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ORIGINAL ARTICLE
Vascular and cardiac imaging

The potential of dynamic ^{99m}Tc-sestamibi cadmium zinc telluride-single-photon emission computed tomography camera assessing myocardial flow reserve in patients with heart failure with preserved ejection fraction

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Aims

Coronary microvascular dysfunction (CMD) is related to the pathophysiology, mortality, and morbidity of heart failure with preserved ejection fraction (HFpEF). A novel single-photon emission computed tomography (SPECT) camera with cadmium zinc telluride (CZT) detectors allows for the quantification of absolute myocardial blood flow and myocardial flow reserve (MFR) in patients with coronary artery disease. However, the potential of CZT-SPECT assessing for CMD has never been evaluated in patients with HFpEF.

Methods and results

The clinical records of 127 consecutive patients who underwent dynamic CZT-SPECT were retrospectively reviewed. Rest and stress scanning were started simultaneously with 3 and 9 MBq/kg of ^{99}mTc-sestamibi administration, respectively. Dynamic CZT-SPECT imaging data were analysed using a net-retention model with commercially available software. Transthoracic echocardiography was performed in all patients. The MFR value was significantly lower in the HFpEF group (mean ± SEM = 2.00 ± 0.097) than that in the non-HFpEF group (mean ± SEM = 2.74 ± 0.14, $P = 0.0004$). A receiver operating characteristic analysis indicated that if a cut-off value of 2.525 was applied, MFR could efficiently distinguish HFpEF from non-HFpEF. Heart failure with preserved ejection fraction had a consistently low MFR, regardless of the diastolic dysfunction

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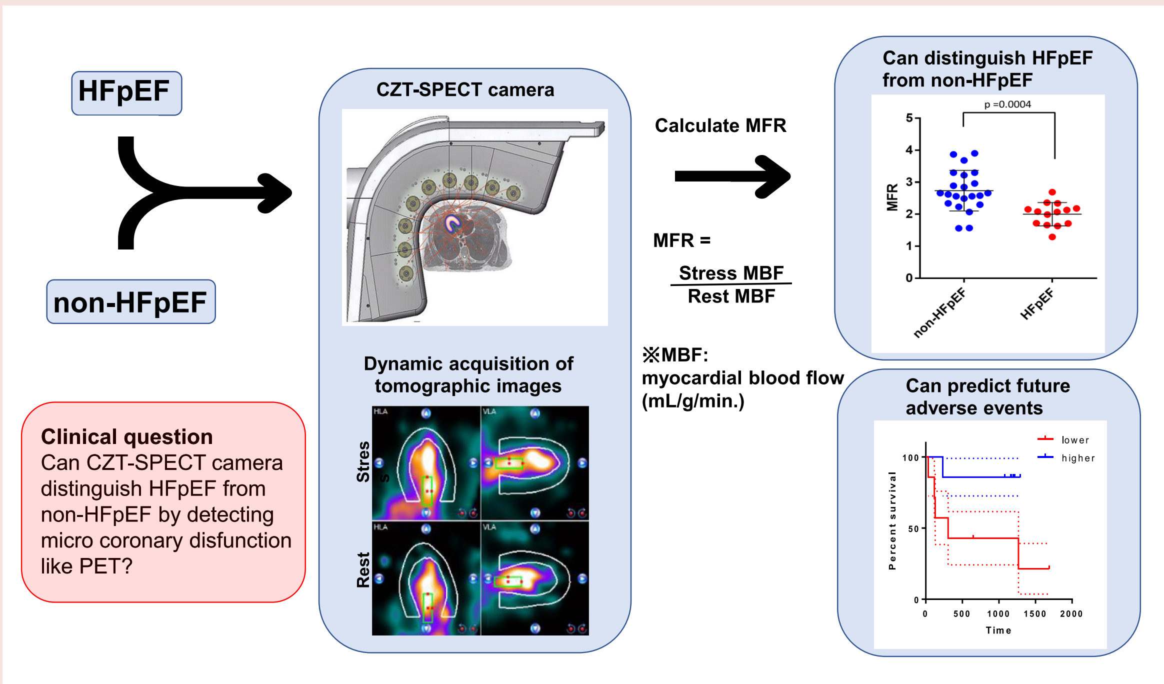
score. Heart failure with preserved ejection fraction patients with MFR values lower than 2.075 had a significantly higher incidence of heart failure exacerbation.

Conclusion Myocardial flow reserve assessed by CZT-SPECT was significantly reduced in patients with HFpEF. A lower MFR was associated with a higher hospitalization rate in these patients. Myocardial flow reserve assessed by CZT-SPECT has the potential to predict future adverse events and stratify the severity of disease in patients with HFpEF.

Graphical Abstract



Keywords Myocardial blood flow • Myocardial flow reserve • Cadmium zinc telluride equipped single-photon emission computed tomography camera • Dynamic scanning • Heart failure with preserved ejection fraction • Coronary microvascular dysfunction

Introduction

Heart failure (HF) is a leading cause of mortality and morbidity worldwide.[1] Approximately half the patients with HF symptoms do not have a marked reduction in left ventricular ejection fraction (LVEF).[2] For a lengthy period, it remained uncovered; however, a new paradigm into the pathophysiology of HF with preserved ejection fraction (HFpEF) has been proposed over the last decade.[3] The key component of this paradigm is that inflammation of the endothelium in the coronary micro-artery, which is compromised by comorbidities including obesity, hypertension, chronic obstructive lung disease, and diabetes, initiates a derangement of the NO-cGMP-PKG pathway, which induces cardiomyocyte hypertrophy or interstitial fibrosis, resulting in diastolic dysfunction.[4–6] Increasing evidence also suggests that the presence of coronary microvascular dysfunction (CMD) is associated with the severity of symptoms[7] or prognosis of patients with HFpEF.[8,9] Therefore, alterations of MFR are associated with CMD in patients with HFpEF, which provides a potential physiologic marker of clinical risk and therapeutic efficacy.

Recently, several reports have shown that myocardial flow reserve (MFR) can be evaluated quantitatively using positron emission tomography (PET)[10,11] and is impaired in patients with HFpEF.[12,13] PET using oxygen-15-labelled water is widely accepted as the gold standard for evaluating myocardial perfusion. However, the use of this apparatus is largely limited to major academic centres or research laboratories.

Single-photon emission computed tomography (SPECT) cameras with cadmium zinc telluride (CZT) detectors (D-SPECT®), which are equipped with a high-speed and high-sensitivity CZT semiconductor camera, enable a dynamic acquisition of tomographic images suitable for the evaluation of absolute myocardial blood flow (MBF).[14] It has also been reported that MFR assessed by a protocol using a ^{99m}Tc-labelled perfusion tracer and CZT-SPECT provided similar results compared with those with ^{15}O-water PET and a high diagnostic value for detecting stable coronary artery disease (CAD).[15,16]

Here, we retrospectively evaluated the potential of CZT-SPECT with a ^{99m}Tc-labelled perfusion tracer to determine whether it can sensitively detect reduced MFR in patients with HFpEF, as previously reported with PET.

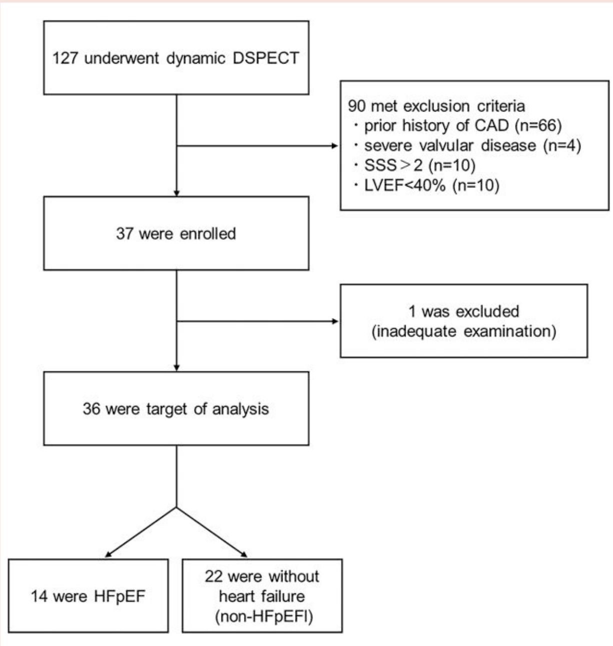


Figure 1 Patient flow diagram. The medical records of 127 patients who underwent dynamic ^{99m}Tc-MIBI perfusion single-photon emission computed tomography using a D-single-photon emission computed tomography camera were retrospectively reviewed. Of these, 90 patients met the exclusion criteria and 1 was excluded because of inadequate examination. The resultant 36 patients were included in the current analysis.

Methods

Study design and patients

We retrospectively reviewed the clinical records of patients who underwent dynamic ^{99m}Tc-sestamibi perfusion SPECT with a D-SPECT camera for evaluation of CAD between October 2017 and October 2020 at the Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Japan. Of the 127 cases reviewed, 90 patients were excluded from the current study due to prior CAD episodes ($n = 66$), severe valvular disease ($n = 4$), LVEF < 40% ($n = 10$), or a summed stress score (SSS) > 2 ($n = 10$) (*Figure 1*). One patient was excluded because of an inadequate examination. The remaining 36 cases were included in this study and divided into 2 groups. Fourteen patients assigned to the HFpEF group had a history of hospitalization due to HF ($n = 11$) or evidence of lung congestion diagnosed by chest radiography and CT in the outpatient clinic ($n = 3$). All 14 patients met the diagnostic criteria recently shown in the guidelines for treating HF patients.[17] The remaining 22 patients, without signs or evidence of HF, were assigned to the non-HFpEF group. Nine patients among non-HFpEF group had chest pain but had no evidence of cardiac origin.

Dynamic ^{99m}Tc-sestamibi cadmium zinc telluride-single-photon emission computed tomography acquisition

All patients were instructed to abstain from caffeine and methylxanthine-containing substrates and medications for at least 24 h before the scan. Rest and stress dynamic images were acquired in the list mode of D-SPECT® (Spectrum Dynamics Medical, Cesare, Israel). All imaging procedures were performed in the supine position. To identify the position of the heart in the scanner's field of view, ∼37 MBq of ^{99m}Tc-sestamibi was administered pre-scanning. Rest scanning was started simultaneously with 3 MBq/kg ^{99m}Tc-sestamibi administration at a rate of 1 mL/s using an automatic injector (Nemoto, Tokyo, Japan) followed by a bolus injection of 30 mL saline and continued for 6 min. The gated perfusion images were acquired for 9 min. Maximum hyperaemia was induced by a continuous intravenous infusion of adenosine (PDRadiopharma Inc., Tokyo, Japan) at a rate of 120 μL/kg/min. Three minutes after the initiation of adenosine administration, a 9 MBq/kg dose of ^{99m}Tc-sestamibi was injected. The injection speed of the radioisotope and the scanning protocol were the same as those in the rest of the scan. Stress-gated perfusion images were also acquired following a stress dynamic scan (see Supplementary material online, *Supplement S1*). Data were parcellated into 32 frames (21×3, 1×9, 1×15, 1×21, 1×27, and 7×30 s frames). Images were reconstructed using an ordered subset expectation maximization algorithm with 4 iterations and 32 subsets.

Dynamic single-photon emission computed tomography image analysis

Details concerning the dynamic SPECT image analysis were previously described by Agostini *et al.*[15] and are described only briefly here. The dynamic CZT-SPECT imaging data were analysed using a net-retention kinetic model[18,19] using commercially available software (Corridor 4DM; Invia, Ann Arbor, MI, USA). A 2 pixel-wide × 6 pixel-long ROI was positioned at the basal valve plane (within the LV and LA) for blood pool sampling (see Supplementary material online, *Supplement S2*). The endocardial and epicardial borders of the LV wall were defined algorithmically using integrated images acquired during heart positioning. The mid-wall between the endocardial and epicardial borders was defined, and its surface was divided into 460 polar sectors. Time activity curves (TACs) were drawn according to the nearest point of each sector across all time frames. TACs globally and in each vessel region (left anterior descending artery, left circumflex artery and right coronary artery) were averaged from the polar map sectors.

Rest echocardiography

Transthoracic rest echo cardiography (EPIQ7; Philips, The Netherlands) was performed for all subjects within 1 month before or after SPECT scanning. The following standard parameters of cardiac function were recorded: septal wall thickness, LV posterior wall thickness, LV mass index, LV ejection fraction by the Simpson method, LA volume index, mitral inflow peak E- and A-wave velocities by pulse wave Doppler (E/A ratio), and tricuspid regurgitation (TR) systolic jet velocity. LV septal e' velocity was measured using the tissue Doppler mode, and LV filling pressure (E/e') was estimated. LV diastolic dysfunction was assessed using the following parameters recommended by the American Society of Echocardiography:[20] average $E/e' > 14$, septal e' velocity <7 cm/s, TR systolic jet velocity >2.8 m/s, and left atrial volume index >34 mL/m^2. Based on these parameters of LV diastolic dysfunction, each subject was classified into one of the following five grades: 0–4.

Statistical analysis

Continuous variables are expressed as mean ± SEM and were analysed by Student's t-test or one-way analysis of variance (ANOVA) if they were compared between two groups or among three or more groups, respectively. When the P-value for ANOVA was statistically significant, Tukey's test was conducted for post-hoc analysis. Fisher's exact test was used to analyse categorical variables between the two groups. The accuracy of MFR in distinguishing HFpEF from non-HFpEF was evaluated using receiver operating characteristic (ROC) curve analysis. A single regression analysis was performed to evaluate the relationship between MFR and clinical variables. If the relationships were statistically significant, they were further evaluated by multiple regression analysis. The log-rank (Mantel–Cox) test was used to compare survival curves. All tests were two-tailed, and P-values ≤0.05 were considered statistically significant. Statistical analyses were performed using the Prism software (GraphPad Software, San Diego, CA, USA).

Table 1 Baseline patient characteristics

Characteristics	Overall (*n* = 36)	Non-HF control (*n* = 22)	HFpEF (*n* = 14)	*P*-value
Demographic characteristics				
Age (years)	71.2 ± 10.3	69.6 ± 9.6	73.7 ± 10.8	0.254
Female, *n* (%)	23 (64)	14 (64)	9 (64)	0.626
Body mass index (kg/m^2)	28.0 ± 32.5	24.1 ± 2.7	33.5 ± 51.3	0.378
Comobidities, *n* (%)				
Hypertension	29 (81)	18 (82)	11 (79)	0.81
Atrial fibrillation	8 (22)	2 (9)	6 (43)	0.018*
Diabetes	9 (25)	9 (41)	0 (0)	0.004*
Dyslipidaemia	19 (53)	13 (59)	6 (43)	0.342
Chronic kidney disease	23 (64)	13 (59)	10 (71)	0.452
Medications, *n* (%)				
Aspirin	11 (31)	10 (45)	1 (7)	0.015*
Statin	16 (44)	12 (55)	4 (29)	0.126
Beta-blocker	12 (33)	3 (14)	9 (64)	0.002*
ACE inhibitor or ARB	20 (56)	12 (55)	8 (57)	0.878
MRA	7 (19)	0 (0)	7 (50)	<0.001*
Ca channel blocker	13 (36)	12 (55)	1 (7)	0.004*
Loop diuretic	13 (36)	2 (9)	11 (79)	<0.001*
Torvaptan	5 (14)	1 (5)	4 (29)	0.042*
Vital signs and laboratory data				
Systolic blood pressure (mmHg)	156.9 ± 22.9	160.5 ± 22.7	151.7 ± 22.2	0.277
Diastolic blood pressure (mmHg)	91.3 ± 15.5	94.1 ± 14.4	87.1 ± 16.2	0.198
Heart rate (b.p.m.)	72.1 ± 13.1	69.2 ± 13.3	76.7 ± 11.9	0.105
Rest rate pressure product	11 319.5 ± 2775.7	11 055.3 ± 2800.5	11 734.7 ± 2684.3	0.488
Haemoglobin (g/dL)	13.5 ± 3.9	13.3 ± 1.7	13.8 ± 5.7	0.687
eGFR (mL/min/1.73 m^2)	52.4 ± 19.5	56.2 ± 21.2	46.7 ± 14.9	0.168
Haemoglobin A1c (%)	6.05 ± 0.82	6.35 ± 0.88	5.66 ± 0.53	0.022*
BNP (pg/mL)	137.1 ± 204.9	76.9 ± 97.2	184.5 ± 249.9	0.208

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; MRA, mineral corticoid receptor antagonist .
*$P < 0.05$.

Table 2 Echocardiographic parameters

Echocardiographic parameters	Overall (*n* = 36)	Non-HF control (*n* = 22)	HFpEF (*n* = 14)	*P*-value
Left heart structure/function				
Septal wall thickness (cm)	9.7 ± 1.9	9.8 ± 1.8	9.3 ± 1.8	0.44
Posterior wall thickness (cm)	9.7 ± 1.6	9.7 ± 1.4	9.8 ± 1.8	0.858
LV mass index	100.4 ± 26.5	92.7 ± 22.6	113.0 ± 27.5	0.031*
LV ejection fraction (%)	61.2 ± 9.4	63.7 ± 7.5	57.5 ± 11.6	0.197
LA volume index (mL/m^2)	40.4 ± 19.0	34.2 ± 12.4	49.8 ± 23.1	0.02*
E velocity (cm/s)	77.8 ± 29.0	76.3 ± 22.9	80.2 ± 36.6	0.713
E/A ratio	0.95 ± 0.42	0.88 ± 0.32	1.10 ± 0.55	0.23
TR systolic jet velocity	2.29 ± 0.47	2.14 ± 0.44	2.51 ± 0.42	0.064
Tissue Doppler indices				
LV septal *e′* velocity (cm/s)	6.3 ± 1.9	6.6 ± 1.8	5.6 ± 1.8	0.127
LV *E/e′* ratio	12.6 ± 3.9	12.0 ± 3.9	13.7 ± 3.9	0.253
Diastolic dysfunction score	1.72 ± 1.28	1.18 ± 0.89	2.57 ± 1.29	0.00073*

For the scoring of diastolic dysfunction, each case was classified into five grades: 0–4. The parameters used for scoring are average $E/e' > 14$, septal e' velocity <7 cm/s, tricuspid regurgitation systolic jet velocity >2.8 m/s and left atrial volume index >34 mL/m^2.
LA, left atrium; LV, left ventricle; TR, tricuspid regurgitation.
*$P < 0.05$.

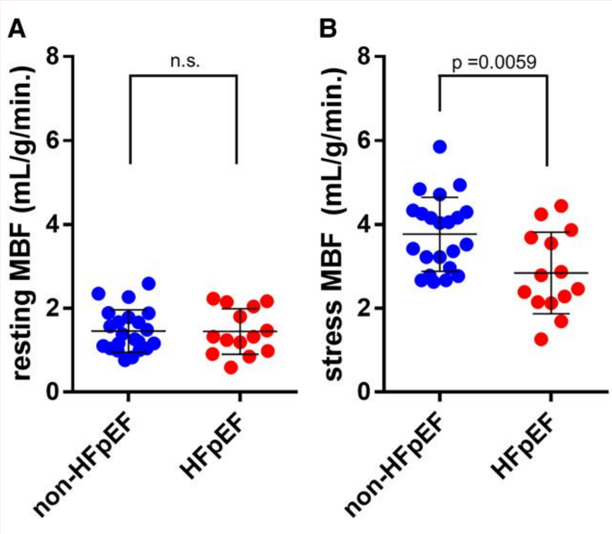


Figure 2 Resting and stress myocardial blood flow (mL/g/min). (*A*) Resting myocardial blood flow: no significant difference. (*B*) Stress myocardial blood flow: mean ± SEM of non-heart failure with preserved ejection fraction ($n = 22$) and heart failure with preserved ejection fraction ($n = 14$) are 3.77 ± 0.19 and 2.84 ± 0.26, respectively. 95% Confidence interval is −1.56 to −0.28. $P = 0.0059$ (two-tailed unpaired *t*-test).

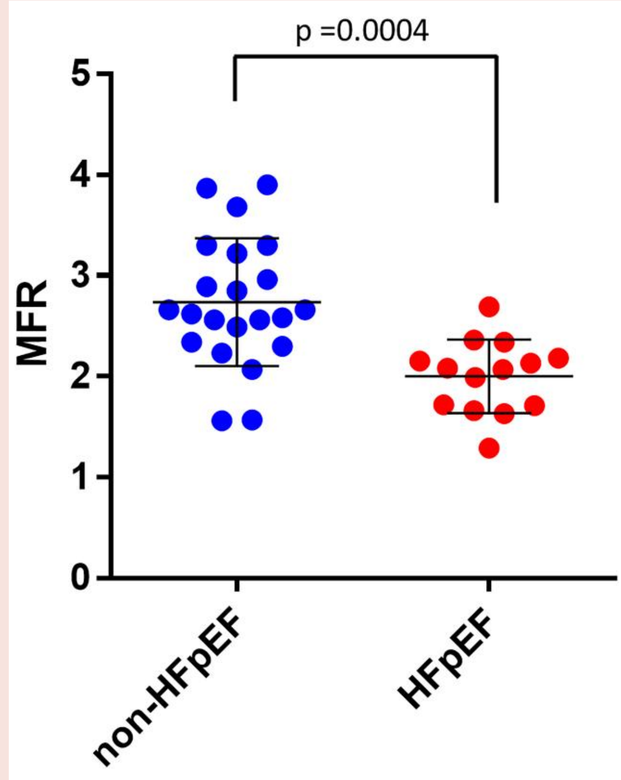


Figure 3 Myocardial flow reserve. Mean ± SEM of non-heart failure with preserved ejection fraction ($n = 22$) and heart failure with preserved ejection fraction ($n = 14$) are 2.74 ± 0.14 and 2.00 ± 0.097, respectively. 95% Confidence interval is −1.12 to −0.35. $P = 0.0004$ (two-tailed unpaired *t*-test).

Result

Baseline characteristics

The baseline characteristics of the 36 patients included in this study are shown in *Table 1*. The mean age of the patients was 71.2 ± 10.3 years; 65% were females, mean body mass index was 28.0 ± 32.5, which was similar between the groups. More cases of HFpEF were complicated by atrial fibrillation (AF) compared with non-HFpEF. No patients with diabetes were included in the HFpEF group. More patients with HFpEF were prescribed beta-blockers, mineral corticoid receptor antagonists, loop diuretics, and torvaptan compared with non-HFpEF. The mean blood pressure, heart rate, haemoglobin level, and renal function were not significantly different between the groups. The BNP levels in the HFpEF group were variably distributed, and the difference between the groups was not statistically significant.

Echocardiographic parameters

Mean LVEF was 63.7 ± 7.5% and 57.5 ± 11.6% for non-HFpEF and HFpEF groups, respectively (*Table 2*). LV mass index and LA volume index in HFpEF were significantly increased compared with the non-HFpEF groups; however, other parameters associated with diastolic dysfunction, such as TR jet velocity or *E/A* ratio, were not significantly different between the groups. In the same fashion, tissue Doppler indices were not significantly different between the groups. Among the parameters of diastolic dysfunction, only the LA volume index was significantly different between the groups. However, the HFpEF group had significantly higher diastolic dysfunction scores (DD scores) than the non-HFpEF group.

Dynamic ^{99m}Tc-MIBI perfusion single-photon emission computed tomography

The resting MBF level was similar between the two groups (*Figure 2A*). In adenosine-induced hyperaemic conditions, the level of MBF in the HFpEF group (mean ± SEM = 2.84 ± 0.26) was significantly impaired compared with that in the non-HFpEF group (mean ± SEM = 3.77 ± 0.19; *Figure 2B*). Accordingly, the value of MFR, which was calculated as stress MBF/resting MBF in each case, was significantly lower in the HFpEF group (mean ± SEM = 2.00 ± 0.097) than in the non-HFpEF group (mean ± SEM = 2.74 ± 0.14, $P = 0.0004$; *Figure 3*). ROC analysis showed that the area under the curve was 0.8409, and the cut-off value was 2.525 (*Figure 4*), indicating that MFR can distinguish patients with HFpEF from the non-HFpEF group with high accuracy. Similar to the total MFR, the regional MFR in each coronary artery vessel was significantly reduced in patients with HFpEF compared with non-HFpEF (*Table 3*). It is reported that loss of atrial stroke performance in patients with AF can decrease cardiac output by up to 25%[21] and could influence the MBF. Among the 36 subjects in the current study, the average of both rest and stress MBF was higher in patients without AF (rest: 1.51 ± 0.49, stress: 3.53 ± 0.88) compared with that with AF (rest: 1.26 ± 0.51, stress: 2.99 ± 1.25) but the difference was not statistically significant.

Relationship between myocardial flow reserve and clinical variables

To explore the relationship between MFR and clinical variables, a single regression analysis was performed. Clinical variables were selected from the patient's background, laboratory data, gated SPECT, and cardiac echo parameters (*Table 4*). Among these variables, patient's age,

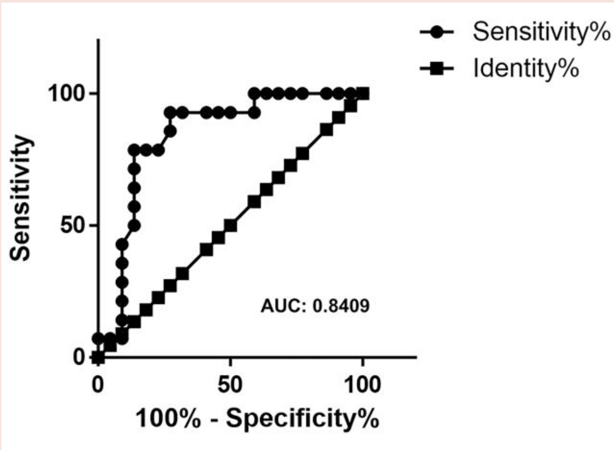


Figure 4 Receiver operating characteristic carve for myocardial flow reserve. AUC, area under the curve, the cut-off value for myocardial flow reserve is 2.525.

Table 3 Regional myocardial flow reserve

MFR	Overall ($n = 36$)	Non-HF control ($n = 22$)	HFpEF ($n = 14$)	P-value
LAD	2.27 ± 0.62	2.63 ± 0.63	1.96 ± 0.30	0.001
LCx	2.38 ± 0.69	2.68 ± 0.68	1.92 ± 0.39	0.0008
RCA	2.44 ± 0.62	2.72 ± 0.57	2.01 ± 0.41	0.0004

LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

Table 4 Single regression analysis

vs. MFR ($n = 36$)	R	P-value
Background		
Age	0.406	0.0138*
Gender	0.282	0.0951
BMI	0.0432	0.802
Smoke	0.0773	0.653
Hypertension	0.0256	0.882
DM	0.227	0.181
Heart failure	0.558	0.000395*
AF	0.295	0.0843
Laboratory data		
BNP	0.238	0.161
HbA1c	0.165	0.335
Gated SPECT parameter		
PFR	0.228	0.18
1/3MFR	0.137	0.424
TTPR/R-R	0.144	0.403
Echo parameter		
EF	0.121	0.478
LVMI	0.266	0.115
LAD	0.233	0.171
E/e'	0.22	0.195
e'	0.183	0.285
TVR velocity	0.544	0.000597*
DD score	0.650523	0.0000174*

AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; DD, diastolic dysfunction; DM, diabetes mellitus; EF, ejection fraction; LAD, left atrial diameter; LVMI, LV mass index; PFR, peak filling rate; 1/3MFR, 1/3 mean filling rate; TTPF, time to peak filling; TVR, tricuspid valve regurgitation.
*$P < 0.05$.

history of HF, tricuspid valve regurgitation (TVR) velocity, and DD score were significantly correlated with MFR. Variables that were significantly correlated with MFR in single regression analysis were selected for multiple regression analysis. TVR velocity and DD score were strongly correlated because TVR velocity is a component of DD score. Considering multicollinearity, TVR velocity was excluded from multiple regression analysis. The result is that history of HF ($P = 0.0473$) and DD score ($P = 0.0150$) were independently correlated with MFR and could pertly predict MFR (multiple R: 0.711, adjusted R^2: 0.46, $P^* < 0.05$). It is reported that peak filling rate (PFR) obtained by gated myocardial perfusion SPECT is correlated with echo LV diastolic parameters and could be an early indicator of LV dysfunction.[22,23] In accordance with these reports, PFR showed a moderate correlation with E/e' in our subjects ($R = 0.519$, $P = 0.00196$); however, it did not show a significant correlation with MFR ($R = 0.228$, $P = 0.180$).

Relationship between myocardial flow reserve and diastolic dysfunction score

It has been reported that decreased MFR in patients with normal ejection fraction assessed by rubidium-82 PET imaging is associated with parameters of diastolic dysfunction on echocardiography.[13] To further explore the relationship between MFR and LV diastolic dysfunction, MFR was compared with DD score (*Figure 5*), which was based on the following four parameters: average $E/e' > 14$, septal e' velocity <7 cm/s, TR systolic jet velocity >2.8 m/s and left atrial volume index >34 mL/m^2. Patients with a higher DD score had a significantly lower MFR compared with those with a lower DD score (*Figure 5*, gathered HFpEF and non-HFpEF). Additionally, among patients with a lower DD score (0 to 2), MFR was significantly lower in patients with HFpEF than in non-HFpEF ($P = 0.011$), indicating that HF itself could be a factor deteriorating MFR.

Myocardial flow reserve as a predictor of future events in heart failure with preserved ejection fraction

In the non-HFpEF group, no hospitalized cases or cardiovascular deaths were observed during the follow-up period. The average follow-up period was 3.5 years in HFpEF group ($n = 14$). During the follow-up period, six patients were hospitalized due to HF with lung congestion, and one patient died of lymphoma. The HFpEF group was divided into two groups according to the median value of MFR (2.075): higher ($n = 7$) and lower ($n = 7$) groups. Kaplan–Meier analysis showed that patients with HFpEF in the MFR-lower group were significantly exacerbated HF more frequently and were hospitalized more often than those in the MFR-higher group (*Figure 6*).

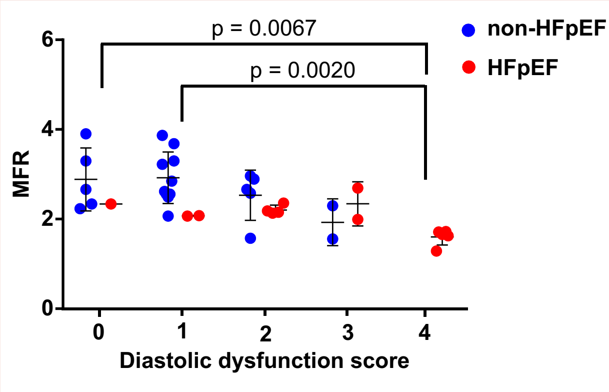


Figure 5 Relationship between myocardial flow reserve and diastolic dysfunction score. Based on echocardiographic parameters, each case was classified into five grades: 0–4. The parameters used for scoring were average *E*/*e*′ > 14, septal *e*′ velocity <7 cm/s, TR systolic jet velocity >2.8 m/s and left atrial volume index >34 mL/m^2. None of the patients in the non-heart failure with preserved ejection fraction group scored 4 points.

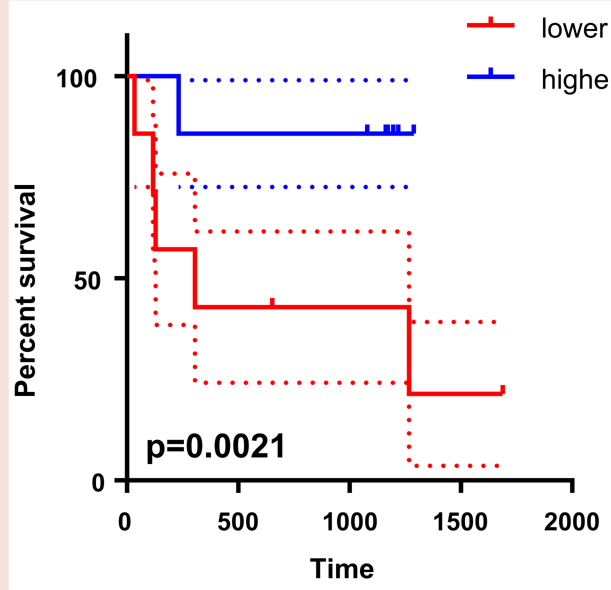


Figure 6 Kaplan–Meier survival analysis for patients with heart failure with preserved ejection fraction. The heart failure with preserved ejection fraction group ($n = 14$) was divided into two groups according to the median value of myocardial flow reserve (2.075): higher ($n = 7$) and lower ($n = 7$) groups. An event was defined as hospitalization due to heart failure or cardiovascular death. The dotted lines show 95% confidence intervals for each group. The log-rank (Mantel–Cox) test was applied to compare survival curves.

Discussion

In the current study, we showed that MFR assessed by CZT-SPECT with a ^{99m}Tc-labelled perfusion tracer decreased in patients with HFpEF compared with non-HFpEF. Moreover, this method has high sensitivity and specificity, similar to PET imaging, and can distinguish patients with HFpEF from non-HFpEF with high accuracy. A significant incidence of adverse events was observed in the MFR-lower group compared with the MFR-higher group (*Figure 6*) and suggests the potential of CZT-SPECT MFR to stratify prognosis in these patients.

D-single-photon emission computed tomography is a novel SPECT system equipped with nine arrays of CZT detectors, which achieves better energy resolution, higher sensitivity, higher count rate, lower radiation exposure, and faster acquisition time than the conventional SPECT system.[14] Several lines of evidence suggest that MBF assessed using CZT-SPECT provides comparable results with that assessed using PET and can be a surrogate modality for PET. Agostini *et al.* reported on over 30 patients with suspected CAD and found a significant correlation between CZT-SPECT and ^{15}O-water PET for the assessment of global MFR.[15,16] Other groups have also reported a significant correlation between dynamic ^{99m}Tc-sestamibi CZT-SPECT and ^{13}N-ammonia PET.[24–26] The correlation between MBF assessed by a dynamic CZT-SPECT scan and that assessed by an invasive coronary fractional flow reserve has also been reported. According to the report, a dynamic CZT-SPECT scan has sufficient ability to detect regional haemodynamic abnormalities.[27] The evidence above indicates that MBF measurement with CZT-SPECT is reliable and can be a surrogate method for PET.

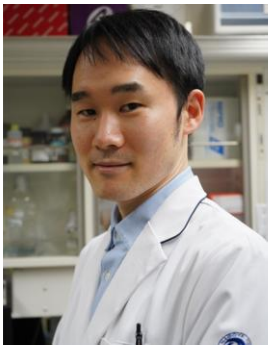
Increasing evidence suggests that a high prevalence of CMD is seen in HFpEF,[8,28] up to 75% of patients with HFpEF also have impaired CFR without epicardial CAD.[7] Furthermore, several reports have suggested that CMD might play a key role in the pathogenesis of HFpEF. Indeed, the systemic inflammatory state induced by risk factors of atherosclerosis such as hypertension, diabetes, or obesity causes endothelial dysfunction, resulting in impairment of NO production,[3,29] which is followed by the derangement of the NO-cGMP-PKG pathway, inducing cardiomyocyte hypertrophy,[30] interstitial fibrosis,[30] or hypophosphorylation of titin,[4] resulting in diastolic dysfunction. It has also been reported that coexisting CMD is associated with the prognosis of HFpEF. It is said that when CMD is defined as having a CFR of <2.5, it is independently associated with primally CV- and HF-specific events.[9] For these reasons, it is important to evaluate CMD in patients with HFpEF.

Currently, in patients without significant epicardial disease, MFR assessed using PET is considered a standard marker of microvascular function and a surrogate for coronary vascular health.[31] Srivaratharajah *et al.*[12] examined a total of 376 individuals, including 78 patients with HFpEF, and reported that MFR assessed by Rb-82 PET in patients with HFpEF was reduced (average = 2.16) compared with non-HF controls with hypertension (average = 2.54) or without hypertension (average = 2.89). Although our non-HFpEF subjects were not divided by blood pressure status, the MFR values of both HFpEF (average = 2.00) and non-HFpEF (average = 2.74) were comparable with the values assessed by Rb-82 PET. Another report evaluating the association between MFR and echocardiographic parameters of diastolic dysfunction in 73 subjects without a history of HF showed that reduced MFR was associated with higher *E*/*e*′ values, higher diastolic dysfunction scores, and decreased left atrial strain.[13] As shown in *Figure 6*, MFR in non-HFpEF subjects appears to decrease as the diastolic dysfunction score increases; however, MFR in patients with HFpEF showed consistently low values regardless of the diastolic dysfunction score, indicating that the diastolic dysfunction score is less reliable than MFR for the evaluation of disease severity in patients with advanced HFpEF. Although the number of patients with HFpEF was only 14 in the current study, patients with lower MFR had a significantly higher incidence of hospitalization due to HF. A large-scale clinical trial is warranted to further clarify whether MFR assessed using D-SPECT can predict adverse cardiac events in patients with HFpEF.

Conclusions

Myocardial flow reserve assessed by CZT-SPECT is significantly reduced in patients with HFpEF compared with that in non-HFpEF subjects. The MFR value is similar to that previously reported for PET. A lower MFR may be associated with a higher hospitalization rate in patients with HFpEF. All data indicate that MFR assessed by CZT-SPECT has the potential to predict future adverse events and stratify the severity of disease in patients with HFpEF.

Lead author biography



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Data availability

The data underlying this article will be shared on reasonable request with the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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