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Original article

Impact of regional functional ischemia on global coronary flow reserve in patients with stable coronary artery disease

Rikuta Hamaya (MD), Tadashi Fukuda (MD), Akinori Sugano (MD), Yoshihisa Kanaji (MD), Masahiro Hada (MD), Yoshinori Kanno (MD), Haruhito Yuki (MD), Masahiro Hoshino (MD), Taishi Yonetsu (MD), Tsunekazu Kakuta (MD, PhD)*

Division of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Ibaraki, Japan

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ABSTRACT

Background: Global coronary flow reserve (g-CFR) provides powerful prognostic information. The relationship between g-CFR and the regional physiological indices of fractional flow reserve (FFR), coronary flow reserve (r-CFR), and the index of microcirculatory resistance remains undetermined. This study aimed to assess the relationship between regional and global physiological indices and determinants of cardiovascular magnetic resonance imaging (CMR)-derived g-CFR.

Methods: A total of 151 patients with single de novo intermediate to stenotic epicardial lesions referred for diagnostic invasive coronary angiography who underwent phase-contrast cine CMR of the coronary sinus (CS) were included. g-CFR was calculated as the ratio of hyperemic and resting CS flow (CSF). Regional and global physiological parameters were compared, and determinants of g-CFR were assessed.

Results: There was a weak linear relationship between FFR and g-CFR ($R^2 = 0.04$, $p = 0.013$), while r-CFR and g-CFR, or combinations of the other regional-global indices were not significantly correlated. When patients were divided into two groups by FFR of 0.80, there were also no significant differences in global physiological indices between the groups (FFR$\leq$0.80 vs. FFR $>$ 0.80; g-CFR: 2.73 vs. 2.61, $p = 0.48$; hyperemic CSF: 3.32 vs. 3.52 ml/min/g, $p = 0.84$). Higher high-sensitivity cardiac troponin-I (hs-cTnI) and higher resting CS flow were independently associated with impaired g-CFR, and the combination could efficiently identify patients with g-CFR $<$ 2.0.

Conclusions: Given weak relationship among global and regional physiological indices, these indices may provide complementary efficacy for prognostication in patients with single-vessel stable coronary artery disease. Combination of hs-cTnI and resting CS flow could estimate g-CFR without pharmacological hyperemic induction.

Introduction

Global coronary flow reserve (g-CFR), calculated as the ratio of hyperemic to rest absolute myocardial blood flow (MBF), is considered as an integrated marker of the hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction on myocardial tissue perfusion [1]. It provides powerful prognostic information in patients with or without obstructive atherosclerotic coronary lesions, frequently using the cut-off value of 2.0 [2,3]. In contrast, fractional flow reserve (FFR) has rapidly gained a consensus as a gold standard of functional stenosis severity specifically for epicardial coronary artery lesions. FFR also holds a prognostic efficacy and a continuous and independent relationship with subsequent outcomes has been demonstrated [4]. A recently reported large, prospective registry study investigated the prognosis of deferred and revascularized lesions based on FFR value [5]. This registry demonstrated that the FFR value was linearly associated with the risk of cardiac events in the deferred lesions. These studies clearly suggested that FFR provides a continuous and independent marker of subsequent future adverse events as modulated by optimal medical therapy or revascularization, not as a dichotomous threshold in decision-making of revascularization. Although both g-CFR and FFR have been reported to be able to provide prognostic information, whether and how regional coronary flow physiology represented

* Corresponding author at: Department of Cardiology, Tsuchiura Kyodo General Hospital, 4-4-1 Otsuno, Tsuchiura city, Ibaraki, 300-0028, Japan.
E-mail address: kaz@joy.email.ne.jp (T. Kakuta).

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by FFR, regional CFR (r-CFR), and the index of microcirculatory resistance (IMR) impacts on global CFR or MBF remains elusive.

The standard tool for noninvasive quantification of absolute hyperemic MBF and flow reserve is positron emission tomography (PET). An alternative promising imaging modality to estimate absolute myocardial flow is cardiovascular magnetic resonance imaging (CMR). Phase-contrast (PC) cine CMR allows noninvasive quantification of coronary sinus blood flow (CSF), without use of ionizing radiation, radioactive tracers, gadolinium, or intravascular catheterization [6,7]. The CS drains approximately 96% of the total MBF and CSF is well correlated with MBF [6]. PC cine CMR of the CS for absolute MBF and coronary flow reserve (CFR) has also been validated against PET [7–9]. This study aimed to evaluate the relationship between regional functional ischemia and global physiological property and to assess the determinants of g-CFR in stable patients with single-vessel disease.

Methods

Study population

We enrolled 159 patients with single-vessel disease showing an intermediate to obstructive stenosis (30–90%) who underwent PC cine CMR study at Tsuchiura Kyodo General Hospital from April 2015 to October 2017. Inclusion criteria were age >20 years and de novo single culprit lesion located at the proximal portion of a native coronary artery. Only patients with non-multivessel disease were included, and when more than two arteries were physiologically investigated due to the intermediate stenosis, vessels with lower FFR value were used in the present analysis. Exclusion criteria were angiographically significant left main disease, previous coronary artery bypass surgery, atrial fibrillation, 2nd or 3rd degree atrioventricular block or previous pacemaker implantation, renal insufficiency with a baseline serum creatinine level >1.5 mg/dl or on dialysis, acute coronary syndrome, cardiogenic shock, congestive heart failure, or a totally occluded culprit lesion. Patients with an impaired systolic ejection fraction (<40%) or severe valvular disease were also excluded. This study complied with the Declaration of Helsinki for investigation in human beings, and was approved by the institutional review board, and all patients provided written informed consent before coronary angiography (CAG) and CMR. Prompt optimal medial therapy was initiated in all patients after enrollment.

Biochemical measurement analysis

Baseline high-sensitivity cardiac troponin-I (hs-cTnI) and N-terminal pro brain natriuretic peptide (NT-proBNP) levels were determined from blood samples obtained before CAG. Sampling was conducted in the morning in clinically stable patients in a fasting state, to reduce diurnal variations of the biomarkers [10]. Hs-cTnI was measured using the ARCHITECT $i2000_{SR}$ STAT hs-cTnI assay (Abbott Laboratories, North Chicago, IL, USA). NT-proBNP levels were determined using the Elecsys proBNP assay (Roche Diagnostics, Basel, Switzerland). Hs-cTnI values were available in 138 out of 151 patients.

Cardiac catheterization and intracoronary physiological studies

Each patient underwent standard CAG via a radial artery by using a 5-French system. No ad hoc percutaneous coronary intervention (PCI) was performed before or after physiological analyses. Physiological indices were measured using a pressure–temperature sensor-tipped wire as described previously [11]. After calibration, a coronary 0.014-inch PressureWire™ (St. Jude Medical, St. Paul, MN, USA) was used to measure the intracoronary pressure distal to the coronary stenosis. Subsequently, 3 ml of room-temperature saline was administered three times, and the baseline mean transit time (Tmn) was determined. For both measurements, hyperemia was induced by an intravenous infusion of adenosine 5′-triphosphate (ATP, 160 $\mu g\,kg^{-1}\,min^{-1}$). FFR was calculated as the ratio of mean distal-to-aortic coronary pressure (Pd/Pa) during hyperemia. CFR was defined as the resting Tmn divided by the hyperemic Tmn values. The index of microvascular resistance (IMR) was defined as $Pd \times Tmn$ or $Pa \times Tmn \times ([1.35 \times Pd/Pa] - 0.32)$ during hyperemia [12].

CMR examination

CMR acquisition and Cine-CMR

CMR image acquisition was performed at median 3 days (range 1–15 days) after CAG. Images were acquired on a 1.5 Tesla scanner (Philips Achieva; Philips Medical Systems, Best, the Netherlands) with 32-channel cardiac coils. Cardiac gating and heart rate were recorded with a vecto-cardiogram device. Blood pressure was monitored throughout the protocol. Cine-CMR was performed using a retrospectively gated steady-state free precession sequence. Twelve short axis slices of left ventricle (LV) were acquired from apex to base. Cine-CMR parameters were: repetition time 4.1 ms, echo time 1.4 ms, slice thickness 6 mm, flip angle 55°, field of view $350 \times 350\,mm^2$, matrix size 128×128, and 20 phases per cardiac cycle. LV mass and volumes were calculated from Simpson's rule using CMR data [8].

Coronary sinus flow measurement

The CS was identified in the atrio-ventricular groove using basal slices of the short-axis stack. The plane for flow measurement by PC cine CMR was perpendicular to the coronary sinus at approximately 1–2 cm from the ostium [8,13]. Velocity-encoded images were acquired with retrospective electrocardiogram (ECG) gating during approximately 15-s breath holds. Imaging parameters were: repetition time 7.3 ms, echo time 4.4 ms, flip angle 10°, field of view $250 \times 250\,mm^2$, acquisition matrix 128×128, 20 phases per cardiac cycle, encoding 50 cm/s, and slice thickness 6 mm. PC cine CMR of CS measurements were performed during hyperemia and at rest. Stable hyperemia was induced by intravenous ATP ($160\,\mu g\,kg^{-1}\,min^{-1}$). All patients were strictly instructed to refrain from caffeinated beverages for more than 24 h before CMR examinations. Total CMR examination time for standard cine CMR and CSF measurement was approximately 15 min.

PC cine CMR image analysis

CSF quantitative analysis by PC cine CMR was performed using proprietary software (Philips View Forum; Philips Medical Systems) in a blinded fashion by 2 observers. The CS contour was traced on the magnitude images throughout the cardiac cycle. CSF quantification was calculated by integrating the flow rates from each cardiac cycle and multiplying by mean heart rate during acquisition. We corrected resting CSF by resting rate pressure product (RPP) using the following formula, for resting MBF linearly correlates with RPP and hyperemic MBF does not [14]:

RPP = systolic blood pressure (mmHg) × heart rate (beats/min); CSF (ml/min/g) = CSF (ml/min)/LV mass (g); and corrected CSF at rest (ml/min/g) = CSF at rest (mL/min/g)/RPP × 10,000. Global CFR (myocardial perfusion reserve) was calculated by CSF during hyperemia/CSF at rest. Coronary vascular resistance (CVR) was defined as mean arterial blood pressure (mmHg)/corrected CSF (ml/min) during hyperemia.

Statistical analysis

Categorical data, expressed as frequencies and percentages, were compared using the χ^2 or Fisher's exact test, as appropriate. Continuous variables were expressed as the median (interquartile range [IQR]) and compared using Student's *t*-test or Mann–Whitney *U* test for variables with a normal or non-normal distribution, respectively. Kruskal–Wallis test was applied in comparisons of three or more groups. Correlations between the two parameters were evaluated by linear regression. Receiver operating characteristic (ROC) curves were analyzed to assess the best cut-off values of clinical and physiological indices to predict g-CFR < 2.0. The optimal cut-off was calculated using the Youden index. Univariate associations with g-CFR as a continuous value or g-CFR < 2.0 were determined by linear or binary logistic regression analyses, respectively. Variables showing values of $p < 0.05$ on univariate models were incorporated into multivariate logistic regression models. A two-sided *p*-value < 0.05 indicated statistical significance.

Results

Patient characteristics and physiological findings

Among 159 patients, 2 patients with claustrophobia, 1 patient with intolerable symptoms during ATP infusion, and 5 patients with suboptimal pressure tracing and/or unsatisfactory CMR imaging quality were excluded from the final analysis. Thus, final analysis was performed in 151 patients with the complete set of intracoronary invasive physiological indices and CMR findings. Fig. 1 shows a representative case of CSF measurements by PC cine CMR. There were no significant complications related to CMR examinations.

The patient baseline characteristics and physiological indices are summarized in Table 1. In total cohort, FFR, regional CFR, and IMR values were 0.74 (0.65–0.80), 2.29 (1.52–3.43), and 21.6 (12.8–37.4), respectively. G-CFR, CSF at rest, CSF at hyperemia, and CVR were 2.72 (1.90–3.70), 1.30 (0.88–1.75) ml/min/g, 3.37 (2.33–4.29) ml/min/g, and 0.30 (0.23–0.40) mmHg min/ml, respectively. Angiographic stenosis severity showed no significant relationship with global indices such as g-CFR and hyperemic CSF ($p = 0.56$ and $p = 0.28$, respectively). Fig. 2 shows the relationships between regional and global physiological indices. FFR had significant albeit weak linear relationships with g-CFR ($R^2 = 0.041$, $p = 0.013$), whereas no significant relationship was found between r-CFR and g-CFR ($R^2 = 0.026$, $p = 0.075$). Both regional IMR and global CVR distributed in the wide ranges, and no significant relationship was detected between IMR and hyperemic CVR ($R^2 = 0.01$, $p = 0.30$).

Physiological property in patients grouped by FFR or global CFR

No significant differences were found in regional physiological factors between patients with g-CFR < 2.0 and g-CFR ≥ 2.0

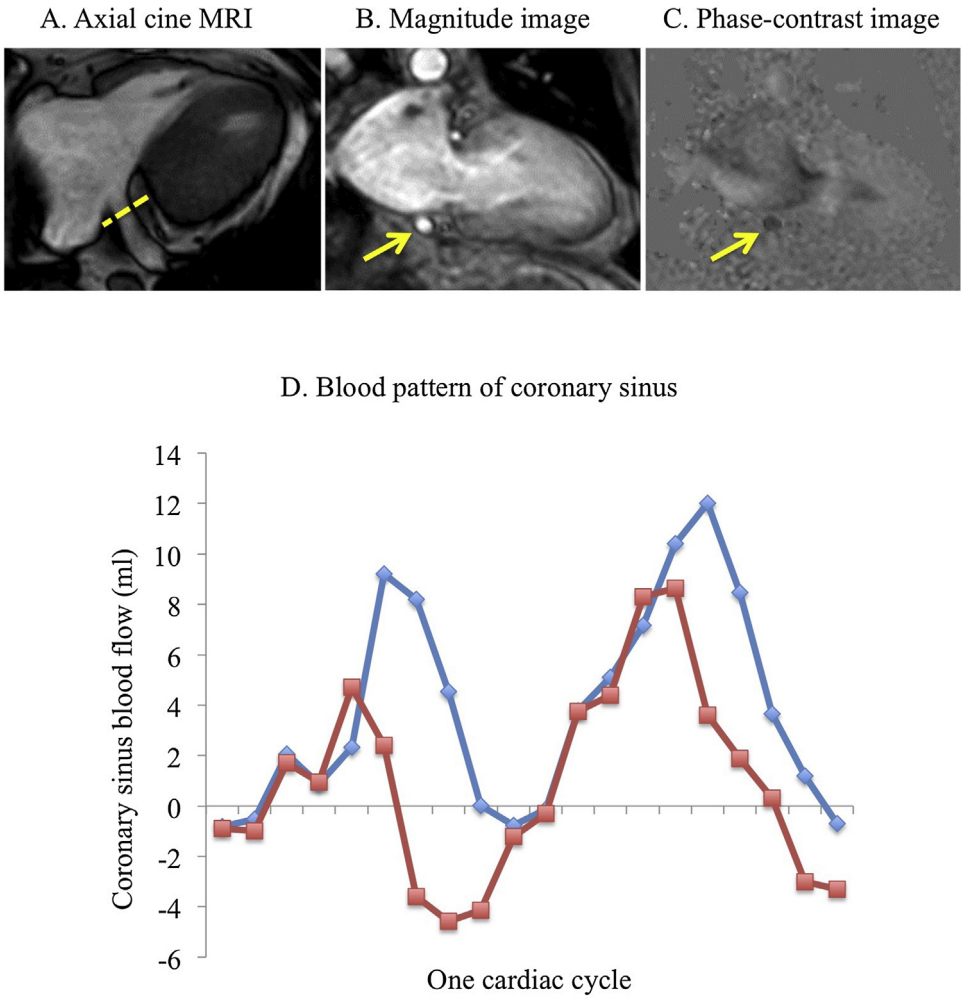

Fig. 1. Representative case of phase-contrast cine cardiovascular magnetic resonance measurement of the coronary sinus. Axial cine magnetic resonance imaging (MRI) (A), magnitude image (B), and phase-contrast image (C) of the coronary sinus. Arrows indicate blood flow in the coronary sinus. Curves of coronary sinus blood flow (CSF) in one cardiac cycle (D) Blue line shows CSF at resting state and red line indicates CSF during adenosine triphosphate infusion.

Table 1
Baseline characteristics and physiological indices.

	Total (n = 151)	g-CFR < 2.0 (n = 45)	g-CFR ≥ 2.0 (n = 106)	p
Demographics				
Age, years	66.4 ± 9.9	68.2 ± 9.3	65.4 ± 10.0	0.94
Male	108 (78.3)	33 (84.6)	75 (75.8)	0.087
Body mass index (kg/m^2)	24.5 (22.7–27.0)	24.0 (22.4–27.0)	24.9 (22.7–26.9)	0.29
Hypertension	109 (72.2)	33 (73.3)	76 (71.7)	0.84
Dyslipidemia	88 (58.3)	30 (66.7)	58 (54.7)	0.17
Diabetes mellitus	62 (41.1)	17 (37.8)	45 (42.5)	0.59
Smoking	34 (22.5)	10 (22.2)	24 (22.6)	0.96
Family history	19 (12.6)	9 (20.0)	10 (9.4)	0.084
Prior PCI	46 (30.7)	14 (31.1)	32 (30.5)	0.94
Prior MI	39 (25.8)	15 (33.3)	24 (22.6)	0.176
Medication				
Aspirin	133 (88.1)	44 (97.8)	89 (84)	0.007
Statin	119 (78.8)	41 (91.1)	78 (73.6)	0.010
Angiotensin inhibitors	97 (64.2)	33 (73.3)	64 (60.4)	0.12
Calcium blocker	68 (45)	20 (44.4)	48 (45.3)	0.93
Beta blocker	73 (48.3)	26 (57.8)	47 (44.3)	0.13
Angiographic data				
Minimum lumen diameter (mm)	1.08 (0.86–1.35)	1.11 (0.79–1.31)	1.06 (0.90–1.43)	0.46
Reference diameter (mm)	2.59 (2.19–3.05)	2.51 (2.19–2.87)	2.67 (2.19–3.10)	0.26
Diameter stenosis (%)	57.4 (48.4–64.9)	55.6 (47.5–68.3)	58.0 (49.5–64.8)	0.63
Lesion length (mm)	11.2 (8.1–16.2)	11.7 (7.3–15.6)	11.0 (8.4–16.3)	0.85
Interrogated location				0.079
RCA	31 (20.5)	14 (31.1)	17 (16.0)	
LAD	112 (74.2)	30 (66.7)	82 (77.4)	
LCx	8 (5.3)	1 (2.2)	7 (6.6)	
Biomarkers				
C-reactive protein (mg/dl)	0.07 (0.03–0.16)	0.09 (0.03–0.17)	0.07 (0.03–0.15)	0.72
Estimated GFR (ml/min/1.73 m^2)	69.0 (59.5–80.5)	69.4 (57.4–76.2)	68.6 (61.1–83.3)	0.25
Hs-cTnI (ng/l)	4 (2–7)	6 (3–10)	3 (2–6)	0.006
NT-proBNP (ng/l)	82 (40–210)	156 (52–482)	73 (38–183)	0.010
Hemodynamic data				
Systolic BP (mmHg)	141.3 ± 19.0	135.9 ± 18.6	143.5 ± 18.8	0.012
Diastolic BP (mmHg)	81.4 ± 10.4	78.1 ± 9.7	82.8 ± 10.5	0.004
Heart rate (beats/min)	64.9 ± 9.3	64.3 ± 10.1	65.1 ± 9.0	0.32
LVEDV (ml)	125.2 (110.0–150.0)	125.5 (110.8–145.9)	125.0 (108.9–158.8)	0.48
LVESV (ml)	51.0 (40.7–65.9)	51.1 (41.3–63.9)	50.7 (38.8–77.7)	0.86
LVEF (%)	58.6 (53.3–63.4)	58.5 (50.5–66.0)	58.8 (55.0–62.7)	0.87
LV mass (g)	95.0 (81.3–108.6)	97.5 (85.8–113.1)	94.9 (79.5–108.5)	0.30
Regional physiology				
FFR	0.74 (0.65–0.80)	0.73 (0.58–0.80)	0.74 (0.67–0.80)	0.38
r-CFR	2.29 (1.52–3.43)	2.14 (1.42–3.46)	2.35 (1.52–3.41)	0.39
IMR	21.6 (12.8–37.4)	21.5 (12.6–37.4)	21.8 (12.8–37.5)	0.95
IMR (corrected)	19.7 (12.2–30.1)	16.8 (11.3–28.0)	20.0 (12.2–32.3)	0.64
Global physiology				
Resting CSF (ml/min/g)	1.30 (0.88–1.75)	1.68 (1.26–2.20)	1.15 (0.78–1.56)	<0.001
Hyperemic CSF (ml/min/g)	3.37 (2.33–4.29)	2.34 (1.68–3.43)	3.64 (2.95–4.57)	<0.001
g-CFR	2.72 (1.90–3.70)	1.41 (1.14–1.87)	3.02 (2.61–4.40)	<0.001
CVR (mmHg/ml/min)	0.30 (0.23–0.40)	0.40 (0.26–0.59)	0.27 (0.21–0.35)	<0.001

Variables are expressed as n (%), median (interquartile range), or mean ± standard deviation. g-CFR, global coronary flow reserve; PCI, percutaneous coronary intervention; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; GFR, glomerular filtration rate; hs-cTnI, high-sensitivity cardiac troponin-I; NT-proBNP, N-terminal pro brain natriuretic peptide; BP, blood pressure; LV, left ventricular; EDV end-diastolic volume; ESV; end-systolic volume; EF, ejection fraction; FFR, fractional flow reserve; r-CFR, regional coronary flow reserve; IMR, index of microvascular resistance; CSF, coronary sinus flow; CVR, coronary vascular resistance.

(g-CFR < 2.0 vs. g-CFR ≥ 2.0; FFR: 0.73 vs. 0.74, p = 0.38; r-CFR: 2.14 vs. 2.35, p = 0.39; IMR: 21.5 vs. 21.8, p = 0.95, respectively) (Table 1). When patients were divided into two groups by FFR of 0.80, there were also no significant differences in global physiological indices between the groups (FFR ≤0.80 vs. FFR >0.80; g-CFR: 2.73 vs. 2.61, p = 0.48; hyperemic CSF: 3.32 vs. 3.52, p = 0.84; CVR: 0.30 vs. 0.30, p = 0.98, respectively). No difference was documented in prevalence of g-CFR <2.0 between patients with FFR ≤0.80 and FFR >0.80 (29.0% vs. 32.4%, p = 0.69).

Determinants of global CFR

In 138 patients (91.4%) whose hs-cTnI levels were available, independent predictors for g-CFR <2.0 or numerical g-CFR values as a continuous variable were identified by univariate and multivariate logistic or linear regression analyses (Table 2). In each model, resting CSF and hs-cTnI were the independent predictors of g-CFR.

ROC curve analysis showed that the best cut-off values of resting CSF and hs-cTnI levels for prediction of g-CFR <2.0 were

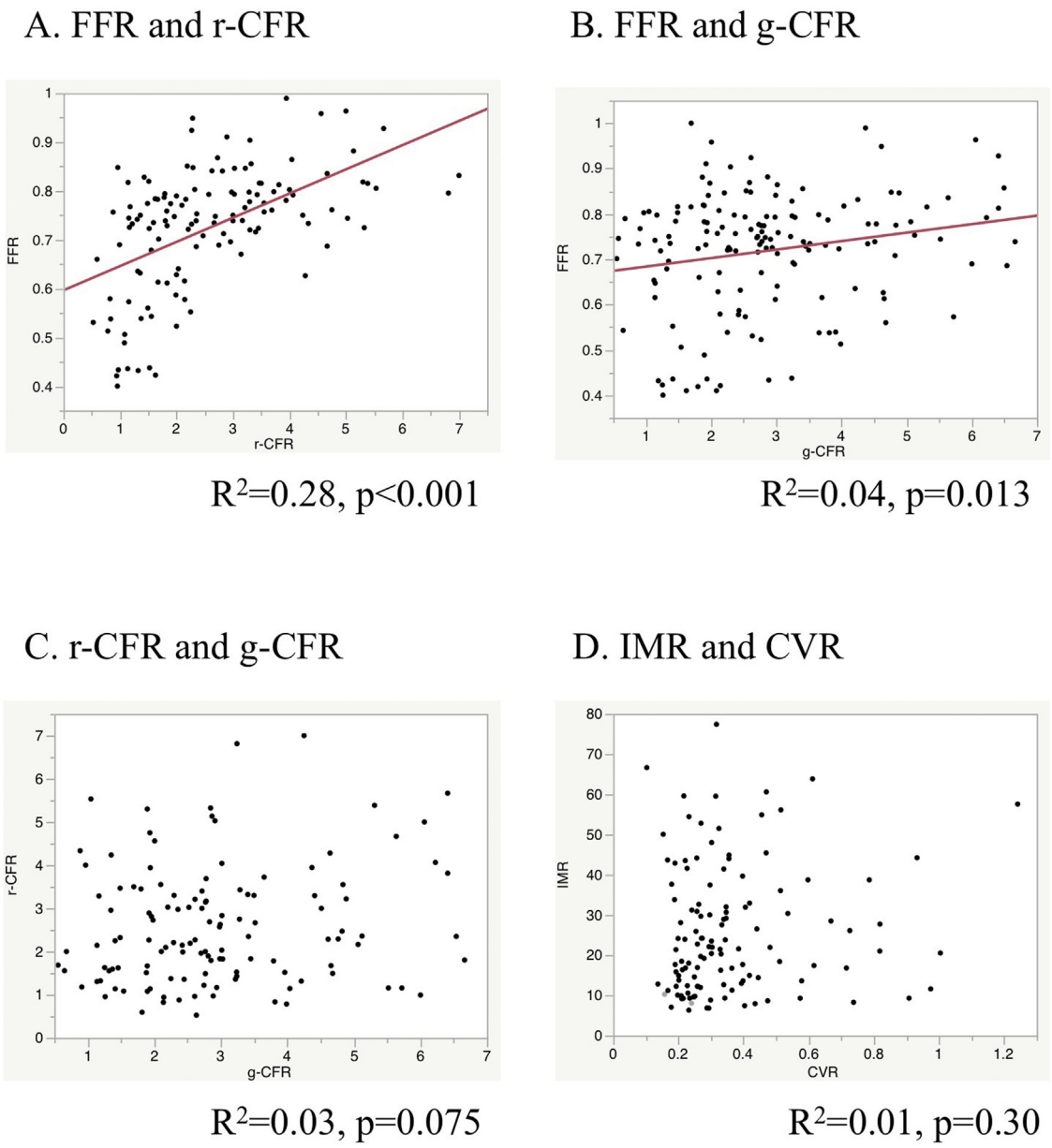

Fig. 2. Correlation between regional and global physiological indices. Linear correlation between fractional flow reserve (FFR) and regional coronary flow reserve (r-CFR) (A), FFR and global CFR (g-CFR) (B), r-CFR and g-CFR (C), and index of microvascular resistance (IMR) and coronary vascular resistance (CVR) (D). Regional FFR and CFR were significantly correlated (R^2 = 0.28, $p < 0.001$). The correlation between FFR and g-CFR was statistically significant albeit weak (R^2 = 0.04, p = 0.013), and there were no linear relationships between r-CFR and g-CFR or IMR and CVR.

1.23 ml/min/g and 7 ng/l, respectively (Table 3). Using these cut-offs, resting CSF was characterized by high sensitivity (82.2%) whereas hs-cTnI had high specificity (76.8%). When patients were divided according to the combination of resting CSF and hs-cTnI, the levels of g-CFR were efficiently stratified (Fig. 3). g-CFR < 2.0 was documented in 57.1% (16/28) patients with high resting CSF and high hs-cTnI, while the prevalence was 6.4% (3/47) in patients with low resting CSF and low hs-cTnI.

Discussion

To our knowledge, this is the first study to report global MBF or flow reserve obtained by PC cine CMR of the CS in relation to regional physiological parameters in stable patients with intermediate to severely stenotic single-vessel coronary artery disease. The principal findings are: (1) a statistically significant albeit weak linear relationship was detected between FFR and g-CFR, whereas no difference was found in g-CFR between the two groups divided by FFR = 0.80; (2) no significant relationship was found between regional hyperemic microvascular resistance and global hyperemic vascular resistance or between regional and global CFR; (3) g-CFR < 2.0 was independently associated with high resting CSF and high hs-cTnI, and these combinations could efficiently identify patients with g-CFR <2.0.

Using PC cine CMR of the CS, our data suggest that the absolute global MBF or flow reserve was not strongly influenced by the regional functional ischemia represented by FFR or r-CFR. Given that g-CFR provides powerful prognostic information in patients with or without obstructive atherosclerotic coronary lesions, our results suggest that g-CFR can provide prognostic information independently of and complementarily with FFR or regional CFR [2,3].

Table 2
Logistic regression models for predicting global CFR.

A. Models for predicting global CFR < 2.0						
	Univariate models			Multivariate model		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Resting CSF	4.189	2.292, 8.317	<0.001	5.270	2.620, 11.829	<0.001
Hs-cTnI	1.084	1.024, 1.154	0.006	1.078	1.006, 1.159	0.033
NT-proBNP	1.013	1.005, 1.023	<0.001	1.007	0.996, 1.020	0.22
B. Models for predicting global CFR						
	Univariate models			Multivariate model		
	Estimate	95% CI	*p*	Estimate	95% CI	*p*
Resting CSF	−1.128	−1.410, −0.846	<0.001	−1.097	−1.383, −0.812	<0.001
Hs-cTnI	−0.057	−0.095, 0.019	0.004	−0.046	−0.081, −0.012	0.009
NT-proBNP	−0.007	−0.012, −0.002	0.003	−0.002	−0.007, 0.003	0.47
FFR	0.021	0.003, 0.039	0.020	0.003	−0.013, 0.019	0.73

These analyses were performed in 138 patients whose hs-cTnI levels were available. Resting CSF: per ml/min/g, hs-cTnI: per ng/l, NT-proBNP: per 10 mg/l, FFR: per 0.01 unit. Factors showing $p < 0.05$ in univariate analyses were incorporated into multivariate models. CI, confidence interval; CFR, coronary flow reserve; CSF, coronary sinus flow; hs-cTnI, high-sensitivity cardiac troponin-I; NT-proBNP, N-terminal pro brain natriuretic peptide; FFR, fractional flow reserve.

Our data showed that higher resting CSF was an independent predictor of g-CFR <2.0. This is in line with the report by Kato et al. in which lower g-CFR obtained by PC cine CMR of the CS predicted the occurrence of major adverse cardiac events [13]. Of note, the difference in g-CFR between patients with and without major adverse cardiac events in their study seemed to be attributed to higher resting CSF in patients with major adverse cardiovascular events (MACE), not the hyperemic CSF. Our results and those of Kato et al. suggest that resting coronary flow might be an important factor for low g-CFR and for MACE, although recent studies consistently showed that hyperemic MBF itself may be superior to g-CFR in detection of functionally significant epicardial stenoses [4,15]. Further study is needed to validate that resting absolute coronary blood flow can identify high-risk patients for future adverse events in patients with stable coronary artery disease. This is worth further investigating since resting CSF by using PC cine CMR can be obtained in less than 10 min without radiation, contrast, and pharmacological vasodilation.

Another potentially intriguing finding is that no significant relationship was detected between hyperemic regional microvas-

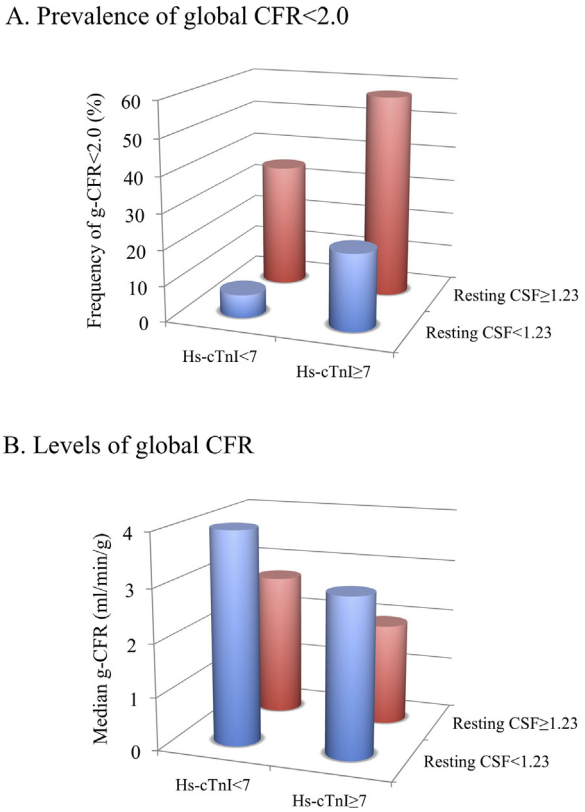

Fig. 3. Global coronary flow reserve (g-CFR) stratification by the combination of high-sensitivity cardiac troponin-I (hs-cTnI) and resting coronary sinus flow (CSF). Frequencies (%) (A) and median values (ml/min/g) (B) of g-CFR in patients divided according to the combination of hs-cTnI and resting CSF. The combination could efficiently stratify the levels of g-CFR ($p < 0.001$). g-CFR <2.0 was determined in 57.1% (16/28) patients with high resting CSF and high hs-cTnI, while the frequency was 6.4% (3/47) in patients with low resting CSF and low hs-cTnI.

Table 3
Predictive accuracy for global coronary flow reserve <2.0.

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Resting CSF	0.74	1.23 ml/min/g	82.2	55.7	44	88.1	63.6
Hyperemic CSF	0.76	2.87 ml/min/g	66.7	76.4	54.5	84.4	73.5
CVR	0.72	0.39 mmHg/ml/min	57.8	82.9	59.1	82.1	75.3
NT-proBNP	0.63	155 ng/l	53.3	72.4	45.3	78.4	66.7
Hs-cTnI	0.65	7 ng/l	48.7	76.8	45.2	79.2	68.8

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; CSF, coronary sinus flow; CVR, coronary vascular resistance; NT-proBNP, N-terminal pro brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin-I.

cular resistance distal to the epicardial lesions and global coronary vascular resistance in the present study population, although methods of measurement were different and two measures were obtained at different time points (median, 3 days). Since current noninvasive methods for the detection of ischemia depends on the assumption of spatial homogeneity in the behavior of hyperemic microvascular resistance, higher regional microvascular resistance is expected to be associated with higher global vascular resistance. Chareonthaitawee et al. demonstrated that there was a large variability of absolute MBF obtained by PET both between and within healthy volunteers [16]. Our findings are in accordance with their study and might suggest the presence of flow heterogeneity in different territories, likely relevant to the spatial hyperemic heterogeneous microvascular resistance.

A recent study demonstrated relationship between PET-derived global CFR and cTn level measured using conventional assays and these independent contributions to MACE prediction in patients without overt coronary artery disease [17]. In line with this study, we demonstrated that impaired CFR was independently associated with minimally elevated troponin measured by a high-sensitive assay. Elevated cTn levels are associated with increased incidence of cardiovascular death and myocardial infarction in patients with stable coronary artery disease, indicating a potential interaction between decreased vasomotor function and subclinical myocardial injury in the course of microvascular dysfunction, diastolic dysfunction, and heart failure [18,19]. In the present study, hs-cTnI independently predicted g-CFR <2.0 with the best cut-off levels of 7 ng/l. Furthermore, the combination of resting CSF and hs-cTnI could efficiently stratify global CFR and identify g-CFR <2.0. Prognostic information of hs-cTnI and resting CFR should be further investigated to elucidate the presence of collinearity or complementary prognostic efficacy. The use of absolute global MBF and CVR measurement integrated with regional physiological assessment may help to identify differentiated patterns of ischemic heart disease with epicardial and microvascular dysfunction, and thus improve decisions on revascularization treatment for individual lesions.

Study limitations

This study included a relatively small number of subjects from a single center. Further, we prospectively enrolled patients with stable angina pectoris based on symptoms and non-invasive test results, and who were referred to our catheter laboratory for diagnosis or treatment. The rigorous exclusion criteria for potential CSF measurement confounders or difficulties also limited the number of the patients in our study, and may have caused selection bias. Further, patients were enrolled with a knowledge of CMR contraindication and importance of ECG-gating. This may cause further selection bias as there were no patients with metallic device implants, bronchospasm, atrial fibrillation, or atrioventricular block. The dose of ATP (160 $\mu g\,kg^{-1}\,min^{-1}$) could not be enough to induce maximum hyperemia. Although our measurement reliability was acceptable for assessing absolute MBF, the current spatial resolution of CMR may have caused partial volume errors, resulting in measurement errors. As there are significant individual variations in MBF under different hemodynamic states, a larger study population is required to confirm our findings. Because of the limited sample size, we could not perform extensive subgroup analyses. The large variation in the presence of epicardial coronary disease and microvascular dysfunction prevented us from a definitive analysis of microvascular and epicardial impairments in our small study population. Nevertheless, our results were consistent with prior PET studies, indicating that MBF was reduced because of microvascular dysfunction, even in territories without significant epicardial stenosis. Finally, we performed PC cine CMR examination at a median 3 days after CAG. Further studies are required using a different CMR time window and to assess the heterogeneity of MBF relevant to age, gender, and other risk factors.

Conclusions

No significant correlation was found between regional and global physiological indices except for a significant albeit weak linear relationship between FFR and global CFR. Impaired global CFR levels were independently associated with high absolute resting CSF and high hs-cTnI, and the combination could efficiently identify patients with global CFR <2.0.

Conflict of interest

None.

Acknowledgments

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