Intramural Needle Ablation for the Treatment of Refractory Ventricular Arrhythmias
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Intramural Needle Ablation for the Treatment of Refractory Ventricular Arrhythmias

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PROTOCOL SUMMARY

Title:	**Intramural Needle Ablation for the Treatment of Refractory Ventricular Arrhythmias**
Objective:	This study will examine the safety and efficacy of intramural needle ablation (INA) in the treatment of intramural ventricular arrhythmias in patients for whom standard RF ablation has been unsuccessful. We hypothesize that the increased current density and improved rates of transmural lesion creation seen with intramural needle ablation will lead to successful arrhythmia termination with minimal or no increased risk of complication.
Design:	This is a prospective, single-center, non-randomized, un-blinded, observational trial.
Enrollment:	Eligible subjects will be consented for participation in the trial prior to undergoing ablation. Patients are considered eligible to undergo intramural needle ablation if they meet the following criteria 1) a) monomorphic ventricular tachycardia (VT); b) frequent ventricular arrhythmia (including unifocal PVCs, couplets, or nonsustained VT) with a PVC burden ≥ 13%, or is causing a decline in left ventricular (LV) ejection fraction to ≤40%; or c) previous failed ablation for one or more of the criteria above, 2) Age 16 or older; 3) Left ventricular (LV) ejection fraction > 10% as estimated by echocardiography, contrast ventriculography or radionuclide imaging within the past 90 days; 4) Clinical indication for catheter ablation of VT; 5) Ventricular arrhythmias not terminable with standard ablation once enrolled in the Intramural Needle Ablation study or previous failed ablation within 6 months prior to enrollment; 6) Able and willing to comply with all pre-, post-, and follow-up testing and requirements; 7) Signed informed consent (for patients < 18 years old, parental consent will be obtained with patient assent); 8) Projected lifespan greater than 1 year. Patients will be excluded from the trial if:1) history of MI or CABG within 6 weeks; 2) Class IV HF; 3) Idiopathic ventricular arrhythmias defined as VT or PVCs that occur without evidence of structural heart disease and that are not causing significant depression of LV function; 4) pregnant; 5) Definite protruding left ventricular thrombus on pre-ablation echocardiography or other imaging modalities; 6) contraindication to heparin; 7) allergy to radiographic contrast dye; 8) unstable angina that is not due to frequent or incessant VT; 9) acute non-cardiovascular illness or systemic infection; 10) thrombocytopenia (platelet count < 50,000 mm^3) or coagulopathy; 11) cardiogenic shock unless it is due to incessant VT; 12) unable to sign consent; 13) projected lifespan of < 1 year. Patients are considered enrolled once consented. Patients who do not undergo ablation of ventricular arrhythmias within 90 days of enrolling will be considered to be screen failures. Patients successfully terminated with standard ablation once enrolled will be followed in a registry for 6 months, (adhering to the same post-procedure schedule as the patients that underwent intramural needle ablation). Two hundred subjects are

	expected to be enrolled in the study.
Clinical Sites:	Mount Sinai Hospital, New York, NY
Time Course:	Expected duration of patient enrollment is approximately 2 years.
Subject Description:	Subjects will only be eligible for this study if they are ≥ 16 years of age and have a history or suspected history of ventricular arrhythmias.
Primary Endpoints:	1. Freedom from recurrent ventricular arrhythmias at 6 months 2. Procedural complications (death, stroke, myocardial infarction, heart failure, conduction abnormalities, pericardial effusion requiring drainage, hematoma, pseudoaneurysm)
Secondary Endpoints:	1. Post-ablation inducibility 2. Time to termination 3. Total duration of intramural needle ablation 4. All-cause mortality *(For patients who have been re-enrolled after the six-month follow-up is complete, primary and secondary endpoints will be re-assessed at six months post-second procedure.)*
Primary Analytical Analysis:	N/A
Secondary Analytical Analysis:	N/A
Study Sponsor:	Vivek Reddy, M.D. Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
Principal Investigator:	Srinivas Dukkipati, M.D. Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
Site, Monitoring, and Data Management Center	Electrophysiology Clinical Research Group Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
Data Monitoring Committee:	TBD

1 CONTACT INFORMATION

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1.1 STUDY SITES & INVESTIGATORS

Site	Principal Investigator
Mount Sinai Hospital	Srinivas Dukkipati, MD

2 STUDY OBJECTIVE

This prospective, single center observational study will examine the role of intramural needle radiofrequency (RF) ablation for the treatment of intramural ventricular arrhythmias in patients who have failed standard RF ablation. We hypothesize that the increased current density and improved rates of transmural lesion creation seen with intramural needle 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 arrhythmias. 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]

RF ablation is also commonly used for the treatment of isolated premature ventricular contractions (PVCs), couplets, and non-sustained VT that occur in patients without structural heart disease. However, when frequent, ventricular ectopy can result in left ventricular dysfunction and increased risk of congestive heart failure. PVC-induced cardiomyopathy appears to be a distinct entity from tachycardia-induced cardiomyopathy. Patients who develop cardiomyopathy have overall heart rates similar to those with PVCs who do not develop LV dysfunction.[3] But higher PVC burdens clearly portend greater risk for cardiomyopathy. One study reported a 24% PVC burden to have the best combination of sensitivity and specificity in identifying patients likely to develop cardiomyopathy, though LV function improvements occur following catheter ablation with PVC burdens as low as 10%.[4] In a four-center study, a 13% PVC burden predicted, with 100 percent sensitivity and 85 percent specificity, an absolute increase of 5% in the LV ejection fraction after catheter ablation.[21]

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. Similarly, activation or pace-mapping is also used to identify the site of origin of PVCs. Typically, 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.[5]

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.[6] 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.[7] 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.[8-12] Transcoronary ethanol ablation has also been employed with moderate success in patients with arrhythmias resistant to endocardial catheter ablation.[13] 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 ablation techniques. 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.

Initial experience with an electrically active needle electrode have demonstrated that radiofrequency ablative energy can effectively create lesions of homogeneous necrosis.[14] Needle electrodes have been used experimentally from the epicardial surface, from the endocardium ex vivo and in vivo in an internally irrigated form.[15-18] It has been shown that the use of a narrow-gauge non-irrigated endocardial needle ablation catheter creates very narrow but deep lesions due to the small electrode size.[19] 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.[20]

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

4 DEVICES AND PROCEDURES

4.1 HARDWARE / SOFTWARE / CATHETERS

The needle-tipped ablation catheter is a deflectable catheter with a distal bipole (dome and ring electrodes) with an extendable/retractable 27-gauge nitinol needle. The needle has a central lumen through which saline can be infused. It has an embedded thermocouple and a position sensor within the tip which is compatible with an electroanatomic mapping system (Carto; Biosense Webster). The needle can be extended or retracted to adjust the depth. It can be locked in position at the desired depth. In its fully retracted position, it is entirely within the catheter tip, whereas, when fully deployed, it extends 12 mm beyond the tip. The depth of extension can be preset and the needle can be locked in position with an adjustable plunge activator. During catheter manipulation, the needle is kept retracted and irrigated with 0.9% saline (with 2 U/mL heparin) at 1 mL/min.

Recording and pacing are possible from both the external electrodes and from the needle. Bipolar recordings are generated between the needle and ring electrode (filtered 30–500 Hz), and between the needle and an inferior vena cava electrode, as well (filtered 30–500 Hz, and separately, filtered 0.5–500 Hz).

At target sites of VT circuits, the catheter tip is placed roughly perpendicular to the endocardial surface. Infusion is discontinued and the needle is extended 7 to 9 mm into the myocardium. One ml of infusate (50% NaCl solution [with 2U/mL heparin], 50% iopamidol [76%]) is injected into the myocardium, after which heparinized saline (2 U/mL, 0.9% NaCl) is infused at 1 mL/min for 60 s. Myocardial staining with contrast is confirmed with fluoroscopy to ensure intramyocardial positioning and to rule out perforation. Temperature-controlled power is delivered for 60 to 90 s with temperature limited to 60°C and power limited to <35 W.

4.2 ABLATION PROCEDURES

Standard Ablation Technique for Ventricular Arrhythmias:
The standard ablation procedure will be performed using the Biosense-Webster Thermocool SF catheter (Diamond Bar, CA, USA). Hemodynamic support to allow for entrainment mapping may be employed with either an intra-aortic balloon pump or with a percutaneous left ventricular assist device. All mapping will be performed with a hybrid magnetic/impedance-based mapping system (Carto, Biosense Webster, Diamond Bar, CA). LV endocardial and epicardial mapping will be 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-cm^3 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 ventricular tachycardia (VT) allows for prolonged mapping during VT. Termination during VT will therefore the preferred initial strategy for these patients, followed by substrate modification. The procedural end point will be non-inducibility of VT.

Intramural Needle Ablation of Ventricular Arrhythmias;
INA will be performed with Intramural Needle Ablation catheter, a retractable needle-tipped catheter (Biosense Webster, Inc., Diamond Bar, CA, USA). The catheter will be positioned at locations determined on the basis of activation or entrainment mapping. Saline solution (0.9% NaCl, 19°C) will be infused through the needle into the myocardium at 1 mL/min for 60 seconds using an automatic injector (Mark V, Medrad, Pittsburgh, PA, USA). Ablation will be initiated with RF energy (500 kHz, Stockert-70 RF Generator, Stockert GMBH, Freiburg, Germany) which will be delivered between the needle and a skin patch electrode. Power will be manually titrated between 30-50 W (limiting catheter tip temperatures to < 60ºC) 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 (within 30 days)	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 (within 3 months)				
CT/MRI (optional)	X (within 3 months, if done)				
***24-Hour Ambulatory Monitor**	X (within 3 months)				X
ICD Interrogation	X				X
Ablation Procedure		X			
EKG	X				X
Medications	X	X	X	X	X
Adverse Events		X	X	X	X

*24-hour ambulatory monitoring will only be required for those undergoing ablation for frequent ventricular arrhythmia (defined as unifocal PVCs, couplets, non-sustained VT) that is causing a decline in LV ejection fraction to $\leq$40%.

Patients whose VT is successfully treated with standard ablation once enrolled 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 intramural needle ablation. Patients whose VT is not inducible and no VT ablation is performed during the procedure will also be considered screen failures. No follow-up will be performed with subjects who have no VT ablation during the procedure.

6 ENDPOINTS

6.1 Primary Endpoint

1. Freedom from recurrent ventricular arrhythmias at 6 months, defined as sustained ventricular tachycardia lasting longer than 30 seconds or a decrease in ventricular arrhythmias (defined as unifocal PVCs, couplets, non-sustained VT) to less than 5000 ventricular beats per 24 hours and identified due to clinical symptoms, device interrogation, or 24-hour ambulatory monitoring.
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 (if performed at procedure conclusion)
2. Time to ventricular arrhythmia termination (if ablation is performed during ventricular arrhythmias).
3. Total duration of intramural needle ablation
4. All-cause mortality

* - For patients who have been re-enrolled after the six-month follow-up is complete, primary and secondary endpoints will be re-assessed at six months post-second procedure.

7 STUDY SUBJECTS

7.1 INCLUSION CRITERIA

1. The study will include patients with any of the following criteria: a) monomorphic ventricular tachycardia (VT); b) frequent ventricular arrhythmia (defined as unifocal PVCs, couplets, non-sustained VT) with a PVC burden ≥13%, or is causing a decline in left ventricular (LV) ejection fraction to ≤40%; or c) previous failed ablation for one or more of the criteria above.
2. ≥ 16 years of age.
3. Left ventricular (LV) ejection fraction > 10% as estimated by echocardiography, CT/MRI, contrast ventriculography, or radionuclide imaging within the past 90 days.
4. Clinical indication for catheter ablation of VT
5. Intramural ventricular arrhythmias not terminable with standard ablation once enrolled in the Intramural Needle Ablation study or previous failed ablation within 6 months prior to enrollment.
6. Ability to understand the requirements of the study and sign the informed consent form. For potential patients aged < 18, parental consent will be required along with subject assent.
7. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.
8. Projected lifespan greater than 1 year.

7.2 EXCLUSION CRITERIA

1. History of MI or CABG within 6 weeks.
2. NYHA Class IV CHF.
3. Patients with idiopathic ventricular arrhythmias defined as VT or PVCs that occur without evidence of structural heart disease and that are not causing significant depression of LV function.
4. Women known to be pregnant or to have positive beta-HCG.

5. Definite protruding left ventricular thrombus on pre-ablation echocardiography or other imaging modalities.
6. Contraindication to heparin
7. Allergy to radiographic contrast dye.
8. Unstable angina that is not due to frequent or incessant VT.
9. Acute non-cardiovascular illness or systemic infection.
10. Thrombocytopenia (platelet count < 50,000 mm^3) or coagulopathy.
11. Cardiogenic shock unless it is due to incessant VT.
12. Unable to sign consent.
13. Projected lifespan of < 1 year.

8 SAMPLE SIZE

This safety and efficacy study will enroll up to 200 patients across 1 US center. This number has been determined on the basis of study feasibility and not by statistical means. In a similar trial, we have experienced a 66% screen failure rate; as such, with 200 patients enrolled, we expect to have approximately 70 evaluable patients who have undergone the INA procedure.

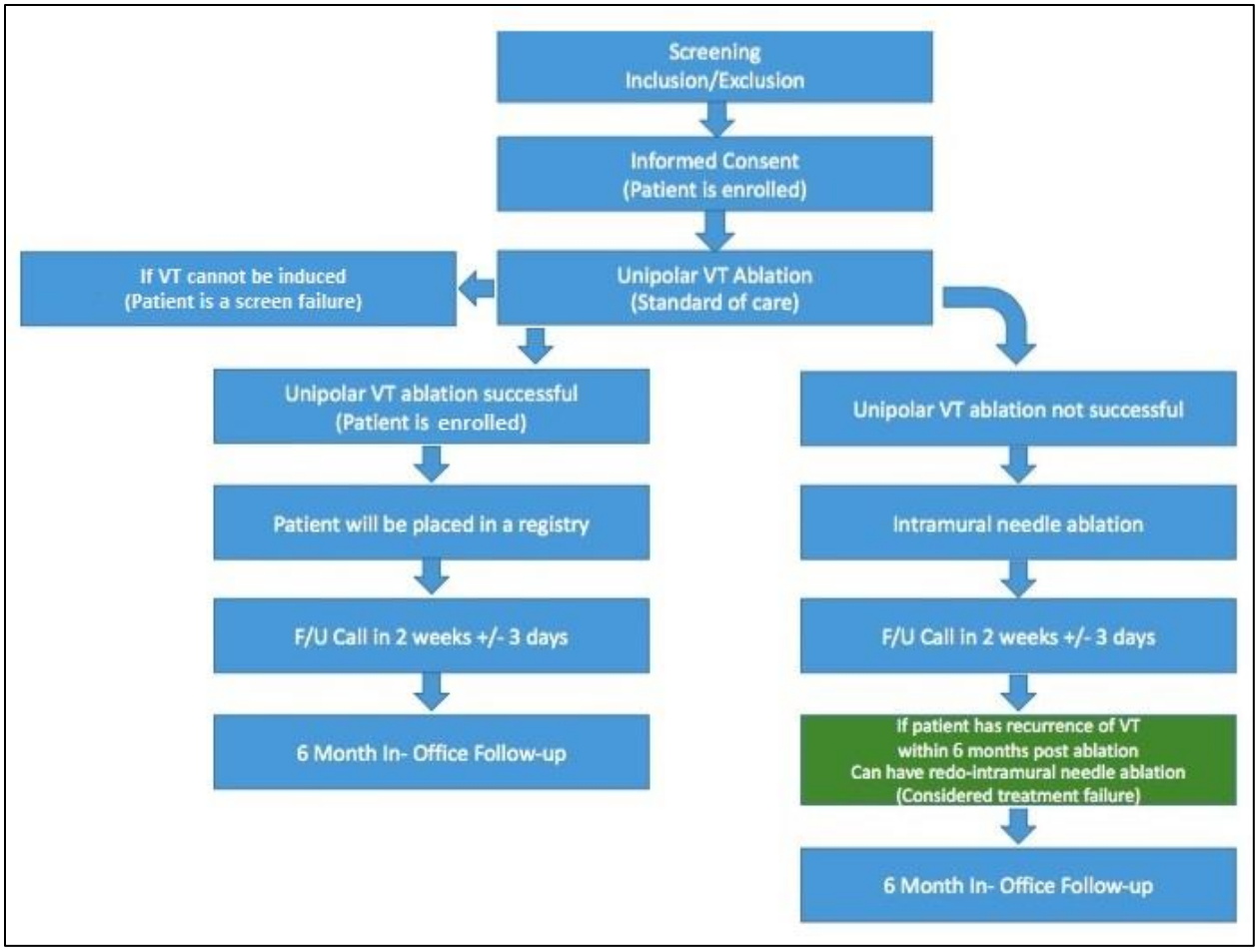
9 PATIENT ENROLLMENT AND WITHDRAWAL

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.

For potential patients aged < 18, parental consent will be required along with subject assent.

Eligible subjects will be consented for participation in the trial prior to undergoing VT ablation. Patients are considered enrolled once consented. Patients whose VT is not inducible and no VT ablation is performed during the procedure will be considered to be screen failures. No follow-up will be performed with subjects who have no VT ablation during the procedure. Patients successfully treated with standard ablation once enrolled will be enrolled and will be followed in a registry for 6 months (adhering to the same post-procedure schedule as the patients that underwent INA).



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 RF energy as part of standard of care in all patients undergoing VT ablation, and INA ablation as an experimental procedure employed only if patient had an unsuccessful ablation within six months prior to enrollment or if the index ablation procedure proves unsuccessful. Unsuccessful ablation is defined as the inability to terminate ventricular arrhythmias or ventricular arrhythmias that are still inducible following ablation.
The following tests and procedures will occur before the ablation as a routine part of pre-procedural medical assessment (all done within 30 days prior to procedure unless noted below):

- 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

- For patients being considered for PVC ablation only: 24-Hour Holter monitoring (within three months)
- Review pre-procedural imaging (within three months): MRI/CT (optional), TTE.
- 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 or conscious sedation 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 ablation or if the patient has failed ablation by standard technique, the patient will undergo INA. The INA 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 standard ablation or intramural needle ablation is performed. Ablation should be stopped when esophageal temperature is ≥38.5ºC.
- Procedural endpoint will be non-inducibility of clinical VT.

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 ≥41.0ºC, 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
    - For PVC ablation patients only: 24-Hour Holter monitoring

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.
- Use of anti-arrhythmic drugs will be at the discretion of the investigator.
- 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

- One repeat intramural needle ablation procedure may be performed within the six-month follow-up period post procedure at the discretion of the physician and the participant will be deemed a treatment failure. Additionally, should a participant finish the six-month follow-up period and require a repeat intramural needle ablation for ventricular arrhythmias at a later date, the patient may be re-enrolled and re-consented in the trial using the same identification number. Primary and secondary endpoints in these re-enrolled patients will be re-assessed at six months post-second procedure. The maximum allowable number of intramural needle ablation procedures for any participant is two, irrespective of the timing of the second procedure.

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 DMC. The DMC 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 DMC.

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 intramural needle VT ablation must be reported to the Data Coordinating Center (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 DMC chair within 72 hours of notification. All SAEs will be reported to the DMC 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 Monitoring Committee

To meet the study's ethical responsibility to its subjects, an independent Data Monitoring Committee (DMC) will monitor results during the study. The committee will consist of a cardiologist who has no formal involvement or conflict of interest with the subjects, the investigators, the sponsor or the DCC. The DMC will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DMC will review interim summary results of the accumulating data every 6 months or on an as needed basis depending on enrollment figures. 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 DMC to the study sponsor related to safety concerns within 10 days. FDA will also be notified within 10 days if the DMC requires changes to the study protocol, procedures or informed consent document. The DMC 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 DMC regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DMC members will not be allowed during DMC closed meetings.

Interim Analyses

An interim analysis will be performed after the enrollment of 20 subjects. This analysis will be presented to the DMC, who has the authority to terminate the study prematurely if an increase in adverse events is encountered. If the DMC determines the trial should be stopped early because of safety concerns, or otherwise modified, the DMC will prepare formal written recommendations to the PI to consider final action. Moreover, any pressing safety concerns that the DMC 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.

The risks associated with an intramural needle ablation catheter are expected to be similar to those for ablation of ventricular arrhythmias with standard ablation catheters.

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 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%).
- Post-procedural hypotension defined as: systolic blood pressure of < 80 mmHg or hypotension that requires administration of vasopressors (~20%).

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 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%).

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 of this clinical study, Srinivas Dukkipati, MD assumes the overall responsibility for the conduct of the study at Mount Sinai. In this study, Srinivas Dukkipati, MD will have certain direct responsibilities and will delegate other responsibilities to his research staff and 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 at 1 site in the United States. 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 ± 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 ± standard deviation, and all categorical variables as a percentage of the total study population.

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