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Original article

Prognostic value of modified coronary flow capacity by ^{13}N-ammonia myocardial perfusion positron emission tomography in patients without obstructive coronary arteries

Shiro Miura MD[a,*], Masanao Naya MD, PhD[b], Hiraku Kumamaru MD[c], Akira Ando CNMT[d], Chihoko Miyazaki MD, PhD[e], Takehiro Yamashita MD, PhD[a]

[a] Department of Cardiology, Hokkaido Ohno Memorial Hospital, Sapporo, Japan
[b] Department of Cardiovascular Medicine, Hokkaido University, Graduate School of Medicine, Sapporo, Japan
[c] Department of Healthcare Quality Assessment, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[d] Division of Diagnostic Radiology Imaging, Hokkaido Ohno Memorial Hospital, Sapporo, Japan
[e] Department of Radiology, Hokkaido Ohno Memorial Hospital, Sapporo, Japan

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ABSTRACT

Background: Vasodilator capacity of coronary circulation is an important diagnostic and prognostic tool in patients with coronary artery disease (CAD). We aimed to clarify the incidence of coronary microvascular dysfunction (CMD), defined as impaired modified coronary flow capacity (mCFC) proposed by Johnson and Gould and measured by ^{13}N-ammonia myocardial perfusion positron emission tomography (PET), in patients without obstructive CAD and to evaluate the risk of future cardiovascular events.

Methods: This retrospective study recruited 407 consecutive CAD-suspected patients who underwent both pharmacological stress/rest ^{13}N-ammonia PET and coronary angiography. Of the 407 patients, 137 patients (median age, 70 years; 63 women) were eligible and followed up (median, 19.8 months). Endpoints were defined as cardiovascular death or major adverse cardiovascular events (MACEs), such as cardiovascular death, nonfatal myocardial infarction, unplanned hospitalization for any cardiac reasons, and unplanned coronary revascularization. The impaired mCFC group included patients with mildly to severely reduced regional CFC in, at least, one vascular territory (n=34), while the remaining patients (n=103) were categorized as having preserved mCFC.

Results: Overall, cardiovascular death and MACEs occurred in five (4%) patients. The Kaplan–Meier curve showed a significant reduction in event-free survival for cardiovascular death (p=0.004) and MACEs (p<0.0001) in the impaired mCFC group, compared to the preserved mCFC group. Impaired mCFC was independently associated with the incidence of both cardiovascular death and MACEs after propensity-score adjustments [hazard ratio (HR), 10.7; 95% confidence interval (CI), 1.0–106.0; p=0.04 and HR, 9.5; 95% CI, 2.5–36.2; p<0.001, respectively].

Conclusions: In CAD-suspected patients without obstructive coronary arteries, impaired mCFC was observed in approximately 25% and was associated with a higher risk of cardiovascular death and MACEs. The mCFC concept can help identify patients who would benefit from specific therapies or lifestyle modifications to prevent future MACEs and can clarify potential mechanisms of CMD.

Introduction

Patients with evident ischemia and no obstructive epicardial coronary artery disease (CAD), named INOCA, are increasingly being recognized [1]; they are frequently referred for coronary angiography (CAG) or coronary computed tomography (CT) angiography (CCTA). One proposed mechanism contributing to INOCA is coronary microvascular dysfunction (CMD), which can occur not only in the absence of obstructive CAD but also in myocardial diseases, obstructive CAD, or during iatrogenic procedures [2]. Cardiac positron emission tomography (PET) has been the gold standard for quantitative myocardial perfusion to define physiological CMD severity [3], which is commonly related to the detrimental effects of cardiovascular risk factors on the arterial wall, vascular smooth muscle cell layer hypersensitivity, or both [4]. In diagnosing CMD, coronary flow reserve [CFR; calculated as the ratio of

* Corresponding author at: Department of Cardiology, Hokkaido Ohno Memorial Hospital, 2-1-16-1 Miyanosawa, Nishi-ku, Sapporo 063-0052, Japan.
E-mail address: s.miura@ohno-kinen.or.jp (S. Miura).

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hyperemic to rest absolute myocardial blood flow (MBF)] reflects the most straightforward assessment of coronary vasodilator capacity [5]. Nonetheless, CFR depends on both resting and vasodilated coronary hemodynamics, and physiological changes in these conditions may inadvertently affect the CFR result [6]. To overcome such CFR limitations, the coronary flow capacity (CFC) concept was introduced by integrating CFR with the maximal flow during coronary vasodilation into a comprehensive framework [7, 8]. Recently, CFC was reported to be associated with the size-dependent highest mortality risk that is meaningfully decreased with revascularization, which was not proven for global CFR [9]. However, because these novel parameters (CFR and CFC) provide a quantitative assessment of the integrated effects of epicardial coronary stenosis, diffuse atherosclerosis, and CMD [10], it might not be straightforward to estimate CMD severity and clarify clinical outcomes, apart from epicardial coronary stenosis, even in patients without obstructive coronary arteries. Thus, we created a modified CFC (mCFC) category by integrating the regional CFC category within each coronary territory into the entire CFC category for each patient.

This study aimed to assess the predictive value of mCFC and flow-based diagnosis for ischemic heart disease based on coronary artery territories utilizing ^{13}N-ammonia PET in patients without obstructive coronary arteries and to characterize the predictors of impaired mCFC to assess microvascular dysfunction.

Materials and methods

Study population

We evaluated 458 consecutive patients who underwent PET myocardial perfusion imaging for the evaluation of suspected CAD based on clinical indications between January 2017 and April 2020 at Hokkaido Ohno Memorial Hospital (Fig. 1). Among them, 407 underwent coronary assessments with CCTA, invasive CAG, or both, within 60 days of PET examination, and 164 patients showed no findings of obstructive CAD in each coronary artery (<50% coronary diameter stenosis or fractional flow reserve >0.80). We further excluded patients with left ventricular (LV) ejection fractions <40% (n=15), known myocardial infarction (n=5), cardiomyopathy (n=3), moderate or severe valvular disease (n=3), or congenital heart disease (n=1), finally resulting in 137 participants. Fig. 2 displays the comprehensive data from a single patient, including CCTA, relative uptake maps, absolute flow, and CFR maps for each coronary territory, and color flow map as a sample. mCFC was defined as “impaired” (n=34), if regional CFC was mildly reduced or worse in any coronary territory among three major coronary-supplied territories, based on a scatter plot CFR versus stress MBF [7]. The remaining patients (n=103) were included in the “preserved” mCFC group. Patients’ medical histories, past or current medication use, and selected laboratory values were ascertained during PET imaging. The Institutional Review Boards (IRB) of Hokkaido Ohno Memorial Hospital approved this study (IRBs number: 2019-7), and all patients provided written informed consent before CAG, CCTA, and PET examination; however, the requirement for consent was waived for this study due to its retrospective nature. This study complied with all IRB requirements based on the Declaration of Helsinki and ethical principles in the Belmont Report.

PET acquisition protocol imaging analysis

All patients underwent single-day stress/rest ^{13}N-ammonia PET with a PET/CT scanner (Biograph mCT Flow 64-4R PET/CT system; Siemens Healthcare, Germany). Dynamic PET at rest and during pharmacologic stress was performed in the 3D list mode, and dynamic frames were reconstructed. CT was used for attenuation correction. Patients were instructed to completely fast for >6 h and refrain from consuming caffeinated beverages and foods for at least 12 h before the examination. The pharmacological stress scan was performed during adenosine triphosphate (ATP)-induced hyperemia for 5 min, at a rate of 160 $\mu g \bullet kg^{-1} \bullet min^{-1}$ [11, 12]. The rest scan was performed with 3 MBq/kg of ^{13}N-ammonia for 30 s after 1 h. After a 3-min ATP infusion, ^{13}N-ammonia was injected at a dose of 3 MBq/kg for 30 s, and the mentioned protocol was followed. Heart rate and blood pressure were recorded during the rest test and every minute during and after ATP infusion, with continuous electrocardiogram monitoring.

PET images were quantitatively analyzed using a commercially available dedicated software package (Syngo MBF®, Siemens Healthcare, Erlangen, Germany). Quantitative analysis was semi-automated using a two-compartment model [13]. The mean MBF values (mL/g/min) were measured for the three regions of the left anterior descending, left circumflex, and right coronary arteries using the 17-segment standard American Heart Association model at rest and during stress. Mean CFR was calculated as the ratio of stress MBF (stress scan) to rest MBF (rest scan) in each region and globally. Originally, Gould et al. advocated that each color-coded pixel is spatially mapped back onto its LV location with percentage of left ventricle calculated for each range of combined CFR and stress perfusion pixel values listed in the CFC color histogram bar [14]. Here, we added a more practical concept of coronary territory onto the original CFC to create a new classification, mCFC, for each patient using scatter plot CFR and stress MBF (Fig. 2). A color flow map of the left ventricle indicated coronary flow in a patient utilizing the CFR and stress MBF for each coronary territory. This allowed for classification into the following six unique categories: normal flow, minimal reduced flow, mildly reduced flow, moderately reduced flow, definite ischemia, and myocardial steal. Preserved mCFC was defined as “normal” or “minimally reduced” flow in every coronary territory within the left ventricle with a color-based interpretation of the flow capacity. Thus, patients with impaired mCFC had “mildly reduced” or less coronary flow in at least one coronary territory.

Outcomes

Patient follow-up was performed using a questionnaire administered by telephone to all patients or their general practitioners or cardiologists, and additional information was gathered from medical charts. The median follow-up period was 19.8 months [interquartile range (IQR): 14.1–31.2] after the PET scan, until the end of June 2020. Endpoints were defined as cardiovascular death or major adverse cardiovascular events (MACEs), such as cardiovascular death, nonfatal myocardial infarction, unplanned hospitalization for any cardiac reasons, and coronary revascularization, including percutaneous coronary intervention (PCI) or coronary artery bypass grafting [15]. Of note, cardiovascular deaths included deaths resulting from myocardial infarction, sudden cardiac death, or death due to heart failure (HF), stroke, cardiovascular hemorrhage, or other cardiovascular causes.

Statistical analysis

Baseline characteristics were reported as counts with percentages for categorical variables and medians with IQRs for continuous variables. We used the Fisher’s exact test and Wilcoxon rank-sum test to assess differences in categorical and continuous baseline characteristics between the preserved and impaired mCFC patients. Survival curves for the primary MACE endpoint and overall survival in both groups were compared. Cox proportional-hazards models were used to examine the association between

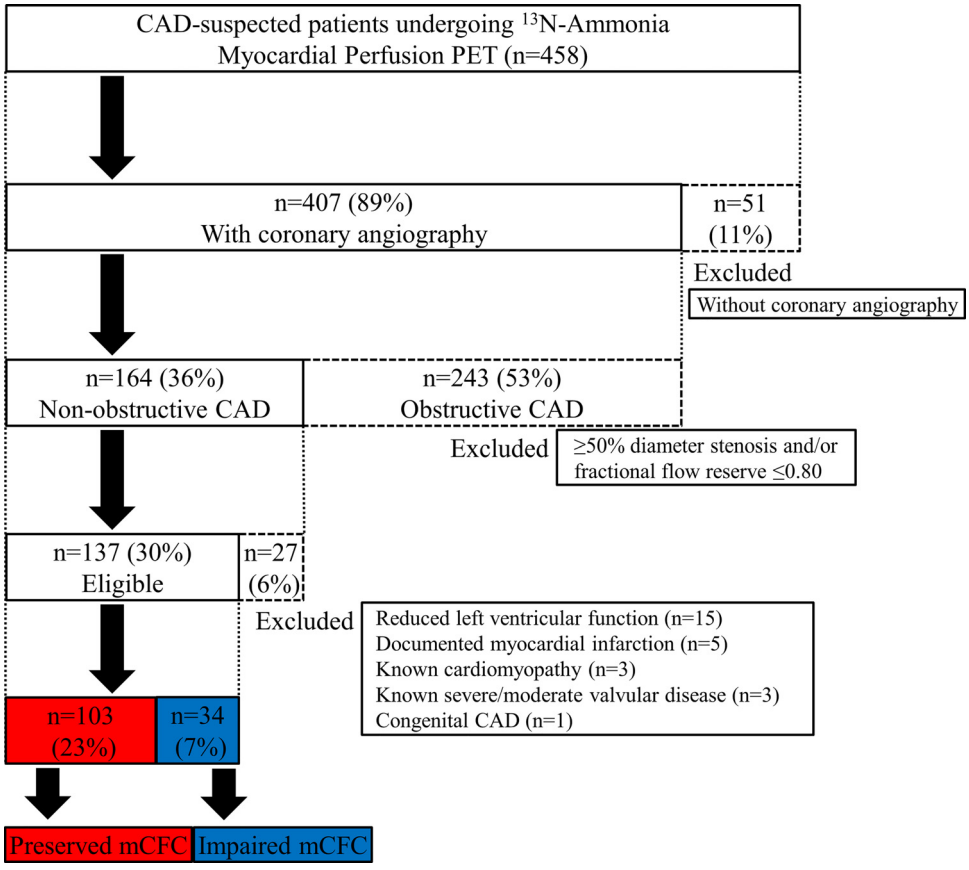

Fig. 1. Patient flow chart. CAD, coronary artery disease; PET, positron emission tomography; mCFC, modified coronary flow capacity.

mCFC and outcome events, with and without controlling for age and sex. Additionally, propensity scores (PS) were estimated for all patients using the following 6 established risk factors based on previous studies [16, 17]: age, sex, diabetes (treatment with glucose-lowering medications or previous diagnosis of diabetes), hypertension (treatment with antihypertensive drugs or hypertension history), chronic kidney disease (CKD) [defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2], and overweight (body mass index >25 kg/m^2). We grouped the patients into five based on the quintiles of PS values and estimated the adjusted hazard ratios (HRs) using Cox regression models for both cardiovascular death and MACEs by including the PS quintiles as a linear term. A p-value<0.05 was considered significant. All statistical analyses were performed using the R statistical software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The clinical characteristics and imaging parameters of the 137 patients are summarized in Tables 1 and 2. The median age was 70 years (IQR, 61–75); 46% were women, and 12% were asymptomatic. The patients with impaired mCFC had a higher rate of hypertension and diabetes mellitus at baseline and underwent more CAG examinations than those with preserved mCFC. The proportion of women did not differ between the two groups. Regarding imaging parameters, the impaired mCFC group had lower LV ejection fraction (rest and stress) and higher summed stress and rest score values. Global CFR and stress MBF were significantly lower in the impaired mCFC group than in the preserved mCFC group [1.81 (IQR, 1.52–2.21) vs. 2.81 (IQR, 2.43–3.32); p<0.001; and 1.66 (IQR, 1.37–1.88) vs. 2.63 mL/g/min (IQR, 2.24–2.92); p<0.001, respectively], while global rest MBF was similar in both groups (p=0.72). The preserved mCFC group showed a normal flow in 55% of the patients and minimally reduced flow in 45%. In the impaired mCFC group, a mildly reduced flow was the most common, occurring in 76% of the patients. Disagreement on the mCFC classification among the three coronary territories was observed in 82% of the impaired mCFC group and only 20% in the preserved mCFC group (p<0.001) (Table 2 and Online Fig. 1). The comparison of stress MBF, rest MBF, and CFR by coronary territories between the two groups is shown in Fig. 3, highlighting that rest MBF was uniformly similar between them across all coronary territories. A significant difference in stress MBF and CFR was observed between the two groups throughout the three coronary territories.

Impact of impaired mCFC on clinical outcome

During the median follow-up period of 19.8 months with a 99% follow-up rate (135/137) until the end of June 2020, when all were administratively censored, cardiovascular death occurred in five (4%) patients, including sudden death in three and HF-related death in two (Table 3). There were unplanned hospitalizations due to cardiac reasons in 11 (8%) patients, specifically HF in 6, and ischemic heart events needing urgent admission but not requiring any coronary revascularizations in 6 patients. One patient developed both HF and an ischemic heart event at different times. Contrarily, nonfatal myocardial infarctions never occurred, and coronary revascularization was performed with PCI in one patient from the preserved mCFC group. Overall, the incidence of unplanned hospitalizations significantly differed between the preserved and impaired mCFC groups (2% and 26%, p<0.001, respectively).

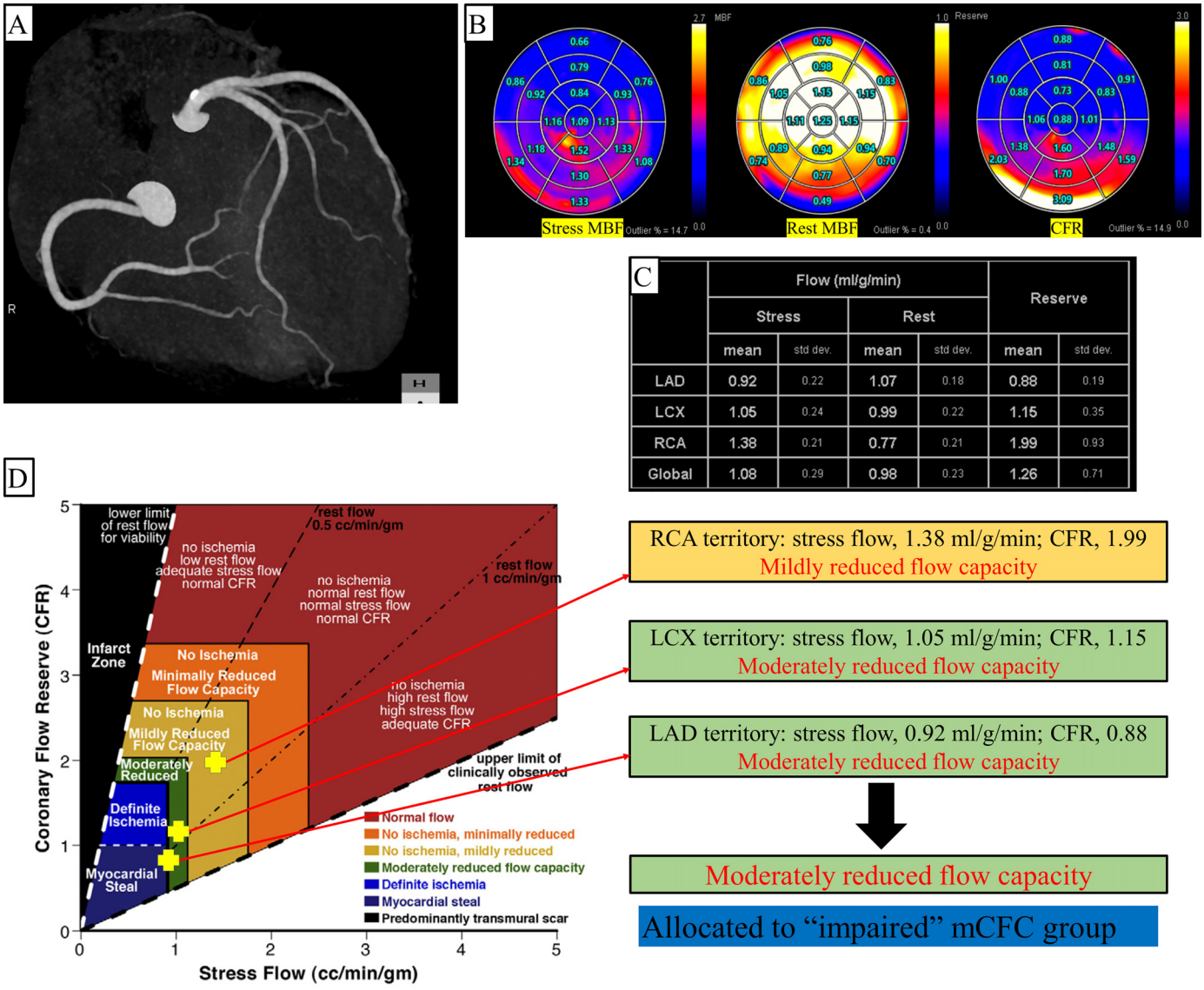

Fig. 2. A representative case of a symptomatic 74-year-old woman in the impaired modified coronary flow capacity (CFC) group. (A) A coronary computed tomography angiography demonstrating no significant epicardial stenosis. (B) Adenosine triphosphate-induced ^{13}N-ammonia positron emission tomography-derived quantification value of stress myocardial blood flow (MBF) (left), rest MBF (center) and, coronary flow reserve (CFR) (right) in the 17-segment standard American Heart Association model and (C) based on the three major coronary territories. A scatter plot of CFR versus absolute stress MBF originally proposed by Johnson and Gould [7] showed that regional CFC was plotted based on stress MBF and CFR in the three coronary territories supplied by the major coronary arteries (right coronary artery, left anterior descending coronary artery, and left circumflex coronary artery), and the worst regional CFC was interpreted as the patient's modified CFC as illustrated in (D). PET, positron emission tomography; MBF, myocardial blood flow; CFR, coronary flow reserve; RCA, right coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending coronary artery; CFC, coronary flow capacity; mCFC, modified coronary flow capacity.

The Kaplan–Meier survival curves indicated that the impaired mCFC group had a significantly higher rate of cardiovascular death (log-rank p=0.004) and MACEs (log-rank p<0.0001) than the preserved mCFC group (Fig. 4). Event-free survival for cardiovascular death at 24 months in the preserved and impaired mCFC groups was 99% and 86%, respectively. In the crude assessment displayed in Table 4, the impaired mCFC group had a significantly high hazard ratio of MACEs [HR, 10.7; 95% confidence interval (95% CI), 2.9–39.2; p<0.001] and cardiovascular death (HR, 12.1; 95% CI, 1.3–108.0; p=0.02). The sex- and age-adjusted (HR, 10.9; 95% CI, 3.0–39.7; p<0.001) and PS-adjusted (HR, 9.5; 95% CI, 2.5–36.2; p<0.001) models showed significant associations between impaired mCFC and MACEs. Similarly, the associations between impaired mCFC and cardiovascular death were significant in the age- and sex-adjusted (HR, 12.4; 95% CI, 1.3–111; p=0.02) and PS-adjusted (HR, 10.7; 95% CI, 1.0–106; p=0.04) analyses.

Discussion

We have demonstrated that in 137 patients without obstructive coronary arteries undergoing myocardial perfusion PET, 25% had impaired mCFC and 23% had lower global CFR (<2.0), while 88% were symptomatic. Patients with impaired mCFC had a higher incidence of hypertension and diabetes at baseline than those with preserved mCFC. Regarding clinical outcomes, patients with impaired mCFC were associated with a 9.5 times greater risk of MACEs after PS adjustments than those with preserved mCFC.

Reportedly, CFC integrates the simultaneous regional size severity of the resting MBF, maximal MBF, and CFR by providing specific patterns that are more accurate than those of CFR alone for distinguishing the effects of focal CAD, diffuse non-obstructive CAD, and CMD by accounting for perfusion heterogeneity [18]. CFC can have some merits in combating potential limitations of CFR. For ex-

Table 1
Baseline Characteristics in Patients with Preserved and Impaired mCFC.

Characteristic	Overall (n=137)	Preserved mCFC (n=103)	Impaired mCFC (n=34)	*p*-value
Demographic characteristics				
Age, years	70 [61, 75]	69 [61, 74]	73 [61, 76]	0.40
Female sex, n (%)	63 (46)	48 (47)	15 (44)	0.84
Body mass index, kg/m^2	24.6 [22.4, 27.0]	24.5 [22.3, 26.5]	25.1 [22.8, 29.0]	0.24
Body mass index >25 kg/m^2, n (%)	56 (41)	39 (38)	17 (50)	0.23
Symptomatic status, n (%)				
Typical angina or exertional dyspnea	80 (58)	59 (57)	21 (62)	0.59
Atypical angina	41 (30)	33 (32)	8 (23)	
Asymptomatic	16 (12)	11 (11)	5 (15)	
Medical history, n (%)				
Hypertension	85 (62)	57 (55)	28 (82)	0.005
Dyslipidemia	73 (53)	52 (51)	21 (62)	0.32
Diabetes mellitus	34 (25)	19 (18)	15 (44)	0.005
Prior percutaneous coronary intervention	26 (19)	16 (16)	10 (29)	0.083
Peripheral arterial disease	7 (5)	4 (4)	3 (9)	0.36
Prior heart failure	14 (10)	7 (7)	7 (21)	0.04
Atrial fibrillation	12 (9)	9 (9)	3 (9)	1.0
Hemodialysis	5 (4)	2 (2)	3 (9)	0.09
Current smoker	30 (22)	24 (23)	6 (18)	0.63
Chronic lung disease	12 (9)	8 (8)	4 (12)	0.49
Malignancy	9 (7)	7 (7)	2 (6)	1.0
Medications, n (%)				
Antiplatelet therapy	48 (35)	33 (32)	15 (44)	0.21
Calcium channel blockers	48 (35)	35 (34)	13 (38)	0.68
β-blockers	32 (23)	21 (20)	11 (32)	0.16
Cholesterol-lowering agents	68 (50)	49 (48)	19 (56)	0.43
ACEI/ARB	57 (42)	40 (39)	17 (50)	0.31
Nitrates	5 (4)	3 (3)	2 (6)	0.59
Diuretic	11 (8)	7 (7)	4 (12)	0.46
Oral hypoglycemic agents	27 (20)	14 (14)	13 (38)	0.005
Insulin	2 (2)	0 (0)	2 (6)	0.06
Laboratory values				
Hemoglobin, g/dl	14 [13, 15]	14 [13, 15]	13 [11, 15]	0.14
eGFR, pg/ml	68 [60, 78]	71 [61, 80]	64 [58, 74]	0.09
eGFR<60, n (%)	32 (24)	22 (22)	10 (29)	0.48
LDL cholesterol, mg/dl	104 [20, 212]	106 [20, 185]	102 [23, 212]	0.81
HbA1c, %	6.0 [5.7, 6.4]	5.9 [5.6, 6.2]	6.3 [5.9, 6.8]	0.004
Fasting glucose, mg/dl	112 [99, 138]	111 [96, 128]	121 [107, 162]	0.01
NT-proBNP, pg/ml	93 [44, 207]	88 [51, 159]	116 [29, 506]	0.58
Coronary assessment, n (%)				
CCTA	95 (69)	76 (74)	19 (56)	0.05
Invasive CAG	80 (58)	54 (52)	26 (77)	0.01
Deferred by fractional flow reserve	21 (15)	14 (14)	7 (21)	0.41

Data are presented as median [interquartile range] or n (%) of patients.
mCFC, modified coronary flow capacity; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro–B-type natriuretic peptide; CCTA, coronary computed tomographic angiography; CAG, coronary angiography.

ample, rest flow may be physiologically elevated in the setting of anxiety or increased myocardial workload, whereas maximal flow in such settings will remain adequate when CFR is low without ischemic signs or symptoms. In this case, CFC would indicate normal flow capacity based on normal maximal flow. Here, we added a unique aspect into the original CFC concept, by examining whether vascular beds perfused by major coronary artery vessels with averaged stress MBF and CFR in that coronary flow are inevitably affected by atherosclerosis burden within each of the arteries. These concepts are already gaining increasing popularity by extrapolation to invasive CFC, assessed in terms of Doppler flow velocity, wherein the magnitude is intrinsically corrected for the amount of perfused myocardial mass in the coronary arterial distribution [8]. Hence, it may be of great importance to explore perfusion-territory specific data to evaluate its diagnostic and prognostic values in CAD-suspected patients undergoing myocardial perfusion PET.

Regarding characteristics of our study population, 243 (60%) of the 407 patients who underwent both CAG and cardiac PET examinations showed obstructive coronary arteries, and one-fourth of the 137 patients without obstructive coronary arteries showed impaired mCFC. The unique relationship between symptoms and mCFC highlighted no statistical difference in symptomatic status between the two groups, and approximately 15% of the impaired mCFC group was asymptomatic. Patients without obstructive coronary arteries are often told that their pain is noncardiac; therefore, no further work-up is often planned, resulting in missed opportunities to diagnose and explore treatments for CMD for both symptom management and risk reduction. Concerning cardiovascular risk factors, baseline hypertension and diabetes had significantly higher incidences in the impaired mCFC group, at 82% and 62%, respectively. The reduction in PET-derived CFR has been found in patients with hypertension regardless of the presence of LV hypertrophy, suggesting that intrinsic microvascular abnormalities (vascular remodeling and endothelial dysfunction) might play a more significant role in CMD development [19]. Similarly, impaired CFR on cardiac PET has been demonstrated in patients with diabetes [20]. Independent of cardiovascular risk factors such as hypertension and diabetes, CKD is proposed as a more significant risk factor in impaired renal function, including even minor renal abnormalities, that may promote cardiovascular diseases [21, 22]. Briefly, endothelial dysfunction is the potential pathophysiological mechanism involved in the association between CMD and CKD [23]. Here,

Table 2
Myocardial Perfusion PET Findings in Patients with Preserved and Impaired mCFC.

	Overall (n=137)	Preserved mCFC (n=103)	Impaired mCFC (n=34)	*p*-value
Hemodynamics conditions during PET				
Rest heart rate, bpm	67 [58, 75]	67 [58, 75]	69 [61, 75]	0.43
Stress heart rate, bpm	77 [70, 85]	80 [70, 85]	75 [70, 83]	0.38
Rest systolic blood pressure, mmHg	132 [117, 147]	128 [117, 147]	136 [118, 149]	0.48
Stress systolic blood pressure, mmHg	116 [101, 128]	116 [104, 127]	107 [94, 132]	0.10
Rest diastolic blood pressure, mmHg	70 [63, 82]	70 [64, 81]	73 [63, 84]	0.49
Stress diastolic blood pressure, mmHg	62 [56, 70]	63 [57, 70]	59 [52, 71]	0.20
Rest rate-pressure product, mmHg*bpm	8400 [7198, 10200]	8580 [7198, 10096]	8347 [7238, 11051]	0.44
Stress rate-pressure product, mmHg*bpm	9116 [7500, 10656]	9348 [7628, 10709]	8105 [6965, 10231]	0.11
Rest EDV (mL)	86 [70, 109]	85 [67, 109]	90 [76, 108]	0.38
Rest LVEF, %	70 [64, 78]	72 [66, 79]	64 [55, 75]	0.001
Stress LVEF, %	70 [62, 76]	71 [65, 76]	62 [55, 72]	0.001
delta LVEF, %	-2 [-4, 1]	-2.00 [-4, 1]	-2 [-4, 2]	0.87
Stress-induced increased LVEF, n (%)	39 (29)	28 (27)	11 (32)	0.66
Summed rest score	1 [0, 3]	1 [0, 2]	2 [1, 6]	0.002
Summed stress score	4 [2, 8]	3 [2, 6]	8 [3, 11]	0.003
Summed difference score	2 [1, 4]	2 [1, 4]	4 [0, 5]	0.19
Rest MBF (mL/g/min)	0.93 [0.77, 1.10]	0.93 [0.77, 1.10]	0.94 [0.72, 1.10]	0.72
Corrected rest MBF, mL/g/min†	1.07 [0.91, 1.27]	1.11 [0.94, 1.27]	0.99 [0.86, 1.20]	0.10
Stress MBF (mL/g/min)	2.34 [1.93, 2.76]	2.63 [2.24, 2.92]	1.66 [1.37, 1.88]	<0.001
CFR	2.63 [2.14, 3.18]	2.81 [2.43, 3.32]	1.81 [1.52, 2.21]	<0.001
CFR <2.0, n (%)	31 (23)	6 (6)	25 (74)	<0.001
Corrected CFR	2.26 [1.83, 2.68]	2.40 [2.06, 2.79]	1.50 [1.26, 2.06]	<0.001
Maximum CFR in 17 segments	3.35 [2.70, 4.00]	3.61 [3.08, 4.14]	2.26 [1.88, 3.07]	<0.001
Minimum CFR in 17 segments	1.94 [1.65, 2.40]	2.11 [1.82, 2.56]	1.48 [1.20, 1.59]	<0.001
Rest CVR, mm Hg/(ml/min/g) ‡	97 [81, 114]	96 [79, 114]	100 [86, 124]	0.33
Stress CVR, mm Hg/(ml/min/g) ‡	34 [28, 43]	32 [26, 38]	48 [40, 59]	<0.001
Interpretation of mCFC, n (%)				
Normal flow capacity	57 (42)	57 (55)	0 (0)	<0.001
Minimally reduced	46 (34)	46 (45)	0 (0)	
Mildly reduced	26 (19)	0 (0)	26 (76)	
Moderately reduced	6 (4)	0 (0)	6 (18)	
Definite ischemia	1 (1)	0 (0)	1 (3)	
Myocardial steal	1 (1)	0 (0)	1 (3)	
Disagreement in regional CFC among three coronary territories§	49 (36)	21 (20)	28 (82)	<0.001

Data are presented as median [interquartile range] or n (%) of patients.
PET, positron emission tomography; mCFC, modified coronary flow capacity; EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; MBF, myocardial blood flow; CFR, coronary flow reserve; CVR, coronary vascular resistance. †Corrected rest MBF is computed by multiplying by the rest rate-pressure product/10 000. ‡Stress/rest coronary vascular resistance (CVR) is calculated by dividing stress/rest mean arterial pressure by CFR. §Disagreement in regional CFC is considered if regional CFC among three coronary territories in a single patient are not uniformly allocated to the same CFC category ranging from normal flow to myocardial steal.

Table 3
Detailed Clinical Outcomes in Patients with Preserved and Impaired mCFC.

	Overall (n=137)	Preserved mCFC (n=103)	Impaired mCFC (n=34)	*p*-value
All-cause death	5 (4)	1 (1)	4 (12)	0.01
Cardiovascular death	5 (4)	1 (1)	4 (12)	0.01
Heart failure-related death	2 (1)	0 (0)	2 (6)	
Sudden death	3 (2)	1 (1)	2 (6)	
MACEs	13 (9)	3 (3)	10 (29)	<0.001
Nonfatal myocardial infarction	0 (0)	0 (0)	0 (0)	NA
Unplanned hospitalization	11 (8)	2 (2)	9 (26)	<0.001
Heart failure	6 (4)	1 (1)	5 (15)	
Ischemic heart event	6 (4)	1 (1)	5 (15)	
Coronary revascularization	1 (1)	1 (1)	0 (0)	1.0
Follow-up period, months	19.8 [14.1 - 31.2]	19.8 [13.9 - 29.3]	21.8 [15.1 - 33.8]	0.38

Data are presented as median [interquartile range] or n (%) of patients.
mCFC, modified coronary flow capacity; MACEs, major adverse cardiovascular events.

Table 4
Crude and Adjusted Effects of Impaired mCFC on Cardiovascular Death and MACEs.

	Crude		Age- and sex-adjusted		PS-adjusted	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Cardiovascular death						
Impaired mCFC	12.1 (1.3 - 108)	0.02	12.4 (1.3 - 111)	0.02	10.7 (1.0 - 106)	0.04
MACEs						
Impaired mCFC	10.7 (2.9 - 39.2)	*p*<0.001	10.9 (3.0 - 39.7)	*p*<0.001	9.5 (2.5 - 36.2)	*p*<0.001

MACEs, major adverse cardiovascular events; mCFC, modified coronary flow capacity; HR, hazard ratio; CI, confidence interval; PS, propensity score.
HRs were calculated with preserved mCFC used as a reference.

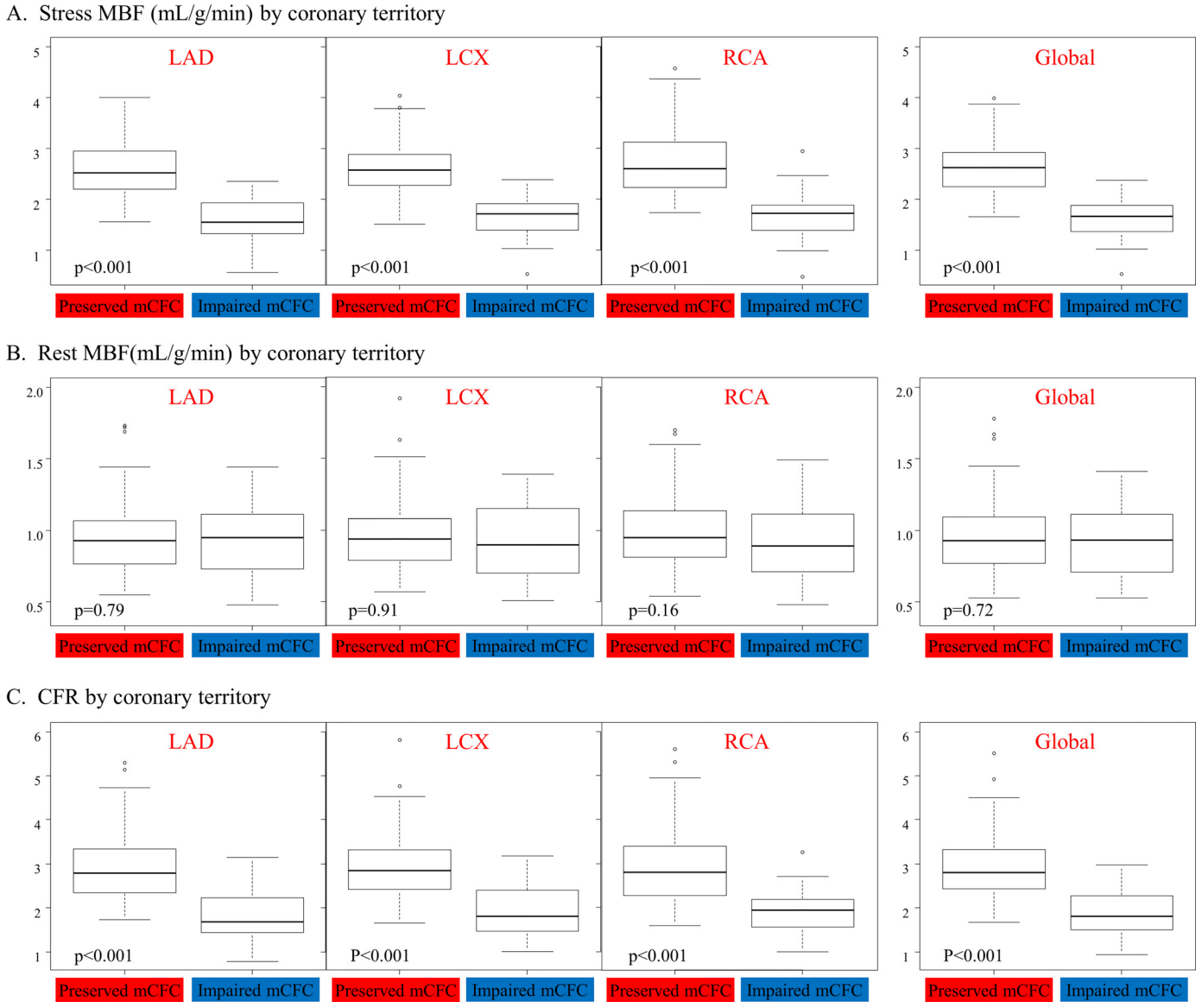

Fig. 3. Adenosine triphosphate-induced ^{13}N-ammonia positron emission tomography-derived quantification measurements by coronary territory. (A) Comparison of stress myocardial blood flow (MBF), (B) rest MBF, and (C) coronary flow reserve in the three coronary territories supplied by the major coronary arteries (right coronary artery, left anterior descending coronary artery, and left circumflex coronary artery), with global left ventricle between the preserved (n=103) and impaired (n=34) modified coronary flow capacity groups. MBF, myocardial blood flow; CFR, coronary flow reserve; RCA, right coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending coronary artery; mCFC, modified coronary flow capacity.

a difference in eGFR value was observed between the preserved mCFC and impaired mCFC groups (eGFR, 71 vs 64 pg/ml; p=0.09), although it was not significant. Interestingly, this finding may be explained partially by a previous study that found that mild-to-moderate CKD was not independently associated with a reduction in peak myocardial flow or CFR, although loss of CFR may accelerate in mild-to-moderate CKD [24]. Overall, we believe that these associations among CMD, CKD, and traditional cardiovascular risk factors could facilitate a deeper understanding of the potential mechanisms of CMD development, as well as the importance of CMD management in patients without obstructive CAD.

Importantly, disagreements in regional mCFC among the three coronary territories were much more frequently observed in the impaired mCFC group (82%) than in the preserved mCFC group (20%), as illustrated in Online Fig. 1, indicating that coronary flow had more heterogeneous distribution in the impaired mCFC group than in the preserved mCFC group. However, the overall median summed difference score on myocardial perfusion imaging (MPI) was low at 2 (interquartile: 2–4), with no difference between both groups. This increases the significance of assessing both regional and global mCFC in addition to absolute indices (stress/rest MBF and CFR) in patients without obstructive CAD, although the "visual analysis" might be close to normal in the MPI study.

Technical problems to measure these PET-derived indices need to be considered. For example, as illustrated in Fig. 2, CFR in the RCA territory may be often calculated relatively higher than the other two territories due to overflow artifact from the adjacent RV blood pool during the early phase of the scan, or motion artifact that is frequently observed in RCA and LAD territories. However, the imbalance/heterogeneity of coronary flow in patients with non-obstructive CAD could result mainly from not only hemodynamically significant epicardial plaque burden in each coronary artery but also from imbalanced distribution of CMD. Reportedly, substantial discordance of classification of CMD among coronary artery territories observed in women with chest pain and non-obstructive CAD was consistent with our findings that CMD is dis-

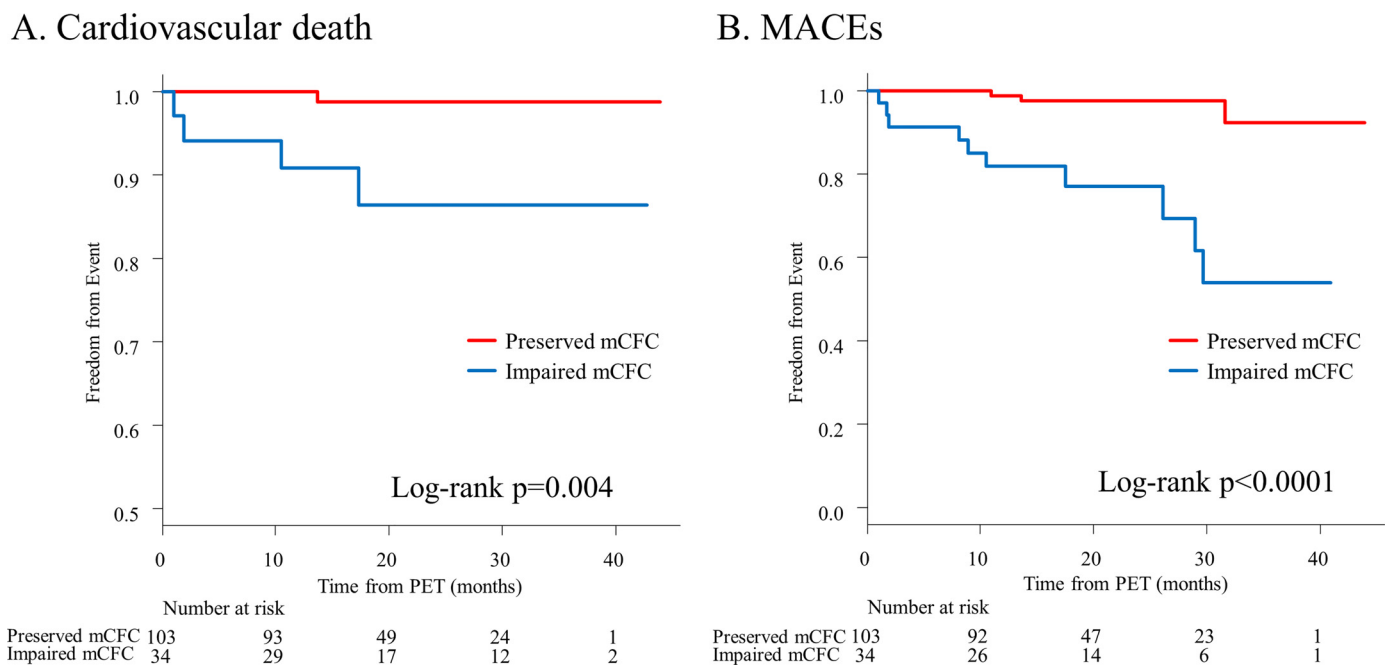

Fig. 4. Kaplan–Meier curves of freedom from cardiovascular death (A) and major adverse cardiovascular events (MACEs) (B) between the patients with impaired and preserved modified coronary flow capacity. MACEs include cardiovascular death, nonfatal myocardial infarction, unplanned hospitalization for any cardiac reasons, and coronary revascularization. mCFC, modified coronary flow capacity; PET, positron emission tomography.

tributed heterogeneously in the myocardium [25]. The patchy distribution of CMD could be explained by transmural heterogeneity, which cannot be assessed with diagnostic imaging. There is also evidence for transmural heterogeneity due to reduced myogenic response in the subendocardium compared with the subepicardium [26]. This may account for the greater vulnerability of the subendocardium to ischemic injury. Since myocardial metabolism is aerobic with high baseline oxygen extraction, there is almost a linear relationship between oxygen demand and coronary blood flow. The local perfusion of the myocardium is highly heterogeneous, with high and low oxygenated areas, even in a normal heart [23]. Therefore, the heterogeneity is more prominent in patients with CMD because heterogeneity results from adaptive processes of microcirculation in response to functional demands. These include fast changes in arteriolar diameter due to changes in smooth muscle tone and slower long-term structural microvascular remodeling with the addition or removal of vessels by angiogenesis or vascular pruning [27]. With these concepts applied, the disagreement between wire-derived regional CFR and cardiovascular magnetic resonance (CMR) imaging-derived global CFR in stable CAD patients may be explained by the heterogeneity of coronary flow [28].

Regarding clinical outcomes, the data on the prognostic value of CMD in patients without obstructive coronary arteries remain scarce. Impaired CFR or CMD has already been shown to predict worse outcomes, irrespective of the cut-off used in recent studies [29], where patients with obstructive CAD were not specifically excluded through CCTA or invasive CAG. In a retrospective study with 79 non-obstructive CAD patients [30], univariable Cox regression analysis showed that CFR <2.0 was a significant predictor of both mortality and MACEs, which is comparable to our observations. Nevertheless, a low sample size that is insufficient for multivariable analysis and a low complete follow-up rate (56%) should be noted as limitations. Additionally, the idea of a regional, rather than global, CFC has been developed recently. Gould et al. have claimed that a severely reduced CFC in only 0.5% of the myocardium contains predictive information [9]. Another unique aspect of clinical events in this study is the significant difference in MACE rates between the two groups, mainly driven by a higher incidence of unplanned hospitalizations for cardiac reasons in the impaired mCFC group. However, a considerable gap in myocardial infarction or revascularization rates was not found between them at reasonably low rates in a relatively short follow-up period. Conversely, unplanned admissions for documented ischemic signs, including typical chest pain attack, ST changes on an electrocardiogram, or newly developed wall motion asynergy on echocardiogram were among the unique manifestations mimicking epicardial coronary ischemic events, often needing CAG. One study has shown that impaired CFR was an independent risk factor for HF development [31], and CFR evaluated by CMR imaging was significantly lower in patients with HF and preserved LVEF (HFpEF) than in hypertensive patients with LV hypertrophy and controls. However, it remains debatable whether the impaired CFR might be a pathophysiological factor for HFpEF or be related to the disease severity.

Study limitations and strengths of our study

First, this study had a relatively small sample size, with few events, and a relatively short follow-up period, although a high complete follow-up rate was achieved. Moreover, we cannot exclude the possibility of recruiting relatively high-risk patients, such as, potentially, those with significant coronary calcium or plaque burden, or undiagnosed silent subendocardial myocardial infarction because myocardial perfusion PET/CT is often applied in Japan when other modalities provide inconclusive findings. This trend may reflect the relatively high event-rate in the study. Second, we derived the global mCFC based on regional CFC analysis, by using the lowest regional MBF estimates for the three main coronary vascular territories. We could not discuss fully whether global mCFC could provide any diagnostic or prognostic advantages compared to other established parameters, such as global CFC, stress MBF, or CFR, although the concept of integrating regional flow evaluation into clinical risk assessment is potentially reasonable. Further studies might be necessary to justify a relevant cut-off for mCFC

classification in justifying CMD diagnosis and its effect on clinical outcomes. Third, according to the stress protocol, we conducted all myocardial perfusion PET examinations with pharmacological stress testing, not exercise stress testing, which can be a more physiologic procedure with the added prognostic value of exercise capacity and electrocardiographic changes. Nevertheless, perfusion PET with exercise stress testing, which is not commercially available in Japan, has a low diagnostic value in patients who cannot achieve an adequate heart rate and blood pressure response due to a noncardiac physical limitation, particularly in the older population such as our study participants. Finally, we should interpret mCFC based on coronary territory with caution because myocardial segments are generally assigned to coronary vascular territories, depending on the most frequent vascular distribution pattern. However, these assumptions may be inaccurate due to individual variability in coronary anatomy [32].

Conclusions

In the 137 patients without obstructive coronary arteries, verified by CCTA or invasive CAG, mCFC integrating regional CFR and regional absolute stress perfusion based on coronary artery territory as a novel quantitative myocardial perfusion measurement utilizing ^{13}N-ammonia PET/CT can be an incremental tool for predicting cardiovascular mortality and MACEs highlighting the high prevalence of CMD defined by mCFC at 25%. Our results showed that mCFC can help cardiologists identify patients who would benefit from specific therapies or lifestyle modifications for preventing future cardiovascular events, and it can help cardiologists understand potential mechanisms of CMD. Future long-term prospective studies are necessary to achieve better classification and to establish potential treatments for patients without obstructive coronary arteries and CMD.

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Declaration of Competing Interest

The other authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2021.09.001.

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