The current concept of re-entrant ventricular tachycardia (VT) in the setting of structural heart disease postulates a complex interplay of triggering mechanisms initiating VT and fixed anatomic substrate capable of maintaining the arrhythmia. Modern ablation approaches primarily target an anatomic substrate that consists of scar with embedded bands of surviving myocardium that represent necessary areas of slow conduction. With this approach, the success rate of VT ablation remains limited, with a VT recurrence rate of 47% during 6 months in a large series despite experienced operators and use of state-of-the-art ablation technology.

A possible explanation for this limited success is that the current anatomic scar–based ablation strategy does not incorporate VT triggers and substrate modulators, such as abnormal innervation, which is known to play an important role in arrhythmogenesis. Abnormal cardiac innervation
WHAT IS KNOWN

• Sympathetic cardiac innervation plays an important role in ventricular arrhythmogenesis and may act as a trigger and substrate modulator of the ventricular tachycardia substrate.
• Current ablation strategies do not incorporate innervation as a potential target during ventricular tachycardia ablations.

WHAT THE STUDY ADDS

• In patients with ischemic cardiomyopathy presenting with drug-refractory ventricular tachycardia, denervated areas are larger =2.5× larger than areas of voltage-defined scar and usually include the inferior wall.
• Although 36% of successful ablation sites demonstrated a bipolar voltage of >1.5 mV, all successful ablation sites were within areas of abnormal innervation. This suggests a possible role of 3-dimensional innervation maps to guide ventricular tachycardia ablation.

has long been associated with an increased risk of sudden cardiac death and ventricular arrhythmias. Decreased reuptake by impaired myocardial presynaptic nerve terminals in patients with ischemic cardiomyopathy results in a buildup of these catecholamines in the synaptic cleft. This leads to a downregulation of postsynaptic β-adrenergic receptors, with resultant worsening cardiomyopathy and increased arrhythmogenesis.

Cardiac sympathetic innervation can be directly imaged with commonly used nuclear radioisotopes, 123I-meta-iodobenzylguanidine (123I-MIBG). As a norepinephrine analogue, 123I-MIBG is similarly released into the synaptic cleft in response to sympathetic input by presynaptic nerve terminals. Recently, global cardiac denervation, as assessed with 123I-MIBG, was demonstrated to correlate with the occurrence of implantable cardioverter-defibrillator (ICD) therapies in both ischemic and nonischemic subjects.

To incorporate this new dimension of ventricular arrhythmogenesis (VT triggers/substrate modulators) into ablation of drug-refractory VT, this study sought to integrate regional sympathetic innervation information in the form of 3-dimensional (3D) innervation maps with standard voltage maps. In addition, it aimed to achieve pathophysiological insights by comparing and integrating 3D 123I-MIBG innervation maps with standard electroanatomic maps.

Methods

Study Protocol
The study was designed as a prospective, single-center feasibility study of patients with ischemic heart disease scheduled for radiofrequency ablation for pharmacologically refractory VT at University of Maryland Medical Center (Baltimore, MD) from January 2010 through January 2014. All study protocols were approved by the University of Maryland Institutional Review Board.

Figure 1. Heart/mediastinal ratio (H/M). Planar 123I-meta-iodobenzylguanidine (123I-MIBG) image with a 7×7 pixel region of interest (ROI) drawn in the mediastinum (yellow square) and an irregular ROI drawn around the cardiac silhouette defining the epicardial border of the heart (yellow outline). To calculate the H/M ratio, the mean counts/pixel in the cardiac region are divided by the mean count/pixel in the mediastinal region.

123I-mIBG Scintigraphy
Preprocedural 123I-mIBG planar and single-photon emission computed tomographic (SPECT) imaging was obtained in 15 patients with ischemic heart disease and drug-refractory VT before VT ablation. Patients were pretreated with either perchlorate (potassium or sodium) or an iodine solution at least 60 minutes before injection to block the uptake of free iodine by the thyroid gland. Patients were then administered 370 MBq (10 mCi) of 123I-mIBG (GE Healthcare, Buckinghamshire, United Kingdom) intravenously. Planar imaging of the anterior thorax (128×128 matrix) was performed 15 minutes later, as was SPECT imaging using a dual-head gamma camera (minimum 30 projections/head, 20–30 seconds/projection, 64×64 matrix, Philips SKYLight SPECT Camera, Philips Medical Systems, Milpitas, CA). Repeat planar and SPECT imaging was performed 4 hours after injection. All camera heads were equipped with low-energy, high-resolution collimators, and all acquisitions were performed with a 20% energy window centered at the 159-keV photopeak of 123I.

Analysis of Planar 123I-mIBG Images
Heart/mediastinal ratio (H/M) was determined on 4-hour planar images from the mean counts/pixel in a visually drawn region of interest over the cardiac silhouette divided by the mean counts/pixel in a 7×7-pixel region of interest placed in the mediastinum (Figure 1).

3D Regional 123I-mIBG Innervation Map Reconstruction and Integration With Voltage Maps
3D reconstructions of the left ventricular myocardium and denervation defects were created using the Amira Visual Imaging software (Visage Imaging, San Diego; Figure 2). On each 2D 123I-mIBG SPECT slice, areas of normally innervated myocardium, denervation, and transition zone (TZ) were traced manually by 2 experienced cardiac nuclear medicine physicians (V.D. and W.C.), who were blinded to the patient’s characteristics. Disagreements were resolved by
were positioned in the RV, along the His bundle and in the coronary sinus. An 8-Fr 3.5-mm irrigated-tip catheter (Navistar Thermocool; Biosense Webster; Diamond Bar) was positioned in the left ventricle (LV) through a retrograde aortic approach (n=11) or transseptal approach (n=4). Intravenous heparin was used during the procedure to maintain an activated clotting time of 300 to 350 s.

Voltage maps were created with a 3.5-mm open irrigated-tip catheter (Thermo-Cool; Biosense Webster) or a multielectrode mapping catheter (PentaRay; Biosense Webster) using a filling threshold of 10 mm. Mapping points, 301±245, were taken per patient. Unipolar signals were filtered at 2 to 240 Hz, and bipolar signals were filtered at 30 to 500 Hz and were acquired during sinus rhythm or ventricular pacing in patients with pacemaker dependency or resynchronization therapy. Standard clinical voltage criteria were used to define scar (bipolar voltage, <0.5 mV), BZs (0.5–1.5 mV), and normal myocardium (>1.5 mV). For unipolar voltage, a cut-off value of 5.8 mV was used to differentiate scar from nonscarred myocardium.13

Near-field bipolar electrograms were analyzed at a speed of 400 mm/s. Fractionated electrograms were defined as having a voltage of ≤0.5 mV, duration of ≥133 ms, and an amplitude/duration ratio of ≤0.005. Isolated potentials were separated from ventricular electrograms by an isoelectric segment and a segment with low-voltage noise (<0.05 mV) >20-ms duration at a gain of 40 to 80 mm/mV.14

Fluoroscopy, local electrogram characteristics, and real-time intracardiac echocardiography were used to confirm stable catheter contact during electroanatomic mapping. Programmed electric stimulation was performed from the RV apex and RV outflow tract, as well as from ≤2 LV sites with additional isoproterenol infusion when VT was not inducible from the RV. This protocol included the use of ≤3-drive train cycle lengths (350, 400, and 600 ms) and ≤3 extra-stimuli with a minimal coupling interval of 200 ms.

**VT Ablation**

The ablation procedures targeted clinical VT as documented by 12-lead ECGs or presumed clinical VT defined by cycle lengths, local RV timing to far-field electrogram, and far-field morphology from ICD recordings.

For hemodynamically unstable or nonsustained VT, pace map matches of 211/12 with the longest Stim-QRS (if multiple sites with identical match found) defining the site closest to central isthmus were used to approximate the VT channel/exit sites, and limited activation mapping was performed if possible. Limited activation mapping of these sites in VT was performed in 4 of the 15 subjects to confirm the site of the earliest activation. Radiofrequency ablation lesions (40–50 W; 60 seconds) were applied at these locations. Additional VT substrate modification was performed as clinically indicated by creating tangential ablation lesions along scar borders or radial lesions transecting the scar toward the scar center or anatomic boundary, such as mitral valve ring. At the end of ablation, programmed electric stimulation was repeated and successful ablation was defined as the inability to induce the clinical or presumed clinical VT.10–15

**Comparison between 3D Innervation Maps and Voltage Maps**

Voltage-defined scar and BZ size and percent of total LV mass were quantified for bipolar and unipolar voltage and compared with the area of denervation and TZ from ¹²³I-mIBG innervation map using the CarotMerg Idaho surface measurement tool. In addition, each 3D reconstructed ¹²³I-mIBG innervation map and voltage maps were analyzed using the standard 17-segment American Heart Association model.12 Individual segments were categorized as myocardium with abnormal voltage or innervation if any such myocardium was present in that segment. Successful ablation points were examined on ¹²³I-mIBG innervation and voltage maps.

**Statistics**

SPSS (IBM) for Windows 16.0 was used for statistical analyses. Continuous variables are expressed as median and quartiles (Q1–Q3).
Results

Patient Characteristics

Fifteen patients with ischemic, drug-refractory VT were enrolled in the study (Table 1). All patients had evidence of previous myocardial infarction by cardiac imaging. All had previous revascularization, with previous coronary artery bypass grafting (n=6), previous coronary stenting (n=8), or both (n=1). No revascularization was performed within 6 months of VT ablation.

Planar and Regional 123I-mIBG Analysis

Four-hour H/M derived from planar images was 1.5 (Q1–Q3, 1.3–1.6). Normalized 123I-mIBG uptake in areas of denervation was 25% (Q1–Q3, 15.3%–31.7%; mean±SD, 24±10%; minimum–maximum, 4%–50%) and increased to 40% (Q1–Q3, 30.2%–43.6%; mean±SD, 38±10%; 14%–72%) in the TZ (P<0.001). Myocardium with preserved sympathetic innervation demonstrated a significantly higher uptake of 67% (Q1–Q3, 52.2%–71.4%; mean±SD, 63±11%; 39%–00%), respectively (P<0.001). Resulting midpoints were 0% to 31%, 31% to 52%, and >52% for denervated area, TZ, and normally innervated myocardium, respectively (Figure 3).

Comparison Between 3D Reconstructed 123I-mIBG Images and Electroanatomic Maps

3D reconstructions of 123I-mIBG SPECT images were successfully performed in all patients. All patients had areas of denervation, TZ, and normal innervation on MIBG innervation maps and areas of voltage-defined scar, BZ, and normal myocardium on bipolar and unipolar electroanatomic maps.

The region of bipolar voltage–defined scar was inferior in 11 patients (73%), anterior in 6 patients (40%), lateral in 10 patients (67%), and septal in 9 patients (60%), whereas denervated areas were found in the inferior wall in 15 patients (100%), anterior wall in 3 patients (20%), the lateral wall in 14 patients (93%), and the septum in 12 patients (80%). The segmental 17-segment analysis showed that the denervated area commonly extended more inferiorly and inferoapically than the bipolar electroanatomic scar, affecting at least parts of the inferior wall in all patients (Figure 4).
123I-mIBG denervated areas were 2.5x larger than bipolar voltage-defined scar (24.6% [Q1–Q3, 18.3%–34.4%] versus 10.6% [Q1–Q3, 3.9%–16.4%]; P<0.001), whereas the size of 123I-mIBG TZ was statistically similar to bipolar-defined BZ with a trend to a larger voltage-defined BZ (11.4% [Q1–Q3, 9.5%–13.2%] versus 16.6% [Q1–Q3, 12.0%–18.8%]; P=0.07). Similarly, in the segmental analysis, denervation was seen in 9 (Q1–Q3, 8–10) segments of the left ventricle, whereas 7 (Q1–Q3, 4–9) segments demonstrated bipolar scar (P=0.09). 123I-mIBG TZ was seen in 10 (Q1–Q3, 9–12) segments and bipolar BZ in 10 (Q1–Q3, 9–16) segments (P=0.16). Seven (Q1–Q3, 3–8) segments only contained bipolar voltage measurements >1.5 mV, whereas 5 (Q1–Q3, 4–6) segments did not contain any areas of either denervation or TZ (a single segment commonly contained areas of both denervation and TZ).

Unipolar scar was significantly larger than bipolar scar (29.2% [Q1–Q3, 17.7%–58%] versus 10.6% [Q1–Q3, 3.9%–16.4%]; P=0.003), which was largely due to 3 patients with diffuse unipolar scar affecting >75% of the LV myocardium. Unipolar scar colocalized with bipolar scar in all patients. No significant differences were found between the 123I-mIBG denervated areas and the unipolar scar area (P=0.55).

Regional analysis revealed that 76% of segments with bipolar scar had severe innervation defects, whereas 84% of bipolar scar had any abnormal innervation (either denervation or TZ). Bipolar and unipolar voltages varied widely within the areas of complete denervation (0.8 mV [Q1–Q3, 0.3–1.7 mV]; mean±SD, 1.3±1.5 mV) and (4.0 mV [Q1–Q3, 2.9–5.6 mV]; mean±SD, 4.4±2.3 mV) and 123I-mIBG TZ (0.8 mV [Q1–Q3, 0.4–1.8 mV]; mean±SD, 1.5±1.8 mV) and (4.6 mV [Q1–Q3, 3.2–6.3 mV]; mean±SD, 5.0±2.6 mV). Bipolar voltage measurements of mapping points in the denervated area and 123I-mIBG TZ were in scar (<0.5 mV), BZ (0.5–1.5 mV) and normal category (>1.5 mV) in 35%, 36%, and 29%, as well as 35%, 35%, and 30%, respectively. The number of mapping points corresponding to scar, BZ, and normal voltage was not statistically different within denervated area or TZ (P>0.05 each), suggesting that voltage was a poor discriminator to predict myocardial innervation state.

Of a total of 1487 points within 123I-mIBG denervated areas, 3.1% (Q1–Q3, 1.1%–5.2%; mean±SD, 5.1±8.7%) demonstrated isolated potentials, with 7.1% (Q1–Q3, 4.6%–15.2%; mean±SD, 11.7±12.1%) demonstrating fractionation. In the MIBG-defined TZ, of a total of 611 mapping points, 0% (Q1–Q3, 0%–0%; mean±SD, 0.7±1.7%) showed isolated potentials, with 7.4% (Q1–Q3, 1.9%–18.6%; mean±SD, 10.8±10.9%) showing fractionation.

**Discussion**

The main findings of the study are (1) using molecular imaging, 3D 123I-mIBG innervation maps could be successfully reconstructed and integrated into clinical mapping systems; (2) denervated areas were 2.5x larger than bipolar scar areas defined by the current gold standard of voltage mapping and commonly extend into the inferior wall; (3) neither bipolar nor unipolar voltage could reliably predict the innervation status of LV myocardium; (4) cut-offs of 0% to 30%, 30% to 50%, and >50% well-approximate denervation, TZ, and normal myocardium; and (5) all successful VT ablation sites were located in areas of abnormal innervation even if those sites demonstrated normal bipolar voltage.
Current Approaches to VT Ablation

Current VT ablation strategies primarily target the anatomic VT substrate, ie, surviving electrically conducting fibers within a myocardial scar. As entrainment mapping is rarely possible because of hemodynamic instability, anatomically based substrate-guided ablation procedures are frequently performed. These use pace mapping, late/diastolic potentials, or local abnormal ventricular activities as electric surrogates for anatomic information of surviving myocardial bundles within the scar.

To further improve the understanding of the scar substrate, cardiac imaging with gadolinium-enhanced MRI, positron emission tomography–computed tomography, and contrast-enhanced multidetector CT has been used to improve the anatomic understanding of scar substrate, BZ, and detailed cardiac anatomy when integrated into 3D mapping systems.

Despite the use of these approaches, the success rate of these anatomically based VT ablation approaches remains suboptimal. In the Thermocool VT Ablation Trial, only slightly more than half of patients with ischemic cardiomyopathy who underwent VT ablation for recurrent monomorphic VT were free of VT after 6 months of follow-up. Therefore, novel approaches incorporating other aspects of arrhythmogenesis, such as VT triggers and substrate modulators, may be beneficial to improve our understanding of VT substrate and to improve the success rate of VT ablation.

Innervation and Arrhythmogenesis

Abnormal innervation has long been associated with an increased risk of sudden cardiac death and ventricular arrhythmias; however, this important dimension of proarrhythmia has thus far not been incorporated clinically to improve substrate characterization and guide ablation therapy of ventricular arrhythmias.

Mechanistically, recent studies have suggested that damaged myocardial presynaptic nerve terminals demonstrate reduced uptake of catecholamines, by the uptake-1 mechanism as has been shown with radiolabeled catecholamines. This leads to accumulation of these neurotransmitters in the synaptic cleft, with consequential overexposure, and down-regulation of postsynaptic β-adrenergic receptors and an imbalance between presynaptic and postsynaptic signaling.

It is thought that this disturbance leads to an increased risk of arrhythmias and contractile dysfunction. This theory is supported by the fact that pharmacological sympathetic blockade decreases the risk for ventricular arrhythmias. Left and bilateral stellate ganglion block with resultant cardiac sympathetic denervation has been shown to decrease the rate of ICD shocks. In addition, nerve sprouting after myocardial injury, which can predispose to sympathetic hypersensitivity, leading to an increased risk of ventricular arrhythmias, may be another important concept linking the sympathetic nervous system and the risk for sudden death. This is supported by the finding that the infusion of nerve growth factor resulted in an upward/leftward shift in the dose–response curves to catecholamines, shortening of refractoriness, and increased risk for ventricular arrhythmias.
Using well validated molecular imaging techniques, visualization of these global and regional sympathetic innervation abnormalities is possible with $^{123}$I-$m$IBG. The decreased reuptake of norepinephrine into presynaptic nerve terminals found in patients with cardiomyopathy results in lower intensity $^{123}$I-$m$IBG signals. This decreased reuptake of $^{123}$I-$m$IBG has been demonstrated across a wide spectrum of subgroups known to be at risk for ventricular arrhythmias, including ischemic and nonischemic cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic RV cardiomyopathy, and VT patients with structurally normal hearts.

Multiple previous studies demonstrated that the global cardiac innervation (H/M and washout rate of $^{123}$I-$m$IBG) correlates with increased risk of ICD therapy, worsening heart failure, and cardiac death. Recent studies have suggested that a regional assessment of innervation can be performed with $^{123}$I-$m$IBG, which was predictive of VT inducibility and ICD shocks. Given the semiquantitative regional analysis used in these previous studies, this study sought to establish quantitative, normalized cut-offs for denervation, TZ, and normal myocardium. The correlating categories of 0% to 30%, 30% to 50%, and >50% may facilitate the transition to a more reproducible use of MIBG for clinical and research applications.

Importantly, this study found that all successful ablation sites demonstrated abnormal innervation patterns. The fact that 36% of successful ablation sites were in areas with preserved bipolar myocardial voltage, conventionally thought to indicate lack of LV scar, suggests that innervation abnormalities could play an important role as a trigger and substrate modulator responsible for ventricular arrhythmogenesis. As traditional voltage mapping is unable to reliably detect denervation, molecular innervation tracers, such as $^{123}$I-$m$IBG, are required. Indeed, the areas of denervation were more than twice the size of voltage-defined scar. This is consistent with animal studies in which innervation imaging postinfarct demonstrated a significantly larger defect than the associated perfusion abnormalities and the extent of innervation/perfusion mismatch correlated with VT inducibility. A likely explanation is that neuronal structures are more sensitive to hypoxemia than myocytes and that neuronal damage may occur in areas without significant myocardial fibrosis.

Limitations
This study has several limitations. This is a first-in-man single-center feasibility study in patients with ischemic cardiomyopathy. It is unclear whether those findings would be applicable in other patients with VT, such as in nonischemic cardiomyopathy. Current $^{123}$I-$m$IBG imaging is limited by the spatial resolution of SPECT camera technology, which is in the range of 10 to 12 mm. However, $^{123}$I-$m$IBG is the most established innervation tracer and most commonly used for innervation imaging and studies.

A 3-point registration algorithm was used to provide a standardized approach to image registration, as opposed to visual alignment. Rotational errors were accounted for by including RV anatomy, as done in previous imaging studies. Despite these measures, registration errors, similar to in other image integration techniques, may have affected the quantitative analysis.

Although technical reasons for the inferior innervation defect cannot be excluded, recent studies demonstrating inferior denervation in patients with syndrome X but preserved innervation in the majority of control patients for a 5±3-month follow up support that the inferior imaging defect is a real phenomenon.

### Table 2. Number of Ablation Sites Categorized by Innervation and Voltage Characteristics

<table>
<thead>
<tr>
<th>Voltage Map</th>
<th>Scar</th>
<th>Border Zone</th>
<th>Normal Voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervation map</td>
<td>Denervated</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Transition zone</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Normal myocardium</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

![Figure 7](https://example.com) Comparison of 3-dimensional innervation map and electroanatomic map: discordant preserved voltage-denervation location of successful ablation site. A, Bipolar electroanatomic map, inferior view, demonstrating inferior scar with ablation site (yellow dot; white arrow) at inferior septal location within the area of preserved bipolar voltage (>1.5 mV). B, Coregistration of electroanatomic bipolar voltage map and innervation map demonstrating significantly larger area of denervation than bipolar voltage scar or border zone. Successful ablation point (yellow dot; white arrow) is located within the area of denervation (red transparent mesh; analogous to Figure 3) close to the denervation/neuronal transition zone interface despite preserved bipolar voltage ($^{123}$I-metaiodobenzylguanidine transition zone in overlying transparent yellow, and normally innervated myocardium in overlying transparent purple).
Finally, the influence of previous VT ablation on innervation is unknown; however, one series that imaged 5 patients 1 to 4 months after ablation of VT in the absence of structural heart disease demonstrated no focal defect in all patients, although one patient had diffusely decreased uptake.\textsuperscript{35}

### Conclusions

To our knowledge, this is the first study to integrate detailed 3D innervation maps derived from \textsuperscript{123}I-IBG to assess a novel dimension of possible VT triggers and substrate modifiers and to define possible quantitative cut-offs for abnormal innervation. Our findings of neuronal damage extending significantly beyond the voltage-defined scar, the inability to predict neuronal health by current voltage criteria, and the finding of abnormal innervation for all successful VT ablation sites (even with preserved voltage) suggest that \textsuperscript{123}I-IBG imaging may provide important information about VT substrate not available from the current anatomic VT substrate model and provide supplemental guidance for VT ablations in patients with ischemic VT.

### Disclosures

Dr Dickfeld received research grants from General Electric and Biosense Webster. In addition, Dr Dilsizian received research grant from General Electric, and A. Turgeman received salary from Biosense Webster. The other authors have no conflicts.

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Three-Dimensional $^{123}$I-Meta-Iodobenzylguanidine Cardiac Innervation Maps to Assess Substrate and Successful Ablation Sites for Ventricular Tachycardia: Feasibility Study for a Novel Paradigm of Innervation Imaging

Thomas Klein, Mohammed Abdulghani, Mark Smith, Rui Huang, Ramazan Asoglu, Benjamin F. Remo, Aharon Turgeman, Olurotimi Mesubi, Sunjeet Sidhu, Stephen Synowski, Anastasios Saliaris, Vincent See, Stephen Shorofsky, Wengen Chen, Vasken Dilsizian and Timm Dickfeld

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