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

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**Background**—Innervation is a critical component of arrhythmogenesis and may present an important trigger/substrate modifier not used in current ventricular tachycardia (VT) ablation strategies.

**Methods and Results**—Fifteen patients referred for ischemic VT ablation underwent preprocedural cardiac $^{123}$I-meta-iodobenzylguanidine ($^{123}$I-mIBG) imaging, which was used to create 3-dimensional (3D) innervation models and registered to high-density voltage maps. 3D $^{123}$I-mIBG innervation maps demonstrated areas of complete denervation and $^{123}$I-mIBG transition zone in all patients, which corresponded to 0% to 31% and 32% to 52% uptake. $^{123}$I-mIBG denervated areas were 2.5-fold larger than bipolar voltage–defined scar (median, 24.6% [Q1–Q3, 18.3%–34.4%] versus 10.6% [Q1–Q3, 3.9%–16.4%]; $P<0.001$) and included the inferior wall in all patients, with no difference in the transition/border zone (11.4% [Q1–Q3, 9.5%–13.2%] versus 16.6% [Q1–Q3, 12.0%–18.8%]; $P=0.07$). Bipolar/unipolar voltages varied widely within areas of denervation (0.8 mV [Q1–Q3, 0.3–1.7 mV] and 4.0 mV [Q1–Q3, 2.9–5.6 mV]) and $^{123}$I-mIBG transition zones (0.8 mV [Q1–Q3, 0.4–1.8 mV] and 4.6 mV [Q1–Q3, 3.2–6.3 mV]). Bipolar voltages in denervated areas and $^{123}$I-mIBG transition zones were <0.5 mV, 0.5 to 1.5 mV, and >1.5 mV in 35%, 36%, and 29%, as well as 35%, 35%, and 30%, respectively ($P>0.05$). Successful ablation sites were within bipolar voltage–defined scar (7%), border zone (57%), and areas of normal voltage (36%), but all ablation sites were abnormally innervated (denervation/$^{123}$I-mIBG transition zone in 50% each).

**Conclusions**—$^{123}$I-mIBG innervation defects are larger than bipolar voltage–defined scar and cannot be detected with standard voltage criteria. Thirty-six percent of successful VT ablation sites demonstrated normal voltages (>1.5 mV), but all ablation sites were within the areas of abnormal innervation. $^{123}$I-mIBG innervation maps may provide critical information about triggers/substrate modifiers and could improve understanding of VT substrate and facilitate VT ablation.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique Identifier: NCT01250912.

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Key Words: cardiac imaging techniques ▶ innervation ▶ tachycardia, ventricular
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 radioisotope, meta-iodobenzylguanidine (123I-IBG). As a norepinephrine analogue, 123I-IBG is similarly released into the synaptic cleft in response to sympathetic input by presynaptic nerve terminals. Recently, global cardiac denervation, as assessed with 123I-IBG, 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-IBG 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.

Preprocedural 123I-IBG 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-IBG (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-IBG 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 located in the mediastinum (Figure 1).

3D Regional 123I-IBG 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-IBG 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

Figure 1. Heart/mediastinal ratio (H/M). Planar 123I-meta-iodobenzylguanidine (123I-IBG) 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-IBG Scintigraphy

123I-IBG Planar and SPECT Imaging

123I-IBG 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-IBG (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.
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 <0.05. 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 extrastimuli 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 transcending 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.15-19

**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 CartoMERGE 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%–100%), 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).

Table 1. Patient Characteristics (n=15)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Age at time of ablation, y</td>
<td>68.5±8.6</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>25.0±12.1%</td>
</tr>
<tr>
<td>Presence of ICD at time of ablation</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Biventricular ICD</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Previous ablations</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Other antiarrhythmic drugs</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>NYHA heart class</td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Class 2</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Class 3</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Class 4</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator; and NYHA, New York Heart Association.

Unless otherwise noted. Comparisons between paired measurements were conducted with a nonparametric test (Wilcoxon signed-rank test) and 2-tailed t test. Differences were considered significant at a level of P<0.05.
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%–58.0%] 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 area 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 denervated Tz were in scar (<0.5 mV), BZ (0.5–1.5 mV) and normal myocardium (>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.

VT Ablation
VT ablation was performed in all patients. No inducible VT was present in 2 patients. In the remaining 13 patients, 57 VTs were induced, including both clinical and nonclinical VTs. Insufficient pace map matches were found in 2 patients leading to substrate modification alone in those cases. In the remaining 11 patients, the 14 clinical VT sites were successfully mapped and localized to the interventricular septum (total n=7; RV side, n=3; LV side, n=4), inferior (n=5), lateral (n=1), and anterior wall (n=1). Clinical VTs had a cycle length of 352 ms (Q1–Q3, 290–410 ms; mean±SD, 372±96 ms) with either right bundle branch block (80%) or left bundle branch block (20%). After ablation, 93% of clinical VTs could no longer be induced.

Electroanatomic and 123I-mIBG Characteristics of Ablation Sites
Successful ablation sites were within bipolar voltage–defined scar in 7% (n=1; 0.4 mV) and BZ in 57% (0.8 mV [Q1–Q3, 0.7–1.3 mV; mean±SD, 1.0±0.3 mV; 0.7–1.4 mV; Figures 5 and 6; Table 2), but they were within areas of normal bipolar voltage in the remaining 36% of cases (4.0 mV [Q1–Q3, 1.9–5.0 mV; mean±SD, 3.4±1.7 mV; 1.8–5.5 mV; Figures 7 and 8). The distance of successful ablation sites within normal myocardium to the nearest BZ was 10.2 mm (Q1–Q3, 3.6–3.7 mm; mean±SD, 11.0±10.0 mm). Successful ablation sites with normal bipolar voltage demonstrated a unipolar voltage of 5.9 mV (Q1–Q3, 5.3–7.6 mV; mean±SD, 7.0±3.0 mV; 4.0–11.4 mV). The unipolar voltage of all successful ablation sites was 5.2 mV (Q1–Q3, 4.2–6.5 mV; mean±SD, 5.6±2.5 mV).

All successful ablation sites demonstrated an abnormal innervation pattern, with 50% within denervated myocardium and 50% within 123I-mIBG TZ. Successful ablation sites with normal bipolar voltage demonstrated denervation or TZ in 40% and 60%, respectively (Table 2).

Successful ablation sites within 123I-mIBG denervation demonstrated a distance to the closest denervation/TZ interface of 3.6 mm (Q1–Q3, 3.3–9.0 mm; mean±SD, 6.3±4.5 mm). Ablation sites in the TZ had a minimum distance to the TZ/normal myocardium interface and the TZ/denervation border of 9 mm (Q1–Q3, 4.5–13.2 mm; mean±SD, 9.3±6.3 mm) and 8 mm (Q1–Q3, 5–8.8 mm; mean±SD, 7.0±3.9 mm), respectively.

Follow-Up
At 6-month follow-up, 1 patient had died of unrelated, noncardiac causes (no ICD interrogation results were available). Six of the remaining 14 patients had recurrent ventricular arrhythmias, either nonsustained VT not requiring any ICD therapy (n=2) or VT treated with antitachycardia pacing (n=3) or ICD shocks (n=1; died before 6-month follow-up visit of heart failure).

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 or 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 bilateralstellate 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-mIBG. The decreased reuptake of norepinephrine into presynaptic nerve terminals found in patients with cardiomyopathy results in lower intensity $^{123}$I-mIBG signals. This decreased reuptake of $^{123}$I-mIBG 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-mIBG) correlates with increased risk of ICD therapy, worsening heart failure, and cardiac death. However, recent studies have suggested that a regional assessment of innervation can be performed with $^{123}$I-mIBG, 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-mIBG, 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-mIBG imaging is limited by the spatial resolution of SPECT camera technology, which is in the range of 10 to 12 mm. However, $^{123}$I-mIBG 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>
<thead>
<tr>
<th>Innervation map</th>
<th>Denervated</th>
<th>Transition zone</th>
<th>Normal myocardium</th>
</tr>
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<tbody>
<tr>
<td>Voltage Map</td>
<td>Scar</td>
<td>Border Zone</td>
<td>Normal Voltage</td>
</tr>
<tr>
<td>Denervated</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Transition zone</td>
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</tr>
<tr>
<td>Normal myocardium</td>
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**Figure 7.** 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.35

Conclusions
To our knowledge, this is the first study to integrate detailed 3D innervation maps derived from 123I-mIBG 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 septal ablation sites (even with normal voltage) suggest that 123I-mIBG 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.

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