Hybrid Epicardial and Endocardial Sinus-Node SpAring AbLation Therapy for Inappropriate Sinus Tachycardia

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This IDE trial is proposed herein to gather clinical data on the safety and effectiveness of a hybridsinus node sparing ablation procedure utilizing the AtriCure ISOLATOR Synergy Surgical AblationSystem to obtain an IST indication.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON56360

Source
ToetsingOnline

Brief title
HEAL-IST IDE-study

Condition

- Cardiac arrhythmias

Synonym
Inappropriate Sinus Tachycardia (IST)

Research involving
Human

Sponsors and support

Primary sponsor: AtriCure, Inc
Source(s) of monetary or material Support: AtriCure;Inc.

Intervention

Keyword: Ablation, heart rhythm, Inappropriate Sinus Tachycardia, IST

Outcome measures

Primary outcome

Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from IST at 12-months. Freedom from IST is defined as mean heart rate of <= 90bpm or at least a 15% reduction in mean heart rate as compared to baseline, in the absence of new or higher dosage of previously failed medications.

Note:

• Mean heart rate will be collected using 7-day continuous monitoring (baseline) and at 12months post procedure (follow-up) within the pre-specified visit windows.

The primary safety endpoint for the study is defined as the incidence of device or procedurerelated major adverse events (MAEs) for subjects undergoing the hybrid sinus node sparing ablation procedure from the index procedure through 30-days post procedure

The following MAEs occurring within 30-days of the ablation procedure will contribute toward the 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 packed red

blood cells (PBRC) transfusion or results in >= 20% decrease in hematocrit (HCT) within 30 days of index procedure)

* Pericarditis requiring surgical treatment (i.e., pericardiotomy)

* Permanent pacemaker implant (e.g., due to lack of sinus node recovery or bradycardia <40bpm)

* New atrial arrhythmia as a result of the hybrid ablation procedure, requiring intervention

* Infection at the surgical site requiring reoperation

The following MAE(s) occurring after 30 days of the procedure and lasting for 12-months will also contribute toward the primary safety endpoint:

* Permanent diaphragmatic paralysis

All MAEs will be adjudicated by the Clinical Events Committee (CEC), thus maintaining the objectivity of the primary safety endpoint.

Secondary outcome

Key secondary effectiveness endpoints include, but may not be limited to:

* Change in 6-Minute Walk Test (6-MWT) from baseline compared to 6-, 12- and 24-months post-procedure

* Change in Borg dyspnea severity of breathlessness and fatigue score from baseline compared to 6-, 12- and 24-months post-procedure. Borg dyspnea score will be assessed at each of the 6-MWT

* Change from baseline in psychological evaluation compared to 6-, 12- and 24-months postprocedure utilizing the Self-Rating Anxiety Scale (SAS)

* IST symptom reduction at baseline, 6-, 12- and 24-months post-procedure

* Change in QoL based on a Short Form Survey (SF-12) domain and component scores at baseline compared to 6-, 12- and 24-months post- procedure

* Change in mean heart rate at 6-, 12- and 24-months post-procedure compared to baseline,using 7-day continuous monitoring

* Freedom from IST or at least 15% reduction in mean heart rate at 12- and 24-months compared to 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-months compared to baseline, regardless of rate control drugs (beta-blockers/calcium channel blockers, ivabradine) and/or AADs

* Device or procedure related Serious Adverse Events (SAEs) through 12-months

* Improved heart rate variability for subjects using 7-day continuous monitoring

* Improved heart rate variability and activity levels for subjects with implantable loop recorders (ILRs)

* Health Economics: ER visits and readmission

Study description

Background summary

Background
Inappropriate Sinus Tachycardia (IST) is a debilitating condition in otherwise healthy patients,
resulting in a significant loss in quality of life. IST is characterized by an elevated heart rate of
>100 bpm at rest with spikes of the heart rate well over the normal range during mild exertion,
very mild stress or even while resting. When the body is under stress from

exercise, psychological
events or other internal and external stressors, it responds with an
exaggerated heart rate.
Clinical manifestations range from patients who are totally asymptomatic to
suffering
incapacitating, incessant tachycardia. Common complaints include palpitations,
lightheadedness,
pre-syncope, syncope, orthostatic intolerance, chest pain/pressure, dyspnea,
and exercise
intolerance (usually caused by issues with heart variability). Low heart rate
variability generally
indicates that the body is under stress from exercise, psychological events, or
other internal or
external stressors. Non-cardiac symptoms are frequent as well, such as anxiety,
depression,
abdominal discomfort, myalgia, insomnia, and headaches. No set criteria exist
for diagnosing
IST, therefore, it commonly is a diagnosis of exclusion, once other possible
causes of tachycardia
have been ruled out. As IST is the presence of a sinus tachycardia in otherwise
healthy patients,
the mechanism is different than for any other tachycardia. Mechanisms for IST
are believed to
amount to a form of dysautonomia, an intrinsic sinus node problem, or both.
However, a
consistent mechanism has yet to be identified.

Prevalence
IST occurs mostly in young females, and there is an associated emotional and
psychological
aspect which can cause severe distress and anxiety. Because IST is not always
recognized,
many patients are misdiagnosed with panic attacks and mental, or emotional
disorders. It is not
uncommon for them to be diagnosed with depression.

The estimates of IST prevalence vary from 1% to 1.2% of the general population.

Inappropriate Sinus Tachycardia Treatment
There are little evidence-based treatment options for IST. Drug treatments such
as beta blockers or calcium channel blockers are generally chosen as the first
line of treatment
but have not proven effective. Ivabradine, an inhibitor of the hyperpolarizing
sodium current,
is a more recent drug that has exhibited better results. Data has suggested
that a combination
of ivabradine and metoprolol might be safe and effective or Ivabradine may also

provide benefits
when added to a beta-blocker therapy.

Radiofrequency (RF) catheter ablation involving sinus node (SN) ablation has been a potential
alternative in patients with IST refractory to medical therapy13. Often, the symptoms worsen or
necessitate a permanent pacemaker. Other complications include phrenic nerve damage or
transient superior vena cava syndrome. It is generally felt that the risks involved outweigh the
benefit of this treatment.
Because of the complex psychosocial relationship to IST, treatment often involves a multidisciplinary
approach. Managing the heart rate does not always relieve the distress the patient has been experiencing1.
Other treatment options have included, erythropoietin, fludrocortisone, volume expansion,
compression garments, phenobarbital, clonidine, psychiatric evaluation, and exercise training.

Much like the treatment of Atrial Fibrillation, multi-disciplinary treatment should only be sought for
symptomatic patients. For the treatment of IST, AtriCure is proposing a novel procedure, whereby
a cardiac electrophysiologist (EP) and a cardiac surgeon (Surgeon) collaborate in a single
procedure. The EP uses an endocardial mapping catheter to identify the location of the sinoatrial
(SA) node, and the Surgeon uses AtriCure ablation devices to create a lesion set designed to
reduce the heart rate while sparing the SA node. The SA node is a complex structure in the heart
that is integral for the regulation of sinus rate. This procedure differs from current forms of ablation
to treat IST performed by an EP alone, in which the SA node is modified or excised. In addition,
AtriCure proposes that this novel procedure should only be considered after lifestyle changes and
drug therapy have been administered and failed. This requirement coincides with our discussions
with experts in the field and current Heart Rhythm Society (HRS) guidelines.

Rationale for Conducting this Clinical Investigation
IST is a prevalent and debilitating condition in otherwise healthy younger patients, resulting in
significant loss of quality of life, lacking effective treatment options or

systematic clinical evidence
to support a therapy.

Study objective

This IDE trial is proposed herein to gather clinical data on the safety and effectiveness of a hybrid
sinus node sparing ablation procedure utilizing the AtriCure ISOLATOR Synergy Surgical Ablation
System to obtain an IST indication.

Study design

This is a prospective, multi-center, pivotal, single arm IDE trial sponsored by AtriCure, Inc.

Intervention

Abblation for all included subjects.

Study burden and risks

The SA node is a complex and tightly controlled structure in the heart that is integral for the regulation of sinus rate. Adverse events that may be anticipated in this clinical trial are believed to be consistent with those associated with other invasive surgical and cardiac procedures.
Complications may occur at any time during the procedure, post procedure or follow-up period.
Possible adverse events may include, but are not limited to, the following:

AEs related to Device Only
Ablation or burns to non-target tissues
Atrial arrhythmia (needing ablation for typical atrial flutter, atypical right atrial flutter, or ectopic atrial tachycardia)
Bradycardia
Junctional rhythm or an atrial escape rhythm (irreversible after hybrid ablation procedure
New Arrhythmia other than IST (abnormal heart rhythm other than atrial fibrillation)
Newly developed second- or third-degree AV block (interruption of heart rhythm) requiring a permanent pacemaker
Pulmonary vein stenosis (narrowing of pulmonary veins that bring oxygen-rich blood from the lungs back to the heart)

AEs related to Procedure Only
Air embolism (small amounts of air often get into the blood circulation)

Anesthesia risks
Aneurysm (a balloon-like bulge in an artery)
Asymptomatic cerebral embolism
Atelectasis (collapsed lung)
Cardiac tamponade (compression of the heart due to blood or fluid build-up in space between the myocardium (the muscle of the heart) and the pericardium (the outer covering sac of the heart)
Deep sternal wound if converted to sternotomy
Drug or Contrast Media Reaction (significant reaction to any medications requiring treatment, including allergic reaction and anaphylactic shock) [serious allergic reaction may include low blood pressure, trouble breathing, seizures and death]
Endocarditis (an inflammation of the heart*s valves or inner lining)
Excessive pain and discomfort
Formation of unwanted scar tissue
Hemothorax (a collection of blood in the space between the chest wall and the lung)
Hemorrhagic stroke secondary to anticoagulant therapy
Hypertension (high blood pressure)
Hypotension (low blood pressure)
Infection or fever
Myocardial Infarction (MI)
Persistent Chest Pain
Pneumonia (inflammation or infection of then lungs)
Pneumothorax (accumulation of air in the space between the lung and the chest wall)
Post-surgical atelectasis (collapse of a lung)
Pseudoaneurysm (collection of blood within the wall of an artery)
Pulmonary Edema (fluid accumulation in the lungs)
Pulmonary embolism (blood clot in the lungs)
Radiation exposure (X-ray)
Reaction to contrast media/ medication (allergic reaction to X-ray dye or medicine)
Renal insufficiency or failure (abnormal kidney function)
Respiratory distress or failure (breathing problems)
Vascular access site complications (complications in the area where the catheter was inserted such as bruising, swelling, or vessel injury, including the development of a hematoma, an AV fistula, or a pseudoaneurysm requiring intervention such as surgical repair)

AEs related to both Device and Procedure
Arterial or venous dissection and/or perforation (a separation of the layers of a blood vessel/a hole in the blood vessel)
Arterial rupture (a tear in the artery)
Atrial rupture (a tear in the upper chamber of the heart)
Bleeding (loss of blood, which may require a transfusion, conversion to sternotomy or thoracotomy or another operation)

Cardiac Perforation (tear to your heart)
Cardiac Valve or Coronary Artery Injury (injury to a heart valve or heart artery)
Cerebrovascular accident (Stroke) or other neurologic event (a stroke or *brain attack* or other neurologic issue)
Chest pain/discomfort from port site or visceral pain from ablation
Damage to adjacent nerve and/or blood vessels
Death
Diaphragmatic paralysis (partial or stopped movement of your diaphragm, resulting in difficulty breathing)
Emergency during the operation requiring change in the planned surgical access (such as opening the chest through the breastbone)
Hematoma (a bruise)
Intercostal nerve injury
Ischemia (lack of blood flow and oxygen to a part of the body)
Pericarditis requiring pericarditis which could cause an effusion that leads to hemodynamic compromise or requires pericardiocentesis or re-operation
Pericardial Effusion (an abnormal accumulation of fluid around the heart)
Phrenic nerve injury (temporary or permanent phrenic nerve paralysis)
Sepsis (a blood infection)
Significant Chest Wound Infection (requiring intervention and/or antibiotics)
Thoracotomy
Ventricular perforation or rupture (a hole in the ventricle)
Wound Infection at surgical site requiring re-operation for wound debridement

There may also be other risks that are unforeseen at this time.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. The risk associated with trial-required testing and assessments are summarized in the table below. Although routine, these tests and assessments may be performed at greater frequency than SOC practices.

History, Clinical Status, QoL, Surveys, 6-Min Walk & Physical Exam: Risks: None, Minimal
Laboratory testing:
Risks: Minimal. Usual risks associated with phlebotomy
ECG:
Risks: None, Minimal
echocardiography, TTE:
Risks: None, Minimal
Computer tomography angiography (CTA) Risks: A separate written informed consent consistent with clinic policies and practices will occur

outside of trial

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >= 18 years and <= 75 years at time of enrollment consent
2. Subject has a diagnosis of IST:
a. Documentation of mean heart rate > 90bpm with 7-day monitor within 90 days of the Index Procedure and;
b. Documentation of a resting heart rate of >100bpm and;
c. Documentation of presence of IST for at least 6-months
d. Documentation of absence of other tachycardia
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 (e.g., 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 cardio-thoracic surgery
5. Left Ventricular Ejection Fraction (LVEF) < 50%
6. Body Mass Index (BMI) >= 35
7. Presence of supraventricular or ventricular tachycardia
8. Presence of Postural Orthostatic Sinus Tachycardia (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 bronchodilators use,
severe asthma or carcinoid syndrome
11. Subjects who have had a previous catheter ablation in the right atrium for IST or other disorders;
Allowed catheter ablation in the right atrium:
a) One previous catheter ablation > 90 days prior to the Index Procedure for AVRT or CTI
b) One previous catheter ablation > 180 days prior to the Index Procedure for AVNRT
12. Life expectancy < 24 months
13. Pregnant or planning to become pregnant during trial
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 trial that may interfere with trial results
18. Not competent to legally represent him or herself (e.g., requires a guardian or caretaker as a legal representative) and;
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

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-09-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	AtriCure ISOLATOR Synergy Surgical Ablation System comprised of: Isolator® Clamp (EMR2/EML2) / Isola
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	22-09-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-12-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05280093
CCMO	NL82643.068.22