Impaired Myocardial Sympathetic Innervation Is Associated with Diastolic Dysfunction in Heart Failure with Preserved Ejection Fraction: 11C-Hydroxyephedrine PET Study

Aikawa, Tadao; Naya, Masanao; Obara, Masahiko; Manabe, Osamu; Tomiyama, Yuuki; Magota, Keiichi; Yamada, Satoshi; Katoh, Chietsugu; Tamaki, Nagara; Tsutsui, Hiroyuki

The journal of nuclear medicine, 58(5): 784-790

2017-05-01

This research was originally published in JNM. Tadao Aikawa, Masanao Naya, Masahiko Obara, Osamu Manabe, Yuuki Tomiyama, Keiichi Magota, Satoshi Yamada, Chietsugu Katoh, Nagara Tamaki and Hiroyuki Tsutsui. Impaired Myocardial Sympathetic Innervation Is Associated with Diastolic Dysfunction in Heart Failure with Preserved Ejection Fraction: 11C-Hydroxyephedrine PET Study. JNM. 2017;58:784-790. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.
Impaired Myocardial Sympathetic Innervation Is Associated with Diastolic Dysfunction in Heart Failure with Preserved Ejection Fraction: 11C-Hydroxyephedrine PET Study

Tadao Aikawa1, Masanao Naya1, Masahiko Obara1, Osamu Manabe2, Yuuki Tomiyama2, Keiichi Magota3, Satoshi Yamada1, Chietsugu Katoh4, Nagara Tamaki2, and Hiroyuki Tsutsui1

1Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan; 2Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan; 3Department of Medical Imaging, Hokkaido University Hospital, Sapporo, Japan; and 4Faculty of Health Sciences, Hokkaido University Graduate School of Medicine, Hokkaido, Japan

Diastolic dysfunction is important in the pathophysiology of heart failure with preserved ejection fraction (HFpEF). Sympathetic nervous hyperactivity may contribute to the development of diastolic dysfunction. The aim of this study was to determine the relationship between myocardial sympathetic innervation quantified by 11C-hydroxyephedrine PET and diastolic dysfunction in HFpEF patients.

Methods: Forty-one HFpEF patients having an echocardiographic left ventricular ejection fraction of 40% or greater and 12 age-matched volunteers without heart failure underwent the echocardiographic examination and 11C-hydroxyephedrine PET. Diastolic dysfunction was classified into grades 0–3 by Doppler echocardiography. Myocardial sympathetic innervation was quantified using the 11C-hydroxyephedrine retention index (RI). The coefficient of variation of 17-segment RIs was derived as a measure of heterogeneity in myocardial 11C-hydroxyephedrine uptake.

Results: Grade 2–3 diastolic dysfunction (DD2–3) was found in 19 HFpEF patients (46%). They had a significantly lower global RI (0.075 ± 0.018 min−1) than volunteers (0.123 ± 0.028 min−1, P < 0.001) and HFpEF patients with grade 0–1 diastolic dysfunction (DD0–1) (0.092 ± 0.024 min−1, P = 0.046). HFpEF patients with DD2–3 had the largest coefficient of variation of 17-segment RIs of the 3 groups (18.4% ± 7.7% vs. 14.1% ± 4.7% in HFpEF patients with DD0–1, P = 0.042 for post hoc tests). In multivariate logistic regression analysis, a lower global RI (odds ratio, 0.66 per 0.01 min−1; 95% confidence interval, 0.38–0.99; P = 0.044) was independently associated with the presence of DD2–3 in HFpEF patients.

Conclusion: Myocardial sympathetic innervation was impaired in HFpEF patients and was associated with the presence of advanced diastolic dysfunction in HFpEF.

Key Words: heart failure with preserved ejection fraction; diastolic dysfunction; 11C-hydroxyephedrine

J Nucl Med 2017; 58:784–790
DOI: 10.2967/jnumed.117.178558

Activation of the sympathetic nervous system (SNS) plays an important role in progression to heart failure (1–3). Impairment of myocardial sympathetic innervation reflecting SNS hyperactivity has been demonstrated to predict adverse cardiac events in patients with heart failure (4,5). Furthermore, regional myocardial denervation quantified by 11C-hydroxyephedrine (11C-HED) PET can predict sudden cardiac death in patients with ischemic cardiomyopathy (6). Although many studies have assessed myocardial sympathetic innervation in patients with heart failure with reduced left-ventricular ejection fraction (LVEF), little information has been shown in patients with heart failure with preserved LVEF (HFpEF) (5,7).

Epidemiologic studies have shown that HFpEF patients account for approximately one-half of patients with heart failure (8). HFpEF is functionally characterized by impaired left-ventricular (LV) relaxation, increased LV stiffness, and elevated LV filling pressure (9). These features of diastolic dysfunction could lead to congestive heart failure (10). The severity of diastolic dysfunction determined by echocardiography has a prognostic impact in HFpEF (11,12). Previous studies showed that SNS hyperactivity can cause diastolic dysfunction in hypertensive patients (13). We, thus, hypothesized that impaired myocardial sympathetic innervation may be related to diastolic dysfunction in HFpEF.

MATERIALS AND METHODS

Study Population

We studied 41 patients with HFpEF, which was defined as having an echocardiographic LVEF of 40% or greater, at Hokkaido University Hospital, Japan, from November 2012 to November 2015. All patients had chronic congestive heart failure diagnosed on the basis of the Framingham criteria (14). Patients who had a renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m2) or severe left-sided valve diseases were excluded. Twelve age-matched volunteers without heart failure served as control subjects. They had neither cardiac symptoms nor a history of cardiovascular disease, and all of them had a normal LVEF without valvular diseases, as determined by echocardiography.

The study protocol was approved by the ethics committee of Hokkaido University Hospital (IBR 012-0098) and registered with the University Hospital Medical Information Network clinical trials registry (UMIN000009386). Written informed consent was obtained from all the participants.
Echocardiographic examinations and measurements were performed by experienced sonographers who were masked to the PET data, using commercially available ultrasound systems in accordance with the guidelines of the American Society of Echocardiography (15). LVEF and left atrial volume were calculated by the biplane method of disks summation using apical 2-chamber and apical 4-chamber views. LV mass was calculated by Devereux’s formula and normalized to body surface area. Color Doppler imaging was performed to screen for valvular diseases. Each participant underwent pulsed-wave Doppler examination of mitral

### TABLE 1
Clinical Characteristics of Study Subjects (n = 53)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 12)</th>
<th>DD ≤ 1 (n = 22)</th>
<th>DD ≥ 2 (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64 ± 12</td>
<td>65 ± 14</td>
<td>63 ± 16</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 ± 4.1</td>
<td>24.3 ± 5.0</td>
<td>24.0 ± 4.2</td>
<td>0.87</td>
</tr>
<tr>
<td>NYHA functional class (I/II/III)</td>
<td></td>
<td>6/13/3</td>
<td>0/11/8</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (83%)</td>
<td>17 (77%)</td>
<td>8 (42%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0%)</td>
<td>10 (45%)*</td>
<td>5 (26%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (58%)</td>
<td>15 (68%)</td>
<td>11 (58%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 (0%)</td>
<td>8 (36%)</td>
<td>7 (37%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0 (0%)</td>
<td>6 (27%)</td>
<td>7 (37%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>0 (0%)</td>
<td>6 (27%)</td>
<td>7 (37%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Heart failure etiologies</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>5 (23%)</td>
<td>7 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>5 (23%)</td>
<td>4 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>6 (27%)</td>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>0 (0%)</td>
<td>5 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (27%)</td>
<td>2 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.0 ± 1.6</td>
<td>12.9 ± 1.9</td>
<td>13.5 ± 1.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.65 (0.57–0.92)</td>
<td>0.81 (0.66–0.99)</td>
<td>0.87 (0.70–1.13)</td>
<td>0.12</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73 m²)</td>
<td>75.6 ± 19.4</td>
<td>66.3 ± 17.2</td>
<td>67.7 ± 33.2</td>
<td>0.56</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL)</td>
<td>11.5 (8.5–19.0)</td>
<td>97.0 (25.2–223.3)*</td>
<td>78.8 (34.1–242.0)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>426 ± 177</td>
<td>367 ± 216</td>
<td>371 ± 199</td>
<td>0.70</td>
</tr>
<tr>
<td>Troponin T (ng/mL)</td>
<td>0.004 (0.003–0.009)</td>
<td>0.016 (0.009–0.045)*</td>
<td>0.038 (0.014–0.058)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-Is or ARBs</td>
<td>5 (42%)</td>
<td>20 (91%)*</td>
<td>13 (68%)</td>
<td>0.009</td>
</tr>
<tr>
<td>β-blockers</td>
<td>1 (8%)</td>
<td>14 (64%)*</td>
<td>18 (95%)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>2 (17%)</td>
<td>1 (5%)</td>
<td>5 (26%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1 (8%)</td>
<td>7 (32%)</td>
<td>9 (47%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>7 (58%)</td>
<td>10 (45%)</td>
<td>6 (32%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Statins</td>
<td>4 (33%)</td>
<td>12 (55%)</td>
<td>10 (53%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0 (0%)</td>
<td>2 (9%)</td>
<td>5 (26%)</td>
<td>0.08</td>
</tr>
<tr>
<td>DOACs</td>
<td>0 (0%)</td>
<td>6 (27%)</td>
<td>3 (16%)</td>
<td>0.13</td>
</tr>
<tr>
<td>SHFM mean life expectancy (y)</td>
<td>10.6 ± 4.9</td>
<td>9.7 ± 3.3</td>
<td></td>
<td>0.50</td>
</tr>
</tbody>
</table>

*P < 0.01 vs. control.
†P < 0.05 vs. control.
‡P < 0.05 vs. DD ≤ 1.

BMI = body mass index; NYHA = New York Heart Association; ACE-Is = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; DOACs = direct oral anticoagulants.

Data are mean ± SD; n, with percentages in parentheses; or median, with interquartile ranges in parentheses.
inflow at rest and Doppler tissue imaging of the mitral annulus. Diastolic
dysfunction was graded as grade 0 (normal function), grade 1 (mild
dysfunction), grade 2 (moderate dysfunction), and grade 3 (severe
dysfunction) on the basis of mean early diastolic annular velocity (e'), left atrial
volume indexed to body surface area, the peak velocity of early-diastolic
mitral flow (E) to peak atrial velocity (A) ratio (E/A), E wave de-
celeration time; LA
9 ratio (E/e
9) in accordance with the recommen-
dations of the American Society of Echocardiography (16).
Subjects should fulfill 2 Doppler criteria consistent with grade 2 or grade 3
diastolic dysfunction. Subjects fulfilling only 1 criterion for grade 2 or grade 3
diastolic dysfunction were classified as having grade 1 or grade 2 diastolic
dysfunction, respectively. HFP EF patients were divided into 2 groups on
the basis of the degree of diastolic dysfunction: grade 0–1 (DD
0–1) and grade 2–3 (DD
2–3). Additionally, the subjects were reclassified using the
more recent published guidelines for diastolic function assessment (17).

11C-HED PET Imaging
PET was performed using a PET/CT scanner (Biograph 64 TruePoint
with TrueV; Siemens Japan). The median interval between echocardiogra-
phy and PET scan was 8 d (range, 0–29 d). The participants fasted for at
least 4 h before PET imaging, and they refrained from taking caffeine-
containing beverages and theophylline-containing medications for at least
24 h before the scan. 11C-HED PET images were acquired as described previously (18). Briefly, after low-dose CT for attenuation and scatter cor-
rection, 185 MBq of 11C-HED were intravenously administered simulta-
neously with a 40-min list-mode acquisition. The list-mode data were
histogrammed into 21 serial frames (9 × 10, 3 × 30, 2 × 60, and 7 ×
300 s). The emission data were reconstructed using filtered backprojection
with gaussian postsmoothing of 10 mm in full width at half maximum. The
image data had a matrix size of 128 × 128 with a voxel size of 3.6 × 3.6 ×
2.0 mm
3.

Data Analysis
All PET images were analyzed using the in-house–developed software.
Short-axis images were used to define a region of interest in the left
ventricle. Myocardial 11C-HED uptake was expressed using the retention
index (RI [min
–1]) that was calculated as the mean myocardial activity in
the last frame (30–40 min) divided by the integral of the arterial blood
time–activity curve derived from a manually placed region of interest at
the basal LV cavity of valve plane (/9,20). Regional PET analyses
were based on the American Heart Association 17-segment model. The

### TABLE 2
Hemodynamics and Echocardiographic Findings

| Parameter                              | Control (n = 12) | DD
0–1 (n = 22) | DD
2–3 (n = 19) | P     |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>121 ± 16</td>
<td>109 ± 21</td>
<td>107 ± 21</td>
<td>0.18</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>67 ± 10</td>
<td>61 ± 12</td>
<td>62 ± 12</td>
<td>0.29</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>58 ± 7</td>
<td>58 ± 11</td>
<td>57 ± 10</td>
<td>0.96</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 (64–69)</td>
<td>51 (43–57)*</td>
<td>45 (42–58)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>46 ± 4</td>
<td>51 ± 8</td>
<td>52 ± 9</td>
<td>0.07</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>28 ± 2</td>
<td>37 ± 10†</td>
<td>41 ± 10*</td>
<td>0.002</td>
</tr>
<tr>
<td>Left atrial end-systolic diameter (mm)</td>
<td>37 (33–39)</td>
<td>42 (39–49)*</td>
<td>43 (34–46)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
| LV mass index (g/m
2)                  | 75 ± 11         | 123 ± 36*  | 133 ± 33*  | <0.001|
| Left atrial volume index (mL/m
2)      | 33 (31–38)      | 42 (35–53) | 43 (31–59) | 0.10  |
| E/A                                    | 0.79 (0.67–0.98) | 0.61 (0.55–0.77) | 1.02 (0.85–1.43)† | 0.002 |
| E wave deceleration time (ms)          | 216 (195–242)   | 219 (184–242) | 182 (167–294) | 0.69  |
| Septal e’ (cm/s)                       | 7.2 ± 2.4       | 6.0 ± 2.4  | 4.7 ± 1.3* | 0.009 |
| Lateral e’ (cm/s)                      | 8.8 ± 1.8       | 8.9 ± 3.9  | 6.9 ± 2.0  | 0.07  |
| E/e’                                   | 8.7 (7.9–9.2)   | 9.2 (8.0–11.1)| 13.0 (10.0–16.3)† | <0.001|

*P < 0.01 vs. control.
†P < 0.05 vs. control.
‡P < 0.01 vs. DD
0–1.
LV = left ventricular; E/A = peak velocity of early-diastolic mitral flow (E) to peak atrial velocity (A) ratio; E/e’ = E to mean early diastolic
annular velocity (e’) ratio.
Data are mean ± SD; n, with percentages in parentheses; or median, with interquartile range in parentheses.
coefficient of variation of 17-segment RIs (CVRI) was derived as a measure of heterogeneity in myocardial $^{11}$C-HED uptake. To quantify perfusion abnormality, we estimated the $^{11}$C-HED influx rate from blood to myocardium ($\text{mL g}^{-1}\text{min}^{-1}$) using a single-tissue-compartment model (21) as an indicator of myocardial blood flow (22).

**Risk Stratification and Biomarkers of HFP EF**

To predict long-term survival in HFP EF patients, we used the validated Seattle Heart Failure Model (SHFM)–based mean life expectancy (23). During PET imaging preparation, venous blood samples at stable and fasting conditions were drawn to measure the levels of plasma norepinephrine and serum troponin T in 50 participants (control subjects, $n = 12$; HFP EF patients, $n = 38$). Plasma norepinephrine levels were measured using high-performance liquid chromatography. Serum troponin T levels were measured by electrochemiluminescence immunoassay.

**Statistical Analysis**

All statistical analyses were performed using JMP Pro (version 12; SAS Institute Inc.). Normally distributed data are presented as mean ± SD and compared among the 3 groups using the 1-way ANOVA with Tukey–Kramer post hoc test. Nonnormally distributed data are presented as medians (with interquartile ranges in parentheses) and compared among the 3 groups using the Kruskal–Wallis test with Steel–Dwass post hoc test. Categoric variables are presented as proportions and compared using the $\chi^2$ test. Correlation between 2 continuous variables was evaluated by linear regression analysis. To identify clinical factors contributing to the presence of DD2–3 in HFP EF patients, multivariate logistic regression analysis was performed using a stepwise variable selection procedure; LVEF was forced into the multivariate model as a clinically meaningful variable, and other variables listed in the univariate analysis were selected on the basis of the corrected Akaike’s information criterion score (model 1). Furthermore, because myocardial ischemia could be a potential confounding factor in this study (6), an additional multivariate analysis including a history of coronary artery disease, LVEF, and stepwise-selected variables was performed (model 2). A $P$ value of less than 0.05 was considered statistically significant.

**RESULTS**

**Clinical Characteristics**

Clinical characteristics of participants are shown in Table 1. Among the 41 HFP EF patients, 22 (54%) were classified into the DD0–1 group and 19 (46%) into the DD2–3 group (Fig. 1). The control group included the following diastolic dysfunctions: grade 0 ($n = 1$), grade 1 ($n = 9$), and grade 2 ($n = 2$). Most of the HFP EF patients (71%) were diagnosed as having nonischemic cardiomyopathy. The SHFM-based mean life expectancy and the levels of plasma norepinephrine and serum troponin T in 50 participants (control subjects, $n = 12$; HFP EF patients, $n = 38$). Plasma norepinephrine levels were measured using high-performance liquid chromatography. Serum troponin T levels were measured by electrochemiluminescence immunoassay.

**TABLE 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control ($n = 12$)</th>
<th>DD0–1 ($n = 22$)</th>
<th>DD2–3 ($n = 19$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global RI (min$^{-1}$)</td>
<td>0.123 ± 0.028</td>
<td>0.092 ± 0.024*</td>
<td>0.075 ± 0.018†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional RI (min$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>0.124 ± 0.028</td>
<td>0.097 ± 0.028‡</td>
<td>0.078 ± 0.019†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal</td>
<td>0.128 ± 0.030</td>
<td>0.099 ± 0.025*</td>
<td>0.085 ± 0.024*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.119 ± 0.029</td>
<td>0.087 ± 0.022*</td>
<td>0.069 ± 0.019†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral</td>
<td>0.119 ± 0.027</td>
<td>0.087 ± 0.027*</td>
<td>0.067 ± 0.016†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVRI (%)</td>
<td>7.9 ± 1.6</td>
<td>14.1 ± 4.7*</td>
<td>18.4 ± 7.7†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$^{11}$C-hydroxyephedrine influx rate (mL.g$^{-1}$.min$^{-1}$)</td>
<td>0.302 ± 0.053</td>
<td>0.231 ± 0.065*</td>
<td>0.189 ± 0.053*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* $P < 0.01$ vs. control.
† $P < 0.05$ vs. DD0–1.
‡ $P < 0.05$ vs. control.
Data are mean ± SD.
The LVEFs were significantly lower, and the LV mass indices were not significantly different between the 2 HFpEF groups. The E/e' group, although the LVEF and LV mass indices were not significantly greater in the 2 HFpEF groups than those in the control group, had a significantly lower global RI (0.068 ± 0.016 vs. 0.096 ± 0.020 min⁻¹), which, however, did not reach statistical significance (P = 0.11). The proportion of diastolic dysfunction grades did not differ between these 2 groups (P = 0.32). In the relationships between 11C-HED PET findings and variables such as the SHFM-based mean life expectancy, B-type natriuretic peptide, norepinephrine, and troponin T, the levels of B-type natriuretic peptide and troponin T were modestly correlated with global RI and CVR (P < 0.05 for all) (Supplemental Fig. 2).

![FIGURE 3. Scatterplots of global RI (A) and CVRI (B) for comparison among the 3 groups. Horizontal lines indicate mean value.](image)

2 HFpEF groups were higher than those in the control group. Hemodynamics and echocardiographic findings are shown in Table 2. The LVEFs were significantly lower, and the LV mass indices were significantly greater in the 2 HFpEF groups than those in the control group, although the LVEF and LV mass indices were not significantly different between the 2 HFpEF groups. The E/e' in the DD₂–₃ group was significantly greater than that in the DD₀–₁ group.

**PET Imaging Results and Relationship with Clinical Variables**

Representative images are shown in Figure 2. The results of PET imaging are summarized in Table 3 and Figure 3. The 2 HFpEF groups showed significantly lower global RIs, all regional RIs, and 11C-HED influx rates and had larger CVRIs than the control group. The DD₂–₃ group had the lowest global RI and regional RIs and the largest CVRI of the 3 groups. After the patients with ischemic heart disease (n = 13) were excluded from the HFpEF patients, the DD₂–₃ group had a significantly lower global RI (0.068 ± 0.016 vs. 0.096 ± 0.016 min⁻¹, P = 0.002) and tended to have a larger CVRI (17.7% ± 7.4% vs. 14.1% ± 4.9%, P = 0.13) than the DD₀–₁ group (Fig. 4). The more recent guidelines for diastolic function assessment classified 37 participants (70%) as grade 0–3 diastolic dysfunction (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org), in which global RI became similar between HFpEF patients with and without advanced diastolic dysfunction.

![FIGURE 4. Scatterplots of global RI (A) and CVRI (B) for comparison between the 2 HFpEF groups with nonischemic heart disease (n = 28). Horizontal lines indicate mean value.](image)

**11C-HED PET as Predictors of DD₂–₃**

Table 4 shows the results of univariate and multivariate logistic regression analysis performed to identify clinical factors contributing to the presence of DD₂–₃ in HFpEF patients. The stepwise variable selection procedure retained a history of hypertension, global RI, and CVRI in models 1 and 2. In multivariate analysis model 1, both a lower global RI and a larger CVRI were independently associated with the presence of DD₂–₃ in HFpEF patients. When a history of coronary artery disease was included in the multivariate analysis (model 2), a lower global RI and a history of hypertension remained independently associated with the presence of DD₂–₃ in HFpEF patients. The studentized residual for each multivariate model had no significant correlation with global RI, indicating acceptable model fit.

**DISCUSSION**

This study showed that myocardial sympathetic innervation was impaired in the presence of HFpEF or advanced diastolic dysfunction. In multivariate logistic regression analysis, reduction in myocardial sympathetic innervation was independently associated with the presence of DD₂–₃ in HFpEF patients. This finding could lead to a new approach to detect the progression of diastolic dysfunction in HFpEF. Furthermore, focal and diffuse changes in myocardial sympathetic innervation might suggest the pathophysiologic process of heart failure across a broad spectrum from normal to diastolic dysfunction.

Reduction in myocardial sympathetic innervation in HFpEF patients was concurrent with previous studies using 123I-metaiodobenzylguanidine imaging (5,7). However, the heart-to-mediastinum ratio on early and delayed planar images and washout rate derived from 123I-metaiodobenzylguanidine imaging were
semiquantitative. In contrast, $^{11}$C-HED is a high-specific-activity PET tracer for SNS presynaptic imaging (19) and enables better regional analysis than $^{123}$I-metaiodobenzylguanidine (20).

The present study demonstrated that reduction in myocardial sympathetic innervation was independently associated with the severity of diastolic dysfunction in HFpEF patients. Meanwhile, heterogeneity of myocardial sympathetic innervation interacted partly with the presence of ischemic heart disease. Diastolic dysfunction plays an important role in the development of HFpEF (9,10). Grassi et al. reported that the presence of diastolic dysfunction augmented the already increased muscle sympathetic nerve activity in hypertensive patients (13). These findings suggest that diastolic dysfunction could increase SNS activity, causing sympathetic denervation in HFpEF as seen in the present study.

Several possibilities are considered to explain the relationship between myocardial sympathetic innervation and diastolic dysfunction in this study. A previous study suggested that regional impairment of sympathetic innervation assessed by $^{11}$C-HED PET is independently associated with hyperemic myocardial blood flow in a non-infarcted myocardium (24). Therefore, both global and regional impairment of sympathetic innervation may reflect heterogeneous microvascular dysfunction in HFpEF. In fact, HFpEF patients showed more severe cardiac hypertrophy and coronary microvascular rarefaction than control subjects in an autopsy study (25). It is possible that microvascular dysfunction may cause heterogeneous reduction in myocardial sympathetic innervation and diastolic dysfunction.

In the present study, we used the algorithm for diastolic function assessment based on the original guidelines (16) because the more recently recommended algorithm (17) does not mention how to deal with patients with atrial fibrillation. The presence of atrial fibrillation is still common in HFpEF patients (8). Actually, in the present study, approximately one-third of the HFpEF patients had paroxysmal or persistent atrial fibrillation. Further analysis is needed to explain the relationship between myocardial sympathetic innervation and diastolic dysfunction in this study.

Several possibilities are considered to explain the relationship between myocardial sympathetic innervation and diastolic dysfunction in this study. A previous study suggested that regional impairment of sympathetic innervation assessed by $^{11}$C-HED PET is independently associated with hyperemic myocardial blood flow in a non-infarcted myocardium (24). Therefore, both global and regional impairment of sympathetic innervation may reflect heterogeneous microvascular dysfunction in HFpEF. In fact, HFpEF patients showed more severe cardiac hypertrophy and coronary microvascular rarefaction than control subjects in an autopsy study (25). It is possible that microvascular dysfunction may cause heterogeneous reduction in myocardial sympathetic innervation and diastolic dysfunction.

In the present study, we used the algorithm for diastolic function assessment based on the original guidelines (16) because the more recently recommended algorithm (17) does not mention how to deal with patients with atrial fibrillation. The presence of atrial fibrillation is still common in HFpEF patients (8). Actually, in the present study, approximately one-third of the HFpEF patients had paroxysmal or persistent atrial fibrillation. Further analysis is needed to explain the relationship between myocardial sympathetic innervation and diastolic dysfunction in this study.
better define the interplay between myocardial sympathetic denervation and diastolic dysfunction based on the new guidelines.

The current study has several limitations. First, HFpEF was defined as having an LVEF of 40% or greater in this study, which is not established criteria for HFpEF. Mildly reduced LVEF (40–50%) might be associated with diastolic dysfunction. However, by multivariate logistic regression analysis, the relationship between diastolic dysfunction and global RI was found independently of LVEF values. Second, the mechanism of the impairment of sympathetic innervation in HFpEF was not clarified in the present study. However, LV mass index and troponin T levels were modestly associated with global RI and CVRI, perhaps providing a pathophysiological link between LV hypertrophy or myocardial damage and cardiac sympathetic function. Third, the control group in the present study had a higher prevalence of grade 1 or higher diastolic dysfunction than the study population in the previous study (11), which may be related to the age and high prevalence of hypertension. Finally, we cannot discuss the prognostic implication of global RI and CVRI in HFpEF patients. We definitely need to conduct a long-term follow-up study in a larger patient group to clarify the prognostic value of quantitative 11C-HED PET and the effects of medical therapies on HFpEF patients with a low global RI.

CONCLUSION

The present study demonstrated that myocardial sympathetic denervation was independently associated with the presence of advanced diastolic dysfunction in HFpEF. The effects of medical therapy targeting sympathetic function on prognosis should be further investigated in HFpEF patients with advanced diastolic dysfunction.

DISCLOSURE

This work was supported by a grant-in-aid for scientific research (JP24591742) from the Ministry of Education, Culture, Sports, Science, and Technology (to Masanao Naya). No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Yoichi M. Ito, PhD, for statistical assistance and Taichi Hayashi, MD, PhD, for technical assistance.

REFERENCES

15. Lang RM, Birrg M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463.