Name of the Study:

Cardiac positron emission tomography for detection of cardiac sympathetic dysinnervation to guide ablation of ventricular tachycardia (PET VT Study)

Principal investigator: Khaled Awad MD (Cardiac Electrophysiology)

Introduction:

Ventricular tachycardia (VT) has become an increasingly prevalent cardiovascular condition. Factors leading to that include aging of the population, increasing use of implantable defibrillators and improved survival of patients with cardiomyopathy. VT ablation has become the cornerstone for treatment of VT.[1,2] Event-free survival following the ablation procedure has been modest adding to the steep cost and associated risks.[1,2] Moreover, patients with more complex scar structure and multiple VTs bear the highest likelihood of VT recurrence.

Identifying critical parts of the VT machinery is key to successful ablation and durable long-term results. VT associated with structural heart disease is usually re-entrant, utilizing areas of slow conduction and unidirectional block caused by conduction barriers. Those barriers can be further classified into structural and functional. Although there have been major strides in the use of CT and MRI for assessing scar structure, current imaging tools still offer very little in terms of functional imaging of scar, with relevance to understanding the pathophysiology of VT.

The role of the autonomic nervous system in the genesis of VT has been studied for decades. [3,4] Several techniques have been used to interrupt sympathetic input to the myocardium at the levels of the spinal cord, sympathetic chain, and renal artery.[5-7] However those measures have been reserved for the most refractory of cases given the lack of standardized techniques, and higher potential for long-term complications. There have been no reports of attempts at terminal cardiac sympathetic modulation in the setting of VT associated with cardiomyopathy in humans.

Fallavollita et al have recently shown that the magnitude of sympathetic dysinnervation associated with hibernating myocardium correlates with the risk for sudden cardiac death and fast VT requiring ICD therapies.[8] [N-13] NH3, [18 F]-fluorodeoxyglucose (FDG), and [C-11] meta-hydroxyephedrine (MHED) were used in that study to determine the relationships between regional myocardial perfusion, metabolism and the distribution of adrenergic receptors with PET imaging.[8] The findings in that study were in alignment with a growing body of evidence derived from studies that used 123I-metaiodobenzylguanidine (MIBG).[9-12] However, that study was the first to demonstrate that PET imaging of cardiac innervation is feasible in large clinical trials. Assessing the anatomic and functional elements reflected by MHED scans, and its relationship to the genesis of VT, seems very intriguing from an electrophysiologic perspective.

Regional denervation associated with cardiomyopathy with hibernating myocardium is usually followed by a process of re-innervation, known as nerve sprouting.[13] Several studies have demonstrated that the presence of inhomogeneity of sympathetic innervation in the setting of cardiomyopathy is associated with sudden cardiac death.[8,13-15] Nerve sprouting induced by infusion of growth factors into the left stellate ganglion in dogs was associated with the occurrence of ventricular arrhythmias.[16] Moreover, there is histologic evidence that VT does

originate from areas with increased density of sympathetic nerve fibers, i.e. areas with nerve sprouting.[14] Therefore, it is plausible that inhomogeneity of sympathetic innervation of scar results from areas with nerve sprouting in the background of denervated scar. The interaction of dynamic changes to spatial distribution of sympathetic innervation, its effects on electrophysiologic properties of scar, and the inhomogeneity of scar structure form the foundation to the machinery needed to sustain VT (i.e. slow conduction and unidirectional block).

Integration of PET/CT imaging of LV scar prior to VT ablation has been reported by Tian et. al.[17] In that study, perfusion was assessed using Rubidium-82, and metabolic activity was assessed by FDG. The authors were able to show correlation between PET and electro-anatomic maps. Ahmad et. al have demonstrated that MIBG can be used to image sympathetic innervation of scar, for use during ablation of VT.[18] In that study, 90% of successful ablation sites were located within dysinnervated areas. Moreover, 10% of successful ablation sites existed in dysinnervated areas with normal bipolar voltage (possibly indicating healthy myocardium). This study was fraught with misalignment of the anatomic models. That would affect the validity of their conclusions and can be avoided by using CT scanning for better definition of cardiac anatomy. The crude resolution of MIBG scans is not adequate to identify more detailed regional details, which would be necessary to identify ablation targets.

Additionally, [C-11] MHED is far superior to MIBG scanning for the following reasons:

1. PET offers superior sensitivity and resolution over SPECT[19]
2. Global down regulation of MIBG uptake in subjects with heart failure makes it hard to make accurate interpretations of MIBG scans[20]

To date, sympathetic dysinnervation has never been assessed using PET for the purpose of guiding VT ablation procedures. Moreover, sympathetic dysinnervation has not been well studied in patients with non-ischemic cardiomyopathy, which is more challenging to manage, given the relatively more obscure substrate.

Study Goals:

A. Demonstrate capability of producing and using the PET agent [C-11] MHED
B. Identify the electrophysiologic properties of areas of relatively increased [C-11] MHED uptake within myocardial scar
C. Identify correlations of preliminary imaging and electrophysiologic data for hypothesis generation. Those shall be investigated with further studies to assess impact on procedural outcomes, and event free survival after VT ablation in future larger studies.

Preliminary hypothesis:

1) PET/CT imaging with [C-11] MHED can guide the identification of elements that are critical to the development of VT, which exhibit abnormal sympathetic influence.
Areas of relative increase in myocardial [C-11] MHED uptake may represent regional nerve sprouting within the background of dysinnervated scar and? represent critical elements to the substrate of VT.

2) Ablation targets detected by conventional electrophysiologic mapping techniques are likely to exist in such areas with dysinnervation, which are likely representative of nerve sprouting.

The data provided by PET/CT imaging could be used to modify the current approaches for VT ablation. Data on the regional adrenergic receptor quantity and distribution could be crucial to improving procedural outcomes and event-free survival in patients with life threatening ventricular arrhythmias.

Brief Protocol:

Study Design:
Pilot, hypothesis generating, nonrandomized study

Number of subjects: 15 patients

Duration of subject participation: Subjects will be enrolled in the study during a pre-ablation visit/consultation and participate in the study from the time consent is obtained, through the PET scan, and for 30 days following ablation.. Patients are not required to attend the follow-up visit in order to be considered complete in the study.

Study Population:
All enrolled patients will be patients referred to Mercy cardiovascular group for consideration of ablation of ventricular tachycardia and have a clinical indication for ablation per standard of care.

Inclusion Criteria:

1. Patients with clinical indication for VT ablation (at least one clinical episode of sustained VT) despite antiarrhythmic drug therapy, or if the patient does not wish to be on one
2. Ischemic or non-ischemic cardiomyopathy (will try to enroll equal number of each)
3. Sustained monomorphic VT is a requirement
4. Age 18-80 years old
5. Ability to provide informed consent

Exclusion criteria:

1. Right ventricular VT
2. Polymorphic VT or VF being the sole detected clinical arrhythmia
3. Pregnancy or lactation (unanticipated, pregnancy test to be done for women in the childbearing age)

Subject Recruitment:
Mercy clinic patients will be recruited by the Principal Investigator, Sub-Investigators, or other designated study team member. Informed consent will be obtained by the Principal Investigator or delegated study personnel. After the informed consent is obtained, the study team will provide the subject's information to the Washington University coordinator for scheduling of the PET/CT scan using the Study Subject Information Sheet by Mercy Secure File Transfer System.

Study Procedures:

Screening/Visit 1	Standard of Care + Research	Discuss ablation and its clinical indication Discuss participation in the study Obtain informed consent Determine eligibility
Optional Cardiac MRI	Standard of Care	Cardiac MRI will be done as per standard of care prior to ablation of ventricular tachycardia. Cardiac MRI is not required for participation on the study
Visit 2	Research	PET/CT scan will be done at Washington University imaging facility up to 21 days before scheduled ablation.
Visit 3	Standard of Care	Cardiac ablation procedure will be done per standard of care
Data-only follow-up	Research	Adverse event and VT recurrence data, when available, will be collected 30 days (+/- 5 days) following cardiac ablation procedure.

Schedule of Events

Procedures	Screening /Visit 1	Optional Cardiac MRI*	Visit 2**	Visit 3	Data-only Follow-up (30 days)
Informed Consent	X				
Demographics	X				
Past Medical History	X				
Inclusion / Exclusion criteria review	X				
PET/CT Scan			X**		
Ablation				X	
MRI		X			
Adverse Events Assessment			X**		X

* Cardiac MRI will be done as per standard of care prior to ablation of ventricular tachycardia. Cardiac MRI is not required for participation on the study.
** Visit 2 occurs at Washington University. Mercy PI/Mercy Research will be notified by Washington University of any adverse events occurring during Visit 2

Criteria for withdrawal of subjects and provision of care after withdrawal

- Patients may cancel participation in the study at any time without penalty. Clinical care will be provided as per standard of care.
- Patients will be removed from the study if they become ineligible at any point before or after the PET scan is performed, or if they become unable or are no longer willing to provide informed consent.

- The investigator(s) may also discontinue or remove a participant from the study for the following:
    - To protect the subject for reasons of safety.
    - If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
    - The subject is determined no longer be able to complete study protocol visit activities.
    - Significant non-compliance by the subject with study requirements.
- The reason for participant discontinuation or withdrawal from the study will be documented.
- It will be documented whether each subject completes the study.
- Information collected up to the last visit will be included in analysis.
- Subjects who sign the informed consent but do not complete the PET/CT scan may be replaced as enrolled subjects.
- Participants who sign the informed consent form and complete the PET/CT scan and subsequently withdraw or are withdrawn or discontinued from the study will not be replaced as enrolled subjects.
- Participants who are unable to complete the PET/CT will be considered withdrawn/incomplete. Their data will be included in summary analysis but will not be used in hypothesis testing.

Study Evaluations and Measurements:

Screening visit activities (i.e., informed consent and eligibility determination) must be completed within 30 days of the scheduled cardiac electrophysiology clinic evaluation and prior to Visit 1 and referral to Washington University for scheduling of the PET/CT scan. No study activity will take place until the subject has provided informed consent.

PET/CT:
PET/CT imaging will be performed at Washington University.
Description of tracers: C11 HED is taken up by neurons like norepinephrine and is stored in presynaptic vesicles. The C11 HED signal is an indicator of sympathetic nerve terminals in the myocardium. This tracer has been used for that purpose for decades, albeit only in research settings given its short half-life, which makes it unsuitable for mass production or transportation, etc.

Imaging is to be performed with PET/CT scanner, after injecting [C-11] MHED.

Please see the Washington University Supplemental Imaging Protocol for further details.

Electroanatomic mapping procedure:
Electroanatomic maps will be created using mapping catheters as performed for standard of care ablation procedures.

High-density electroanatomic maps (>150 points for the LV) will be acquired using the Thermocool SmartTouch or Thermocool SF catheters or similar mapping catheters.

The areas of interest will be mapped in detail using conventional electrophysiologic techniques. Signal amplitude, electrogram characteristics (low amplitude, late, fractionated, etc.) will be noted. Entrainment mapping of VT will be pursued whenever possible.

Maps will be merged offline after the ablation case has ended, which is typically done on the mapping computers. Correlations between PET uptake values and electro-anatomic data obtained during ablation (data regularly obtained during the course of an ablation case including refractory periods, voltage measurements, roles in VT circuit) will be made as part of final data analysis.

Post-procedural follow up will be arranged for subjects based on current standards of care. Antiarrhythmic drugs will be required for, at least, the first 8 weeks unless there is a contraindication.

Data Collection:
Demographics and data regarding type of cardiac disease will be collected from patients. Electroanatomic PET maps are the main form of data that will be collected during the study.

Analysis:

Baseline and demographic characteristics will be summarized.

In addition to the standard clinical analysis of electroanatomic maps, further offline analysis will be performed at the end of the study. This analysis will include fusing them with the PET scans to make correlations as to the physiologic properties of ablation targets. Ablation targets will be classified to three categories:

1. Isthmus sites / isthmus site equivalents
2. Exit and entrance sites
3. Local abnormal electrograms that do not fall under either of the prior two categories

The investigators will try to make correlations between PET uptake values and electro-anatomic data obtained during ablation (data regularly obtained during the course of an ablation case including, for example, refractory periods, voltage measurements, roles in VT circuit). These data are not part of the study CRFs and will be evaluated after all participants have completed the study.

Safety Evaluation:

Standard safety procedures during synthesis and injection of the tracers will be followed. This will be monitored by the radioactive drug research committee at Washington University. Those measures are implemented and monitored by the FDA and the local radioactive drug research committee to ensure the drugs are pyrogen free, and that the dose is properly measured, etc. Injection of the tracer is done under the supervision of a physician and could

entail monitoring for vitals, cardiac rhythm, etc. Please see the Washington University Supplemental Imaging Protocol for further details.

Safety Management:
Adverse events will be monitored at the time points specified in the schedule of events and reported to the PI and the IRB, as required per policy. During the PET/CT, patients will be under the care of Dr. Gropler at Washington University. Following the PET/CT, patients can contact Dr. Awad / Mercy Research team. If an unanticipated problem occurs, study team will notify Mercy IRB, Washington University study team and Washington University IRB, and the radioactive drug research committee or FDA, as applicable.
All related, serious adverse events will be followed until resolution or stabilization as evaluated by the Principal Investigator.

Definition of an Adverse Event
Definitions of adverse events, serious adverse events and unanticipated problems per Mercy policies and procedures. Serious adverse events and unanticipated problems related to the PET/CT scan and tracer injection will be documented and reported for this study. Adverse event screening will begin at the beginning of visit 2 through 30 days following the ablation procedure.

Adverse Event Reporting (Mercy and Washington University)
If unanticipated problems related to the research involving the risks to subjects or others occur during the course of the study, these will be reported to the Mercy IRB in accordance with Institutional Review Board policies and to the Washington University study team for reporting to the Washington University Institutional Review Board, Human Research Protection Office and/or Radioactive Research Drug Committee, as applicable.
Adverse events that are not serious but that are notable, in the opinion of the Principal Investigator, and could involve increased risks to subjects will be summarized and submitted to the IRB at the time of continuing review.

Data Management:
Data will be maintained by Mercy Research according to Mercy and Mercy Research policies and procedures. Case Report Forms will be stored on secured computers.
Data will be stored at a Mercy Research office at Mercy Hospital St. Louis.
Investigators will have access to data / images.
Data will be shared between investigators. Unidentified data could be used for publication in peer review journals, etc.
Images and study data will be shared with Washington University investigators. Data of interest from CRFs for completed subjects will be entered into an Excel spreadsheet at the end of the study to create a study dataset to be shared with Washington University investigators. The study dataset will be sent via Mercy Secure File Transfer system. Images may be accessed by the Mercy Principal Investigator using the Washington University Central Neuroimaging Data Archive (CDNA) and may be shared amongst the Washington University and Mercy study teams for analysis in a secure manner, via the Washington University CDNA system, secure email or CD through mail or hand delivery. PET/CT images will not be loaded into patient medical records.

Confidentiality and Privacy:

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA and subject privacy.
The investigators and other research personnel will not use such data and records for purposes other than study conduct.

Potential risk to Subjects:
Risks associated with the PET/CT scan include:
-Radiation exposure
-the radiotracer is known to have no significant physiologic effect according to published data
-Venipuncture
-Breach of confidentiality

Potential Benefits to Subjects
Advancing methods and approaches to ablation of ventricular tachycardia. The PET/CT scans can advance our understanding of a given patient's scar structure, which could provide some guidance for future ablation procedures.

Subject Payment
Patients will be paid $150 following Visit 2, provided they sign the Washington University Supplemental Consent for Imaging. Subjects who are unable to complete the PET/CT due to technical or quality failures will be paid. Subjects who withdraw or screen fail in advance of Visit 2, or those who choose not to consent to imaging, will not be paid. Payment will be provided by Washington University.

Recruitment Methods
Recruited subjects will be patients referred to Mercy cardiovascular group for management of ventricular tachycardia in whom ablation is determined to be the patient's preferred therapeutic option. Patients will be consented during evaluation in the cardiac electrophysiology clinic, satellite clinics or remotely. The informed consent will be obtained by the Principal Investigator or delegated study personnel. Subjects will be given as much time as they like to make a decision on whether they would like to participate in the study. The investigator will ensure that the patient understands the study's risk and benefits, etc.
PI and study personnel will follow the Mercy Research SOP for informed consent including remote consent procedures.

Partial Waiver of HIPAA Authorization
A partial waiver of HIPAA authorization is being requested for this study. The protected health information used for this research does not pose more than minimal risk to the privacy of individuals and will be managed in accordance with what the data management section of this protocol describes. Additionally, address information may be accessed to provide the consent form for remote consenting procedures prior to the patient's telemedicine visit where the informed consent discussion occurs. Shared data will be de-identified, and any identifiable data will be stored on secured computers which the investigators have access to. The research could not be practicably conducted without this partial waiver of HIPAA authorization as recruitment would be limited to a smaller population than what this protocol has designated as the study population. Additionally, access to protected health information is necessary to determine eligibility of potential research participants.

Protected health information used as part of this research study will not be reused or disclosed by any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart.

Federal Regulatory Requirements for Waiver or alteration of HIPAA Authorization 45 CFR 164.512(i.)(2)(ii):
A) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
1) an adequate plan to protect the identifiers from improper use and disclosure
2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
3) adequate written assurances that the protected health information will not be reused or disclosed by any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart
B) The research could not practicably be conducted without the waiver or alteration; and
C) The research could not practicably be conducted without access to and use of the protected health information

Study Merits and Innovation:

a. Using CT to perform accurate merging of PET imaging data with the electro-anatomic maps routinely used during ablation procedures
b. Aims at examining the applicability of cutting edge imaging techniques and agents, to improve techniques used in routine, yet costly, ablation procedures and improve patient outcomes
c. Will be the first study to obtain [C-11] MHED in patients who already have clinical VT, which might reveal findings that might not be readily apparent in prospective upstream scans reported in recent studies, which could have been obtained years prior to the development of clinical VT.
d. Examines the distribution and characteristics of sympathetic dysinnervation in non-ischemic cardiomyopathy, which has not been the focus of other of the studies done with myocardial adrenergic receptor imaging with SPECT or PET.
e. Eventually, findings could be applied in everyday clinical practice, to improve outcomes and improve the understanding of VT.

Future Direction:

1. Randomized clinical study to examine the impact of more detailed imaging of scar innervation on clinical outcomes during VT ablation.
2. Develop similar imaging agent labeled with F19. The longer half-life of F19 would allow for wide commercial use for pre-ablation imaging, risk stratification for sudden cardiac death, etc.
3. Explore utility in defining risk of sudden cardiac death in the setting of cardiac syncope, and in patients who do not readily quality for ICD therapy, i.e. those with mildly reduced ejection fraction, while being at significant risk for sudden death.

4. Assess the feasibility of imaging the autonomic input to the left atrium, particularly the antral aspect of the pulmonary veins, which could be used to identify targets for ablation of atrial fibrillation. That could be fully investigated in a separate future study.

References:

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