guardian or caretaker as a legal representative) 19. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions, that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results

AAD = antiarrhythmic drug; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; IST = inappropriate sinus tachycardia; LVEF = left ventricular ejection fraction; POTS = postural orthostatic sinus tachycardia.

consolidation period will not be considered a primary effectiveness failure.

Statistical analysis

Standard descriptive statistics will be used to summarize numeric variables, including the number of observed values, mean, standard deviation, median, and minimum and maximum values. Summaries of categorical variables will include the number and percentage of observed values, at each level of the categorical variable.

Baseline and demographic information, including age, sex, race, ethnicity, height, weight, body mass index, and medical history will be summarized with standard descriptive statistics. Primary and secondary effectiveness endpoints, including mean heart rate and rate control drugs, ivabradine status, psychological evaluation (Self-Rating Anxiety Scale scores), IST symptoms, and change in QoL, will be summarized by visit. Categorical summaries will be based on the number of subjects with an available assessment. QoL measures will be summarized numerically including change from baseline and percent change from baseline to 12 and 24 months postprocedure follow-up.

Two-sided 95% and 90% confidence intervals will be provided for point estimates as appropriate.

Bayesian adaptive design

A Bayesian adaptive design will be used for the HEAL-IST IDE trial. This trial will have an adaptive sample size referred to as the "Goldilocks" design.[15] Interim analyses will be performed for the purpose of sample size selection and will start at 80 subjects treated and every additional 20 subjects treated thereafter: 100, 120, and 142. At each interim analysis, subjects will be at various stages of follow-up (12 months, 6 months, 30 days, newly enrolled, etc.). Beta-binomial models with noninformative prior distributions will be used to calculate the probability of trial success at each interim analysis. Based on the MAE rate and

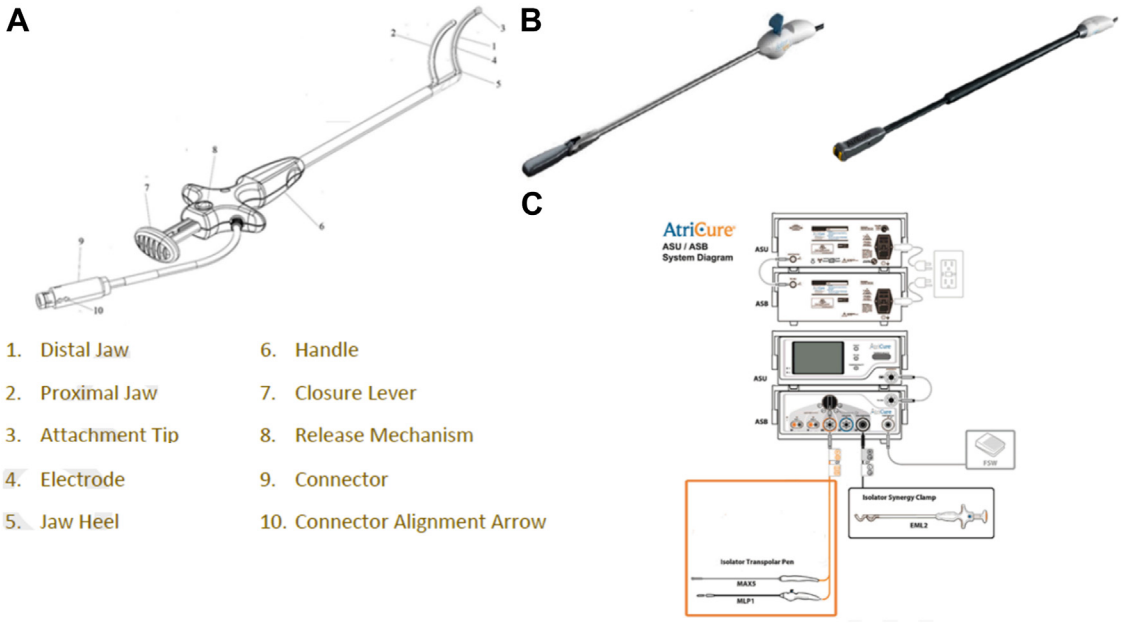

Figure 1 AtriCure ISOLATOR Synergy Surgical Ablation System. **A:** ISOLATOR clamps (EMR2/EML2): each jaw contains 2 linear electrodes located medially and axially on the centerline of each insulated jaw of the end effector. Each of the electrodes on each opposing jaw in the EMR2/EML2 is spaced 0.5 mm (0.02 inch) from the center line of the jaw and 1.0 mm (0.04 inch) apart from each other. **B:** ISOLATOR pen devices (MAX5 and MLP1) utilize radiofrequency (RF) energy from the RF generator (ablation and sensing unit [ASU]) to create lines of ablation on cardiac tissue. The devices apply the energy in a unidirectional manner and can create spot lesions the length of the end effector portion. **C:** The ASU (ASU2/ASU3/ASB3) is a portable reusable radiofrequency generator that is designed to deliver RF bipolar energy to ablate biological tissue. The ASU limits the amount of voltage, current, and time at which power is output to the handpiece.

effectiveness rate, one of the following decisions will be made with respect to sample size at each interim analysis: (1) stop accrual based on predicted futility; (2) stop accrual based on predicted success and follow all treated subjects to 12 months (primary effectiveness endpoint), at which time the decisive primary analysis is conducted; or (3) continue enrolling subjects for the next interim analysis or up to the maximum sample size (142 subjects). Subjects meeting the primary effectiveness endpoint will be labeled as responders, and the proportion of responders will be compared with a performance goal of 40%.

Sample size calculation

Based on a 40% performance goal and assuming an effectiveness success rate of 55% in the treated population, with a sample size of up to 142 subjects, the study has at least 90% power to show that the primary effectiveness success rate exceeds the 40% performance goal. For the primary safety endpoint, the MAE rate for this trial will be shown not to exceed 23.5%. The type I error for the primary effectiveness endpoint is $\leq$0.025 and for the primary safety endpoint is $\leq$0.05. The primary effectiveness analysis will be conducted

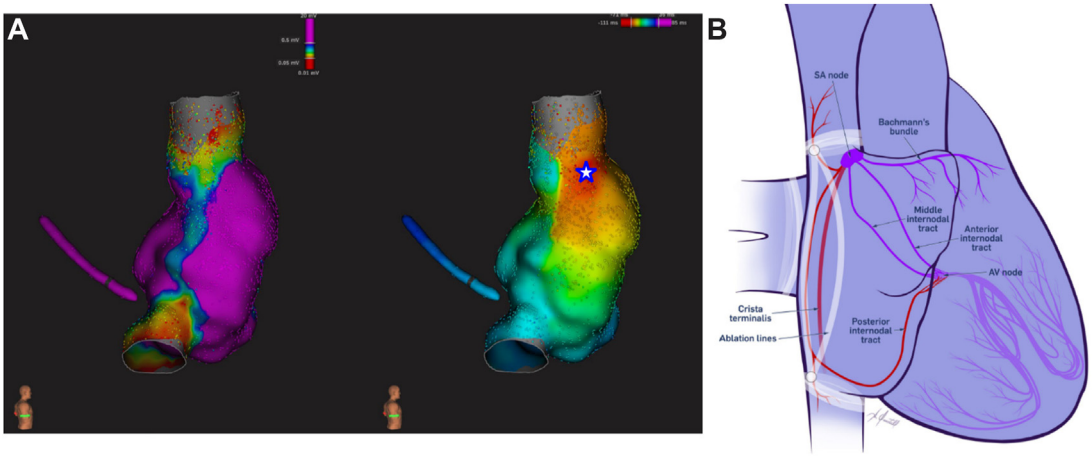

Figure 2 Hybrid sinus node–sparing ablation lines. A: Example of postablation right atrial electroanatomical voltage (left) and activation mapping (right). Ablation-induced isolation of the superior vena cava and inferior vena cava and intercaval line conduction block. The earliest atrial activation site (blue star) is consistent with physiological sinoatrial (SA) node activation. B: Anatomical representation of the ablation lesions at the superior vena cava, inferior vena cava, and intercaval region. Reprinted with permission from de Asmundis and colleagues.[14]

when all subjects have completed their 12-month post-procedure visit, or after the last 12-month visit window closes. Assuming a 36-month enrollment period, the primary effectiveness analysis is estimated to occur 48 months after the first subject is enrolled in the trial.

Organizational structure

The conduct of the clinical investigation will be approved by the appropriate IRB and EC of the respective investigational site and by the applicable regulatory authorities. This clinical investigation is funded by AtriCure.

Steering Committee

The Steering Committee consists of a group of at least 2 cardiac surgeons and 2 electrophysiologists with expertise in the treatment of IST using the hybrid sinus node–sparing ablation procedure and is responsible for overseeing the scientific and operation aspects of the clinical investigation.

Subject Selection Committee

As IST is a disease of elimination, a Subject Selection Committee comprising cardiac surgeons and electrophysiologists is instituted to review and approve subject eligibility to ensure appropriate subject selection for the trial. The Subject Selection Committee will confirm that each subject meets trial entrance criteria. This will ensure that patients with postural orthostatic tachycardia syndrome are not enrolled and to help standardize definitions between sites and countries, in which medical practices may differ.

Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) comprise independent leading physician practitioners (electrophysiologist and cardiac surgeon) and a biostatistician who are not trial investigators. Aside from being compensated for their duties as DSMB members, the DSMB members do not have any ongoing financial relationship with the Sponsor and are not involved in the conduct of the trial in any role other than that of a DSMB member. The membership of the DSMB will remain anonymous to the investigational sites to reduce any potential bias.

The DSMB will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those subjects yet to be enrolled, as well as for the purpose of the continuing validity and scientific merit of the clinical investigation.

Clinical Events Committee

The Clinical Events Committee (CEC) comprises an independent, board-certified electrophysiologist, cardiac surgeon, and neurologist who are not trial investigators. The CEC will review and adjudicate prespecified events reported by investigators or identified by safety personnel. The CEC adjudicator(s) will classify each of these adverse events based on severity and association to the device or procedure. The CEC will adjudicate the following events up to 12 months postprocedure: all MAEs included in the primary safety endpoint, regardless of seriousness; unanticipated device effects; and all adverse events potentially related to the procedure or any AtriCure devices used in the trial. Additionally, all primary safety endpoints and other adverse events determined by the CEC to be relevant will be adjudicated until the subject exits the trial.

Data collection

The Sponsor and its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation. Data will be collected via case report form (CRF) through a secure Web-based electronic data capture system accessed only by authorized personnel. The data will be subjected to consistency and validation checks within the electronic data capture system and supplemental review by the Sponsor.

Complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed informed consent forms, correspondence with the IRB and EC and clinical investigation monitor or Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation will be maintained by investigators throughout the trial. The investigator will assure the accuracy, attribution, completeness, legibility, and timelines of the data reported to the Sponsor on the CRFs and in all required reports.

Discussion

Rodríguez-Mañero and colleagues[16] performed a retrospective review of 9 studies of catheter ablation for IST with 153 patients. They not only found that, at a mean follow-up interval of 28.1 $\pm$ 12.6 months, 86.4% of patients experienced relief in symptoms, but also reported that on long-term follow-up, successful symptom relief dropped off substantially with a corresponding high recurrence rate. The results of this publication support the current class III recommendation indicated in the 2015 Heart Rhythm Society Expert Consensus on Diagnosis and Treatment of IST. The standard endocardial SAN modification approach is associated with a pacemaker implantation rate as high as 50%.[12] Endocardial only SAN ablation in symptomatic IST patients can be technically challenging; failure of endocardial SAN ablation may be either due to inadequate lesion transmurally to affect the intramural SAN pacemaker compartments within thick (>10 mm) thickness of superior crista terminalis or limited by the proximity of the phrenic nerve.[16] Jacobson and colleagues[17] suggested that due to the 3-dimensional intramural structure of the human SAN, a combined epicardial and endocardial approach to SAN ablation should be considered for refractory IST patients.

The HEAL-IST IDE trial will investigate the novel hybrid SAN-sparing ablation approach for IST; epicardial lesions are applied to electrically isolate the SAN from SVC and IVC, and an intercaval line is added.[12–14] The IVC line is performed to eliminate the potential of creating iatrogenic

atrial flutter caused by the intercaval line. The SVC ablation eliminates any superior extensions of the sinus node extending into the SVC. The main body of the sinus node is demarcated during the endocardial mapping and marked epicardially with dye, thus sparing the main body of the sinus node.[18] The efficiency of this strategy could be due to its potential targeting of increased automaticity (through local modulation of autonomic ganglia within the fat pad near the base of SVC and right pulmonary veins), SAN re-entry (through SVC, IVC and intercaval ablation lines targeting sinoatrial conduction pathways), and eventually, caval latent pacemakers or micro–re-entries (through electrical isolation of SVC and IVC).

Because of the poor success rate of endocardial ablation; high incidence of adverse events, especially pacemaker implantation; and class III indication from the HRS guidelines, a randomized trial of endocardial ablation vs the described hybrid approach in this article was not warranted. Instead, a single-arm study with a performance goal was deemed most appropriate.

The presented trial is therefore eagerly awaited to evaluate the safety and long-term effectiveness of the hybrid sinus node–sparing approach for the treatment of IST.

Conclusion

The HEAL-IST IDE trial is the first multicenter trial evaluating ablation treatment in patients diagnosed with symptomatic IST and who are refractory or intolerant to rate control drugs (eg, beta-blocker, calcium-channel blockers, ivabradine) or AADs. The results of this study will help guide medical decision making regarding the best management in this challenging population. Furthermore, long-term results of the novel hybrid sinus node–sparing ablation for the treatment of IST will be provided.

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Ethics Statement: The conduct of the clinical investigation will be conducted in accordance with the Declaration of Helsinki, applicable Good Practices and regulations, including ISO 14155: 2020, and will be approved by the appropriate IRB/EC of the respective investigational site and by the applicable regulatory authorities.

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