Iodine-123 Metaiodobenzylguanidine Imaging and Carbon-11 Hydroxyephedrine Positron Emission Tomography Compared in Patients With Left Ventricular Dysfunction

Ichiro Matsunari, MD, PhD; Hirofumi Aoki, MD; Yusuke Nomura, MD, PhD; Nozomi Takeda, RN; Wei-Ping Chen, MD, PhD; Junichi Taki, MD, PhD; Kenichi Nakajima, MD, PhD; Stephan G. Nekolla, PhD; Seigo Kinuya, MD, PhD; Kouji Kajinami, MD, PhD

Background—Although both 123I-metaiodobenzylguanidine (123I-MIBG) imaging and 11C-hydroxyephedrine (11C-HED) positron emission tomography (PET) are used for assessing cardiac sympathetic innervation, their relationship remains unknown. The aims were to determine whether 123I-MIBG parameters such as heart-to-mediastinum ratio (H/M) are associated with quantitative measures by 11C-HED PET and to compare image quality, defect size, and location between 123I-MIBG single-photon emission computed tomography (SPECT) and 11C-HED PET.

Methods and Results—Twenty-one patients (mean left ventricular ejection fraction, 39%±15%) underwent 123I-MIBG imaging and 11C-HED PET. Early (15-minute), late (3-hour) H/M, and washout rate (WR) were calculated for 123I-MIBG. Myocardial retention and WR was calculated for 11C-HED. Using a polar map approach, defect was defined as the area with relative activity <60% of the maximum. Both the early (r=0.76) and late (r=0.84) 123I-MIBG H/M were correlated with 11C-HED retention. 123I-MIBG WR was correlated with 11C-HED WR (r=0.57). Defect size could not be measured in 3 patients because of poor quality 123I-MIBG SPECT, whereas 11C-HED defect was measurable in all patients. Although defect size measured by early or late 123I-MIBG SPECT was closely correlated with that by 11C-HED PET (early: r=0.94; late: r=0.88), the late 123I-MIBG overestimated defect size particularly in the inferior and septal regions.

Conclusions—123I-MIBG H/M gives a reliable estimate of cardiac sympathetic innervation as measured by 11C-HED PET. Furthermore, despite the close correlation in defect size, 11C-HED PET appears to be more suitable for assessing regional abnormalities than does 123I-MIBG SPECT. (Circ Cardiovasc Imaging. 2010;3:595-603.)

Key Words: nervous system ▪ sympathetic ▪ radioisotopes ▪ tomography

Iodine-123 metaiodobenzylguanidine (123I-MIBG, a norepinephrine analogue) imaging is known to provide important clinical information on cardiac sympathetic neuronal function in various cardiac disorders such as heart failure (HF), coronary heart disease (CHD), and arrhythmogenic heart diseases. In particular, planar imaging–derived semiquantitative parameters of 123I-MIBG such as heart-to-mediastinum uptake ratio (H/M) or myocardial washout rate (WR) are of prognostic significance in HF patients, as demonstrated by a number of studies. Furthermore, regional denervation, which may be linked to ventricular arrhythmia, can be assessed by single-photon emission computed tomography (SPECT) imaging, although the low myocardial uptake of 123I-MIBG, particularly in HF patients, may pose limitation for accurate measurement of denervated area.

Clinical Perspective on p 603

Positron emission tomography (PET) using tracers for sympathetic innervation such as 11C-hydroxyephedrine (11C-HED) or 11C-epinephrine is a more sophisticated imaging technique as compared with 123I-MIBG imaging with higher sensitivity, spatial resolution, and the possibility of absolute quantification by routine use of attenuation/scatter correction. However, its clinical experience is limited because it is methodologically demanding, including the necessity for an on-site cyclotron. Therefore, interpretation of 11C-HED PET is still a challenge from the viewpoint of clinical significance because of the lack of large clinical data. In this regard, it would be useful to know how 11C-HED PET measurements are associated with those of more widely available techniques such as 123I-MIBG imaging.

Received November 3, 2009; accepted May 27, 2010.

From The Medical and Pharmacological Research Center Foundation (I.M., N.T., W.-P.C.), Hakui, Japan; the Department of Cardiology (H.A., Y.N., K.K.), Kanazawa Medical University, Uchinada, Japan; the Department of Nuclear Medicine (J.T., K.N., S.K.), Kanazawa University Hospital, Kanazawa, Japan; and the Department of Nuclear Medicine (S.G.N.), Technical University Munich, Munich, Germany.

Correspondence to Ichiro Matsunari, MD, The Medical and Pharmacological Research Center Foundation, W32, Inoyama, Hakai, Ishikawa, 925-0613, Japan. E-mail matsunari@mprcf.or.jp

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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.109.920538

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The purposes of this study were to determine whether planar $^{123}$I-MIBG imaging–derived parameters such as H/M or WR are associated with quantitative parameters measured by $^{11}$C-HED PET, and to directly compare image quality, defect size, and location between $^{123}$I-MIBG SPECT and $^{11}$C-HED PET.

### Methods

#### Study Population

This was a retrospective analysis of observational study to characterize HF using imaging biomarkers. Although the imaging protocol included $^{11}$C-acetate PET to assess oxidative metabolism, this part was not used in this study. $^{123}$I-MIBG imaging was performed when it is clinically indicated by referring physician. We consecutively screened 38 patients who had been referred to The Medical and Pharmacological Research Center Foundation as potential candidates of the study using the following criteria: (1) angiographically proven CHD or nonischemic symptomatic HF, because both disease conditions are known to cause abnormalities in cardiac sympathetic innervation,7,15 (2) regional or global (left ventricular ejection fraction [LVEF] of <50%) left ventricular (LV) dysfunction documented by echocardiography or ECG-gated myocardial perfusion SPECT at entry, and (3) both $^{123}$I-MIBG imaging and $^{11}$C-HED PET having been performed under stable general condition within 1 month after the entry. The first criterion was met in all 38 patients; the second criterion was met in 31 patients. Of these, 21 patients met the third criterion and thus were included in the study. Patients were excluded if they (1) had decompensated HF, (2) had acute coronary events (<10 days) such as myocardial infarction or unstable angina before the imaging study, (3) had any cardiac event or clinical instability requiring changes in medical treatment between the 2 imaging visits, or (4) were premenopausal women. All cardiac medications such as β-blockers were continued during the study period for safety reasons. All patients underwent $^{123}$I-MIBG imaging and $^{11}$C-HED PET within a mean of 5.7 days (1 to 15 days). The study protocol was approved by the institutional ethical committee and written informed consent was obtained from all the participants at the time of screening.

#### $^{123}$I-MIBG Imaging

Anterior planar imaging for 5 minutes was performed 15 minutes and 3 hours after intravenous injection of 111 MBq of $^{123}$I-MIBG using a triple-head camera system (Prism 3000, Picker, Cleveland, Ohio) equipped with low-energy parallel-hole collimators. Images were acquired for 5 minutes using 512×512 matrices. After completion of planar imaging, SPECT was acquired for 15 minutes in 64×64 matrices over 360° with an acquisition time of 30 seconds per projection in 4° increments. An energy window centered on the 159±15.9 keV. The image data were reconstructed by use of a standard filtered back-projection with a Butterworth filter (cutoff frequency, 0.24; order 8). Neither attenuation nor scatter correction was performed.

The H/M was measured for both early (15-minute) and late (3-hour) images by placing the regions of interest on the entire LV myocardium and upper mediastinum. Additionally, background and decay corrected WR from the early to delayed images was calculated.6

#### Positron Emission Tomography

PET imaging was performed using a full-ring PET scanner (Advantage, GE Healthcare). After positioning the subject in the supine position in the gantry, transmission scan for 15 minutes was performed using $^{68}$Ge/$^{68}$Ga pin sources for attenuation correction. After completion of transmission scan, 600 MBq of $^{11}$C-HED was intravenously injected, and a dynamic imaging sequence (14 frames, 6×30, 2×60, 2×150, 2×300, and 2×600 seconds) was acquired. Additionally, venous blood samples were drawn to measure plasma norepinephrine (NE) and brain natriuretic peptide (BNP) as the neurohormonal markers of HF severity.

#### Processing of PET Data

A volumetric sampling procedure was used to create polar maps of activity distribution throughout the entire LV myocardium. From the dynamic PET images, global myocardial $^{11}$C-HED retention fraction was calculated as the LV myocardial activity at the last frame (30 to 40 minutes) divided by the integral of the arterial blood activity curve, which was derived from a small circular region of interest in the left ventricular cavity. Additionally, $^{11}$C-HED WR was obtained as the difference in activity between the early (10- to 15-minute) and the late (30- to 40-minute) images divided by the early image.16

#### Comparison of $^{123}$I-MIBG SPECT and $^{11}$C-HED PET

For tomographic data, image quality was assessed by 2 readers. Each SPECT or PET image data set was assigned good, fair, or poor (suboptimal). The disagreements in image quality assignment was resolved by consensus. The patients with poor image quality in at least 1 of the 3 image data sets (ie, early and late $^{123}$I-MIBG SPECT, and $^{11}$C-HED PET) were excluded from further analysis because reliable defect size quantification would not be possible in such patients.

Comparison of defect size and location between $^{123}$I-MIBG SPECT and $^{11}$C-HED PET was performed using a semi-quantitative polar map approach, which was developed and validated at the Technical University of Munich.17 The SPECT and PET images were normalized to the mean of 6 connected sectors showing the highest overall uptake in the LV myocardium. A pixel in the patient’s map was considered abnormal if its count activity was <60% of the maximum.18 The defect size was measured for the apical, anterior, septal, lateral, and inferior regions and for the whole LV, and was expressed as the percentage of LV myocardium (%LV).

#### Intraobserver and Interobserver Agreements

To test intraobserver agreement of defect size measurements, a single reader analyzed both $^{123}$I-MIBG SPECT and $^{11}$C-HED PET twice in every patient. To reduce recall bias, the second analysis was performed at least 1 month after the first analysis. Additionally, the data were analyzed independently by another reader to test interobserver agreement.

#### Echocardiography

Echocardiography was performed in all patients on the same day of PET imaging using Vivid 7 (GE Healthcare) with a 4-MHz transducer. LVEF was measured using the Simpson biplane method.

#### Statistical Analysis

Data are expressed as mean±1SD. A paired $t$ test was used for comparison of hemodynamic variables between the 2 imaging visits. Correlations of variables were analyzed by linear regression. The defect size between $^{123}$I-MIBG SPECT and $^{11}$C-HED PET was compared using repeated-measures ANOVA, followed by the Dunnett multiple comparison test. For correlation analysis of imaging versus neurohormonal parameters, the logarithmical transformation of BNP was performed to normalize the distribution of its plasma concentration because BNP is known to be rarely normally distributed.19,20 Intraobserver and interobserver agreements were assessed by intraclass correlation coefficient and Bland-Altman plots. Analysis was performed using SPSS 18, JMP 8, or GraphPad Prism 5, where appropriate.

#### Results

Patient Characteristics

Patient characteristics are summarized in Table 1. There were 15 men and 6 women with a mean age of 66±8 years. In this study, none of the 21 patients met the exclusion criteria and had to be excluded from the study because they were in stable...
| Age, y | Sex | Diagnosis | Infarct-Related Artery in Mi (or Stenosed Artery in Non-MI) | Complicated Diseases | NYHA Functional Class | LVEF, % | NE, pg/mL | BNP, pg/mL | ACEI or ARB | p-Blocker | Digitalis | Diuretic | Nitrate | Ca Antagonist | Spironolactone | Mean RPP on \(^{123}\)I-MIBG | Mean RPP on \(^{11}C\)-HED |
|-------|-----|-----------|------------------------------------------------------------|----------------------|---------------------|--------|--------|-----------|------------|-----------|-----------|---------|---------|--------|----------|-----------------|----------------|-----------------|----------------|
| 1     | 59  | F         | MI | LCx |                          | 1   | 55    | 210    | 98.0       | X         | X         | X       | X       | X      | X        | 3813            | 3583            |
| 2     | 66  | M         | MI | LAD |                          | 4   | 38    | 300    | 121        | X         | X         | X       | X       | X      | X        | 6240            | 6720            |
| 3     | 47  | M         | MI | LAD |                          | 2   | 33    | 179    | 132        | X         | X         | X       | X       | X      | X        | 6167            | 7553            |
| 4     | 76  | M         | MI | LAD | HT                        | 2   | 46    | 270    | 53.4       | X         | X         | X       | X       | 5743           | 5461            |
| 5     | 60  | M         | MI | LAD | DM, HT                    | 3   | 27    | 798    | 529        | X         | X         | X       | X       | X      | X        | 4473            | 4444            |
| 6     | 64  | M         | MI | RCA | DM, Asthma                | 3   | 26    | 592    | 748        | X         | X         | X       | X       | 4520           | 5544            |
| 7     | 66  | F         | MI | LAD | DM                        | 2   | 43    | 373    | 67.8       | X         | X         | X       | X       | X      | X        | 5621            | 5544            |
| 8     | 56  | M         | MI | LAD |                          | 3   | 16    | 448    | 150        | X         | X         | X       | X       | X      | X        | 5180            | 4532            |
| 9     | 78  | F         | MI | LAD | DM, HT, HL                | 2   | 59    | 427    | 359        | X         | X         | X       | X       | 6347           | 6880            |
| 10    | 68  | M         | MI | LAD | DM                        | 1   | 55    | 134    | 54.5       | X         | X         | X       | X       | 4667           | 4911            |
| 11    | 60  | M         | MI | RCA | VF                        | 2   | 27    | 582    | 230        | X         | X         | X       | X       | 6080           | 6058            |
| 12    | 67  | M         | MI | LAD |                          | 1   | 40    | 427    | 235        | X         | X         | X       | X       | 5040           | 4875            |
| 13    | 67  | M         | MI | LCx |                          | 1   | 40    | 255    | 72.6       | X         | X         | X       | X       | 4712           | 4629            |
| 14    | 59  | M         | Non-MI | RCA | DM, HT                    | 1   | 58    | 105    | 16.4       | X         | X         | X       | X       | 5670           | 5922            |
| 15    | 69  | F         | Non-MI | LAD |                          | 1   | 66    | 214    | 10.0       | X         | X         | X       | X       | 4320           | 4640            |
| 16    | 58  | M         | Non-MI | LCx |                          | 1   | 49    | 309    | 24.9       | X         | X         | X       | X       | 5120           | 5301            |
| 17    | 61  | F         | Valvular disease | ... |                          | 3   | 31    | 394    | 133        | X         | X         | X       | X       | 8507           | 8836            |
| 18    | 75  | M         | Amyloid CM | ... |                          | 2   | 30    | 627    | 84.2       | X         | X         | X       | X       | 8464           | 7245            |
| 19    | 76  | M         | Amyloid CM | ... |                          | 3   | 26    | 483    | 174        | X         | X         | X       | X       | 5588           | 5058            |
| 20    | 81  | F         | Unknown etiology | ... |                          | 3   | 22    | 1950   | 4253       | X         | X         | X       | X       | 5749           | 5592            |
| 21    | 70  | M         | Unknown etiology | ... | HT                        | 2   | 30    | 471    | 15.4       | X         | X         | X       | X       | 5757           | 5893            |

Mean (SD) 39 (14) 455 (385) 360 (910) 5608 (1181) 5677* (1224)

Mi indicates CHD with prior myocardial infarction; non-MI, CHD without prior myocardial infarction; CM, cardiomyopathy; LCx, left circumflex artery; LAD, left ascending artery; RCA, right coronary artery; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and mean RPP, product of mean blood pressure and heart rate.

*P=0.57 versus mean RPP on \(^{123}\)I-MIBG.
Sixteen patients had CHD (13 had a history of myocardial infarction, and subsequent percutaneous coronary intervention on their infarct-related arteries) and 5 had nonischemic HF (1 valvular disease, 2 amyloid cardiomyopathy, and 2 HF of unknown underlying disease). The mean LVEF as measured by echocardiography was 39±14%. Functional status as assessed by New York Heart Association functional class and medication regimens remained unchanged in all patients. Similarly, hemodynamic variables did not differ significantly during the study period.

Planar 123I-MIBG Imaging Parameters and 11C-HED PET
As illustrated in Figure 1, both the early and late 123I-MIBG H/M were significantly correlated with 11C-HED retention. Additionally, there was a significant correlation between 123I-MIBG WR and 11C-HED WR ($r=0.57$, $P<0.01$).

The relationships between 123I-MIBG or 11C-HED parameters versus functional or neurohormonal measures of HF severity are summarized in Table 2. LVEF was significantly correlated with most of the image-derived parameters except for early 123I-MIBG H/M. Plasma NE showed a close correlation with 11C-HED WR (0.78) and a moderate correlation with 123I-MIBG WR (0.44) but did not with 123I-MIBG H/M or 11C-HED retention. Additionally, 123I-MIBG H/M or 11C-HED retention was negatively correlated with logarithm of plasma BNP, whereas 123I-MIBG WR or 11C-HED WR was positively correlated with it.

123I-MIBG SPECT and 11C-HED PET

Image Quality Assessment of Tomographic Data
By visual inspection, the quality of 11C-HED images was judged as good in all 21 patients. For the early 123I-MIBG SPECT, the image quality was fair in all 21 patients. For the late 123I-MIBG SPECT, the quality was fair in 18 patients and was poor in 3 patients. These 3 patients with poor-quality late 123I-MIBG images were considered to be suboptimal for defect size quantification and were therefore excluded from the further analysis, whereas 11C-HED defect was measurable in all patients. The mean late H/M in this subgroup was 1.57±0.19, as compared with 1.90±0.29 ($P=0.08$) in the remaining patients with acceptable image quality. An example of poor 123I-MIBG image quality is presented in Figure 2.

Intraobserver and Interobserver Reproducibility
Intraobserver and interobserver agreements were good for both PET and SPECT, with intraclass correlation coefficients of 0.98 to 0.99 for intraobserver and 0.95 to 0.99 for interobserver agreement. Bland-Altman plots demonstrated no evidence of systemic bias for both 123I-MIBG SPECT and 11C-HED PET (Figure 3), although the limits of 2SDs of the difference of 123I-MIBG SPECT tended to be wider as compared with those of 11C-HED PET.

Comparison of Defect Size and Location Between 123I-MIBG SPECT and 11C-HED PET
The relationships of defect size between 123I-MIBG SPECT and 11C-HED PET are shown in Figure 4. The defect size measured by either early or late 123I-MIBG SPECT was closely correlated with that measured by 11C-HED PET. Figure 5 illustrates a representative case example with a more extensive inferior defect with 123I-MIBG SPECT than with 11C-HED PET.

Discussion
To the best of our knowledge, this is the first study that compared 123I-MIBG imaging and 11C-HED PET in the same individual patients. The major findings of this study were that (1) 123I-MIBG H/M were significantly correlated with quan-
titative measure of sympathetic innervation (ie, $^{11}$C-HED retention) by PET, (2) cardiac $^{11}$C-HED WR was significantly correlated with $^{123}$I-MIBG WR and plasma NE level, (3) $^{11}$C-HED PET consistently showed better image quality than $^{123}$I-MIBG SPECT, and (4) late $^{123}$I-MIBG SPECT overestimated the defect area particularly in the inferior and septal regions as compared with $^{11}$C-HED PET.

$^{123}$I-MIBG and $^{11}$C-HED as Tracers for Assessing Cardiac Sympathetic Innervation

$^{123}$I-MIBG and $^{11}$C-HED are currently the most established single-photon and positron-emitting tracers for assessing cardiac presynaptic sympathetic neuronal integrity.7,15 Both tracers are analogs of NE, not metabolized, and thus marks the location of functioning nerve terminals.11,21 Our prior

![Image of PET and SPECT images showing early and late myocardial tracer uptake and liver activity](http://circimaging.ahajournals.org/)

**Figure 2.** $^{123}$I-MIBG SPECT and $^{11}$C-HED PET images from a male patient with anterior myocardial infarction. The quality of early and late $^{123}$I-MIBG SPECT and $^{11}$C-HED PET images were judged as fair, poor, and good, respectively. In particular, the low myocardial tracer uptake and intense adjacent liver activity on the late $^{123}$I-MIBG SPECT degrades the image quality. SA indicates short axis; VLA, vertical long axis; and HLA, horizontal long axis.

![Intraobserver agreement plots](http://circimaging.ahajournals.org/)

**Figure 3.** Bland-Altman plots and intraclass correlation coefficients with 95% confidence intervals in parentheses for $^{11}$C-HED PET and $^{123}$I-MIBG SPECT defect size showing interobserver and intraobserver variabilities. Solid lines indicate mean difference; dotted lines, limits of 2 SDs of the difference.
experimental study using rabbit hearts has shown that both tracers are highly specific for sympathetic neurons. From a technical viewpoint, however, there are many differences between planar imaging and PET. The former only gives semiquantitative parameters such as H/M, whereas the later provides truly quantitative measures of neuronal density. Despite this, 123I-MIBG H/M, particularly late H/M, were well correlated with 11C-HED retention, supporting the concept that the simple semiquantitative H/M gives a reliable estimate of cardiac sympathetic innervation.

In the present study, we measured plasma NE and BNP as neurohormonal makers of HF severity because these markers reflect different pathophysiologic aspects of HF. BNP is released from the myocardium and its plasma level reflects myocardial wall stress, whereas plasma NE is a marker of systemic sympathetic nerve activation. Although plasma NE is elevated only at a later stage of HF, both markers are known to provide important prognostic information in HF patients. It should also be noted that unlike the imaging parameters tested in this study such as 123I-MIBG H/M and 11C-HED retention, plasma NE is not specific for cardiac sympathetic function. When the imaging parameters were compared with functional or neurohormonal parameters, 11C-HED retention showed a similar correlation pattern (ie, significant correlations with LVEF and plasma BNP, but not with NE) to late 123I-MIBG H/M, suggesting that 11C-HED retention and late 123I-MIBG H/M may reflect similar physiological aspects of HF. It is also notable that 11C-HED WR was significantly correlated with plasma NE. To date, only little attention has been given to 11C-HED WR in literature. Besides the short physical half-life of 11C, a possible reason for this is that 11C-HED binding to storage vesicles is considered to be relatively low as compared with that of NE. However, our prior experimental study in rabbit hearts has shown that reserpine inhibitable fraction of 11C-HED is greater than that of 123I-MIBG, suggesting that the former is more specific for intravesicular uptake than the later. In this regard, it is conceivable that 11C-HED PET may reflect cardiac sympathetic nerve activity at least to some degree, as does 123I-MIBG PET, although the clinical value of 11C-HED WR remains to be elucidated by further studies. This is also supported by the significant correlation between 11C-HED WR and 123I-MIBG WR observed in this study.

Tomographic Imaging

There is a general agreement that the sympathetic nervous system plays an important role in the genesis of ventricular arrhythmias and an increased risk of sudden death. Recent studies have shown that the regional variation of presynaptic sympathetic function as assessed by SPECT or PET may be linked to some forms of lethal ventricular arrhythmias. However, image quality is a critical issue for reliable measurement of such regional abnormalities on tomographic data. Our results demonstrated that 11C-HED PET consistently showed better image quality than 123I-MIBG SPECT. More importantly, a small but not negligible number of patients (14%) showed poor-quality late 123I-MIBG images, where measurement of regional abnormalities was not possible in a reliable manner. The quality of 11C-HED PET images was still good in all such patients, indicating that 11C-HED PET is more suitable for assessment of regional abnormalities than 123I-MIBG SPECT. In other words, regional analysis with 123I-MIBG SPECT may be difficult when its image quality is suboptimal. It is also important to note that image quality may affect reproducibility of measurements, which is supported by our data showing a trend toward lower variability with 11C-HED PET than with 123I-MIBG SPECT. The better

**Table 3. Defect Size and Location Assessed by 123I-MIBG SPECT and 11C-HED PET**

<table>
<thead>
<tr>
<th></th>
<th>Early 123I-MIBG</th>
<th>Late 123I-MIBG</th>
<th>11C-HED</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>2.8±3.8</td>
<td>2.6±3.7†</td>
<td>4.1±5.1</td>
<td>0.036</td>
</tr>
<tr>
<td>Inferior</td>
<td>8.0±5.6</td>
<td>11.3±5.0†</td>
<td>6.2±6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal</td>
<td>7.3±5.6</td>
<td>8.2±5.7†</td>
<td>5.9±6.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Lateral</td>
<td>3.8±5.0</td>
<td>5.2±4.8</td>
<td>5.9±6.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Apex</td>
<td>9.7±8.0†</td>
<td>12.7±7.0</td>
<td>11.7±8.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Total</td>
<td>31.6±23.2</td>
<td>39.9±20.1†</td>
<td>33.8±25.4</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Values are expressed as %LVM (mean±SD).
*P values by repeated-measures ANOVA.
†P<0.05 versus 11C-HED.
The image quality of PET than SPECT is not surprising considering the technical advantages of PET over SPECT. Additionally, the lower injected dose of $^{123}$I-MIBG (111 MBq) relative to that of $^{11}$C-HED (600 MBq) may have contributed to the lower image quality. However, this reflects the standard $^{123}$I-MIBG imaging protocol practiced in Japan, where 111 MBq is the maximum dose limit for this tracer. Furthermore, the intense adjacent liver uptake relative to the myocardium, as illustrated in Figure 2, is not likely to be improved by increasing the $^{123}$I-MIBG dose.

Despite the image quality differences described above, the defect size measured by $^{123}$I-MIBG SPECT was closely correlated with that measured by $^{11}$C-HED PET, indicating that $^{123}$I-MIBG SPECT provides measures of regional sympathetic innervation if the image quality is acceptable. However, the late $^{123}$I-MIBG SPECT significantly overestimated defect area as compared with $^{11}$C-HED PET, particularly in the inferior and septal regions. In addition to possible differences in tracer kinetics between $^{123}$I-MIBG and $^{11}$C-HED, attenuation artifacts may certainly have contributed to the results. Inferior and septal regions are known to be susceptible to attenuation artifacts, which is particularly true in patients with dilated LV such as those encountered in HF. Furthermore, intense liver activity may have further lessened the inferior myocardial activity during image reconstruction.

**Limitations**

There are limitations of the study to be described. First, the most significant limitation of the study is the lack of attenuation correction for $^{123}$I-MIBG SPECT, which would have had a significant impact on SPECT image quality and would make a proper comparison of the 2 tracers difficult. Additionally, relatively low spatial resolution of current SPECT system limits the clear delineation of myocardium from the liver, which may be further enhanced after correction. Perhaps for this reason, attenuation correction for cardiac $^{123}$I-MIBG SPECT has not yet been used in any of published data. Nevertheless, we believe that further instrumental work should be directed toward implementation of attenuation correction together with improved spatial resolution and counting sensitivity. This would improve SPECT image quality and enable more accurate $^{123}$I-MIBG SPECT measurements, which may be possible using newer generation cameras. Second, both PET and SPECT images were normalized to the maximum of LV myocardium and a simple 60% threshold was used to define defect area, which abolishes any difference in global tracer retention because the maximum is always set to 100%. This is unavoidable with $^{123}$I-MIBG due to the nonquantitative nature of SPECT. A true regional defect versus normal will thus be underestimated in case of overall downregulation of innervation that includes remote myocardium. Thus, if PET is used and regional absolute retention is compared with normal, defect size will be more accurately assessed. We could not cover this issue in the present study because we did not include normal data bases for comparison.

Third, we relied on $^{11}$C-HED retention/washout as PET measures of presynaptic sympathetic function because they are simple and stable. More sophisticated compartment kinetic models have also been used for $^{11}$C-HED. Although they are technically more demanding, the model based quantitative parameters such as volume of distribution may be more specific to presynaptic uptake-1 function than is $^{11}$C-HED retention. The comparative clinical significance of these $^{11}$C-HED parameters remains to be investigated in further studies. Furthermore, we assessed only presynaptic neuronal function in the current study. The combination of presynaptic and postsynaptic functions using PET has been reported in patients with arrhythmogenic heart diseases and HF, which would provide more comprehensive understanding of underlying pathophysiology.

Fourth, plasma BNP, NE, and LVEF were measured on the day of $^{11}$C-HED PET, and therefore it is possible that these measurements would have been more favorably correlated with $^{11}$C-HED results than with $^{123}$I-MIBG. Although the both imaging procedures were performed under stable clini-
cal conditions with relatively short intervals (mean 5.7 days), this possibility cannot be ruled out. Fifth, the study patients were heterogeneous in underlying etiology, including ischemic and nonischemic cardiac diseases. However, it has been shown that sympathetic neuronal imaging reflects the disease severity independent of underlying cause,1 which was true in the current study as demonstrated by the relationship between imaging parameters and functional or neurohormonal markers of HF. Finally, outcome data were not obtained in this study and therefore comparative prognostic value of 123I-MIBG imaging and 11C-HED PET is unknown.

Conclusion
Semiquantitative 123I-MIBG H/M gives a reliable estimate of cardiac sympathetic innervation as measured by 11C-HED PET. Additionally, 11C-HED WR may serve as an index of cardiac sympathetic neuronal activity, as does 123I-MIBG WR, although this must be validated in further studies. As for tomographic imaging, although there is a close correlation in measured defect size between SPECT and PET, the later 121I-MIBG SPECT overestimates defect size particularly in the inferior and septal regions. More importantly, 11C-HED PET consistently yields better quality images and appears to be more suitable for assessing regional abnormalities than 123I-MIBG SPECT. In other words, regional analysis with 123I-MIBG SPECT may be difficult when its image quality is suboptimal.

Sources of Funding
This work was supported by Ishikawa prefectoral government.

Disclosures
None.

References
28. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, Masuda M, Okuda K, Iwasaki Y, Yasui T, Hori M, Fukunami M. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with...


CLINICAL PERSPECTIVE

Iodine-123 metaiodobenzylguanidine (123I-MIBG) imaging provides information on cardiac sympathetic neuronal function, which may be clinically useful in a variety of conditions including diabetes and heart failure. This study was performed to determine whether semiquantitative 123I-MIBG parameters such as heart-to-mediastinum ratio (H/M) are associated with quantitative measures of cardiac sympathetic innervation by 11C-hydroxyephedrine (11C-HED) positron emission tomography (PET) and to compare image quality, defect size, and location between 123I-MIBG single-photon emission computed tomography (SPECT) and 11C-HED PET in patients with regional or global left ventricular dysfunction (mean left ventricular ejection fraction, 39±15%). We found that both the early (r=0.764) and late (r=0.844) 123I-MIBG H/M were correlated well with 11C-HED retention. Myocardial 123I-MIBG washout rate was also correlated with 11C-HED washout rate (r=0.569). For tomographic imaging, however, 123I-MIBG defect size could not be measured in 3 patients because of poor SPECT image quality, whereas 11C-HED defect was measurable in all patients. Furthermore, although defect size measured by early or late 123I-MIBG SPECT was significantly correlated with that by 11C-HED PET, the late 123I-MIBG overestimated defect size particularly in the inferior and septal regions. Thus, 123I-MIBG H/M gives a reliable estimate of cardiac sympathetic innervation as measured by 11C-HED PET. However, regional analysis with 123I-MIBG SPECT may be difficult when its image quality is suboptimal.
Iodine-123 Metaiodobenzylguanidine Imaging and Carbon-11 Hydroxyephedrine Positron Emission Tomography Compared in Patients With Left Ventricular Dysfunction
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_Circ Cardiovasc Imaging_. 2010;3:595-603; originally published online June 9, 2010; doi: 10.1161/CIRCIMAGING.109.920538
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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