123I-mIBG Scintigraphy to Predict Inducibility of Ventricular Arrhythmias on Cardiac Electrophysiology Testing
A Prospective Multicenter Pilot Study

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Background—Disturbances of autonomic function after infarction are associated with both total mortality and sudden death. Although many imaging techniques for assessing the cardiac autonomic nervous system have been studied, the clinical usefulness of these techniques remains uncertain. This exploratory pilot study examined the relationship between abnormalities of ventricular sympathetic innervation delineated by scintigraphic imaging with 123I-mIBG and inducible ventricular tachyarrhythmias in patients with left ventricular dysfunction and previous myocardial infarction.

Methods and Results—Fifty patients underwent electrophysiological (EP) testing and 15-minute and 4-hour planar and single photon emission computed tomography (SPECT) imaging with 123I-mIBG and SPECT imaging with 99mTc-tetrofosmin. The primary efficacy variables were the 4-hour heart:mediastinum ratio (H/M) and the 123I-mIBG/99mTc-tetrofosmin SPECT mismatch score. EP studies were categorized as positive (EP+) or negative (EP-) for inducibility of sustained (>30 seconds) ventricular tachyarrhythmias. Thirty patients were EP+, and 20 were EP-. There were no significant differences in the 4-hour H/M ratios or 123I-mIBG/99mTc-tetrofosmin SPECT mismatch scores between the two groups. In a multivariable analysis using all 123I-mIBG and 99mTc-tetrofosmin SPECT measurements, the only variable that showed a significant difference between EP+ and EP- patients was the 4-hour 123I-mIBG SPECT defect score. A 4-hour 123I-mIBG SPECT defect score of ≥37 yielded a sensitivity of 77% and specificity of 75% for predicting EP results.

Conclusions—The standard indices of 123I-mIBG imaging (H/M and innervation-perfusion mismatch score) are not predictive of EP test results. The association of 123I-mIBG SPECT defect severity with EP test inducibility in this exploratory study will require confirmation in a larger cohort of patients. (Circ Cardiovasc Imaging. 2008;1:131-140.)

Key Words: electrophysiology ■ scintigraphy ■ tachyarrhythmias

Ventricular tachycardia and ventricular fibrillation are recognized as the primary causes of sudden death in survivors of myocardial infarction.1 Programmed ventricular stimulation performed at electrophysiological (EP) testing is an effective tool to identify most patients at risk for sustained monomorphic ventricular tachycardia but does not identify all patients at risk for sudden death.2 Ventricular tachycardia inducible by programmed stimulation is thought to identify reentrant circuits that form as a result of the healing process after infarction. Although dysfunction of the autonomic nervous system is thought to play a prominent role in modulating occurrence of ventricular tachyarrhythmias,3,4 its relationship with the factors responsible for spontaneous activation of reentrant circuits, and therefore the results of EP testing, is uncertain.

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123I-mIBG is a norepinephrine analogue, and myocardial uptake reflects the extent of sympathetic innervation. Reduced myocardial uptake of 123I-mIBG is observed in asso-
cation with most diseases that result in left ventricular (LV) dysfunction and potentially lethal ventricular arrhythmias.\(^5\)\(^–\)\(^15\) In small observational studies, dysfunction of the myocardial autonomic nervous system as evaluated by using \(^123\)I-

mIBG has been shown to be associated with the occurrence of arrhythmias.\(^14\)\(^–\)\(^18\) However, the explanation for this association is not yet clear. One potential link between abnormalities of sympathetic innervation and the occurrence of potentially lethal ventricular arrhythmias is the fact that denervated myocardium may be viable and hyperresponsive to circulating catecholamines.\(^3\) It is also possible that denervated but viable myocardium on the border zone of infarctions is prone to the development of reentrant ventricular tachycardia circuits. Both single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging have been used to demonstrate the presence of denervated but still viable myocardium (as can be observed after myocardial infarction) that could contribute to the development of ventricular arrhythmias.\(^18\)\(^–\)\(^26\)

The present exploratory pilot study was designed to examine whether alterations in cardiac sympathetic innervation as measured by \(^123\)I-
mIBG scintigraphy were related to the inducibility of ventricular arrhythmias during EP testing in patients with previous infarction. The primary objective was to evaluate results by using planar \(^123\)I-
mIBG imaging and the combination of SPECT \(^123\)I-
mIBG innervation and \(^99m\)Tc-tetrofosmin perfusion imaging (providing information on extent of denervated myocardium and infarct size, respectively).

Methods

Patient Selection

This was a phase 2, open-label, multicenter exploratory study conducted at 13 centers in Europe and one center in the United States, investigating the association between findings on planar and SPECT \(^123\)I-
mIBG imaging and the results of cardiac EP testing. The protocol was approved by the ethical committees or institutional review boards at each participating institution. All patients provided written informed consent before the performance of any study procedures.

Primary inclusion criteria at the inception of the study included a history of myocardial infarction, LV dysfunction (left ventricular ejection fraction [LVEF] ≤ 40%, measured within 30 days of study entry), and referral for a clinically indicated cardiac EP study because of syncope or nonsustained Vt. Patients with a functioning pacemaker and those who had ever received defibrillation to treat a previous arrhythmic event were excluded because of the potential for artifactual suppression of neuronal uptake of \(^123\)I-
mIBG. Because of slow enrollment, the study protocol was amended (toward the end of the study) to allow the inclusion of patients with LVEF between 41% and 49% and those who had undergone a clinically indicated cardiac EP study, which was positive for inducible ventricular tachyarrhythmias within the 12 months preceding study entry and subsequently had undergone implantable cardioverter-defibrillator (ICD) implantation. Ten subjects were enrolled under the auspices of this amendment.

A total of 63 patients were enrolled in the study and completed the imaging protocol. However, six patients did not undergo EP testing and were excluded from further analysis. One additional patient completed all imaging and EP procedures but was withdrawn thereafter because of a protocol violation (previously undocumented history of defibrillation). Therefore, the final study population consisted of 56 patients.

Study Protocol

Per protocol, the patients underwent screening assessment, including medical history and blood samples for biochemistry, hematology, and plasma brain natriuretic peptide (BNP) and norepinephrine (NE) levels within 21 days of the scheduled date for cardiac EP testing. Patients then underwent resting imaging with \(^123\)I-
mIBG (to assess cardiac innervation) and \(^99m\)Tc-tetrofosmin (to assess myocardial perfusion and infarct size).

Investigational sites sent copies of all digital image files from the scintigraphic studies to an imaging core laboratory for central evaluation and analysis. Similarly, selected ECG recordings (surface and intracardiac) obtained during the EP procedure were submitted on paper or digital media for central review. Notations were provided on the submitted material to indicate the timing of each stimulus during the EP procedure and any intervention required as a result of induced arrhythmias (medications, electric shock, etc).

\(^{123}\)I-
mIBG Imaging: Data Acquisition

All subjects were 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) was administered intravenously, and a 10-minute planar image of the anterior thorax (128×128 matrix) was acquired beginning 15 minutes after tracer injection. A SPECT study was then acquired using either a dual- or triple-head gamma camera (minimum 30 projections/heart, 20 to 30 seconds/projection, 64×64 matrix). Repeat planar and SPECT studies were acquired at ~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 \(^123\)I.

\(^{123}\)I-
mIBG Imaging: Data Analysis

All image processing was performed by an experienced technologist at a central image core laboratory (GE Healthcare Image Review Center, Oslo, Norway). Early (15 minutes postinjection) and late (4-hour delayed) planar images were processed to determine the H/M ratio. A whole-heart region of interest (ROI) was drawn manually to include both ventricles; to avoid truncating ventricular activity, no attempt was made to exclude atrial activity that might occasionally have been visible. A square mediastinal ROI (7×7 pixels) was drawn in the upper mediastinum, using the apices of the lungs as anatomic landmarks. The H/M ratio was calculated as the ratio of the counts per pixel in the two ROIs.

All SPECT images were processed using filtered back-projection and displayed as reconstructed short- and long-axis (horizontal and vertical) slices according to the ACC/AHA/ASNC standards.\(^27\)\(^–\)\(^28\) The early and late \(^{123}\)I-
mIBG SPECT images were presented side by side on a single video screen.

All images (early and late planar and SPECT) were reviewed independently by three nuclear cardiologists, each with at least 10 years experience in the interpretation of myocardial perfusion and innervation imaging studies. The readers were blinded to all clinical information. Each reader assessed each image or image set as either diagnostic (optimal or suboptimal) or nondiagnostic, with the latter removed from the efficacy analyses. All reviews were performed at the same image core laboratory where the images were processed.

For each planar image, the readers examined the ROIs and the resultant H/M ratio to determine whether the value accurately reflected the visual assessment of \(^123\)I-
mIBG uptake. If the ROIs were judged to be incorrectly positioned, they were resized or repositioned and a new H/M was determined. Based on the H/M ratios accepted by each reader, a single aggregate H/M was derived for each image, either the value accepted by at least two blinded readers, or if this criterion was not satisfied, the average H/M for all readers.

In addition, the H/M data were used to calculate myocardial washout using two formulas. Uncorrected washout was calculated as

\[
\frac{[H/M(\text{early})-H/M(\text{late})]}{H/M(\text{early})}.
\]
Background corrected washout was calculated as

\[ \left[ \frac{H(\text{early}) - M(\text{early})}{H(\text{late}) - M(\text{late})} \right] \left[ \frac{H(\text{early})}{H(\text{late})} \right]. \]

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

For the SPECT image sets, segmental myocardial activity was scored using a 17-segment model. Each segment was 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 (17 × 4).

To create a single aggregate SPECT SS, the average of individual reader scores was calculated, excluding SS values based on <17 segments (at least one segment scored NA). In addition, aggregate SS results for each of the three coronary vascular territories were determined based on the seven segments assigned to the left anterior descending artery (LAD) and five each to the right coronary artery (RCA) and left circumflex (LCx) territories in the 17-segment model.

Before the first 123I-mIBG reading session, all readers received training on the image display systems and the appearance of normal and abnormal 123I-mIBG planar and SPECT images, supplementing their prior experience in examining such studies. The training cases included approximately five 123I-mIBG SPECT studies on normal volunteers (derived from previous investigator-initiated studies) to provide the readers with an adequate basis for visual assessment of severity of abnormalities on study subject images. As a further element of the training, the readers were instructed that the unprocessed projection images should be used as a guide to the overall myocardial uptake of 123I-mIBG. This was done because, unlike for MPI SPECT, where there is usually at least one myocardial region with preserved uptake, 123I-mIBG imaging abnormalities can involve all wall segments. In such a circumstance, global uptake as judged on the projection images can be used as an aid for determining the score of the myocardial segment with the best uptake. In addition, the readers were advised to consider the relation of myocardial background (eg, lung) activity on SPECT images as another means to assess the presence of global reduction in myocardial 123I-mIBG uptake.

Planar and SPECT images were presented to the readers in separate sessions. Scoring of SPECT images was performed without explicit knowledge of H/M ratio results.

99mTc-Tetrofosmin Imaging: Data Acquisition

For subjects who had undergone a rest, 99mTc-Tetrofosmin study as part of clinical care within 14 days before 123I-mIBG administration, this examination was obtained for review. For all other subjects, 99mTc-Tetrofosmin imaging was performed either immediately after the completion of 123I-mIBG imaging or on a different day. These subjects received an intravenous administration of 555 to 740 MBq (15 to 20 mCi) 99mTc-Tetrofosmin (MYOVIE, GE Healthcare) at rest, and ECG-gated SPECT imaging was started 15 minutes later. Imaging was performed using low-energy, high-resolution collimators and a 20% energy window centered at the 140 keV photopeak of 99mTc for studies performed on a different day from 123I-mIBG and a 10% energy window for studies performed on the same day as 123I-mIBG.

For subjects who underwent both 123I-mIBG and 99mTc-Tetrofosmin imaging on the same day, 123I-mIBG imaging was always performed first, eliminating any possibility of degradation of these images. There was no visual evidence of significant spillover of 123I photons affecting the interpretation of the 99mTc-Tetrofosmin images acquired with 123I-mIBG still present.

99mTc-Tetrofosmin Imaging: Data Analysis

The rest 99mTc-Tetrofosmin SPECT images were processed and presented to two blinded readers (two of the same readers who interpreted the 123I-mIBG images) as single image sets. The same scoring system was used as for the 123I-mIBG images, including the creation of a single aggregate SS. There was no association between the 99mTc-Tetrofosmin and 123I-mIBG images for a given patient, because the different SPECT studies were presented in separate sessions (only one image type per session) and with random code identifiers.

In addition to the aggregate 99mTc-Tetrofosmin SS, the mismatch score for each subject was calculated as the difference between the 123I-mIBG and 99mTc-Tetrofosmin SS values. For consistency, the 123I-mIBG SS used in this calculation was the mean of the scores from the two readers who interpreted the 99mTc-Tetrofosmin images.

Cardiac Electrophysiological Testing

The cardiac EP study (if not performed before subject enrollment) was performed no earlier than 24 hours after 123I-mIBG administration. The cardiac EP study was performed according to each site’s standard clinical practice. Recommendations for the EP test included (1) Use of a stimulation protocol with two right ventricular sites (right ventricular apex and outflow tract); (2) Use of programmed stimulation with two drive cycle lengths (600 and 400 ms) progressing from the longer to the shorter length and 1.2, and 3 extrastimuli; (3) Use of an initial S2 coupling interval in each stimulation sequence of at least 300 ms; and (4) Use of no coupling interval of <200 ms.

The number and location of sites stimulated, characteristics of the stimulation signal, and pro- or antiarrhythmic drugs administered were recorded on the appropriate case report form.

For submission of EP study results, the following guidelines were followed. For each stimulation sequence recorded on the case report form, at least one surface ECG tracing was submitted. If no ventricular tachyarrhythmia (defined as a series containing at least six beats) occurred, tracings showing the first and last stimulations in the sequence (longest and shortest terminal coupling intervals) were submitted. If a tachyarrhythmia was induced, one or more ECG tracings were required, sufficient to demonstrate the stimulation sequence (S1, S2, etc), the beginning of the ventricular tachyarrhythmia induced by the stimulation sequence, and the termination of the ventricular tachyarrhythmia. The submitted tracings were sufficient in duration to document the basic cycle length and extrastimuli (S1, S2, etc)+5 seconds and the last 5 seconds of the tachyarrhythmia +5 seconds after termination. For a sustained (≥30 seconds) tachyarrhythmia, tracings for the entire duration of the arrhythmia were required.

A clinical adjudication committee consisting of three cardiologists with specialty training in electrophysiology performed an independent review of all EP test data. Before the first clinical adjudication committee review meeting, the committee agreed on the criteria for determining whether an EP study was positive, negative, or indeterminate. The remit of the committee included determining whether a sustained tachycardia had a single stable QRS morphology (monomorphic) or a changing QRS morphology (polymorphic). Although the clinical adjudication acknowledged that sustained monomorphic VT was a definitive positive finding on EP testing, the committee decided that for the purposes of this study, any sustained VT should be considered positive (particularly given uncertainties with regard to use of the test results in making decisions regarding insertion of an ICD). The committee therefore designated two subcategories within the positive category: Sustained monomorphic VT; and sustained polymorphic VT, including ventricular flutter and fibrillation.

A positive EP study required induction of sustained VT (lasting at least 30 seconds or requiring termination in <30 seconds because of hemodynamic instability). A negative EP study was one in which no sustained tachyarrhythmia was induced. An indeterminate study was one for which the EP protocol or the submitted data were judged inadequate to reach a definitive conclusion on inducibility.

All clinical adjudication committee deliberations were performed without the knowledge of clinical or nuclear data.

Statistical Analysis

This study was designed to explore the relationship between cardiac EP test results and myocardial sympathimetric innervation as represented by findings on 123I-mIBG planar and SPECT imaging. Based on
extensive published results using H/M ratios on planar imaging and numerous comparisons of 123I-
MIBG and MPI SPECT, the late planar H/M ratio and the late 123I-
MIBG/tetrofosmin SPECT mismatch score were considered as the initial primary analysis targets. However, as an exploratory investigation, the ultimate objective was to identify any parameter of 123I-
MIBG imaging that demonstrated predictive capability for EP test results.

The primary analyses were performed on the data from subjects with diagnostic images (ie, not judged nondiagnostic by at least two blinded readers) and definitive cardiac EP test results (positive or negative) as per the clinical adjudication committee.

All continuous variables approximated a normal distribution (as evaluated by Kolmogorov-Smirnov tests) and are presented as mean values ± one SD. Differences between groups of patients were evaluated by one-way analysis of variance and Student’s t tests. In case of post hoc comparisons, Bonferroni method was applied to adjust for inflation of the type I error with multiple comparisons, and adjusted probability values are presented. Categorical data are summarized as frequencies and percentages, and differences between groups of patients were evaluated by χ² tests as appropriate.

Univariate and multivariable analyses were performed to identify variables that could potentially predict inducibility of ventricular arrhythmias during EP testing; the tested variables are listed in Table 1. All statistical analyses were performed using SAS software (SAS Inc, Cary, NC) or MINITAB for Windows. A P value of <0.05 was considered significant for all tests.

### Results

#### Patients

Fifty-six patients completed the entire study protocol and had data reviewed by the clinical adjudication committee. The EP study was considered indeterminate in six patients, five based on inadequate EP protocols with only one stimulation site documented (without induction of a sustained arrhythmia), and one patient for whom no tracings of the EP study could be retrieved. The six indeterminate patients were removed.

#### Table 2. Characteristics of Patients With Positive (EP⁺) and Negative (EP⁻) Electrophysiologic Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=50)*</th>
<th>EP⁺ (n=30)*</th>
<th>EP⁻ (n=20)*</th>
<th>P(EP⁺ vs EP⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male</td>
<td>48</td>
<td>29</td>
<td>19</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.1 ± 9.2</td>
<td>65.0 ± 9.0</td>
<td>65.2 ± 9.6</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Medication: ACEI/ARB</td>
<td>46 (92%)</td>
<td>26 (87%)</td>
<td>20 (100%)</td>
<td>0.12</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>45 (90%)</td>
<td>28 (93%)</td>
<td>17 (85%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Ca channel blocker</td>
<td>10 (20%)</td>
<td>6 (20%)</td>
<td>4 (20%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Statin</td>
<td>44 (88%)</td>
<td>25 (83%)</td>
<td>19 (95%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>9 (18%)</td>
<td>9 (30%)</td>
<td>0 (0%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (32%)</td>
<td>7 (23%)</td>
<td>9 (45%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (68%)</td>
<td>19 (63%)</td>
<td>15 (75%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>5 (10%)</td>
<td>3 (10%)</td>
<td>2 (10%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>NYHA II</td>
<td>24 (48%)</td>
<td>14 (47%)</td>
<td>10 (50%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>NYHA III</td>
<td>10 (20%)</td>
<td>7 (23%)</td>
<td>3 (15%)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>LVEF (%) (range)</td>
<td>32.3 (15–48)</td>
<td>32.1 (16–48)</td>
<td>32.7 (15–40)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>No. previous infarctions: 1</td>
<td>31 (62%)</td>
<td>17 (57%)</td>
<td>14 (70%)</td>
<td>0.41</td>
</tr>
<tr>
<td>No. ≥2</td>
<td>19 (38%)</td>
<td>13 (43%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmia history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSVT</td>
<td>27 (54%)</td>
<td>12 (40%)</td>
<td>15 (75%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>9 (18%)</td>
<td>9 (30%)</td>
<td>0 (0%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Mean NE (nmol/L)†</td>
<td>1.37</td>
<td>1.30</td>
<td>1.90</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean BNP (pmol/L)†</td>
<td>61.7</td>
<td>62.4</td>
<td>82.4</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Percentage of subjects with specified EP findings.
†Data based upon 28 EP⁺ and 17 EP⁻ subjects with adequate blood samples
ACEI indicates ACE inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; NYHA, New York Heart Association; NE, norepinephrine; NSVT, nonsustained ventricular tachycardia.
from the analyses. The remaining 50 patients (48 men, two women) represent the evaluable study population. According to the study inclusion criteria, all had a history of myocardial infarction; details concerning characteristics (eg, STEMI versus non-STEMI) and location were not specifically collected. Forty-nine patients (98%) had an LVEF ≥ 40%. One patient enrolled under the amendment described in Methods had an LVEF of 48% but was included in the analyses, as removal of these data had no impact on study results calculations not shown). Nine patients had a cardiac medical history that included an episode of sustained VT; but these were remote events (most recent infarction from 3 to 25 years before study participation) that were not the basis for referral for EP testing. The clinical characteristics of the evaluable study population are summarized in Table 2.

According to the clinical adjudication committee, 30 patients (60%) were classified as EP-positive (+), and 20 patients (40%) were classified as EP-negative (−). Of the 30 EP+ patients, 19 had monomorphic and 11 had polymorphic VT. Sustained monomorphic VT was somewhat more likely to be produced by stimulation at the right ventricular apex (13/19 [68%] patients versus 6/11 [55%] for polymorphic VT), but there was no apparent association between the aggressiveness of the EP protocol and the timing and characteristics of the induced tachycardia.

Demographic and clinical data for the 50 patients divided according to the EP results are presented in Table 2. There was no difference in demographic data or cardiac medical history between the EP+ and EP− groups. EP+ patients were more likely to have a history of sustained VT or to be treated with amiodarone (only one patient was common to the two groups), whereas EP− patients more often had a history of nonsustained VT only. Seven of the nine patients (78%) receiving amiodarone were being treated for atrial fibrillation; the other two (22%) were being treated for nonsustained VT.

### Scintigraphic Variables Versus Electrophysiological Testing

All three readers considered all planar and SPECT 123I-mIBG images as diagnostic and interpretable. Of the SPECT images, the three readers considered 38%, 88%, and 94%, respectively, to be of optimal quality. In this regard, the first reader (62% of images diagnostic but suboptimal) judged the 123I-mIBG SPECT images of 16 patients to have one to seven NA myocardial segments because of high background or adjacent liver activity. The other two readers scored all 17 myocardial segments in all 123I-mIBG SPECT studies.

A summary of the aggregate reader imaging results is presented in Table 3. There was no difference between the results of the EP+ and EP− patient groups for either of the primary efficacy variables 4-hour H/M and 123I-mIBG/99mTc-tetrofosmin SPECT mismatch score. There was also no difference between EP+ patients with monomorphic and polymorphic VT (mean 4-hour H/M 1.43 ± 0.22 versus 1.45 ± 0.21, P > 0.50; mean 4-hour 123I-mIBG/99mTc-tetrofosmin SPECT mismatch score 22.3 ± 10.4 versus 29.8 ± 14.3, P = 0.12).

On the secondary analysis of all 123I-mIBG and 99mTc-tetrofosmin measurements, only the 4-hour 123I-mIBG SPECT studies showed a statistically significant difference between EP+ and EP− patients (mean 42.7 ± 8.8 versus 34.9 ± 9.8, P = 0.005; Figure 1). Patients with EP+ for monomorphic VT also had significantly higher scores (mean 41.8 ± 7.7) than EP− patients (P = 0.040). There was no difference between EP+ patients with monomorphic and polymorphic VT (mean SS 44.1 ± 10.7 for the latter; P = 0.50).

The 99mTc-tetrofosmin defect scores (reflecting infarct size) tended to be larger for EP+ than EP− patients, but the

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### Table 3. 123I-mIBG and 99mTc-Tetrofosmin Imaging Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>EP+ Patients (n=30) mean±1 SD (95% Confidence Interval)</th>
<th>EP− Patients (n=20) mean±1 SD (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early planar 123I-mIBG H/M ratio</td>
<td>1.58±0.16 (1.52–1.64)</td>
<td>1.60±0.14 (1.54–1.66)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Late planar 123I-mIBG H/M ratio</td>
<td>1.44±0.21 (1.36–1.51)</td>
<td>1.47±0.13 (1.41–1.53)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Washout (uncorrected) (%)</td>
<td>9.3±7.3 (6.7–11.9)</td>
<td>8.0±6.2 (5.3–10.7)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Washout (corrected) (%)</td>
<td>47.1±15.6 (41.5–52.7)</td>
<td>43.5±12.3 (38.1–48.9)</td>
<td>0.39</td>
</tr>
<tr>
<td>Early 123I-mIBG SPECT summed score</td>
<td>37.4±9.6 (34.0–40.8)</td>
<td>32.3±10.3 (27.8–36.8)</td>
<td>0.082</td>
</tr>
<tr>
<td>Late 123I-mIBG SPECT summed score</td>
<td>42.7±8.8 (39.6–45.8)</td>
<td>34.9±9.8 (30.6–39.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>99mTc-tetrofosmin SPECT summed score</td>
<td>17.6±9.0 (14.4–20.8)</td>
<td>12.7±10.4 (8.1–17.3)</td>
<td>0.086</td>
</tr>
<tr>
<td>Late 123I-mIBG/99mTc-tetrofosmin mismatch score</td>
<td>21.4±13.1 (16.7–26.1)</td>
<td>17.3±11.1 (12.4–22.2)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
difference did not reach significance, indicating that the difference in $^{123}$I-mIBG SPECT results did not merely reflect a difference in infarct size between EP$^+$ and EP$^-$ patients. EP$^+$ patients tended to have more perfusion defects in the LAD territory than EP$^-$ subjects (regional SS $>4$: LAD: EP$^+$ 20/30 [67%]; EP$^-$ 7/20 [35%]), but the difference in mean SS values was not significant (EP$^+$: 8.8±7.2; EP$^-$: 5.6±7.8; P=0.150). Almost half the patients had mild to moderate abnormalities (SS <14, ie, <20% of maximum) on $^{99m}$Tc-tetrofosmin SPECT (n=23, 46%). By comparison, 98% (n=49) of patients had more severe abnormalities (SS >14) on delayed $^{123}$I-mIBG SPECT imaging.

Localization of 4-hour $^{123}$I-mIBG SPECT abnormalities in terms of regional vascular territories is presented in Table 4.

Although there was evidence of reduced innervation in all three territories in almost all patients (16/20 EP$^+$ and 28/30 EP$^-$ patients with total SS >30), the severity of abnormalities in the LAD territory was significantly greater in EP$^+$ than EP$^-$ patients.

With respect to the perfusion-innervation mismatch data, the 4-hour $^{123}$I-mIBG/$^{99m}$Tc-tetrofosmin SPECT mismatch score ranged from −3 to +44 (mean 20), with the SS being higher for $^{123}$I-mIBG than for $^{99m}$Tc-tetrofosmin in 47 patients (94%; Figure 2). Representative imaging examples are shown in Figure 3.

On multivariable analysis, only the late $^{123}$I-mIBG SPECT SS was identified as a predictor of inducible ventricular tachyarrhythmias during EP testing. An ROC curve was also constructed based on the late $^{123}$I-mIBG SPECT data (Figure 4).
Figure 4. Late $^{123}$I-mIBG SPECT ROC curve. Cutoff values of 37 and 39 yielded sensitivities of 77% and 67% and specificities of 75% and 90%, respectively. The area under the curve was 0.76.

A SS threshold of 37 yielded a sensitivity of 77% and a specificity of 75%, whereas the Youden index (sensitivity + specificity – 1) was maximized at SS = 39 (sensitivity 67%, specificity 90%, positive predictive value 89%, negative predictive value 64%). The area under the ROC curve was 0.76 ($P < 0.01$).

Discussion

The main findings of the current study can be summarized as follows. Of 50 patients with coronary artery disease, previous infarction, and LV dysfunction, 60% had inducible sustained ventricular arrhythmias at EP testing. EP+ and EP− patients were not different in baseline characteristics, and the most commonly used parameters of $^{123}$I-mIBG imaging (4-hour planar H/M and $^{123}$I-mIBG/$^{99m}$Tc-tetrofosmin SPECT mismatch score) did not differentiate between the two populations. The only imaging variable on univariate and multivariable analyses that differed between EP+ and EP− patients was the 4-hour $^{123}$I-mIBG SPECT SS. A summed defect score of 37 on 4-hour $^{123}$I-mIBG SPECT yielded a sensitivity of 77% and a specificity of 75% for the prediction of inducibility on programmed stimulation, whereas a SS of 39 had a sensitivity of 67% and a specificity of 90%. The difference in global innervation between EP+ and EP− patients primarily reflected more severe reduction in the LAD territory (anterior wall, anterior septum, apex). There was no difference in the severity of late $^{123}$I-mIBG SPECT defects between patients with inducible monomorphic versus polymorphic VT.

Innervation Imaging

A characteristic of the myocardium that may play a role in the occurrence of (potentially) lethal ventricular tachyarrhythmias is innervation and denervation.4,17 Experimental work has demonstrated that ischemia and myocardial infarction result in myocardial denervation.29 Cardiac sympathetic nerve fibers run over the epicardial surface and follow the coronary arteries. Sympathetic nerve fibers are more susceptible to oxygen deprivation than are cardiomyocytes,29 and it has been demonstrated that myocardial ischemia and infarction cause transient or permanent sympathetic denervation. Regions of denervation respond differently to sympathetic stimulation than normal myocardium, and this electrophysiological heterogeneity may be a substrate for both ventricular tachycardia and fibrillation. In an early animal study, denervated myocardium with catecholamine supersensitivity developed within 5 to 10 days after infarction.30

Both PET and SPECT tracers have been developed to image cardiac sympathetic innervation.18–25,31 Allman et al25 evaluated 16 patients with previous infarction and C11-HED PET and demonstrated extensive regions of denervation. Moreover, Calkins et al30 used C11-HED PET to evaluate 11 patients with a history of sustained VT and showed that scintigraphic denervation was related to ventricular refractoriness.

$^{123}$I-mIBG is a SPECT tracer that can be used for assessment of cardiac sympathetic innervation. $^{123}$I-mIBG is a norepinephrine analogue and has storage, transport, and uptake characteristics similar to that of norepinephrine. The early work by Minardo et al21 demonstrated in a canine model that sympathetic denervation following infarction related closely to defects on $^{123}$I-mIBG imaging. Mitrani et al29 evaluated 18 patients with cardiac disease presenting with ventricular tachyarrhythmias using $^{123}$I-mIBG SPECT and confirmed that $^{123}$I-mIBG imaging could demonstrate regional denervation. Various studies have subsequently evaluated patients with previous infarction and showed significantly larger innervation than perfusion defects.33,34 It has been suggested that this viable but denervated myocardium is very sensitive to sympathetic stimulation and may play a role in arrhythmogenesis in ischemic heart disease.

The current “proof-of-principle” study was designed to assess the capability of $^{123}$I-mIBG imaging to predict inducibility of ventricular tachyarrhythmias on EP testing as a first step in the direction of better selection of patients with coronary artery disease and LV dysfunction at risk for ventricular tachyarrhythmias. Parameters commonly derived from $^{123}$I-mIBG imaging, including the early and delayed H/M ratio and washout on planar imaging, the $^{123}$I-mIBG defect size on early and delayed SPECT imaging, and the $^{123}$I-mIBG-perfusion mismatch were examined. Among all these variables, only the $^{123}$I-mIBG defect size on late SPECT imaging was associated with ventricular tachyarrhythmia inducibility during EP testing.

Numerous studies on $^{123}$I-mIBG imaging in patients with LV dysfunction have demonstrated that the H/M ratio on planar $^{123}$I-mIBG imaging is predictive of prognosis in both ischemic and nonischemic heart failure.8,12–15 In several such studies, the H/M ratio was superior to LVEF in predicting of the outcome.10,11 The strong prognostic value of the H/M ratio was recently confirmed in a multicenter trial including 290 heart failure patients.35 Most deaths in these studies, however, were due to heart failure, and very few data are available on the value of the H/M ratio to predict sudden cardiac death. Arora et al10 evaluated 17 patients with an ICD, 10 of whom had previously experienced appropriate ICD discharges for ventricular tachyarrhythmias. These patients had a significantly lower H/M ratio and larger $^{123}$I-mIBG SPECT defect size, as compared with patients without discharges. More recently, Kioka et al36 demonstrated that the H/M ratio was predictive of sudden death in a population of 97 patients with mild-to-moderate heart failure, and Nagahara et al17 showed a relationship between appropriate ICD dis-
charge and reduced H/M ratio in combination with elevated plasma brain natriuretic peptide concentration. Although adverse cardiac outcomes, including sudden death, are more frequent in heart failure patients with significantly reduced H/M ratios, there are no definitive data indicating that this global measure of cardiac sympathetic innervation is specifically predictive of either spontaneous occurrence of VT or its inducibility on EP testing. The results of the present study suggest that planar $^{123}$I-$m$IBG imaging may be less effective for identifying risk for occurrence of a ventricular arrhythmia than for identifying the population most likely to die from such an event. In particular, if the regional distribution of denervation plays a significant role in the genesis of more serious arrhythmias, a three-dimensional imaging technique such as SPECT might be essential for an assessment intended to determine the most appropriate therapeutic intervention.

At present, there are few data on $^{123}$I-$m$IBG imaging in predicting inducibility of ventricular tachyarrhythmias during EP testing, and as most previous studies mainly used planar imaging, it is difficult to make comparisons with the current study. Nevertheless, as the present study failed to show a relationship between EP results and commonly used measures of $^{123}$I-$m$IBG abnormality, including H/M, perfusion-$m$IBG mismatch score, and washout, this imaging procedure may not be useful as an adjunct for patients being considered for EP testing.

It was somewhat surprising that the perfusion-$m$IBG mismatch score was not predictive of EP inducibility. Although there was a trend toward a larger mismatch in the patients with inducible ventricular tachyarrhythmias, there was a similar trend toward larger LAD territory perfusion defects in patients with EP+ results. Dae et al. demonstrated in a canine model that transmural infarction was associated with a match in the extent of perfusion defect and $m$IBG defect, but that nontransmural infarction resulted in areas of extensive denervation on $m$IBG imaging but significantly smaller perfusion defects. It has been hypothesized that these areas of viable, but denervated tissue may be susceptible to ventricular tachyarrhythmias. Matsunari et al. demonstrated that these areas of mismatch occur frequently after infarction, and Simoes et al. subsequently demonstrated a significant relationship between the extent of perfusion-$m$IBG mismatch and EP parameters characterizing repolarization and depolarization. Nerve sprouting after infarction, which has been demonstrated in various animal models, may also play a role in creating instability that can result in occurrence of arrhythmias.

**Limitations**

The current study has a number of limitations. The sample size was relatively small, because of the strict inclusion criteria and design of the study; the population studied was heterogeneous, including patients who had already experienced spontaneous sustained VT; and follow-up data were not collected to determine outcomes, including the occurrence of ICD firings. In addition, visual scoring of $^{123}$I-$m$IBG SPECT images is challenging, especially in patients with more severe LV dysfunction, and semiquantitative comparisons to normal data files were not available to assist the readers. The study results can only be judged in terms of the methods used and the relatively narrow patient population included. Also, inducibility of ventricular tachyarrhythmias during EP testing (both monomorphic and polymorphic) was used as the end point in the current study. It is known that inducibility during EP testing has only modest predictive value for sudden cardiac death. Future studies will need to include longitudinal follow-up to determine whether any parameters from $^{123}$I-$m$IBG imaging (such as 4-hour SPECT defect scores) are predictive of arrhythmic events or sudden death.

**Conclusions**

In this prospective, multicenter study, neither the late planar H/M nor $^{123}$I-$m$IBG/$^{99m}$Tc-tetrofosmin SPECT mismatch score were associated with inducibility on EP testing. There was an association between $^{123}$I-$m$IBG SPECT defect severity and results of EP testing. Our findings suggest that further investigation of the relationship between abnormal findings on $^{123}$I-$m$IBG SPECT imaging and the occurrence of spontaneous ventricular tachyarrhythmias is warranted.

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**Disclosures**

Jeroen Bax has received research grants from GE Healthcare. Otakar Kraft and Denis Agostini are principal investigators in an ongoing multicenter clinical study using $^{123}$I-$m$IBG sponsored by GE Healthcare. Gopa Banerjee and Arnold Jacobson are employed by GE Healthcare. None of the other authors reports any relationships to disclose.

**Appendix**

The following investigators and institutions enrolled subjects in this multicenter study, listed in the order of number of subjects enrolled (highest first).

- Dr Otakar Kraft
- University Hospital Ostrava
- Czech Republic
- Dr Otakar Belohlavek
- Na Homolce Hospital
- Prague, Czech Republic
- Professor Laszlo Galuska
- University of Debrecen
- Debrecen, Hungary
- Dr Holger Amthauer
- Centre Hospitalier Universitatsmedizin Berlin
- Germany
- Dr Jaroslav Vizda
- Dr Petr Parizek
- University Hospital, Hradec Kralove
- Czech Republic
- Dr Jeroen Bax
- Leiden University Medical Centre
- Leiden, The Netherlands
- Dr Alfred E. Buxton
- Rhode Island Hospital
- Providence, RI
- Dr Jan Gunnar Fjeld
- Rikshospitalet University Hospital
Oxlo, Norway
Professor Karl Theisen
Klinikum der Universität Muenchen
Germany
Dr Africa Muxi
Hospital Clinic i Provincial
Barcelona, Spain
Professor Christoph Eilles
University Clinic Regensburg
Germany
Dr Marie-Jeanne Albelli
Centre Hospitalier Universitaire Rangueil
Toulouse, France
Professor Dominique Le Guludec
Bichat Public Hospital
Paris, France
Professor Markus Schwaiger
Universität Munchen Klinikum rechts der Isar
Munich, Germany

References


CLINICAL PERSPECTIVE

Because dysfunction of the cardiac autonomic nervous system is associated with risk for ventricular arrhythmias, methods for assessing this system are of considerable research interest. The present pilot study examined scintigraphic imaging findings with the norepinephrine analog $^{123}$I-mIBG in a series of 50 ischemic heart disease patients who underwent cardiac electrophysiology (EP) testing. The commonly used index of cardiac $^{123}$I-mIBG uptake, the heart/mediastinum ratio, was not predictive of inducibility on EP testing. The mismatch between myocardial viability (assessed with myocardial perfusion imaging) and innervation (assessed with $^{123}$I-mIBG single photon emission computed tomography [SPECT]) was also unsuccessful at discriminating patients with positive and negative EP results. On multivariable analysis, the only $^{123}$I-mIBG imaging parameter significantly associated with EP results was the severity of $^{123}$I-mIBG SPECT defect on 4-hour delayed imaging. These findings suggest that the complex relationships that underlie inducibility of re-entrant tachycardias on EP testing cannot be readily explained based on patterns of myocardial sympathetic innervation alone. Further research is needed to determine whether $^{123}$I-mIBG SPECT has clinical utility for evaluation of patients at risk for ventricular arrhythmias.
123I-mIBG Scintigraphy to Predict Inducibility of Ventricular Arrhythmias on Cardiac Electrophysiology Testing: A Prospective Multicenter Pilot Study
Jeroen J. Bax, Otakar Kraft, Alfred E. Buxton, Jan Gunnar Fjeld, Petr Parízek, Denis Agostini, Juhani Knuuti, Albert Flotats, James Arrighi, Africa Muxi, Marie-Jeanne Alibelli, Gopa Banerjee and Arnold F. Jacobson

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In the article by Bax et al, “\(^{123}\)I-mIBG Scintigraphy to Predict Inducibility of Ventricular Arrhythmias on Cardiac Electrophysiology Testing: A Prospective Multicenter Pilot Study,” which appeared in the September 2008 issue of the journal (Circ Cardiovasc Imaging, 2008;1:131–140), the following corrections should be made on page 136.

The last column (P) of Table 4 is now aligned properly, with the following values under P and LAD territory reading: 0.013; 0.004; 0.030.

The legend to Figure 3 has the word tetrosmin misspelled several times and should be correctly spelled tetrofosmin.

These errors have been corrected in the current online version of the article (http://circimaging.ahajournals.org/cgi/content/full/1/2/131).