REnal Sympathetic dEnervaTion as an adjunct to catheter-based VT Ablation
RESET-VT
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VERSION 1.3

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PROTOCOL SUMMARY

Title:	**RESET-VT**
Objective:	The goal of this trial is to test the impact of catheter-based renal sympathetic denervation (RSDN) as an adjunctive treatment for patients with either ischemic or non-ischemic cardiomyopathy undergoing catheter ablation of ventricular tachycardia (VT). The proposed study is a prospective, multicenter, randomized control trial. Patients undergoing VT ablation will be randomized to either VT ablation alone or VT ablation + RSDN.
Design:	This study is a prospective, multicenter, single-blinded, randomized (1:1) control trial evaluating the effectiveness of RSDN in the prevention of recurrent VT in patients with ischemic or non-ischemic ventricular dysfunction who are undergoing catheter ablation for VT. These patients will be randomized to ablation alone or ablation + RSDN. Subjects will only be eligible for this study if they are ≥ 18 years of age and have a history of structural heart disease (post-MI, dilated cardiomyopathy, sarcoid myopathy, hypertrophic cardiomyopathy, etc.), have an existing ICD and are planned for catheter-based VT ablation. In addition, eligible patients will have accessible renal vasculature (as determined by renal angiography). The patient will be blinded to the results of randomization. Once randomized, study group subjects will undergo a strategy of catheter-based renal sympathetic denervation + VT ablation. Follow-up will be conducted in regular intervals over a 24-month period.
Enrollment:	Total: 202 subjects Pilot Phase: 20 subjects (~10 control group, ~10 study group)
Clinical Sites:	• Mount Sinai School of Medicine (PILOT) • Homolka Hospital, Prague, Czech Republic (PILOT) • Other Sites TBD (total up to 25 sites)
Time Course:	Initial enrollment: December 2012

Last enrollment: July 2013 (Pilot)
Last 24-month follow-up: July 2015 (Pilot)

Subject Description: Eligible subjects include those ≥ 18 years of age with a history of structural heart disease (post-MI, dilated cardiomyopathy, sarcoid myopathy, hypertrophic cardiomyopathy, etc.), have an existing ICD and are planned for catheter-based VT ablation. In addition, eligible patients will have accessible renal vasculature (as determined by renal angiography).

Study Group: In addition to VT ablation, the subjects in this group will undergo catheter-based renal sympathetic denervation.

Control Group: Subjects in the control group will undergo a standard procedure for catheter-based VT ablation.

Primary Endpoint:

1. Time to first event requiring appropriate ICD therapy for ventricular arrhythmia or Incessant VT (VT occurring below the ICD rate cut-off)

Secondary Endpoints:

1. Appropriate ICD therapy for ventricular arrhythmia
2. Appropriate ICD Shocks ventricular arrhythmia
3. Inappropriate ICD therapy
4. All ICD therapy (Appropriate + Inappropriate)
5. A composite of Mortality, ICD storm, and Incessant VT (VT occurring below the ICD rate cut-off)
6. Number of Hospitalizations for Cardiovascular Causes.
7. Total VT burden (Number of episodes).
8. All-Cause Mortality.
9. The occurrence of ICD storm, defined as ≥3 appropriate shock therapies within 24 hours.
10. Differences in blood hormone measurements (including norepinephrine, aldosterone, renin, and BNP).
11. Differences in BUN/creatinine measurements.
12. Differences in cardiac parameters, including LV size (septal and free wall thickness) and mitral inflow (E&A velocity), as measured by trans-thoracic echocardiography.
13. Procedure related adverse events including, but not limited to hematomas, pseudoanuerysms, renal artery stenosis, renal impairment, thromboembolic events, stroke, pericardial bleeding including tamponade and myocardial infarction
14. Change in blood pressure

15. Development of orthostatic hypotension
16. Other individual complication rates including, but not limited to MI and death.
17. 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer);
18. Procedure time

Primary Analytical Analysis:	Intent to treat analysis
Secondary Analytical Analysis:	Per protocol analysis
Principal Investigator:	Vivek Y. Reddy, M.D. Mount Sinai School of Medicine One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
Site, Monitoring, and Data Management Center	Electrophysiology Clinical Research Group Mount Sinai School of Medicine One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
Data Safety and Monitoring Board:	TBD

1 CONTACT INFORMATION

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1.1 STUDY SITES & INVESTIGATORS

Site	Principal Investigator
1. Mount Sinai School of Medicine	Vivek Y. Reddy, MD
2. Homolka Hospital, Prague, Czech Republic	Petr Neuzil, MD
3. TBD	

2 STUDY OBJECTIVE

The goal of this trial is to test the impact of catheter-based renal sympathetic denervation (RSDN) as an adjunctive treatment for patients with either ischemic or non-ischemic cardiomyopathy undergoing catheter ablation of ventricular tachycardia (VT). The proposed study is a prospective, single-blind, multicenter, randomized control trial. Patients undergoing VT ablation will be randomized to either ablation alone or ablation + RSDN.

3 INTRODUCTION, RATIONALE

Sudden cardiac death (SCD), defined as an unexpected death from a cardiac cause occurring within ≤ 1 hour of the onset of symptoms, accounts for 300,000 to 400,000 deaths in the United States annually, or 5.6% of annual mortality.[1-3] SCD is most commonly caused by ventricular tachy-arrhythmias, including ventricular tachycardia (VT). Several therapies exist for the prevention of VT, including implantable cardioverter-defibrillator therapy (ICD), anti-arrhythmic drug therapy (AAD), and the use of catheter based ablation.

Current guidelines recommend the use of implantable cardioverter-defibrillator (ICD) as therapy to prevent SCD in patients who have survived a prior cardiac arrest due to unstable VT or who have had a previous episode of spontaneous sustained VT.[4] Several trials have demonstrated the efficacy of ICD therapy in preventing SCD.[5,6] The MADIT II trial, a randomized trial of patients with prior myocardial infarction and left ventricular ejection fraction ≤30%, demonstrated a 31% reduction in the relative risk of death in the defibrillator group. [6] However, ICD therapy does not prevent VT, and a significant proportion of patients may still experience appropriate shocks. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial, 60% of patients had ≥1 appropriate ICD therapy for VT/VF during follow-up (31±13 months), and the first arrhythmia resulting in a shock during follow up was frequently identified as VT (63%). Unfortunately, these ICD shocks are associated with both a significant reduction in quality of life and increased

mortality. In a study examining quality of life in patients who had received ICD shocks, at 5.5 years post ICD implantation 19% of patients demonstrated signs of post-traumatic stress disorder.[7] In the MADIT II trial, patients who experienced VT/VF had an increased risk of death, with a hazard ratio of 2.5.[6] Thus, while ICDs have a clear overall mortality benefit in patients with a reduced ejection fraction, the ICD shocks themselves clearly reduce the quality-of-life of these patients and may have a negative impact on longevity.

Antiarrhythmic drugs (AADs) are another therapy available for the prevention of VT, but unfortunately they have little effect on ventricular arrhythmia recurrence, and may increase mortality when used in high-risk patients. In the OPTIC trial, 412 patients who had an ICD implanted within 21 days for inducible or spontaneously occurring VT/VF were randomized to either amiodarone plus beta-blocker, sotalol alone, or beta-blocker alone. Although patients in the amiodarone plus beta blocker group were less likely to receive shocks (HR, 0.27; 95% CI, 0.14-0.52; P<.001), shocks still occurred in 10.3% of these patients. In addition, serious adverse effects associated with amiodarone resulted in study drug discontinuation in 18.2% of patients at 1 year.[8]

More recently, catheter ablation has emerged as a new option for the primary prevention of ICD shocks. Current guidelines recommend catheter ablation for symptomatic sustained monomorphic VT, including VT terminated by an ICD, that recurs despite AAD therapy or when AADs are not tolerated. In addition, ablation is indicated for control of VT storm refractory to drug therapy when there is a suspected trigger than can be targeted for ablation.[9] The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia Study (SMASH-VT) randomized patients with a history of myocardial infarction who underwent defibrillator implantation for spontaneous VT or VF, to either defibrillator implantation alone or defibrillator implantation plus substrate-based catheter ablation. In patients who underwent defibrillator implantation alone 33% received ICD therapies (anti-tachycardia pacing or shocks), compared to 12% in patients who received defibrillator implantation plus substrate-based catheter ablation (Hazard ratio in the ablation group, 0.35; 95% confidence interval, 0.15 to 0.78, P=0.007).[10] Similar results were seen in another multicenter randomized trial of similar design, VTACH. Despite the efficacy of VT ablation in these trials, there remain a significant number of patients how have recurrent arrhythmic events after catheter ablation procedures. This is particularly true in patients who present with ventricular arrhythmias refractory to anti-arrhythmic drugs and device therapies.

Thus, anti-arrhythmic drugs and catheter ablation each have limitations as sole therapies in patients at risk for recurrent ICD shocks. One adjunctive strategy under investigation is renal sympathetic denervation (RSDN). Recently, RSDN has been developed as a therapy to treat hypertension in patients resistant to anti-hypertensive drug therapy. In the Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension: a multicentre safety and proof-of-principle cohort study, 45 patients with a mean office blood pressure of 177/101 mm Hg (SD 20/15), (mean 4.7 antihypertensive medications) underwent renal sympathetic denervation with radiofrequency based catheter ablation. After the procedure, these patients experienced a mean decrease in office blood pressure of -27/-17 mm Hg at 12 months, as well as a 47% reduction in renal noradrenaline spillover.[11] In the Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension (Symplicity HTN-2) Trial, a multi-center prospective trial that

randomized 106 patients to RSDN or medical management, at 6 months, 84% of patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 35% of controls ($p<0{\cdot}0001$).

RSDN is thought to decrease blood pressure by a number of mechanisms including its ability to favorably affect whole body norepinephrine spillover and decrease central sympathetic tone. Indeed, RSDN has been shown to reduce whole body norepinephrine spillover by 42%, and efferent muscle sympathetic nerve activity by 66%.[12] Interestingly, increased catecholamine and sympathetic activity are both important factors in the development of ventricular arrhythmias.[13-18] In addition, chronic hypertension is believed to mediate pathogenesis and progression of cardiac arrhythmias via its remodeling effects on cardiac anatomy through the renin-angiotensin-aldosterone system.[19]

Logically, RSDN may be an effective therapy in the prevention of SCD from VT. Interestingly, there is at least one case report examining the impact of RSDN for the treatment of recurrent appropriate ICD shocks; two patients with ICDs for scar-related VT and CHF underwent RSDN for therapy resistant electrical storm. [20] One patient with hypertrophic cardiomyopathy had recurrent monomorphic VT despite multiple endocardial and epicardial ablations, while the second patient with dilated non-ischemic cardiomyopathy suffered from recurrent polymorphic VT, and had declined catheter ablation therapy. After undergoing RSDN, both patients experienced significantly less episodes of VT requiring ATP or shocks. Importantly, despite normal to low blood pressure at baseline, both patients maintained a stable blood pressure at 6 months of follow up post procedure.

Rationale for RESET-VT:

Despite significant advances in the management of ventricular arrhythmias through the use of ICD therapy, AADs, and catheter-based ablation strategies, considerable challenges remain. The optimal method for the prevention of recurrent VT following catheter ablation remains unclear. RSDN may be an effective tool for preventing ventricular arrhythmias, and associated ICD therapies, by reducing central sympathetic tone, catecholamine levels, and the renin-angiotensin-aldosterone system and promoting ventricular remodelling. Although RSDN has been shown to reduce the recurrence of VT in a case report of 2 patients suffering from electrical storm, to date no large prospective randomized study has evaluated the impact of RSDN in the prevention of recurrent VT in patients following catheter ablation of VT with ischemic or non-ischemic ventricular dysfunction. This study will specifically evaluate the safety and efficacy of adjunctive RSDN in the prevention of ICD therapy in patients with ischemic or non-ischemic ventricular dysfunction who are to receive a catheter-based VT ablation.

4. Schedule of Treatment and Tests:

TABLE 1: SCHEDULE OF TREATMENTS AND TESTS:

	Baseline	Procedure*	Discharge	1 month	6,12,18 & 24 months
Type of visit	Office	Hospital		Office	Office or Transtelephonic
Informed Consent	X				
Brief History & Physical	X			X	
Blood Laboratory Testing: CBC, Electrolytes, BUN/Creatinine, BNP	X				X (12, 24m)
NIH Stroke Scale	X		X		
Blood for Renal Hormones (OPTIONAL)	X				X (12m)
TTE	X				X (12 m)
Renal Angiography		X			
Ultrasound or MR/CT Angiography					X (6 m)
Randomization		X			
Renal Sympathetic Denervation		X			
ICD Interrogation/remote transmission	X			X	X
EKG	X				X (12m)
Office BP Measurements (including orthostatic BPs)	X			X	X (12m)
Medications	X		X	X	X
Adverse Events		X	X	X	X

5. **Endpoints:**

5.1: Primary Endpoint:

The following primary endpoint will be assessed: Time to first event requiring appropriate ICD therapy or Incessant VT (VT occurring below the ICD rate cut-off); this will be assessed in the on-treatment patient cohort.

5.2: Secondary Endpoints:

The following secondary endpoints will be assessed:

1) Appropriate ICD therapy for ventricular arrhythmia assessed in the full intention-to-treat patient cohort
2) Appropriate ICD Shocks for ventricular arrhythmia
3) Inappropriate ICD therapy
4) All ICD therapy (Appropriate + Inappropriate)
5) A composite of Mortality, ICD storm, and Incessant VT (VT occurring below the ICD rate cut-off)
6) Number of Hospitalizations for Cardiovascular Causes.
7) Total VT burden (Number of episodes).
8) All-Cause Mortality.
9) The occurrence of ICD storm, defined as ≥3 appropriate shock therapies within 24 hours.
10) Differences in blood hormone measurements (including norepinephrine, aldosterone, renin, and BNP).
11) Differences in BUN/creatinine measurements.
12) Differences in cardiac parameters, including LV size (septal and free wall thickness) and mitral inflow (E&A velocity), as measured by trans-thoracic echocardiography.
13) Procedure related adverse events including, but not limited to hematomas, pseudoanuerysms, renal artery stenosis, renal impairment, thromboembolic events, stroke, pericardial bleeding including tamponade and myocardial infarction.
14) Development of orthostatic hypotension
15) Changes in blood pressure
16) Other individual complication rates including, but not limited to MI and death.
17) 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer);
18) Procedure time

6. STUDY SUBJECTS

6.1 INCLUSION CRITERIA

State inclusion criteria for enrollment in study:

1. ≥ 18 years of age
2. Structural heart disease (post-MI, dilated cardiomyopathy, sarcoid myopathy, hypertrophic cardiomyopathy, chagas-related cardiomyopathy, etc.)
3. Planned for catheter-based ablation of VT
4. All patients will have an existing ICD
5. Accessibility of renal vasculature (determined by renal angiography)
6. Ability to understand the requirements of the study
7. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements

6.2 Exclusion Criteria

Clinical Exclusion Criteria:

1) MI or CVA within 30 days
2) Coronary Artery Bypass Graft (CABG) within 30 days of this procedure
3) Known renovascular abnormalities that would preclude RSDN (eg, renal artery stenosis)
4) GFR <30 ml/min (unless receiving dialysis)
5) Life expectancy <1 year for any medical condition
6) Any condition resulting in a contraindication to anticoagulation (e.g. GI bleeding)
7) Inability to give informed consent
8) Known pregnancy or positive β-HCG within 7 days of procedure.

7. Sample Size Calculation:

We generated our sample size using the following key assumptions:

1. In patients receiving catheter ablation for VT alone, the estimated success rate (absence of ICD therapy) at 2 years is 65%
2. In patients receiving RSDN in addition to VT ablation, we expect a 30% improvement such that the estimated 2 year success rate is 85%

The power analysis revealed that a 30% improvement in therapy with RSDN would be detected with 83 patients per arm (80% power, 2-sided alpha error of 0.05). This would require an enrollment of a total of 168 patients, with follow-up of 2 years. We expect an ~10% loss to follow-up. Accordingly, we will plan to enroll an additional ~10% of patients so as to have sufficient number of randomized patients: this would require 184 patients. In addition, we expect 10% of patients will have renal vasculature inappropriate for the RSDN procedure (these are patients that will be consented pre-procedure, but will screen out after renal angiography during the VT ablation procedure). Accordingly, we will ultimately plan to include a total of 202 patients: ~18 patients would screen out after renal angiography, and there would remain a total of 92 patients randomized to each arm.

This study is divided into two phases: a PILOT phase (to include 20 patients) followed by the remaining 182 patients to a total of 202 patients. The PILOT phase will be conducted at 2 sites: Homolka Hospital (Prague, Czech Republic) and Mount Sinai Medical Center. An interim safety

analysis for the primary endpoint will be conducted when all patients in the PILOT phase (20 subjects) have completed the 1-month follow up visit.

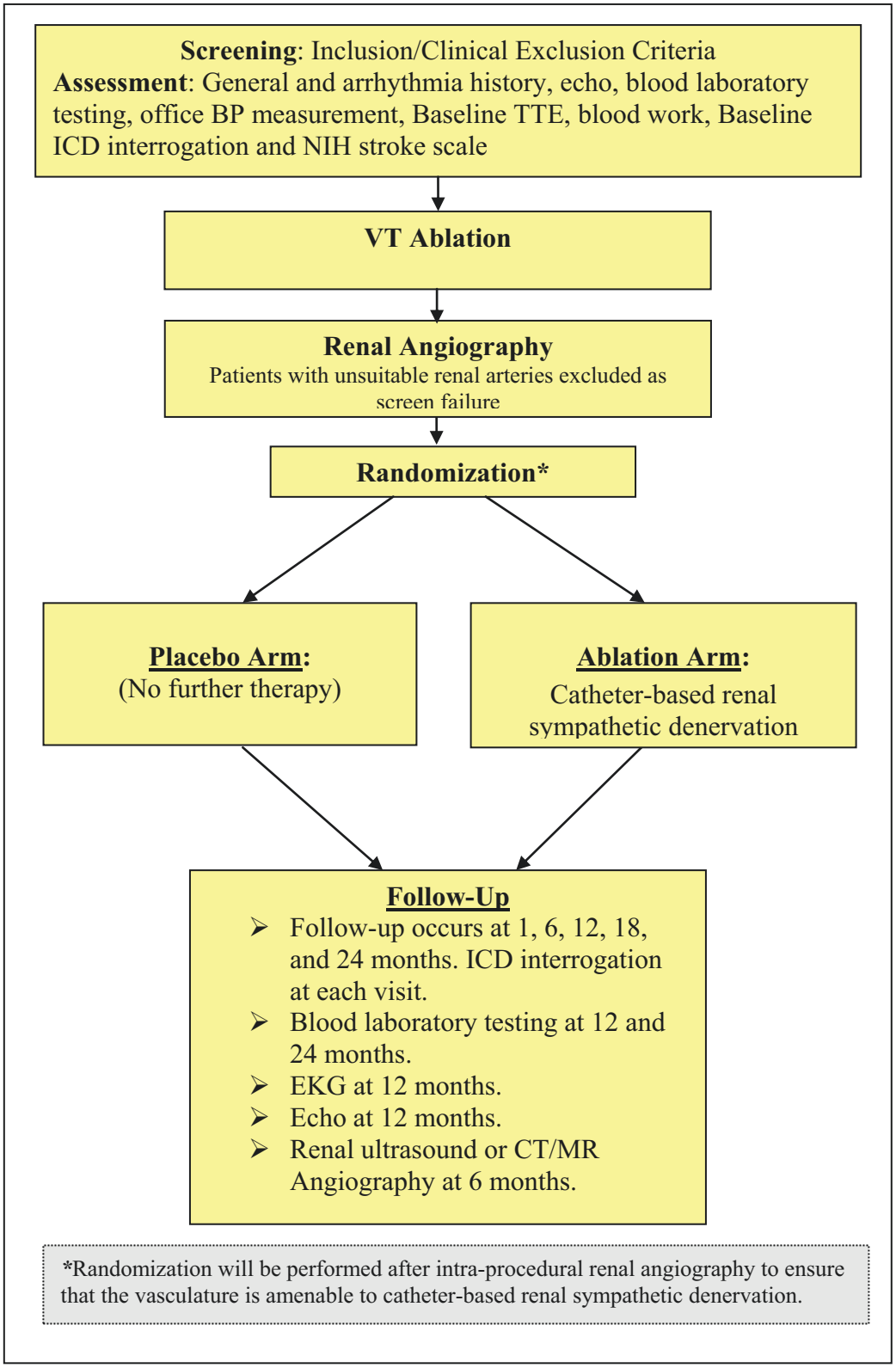
8. Patient Enrollment and withdrawal:

This will be a multicenter trial. 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.

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 allowed to take a copy of the consent form home to contemplate whether they would like to be enrolled in the study. A sample consent form can be found in Appendix 1. 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.

Consent must be obtained before the VT ablation procedure.

9. **Pre-Procedure and Ablation Study Design Flow-Chart**



PRE- AND ABLATION PROCEDURE

9.1.1 PRE-PROCEDURE

The following tests and procedures will occur before the ablation:

- Recording of patient medical history (including details of VT both clinical/ICD)
- Recording medication history (including all AAD ever used, 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
- Baseline NIH stroke scale
- If performed for any reason, collect any pre-procedural imaging: MRI/CT and Renal Ultrasounds within 6 months of procedure
- Baseline laboratory, including complete blood count, standard electrolyte panel, renal function, and brain natriuretic peptide levels.
- Baseline Transthoracic Echocardiogram
- Baseline blood pressure. Proper blood pressure measurement technique is essential: i) patient should sit quietly in a chair with his/her back supported for 5 minutes before taking the measurement; ii) use of the correct cuff size with the air bladder encircling at least 80% of the arm (the adult large cuff for the majority of patients); iii) support the arm at heart level during the cuff measurement; iv) a minimum of 2 readings should be taken at intervals of at least 1 minute and the average of those readings should be taken to represent the patient's blood pressure; v) the blood pressure should be measured
- Consent must be obtained before the VT ablation procedure.
- Randomization into one of two groups will be performed by opening the Randomization envelope after Renal Angiography.

  Study/Experimental Group: These subjects will undergo catheter-based sympathetic renal denervation.

  Placebo Control Group: These subjects will receive no further intervention..

9.1.2 PRE-PROCEDURE MEDICATION MANAGEMENT

After the ablation procedure, patients should receive either an antiplatelet agent (aspirin, clopidogrel, etc) or anticoagulant (warfarin, dabigatran, etc) for at least 1 week. Further decisions regarding the peri-procedural management of other cardiovascular (including anti-coagulant and anti-thrombotic agents) and non-cardiovascular medications should be as per clinical practice – but every effort should be made to maximize beta-blocker therapy, ACEI/ARB, and spironolactone therapy as per the guidelines.

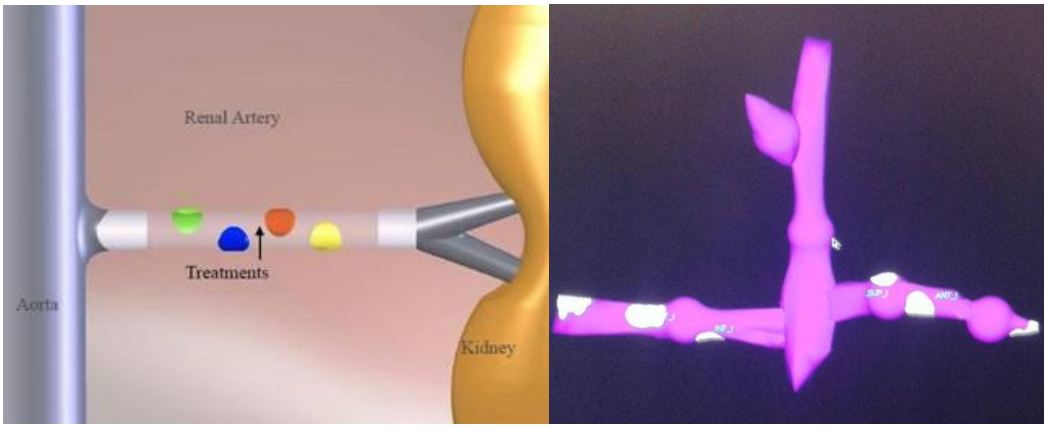
9.1.3 VT ABLATION PROCEDURAL DETAILS

- Patients will be brought to the electrophysiology laboratory in a fasting state
- General anesthesia/conscious sedation will be used according to operator preference
- Patients will undergo electrophysiology study and VT ablation as per standard practice
- Therapeutic anticoagulation will be administered with intravenous heparing with a target ACT of 300 seconds or greater.

9.1.4 RENAL SYMPATHETIC ABLATION PROCEDURAL DETAILS

- In patients randomized to receive RSDN, the procedure will be performed after the VT ablation on therapeutic anticoagulation with intravenous heparin.

- Abdominal aortography will be performed to assess the renal arteries for the suitability of catheter-based renal denervation in all patients. For those patients in whom the angiogram demonstrates that the renal anatomy is inappropriate for the RSDN procedure (small renal arteries, extensive atherosclerosis, renal stenosis, etc), the patient will be excluded from the study as a screen failure. The patient's baseline information will be collected but no further follow-up required (beyond assessing for any adverse events related to the procedure). If the renal arteries are deemed suitable for RSDN, the patient will then undergo randomization.
- Randomization will be done by permuted-block randomization centrally and will be stratified by site. Allocation concealment shall be maintained at all sites by the use of a web-based central randomization scheme. The operating physician controlling the delivery of ablative energy will be aware of the outcome. This approach has been selected to minimize (1) study bias and (2) placebo effect. The randomization schema will be blocked by size for each site.
- After confirmation of eligibility, an irrigated radiofrequency ablation catheter will be introduced sequentially into each renal artery.
- The ablation catheter is placed within a long vascular sheath and advanced into the renal artery. The sheath is advanced over the catheter to engage the renal artery ostium and allow for contrast injection and visualization of the vessel during catheter manipulation.
- After completion of the measurement, no more than six radiofrequency ablation lesions separated both longitudinally and rotationally (a ―spiral pattern", see figure) will be placed per renal artery. The power will be started at 10 W and titrated to a maximum 20 W, as deemed appropriate by the impedance drop (goal 10% drop). Each lesion should be between 30-120 seconds in duration (no more than 120 seconds per lesion).



9.1 POST-PROCEDURE

9.2.1 POST-PROCEDURE FOLLOW UP

- All patients will be monitored to verify vascular hemostasis prior to discharge from the hospital.
- All patients will receive either oral aspirin (81-325 mg QD) or clopidogrel (75 mg QD) or warfarin or dabigatran or rivaroxiban for at least 1 week upon discharge.
- Medication and adverse event review will be performed prior to discharge.
- Complications including vascular, stroke, heart failure etc, and presence of ventricular arrhythmias will be documented.
- NIH stroke scale will be repeat post-procedure
- ICD programming: (see below section 9.2.3)

- The total number of episodes of VT, ATP, and Shocks will be documented at all visits.
- The follow-up includes:
    - 1 Months
        - History and Physical
        - ICD interrogation (may be trans-telephonic)
        - Office BP measurements (x2) including orthostatics
        - Review of Medications and Adverse events
    - 6 Months
        - ICD interrogation (may be trans-telephonic)
        - Review of Medications and Adverse Events
        - Repeat Renal Ultrasound or MR/CT Angiography
    - 12 Months:
        - ICD interrogation (may be trans-telephonic)
        - EKG
        - Office BP measurements (x2) including orthostatics
        - Lab tests (CBC, Electrolytes, BUN/Cr)
        - Blood for Renal Hormones (OPTIONAL)
        - BNP Level.
        - Review of Medications and Adverse Events
        - Repeat TTE
    - 18 Months:
        - ICD interrogation (may be trans-telephonic)
        - Review of Medications and Adverse Events
    - 24 Months:
        - ICD interrogation (may be trans-telephonic)
        - Lab tests (CBC, Electrolytes, BUN/Cr)
        - BNP Level
        - Review of Medications and Adverse Events

9.2.2 POST-PROCEDURE MEDICATION MANAGEMENT

- Standard cardiovascular medications are left up to the discretion of the investigator – but BBLs, ACEI, ARBs and aldosterone antagonist use is recommended as per standard guidelines.
- Therapeutic anticoagulation (example Warfarin or equivalent agent) beyond the requisite 1 week post-procedure timepoint is at the discretion of the patient's physician.

9.2.3 ICD PROGRAMMING

The following programmed detection and therapy parameters should be used to optimize therapy delivered to the subject during the course of the study for both the Catheter Ablation Group (Treatment) and Control Group:

ICD Programming Requirements

Arrhythmia	Programming Strategy
VT Zone	175-195 bpm
VF Zone	*200* bpm. ATP to 250 bpm
Monitor Zone	130-170 bpm
VT Therapy	ATP – recommended. Programmed at investigators discretion

SVT Discriminators	Should be ~~O~~N" in VT zone. Programmed at investigators discretion.

Device Specific Detection Parameters

Arrhythmia	Medtronic	Boston-Scientific	St. Jude	Biotronik
VF	18/24 beats	5s (1-25s std, but would be approx.3-10 beats)	18 intervals (uses binned counter)	18/24
VT	18-20 beats	5s	18-20	18-20 (must be VF)
Monitor	No effect (on newer devices)		Monitor may affect detection	
Comments				Uses the same criteria for detection and redetection

9.2 SAFETY

We anticipate no significant increase in adverse events as compared to the VT ablation or renal angiography procedure. The local site primary investigator will oversee the safety of the study at his/her site. All adverse events will be reported to the Data Coordinating Center (Mount Sinai School of Medicine). Adverse events will be monitored and tallied for each 50 patients enrolled in the study (after the 20 patients enrolled during the PILOT phase), and presented to an independent Cardiologist (who will serve as the Data Safety Monitoring individual). All adverse events will be adjudicated as being either: 1) related to the renal denervation procedure; 2) related to the VT ablation procedure or 3) unrelated to either procedure. Because of the small size of this study, the DSMB will consist of one Cardiologist; 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

9.3.1 Interim and Futility Analyses

An interim or futility analyses will be performed after completion of the PILOT phase of this study: after the enrollment of 20 subjects (10 controls, 10 study group). 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 in the treatment arm.

9.3.2 Clinical Events Committee

A separate Clinical Events Committee (CEC) composed of 2 independent electrophysiologists will adjudicate all ICD events in this study.

9.3 RISKS

VT ablation will occur according to standard procedure, and therefore the risk includes that of a standard VT ablation. These risks include:

Common:

- Discomfort at the site of vascular access
- Groin hematoma

Uncommon:

- Bleeding
- Vascular injury
- Thromboembolism, including renal infarction and peripheral atheroembolism. This risk is minimized considerably by the short duration of the procedure, as well as the use of a saline-irrigated ablation catheter.
- Risks associated with sedatives/anesthesia.
- Injury to adjacent structures (phrenic nerve, cardiac valves)
- Vascular complications (including pseudoaneurysm, AV fistula requiring surgical intervention)
- Radiation burns
- Pneumonia and/or sepsis
- Death
- Discomfort in the throat region
- Cardiac Perforation requiring drainage or surgery
- Injury to adjacent structures (phrenic nerve, esophagus, lung, cardiac valves)
- Congestive heart failure
- Myocardial infarction
- Radiation burns

The potential additional risks of the RSDN procedure are anticipated to be uncommon but may include:

- Renal artery dissection
- Renal artery stenosis or occlusion
- Renal dysfunction potentially needing hemodialysis
- Thromboembolism, including renal infarction and peripheral atheroembolism. This risk is minimized considerably by the short duration of the procedure, as well as the use of a saline-irrigated ablation catheter.

10.0 STUDY MANAGEMENT

10.1 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 at his/her site: 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.

10.2 Confidentiality

Patient information will be kept confidential and managed according to the 1996 HIPAA guidelines. All patient information will be de-identified and stored in a secure, locked environment. 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.

10.3 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.

10.4 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.

10.5 Economic Impact on Subjects

The catheter-based renal sympathetic denervation procedure is part of a research study and is investigational. The cost of the renal sympathetic denervation procedure and follow-up will be the responsibility of the subject or the subject's insurance carrier. No payment will be made to the subject for taking part in this study.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Risk to subjects: Although it is unlikely, it is possible there may be loss of confidentially. This is a typical risk of any research study. Stenosis, dissection, and groin complications are possible clinical risks however they are not anticipated risks in this trial.

11.2 Potential Benefits to Subjects: After undergoing RSDN, patients may experience less episodes of VT requiring ATP or shocks a result of the expected reduction in whole body norepinephrine spillover and sympathetic nerve activity.

11.3 Role of the Coordinating Center

As principal investigator and study sponsor of this clinical study, Vivek Y. Reddy, 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, Vivek Y. Reddy, MD will have certain direct responsibilities and will delegate other responsibilities to his staff at the Coordinating Center, the Mount Sinai Hospital. Together, 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.

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

The Coordinating center will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial.

11.5 Site Record Retention Policy

All clinical sites will maintain study records for two years after research termination.

11.6 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.

12.0 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 the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled registry period.

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 location. The research study coordinators, principal investigator and co-investigators will be the only people with access to this data. All data will be stored without any patient information apart from the unique three digit patient identifier. There will be a code sheet that will link the de-identified data back to the subjects. This will be encrypted and password-protected. One copy will be stored in the primary investigator's computer, and another in the research coordinator's computer.

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