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

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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 ^{11}C-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 ^{11}C-hydroxyephedrine PET. Diastolic dysfunction was classified into grades 0–3 by Doppler echocardiography. Myocardial sympathetic innervation was quantified using the ^{11}C-hydroxyephedrine retention index (RI). The coefficient of variation of 17-segment RIs was derived as a measure of heterogeneity in myocardial ^{11}C-hydroxyephedrine uptake. **Results:** Grade 2–3 diastolic dysfunction (DD_{2-3}) 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 (DD_{0-1}) (0.092 ± 0.024 min^{-1}, $P = 0.046$). HFpEF patients with DD_{2-3} had the largest coefficient of variation of 17-segment RIs of the 3 groups ($18.4\% \pm 7.7\%$ vs. $14.1\% \pm 4.7\%$ in HFpEF patients with DD_{0-1}, $P = 0.042$ 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 DD_{2-3} 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; ^{11}C-hydroxyephedrine

J Nucl Med 2017; 58:784–790
DOI: 10.2967/jnumed.116.178558

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 ^{11}C-hydroxyephedrine (^{11}C-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/1.73m^2) 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 (IRB 012-0098) and registered with the University Hospital Medical Information Network clinical trials registry (UMIN000009386). Written informed consent was obtained from all the participants.

Received May 23, 2016; revision accepted Oct. 17, 2016.
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Published online Nov. 3, 2016.

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

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

*P < 0.01 vs. control.
†P < 0.05 vs. control.
‡P < 0.05 vs. $DD_{0–1}$.
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.

Echocardiography

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

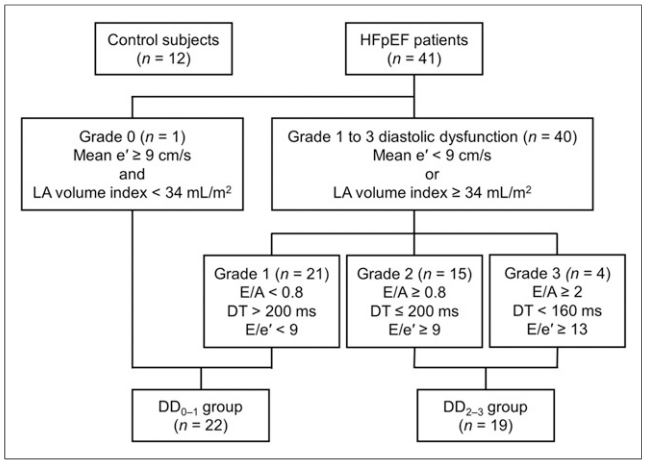

FIGURE 1. Participant flowchart and diastolic dysfunction grading of HFpEF patients. DT = deceleration time; LA = left atrial.

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 the peak atrial velocity (A) ratio (E/A), E wave deceleration time, and E to e′ ratio (E/e′) in accordance with the recommendations 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. HFpEF 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*).

^{11}C-HED PET Imaging

PET was performed using a PET/CT scanner (Biograph 64 TruePoint with TrueV; Siemens Japan). The median interval between echocardiography 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. ^{11}C-HED PET images were acquired as described previously (*18*). Briefly, after low-dose CT for attenuation and scatter correction, 185 MBq of ^{11}C-HED were intravenously administered simultaneously 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 ^{11}C-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 (*19,20*). Regional PET analyses were based on the American Heart Association 17-segment model. The

TABLE 2
Hemodynamics and Echocardiographic Findings

Parameter	Control (*n* = 12)	HFpEF		*P*
		$DD_{0–1}$ (*n* = 22)	$DD_{2–3}$ (*n* = 19)	
Systolic blood pressure (mm Hg)	121 ± 16	109 ± 22	107 ± 21	0.18
Diastolic blood pressure (mm Hg)	67 ± 10	61 ± 12	62 ± 12	0.29
Heart rate (bpm)	58 ± 7	58 ± 11	57 ± 10	0.96
LVEF (%)	67 (64–69)	51 (43–57)*	45 (42–58)*	<0.001
LV end-diastolic diameter (mm)	46 ± 4	51 ± 8	52 ± 9	0.07
LV end-systolic diameter (mm)	28 ± 2	37 ± 10†	41 ± 10*	0.002
Left atrial end-systolic diameter (mm)	37 (33–39)	42 (39–49)†	43 (34–46)	0.03
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.

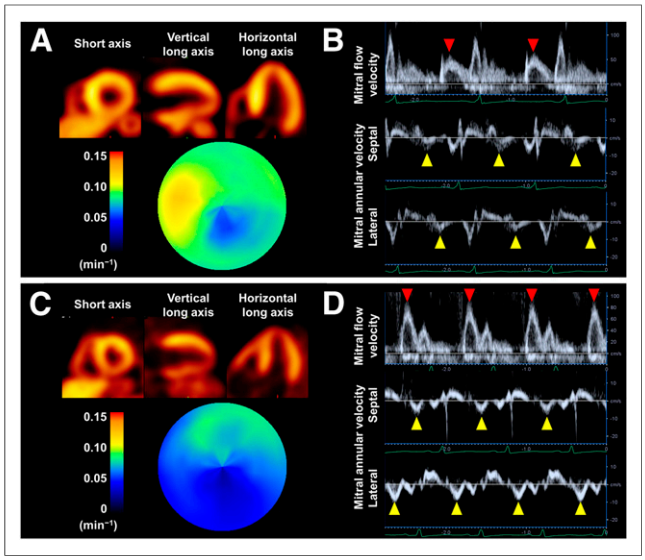

FIGURE 2. Representative images of ^{11}C-HED PET (A and C) and Doppler echocardiography (B and D) in 2 HFpEF patients (patient 1 with hypertensive heart disease and grade 1 diastolic dysfunction [A and B]). In patient 2 with cardiac amyloidosis and grade 2 diastolic dysfunction (C and D), the polar map of ^{11}C-HED RI (C) shows more extensive impairment of myocardial sympathetic innervation than that of patient 1 (A). Red arrowheads indicate E wave, and yellow arrowheads indicate e′.

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 (mL·g^{-1}·min^{-1}) using a single-tissue-compartment model (*21*) as an indicator of myocardial blood flow (*22*).

Risk Stratification and Biomarkers of HFpEF

To predict long-term survival in HFpEF 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; HFpEF 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 χ^2 test. Correlation between 2 continuous variables was evaluated by linear regression analysis. To identify clinical factors contributing to the presence of $DD_{2–3}$ in HFpEF 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 HFpEF patients, 22 (54%) were classified into the $DD_{0–1}$ group and 19 (46%) into the $DD_{2–3}$ 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 HFpEF patients (71%) were diagnosed as having nonischemic cardiomyopathy. The SHFM-based mean life expectancy and the levels of plasma B-type natriuretic peptide did not differ between the 2 HFpEF groups. The $DD_{2–3}$ group less frequently had a history of hypertension, and had higher New York Heart Association functional classes than the $DD_{0–1}$ group. The levels of troponin T in the

TABLE 3
PET Imaging Results

Parameter	Control (n = 12)	HFpEF		P
		$DD_{0–1}$ (n = 22)	$DD_{2–3}$ (n = 19)	
Global RI (min^{-1})	0.123 ± 0.028	0.092 ± 0.024*	0.075 ± 0.018*†	<0.001
Regional RI (min^{-1})				
Anterior	0.124 ± 0.028	0.097 ± 0.028‡	0.078 ± 0.019*†	<0.001
Septal	0.128 ± 0.030	0.099 ± 0.025*	0.085 ± 0.024*	<0.001
Inferior	0.119 ± 0.029	0.087 ± 0.022*	0.069 ± 0.019*†	<0.001
Lateral	0.119 ± 0.027	0.087 ± 0.027*	0.067 ± 0.016*†	<0.001
CVRI (%)	7.9 ± 1.6	14.1 ± 4.7*	18.4 ± 7.7*†	<0.001
^{11}C-hydroxyephedrine influx rate (mL·g^{-1}·min^{-1})	0.302 ± 0.053	0.231 ± 0.065*	0.189 ± 0.053*	<0.001

*P < 0.01 vs. control.
†P < 0.05 vs. $DD_{0–1}$.
‡P < 0.05 vs. control.
Data are mean ± SD.

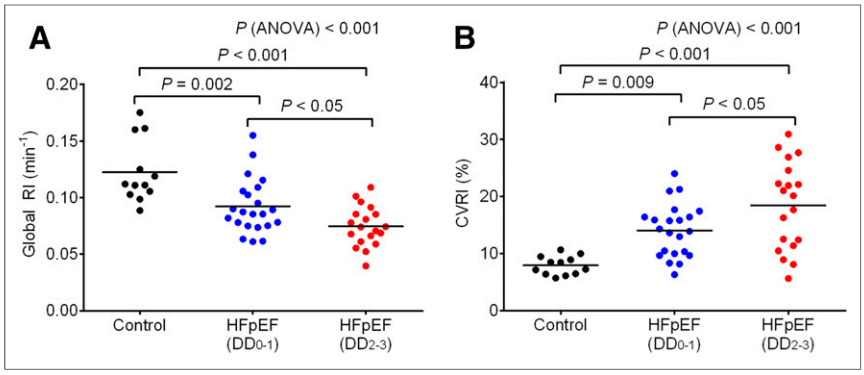

FIGURE 3. Scatterplots of global RI (A) and CVRI (B) for comparison among the 3 groups. Horizontal lines indicate mean value.

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 $DD_{2–3}$ group was significantly greater than that in the $DD_{0–1}$ 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 ^{11}C-HED influx rates and had larger CVRIs than the control group. The $DD_{2–3}$ 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 $DD_{2–3}$ 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 $DD_{0–1}$ group (Fig. 4). The more recent guidelines for diastolic function assessment reclassified 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.

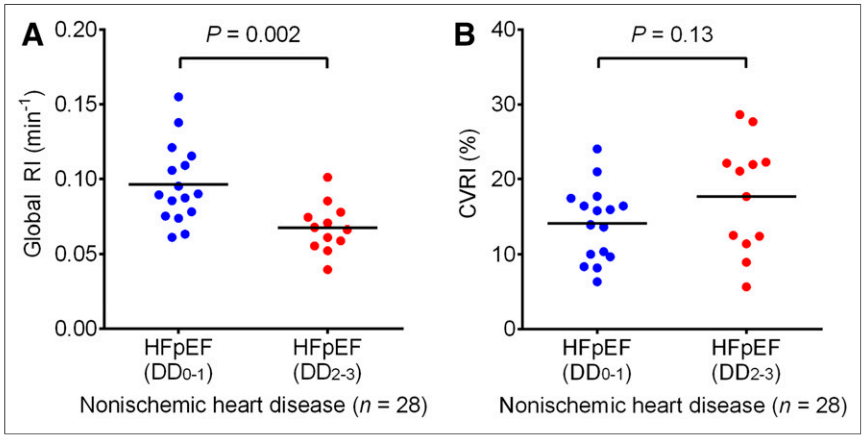

FIGURE 4. Scatterplots of global RI (A) and CVRI (B) for comparison between the 2 HFpEF groups with nonischemic heart disease (n = 28). Horizontal lines indicate mean value.

Figure 5 shows scatterplots of interplay between ^{11}C-HED PET parameters and echocardiographic variables. A simple linear regression analysis revealed a significant positive correlation between LVEF and global RI and a significant negative correlation between LV mass index and global RI. CVRI also significantly correlated with LVEF and LV mass index. HFpEF patients with an LVEF of less than 50% tended to have a lower RI (0.078 ± 0.025 min^{-1}) than those with an LVEF of 50% or greater (0.090 ± 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 ^{11}C-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 CVRI (P < 0.05 for all) (Supplemental Fig. 2).

^{11}C-HED PET as Predictors of $DD_{2–3}$

Table 4 shows the results of univariate and multivariate logistic regression analysis performed to identify clinical factors contributing to the presence of $DD_{2–3}$ 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 $DD_{2–3}$ 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 $DD_{2–3}$ 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 $DD_{2–3}$ 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 concordant with previous studies using ^{123}I-metaiodobenzylguanidine imaging (*5,7*). However, the heart-to-mediastinum ratio on early and delayed planar images and washout rate derived from ^{123}I-metaiodobenzylguanidine imaging were

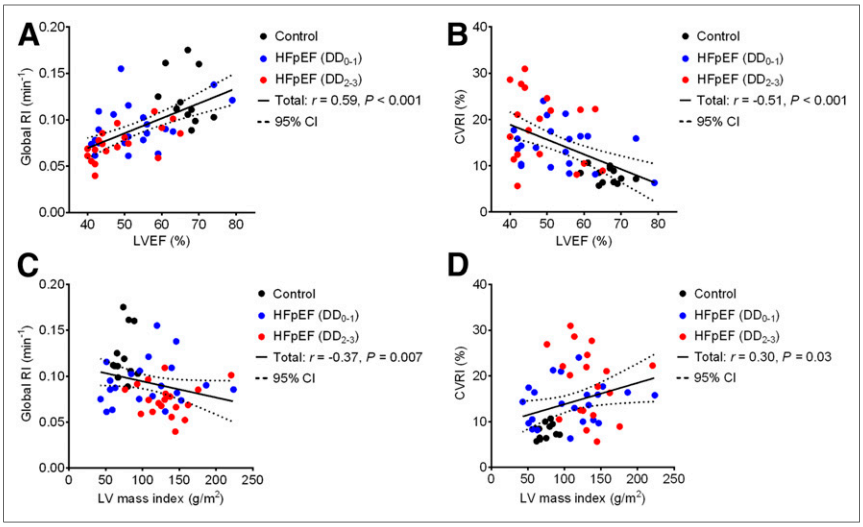

FIGURE 5. Scatterplots demonstrate association of LVEF (A and B) and LV mass index (C and D) with global RI and CVRI in study subjects. CI = confidence interval.

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 noninfarcted 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

TABLE 4
Logistic Regression Analysis to Identify Clinical Factors Contributing to Presence of DD_{2-3} in HFpEF Patients

Factor	Univariate		Multivariate model 1		Multivariate model 2	
	OR	*P*	OR	*P*	OR	*P*
Age (per 10 y)	0.92 (0.59–1.43)	0.72	–	–	–	–
Sex (male)	1.94 (0.53–7.77)	0.32	–	–	–	–
BMI (kg/m^2)	0.99 (0.86–1.13)	0.88	–	–	–	–
Hypertension	0.21 (0.05–0.79)	0.02	0.29 (0.06–1.37)	0.12	0.18 (0.03–0.98)	0.048
Diabetes	0.43 (0.11–1.56)	0.20	–	–	–	–
Coronary artery disease	1.56 (0.41–6.03)	0.51	–	–	3.41 (0.59–25.2)	0.17
Atrial fibrillation	1.02 (0.28–3.68)	0.97	–	–	–	–
B-type natriuretic peptide (per 100 pg/mL)	1.19 (0.87–1.81)	0.29	–	–	–	–
SHFM mean life expectancy (y)	0.95 (0.81–1.10)	0.49	–	–	–	–
LVEF (per 5%)	0.76 (0.51–1.08)	0.13	1.04 (0.60–1.83)	0.89	1.08 (0.60–2.05)	0.80
LV mass index (per 10 g/m^2)	1.08 (0.90–1.32)	0.39	–	–	–	–
Global RI (per 0.01 min^{-1})	0.64 (0.41–0.90)	0.008	0.66 (0.38–0.99)	0.044	0.62 (0.33–0.98)	0.042
CVRI (per 5%)	1.76 (1.06–3.20)	0.03	1.88 (1.01–3.95)	0.046	1.79 (0.94–3.88)	0.08

OR = odds ratio; model 1 = including LVEF and stepwise-selected variables; model 2 = including coronary artery disease, LVEF, and stepwise-selected variables; BMI = body mass index.
Data in parentheses are 95% confidence intervals.

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 pathophysiologic 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 ^{11}C-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.

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