Ablation at Virtual-hEart pRedicted Targets for VT

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JHM IRB - eForm A – Protocol

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1. Abstract

Ventricular tachycardia (VT), a life-threatening fast heart rhythm, occurs frequently in patients with myocardial infarction, leading to sudden cardiac death. Catheter-based ablation, the delivery of energy to destroy the ability of cardiac tissue to conduct electrical signals, offers the possibility of permanent cure by interrupting the VT reentrant circuit. Unfortunately, eliminating infarct-related VT with ablation has achieved only modest success, 50-88%, and with complication rates as high as 8% of the treated population. This stems from limitations in current electrical mapping techniques used to identify the target locations for ablation. These include limited sampling during mapping, with resolution often insufficient to identify critical arrhythmia circuits, the hemodynamic intolerance during VT induction, and the ambiguities in correlating electrical maps with heart anatomy. Furthermore, the complex three-dimensional pathways of cardiac impulse propagation around/through the zone of infarct during VT are difficult to reconstruct by mapping the ventricular surfaces only. These limitations translate into inaccurate ablation targets and extensive unnecessary lesions, and into prolonged duration of the procedure, dramatically increasing the risk of chamber injury, thromboemboli, bleeding, and radiation overexposure. Our Hopkins team has developed a novel "virtual-heart" methodology that could eliminate the need for invasive electrical mapping in determining the optimal targets for infarct-related VT ablation. The approach is based on cardiac imaging and computational modeling, and is personalized to each patient. The methodology involves constructing three-dimensional computer models from patients' CMR data. We then execute simulations with each virtual heart to evaluate all possible patient-specific VTs, and to determine automatically, using a novel algorithm, the optimal ablation targets that render, with minimum lesion size, each heart not inducible for VT.. The approach thus targets termination not only of VTs that are clinically manifested or induced at the time of procedure, but of all VTs that could arise from the given post-infarction substrate, including those that might arise following initial ablation, thus potentially eliminating the need for repeated ablations and offering long-term freedom from VT.

2. Objectives (include all primary and secondary objectives)

The goal of this study is to test the efficacy of the new imaging/simulation ("virtual heart") approach for determining the optimal ablation sites in patients with VT, which render post-

infarction VT non-inducible. The study will test both the acute outcome of the ablation procedure, and the effect the use of the predicted targets has upon procedure time.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

We use a novel "virtual-heart" methodology that could eliminate the need for invasive electrical mapping in determining the optimal targets for ablation of VT in structural heart disease. The approach is based on cardiac imaging and computational modeling, and is personalized to each patient. The methodology involves constructing three-dimensional (3D) models of the patient's ventricles, including all structural remodeling from patients' clinical MRI data. We then execute simulations with each virtual heart to evaluate all possible patient-specific VTs, and to determine automatically, using a novel algorithm, the optimal ablation targets that render, with minimum lesion size, each heart not inducible for VT. The approach thus targets termination not only of VTs that are clinically manifested or induced at the time of procedure, but of all VTs that could arise from the given arrhythmogenic substrate, including those that might arise following initial ablation, thus potentially eliminating the need for repeated ablations and offering long-term freedom from VT. Retrospective studies have demonstrated an excellent correspondence between predicted targets in patients with VT and the lesions that successfully terminated VT. The methodology for constructing the patient's 3D virtual heart and assessing the arrhythmogenic propensity of the substrate has been published by our team in *Nature Communications*. May 10;7:11437. doi: 10.1038/ncomms11437, 2016.

Once all possible VT that the arrhythmogenic substrate can sustain are determined, in each personalized virtual heart we determine the minimum-size (i.e.optimal) ablation lesions that render it not inducible for VT from any pacing location. These optimal targets are determined using a novel automatic algorithm we developed and validated recently (*Heart Rhythm* **13**, 1687-1698, doi:10.1016/j.hrthm.2016.04.009 (2016). The algorithm represents reentrant wave propagation as a flow network and identifies the smallest amount of tissue that, when eliminated from the network, disrupts and terminates the flow.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

1. Potential participants will be obtained from the Johns Hopkins Hospital electrophysiology lab inpatient and outpatient schedule and from the Johns Hopkins outpatient cardiac electrophysiology clinic, who have a planned procedure for catheter ablation of ventricular tachycardia.
2. Participants will undergo written consent.
3. The participant will then undergo a cardiac MRI scan performed with a 1.5-T MRI scanner, with delayed late gadolinium enhancement. Cardiac MRIs or CTs are part of the routine care at Johns Hopkins among patients presenting for a ventricular tachycardia catheter ablation.
4. MRIs should be acquired no more than 30 days and no fewer than 24 hours prior to a scheduled ablation procedure. If the patient has prior MRI data available matching the specified image parameters, from fewer than 30 days prior to the procedure, those data may be used instead.
5. The cardiac MRI will then be processed and simulations performed with each virtual heart to evaluate all possible patient-specific VTs, and to determine the optimal ablation targets.
6. In the event that a patient is enrolled, but a satisfactory, good quality MRI cannot be obtained, the patient will remain enrolled, but the guided ablation procedure will not be performed and the patient will undergo a standard ablation procedure. Other than this

notation of data, the procedure will be the same as if the subject were not enrolled in the study.

7. If a good quality cardiac MRI is obtained and a virtual heart model with the ablation targets is generated, the operating physician will merge the virtual heart lesion map to the invasive electroanatomical navigation system. After the patient has been catheterized, an attempt should be made to induce VT. The physician should then navigate the catheter to each of the ablation targets specified, and place a lesion as per his or her training and experience, confirming when done that the lesion marker in the mapping system coincides with the target. This will be done for each lesion.
8. Once ablation lesions have been delivered at all of the suggested targets as described above, an attempt should be made once again to induce ventricular tachycardia, and the result recorded. If the operator feels the virtual heart guided ablation is an area to be unsafe, then no ablation will be performed.
9. Following the investigational portion of the procedure, the operator will continue to perform the rest of the VT ablation procedure per their discretion.

b. Study duration and number of study visits required of research participants.
We expect to enroll 10 participants over a one year period. Only two study visits would be required at this time, and this will coincide with the participant's normal pre procedure cardiac MRI study and catheter ablation procedure.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
This study is not blinded as the goal is to determine the acute procedural outcome of the inability to induce ventricular tachycardia.

d. Justification of why participants will not receive routine care or will have current therapy stopped.
The participants will receive routine care in regards to catheter ablation for the management of their arrhythmia.

e. Justification for inclusion of a placebo or non-treatment group.
There will be no placebo group.

f. Definition of treatment failure or participant removal criteria.
Participant failure would occur if the virtual heart modeling was unable to be performed secondary to a poor cardiac MRI study.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
N/A

5. Inclusion/Exclusion Criteria

Patients that exhibit monomorphic VT secondary to scarring will be eligible for the study. Patients with implanted cardiac devices may also be enrolled based on standard protocol in the Radiology Departments at Johns Hopkins University. Due to the use of gadolinium as an MRI contrast agent, patients with GFR < 30 mL/min should not be enrolled in the study.

Inclusion Criteria

Patients must meet all of the following inclusion criteria:

- Eligible patients must be at least 18 years old at the time of enrollment.
- A Pre-Op cardiac MRI including LGE must be performed prior to ablation. As JHU performs MRIs with ICD or pacemaker implanted, patients with these devices may be enrolled.
- Eligible patients must suffer from VT, thought to be secondary to structural heart disease (scarring).

- Eligible patients must be determined to be suitable candidates for ablation to treat VT by their cardiologist and/or electrophysiologists regardless of this protocol.

General Exclusion Criteria

- Patients with GFR < 30 mL/min should not be enrolled in the study due to the use of intravenous gadolinium as an MRI contrast agent
- If a pre-procedure MRI cannot or likely will not be performed for any reason (such as claustrophobia), the patient must be excluded.
- Pregnant women may not participate in the study because gadolinium MRI contrast is contraindicated in these patients.
- Any subject that, during the course of the pre-procedure imaging, is discovered to have VT not related to scarring, he/she must be de-enrolled from the study.

6. Drugs/ Substances/ Devices

N/A

7. Study Statistics

Primary Endpoint

The primary endpoint of this study is conversion from acute inducibility of VT to acute non-inducibility of VT using only the lesions indicated by our methodology.

Secondary Endpoints

The secondary endpoints are how many additional lesions were needed to terminate VT, if any, and procedure duration.

a. We anticipate that 10 participants will be adequate to describe the association of the virtual heat guided ablation lesions and acute VT non inducibility.
b. Early stopping rules. We anticipate no untoward effects from this research. However, if any adverse events are noted the study will be terminated.

8. Risks

Ablation Risks

Standard ablation procedures include all of the operations that will be performed as part of the study, including induction of VT and termination of VT, pace mapping, and creation of lesions via radiofrequency energy. The study requires one additional attempt to induce VT, out of multiple attempts typically done during such a procedure. The study requires that the ablating physician ablate the predicted lesion sites first. If the hypothesis of this trial is correct, the number of lesions delivered will be smaller than usual. It is possible that several lesions might be added to the total number normally done during such a procedure. However, frequently multiple lesions are placed during such a procedure.

The acute harm associated with induction of ventricular tachycardia is patient hemodynamic instability. The acute harm associated with ablation lesions are in line with the risk of the procedure which includes pain, damage to heart valve, lung or heart perforation which could require emergency intervention or surgery, heart block, stroke or TIA, pulmonary embolism, myocardial infarction, phrenic nerve paralysis and death.

There is no clear long term harm from induction of ventricular tachycardia during an electrophysiology procedure. The long term harm associated with unnecessary ablation lesions in areas of diseased myocardial tissue is not clear.

In order to minimize risk, all procedures will be performed with cardiac anesthesiology support. Throughout the procedure, continuous hemodynamic monitoring including non-invasive/invasive measurements of blood pressure, heart rate, oxygen saturation and respiratory status will be performed. Ablation will only be performed by an experience operator, using tools approved for the indication on diseased tissue which is important in the substrate for ventricular tachycardia.

All adverse events related to an electrophysiology procedure at the Johns Hopkins Hospital is recorded in a HIPAA secure RedCap database. Adverse events are assessed at the time of the procedure and at each subsequent clinic visit. Any unanticipated problems involving risk to subjects or others will be reported to FDA within 10 working days after receiving notice of the adverse effect
Major complications are defined as life-threatening, leading to permanent harm, or necessitating intervention or prolonged hospitalization within 30 days of ablation.

a. Plan for reporting unanticipated problems or study deviations.

   Unanticipated problems will be reported to the study investigators along with the referring physician. Study deviations will be communicated with the study participant.

b. Legal risks such as the risks that would be associated with breach of confidentiality.

   Not applicable.

c. Financial risks to the participants.

   There are no financial risks to the participant.

9. Benefits

There are no direct benefits from participation in this study. The benefit of this study is to better understand the mechanism and optimal ablation sites for those presenting to the electrophysiology lab for the catheter ablation of VT. The goal is using our protocol will lead to decreased procedural times, decrease patient risk and improved efficacy for the catheter ablation management of VT.

10. Payment and Remuneration

Monetary compensation will not be provided to the participants.

11. Costs

There will be no cost for the participant in this study.