

Bipolar Catheter Ablation for the Treatment of Refractory Scar-Related Ventricular Arrhythmia

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PROTOCOL SUMMARY

Title:

Bipolar Catheter Ablation for the Treatment of Refractory Scar-Related Ventricular Arrhythmia

Objective:

This study will examine the safety and efficacy of irrigated bipolar radiofrequency (RF) ablation in the treatment of intramural ventricular tachycardia (VT) in patients for whom standard VT unipolar RF ablation has been unsuccessful. We hypothesize that the increased current density and improved rates of transmural lesion creation seen with bipolar RF ablation will lead to successful arrhythmia termination with minimal or no increased risk of complication.

Design:

This is a prospective, multi-center, non-randomized, un-blinded, observational trial.

Enrollment:

Eligible subjects will be consented for participation in the trial prior to undergoing VT ablation. Patients are considered eligible to undergo bipolar ablation if they meet the following criteria 1.) evidence of ischemic or non-ischemic VT; 2.) intramural VT not terminable with unipolar ablation once enrolled in the Bipolar study, OR 3.) failed unipolar VT ablation within the past 6 months prior to enrollment. Patients will be excluded from the trial if: 1.) history of MI or CABG within 6 weeks; 2.) Class IV HF; 3.) pregnant; 4.) unable to sign consent; 5.) projected lifespan of < 1 year; Patients are considered enrolled once consented. Patients who do not undergo VT ablation within 90 days of enrolling will be considered to be screen failures. Patients successfully terminated with unipolar ablation once enrolled will be followed in a registry for 6 months, (adhering to the same post-procedure schedule as the patients that underwent bipolar ablation).. Two hundred subjects are expected to be enrolled in the study.

Clinical Sites:

1. Mount Sinai Hospital, New York, NY
2. Loyola University Health System, Maywood, IL
3. Brigham and Women's Hospital, Boston, MA
4. University of Pennsylvania, Philadelphia, PA
5. Texas Cardiac Arrhythmia Research Foundation
6. Beth Israel Hospital, Boston, MA
7. Homolka Hospital, Prague, Czech Republic

Time Course:

Expected duration of patient enrollment is approximately 2 years.

Subject Description:

Subjects will only be eligible for this study if they are ≥ 18 years of age and have a history or suspected history of VT.

Primary Endpoints:

1. Freedom from recurrent VT at 6 months
2. Procedural complications (death, stroke, myocardial infarction, heart failure, conduction abnormalities, pericardial effusion requiring drainage, hematoma, pseudoaneurysm)

Secondary Endpoints:	<ol style="list-style-type: none"> 1. Post-ablation inducibility 2. Time to termination 3. Total duration of bipolar ablation 4. All-cause mortality
Primary Analytical Analysis:	N/A
Secondary Analytical Analysis:	N/A
Principal Investigator:	<p>Srinivas Dukkipati, M.D. Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA</p>
Site, Monitoring, and Data Management Center	<p>Electrophysiology Clinical Research Group Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA</p>
Events Adjudication Committee:	TBD
Data Safety and Monitoring Board:	<ul style="list-style-type: none"> • Dr. Jonathan Halperin Icahn School of Medicine at Mount Sinai New York, NY Cardiologist • Dr. Arash Aryana Regional Cardiology Associates Medical Group Sacramento, Ca. Electrophysiologist • Dr. Shephal Doshi Pacific Heart Institute Santa Monica, Ca. Electrophysiologist

1 CONTACT INFORMATION

PRINCIPAL INVESTIGATOR:

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1.1 STUDY SITES & INVESTIGATORS

Site	Principal Investigator
1. Mount Sinai Hospital	Srinivas Dukkipati, MD
2. Loyola University Health System	David Wilber, MD
3. Brigham and Women's Hospital	Usha B. Tedrow, MD, M.Sc.
4. Penn Cardiovascular Institute	Pasquale Santangeli,MD
5. Texas Cardiac Arrhythmia Research Foundation	Andrea Natale, MD
6. Beth Israel Hospital	Elad Anter, MD
7. Homolka Hospital	Petr Neuzil, MD

2 STUDY OBJECTIVE

This prospective, multicenter observational study will examine the role of irrigated bipolar radiofrequency (RF) ablation for the treatment of intramural ventricular tachycardia in patients who have failed standard unipolar RF ablation. We hypothesize that the increased current density and improved rates of transmural lesion creation seen with bipolar RF ablation will lead to successful arrhythmia termination with minimal or no increased risk of complication.

3 INTRODUCTION, RATIONALE

Radiofrequency (RF) ablation is the most commonly employed method for the catheter treatment of cardiac arrhythmias. Myocardial scar serves as the most frequent substrate for the genesis of both atrial and ventricular arrhythmia. Such scar frequently contains surviving myocyte bundles interspersed with fibrotic tissue, which leads to slow conduction. Areas of denser fibrosis cause conduction block. When appropriately arranged, conduction through or around these scars leads to the creation of a “reentry” circuit through which an arrhythmia is generated and maintained.¹ Each reentry circuit contains within it an area called the isthmus, a portion of the circuit located in a position intimately related to the scar border zone. Electrical activation travels slowly through the isthmus before breaking out into normal myocardium. Ablation at the site of an isthmus will terminate a reentrant tachycardia.²

A variety of techniques, including electroanatomic mapping and activation, entrainment, and substrate mapping, are employed during electrophysiologic (EP) study to identify areas of myocardial scar and potential isthmus sites. Points or lines of ablation using RF energy are then created in an attempt to interrupt the reentry circuit. Typically, unipolar RF energy is applied via a catheter tip electrode to the

endocardial or epicardial surface of the heart and grounded via an electrode pad placed on the patient's skin. RF energy in this setting is dispersed through the entirety of the tissue between catheter tip and grounding pad. The standard 7-French, 4-mm tip catheters are highly successful at ablating circuits located within a few millimeters of the catheter tip. A focal, 1mm area of resistive heating occurs within the myocardium immediately in contact with the catheter tip; myocardial cell death occurs several millimeters more deeply through passive, conductive heating, which spreads outward from the contact point.³

While the standard catheter is effective at the ablation of superficial arrhythmias, it has proven more problematic when used for deep myocardial sites or for creating transmural lesions. A number of alternatives have been developed in an attempt to access these sites. 8-mm or 10-mm catheter tips are able to create larger zones of resistive heating, delivering direct RF energy to a larger area of myocardium. A larger interface between catheter tip and blood improves cooling and allows for the delivery of more power without a rise in impedance.⁴ The clinical use of these larger catheters can, however, be limited by rapid temperature rises at the catheter-tissue interface, resulting in thrombus formation, char, and "steam pop" rupture of the endocardial surface.⁵ The use of irrigated ablation catheters have improved upon the ability to deliver RF energy without a sustained rise in impedance. Both open irrigated- and closed-loop irrigated catheters circulate saline along the catheter tip-myocardial interface, allowing for continued delivery of RF current without thrombus formation at the endocardial surface. Intramyocardial temperature rises accordingly without a concomitant endocardial temperature surge, creating larger and deeper myocardial ablation zones.⁶⁻¹⁰ Catheters featuring a retractable needle tipped electrode with intramyocardial saline infusion have also shown promise as a means of accessing deep myocardial circuits in ventricular tachycardia ablation, but are not currently available in the US.¹¹⁻¹³ Transcoronary ethanol ablation has also been employed with moderate success in patients with arrhythmias resistant to endocardial catheter ablation.¹⁴ This technology, however, grants only limited control over the size of the resulting infarct and is restricted by the need for perfusion of the scar zone by an accessible coronary artery.

Nevertheless, there remain occasions in which an arrhythmia cannot be eliminated by standard unipolar ablation technique. This is seen most frequently due to deep intramural ventricular tachycardia, sometimes encountered following myocardial infarction. Both standard and alternative ablation strategies are frequently either unavailable or inadequate for termination of these arrhythmias.

Recently, several centers have employed irrigated bipolar ablation (BA) to target arrhythmias not amenable to unipolar ablation. During BA, two catheters are connected to either pole of an RF generator, allowing either catheter to function as the "active" catheter and the other the "return" catheter. Rather than being dispersed between the catheter tip and a distant grounding pad, BA concentrates energy between two catheter tips positioned on opposing sides of a target scar. BA may thus improve lesion transmurality through synergistic, simultaneous heating and increased current density leading to concentrated thermal injury.¹⁵⁻¹⁷

Initial experience in the use of BA technology in mammalian hearts demonstrated that it could successfully be applied to create discrete areas of myocardial necrosis with minimal risk of complication. When compared to unipolar ablation, several studies suggested that BA could create larger areas of necrosis and transmural lesions with only rare episodes of perforation.¹⁵⁻²⁷ Subsequent experience in human hearts was predominantly surgical: a large number of observational studies and reviews demonstrated the effectiveness and safety of BA in patients undergoing pulmonary vein isolation and Cox-Maze surgery as either isolated procedures or as adjuncts to valve replacement or coronary artery bypass surgery.^{24, 28-50}

Despite its broad use during surgical ablation, the application of BA during catheter-based therapies is limited. Recently, our group demonstrated the utility of BA in both an in vitro model and in a series of patients with arrhythmia resistant to unipolar ablation.⁵¹ When compared to unipolar RF ablation, BA was found to be more likely to achieve transmural lesions in a porcine heart model (33% vs 82%, respectively, $p = 0.001$) and could do so in tissue up to 25 mm thickness. Clinically, all septal atrial flutters, 5 of 6 septal VTs, and 2 of 4 free-wall VTs were successfully acutely terminated.

The proposed study will further examine the role of BA in patients with ventricular tachycardia resistant to standard ablation techniques.

4 DEVICES AND PROCEDURES

4.1 HARDWARE / SOFTWARE / CATHETERS

The product consists of the CARTO V3 system (Biosense Webster, Inc.) preserving all existing functionalities with small software and hardware changes to allow the connection of an additional ablation catheter as an indifferent electrode for use of a bipolar ablation mode.

Hardware:

The bipolar ablation mode objective is to enable the performance of bipolar ablation between two therapeutic catheters. This mode is enabled by a special cable solution that allows the connection of a second therapeutic catheter to the Stockert 70 radiofrequency generator through the PIU REF/DECA port. The cable is based on the regular ablation catheter, modified to allow ablation while maintaining the magnetic location and all other existing capabilities.

Software:

The system displays the distance (tip to tip) between the Map and Ref/Decca catheters in the map viewer in order to simplify the position of the two catheters when ablating. The distance indication includes a connecting line between the two catheters, numerical value (in mm) and color change according to a user-defined threshold. The conventional ablation tag on the ablation catheter is replaced by new —bipolar ablation mode tag that is displayed for each of the ablation catheters (dual point). The —ablation mode can be activated/deactivated by the user and has additional safety protections.

Catheters:

Two of four types of Biosense Webster Thermocool catheters will be used during bipolar ablation in the following configuration:

1. THERMOCOOL®SMARTTOUCH® Catheter, NAVISTAR® THERMOCOOL® Catheter, Or THERMOCOOL® SF or SF NAV Catheter, connected to the MAP socket of the PIU
2. THERMOCOOL® SF Catheter (D-1313-XX or D-1315-XX), connected to the REF/DECA socket of the PIU

The Diagnostic/Ablation Deflectable Tip Catheters are 7.5 F luminal catheters with deflectable tips designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency current to the catheter tip electrode for ablation purposes. For ablation, the catheters are used in conjunction with a radiofrequency generator (Stockert 70, described above) and a dispersive pad (reference electrode). The catheters have a high-torque shaft with a deflectable tip section containing an array of platinum electrodes. All of the electrodes may be used for recording and stimulation purposes. The tip electrode

serves to deliver radiofrequency current from the radiofrequency generator to the desired ablation site. The tip electrode and ring electrodes are made from platinum-iridium. The catheters incorporate either a thermocouple or thermistor temperature sensor that is embedded in the 3.5 mm tip electrode.

The Thermocool Navistar and SmartTouch catheters are currently FDA-approved for ventricular tachycardia ablation. The Thermocool SF catheters are currently FDA-approved only for ablation of atrial arrhythmias.

4.2 ABLATION PROCEDURES

Unipolar Ventricular Tachycardia Ablation

Hemodynamic support to allow for entrainment mapping will be employed with either an intra-aortic balloon pump or with a percutaneous left ventricular assist device (Impella 2.5, Abiomed, Inc, Danvers, MA). All mapping will be performed with a hybrid magnetic/impedance-based mapping system (Carto, Biosense Webster, Diamond Bar, CA). LV endocardial and epicardial mapping was performed by utilizing a transseptal and subxiphoid puncture approach, respectively. Prolonged, split, or isolated late potentials will be tagged. For unipolar RF, power will be set to 30–50 W at 30-cm³ irrigation, targeting an impedance drop of >10 Ω. In the epicardium, power will be set to 15–30 W with 5-ml/min irrigation. The use of the percutaneous left ventricular assist device in patients with VT allows for prolonged mapping during VT. Termination during VT was therefore the preferred initial strategy for these patients, followed by substrate modification. The procedural end point was the non-inducibility of VT.

Bipolar Ventricular Tachycardia Ablation

BA will be performed across two 3.5-mm externally irrigated catheters (Thermocool). Catheters will be positioned at locations determined on the basis of activation or entrainment mapping. The catheter on the left side of the heart (in the left ventricle) will connect to the ablation catheter connection on the RF generator (Stockert, Biosense Webster, Diamond Bar, CA). The second catheter, located in the right heart (right ventricle) or epicardium will be connected to the indifferent electrode connection via a custom cable, which allows visualization of electrograms from 4 poles of the second catheter while simultaneously allowing the distal electrode to be the indifferent electrode. Ablation will be initiated with a power of 30 W in the ventricle (limiting catheter tip temperatures to < 42-45°C) and then titrated to a maximum of 35 W over 60-90 seconds for an impedance drop of up to 30-40 Ω. Ablation will be terminated or the power down-titrated if a sudden rise in temperature or a rapid fall or rise in impedance is seen.

5 SCHEDULE OF TREATMENT AND TESTS

TABLE 1: SCHEDULE OF TREATMENTS AND TESTS:

	Baseline	Procedure	Discharge	Telephone Follow-up (2 weeks +/- 3 days)	Follow-up Visit (6mo, +/- 2 weeks)
Type of visit	Office	Hospital		N/A	Office
Informed Consent	X				
Brief History & Physical	X				X
Blood Laboratory Testing: CBC, Electrolytes, BUN/Creatinine, BNP, INR, LFTs	X				X (as indicated)
TTE	X				
CT/MRI	X				
ICD Interrogation	X				X
EKG	X				X
Medications	X	X	X	X	X
Adverse Events		X	X	X	X

* Patients who screen fail will be placed in a registry and will continue to be followed throughout the study, adhering to the same post-procedure schedule as the patients who underwent bipolar ablation.

6 ENDPOINTS

6.1 Primary Endpoint

1. Freedom from recurrent VT at 6 months, defined as sustained ventricular tachycardia lasting longer than 30 seconds and identified due to clinical symptoms or during device interrogation.
2. Procedural complications (death, stroke, myocardial infarction, heart failure, conduction abnormalities, pericardial effusion requiring drainage, hematoma, pseudoaneurysm)

6.2 Secondary Endpoints

1. Post-ablation inducibility
2. Time to termination
3. Total duration of bipolar ablation
4. All-cause mortality

7 STUDY SUBJECTS

7.1 INCLUSION CRITERIA

1. ≥ 18 years of age.
2. The study will include all forms of scar VT--both ischemic (post-myocardial infarction) and non-ischemic (e.g. sarcoid, amyloid, dilated)--as determined by cardiac MRI and/or voltage mapping at the time of VT ablation.
3. Intramural VT not terminable with unipolar ablation once enrolled in the Bipolar study or previous failed unipolar ablation within 6 months prior to enrollment.
4. Ability to understand the requirements of the study and sign the informed consent form.
5. Willingness to adhere to study restrictions and comply with all post- procedural follow-up requirements
6. Projected lifespan greater than 1 year.

7.2 EXCLUSION CRITERIA

1. Tissue Thickness less than 5 mm as assessed by electroanatomic mapping, CT, or MRI.
2. MI or CABG within 6 weeks.
3. NYHA Class IV CHF.
4. Women known to be pregnant or to have positive beta-HCG.
5. Participation in another study that would interfere with this study.

8 SAMPLE SIZE

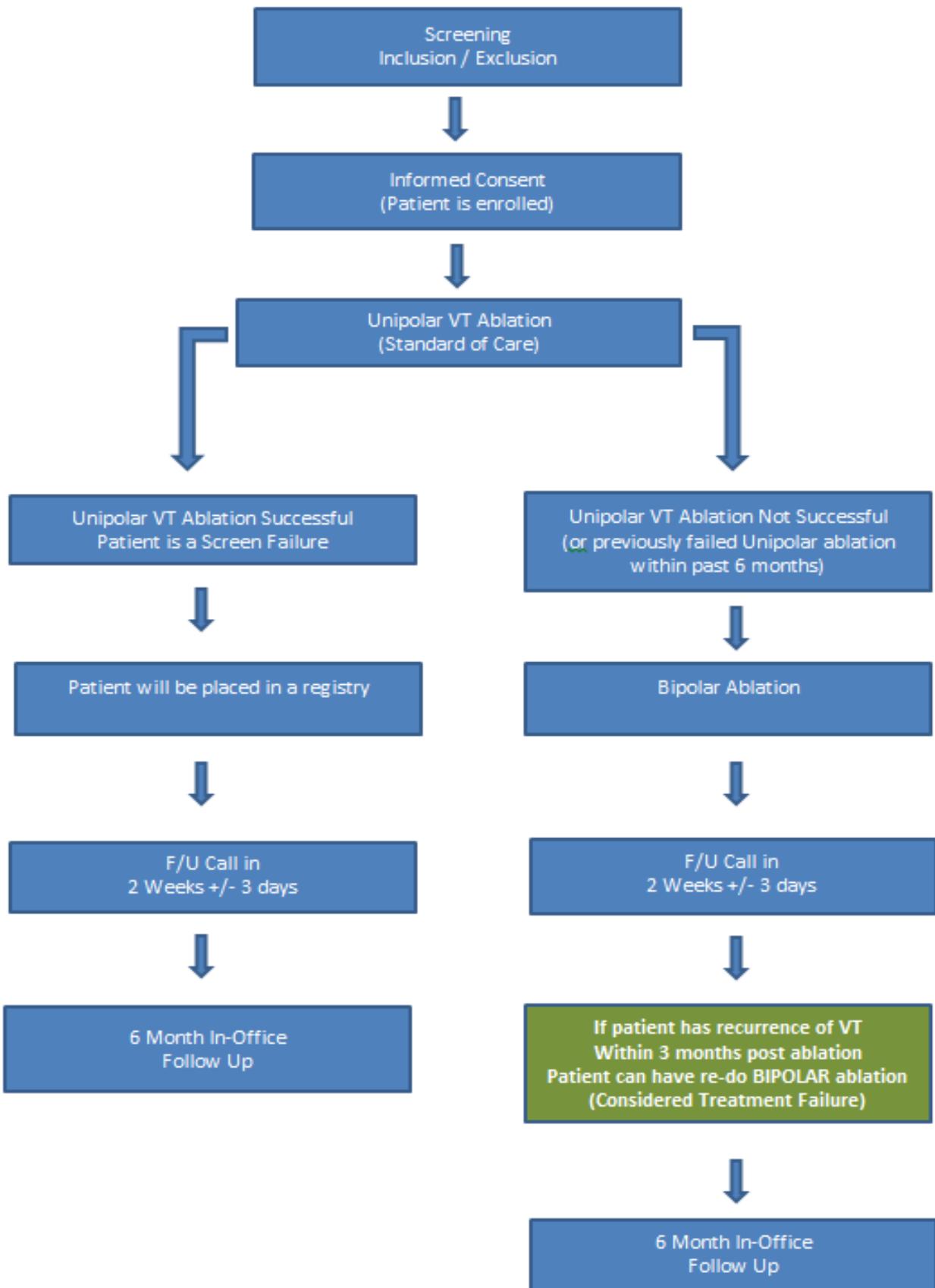
This safety and efficacy study will enroll 200 patients across 6 US centers and 1 OUS center. This number has been determined on the basis of study feasibility and not by statistical means.

9 PATIENT ENROLLMENT AND WITHDRAWAL

Patients meeting the study inclusion criteria will be identified in the outpatient or inpatient setting by one of the study sites' primary or co-investigators. Patients will be followed by one of the study site primary or co-investigators. Approximately 100 patients are expected to participate each year, with an expected total enrollment of 200 patients.

The study will typically be described (including the risks and benefits) during the initial clinic or hospital visit. Consent will typically be obtained at the time of the initial assessment if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be encouraged to take a copy of the consent form home to contemplate whether he/she would like to be enrolled in the study (see Appendix 1 for informed consent form.) Only patients who voluntarily provide consent will be included in this study. Consent will be obtained prior to undergoing the ablation procedure. Patients will be able to withdraw from the study at any point without compromising their medical care. All data will be de-identified and protected in accordance with institutional and HIPAA guidelines, including 1) de-identification of all geographic subdivisions smaller than a state; 2) all elements of dates related to the individual; 3) telephone and fax numbers; 4) email addresses; 5) social security, medical record, health plan beneficiary, account, and certificate/license numbers; 6) vehicle identifiers; 7) device identifiers; 8) URLs and IP addresses; 9) biometric identifiers; and 10) photographic images.

Eligible subjects will be consented for participation in the trial prior to undergoing VT ablation. Patients are considered eligible to undergo bipolar ablation if they meet the following criteria 1.) evidence of ischemic or non-ischemic VT; 2.) intramural VT not terminable with unipolar ablation once enrolled in the Bipolar study, OR 3.) failed unipolar VT ablation within the past 6 months prior to enrollment. Patients are considered enrolled once consented. Patients who do not undergo VT ablation within 90 days of enrolling will be considered to be screen failures. Patients successfully terminated with unipolar ablation once enrolled will be followed in a registry for 6 months (adhering to the same post-procedure schedule as the patients that underwent bipolar ablation).



10 STUDY PROCEDURES

10.1. PRE-PROCEDURE EVALUATION

Patients will be consented for the study in either the inpatient or outpatient setting. The consent will detail the use of unipolar RF energy as part of standard of care in all patients undergoing VT ablation, and bipolar ablation as an experimental procedure employed only if patient had an unsuccessful unipolar ablation within six months prior to enrollment or if the index unipolar ablation procedure proves unsuccessful. Unsuccessful unipolar ablation is defined as the inability to terminate VT or VT that is still inducible following unipolar ablation.

The following tests and procedures will occur before the ablation as a routine part of pre-procedural medical assessment:

- Recording of patient medical history (including details of VT both clinical/ICD)
- Recording medication history (including all anti-arrhythmic drugs used and duration of use)
- Obtain β -HCG in females of child bearing age the morning of the procedure as per usual clinical practice
- Baseline assessment of arrhythmia burden and type: Office/inpatient records, ICD interrogation report
- If performed for any reason, review and collect any pre-procedural imaging: MRI/CT, echocardiograms
- Baseline laboratory, including complete blood count, standard electrolyte panel, renal function, and brain natriuretic peptide levels.
- Consent must be obtained before the VT ablation procedure.

10.2 PRE-PROCEDURE MEDICATION MANAGEMENT

Management of pre-procedural anti-platelet and anti-thrombotic medications will be at the discretion of the primary operator. Typically, however, these medications will be continued through the procedure. Every effort will be made to maximize beta-blocker, ACE-i/ARB, and aldosterone antagonist therapy per current guidelines.

10.3 VT ABLATION PROCEDURAL DETAILS

- Patients will be brought to the electrophysiology laboratory in a fasting state.
- General anesthesia will be used for sedation.
- Patients will undergo electrophysiology study and VT ablation as per standard practice.
- If a patient's arrhythmia cannot be eliminated with standard unipolar ablation or if the patient has failed unipolar ablation within the previous six months the patient will undergo a bipolar ablation. The bipolar hardware/software will be employed as described above.
- Therapeutic anticoagulation will be administered with intravenous heparin with a target ACT of 300 seconds or greater.
- Esophageal temperature monitoring is required when ablation is performed in the coronary sinus or epicardium irrespective of whether unipolar or bipolar ablation is performed. Ablation should be stopped when esophageal temperature is $\geq 38.5^{\circ}\text{C}$.

10.4 POST-PROCEDURE

10.4.1 POST-PROCEDURE FOLLOW UP

- All patients will be monitored to verify vascular hemostasis prior to discharge from the hospital.
- The majority of patients will receive either warfarin or a novel oral anti-coagulant (dabigatran, rivaroxaban, or apixaban) for 4-6 weeks post-procedure. Those patients with less extensive ablations may receive oral aspirin (81-325 mg daily) or clopidogrel (75 mg daily). These decisions will be made at the discretion of the primary operator per current guidelines.
- A proton pump inhibitor is recommended for any significant esophageal temperature rises noted during the procedure as determined by the treating physician. However, if the esophageal temperature is noted to have been $\geq 41.0^{\circ}\text{C}$, a proton pump inhibitor is required for a minimum of 4 weeks following the ablation procedure.
- Medication and adverse event review will be performed prior to discharge.
- Complications including vascular, stroke, heart failure, pericardial effusion, tamponade, bleeding, and death will be documented.
- The total number of episodes of VT, ATP, and shocks will be documented at all visits.
- The follow-up includes:
 - 2 weeks: Telephone follow up
 - Assessment for adverse events or recurrent arrhythmia.
 - 6 months: In-office follow up
 - History and Physical
 - Electrocardiogram
 - ICD interrogation (may be trans-telephonic)
 - Review of medications and adverse events

10.4.2 POST-PROCEDURE MEDICATION MANAGEMENT

- Standard cardiovascular medications are left up to the discretion of the investigator. Beta-blockers, ACE-i/ARBs, and aldosterone antagonist use is recommended as per standard guidelines.
- Therapeutic anticoagulation beyond the requisite 4-6 week post-procedure time point will be at the discretion of the patient's physician.

10.4.3 REPEAT VT ABLATION PROCEDURES

- A repeat bipolar VT ablation may be performed within 90 days post procedure at the discretion of the physician and will be deemed a treatment failure.

11 SAFETY

We anticipate no significant increase in adverse events as compared to the standard VT or AT ablation procedures. The local site primary investigator will oversee the safety of the study at his/her site. All adverse events will be reported to the DSMB. The DSMB will consist of one Cardiologist and two electrophysiologists. The PI will also be present at the meetings to relate any pertinent trial information. However, recommendations are solely up to the discretion of the DSMB.

Adverse Events

An adverse event is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an adverse event unless there is a change in the nature, severity or degree of the condition.

Serious Adverse Event

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

Unanticipated Serious Adverse Event

An unanticipated (unexpected) serious adverse event is any serious adverse event that is not protocol-defined or documented in the patient consent form. Expedited reporting is required for serious adverse events that are unexpected.

Unanticipated Adverse Device Effects

An unanticipated adverse device effects (UADE) is any serious adverse effect on health or safety or any life-threatening problem caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

Event Recording

The following adverse events will be captured throughout the period of trial participation:

- Protocol-defined (as described below)
- Serious unanticipated events (serious “*Other*” adverse events)

Causality

The investigator will assess the relationship of an adverse event to the intervention. Causality will be defined as follows:

Probable

Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the ablation procedure. The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the intervention, and
- The event is a known reaction to the intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

Possible

Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after intervention, and
- The event is not a known reaction to intervention, but cannot be explained by a commonly occurring alternative etiology

Unlikely

Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to intervention and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the intervention, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the intervention.

Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects

All investigators must report both expected (protocol-defined) and unexpected SAEs. All protocol defined SAEs must be reported directly to the clinical center's IRB and the DCC within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths, UADEs, and unexpected SAEs that are possibly or probably related to the BIPOLAR VT ablation must be reported to the DCC and the clinical center's IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All *unexpected SAEs* that are *unlikely related to the study intervention* must be reported to the DCC and the clinical center's IRB within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

The DCC will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

Reporting of Unanticipated Problems

All *UPs* that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All UPs that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

DCC Reporting to FDA

The DCC will report unexpected SAEs that are possibly or probably related to the investigational device or UADEs to FDA as appropriate. The DCC will send an initial IDE safety report communication to the FDA within 2 business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of a UADE for this IDE trial.

Data and Safety Monitoring Board

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The DSMB will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. The FDA will be provided a copy of any written communication from the DSMB to the study sponsor related to safety concerns within 10 days. FDA will also be notified within 10 days if the DSMB requires changes to the study protocol, procedures or informed consent document. The DSMB will be provided a copy of any letter from the FDA to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The clinical centers will have no contact with the members of DSMB regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DSMB members will not be allowed during DSMB closed meetings.

Event Adjudication Committee

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all adverse events and causes of mortality. The individuals who will serve on the committee are unaffiliated with the clinical sites and the DCC, and will be appointed by the DCC. The committee will consist, at least, of a statistician, a cardiologist, and an electrophysiologist. The EAC will meet every 6 months or as needed to review outcomes data for each subject enrolled.

Interim and Futility Analyses

An interim or futility analyses will be performed after the enrollment of 20 subjects. This analysis will be presented to the DSMB, who has the authority to terminate the study prematurely if an increase in adverse events is encountered. If the DSMB determines the trial should be stopped early either because of efficacy or safety concerns, or otherwise modified, the DSMB will prepare formal written recommendations to the PI to consider final action. Moreover, any pressing safety concerns that the DSMB identifies will be verbally communicated to the PI as soon as possible, prior to written documentation. The trial will be terminated early if severe procedure-related adverse events occur in more than 15% of patients.

12 RISKS

Patient confidentiality risks associated with any research study are minimal and include: breach of confidentiality and loss of personal data.

As the protocol includes a *standard of care* VT ablation procedure, *the risks of the procedure are generic to a standard VT procedure, and include the following:*

Potential Risks Associated with VT Ablation

- Death: End of Life (1%).
- Cardiogenic shock: when the heart has been damaged so much that it is unable to supply enough blood to the organs of the body (<1%).
- Complete Heart Block: complete absence of conduction from the atria to the ventricles during a stable supraventricular rhythm (2%).
- New incessant VT/VF: new arrhythmias may occur as a result of damage to the heart's electrical system. It may be necessary to shock your heart to stop the rhythm (<1%).

- Acute Myocardial Infarction (MI): blocked blood supply to the heart that may cause damage to the heart muscle and affect how you feel and how well your heart can pump blood. This is often treated with drugs or may require surgical repair (1.5%).
- Stroke (also called Cardiovascular Accident or CVA): may cause an interruption in the blood supply to a part of the brain (~2-4%).
- Pericarditis: inflammation may occur in the outer lining of the heart (<1%).
- Cardiac perforation causing pleural effusion or tamponade: fluid build-up around the heart. A hole in your heart wall (*perforation*) could result in bleeding into the sac, called the pericardium, which surrounds your heart (*cardiac tamponade*). This may be treated by insertion of a needle, through your chest wall, into the sac and removal of the blood. This type of hole sometimes requires surgical repair (1.5%).
- Adverse effects on implantable pacemakers, cardioverters, and defibrillators. An example is dislodgement of ICD leads: (<1%).
- Coronary artery occlusion: a partial or complete block of blood flow in a coronary (heart) artery (<1%).
- Heart Valve injury (also called Valvular Damage/Insufficiency): an injury to a valve structure resulting in a loss and/or worsening of function (e.g., worsening of regurgitation score or prolapse) (<1%).
- Acute Pulmonary edema: fluid accumulation (build-up) in the lungs (<1%).
- Pulmonary embolism: blockage of a pulmonary artery; a blood clot from a vein may get stuck in the lungs. This is usually treated with drugs (<1%).
- Vascular access complications: an obstruction or perforation or damage to the vascular (blood vessel) system (2%).
- Arterial/venous thrombus: clot formation in the artery or vein (1.5%).
- AV fistula: an abnormal passageway (such as a hole) between an artery and a vein; this may allow blood to go between the arteries and veins and not through the entire body. This may cause some part of the body to not receive the usual amount of blood. This may heal on its own, but may require surgical repair (1.5%).
- Catheter insertion site hematoma: bleeding or bruising from the site of catheter placement. This may go away without treatment, but may require manual compression or surgical repair. If excessive bleeding at the site of the catheter placement continues, this could result in anemia requiring medical intervention (2%).
- Esophageal injury: the esophagus is located in close proximity to the left atrium and ventricles. Esophageal injury may occur from radiofrequency ablation and most often heals on its own. In rare situations, a communication may develop between a cardiac chamber and the esophagus. This may present as fever, hematemesis, gastrointestinal bleeding, or stroke. This complication requires emergency surgical repair and is associated with a high mortality. The incidence of a fistula forming between a cardiac chamber and the esophagus following ventricular tachycardia ablation is very rare (<0.1%).
- Hemo-pneumothorax: bleeding in the chest (also called hemothorax); blood may leak into the chest cavity putting pressure on internal organs like your lungs (also called hemo-pneumothorax). This may be treated by using a needle or suction to remove the excess blood or it may require surgical repair. Pneumothorax may also occur when gas or air is present in the pleural (chest) cavity (<1%).
- Hypoxia: reduced oxygen supply to tissue (<1%).
- Infection, Localized or systemic: an infection may occur anywhere an incision or cut is made during the procedure (<1%).
- Peripheral venous thrombosis: blood clots in the vein (<1%).

- Phrenic nerve damage: damage to the nerve that controls the diaphragm and may affect your breathing. Symptoms may be temporary but in some cases can be permanent (respiratory arrest) (<1%).
- Pneumonia: infection of lungs or gathering of fluid in the lungs (<1%).
- Pseudoaneurysm: development of a false pouch in the vessel wall. This can be caused by movement of catheters in the blood vessels. This may heal on its own, but sometimes need surgical repair (<1%).
- Radiation injury resulting in dermatitis (skin burns): (<1%).
- Respiratory failure: damage to breathing that can be permanent (respiratory arrest) (<1%).
- Radiation exposure during the fluoroscopic imaging of the catheters during ablation: this may slightly increase the lifetime risk of developing a fatal malignancy or a genetic defect in offspring (<1%).
- Fluid overload: excessive fluid built up could result in pulmonary (lung) edema; congestive heart failure (CHF) may occur or may be exacerbated (worsened) due to delivery of sterile salt water (saline) during the procedure (these risks are specific to open irrigated ablation catheters) (1.5%).

There are risks associated with an epicardial ablation if this is performed

- RV puncture with no clinical consequence: a rupture or hole (perforation) in the right ventricular heart of no clinical significance (15%).
- Pericardial bleeding: blood in the pericardial sac (~7%).
- Hemoperitoneum: blood in the peritoneal cavity due to damage to abdominal vessel / organ (<1%).
- Coronary Artery Damage: see definition for Coronary Artery Occlusion above (~0.6%).
- Phrenic Nerve Damage: see definition for Phrenic Nerve Damage above (~0.6%).
- Pleural damage: see definition for Hemo-pneumothorax above (~1.5%).
- MI: see definition for acute myocardial infarction above (~0.6%).
- Tamponade: see definition for Cardiac Perforation above (~4%).
- Abdominal bleeding: uncontrolled bleeding in the abdomen (~ 0.5%).
- Pericarditis: see definition of Pericarditis above (~21%).
- Esophageal injury: the esophagus is located in close proximity to the left atrium and ventricles. Esophageal injury may occur from radiofrequency ablation, particularly in the epicardium and the coronary sinus. This most often heals on its own. In rare situations, a fistula may develop between a cardiac chamber and the esophagus. This may present as fever, hematemesis, gastrointestinal bleeding, or stroke. This complication requires emergency surgical repair and is associated with a high mortality. The incidence of a fistula forming between a cardiac chamber and the esophagus following ventricular tachycardia ablation is very rare (<0.1%).
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13 STUDY MANAGEMENT

13.1 Study Data Collection and Processing

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Patients will be identified by a 5-digit number and their initials. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers) for their own reference. All study-related documents

(CRFs, source medical records, regulatory binder) must be kept in a secure, locked environment with access limited to study personnel only.

The PI is responsible for ensuring the following: 1) adherence to the protocol; 2) verifying adherence to local regulations on the conduct of clinical research; and 3) ensuring completeness, accuracy, and consistency of the data entered in the CRF.

Final CRFs in human readable format must be reviewed and verified for accuracy by the study site Principal Investigator and signed-off. A copy of the final CRF will remain at the investigator's site at the completion of the study.

The CRF numbering convention is as follows:

01 - 2 3 4 A -B -A

01: Site # must be 2 digits (use leading zero) --- (sites 01-10)

2 3 4: patient screening/enrollment # (001 – 500)—must be 3 digits

A-B-A: Patient initials (if no middle initial, use dash)

Total 5 digits and initials for enrolled patients.

13.2 Confidentiality

Patient information will be kept confidential and managed according to the 1996 HIPAA guidelines. Each patient will be given a unique subject number and will be identified by this number and their initials. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is protected.

13.3 Deviations from Protocol

The investigator will not deviate from the protocol except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the IRB/EC must be notified within five days of the incident.

13.4 Role of the Coordinating Center

As principal investigator and study sponsor of this clinical study, Srinivas Dukkipati, MD assumes the overall responsibility for the conduct of the study, including assurance that the study meets national and institutional guidelines for study conduct. In this study, Srinivas Dukkipati, MD will have certain direct responsibilities and will delegate other responsibilities to his staff at the Coordinating Center, the Icahn School of Medicine at Mount Sinai. The coordinating center will: 1) ensure adherence to the national and institutional regulations; 2) develop and distribute protocols and case report forms; 3) coordinate data organization; 4) perform statistical analyses; 5.) provide on-site and remote monitoring.

13.5 Withdrawal of Subjects

A subject may withdraw from the study at any time should they choose to do so. Additionally, subjects may be withdrawn by the investigator if deemed appropriate due to safety or compliance issues.

13.6 Economic Impact on Subjects

There are no additional costs related to involvement in this study. Since the cost of the procedure will be included within the Disease Related Group (DRG) charge, neither patient nor insurance provider will incur additional cost.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Maintaining Records (21 CFR 812. 140 (B))

All clinical sites will maintain study records for two years after research termination. The Coordinating center will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial.

14.2 Institutional Review Board (IRB) / Ethics Committee (EC) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by the IRB/EC before the change is made.

The study site Principal Investigator(s) is responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

15 CLINICAL CENTERS

The study will be conducted in up to 6 sites in the United States and 1 in Europe. Each clinical center will be required to obtain IRB/EC approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the DCC with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile

All cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

Qualifications and Training

Clinical investigators will be electrophysiologists with expertise in VT ablation. The certified operator will either perform the ablation on their own patient, or participate in the ablation of an enrolled patient. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

16 DATA HANDLING

Information about patients will be kept confidential and managed according to the requirements of the United States of American Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

1. What protected health information (PHI) will be collected from patients.
2. Who will have access to that information and why.
3. Who will use or disclose that information.
4. The rights of a research patient to revoke their authorization for use of their PHI.

In order to ensure patient confidentiality, all case report forms and patient information (CT / MRI, if reviewed), fluoroscopic and endoscopic images, ECGs) will be de-identified and replaced with a unique patient identifier. Information will be stored in the office of the local study coordinator, which will be kept in a secure, locked location. The research study coordinators, principal investigator and co-investigators will be the only personnel with access to this data. All data will be stored without any patient information apart from the unique three digit patient identifier. Electronic data will be encrypted and password-protected.

17 DATA ANALYSIS

Baseline clinical characteristics (e.g. age, gender, renal function) and procedural characteristics (e.g. surface intracardiac electrogram, and imaging findings) of the patients will be collected and analyzed. All continuous variables will be performed as the mean \pm standard deviation, and all categorical variables as a percentage of the total study population.

The co-primary endpoints of safety and efficacy will display events as a percentage of the total study population. Bar charts may be employed to demonstrate such data.

Secondary data analysis will display continuous variables as the mean \pm standard deviation, and all categorical variables as a percentage of the total study population.

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