ORIGINAL RESEARCH

Impairment of Coronary Flow Reserve Evaluated by Phase Contrast Cine-Magnetic Resonance Imaging in Patients With Heart Failure With Preserved Ejection Fraction

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***Background*—**Phase contrast (PC) cine-magnetic resonance imaging (MRI) of the coronary sinus allows for noninvasive evaluation of coronary flow reserve (CFR), which is an index of left ventricular microvascular function. The objective of this study was to investigate coronary flow reserve in patients with heart failure with preserved ejection fraction (HFpEF).

***Methods and Results*—**We studied 25 patients with HFpEF (mean and SD of age: 73±7 years), 13 with hypertensive left ventricular hypertrophy (LVH) (67±10 years), and 18 controls (65±15 years). Breath-hold PC cine-MRI images of the coronary sinus were obtained to assess blood flow at rest and during ATP infusion. CFR was calculated as coronary sinus blood flow during ATP infusion divided by coronary sinus blood flow at rest. Impairment of CFR was defined as CFR <2.5 according to a previous study. The majority (76%) of HFpEF patients had decreased CFR. CFR was significantly decreased in HFpEF patients in comparison to hypertensive LVH patients and control subjects (CFR: 2.21±0.55 in HFpEF vs 3.05±0.74 in hypertensive LVH, 3.83±0.73 in controls; $P<0.001$ by 1-way ANOVA). According to multivariable linear regression analysis, CFR independently and significantly correlated with serum brain natriuretic peptide level ($\beta=-68.0$; 95% CI, −116.2 to −19.7; $P=0.007$).

***Conclusions*—**CFR was significantly lower in patients with HFpEF than in hypertensive LVH patients and controls. These results indicated that impairment of CFR might be a pathophysiological factor for HFpEF and might be related to HFpEF disease severity.
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Key Words: coronary flow reserve • heart failure with preserved ejection fraction • hypertension • left ventricular hypertrophy

Approximately half of all heart failure patients have preserved ejection fraction (HFpEF).[1–3] Prevalence of HFpEF will continue to increase as life expectancies increase.[4–6] Outcomes for patients with HFpEF are poor and are similar to those of heart failure (HF) patients with reduced ejection fraction (EF).[1,4] However, an effective treatment of HFpEF has not been identified because the precise pathophysiological mechanisms of HFpEF have not been fully elucidated.[7] The pathophysiology of HFpEF is complex and multifactorial and includes diastolic dysfunction,[8] myocardial ischemia, cardiomyocyte hypertrophy, cardiac inflammation,[9] and endothelial dysfunction.[10,11]

Noncontrast phase-contrast (PC) cine-magnetic resonance imaging (MRI) of the coronary sinus has emerged as a noninvasive method to evaluate global left ventricular (LV) myocardial blood flow.[12–16] Validation studies of this imaging technique have been performed using phantom models,[17] animal experimental model using flow probes,[15] and myocardial positron emission tomography (PET).[13] Coronary flow reserve (CFR) can be calculated from coronary sinus blood flow augmentation by ATP infusion. Previous studies showed that CFR is impaired in hypertrophic cardiomyopathy,[12] HF,[18] and dilated cardiomyopathy.[16] In HFpEF patients, a subtle abnormality of resting myocardial function becomes apparent during the stress condition.[19–21] Therefore, we hypothesized that CFR might be decreased in patients with HFpEF.

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The purpose of this study was to analyze CFR using coronary sinus blood flow measurement by PC cine-MRI in HFpEF patients.

Materials and Methods

Study Subjects

We prospectively enrolled 27 patients with HFpEF, 13 with hypertensive left ventricular hypertrophy (LVH), and 18 control subjects. We applied the diagnostic criteria of the European Working Group for the diagnosis of HFpEF.[22] Briefly, we defined HFpEF as follows: patients with heart failure syndrome and (1) left ventricular ejection fraction (LVEF) >50% and (2) $E/e' \geq 15$ or $8<E/e'<15$ and brain natriuretic peptide (BNP) >200 pg/dL. LVH was defined by the linear method formula using echocardiographic data. Two patients with more than moderate valvular heart disease were excluded from analysis (Figure 1). Finally, 25 HFpEF patients were included in the analysis. Control subjects were free from any HF symptoms and had no history of any cardiovascular disease. Control subjects were referred for echocardiography and MRI for evaluation of cardiac function, and they had no cardiovascular abnormalities either on echocardiography or MRI. All study subjects underwent coronary computed tomography (CT) to exclude significant coronary artery disease (CAD). None of the study subjects had significant coronary artery stenosis on CT. This study was approved by the institutional review board of Kanagawa Cardiovascular and Respiratory Center. All patients gave written informed consent to participate in this study.

Echocardiography

Echocardiography was performed using a commercially available system equipped with a 3.3-MHz transducer (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). Conventional echocardiographic analysis, including 2-dimensional (2D), Doppler, and tissue Doppler measurements, was performed. Ventricular volumes and LVEF were calculated by the modified Simpson method using apical 4- and 2-chamber views. Early transmitral velocity (E wave) was obtained by pulse wave Doppler from the apical 4-chamber view with the sample volume positioned at the tip of the mitral leaflet. Peak LV velocity (e′) was measured from the lateral and septal mitral annulus and was averaged. The E/e′ ratio was calculated as the E wave divided by the e′ velocity. LV mass was calculated by linear method formula:

$$\text{LV mass} = 0.8 \times 1.04 \times [(\text{IVS+LVID+PWT})^3] + 0.6\text{g}$$

where IVS is the interventricular septum, LVID is the LV internal diameter, and PWT is the inferolateral wall thickness. Based on a report published by the American Society of Echocardiography and the European Association of Cardiovascular Imaging,[23] LVH was defined as LV mass >95 g/m^2 for women and >115 g/m^2 for men.

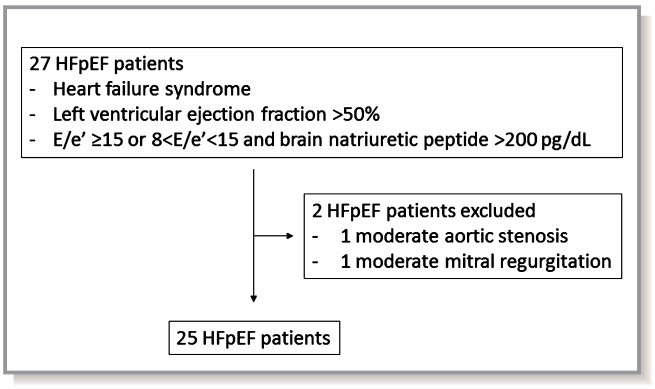

Figure 1. Flow chart of patients' enrollment. HFpEF indicates heart failure with preserved ejection fraction.

Magnetic Resonance Imaging

Acquisition of MRI was performed using a 1.5-T MRI scanner equipped with 32-channel cardiac coils (Achieva; Philips Healthcare, Best, The Netherlands). Cine-MRI images and PC cine-MRI images were acquired in all study participants. Vector-electrocardiographic (VCG) monitoring leads were positioned on patients while in the supine position. Scout images were acquired in 3 orthogonal planes for cardiac orientation. Vertical and horizontal long-axis cine-MRI images of the LV were acquired using a steady-state free precession sequence. Short-axis cine-images of the LV were acquired from the apex to the base (repetition time, 4.1 ms; echo time, 1.7 ms; flip angle, 55 degrees; field of view, 350×350 mm; acquisition matrix, 128×128; slice thickness, 10 mm; and number of phases per cardiac cycle, 20).

For acquisition of the coronary sinus, cine-MRI images in the axial plane were obtained through the atrioventricular groove to locate the coronary sinus (Figure 2). The imaging plane for blood flow measurement by PC cine-MRI images was positioned perpendicular to the coronary sinus at 2 cm from the ostium of the coronary sinus. Phase-contrast cine-MRI of the coronary sinus was acquired during suspended shallow breath-holding using a VCG-triggered gradient echo sequence (repetition time, 7.3 ms; echo time, 4.4 ms; flip angle, 10 degrees; field of view, 240×194 mm; acquisition matrix, 128×128; number of phases per cardiac cycle, 20; velocity encoding, 50 cm/s; and slice thickness, 6 mm). Pharmacological stress was achieved by injecting ATP (160 $\mu g \cdot kg^{-1} \cdot min^{-1}$) into the left antecubital vein for 4 minutes. PC cine-MRI images of the coronary sinus were acquired during ATP infusion and at rest. Duration between

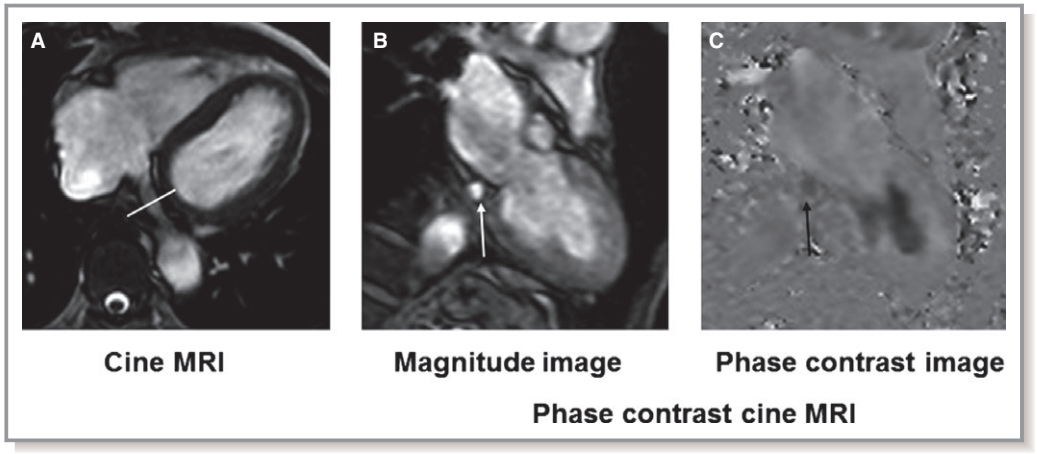

Figure 2. Phase-contrast cine-MRI images of coronary sinus. A, Axial image of the coronary sinus acquired by steady-state free precession (white solid line). B, Magnitude image of coronary sinus (white arrow). C, Phase-contrast image of coronary sinus. Blood flow in the coronary sinus appears as a low-signal-intensity area in (C), (black arrow). MRI indicates magnetic resonance imaging.

stress and resting image acquisition was at least 10 minutes. All patients were asked to refrain from caffeinated beverages for at least 24 hours before MRI scanning. In line with other studies, we corrected coronary sinus blood flow using rate pressure products (RPPs), as follows[13,16,24–28]:

$$\text{RPP (mm Hg/min)} = \text{Systolic blood pressure (mm Hg)} \times \text{Heart rate (beats/min)}$$

$$\text{Corrected coronary sinus flow (mL/min)} = \text{coronary sinus flow (mL/min)} / \text{RPP (mm Hg/min)} \times 7500$$

The Δ coronary sinus flow and CFR were calculated as:

$$\Delta\text{ Coronary sinus flow (mL/min)} = \text{Corrected coronary sinus flow during ATP infusion (mL/min)} - \text{Corrected coronary sinus flow at rest (mL/min)}$$

$$\text{CFR} = \text{Corrected coronary sinus flow during ATP infusion (mL/min)} / \text{Corrected coronary sinus flow at rest (mL/min)}$$

Statistical Analysis

Data were statistically analyzed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL) and MedCalc for Windows (version 14.8.1; MedCalc Software, Ostend, Belgium). Continuous values are presented as means±SD. Normality was determined using the Shapiro–Wilk test. Normally distributed values were compared using an unpaired *t* test, and non-normally distributed values were compared using the Mann–Whitney *U* test. The difference between the 3 groups was calculated by 1-way ANOVA with Tukey's post-hoc test. Significance of difference in categorical variables was calculated by chi-square test. Uni- and multivariable linear regression analyses were used to evaluate the relationship between CFR and echocardiographic parameters and between serum BNP level and cardiac functional parameters. Intra- and interobserver variability was assessed using intraclass correlation coefficients (ICCs). All *P* values were 2-sided, and a $P<0.05$ was considered to indicate statistical significance.

Results

Characteristics of Study Subjects

Table 1 summarizes the characteristics of the 25 patients with HFpEF. Average age was 73±7 years, and 17 of 25 (44%) patients were female. Prevalence of hypertension, dyslipidemia, diabetes mellitus, and current smoker were 44%, 32%, 32%, and 8%, respectively. Prescription rate of calcium-channel blocker (CCB), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE/ARB), beta-blockers, diuretics, and statins were 28%, 40%, 24%, 16%, and 28%, respectively. Serum BNP concentration was 251±180 pg/dL. In hypertensive LVH subjects (n=13), mean age was 67±10 years, and 3 of 13 (23%) patients were female. A significant difference was found between the HFpEF and LVH groups with regard to sex ($P=0.009$), prevalence of hypertension ($P=0.006$), prescription rate of CCB ($P<0.001$) and ACE/ARB ($P=0.031$), and serum BNP concentration ($P=0.007$). In control subjects (n=18), mean age was 65±15 years. Five of eighteen (28%) subjects were female. The proportion of females, prevalence of hypertension, prescription rate of CCB,

Table 1. Characteristics of Study Subjects

	HFpEF, N=25	LVH, N=13	Controls, N=18	*P* Value HFpEF vs Control	*P* Value LVH vs Control	*P* Value HFpEF vs LVH
Female (%)	17 (68)	3 (23)	5 (28)	0.009	0.77	0.009
Age, y	73±7	67±10	65±15	0.21	0.99	0.33
SBP, mm Hg	131±22	142±14	131±11	0.99	0.16	0.17
DBP, mm Hg	73±15	74±9	75±7	0.92	0.95	1.00
CAD risk factors (%)						
Hypertension	11 (44)	13 (100)	1 (6)	<0.001	<0.001	0.006
Dyslipidemia	8 (32)	4 (31)	2 (11)	0.11	0.17	0.94
Diabetes mellitus	8 (32)	4 (31)	3 (17)	0.26	0.35	0.94
Current smoker	2 (8)	1 (8)	0 (0)	0.92	0.23	0.97
Medication (%)						
Calcium-channel blocker	7 (28)	12 (93)	0 (0)	0.014	<0.001	<0.001
ACE/ARB	10 (40)	10 (77)	1 (6)	0.011	<0.001	0.031
Beta-blocker	6 (24)	7 (54)	0 (0)	0.025	<0.001	0.065
Diuretics	4 (16)	4 (31)	0 (0)	0.075	0.012	0.29
Statin	7 (28)	4 (31)	1 (6)	0.062	0.059	0.86
Blood test result						
BNP, pg/dL	251±180	51±42	52±70	<0.001	0.99	0.007

The difference between the 3 groups was calculated by 1-way ANOVA with Tukey's post-hoc test. Significance of difference in categorical variables was calculated by chi-square test. ACE indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

ACEI/ARB, beta-blockers, and serum BNP concentration were significantly higher in the HFpEF group than in the control group (all $P<0.05$).

Standard echocardiographic data obtained from 2D, Doppler, and tissue Doppler measurements are shown in Table 2. Mean LVEF was 69±7% in HFpEF patients, 63±6% in hypertensive LVH patients, and 67±8% in control subjects. No significant difference was found in LVEF between the 3 groups (all $P\geq0.05$). LV mass (LVM) index was 111±36 g/m^2 in HFpEF patients, 132±21 g/m^2 in hypertensive LVH patients, and 60±26 g/m^2 in control subjects. Left atrial (LA) dimension was largest in hypertensive LVH patients, and

Table 2. Echocardiographic Parameters

	HFpEF, N=25	LVH, N=13	Controls, N=18	*P* Value HFpEF vs Control	*P* Value LVH vs Control	*P* Value HFpEF vs LVH
LV EDVI, mL/m^2	77±26	86±9	67±17	0.38	0.020	0.19
LV ESVI, mL/m^2	25±15	33±8	23±11	0.86	0.10	0.20
LV SVI, mL/m^2	52±12	53±5	44±7	0.12	0.012	0.88
LVEF, %	69±7	63±6	67±8	0.93	0.40	0.24
LVM index, g/m^2	111±36	132±21	60±26	<0.001	<0.001	0.051
LAD, mm	40±7	44±4	35±8	0.023	0.001	0.31
HR, bpm	61±12	64±9	65±13	0.90	0.99	0.96
E wave, ms	82±30	82±42	62±14	0.030	0.15	0.94
e′	5.9±2.1	7.5±2.3	8.3±2.5	0.082	0.62	0.59
E/e′	15.3±7.6	10.6±3.5	8.1±2.9	0.001	0.40	0.11

The difference between the 3 groups was calculated by 1-way ANOVA with Tukey's post-hoc test. bpm indicates beats per minute; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HFPEF, heart failure preserved ejection fraction; HR, heart rate; LAD, left atrial dimension; LV, left ventricle; LVH, left ventricular hypertrophy; LVM, left ventricular mass.

Table 3. Magnetic Resonance Imaging Cardiac Parameters

	HFpEF, N=25	LVH, N=13	Controls, N=18	*P* Value HFpEF vs Control	*P* Value LVH vs Control	*P* Value HFpEF vs LVH
LV EDVI, mL/m^2	75±23	87±10	67±17	0.37	0.015	0.16
LV ESVI, mL/m^2	26±14	32±8	23±11	0.84	0.096	0.19
LV SVI, mL/m^2	49±12	54±5	43±7	0.11	0.007	0.29
LVEF, %	67±9	63±6	66±8	0.97	0.39	0.25
LVM index, g/m^2	109±32	132±20	60±25	<0.001	<0.001	0.082
HR, bpm	63±12	64±8	65±12	0.91	0.99	0.95
RV EDVI, mL/m^2	75±18	79±7	68±8	0.24	0.058	0.56
RV ESVI, mL/m^2	25±6	27±3	23±3	0.35	0.075	0.50
RV SVI, mL/m^2	49±11	52±4	45±5	0.20	0.056	0.60
RVEF, %	66±2	65±2	66±2	0.76	0.98	0.88

The difference between the 3 groups was calculated by 1-way ANOVA with Tukey's post-hoc test. bpm inidcates beats per minute; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HFPEF, heart failure preserved ejection fraction; HR, heart rate; LV, left ventricle; LVH, left ventricular hypertrophy; LVM, left ventricular mass; RV, right ventricle.

E/e′ was highest in HFpEF patients. Table 3 summarizes the results of MRI parameters. No significant difference was found in right ventricular (RV) end-diastolic volume, RV end-systolic volume, RV stroke volume index, and RV ejection fraction (RVEF). Similar to the result of echocardiography, LVEF was similar between the 3 groups, and LVM index was highest in LVH patients.

Comparison of Coronary Flow Reserve

Figure 3 shows the comparison of CFR between the 3 groups. Mean CFR was significantly lower in the HFpEF group than in the control group (CFR: 2.21±0.55 vs 3.83±0.73; *P*<0.001).

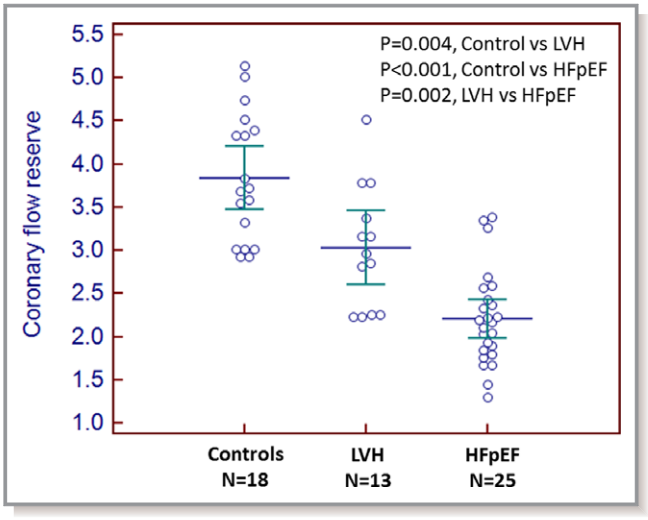

Figure 3. Comparison of coronary flow reserve between HFpEF, LVH, and controls. HFpEF indicates heart failure with preserved ejection fraction; LVH, left ventricular hypertrophy.

In addition, CFR was significantly lower in the HFpEF group than in the hypertensive LVH group (CFR: 2.21±0.55 v 3.05±0.74; *P*=0.002). The reproducibility of coronary sinus blood flow measurements was sufficient in terms of intraobserver reproducibility analysis (ICC: 0.87 for coronary sinus flow at rest) and interobserver reproducibility analysis (ICC: 0.86 for coronary sinus flow at rest).

Figure 4 shows an example of the blood flow pattern of the coronary sinus in an HFpEF patient. Coronary sinus blood flow was 108 mL/min and increased to 180 mL/min in response to ATP infusion, resulting in CFR of 1.67. In this HFpEF patient, CFR was substantially lower than that in healthy subjects (the lower limit normal healthy CFR is 2.5, as previously reported[29]).

Table 4 summarizes the results of coronary sinus blood flow and CFR. Corrected coronary sinus blood flow at rest was substantially higher in both HFpEF and hypertensive LVH than in control subjects. During ATP infusion, a significant increase in coronary sinus blood flow was observed in all 3 groups. However, the Δ corrected sinus blood flow and CFR were lower in HFpEF patients than in hypertensive LVH patients or in controls. A significant difference was found in CFR between the 3 groups (2.21±0.55 in HFpEF; 3.03±0.71 in hypertensive LVH; 3.83±0.73 in control subjects; all *P*<0.05). Prevalence of CFR impairment (CFR <2.5) was significantly higher in HFpEF patients than in the other groups (19 of 25 [76%] in HFpEF; 4 of 13 [31%] in hypertensive LVH; and 0 of 18 [0%] in normal subjects; *P*<0.001 in HFpEF vs hypertensive LVH; *P*=0.012 in hypertensive LVH and controls).

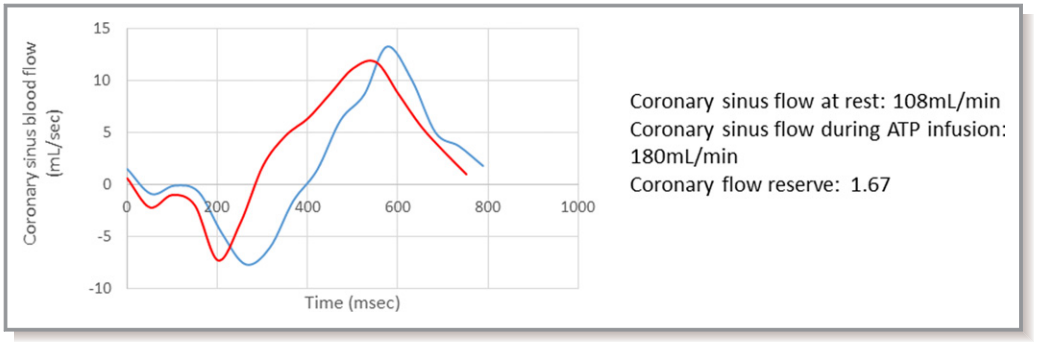

Figure 4. Representative pattern of coronary sinus blood flow curve in an HFpEF patient. Blue line indicates the curve of coronary sinus blood flow at rest, whereas the red line indicates the curve of coronary sinus blood flow during pharmacological stress by ATP infusion. Coronary sinus flow is 108 mL/min at rest and increased to 180 mL/min during ATP infusion, resulting in coronary flow reserve of 1.67. HFpEF indicates heart failure with preserved ejection fraction.

Relationship Between Serum BNP Level and Cardiac Functional Parameters

Figure 5 shows the results of univariable linear regression analysis between serum BNP and cardiac functional parameters. A significant negative correlation was found between serum BNP and coronary flow reserve ($y=-74.3x\pm362.5$; $P<0.001$). No significant relationship was found between serum BNP and EF, BNP and E/e′, or BNP and LA dimension. Table 5 shows the results of multivariable linear regression analysis between serum BNP and cardiac functional and structural parameters by MRI and echocardiography. Multiple regression analysis showed that only CFR was significantly and independently related to BNP level. However, LVEF, E/e′, and LA dimension were not independently related to BNP level.

Discussion

This is the first study showing decreased CFR in HFpEF patients. The major findings are as follows: (1) CFR was significantly lower in HFpEF patients than in LVH patients or control subjects; (2) the majority (76%) of HFpEF patients had impairment of CFR; and (3) decreased CFR was significantly associated with elevated serum BNP concentration. These results indicate that decreased CFR might play an important role in the pathophysiology of HFpEF and might reflect disease severity.

Utility of Phase-Contrast Cine-MRI to Evaluate CFR in HFpEF Patients

In the current study, we used PC cine-MRI of the coronary sinus both at rest and during ATP infusion for evaluation of CFR. The coronary sinus drains ≈96% of total LV myocardial blood flow,[30] and we can estimate global LV blood flow by measuring blood flow in the coronary sinus. A previous study showed that PC cine-MRI–derived myocardial blood flow was well correlated with LV myocardial blood flow measured by PET.[13] Therefore, PC cine-MRI derived CFR is considered as a noninvasive, reliable measure of LV myocardial blood flow. In addition, an important advantage

Table 4. Coronary Sinus Blood Flow and Coronary Flow Reserve

	HFpEF, N=25	LVH, N=13	Controls, N=18	*P* Value HFpEF vs Control	*P* Value LVH vs Control	*P* Value HFpEF vs LVH
Corrected coronary sinus flow at rest, mL/min	80.9±31.1	84.8±15.3	59.8±18.8	0.020	0.019	0.89
Corrected coronary sinus flow during ATP infusion, mL/min	183.7±95.0*	253.5±62.7*	225.3±71.0*	0.23	0.61	0.039
Δ Corrected coronary sinus flow, mL/min	102.8±70.9	168.7±55.4	165.4±57.4	0.007	0.99	0.10
Coronary flow reserve	2.21±0.55	3.03±0.71	3.83±0.73	<0.001	0.004	0.002

Data are expressed as mean±SD. Δ Corrected coronary sinus flow=Corrected coronary sinus flow during ATP infusion−Corrected coronary sinus flow at rest. Coronary flow reserve=Corrected coronary sinus flow during ATP infusion/Corrected coronary sinus flow at rest×100. The difference between the 3 groups was calculated by 1-way ANOVA with Tukey's post-hoc test. HFPEF indicates heart failure with preserved ejection fraction.
*$P<0.05$ vs corrected coronary sinus flow at rest.

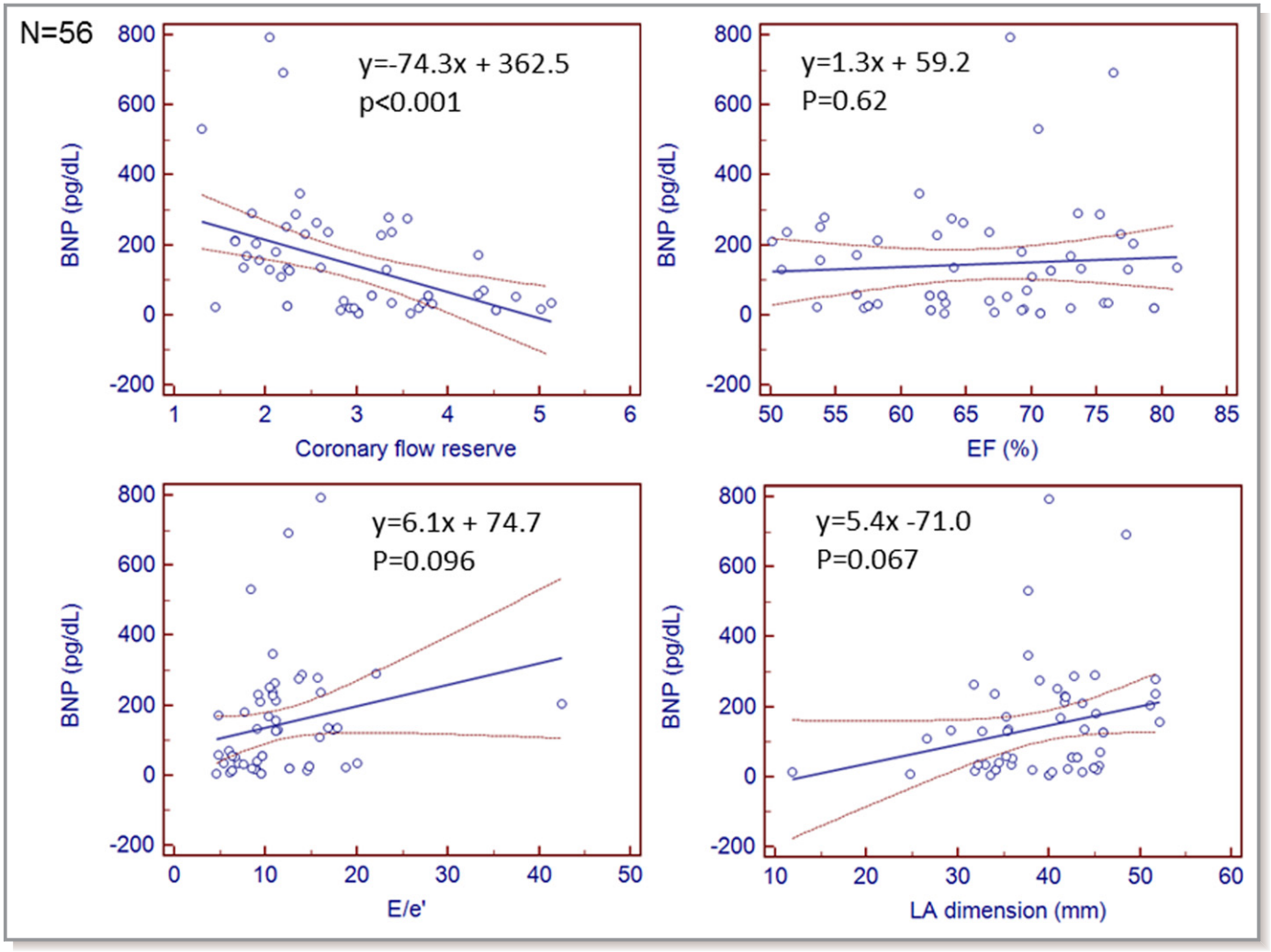

Figure 5. Relationship between serum BNP and cardiac functional parameters. Significant negative correlation is noted between serum BNP and coronary flow reserve. No significant relationship is noted between BNP and EF, BNP and E/e′, BNP, and LA dimension. BNP indicates brain natriuretic peptide; EF, ejection fraction; LA, left atrium.

of PC cine-MRI flow measurement is that it does not necessitate any gadolinium contrast injection and does not expose patients to radiation.

Table 5. Multivariable Linear Regression Analysis of the Relationship Between Serum Brain Natriuretic Peptide Level and Cardiac Functional Parameters

	β	SE	95% CI for β	*P* Value
Coronary flow reserve	−68.0	24.0	−116.2 to −19.7	0.007
LVEF	0.98	2.61	−2.9 to 9.4	0.30
E/e′	−0.59	4.08	−8.7 to 7.5	0.88
LA dimension	3.22	3.09	−4.2 to 6.2	0.70

Other variables included in multiple regression analysis are as follows: age; systolic and diastolic blood pressure; and body mass index. LA indicates left atrium; LVEF, left ventricular ejection fraction.

Basically, CFR is considered as an integrated functional measure of epicardial coronary artery and intramyocardial microvessels. Therefore, in the absence of obstructive coronary artery stenosis in the epicardial coronary artery, decreased CFR could be a measure of coronary microvascular dysfunction.[31] In this study, all study participants underwent coronary CT and no significant coronary artery stenosis was detected in any subject. Because the negative predictive value of coronary CT is high, impairment of CFR in LVH and HFpEF patients could be explained by decreased microvascular function. In previous reports, HFpEF patients were predominantly female. Our result is in line with previous studies. However, in the LVH and control groups, sex was predominantly male. Sex difference between HFpEF and the other 2 groups may bias the results of this study.

Apparently, HFpEF is not simply caused by one pathophysiological factor, but complex and multifactorial abnor-

malities of cardiac and vascular system capacity. In addition, previous studies showed that diastolic dysfunction is not common at resting status, but becomes apparent during exercise stress.[32,33] In this study, coronary sinus blood flow is higher, both in HFpEF patients and hypertensive LVH patients, than that of control subjects at rest, but CFR is significantly lower in HFpEF patients in comparison to hypertensive LVH and control subjects. One possible explanation for this phenomenon is that coronary sinus blood flow is already elevated at rest to account for microvascular dysfunction in HFpEF patients, whereas their reserve myocardial capacity for pharmacological stress is decreased in comparison to healthy subjects. In addition, CFR was significantly lower in HFpEF patients than in LVH patients, suggesting that the reduction of CFR in HFpEF patients is not simply induced by LVH, but also by other unknown pathophysiological factors. In addition, we found that prevalence of coronary microvascular dysfunction was significantly higher in HFpEF patients than in hypertensive LVH patients or control subjects (76% vs 31% vs 8%; $P<0.05$). This finding suggests that CFR might play a key role in pathophysiology of HFpEF patients. Furthermore, a significant correlation between serum BNP level and CFR was also observed in this study. A previous study showed that BNP level is a prognostic marker for HFpEF.[7] Our finding suggests that impairment of CFR might predict future cardiovascular events in HFpEF patients.

Clinical Implication

The pathophysiology of HFpEF has been postulated to involve myocardial fibrosis and myocyte hypertrophy, leading to impaired LV filling and decreased diastolic distensibility and stiffness.[34–36] The present study utilized a noninvasive diagnostic tool to evaluate coronary flow reserve (phase-contract cine-MRI of the coronary sinus), and this modality might allow more-accurate diagnosis of HFpEF. Distinguishing HFpEF from other etiologies of exertional shortness of breath, such as chronic pulmonary disorders, is of clinical interest. It remains to be shown whether coronary flow reserve differs between HFpEF patients and those with normal EF and nonmyocardial causes of dyspnea. In addition, no data are available as to whether CFR can predict outcomes in HFpEF patients. Furthermore, large-scale follow-up study is necessary to elucidate the clinical utility of CFR measurement to predict outcomes in HFpEF patients.

Study Limitations

First, this study was a small, single-center, cross-sectional study. Therefore, a large-scale, multicenter study is warranted to validate the results of our study. Second, MRI is contraindicated for patients with mechanical devices (eg, pacemaker implantation and implantable cardioverter defibrillator implantation) and claustrophobia, and these patients were excluded from this study. Third, the LVH group and controls had comorbidities (eg, hypertension, dyslipidemia, diabetes mellitus, and smoking) that may impair coronary flow reserve. Fourth, CAD was only assessed by coronary CT and not by conventional coronary angiography. Therefore, we cannot completely exclude the presence of coronary artery stenoses and their impact on coronary flow reserve in the study population. Fifth, in previous reports, HFpEF patients were predominantly female, which was also true in the present study. However, in the LVH and control groups, sex was predominantly male, and sex differences between the study groups may bias the results of this study. Sixth, there were many statistical tests and lots of *P* values were reported. However, we did not perform any adjustment for multiple hypotheses testing.

Conclusion

CFR were significantly lower in HFpEF patients than in control subjects. CFR was independently correlated with serum BNP level. These results indicated that microvascular dysfunction might play an important role in the pathophysiology of HFpEF.

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Disclosures

None.

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