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Three Dimensional Neuro-cardiac Imaging Using ^{123}I-metaiodobenzylguanidine Single Photon Emission Computed Tomography to Guide Ventricular Tachycardia Ablations

Protocol **09/16/09**

Background

VT is the next frontier in electrophysiology. An increasing number of patients require VT ablation despite optimal medical therapy. Myocardial scars are present in the majority of patients with ischemic and nonischemic cardiomyopathy and usually act as the substrate for reentrant VT. According to pathological findings, rather than being homogeneous tissue, cardiac scars often contain many “channels” of surviving myocardium within the area, which enable electricity to enter, traverse, and exit the scar via different connections within this network and form a “reentry loop” maintaining reentrant VT. Cauterizing the myocardial channels along the scar border in order to interrupt those loops and clinical VT, therefore, is the aim for most reentrant VT ablations. Because of hemodynamic intolerance as well as the pre-existing alternative channels and exit sites, an approach targeting single VT channels identified by their electrical characteristics will not be applicable for the majority of patients. A “substrate-guided” ablation approach is frequently conducted to treat such arrhythmias and involves the placement of linear ablation lesions along the scar

border in order to interrupt as many channels as possible. These are the most commonly used and accepted treatment strategies.

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A detailed anatomic knowledge of scar location and exact scar borders is necessary to accurately place curative ablation lines. 3D mapping systems are currently used to create a “voltage map” of the left ventricle (LV) to obtain such anatomic information (current “gold standard”). The amplitude of endocardial voltages is measured and recorded in real time by a roving mapping catheter moved along the endocardial LV surface. However, voltage mapping has several important limitations: First, endocardial voltage is limited in distinguishing between nonviable and damaged but viable myocardium. Second, a single endocardial voltage measurement cannot differentiate between endocardial and epicardial scar components. Third, suboptimal catheter contact can result in falsely low voltage measurements leading to an overestimation of ventricular scar and unnecessary ablation lesions. Fourth, the limited spatial resolution of the catheter tip and the mapping density of the voltage map can make the detection of isolated scar areas or small patches of surviving myocardium (which could represent viable VT channels)

difficult.[12] Finally, detailed voltage mapping is quite time consuming, which increases procedure length and complication rates.

Current research focuses mostly on better defining the myocardial scar with metabolic or anatomic imaging. However, this has multiple limitations. Magnetic resonance (MR) imaging has been validated to assess anatomic information about scar but is currently contraindicated after implantable cardioverter-defibrillator placement and thus unavailable in nearly all patients requiring VT ablations. Metabolic imaging can provide an alternative definition of myocardial scar to voltage mapping, but will still rely

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on the same therapeutic approach of creating linear lesion along the scar border, which has only a limited long-term success rate of 53%.

Abnormal sympathetic cardiac innervation has been shown to have prognostic value for different heart diseases, e.g. heart transplant, coronary artery disease, heart failure, arrhythmias, etc. Importantly, there is a clear association with an increased cardiac morbidity and mortality in ischemic heart diseases. ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) allows visualization of the cardiac innervation, which could provide additional information to understand VT.

Therefore, the clinical need exists for a novel approach, which could provide new pathophysiological insights and may provide

innovative treatment strategies. Given a well established relationship between ventricular arrhythmias/sudden cardiac death and the cardiac innervation we propose to investigate the relationship between MIBG innervation imaging and ventricular ablation procedures.

Objective of the study

The purpose of this study is to assess if Single Photon Emission Computed Tomography (SPECT) demonstrating cardiac innervation can be integrated into current electrophysiology voltage mapping system and provide improved guidance for ablation of ventricular tachycardia.

Benefits to the Patient

Direct benefits to the participant would be the possibility of reducing VT ablation procedure time. Indirect benefits include the possibility of reducing VT ablation procedure time and increasing the accuracy of the ablation location with an overall improvement in the quality of life.

Study Population

Inclusion Criteria:

1**.** Patients with ventricular arrhythmias requiring VT ablation
2. Age 18 y and above;
3. Ability to sign informed consent.

Exclusion criteria:

1. Younger than 18 y;
2. Inability to sign informed consent.

Procedures

^{123}I-MIBG Imaging Acquisition

All subjects will be pretreated with either perchlorate (potassium or sodium) or an iodine solution to block uptake of free iodine (^{123}I) by the thyroid gland. For the imaging study, an activity of 370 MBq (10 mCi) ^{123}I-mIBG (GE Healthcare) will be administered intravenously, and a 10-minute planar image of the anterior thorax (128_128 matrix) will be acquired beginning 15 minutes after tracer injection. A SPECT study will then be acquired using either a dual- or triple-head gamma camera (minimum 30 projections/head, 20 to 30 seconds/ projection, 64_64 matrix). Repeat planar image and SPECT studies will be acquired at 4 hours after injection. All camera heads will be equipped with low-energy, high-resolution collimators, and all acquisitions will be performed with a 20% energy window centered at the 159 keV photopeak of ^{123}I. Images will be reacquired 6 months after the ablation.

^{123}I-MIBG Imaging Reconstruction and Integration

The SPECT dataset will undergo post-procedural DICOM3 formatting analogous to the CT or MRI datasets using MATLAB 7.6.0 (The Mathworks Inc.). The formatted SPECT dataset will be transferred into the electrophysiology mapping system using the CartoMERGE Image Importation algorithm.

Voltage Map Dataset

All voltage maps will be created by an electrophysiologist using a Carto 3D mapping system and a 3.5-mm Navistar cooled-tip catheter. Bipolar electrograms will be filtered at 10–30 to 400–500 Hz. Standard clinical voltage criteria will be used to define scar (<0.5 mV), abnormal (0.5–1.5 mV), and normal (>1.5 mV) myocardium. Each voltage map will be divided into 17 segments according to the AHA LV model to conduct visual analysis as well as quantitative analysis.

123I-MIBG Imaging Dataset

For the planar images a whole-heart region of interest (ROI) will be drawn manually to include both ventricles. A square mediastinal ROI (7x7 pixels) will be drawn in the upper mediastinum, using the apices of the lungs as anatomic landmarks. The H/M ratio will be calculated as the ratio of the counts per pixel in the two ROIs. H/M data will be used to calculate myocardial washout using two formulas. Uncorrected washout will be calculated as

H/M (early)–H/M (late)/H/M (early).

Background corrected washout will be calculated as

H (early)–M (early)–H (late)–M (late)/H (early)–M (early)

Single aggregate values for each washout parameter will be determined as described above.

For the SPECT image sets, segmental myocardial activity will be scored using a 17–segment model. Each segment will be scored using the following scale: 0 normal tracer uptake, 1 mildly reduced uptake, 2 moderately reduced uptake, 3 severely reduced uptake, 4 absent tracer uptake, NA not assessable. Accordingly, the summed score (SS) for each study could range from 0 to 68 (17x4).

Heart Rate Variability

All the patients will undergo 24-hour ambulatory electrocardiographic monitoring on entrance into the study in order to investigate the prognostic value of heart rate variability (HRV). Time and frequency domain HRV parameters will be calculated from those recordings. Traditional measurements of HRV will be analyzed according to the Task Force of the European Society of Cardiology and the North American society of Pacing and Electrophysiology Time domain analysis of HRV will include the mean duration of

all normal-to-normal (NN) intervals (mean RR), standard deviation of all normal-to-normal intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments, mean of SDNN in all 5-min segments (SDNN index), square root of the mean of the sum of the squares of differences between adjacent NN intervals, number of NN intervals differing by more than 50 ms from the adjacent interval divided by the total number of NN intervals, and HRV triangular index. HRV parameters will be reacquired 6 months after the ablation.

Patient Characteristics

Patient clinical characteristics (gender, age, ejection fraction, comorbidities, anti-arrhythmia medications) and their clinical VT characteristics (morphology, frequency, duration, cycle length, termination strategy, previous ICD shocks) will be collected.

Research Part of the Protocol

Four specific aims were plan to achieved for this research. Specific Aim 1: Evaluate if areas of left ventricular (LV) denervation measured by cardiac 123I-metaiodobenzylguanidine (MIBG) SPECT imaging (innervation map) can be integrated into the CartoXP electrophysiology mapping system. Specific Aim 2: Evaluate, in a group of 20 patients, if areas of denervation in the 3D maps reconstructed from MIBG SPECT imaging correlate with the voltage-map defined scar targeted during VT ablations Specific Aim 3: Determine the changes of cardiac innervation before and 6 months after the VT ablation in 20 patients. Specific Aim 4: Investigate the possible predicting factors for VT reoccurrence within six month after the ablation.

Risks

Ventricular tachycardia ablation procedures have a definite morbidity and mortality, with a major complication rate of endocardial procedures ranging from 2.5 to 6 %. This is to due to both patient-related and procedure-related factors. Patients typically suffer from congestive heart failure and other comorbidities and the procedures are long, requiring the patient to lie flat for up to eight hours at times. It must be emphasized that both procedures are currently performed on patients as indicated.

In addition to the risks of sedation, standard risks of an endocardial procedure include bleeding and other vascular access complications, stroke, myocardial infarction and rarely myocardial rupture and pericardial tamponade, aortic valve avulsion, and entanglement of the catheter in the mitral valve apparatus requiring surgical intervention, and death. Attempts to ablate VT using an endocardial-only approach in patients with a high likelihood of having an epicardial origin would lead to unnecessarily prolonged endocardial procedures and failed ablation. This would lead to a second, epicardial, procedure.

Measures to Reduce Risks

Our approach will be to conduct the cardiac imaging scan and reconstruction for the patients first. This will be followed by endocardial mapping. The imaging information known before the endocardial procedure will help reduce the mapping time, improve the mapping/ablation accuracy and reduce the risk due to the long procedure time. It is our belief that, with this imaging guidance approach, we can improve the success rate of VT ablation in VT patients.

Data Analysis

Means and standard deviations will be calculated for each of the four registration strategies, i.e. LM, LM and SF, VA, VA and SF, in order to identify the best registration method.

Differences in scar size, morphology and severity between 3D MIBG innervation maps and EP voltage maps will be analyzed using Student T-test. Segments where diastolic potentials, fractionated potentials and successful ablation sites are located will be investigate in order to indentify the characteristics of the MBIG imaging in those segment, e.g heterogeneity, etc. Segmental/regional washout rate, normalized MIBG activities as well as SS scores will be compared with segmental/regional voltage values in order to indentify the relationship between cardiac denervation areas and abnormal endocardial voltage areas.

Differences in size, morphology and severity, regional/global washout from planer images, normalized regional intensities, regional activity summed scores between pre and post ablation 3D MIBG innervation maps will be analyzed using Paired T-test. Global wash out rate will be correlated with HRV indexes before and after the ablation to investigate the relationship between them. Normalized regional MIGB intensities, regional wash out rate and regional SS score both before and after ablations will be compared between VT exit sites segments and other segments with independent sample T-test in order to identify the innervation characteristics of the exit site segments.

Measurements and results will be reported as mean ± standard deviation if a normal distribution can be assumed. P values at a level of <0.05 will be considered as statistically significant. Pearson correlation will be conducted to investigate the relationship between two sets of images. The logistic regression will be conducted to investigate the relationship between 3D innervation morphologies, HRV parameters, patient characteristics, clinical VT characteristics and the VT recurrence within the six month

follow-up period. Receiver operating characteristics (ROC) curves will be used to assess best correlation performed with innervation and voltage map.

C.6.1. Publications

1. Dickfeld T, Lei P, Dilsizian V, et al. Integration of Three-Dimensional Scar Maps For Ventricular Tachycardia Ablation Using Positron Emission Tomography/Computed Tomography (PET/CT). JACC Imaging 2008; 1:73-82

2. Tian J, Smith MF, Chinnadurai P et al. Clinical application of PET/CT fusion imaging for three-dimensional myocardial scar and left ventricular anatomy during ventricular tachycardia ablation. J Cardiovasc Electrophysiol. Published January 13, 2009; DOI: 10.1111/j.1540-8167.2008.01377.x

3. Tian J, Smith MF, Jeudy J, Dickfeld T. Multi-Modality Fusion Imaging Using Delayed-Enhanced Cardiac Magnetic Resonance Imaging, Computed Tomography, Positron Emission Tomography and Real-Time Intracardiac Echocardiography to Guide Ventricular Tachycardia Ablation in Implantable Cardioverter-Defibrillator Patients. Heart Rhythm 2009; In Press

C.6.2. Published Research Abstracts

1. Tian J, Smith MF, Turgeman A, Dilsizian V, Abbo A, Peters R, Saba M, Shorofsky S, Dickfeld T. (2009) Comparison of PET Metabolic Activities among Scar, Border Zone and Healthy Myocardium in Patients Undergoing Ischemic VT Ablation. Heart Rhythm, In press

2. Tian J, Smith MF, Dilsizian V, Abbo A, Peters R, Saba M, Shorofsky S, Dickfeld T. (2009) Integration of 3D Scar Maps using SPECT to Guide Ventricular Tachycardia Ablation. Heart Rhythm, In press

3. Dickfeld T, Tian J, O'Donnell T, Anand A, Hussein A, Peters R, Saba M, Shorofsky S, Jeudy J. (2009) Integration of Three-dimensional, Delayed Enhancement MRI Scar in Patients with ICD for Guidance of Ventricular Tachycardia Ablation. Heart Rhythm, In press

4. Tian J, Smith MF, Chinnadurai P, Dilsizian V, Turgeman A, Abbo A, Plotnick D, Hood R, Peters R, Saba M, Shorofsky S, Dickfeld T. (2008) First Clinical Experience Using PET/CT Fusion Imaging of Three-Dimensional Myocardial Scar and Left Ventricular Anatomy for Ventricular Tachycardia Ablation. Circulation, 118, 18, (S2) S690

5. Tian J, Smith MF, Turgeman A, Abbo A, Bruce P, Hood R, Peters R, Saba M, Shorofsky S, Dickfeld T. (2008) Comparison of Anatomical and Dynamic CT-

derived Parameters between Scar, Border zone and Healthy Myocardium in Patients Undergoing Ischemic VT Ablation. Circulation, 118, 18, (S2) S937

6. Dickfeld TM, Read K, Gotman S, Tian J, Peters R, Hood R, Saba M, Shorofsky S, Fleiter T. (2008) Catheter Navigation, Ablation and Lesion Visualization Using Real-Time Computer Tomography Guidance. Circulation, 118, 18, (S2) S831

7. Dickfeld, TM, Hodefi D, Read K, Plotnick D, Tian J, Akella J, Nillas M, Johnson A, Saba M, Shorofsky S and Fleiter T. (2008) Real-Time CT Guided Ablation Procedures: Radiation Exposure, Safety and Feasibility. Heart Rhythm 5, (5S), S272