ORIGINAL RESEARCH

Prevalence and Clinical Significance of Discordant Changes in Fractional and Coronary Flow Reserve After Elective Percutaneous Coronary Intervention

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***Background*—**Fractional flow reserve (FFR) and coronary flow reserve (CFR) are well-validated physiological indices; however, changes in FFR and CFR after percutaneous coronary intervention (PCI) remain elusive. We sought to evaluate these changes and to investigate whether physiological indices predict cardiac event-free survival after PCI.

***Methods and Results*—**Physiological assessment of 220 stenoses from 220 patients was performed before and after PCI. The changes in FFR and CFR were studied, and factors associated with CFR change were investigated. Follow-up data were collected to determine the predictor of cardiac events. CFR increase was found in 158 (71.8%) territories, and 62 (28.2%) presented a decrease, whereas FFR increased in all 220 (100%) territories. Pre- and post-PCI percentage diameter stenoses were 57.7±11.2% and 7.48±4.79%, respectively. Post-PCI CFR increase was associated with pre-PCI indices including low FFR, low CFR and high microvascular resistance, and post-PCI hyperemic coronary flow increase. Post-PCI CFR decrease was not associated with significant post-PCI hyperemic coronary flow increase. At a median follow-up of 24.3 months, adverse event–free survival was significantly worse in patients with lower pre-PCI CFR (log-rank test λ^2=7.26; *P*=0.007). Cox proportional hazards analysis showed that lower pre-PCI CFR (hazard ratio 0.73; 95% CI 0.55–0.97; *P*=0.028) was an independent predictor of adverse cardiovascular events after PCI.

***Conclusions*—**CFR decrease after PCI was not uncommon, and discordant change in FFR and CFR was associated with high pre-PCI CFR, low pre-PCI microvascular resistance, and no significant post-PCI hyperemic coronary flow increase. Pre-PCI CFR, not post-PCI physiological indices, may help identify patients who require adjunctive management strategy after successful PCI. **(*J Am Heart Assoc*. 2016;5:e004400 doi: 10.1161/JAHA.116.004400)**

Key Words: coronary artery disease • coronary flow reserve • fractional flow reserve • microvascular dysfunction • microvascular resistance • percutaneous coronary intervention

Fractional flow reserve (FFR) is the standard in decision making for revascularization in the catheter laboratory and has become a part of the clinical guidelines for assessing the physiological significance of epicardial coronary stenosis based on a sound concept and randomized clinical trials.[1–4] A recent study also suggested that FFR measured after percutaneous coronary intervention (PCI) has prognostic value, with an inverse relationship to subsequent clinical events.[5] The purpose of PCI is to increase coronary flow by modifying epicardial stenosis, and FFR-guided PCI results in better outcome compared with angiographic guidance,[2,3] suggesting that FFR-guided PCI may benefit from hyperemic coronary flow increase. Recently, recognition of the significant relevance of myocardial blood flow with adverse clinical outcome urges a comprehensive approach to ischemic heart disease with incorporation of coronary flow impairment and microvascular resistance as well as FFR.[6–10] Given that PCI is optimally performed without significant complications, post-PCI FFR and CFR may similarly increase with less influence from epicardial stenosis, provided that microvascular resistance is minimized and constant before and after PCI and that basal coronary flow is not significantly different before and after PCI.[11,12] Coronary flow reserve (CFR) is a well-validated index that can assess coronary flow impairment originating from epicardial stenosis, diffuse coronary disease, or

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microvascular dysfunction.[13,14] Furthermore, CFR has been shown to provide a substantial ability to stratify the risk for cardiac events.[7,15,16] PCI increases FFR value; however, post-PCI CFR change and its relationship with FFR improvement remains elusive. The purpose of this study is to investigate the relationship between FFR and CFR changes after successful PCI. We hypothesized that FFR increase may not necessarily result in CFR increase after PCI and that pre-PCI physiological indices might predict concordant improvement in FFR and CFR. Furthermore, we assessed whether pre-PCI physiological indices may predict event-free survival after PCI.

Methods

Study Population

This study prospectively but nonconsecutively investigated physiological data collected from patients scheduled for elective PCI who had stable coronary artery disease and who met the following criteria at Tsuchiura Kyodo General Hospital from January 2012 to July 2015: age >20 years and detection of an identifiable, de novo, single-culprit lesion located at the proximal portion of a native coronary artery. Patients were also included if they had stable angina pectoris or nonculprit lesions in other vessels after previous acute coronary syndrome (>2 weeks after PCI) culprit-lesion treatment. Stable angina pectoris was defined as no change in the frequency, duration, or intensity of anginal symptoms within 6 weeks before PCI. The target lesion was identified by a combination of coronary angiograms, ECG findings, angiographic lesion morphology, scintigraphic findings, perfusion cardiac magnetic resonance imaging, or FFR measurements. All included patients had angina, documented myocardial ischemia, or both. All patients underwent 2-dimensional echocardiography before enrollment. The exclusion criteria were angiographically significant left main disease, previous coronary artery bypass surgery, dialysis, renal insufficiency with a baseline serum creatinine level >1.7 mg/dL, culprit lesion of acute coronary syndrome, cardiogenic shock, congestive heart failure, a totally occluded culprit lesion, and difficult culprit-lesion identification. Patients with severely impaired systolic ejection fraction (<25%) were also excluded from the study. Of 242 patients who were initially included, 8 were excluded because of failure of the guidewire (St. Jude Medical) in crossing the lesion or unsatisfactory quality of physiological data tracing either before or immediately after PCI. In the present study, all patients showed FFR ≤0.80. All patients had antiplatelet treatment with aspirin (200 mg/day) and clopidogrel (75 mg/day; loading dose 300 mg) ≥24 hours before cardiac catheterization. The study protocol was approved by the institutional review board, and all patients provided written informed consent before PCI.

Cardiac Catheterization

Each patient initially underwent standard selective coronary angiography for assessment of coronary anatomy via the radial artery using a 6F system. Coronary angiograms were analyzed quantitatively using a CMS-MEDIS system (Medis Medical Imaging Systems) to measure lesion length, minimum lumen diameter, reference lumen diameter, and percentage diameter stenosis at the target lesion. All patients received a bolus injection of heparin (5000 IU) before the procedure and an additional bolus injection of 2000 IU every hour if the procedure required >1 hour. An intracoronary bolus injection of nitroglycerin (0.2 mg) was administered at the start of the procedure and repeated every 30 minutes. All patients underwent coronary stent implantation (drug-eluting, 92%; bare metal stent, 8%) with predilatation. The type of stent was selected at the operator's discretion, and the strategy was determined by the interventionist. To avoid aggressive stent expansion, online quantitative coronary angiography was used to help determine the proper stent size. Successful PCI was defined as <20% residual stenosis with thrombolysis in myocardial infarction grade 3 flow. Decisions about further treatment and medication during follow-up were left to the discretion of the treating cardiologist.

Intracoronary Physiological Indices

Before and after elective stenting, FFR, CFR, mean transit time (Tmn), and the index of microcirculatory resistance (IMR) were determined using a RadiAnalyzer Xpress instrument with a Certus coronary pressure wire (St. Jude Medical), as described previously.[17–19] FFR was calculated as the ratio of distal coronary pressure to proximal coronary pressure at stable hyperemia induced by intravenous adenosine (140 μg/kg per minute through a central vein). CFR was measured simultaneously with FFR using the thermodilution method, as described elsewhere.[19] Resting and hyperemic thermodilution curves (3 times each) were obtained, and CFR was calculated as the ratio of basal Tmn divided by hyperemic Tmn. IMR was calculated as the product of mean distal coronary pressure during stable hyperemia and Tmn.[18] With significant epicardial stenosis and/or collateral flow, accurate determination of IMR requires measurement of coronary wedge pressure.[20] Consequently, IMR has been reported to be calculated as $IMR=P_a\times Tmn\times([P_d-P_w]/[P_a-P_w])$, in which P_d is distal coronary pressure, P_a is proximal coronary pressure, and P_w is coronary wedge pressure. In the present study, both corrected pre-PCI IMR values using wedge pressure during predilatation ballooning and uncorrected pre-PCI IMR values were presented and studied. Because the inverse value of mean hyperemic Tmn has been validated to correlate with absolute coronary blood flow,[10,19,21] the shorter hyperemic Tmn suggests higher coronary flow, and the increase in

coronary flow after PCI may be presented by a positive value calculated by the formula of pre-PCI Tmn minus post-PCI Tmn within each participant. In the present study, Tmn was considered a surrogate of coronary flow.

Data Analysis

Data were analyzed as serial measurements before and after PCI. The relationships between FFR and CFR before and after PCI were studied. We further investigated for a significant relationship between the changes in FFR and CFR. To investigate the details of serial change in CFR, lesions were divided into 2 groups based on whether post-PCI CFR increased or decreased in comparison with pre-PCI CFR, and patient characteristics, angiographic data, and intracoronary physiological indices were compared between these 2 groups. Because FFR increase was obtained in all territories in the present cohort, territories with CFR increase indicated concordant change of FFR/CFR after PCI, and those showing CFR decrease indicated discordant FFR/CFR change. We further evaluated the determinant factors of absolute CFR change after PCI (pre-PCI minus post-PCI CFR). Long-term clinical follow-up data were collected. The cumulative incidence of adverse cardiac events (cardiac death, myocardial infarction, revascularization of any vessels, hospitalization for heart failure, clinically significant arrhythmia, and stroke) was followed.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp) and EZR version 1.32 (Saitama Medical Center, Jichi Medical University). Categorical data are expressed as absolute frequencies and percentages and were compared using chi-square or Fisher exact tests, as appropriate. Continuous variables are expressed as mean±SD for normally distributed variables or as median (25th–75th percentile) for nonnormally distributed variables and compared using Student *t* tests and Mann–Whitney *U* tests, respectively. The correlation between the 2 parameters was evaluated using linear regression analysis. The relationships between change in CFR and clinical, angiographic, and physiological indices and other potential confounders before PCI were assessed using univariate and multivariate logistic regression analyses. Linear multivariate regression analysis was also used to evaluate the predictors of change in absolute CFR values. The associated variables in univariate analysis ($P \leq 0.10$) were analyzed using stepwise methods, and independent variables in the final multivariate models are presented in the tables. Receiver operating characteristic curve analysis was used to determine the optimal cutoff values. At follow-up data analysis, differences in combined adverse events between patients with lower pre-PCI CFR and those with higher pre-PCI CFR were analyzed with the Kaplan–Meier method. Event-free survival curves were compared using the Mantel-Cox test. Cox proportional hazards regression analyses for combined adverse events using the presence of low pre-PCI CFR and other clinical and angiographic variables were performed to identify predictors of adverse events during follow-up periods. Hazard ratios with corresponding 95% CIs are reported. All variables associated with adverse events at the $P<0.10$ level in univariate analysis were tested in a stepwise multivariable Cox regression analysis. $P<0.05$ indicated statistical significance.

Results

Patient Characteristics

No significant complication related to physiological measurements was documented. In 234 territories from 234 patients, 63 patients (26.9%) showed a post-PCI cardiac troponin I (cTnI) level >5 times the upper reference limit (≥1.0 ng/mL) based on blood samples taken at an average of 20.1±2.4 hours after PCI. The institutional 99th percentile upper reference limit for diagnosing acute coronary syndrome is 0.20 ng/mL, and PCI-related myocardial injury was defined as a cTnI level >1.0 ng/mL (0.20 ng/mL; institutional upper reference limit ×5) based on the third universal definition of myocardial infraction.[22] In these 63 patients, 4 had distal embolization exhibiting a transient slow flow or no reflow at the time of PCI with ECG changes, and 10 showed side-branch occlusion (>1.5 mm in diameter) during PCI with wall motion abnormality detected by ultrasound examination after PCI and/or ECG changes. Consequently, these 14 patients fulfilled the definition of type 4A myocardial infarction in the present cohort and were excluded from this study because significant microvascular injury and/or myocardial necrosis was expected in these cases, resulting in worse post-PCI CFR. Patients with isolated minor cTnI elevation without other clinical presentation (otherwise successful PCI) were not excluded. In total, 220 territories from 220 patients were studied to assess the acute effect of PCI on physiological indices. No patient had angiographically visible epicardial collaterals.

Patient Characteristics and Angiographic, Procedural, and Hemodynamic Results

The baseline patient characteristics and angiographic findings divided based on CFR increase or decrease are summarized in Tables 1 and 2. FFR increased in all studied territories (220 of 220, 100%), in contrast with a 71.8% (158 of 220) CFR increase after PCI, indicating that concordant increase was observed in 71.8% of all studied territories. Pre- and post-PCI FFR values were 0.73 (0.65–0.78) and 0.87 (0.84–0.92),

Table 1. Patient Baseline Characteristics

	Total (N=220)	CFR Increase (n=158)	CFR Decrease (n=62)	*P* Value*
Age, y	66.4±9.6	66.4±9.6	66.2±9.4	0.858
Male	189 (85.9)	131 (82.9)	58 (93.5)	0.052
Hypertension	163 (74.1)	118 (74.7)	45 (72.6)	0.736
Hyperlipidemia	134 (60.9)	94 (59.5)	40 (64.5)	0.541
Diabetes mellitus	83 (37.7)	56 (35.4)	27 (43.5)	0.282
Current smoker	48 (21.8)	35 (22.2)	13 (21.0)	1.000
eGFR, mL/min/1.73 m^2	70.6±18.7	70.9±19.1	69.9±17.6	0.723
CRP, mg/dL	0.08 (0.00–0.23)	0.09 (0.00–0.25)	0.06 (0.00–0.20)	0.192
WBC, counts/μL	5605±1427	5607±1444	5599±1395	0.970
Total cholesterol, mg/dL	167±35	168±36	163±34	0.289
LDL-C, mg/dL	95±29	96±30	94±28	0.698
HDL-C, mg/dL	46±11	46±11	46±11	0.750
Medication				
Statin	177 (80.5)	121 (76.6)	56 (90.3)	0.023
ACEI or ARB	158 (71.8)	114 (72.2)	44 (71.0)	0.869
β-blocker	87 (39.5)	57 (36.1)	305 (48.4)	0.125
Diuretics	28 (12.7)	22 (13.9)	6 (9.7)	0.503
Calcium blocker	108 (49.1)	81 (51.3)	27 (43.5)	0.369
Ejection fraction, %	63.1±10.0	62.8±10.4	63.7±9.1	0.570

Values are mean±SD, median (interquartile range), or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CFR, coronary flow reserve; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; WBC, white blood cell.
*All categorical variables were compared by chi-square test; continuous variables were compared by *t* test or Mann–Whitney *U* test.

respectively, and pre- and post-PCI CFR values were 2.34 (1.56–3.27) and 3.41 (2.29–5.16), respectively. Pre- and post-PCI percentage diameter stenoses were 57.7±11.2% and 7.48±4.79%, respectively. Distributions of pre- and post-PCI FFR and CFR and changes in FFR and CFR after PCI are shown in Figure 1. A moderately significant relationship was observed between pre-PCI FFR and CFR ($P<0.001$, $R^2=0.15$) (Figure 2), but there was no relationship between post-PCI FFR and CFR ($P=0.41$, $R^2=0.003$) (Figure 3). There was a statistically significant but weak relationship between change in FFR and CFR before and after PCI ($P=0.001$, $R^2=0.054$) (Figure 4). Post-PCI CFR increase was associated with pre-PCI physiological indices including low FFR ($P=0.019$), low CFR ($P<0.001$), high IMR ($P=0.001$), and angiographic parameters of the percentage diameter stenosis ($P=0.001$), pre-PCI reference diameter ($P=0.005$), and stent size ($P=0.001$) (Table 2). Of note, in territories with post-PCI CFR decrease, no significant post-PCI hyperemic coronary flow increase was detected (Table 2) (pre-PCI Tmn 0.26 versus post-PCI Tmn 0.26, *P* value not significant) (Figure 5) in contrast with significant post-PCI coronary flow increase observed in territories showing post-PCI CFR increase (Table 2) (pre-PCI Tmn 0.38 versus post-PCI Tmn 0.20, $P<0.001$) (Figure 5). In the multivariate analysis, pre-PCI CFR (odds ratio 0.67; 95% CI 0.55–0.81, $P<0.001$) and pre-PCI reference diameter (odds ratio 3.09; 95% CI 1.47–6.52, $P=0.003$) were independent predictors of CFR increase after PCI (Table 3). When an absolute increase in CFR after PCI (post-PCI CFR minus pre-PCI CFR) was evaluated as a determinant physiological outcome, pre-PCI CFR (β=−0.30; 95% CI −0.60 to −0.25, $P<0.001$), pre-PCI IMR (β=0.26; 95% CI 0.021–0.061, $P<0.001$), and diabetes mellitus (β=−0.16; 95% CI −1.38 to −0.19, $P=0.010$) were independent predictors (Table 4). Figure 6 shows the relationship between pre-PCI CFR and absolute CFR change (post-PCI CFR minus pre-PCI CFR). Lower pre-PCI CFR was significantly associated with greater change in CFR after PCI. When IMR was compared between the 2 groups showing concordant change in FFR and CFR and discordant change, territories with concordant change showed both significant IMR decrease after PCI ($P<0.001$) (Figure 5), regardless of P_w correction, and significant increase in coronary flow represented by hyperemic Tmn decrease in comparison with those with discordant change ($P<0.001$) (Table 5). In the present cohort, no significant relationship was observed between cTnI elevation after PCI and change in CFR ($P=0.72$).

Table 2. Patient Angiographic and Physiological Parameters

	Total (N=220)	CFR Increase (n=158)	CFR Decrease (n=62)	*P* Value*
Lesion location				
RCA	28 (12.7)	17 (10.8)	11 (17.7)	0.366
LAD	152 (69.1)	112 (70.9)	40 (64.5)	
LCX	40 (18.2)	29 (18.4)	11 (17.7)	
Quantitative coronary angiography before PCI				
Pre-MLD, mm	1.12±0.34	1.11±0.34	1.14±0.33	0.520
Pre-RD, mm	2.65±0.50	2.70±0.51	2.53±0.45	0.029
Stenosis, %	57.7±11.2	58.8±11.6	54.8±10.0	0.019
Lesion length, mm	11.7 (8.49–15.9)	11.3 (8.37–16.0)	12.7 (8.69–16.0)	0.338
Quantitative coronary angiography after PCI				
Post-MLD, mm	2.98±0.44	3.01±0.43	2.90±0.47	0.076
Post-RD, mm	3.22±0.42	3.25±0.41	3.14±0.45	0.081
Stent size, mm	3.50 (3.00–3.50)	3.50 (2.50–4.00)	3.00 (2.50–4.00)	0.001
Stent total length, mm	24.0 (18.0–32.3)	24.0 (9.0–72.0)	24.0 (12.0–56.0)	0.933
Drug eluting stent	205 (93.2)	146 (92.4)	59 (95.2)	0.829
Physiological parameters before PCI				
Pre-PCI FFR	0.73 (0.65–0.78)	0.73 (0.62–0.78)	0.75 (0.70–0.78)	0.019
Pre-PCI CFR	2.34 (1.56–3.27)	2.13 (1.44–2.88)	3.11 (2.10–3.99)	<0.001
Pre-PCI IMR with P_w correction	18.1 (12.0–25.7)	19.0 (13.2–29.7)	15.3 (9.9–20.1)	0.001
Pre-PCI IMR without P_w correction	20.5 (13.4–31.9)	21.8 (15.4–35.5)	16.2 (11.3–22.6)	<0.001
Tmn (pre-PCI)				
At rest, second	0.90 (0.59–1.27)	0.89 (0.61–1.31)	0.94 (0.58–1.16)	0.681
At hyperemia, second	0.35 (0.23–0.56)	0.38 (0.26–0.65)	0.26 (0.18–0.39)	<0.001
Physiological parameters after PCI				
Post-PCI FFR	0.87 (0.84–0.92)	0.87 (0.84–0.92)	0.87 (0.85–0.92)	0.962
Post-PCI CFR	3.41 (2.29–5.16)	4.04 (3.04–5.87)	2.10 (1.46–2.88)	<0.001
Post-PCI IMR	15.3 (11.8–22.1)	14.7 (10.7–20.5)	20.1 (13.7–28.4)	<0.001
Tmn (post-PCI)				
At rest, second	0.80 (0.56–1.11)	0.83 (0.62–1.23)	0.70 (0.37–0.94)	<0.001
At hyperemia, second	0.22 (0.16–0.30)	0.20 (0.15–0.28)	0.26 (0.21–0.38)	<0.001
cTnI elevation after PCI				
cTnI >1.0 ng/mL	49 (22.3)	34 (21.5)	15 (24.2)	0.720

Values are mean±SD, median (interquartile range), or n (%). CFR indicates coronary flow reserve; cTnI, cardiac troponin I; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LAD, left anterior descending; LCX, left circumflex; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; P_w, mean coronary wedge pressure; RCA, right coronary artery; RD, reference diameter; Tmn, mean transit time.

*All categorical variables were compared by chi-square test; continuous variables were compared by *t* test or Mann–Whitney *U* test.

Clinical Outcome at Long-Term Follow-up

At a median follow-up of 24.3 months (interquartile range 10.5–36.4 months), 2 patients were lost to follow-up; therefore, follow-up data were analyzed in 218 (99.1%) patients. During the long-term follow-up period, 1 patient with post-PCI died because of ventricular arrhythmia. The cumulative rate of adverse events was 17.4% (38 of 218) (Table 6). When baseline clinical and instrumental findings in patients with and without adverse cardiac events during follow-up were compared, no significant differences were observed regarding risk factors, clinical characteristics, medication, coronary anatomy, angiographic findings, and elevation of cTnI after PCI. Pre-PCI CFR (*P*=0.008), pre-PCI FFR

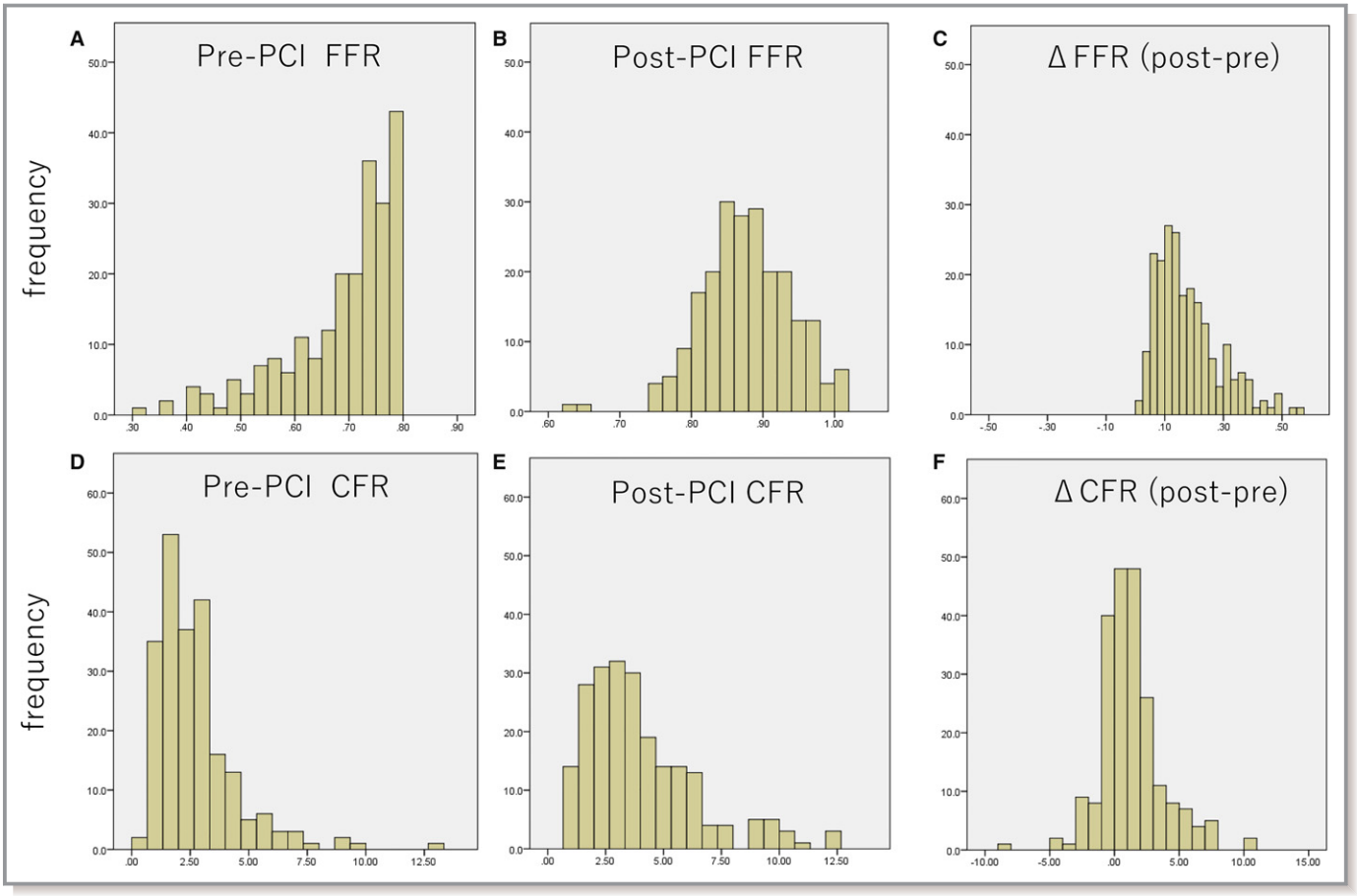

Figure 1. Distributions of pre- and post-PCI coronary flow reserve (CFR) and fractional flow reserve (FFR). A, Pre-PCI FFR. B, Post-PCI FFR. C, ΔFFR. D, Pre-PCI CFR. E, Post-PCI CFR. F, ΔCFR. ΔCFR represents post-PCI CFR minus pre-PCI CFR. ΔFFR represents post-PCI FFR minus pre-PCI FFR. PCI indicates percutaneous coronary intervention.

(*P*=0.033), and pre-PCI Tmn (*P*=0.017) were significantly different between patients with adverse events and those without (Table 7). Stepwise multivariable Cox regression analysis showed that low pre-PCI CFR (hazard ratio 0.73; 95% CI 0.55–0.97; *P*=0.028) was an independent predictor of adverse events during follow-up (Table 8). Receiver operating

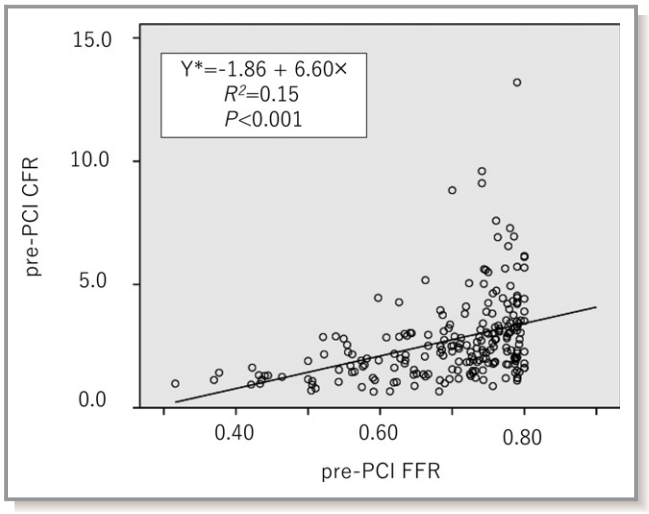

Figure 2. Relationship between pre-PCI fractional flow reserve (FFR) and pre-PCI coronary flow reserve (CFR). Y* was defined as pre-PCI CFR. PCI indicates percutaneous coronary intervention.

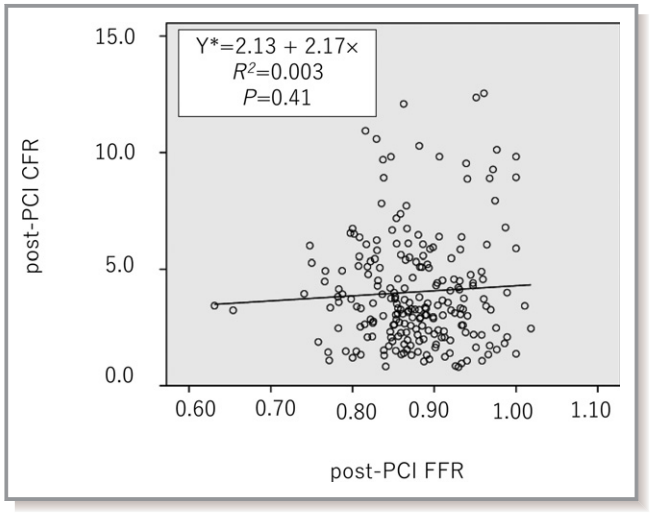

Figure 3. Relationship between post-PCI fractional flow reserve (FFR) and post-PCI coronary flow reserve (CFR). Y* was defined as pre-PCI CFR. PCI indicates percutaneous coronary intervention.

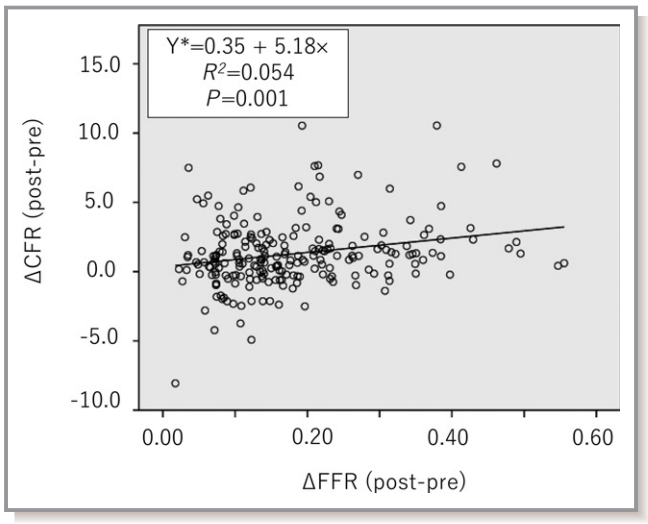

Figure 4. Relationship between change in fractional flow reserve (FFR) and change in coronary flow reserve (CFR) after percutaneous coronary intervention (PCI). ΔCFR represents post-PCI CFR minus pre-PCI CFR. ΔFFR represents post-PCI FFR minus pre-PCI FFR. Y* was defined as pre-PCI CFR.

characteristic curve analysis revealed that the optimal cutoff value of pre-PCI CFR to predict adverse events was 2.42 (area under the curve 0.637; 95% CI 0.541–0.734) for pre-PCI CFR. Event-free survival was significantly worse in patients with lower pre-PCI CFR (lower than the optimal cutoff value determined by receiver operating characteristic analysis; log-rank test λ^2=7.26; *P*=0.007) (Figure 7).

Discussion

The main findings of the present study were as follows: (1) FFR and CFR increases after PCI were not necessarily concordant; (2) CFR increase after otherwise successful PCI was associated with low pre-PCI CFR, low pre-PCI FFR, pre-PCI high microvascular resistance, and hyperemic coronary flow increase after PCI; and (3) during long-term follow-up after PCI, patients with low pre-PCI CFR showed a worse clinical course after successful PCI than those without low pre-PCI CFR.

Our results indicate that no physiological indices after PCI or changes in these parameters were associated with event-free survival after PCI, and pre-PCI CFR may help identify patients at high risk of subsequent events. Global reduction of CFR, which may reflect the greater burden of diffuse atherosclerosis, suggests the presence of high cardiovascular risk, not limited to the events of revascularized vessels, and susceptibility to major adverse cardiac events. To the best of

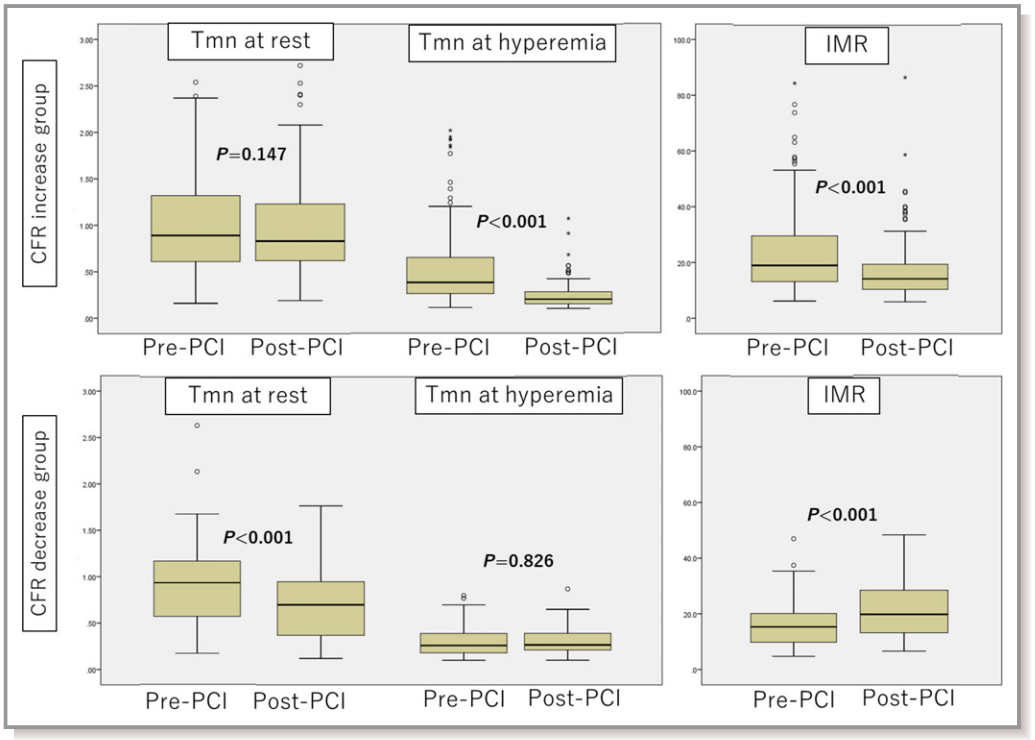

Figure 5. Comparison between coronary flow reserve (CFR) increase and CFR decrease territories. Change in basal flow and hyperemic flow represented by basal mean transit time (Tmn) and hyperemic Tmn and change in index of microcirculatory resistance (IMR) before and after percutaneous coronary intervention (PCI).

Table 3. Predictors of Increased CFR After PCI

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Pre PCI FFR	0.004	0.00–0.16	0.004			
Pre PCI CFR	0.69	057–0.83	<0.001	0.68	0.56–0.82	<0.001
Pre PCI IMR with P_w correction	1.05	1.02–1.09	0.002			
Pre-MLD	0.75	0.31–1.80	0.518			
Pre-RD	1.99	1.07–3.71	0.031	2.15	1.11–4.18	0.024
Diameter stenosis	1.03	1.01–1.06	0.021			
Lesion length	0.99	0.94–1.04	0.603			

Values were assessed by using univariate and multivariate logistic regression analyses. The associated variables in univariate analysis ($P \leq 0.10$) were entered into the final multivariate model. CFR indicates coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; MLD, minimal lumen diameter; OR, odds ratio; PCI, percutaneous coronary intervention; P_w, mean coronary wedge pressure; RD, reference diameter.

our knowledge, this study is the first to show that CFR decrease (28.2%, 62 of 220) occurred in a nonnegligible proportion of patients undergoing otherwise successful PCI in contrast to the prevalence (100%) of FFR increase. CFR decrease was associated with lower pre-PCI microvascular resistance represented by lower IMR values and increased microvascular resistance after PCI. We further demonstrated that pre-PCI CFR—not post-PCI parameters such as post-PCI physiological indices and patient and procedural characteristics—might allow identification of patients who are likely to have adverse cardiac events and who may require adjunctive therapeutic interventions despite otherwise successful PCI.

Effect of PCI on Changes in Physiological Indices

FFR and CFR are both well-validated physiological indices for guiding PCI indication.[2–4,11] A recent study also suggested

Table 4. Predictors of Absolute Increase in CFR* After PCI

	Univariate Analysis			Multivariate Analysis		
	β	95% CI	*P* Value	β	95% CI	*P* Value
Hypertension	0.011	−0.68 to 0.80	0.875			
Diabetes mellitus	−0.14	−1.38 to −0.06	0.033	−0.16	−1.39 to −0.19	0.010
Hyperlipidemia	−0.074	−1.03 to 0.30	0.276			
Medication						
Statin	−0.13	−1.58 to 0.44	0.064			
β-blocker	−0.075	−1.03 to 0.29	0.267			
Physiological indices before PCI						
Pre-PCI FFR	−0.14	−6.46 to −0.18	0.038			
Pre-PCI CFR	−0.37	−0.69 to −0.34	<0.001	−0.30	−0.60 to −0.25	<0.001
Pre-PCI IMR with P_w correction	0.36	0.037–0.077	<0.001	0.26	0.021–0.061	<0.001
Quantitative coronary angiography before PCI						
Pre-MLD	−0.10	−1.70 to 0.23	0.133			
Pre-RD	0.12	−0.075 to 1.21	0.083			
Diameter stenosis	0.17	0.008–0.063	0.012			
Lesion length	−0.073	−0.08 to 0.024	0.281			
Ejection fraction	0.048	−0.02 to 0.04	0.476			

Values were assessed by using linear univariate and multivariate regression analysis. The associated variables in univariate analysis ($P \leq 0.10$) were entered into the final multivariate model. CFR indicates coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; P_w, mean coronary wedge pressure; RD, reference diameter.
*Post-PCI CFR minus pre-PCI CFR.

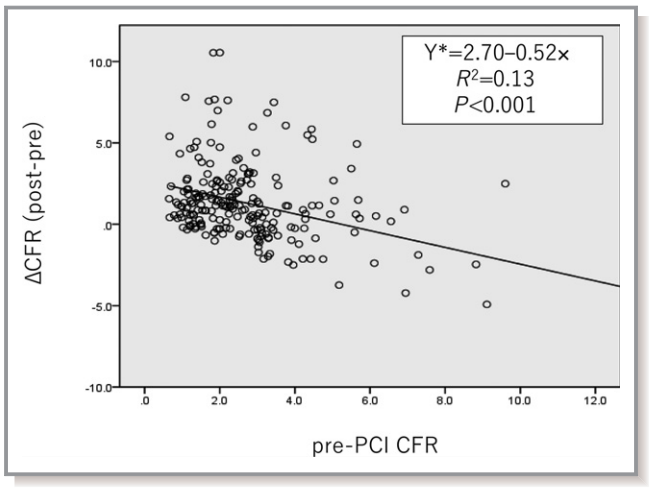

Figure 6. Change in coronary flow reserve after percutaneous coronary intervention (PCI) as a function of pre-PCI coronary flow reserve (CFR) value. ΔCFR represents post-PCI CFR minus pre-PCI CFR. Y* was defined as pre-PCI CFR.

Table 6. Incidence of Adverse Events

	All Patients (n=218)
All adverse events	38 (17.4)
Cardiac death	1 (0.5)
Myocardial infarction	2 (0.9)
Any revascularization	23 (10.5)
Target vessel revascularization	8 (3.7)
Non target vessel revascularization	14 (6.4)
Hospitalization of heart failure	7 (3.2)
Arrhythmia	4 (1.8)
Stroke	1 (0.5)

Values are n (%).

that FFR measured after PCI has prognostic value, with an inverse relationship to subsequent clinical events.[5] Mehta et al reported that lower FFR values among acute coronary syndrome patients with coronary lesions deferred revascularization based on FFR are associated with a significantly higher rate of adverse cardiac events.[23] The principle of CFR has been vigorously applied to a number of diagnostic tests, although its sensitivity toward resting hemodynamic relevance has been considered an important limitation in its use to consider myocardial flow impairment, despite reported evidence of powerful efficacy to stratify the risk of adverse cardiac events.[7,16,24,25] Our results indicated that CFR decrease after successful PCI was not uncommon, and CFR decrease was associated with pre-PCI physiological indices including high CFR, high FFR, low IMR, and no significant coronary flow increase after successful PCI. In the present study, when comparing the 2 groups (based on CFR increase or decrease after PCI), hyperemic coronary flow increase represented by decrease in Tmn was observed in the group with CFR increase. In contrast, basal flow increase was observed and no significant hyperemic flow increase was detected in the group with CFR decrease (Table 2, Figure 5). In territories with CFR decrease after PCI, pre-PCI hyperemic Tmn was significantly shorter than in territories with CFR increase, and post-PCI resting Tmn was shorter than in territories with pre-PCI resting values and no significant increase in coronary flow after PCI (Table 2). These phenomena explained post-PCI CFR decrease in these territories (Figure 5). This means that these lesions with CFR decrease likely correspond to non–flow-limiting stenosis, although, in all of the lesions, FFR indicated physiologically significant stenoses. Of note, pre-PCI FFR values showed significantly lower values in the group with CFR increase compared with those with CFR decrease. Figure 5 also explained the relationship between IMR change and coronary flow increase. In the vessels with an IMR decrease from before to after PCI, coronary flow increased immediately after PCI. The acute IMR decrease with coronary flow increase could be explained by the dilatation of microvasculature after PCI caused by distal pressure restoration. A higher pre-PCI IMR might reflect not only various chronic microvascular alterations but also the reduced passive distention of microvasculature due to loss of perfusion pressure. In this condition, coronary flow increased immediately after PCI due to microvascular distention caused by the acute effect of coronary perfusion pressure restoration. Consequently, the vessels with high IMR before PCI could be capable of vasodilatation resulting in coronary flow increase after PCI. In contrast, the territories with lower pre-PCI microvascular resistance showed higher coronary flow even under the presence of epicardial stenosis. Microvasculature

Table 5. Change in IMR and Tmn Before and After PCI

	CFR Increase (n=158)	CFR Decrease (n=62)	*P* Value*
ΔIMR (pre-IMR minus post-IMR)	3.73 (−0.77 to 11.8)	−6.28 (−9.25 to 0.16)	<0.001
ΔTmn (pre-Tmn minus post-Tmn) at hyperemia	0.17 (0.07–0.39)	−0.01 (−0.07 to 0.07)	<0.001

Values are median (interquartile range). CFR indicates coronary flow reserve; IMR, index of microcirculatory resistance; PCI, percutaneous coronary intervention; Tmn, mean transit time. *All continuous variables were compared by Mann–Whitney *U* test. Pre-IMR was corrected with wedge pressure.

Table 7. Patients and Lesion Characteristics of Patients With and Without Adverse Events

	Total (n=218)	Adverse Event (n=38)	No Adverse Event (n=180)	*P* Value*
Age, y	66.3±9.6	68.5±10.8	65.8±9.3	0.118
Male	188 (86.2)	36 (94.7)	152 (84.4)	0.121
Hypertension	161 (73.9)	32 (84.2)	129 (71.7)	0.154
Hyperlipidemia	133 (61.0)	22 (57.9)	111 (61.7)	0.716
Diabetes mellitus	81 (37.2)	18 (47.4)	63 (35.0)	0.196
Current Smoker	48 (22.0)	7 (18.4)	41 (22.8)	0.669
eGFR, mL/min/1.73 m^2	70.5±18.7	68.7±22.2	70.9±18.0	0.509
CRP, mg/dL	0.08 (0.00–0.24)	0.06 (0.00–0.26)	0.08 (0.00–0.22)	0.904
WBC, counts/μL	5608±1420	5308±1564	5672±1384	0.151
Total cholesterol, mg/dL	167±35	166±36	167±35	0.874
LDL-C, mg/dL	95±29	98±29	95±29	0.577
HDL-C, mg/dL	46±11	46±12	46±11	0.898
Medication				
Statin	175 (80.3)	29 (76.3)	146 (81.1)	0.505
ACEI or ARB	157 (72.0)	29 (76.3)	128 (71.1)	0.558
β-blocker	87 (39.9)	12 (31.6)	75 (41.7)	0.278
Calcium blocker	108 (49.5)	22 (57.9)	86 (47.8)	0.287
Ejection fraction, %	63.1±10.1	60.7±11.4	63.6±9.7	0.108
Lesion location				
RCA	28 (12.8)	5 (13.2)	23 (12.8)	0.160
LAD	150 (68.8)	22 (57.9)	128 (71.1)	
LCX	40 (18.9)	11 (28.9)	29 (16.1)	
Quantitative coronary angiography before PCI				
Pre-MLD, mm	1.12±0.34	1.19±0.38	1.11±0.32	0.182
Pre-RD, mm	2.66±0.50	2.81±0.57	2.63±0.49	0.143
Stenosis, %	57.7±11.6	57.7±11.4	57.7±11.6	0.990
Lesion length, mm	11.6 (8.46–15.8)	13.0 (9.5–17.7)	11.2 (8.21–15.6)	0.100
Quantitative coronary angiography after PCI				
Post-MLD, mm	2.98±0.44	3.04±0.44	2.97±0.44	0.342
Post-RD, mm	3.22±0.43	3.30±0.45	3.20±0.42	0.214
Stent size, mm	3.50 (3.00–3.50)	3.50 (3.50–3.50)	3.25 (3.00–3.50)	0.009
Stent total length, mm	24.0 (18.0–32.0)	28.0 (23.3–32.8)	24.0 (18.0–32.0)	0.078
Drug-eluting stent	203 (93.1)	35 (92.1)	168 (93.3)	0.766
Physiological parameters before PCI				
Pre-PCI FFR	0.73 (0.65–0.78)	0.69 (0.62–0.75)	0.74 (0.66–0.78)	0.033
Pre-PCI CFR	2.34 (1.61–3.28)	1.91 (1.29–2.41)	2.52 (1.75–3.39)	0.008
Pre-PCI IMR with P_w correction	18.1 (12.0–25.6)	20.2 (12.6–31.6)	17.7 (11.9–24.9)	0.129
Pre-PCI IMR without P_w correction	20.5 (13.5–31.8)	24.9 (17.6–38.7)	19.6 (13.1–29.9)	0.035
Tmn (pre-PCI)				
At rest, second	0.90 (0.60–1.27)	0.83 (0.61–1.33)	0.92 (0.60–1.24)	0.722
At hyperemia, second	0.35 (0.23–0.56)	0.44 (0.34–0.61)	0.33 (0.22–0.52)	0.017

Continued

Table 7. Continued

	Total (n=218)	Adverse Event (n=38)	No Adverse Event (n=180)	*P* Value*
Physiological parameters after PCI				
Post-PCI FFR	0.87 (0.84–0.92)	0.86 (0.84–0.93)	0.87 (0.84–0.92)	0.798
Post-PCI CFR	3.42 (2.32–5.20)	3.15 (2.08–4.28)	3.49 (2.46–5.32)	0.183
Post-PCI IMR	15.3 (11.8–22.0)	15.0 (13.0–22.0)	15.5 (11.5–22.5)	0.830
Tmn (post-PCI)				
At rest, second	0.80 (0.56–1.12)	0.72 (0.43–1.05)	0.80 (0.58–1.13)	0.218
At hyperemia, second	0.22 (0.16–0.30)	0.22 (0.16–0.29)	0.22 (0.15–0.30)	0.911
cTnI elevation after PCI				
cTnI >1.0 ng/mL	47 (21.6)	10 (26.3)	37 (20.6)	0.515

Values are mean±SD, median (interquartile range), or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CFR, coronary flow reserve; CRP, C-reactive protein; cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HDL-C, high-density lipoprotein cholesterol; IMR, index of microcirculatory resistance; LAD, left anterior descending; LCX, left circumflex; LDL-C, low-density lipoprotein cholesterol; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; P_w, mean coronary wedge pressure; RCA, right coronary artery; RD, reference diameter; Tmn, mean transit time; WBC, white blood cell.
*All categorical variables were compared by chi-square test; Continuous variables were compared by *t* test or Mann–Whitney *U* test.

in such a condition might already be fully dilated and have decreased microvascular resistance; therefore, coronary flow may not increase after PCI. In these territories, a possible coronary flow increase after PCI might be limited by responsive microvascular resistance increases. Currently, controversy exists about whether hyperemic microvascular resistance in the presence of functionally significant stenosis is equivalent to that after stenosis removal by PCI.[9,10,26–28] Our results clearly demonstrated that microvascular resistance was affected by PCI, and its direction of change had an impact on CFR change and hyperemic coronary flow after successful PCI. Multifactorial mechanisms between microvascular resistance and hemodynamics may be involved in the determination of individual functional status of coronary circulation before and after PCI, although precise mechanisms relating microvascular resistance and hemodynamics remain elusive. In general, blood pressure increase will decrease microvascular resistance; however, as the flow increases or by the hyperemic induction, pressure gradient across the epicardial stenosis increases, resulting in the distal coronary pressure decrease, and microvascular resistance may increase to maintain the perfusion pressure. If PCI decreases microvascular resistance, then coronary blood flow might significantly increase through the combination of reduced epicardial stenosis and decreased microvascular resistance. In contrast, hyperemic coronary flow might not significantly increase when microvascular resistance increases after PCI. Furthermore, any impact of a post-PCI change in microvascular resistance on the change in coronary flow is unknown. In the natural history of atherosclerosis, microvascular remodeling may occur independently or dependently of epicardial stenosis progression, resulting in the more complex and multifactorial interactions between microvascular status and hemodynamics. Further study is needed to clarify the relationship between PCI and its effect on microvascular status and hemodynamics.

Relationship Between Hemodynamic Indices and Clinical Outcome

Our results showed that pre-PCI physiological index of CFR, not patients' baseline characteristics or procedural and angiographic factors, was an independent predictor of adverse events after otherwise successful PCI. Taqueti et al reported that CFR was associated with adverse cardiac outcomes independent of revascularization.[25] They also suggested that revascularization might favorably affect only patients with low CFR. In their results, there was a significant interaction between CFR and early revascularization by coronary artery bypass grafting, such that patients with low CFR who underwent coronary artery bypass grafting —but not percutaneous coronary intervention—experienced event rates comparable to those with preserved CFR, independent of revascularization. These results were in line with our results and strongly support the concept of the currently ongoing clinical trial (DEFINE-FLOW; NCT02328820) with regard to the benefit of coronary flow increase by PCI. CFR may play an important role in diagnosing the pathophysiological abnormalities leading to adverse cardiac events in patients undergoing PCI. Revascularization procedures may not alter the natural history of atherosclerotic disease burden. Coronary artery disease exists diffusely in addition to a local isolated stenosis, so that localized mechanical intervention may fail to alter long-term disease outcome. Information on coronary physiology and myocardial blood flow in patients with coronary heart disease has been rigorously debated recently as to whether it informs treatment decisions.[6,8,12,14,24,25] Despite

Table 8. Cox Regression Analysis for Prediction of Adverse Events

	Univariate Analysis		
	HR	95% CI	*P* Value
Patient characteristics			
Ejection fraction	0.98	0.95–1.00	0.072
Hypertension	2.20	0.92–5.27	0.076
Hyperlipidemia	0.90	0.47–1.71	0.745
Diabetes mellitus	1.60	0.84–3.02	0.151
eGFR	1.00	0.98–1.01	0.707
Quantitative coronary angiography			
Pre-MLD	2.20	0.83–5.87	0.115
Pre-RD	1.48	0.77–2.85	0.238
Diameter stenosis	0.99	0.96–1.02	0.523
Lesion length	1.01	0.97–1.05	0.737
Post-MLD	1.30	0.63–2.66	0.478
Post-RD	1.63	0.76–3.50	0.207
Pre-PCI physiological parameters			
Pre-PCI FFR	0.078	0.01–1.16	0.064
Pre-PCI CFR	0.73	0.55–0.97	0.028
Pre-PCI IMR with Pw correction	1.01	0.99–1.02	0.378
Tmn (pre-PCI)			
At rest	1.07	0.57–2.00	0.835
At hyperemia	1.72	0.86–3.45	0.129
Post-PCI physiological parameters			
Post-PCI FFR	0.289	0.00–51.7	0.639
Post-PCI CFR	0.98	0.85–1.13	0.808
Post-PCI IMR	1.00	0.96–1.03	0.767
Tmn (post-PCI)			
At rest	0.76	0.36–1.59	0.465
At hyperemia	0.48	0.03–6.75	0.583
Change in physiological parameters			
ΔFFR (pre-post)	0.13	0.01–1.90	0.136
ΔCFR (pre-post)	0.91	0.80–1.04	0.159
ΔIMR (pre-post)	1.01	0.99–1.03	0.231

Values were assessed by using univariate Cox regression analyses. The associated variables at the $P<0.10$ level in univariable analysis were then tested in a multivariable Cox regression analysis. Pre-PCI CFR was only predictor of adverse events in multivariate analysis (HR, 0.73; 95% CI, 0.55–0.97; $P=0.028$). CFR indicates coronary flow reserve; CI, confidence interval; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HR, hazard ratio; IMR, index of microcirculatory resistance; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; Pw, mean coronary wedge pressure; RD, reference diameter; Tmn, mean transit time.

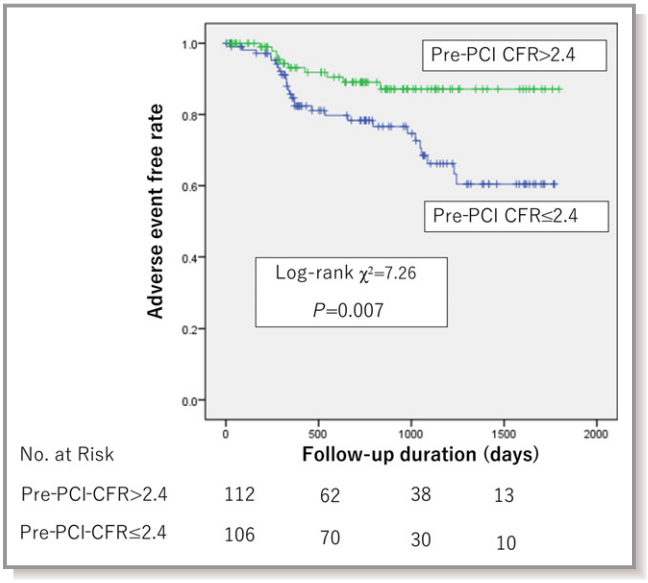

Figure 7. Kaplan–Meier plots estimating probability of event-free survival for patients with CFR cutoff values >2.4 and ≤2.4. CFR indicates coronary flow reserve; PCI, percutaneous coronary intervention.

incorporation into contemporary guidelines, these techniques are still poorly understood, and their interpretation to guide revascularization decisions is often inconsistent (eg, FFR/CFR discordant). A prospective large clinical study is required to evaluate the efficacy of CFR or other physiological indices to risk stratify patients at higher risk of future events in the presence of epicardial stenosis, regardless of PCI performance.

Study Limitations

The results of the present study should be interpreted with consideration of some limitations. First, this study included a relatively small number of participants from a single center. Exclusion of patients with significant left main disease, renal impairment, heart failure, or acute coronary syndrome may have resulted in selection bias. This study prospectively enrolled patients with stable angina pectoris based on symptoms and noninvasive test results who were referred to the catheter laboratory for treatment or diagnosed by diagnostic catheterization at our institution. Currently, there is no solid scientific basis for defining a biomarker threshold for diagnosis of periprocedural myocardial infarction. In this study, periprocedural myocardial injury was arbitrarily defined as a post-PCI cTnI level >5 times the upper reference limit (>1.0 ng/mL). We cannot exclude the possibility that a smaller amount of myocardial necrosis also might affect the change in microvascular resistance after PCI and affect the change in CFR, although no significant relationship was observed between cTnI elevation after PCI and CFR change in the present study. Corrected and uncorrected pre-PCI IMR values were both used in the analysis, whereas no correction was performed for post-PCI IMR. This was based on the fact that microcirculatory resistance without incorporation of

collateral flow will be increasingly overestimated as epicardial stenosis severity increases, and in patients with functionally nonsignificant stenosis, the amount of IMR correction is minimal and negligible. Coronary physiological measurements were performed ≈10 minutes after the final balloon inflation in all cases. Examination at a different time may alter hemodynamic indices.

Conclusions

CFR decrease after PCI was not uncommon, and discordant change in FFR and CFR was associated with high pre-PCI CFR, low pre-PCI microvascular resistance, and no significant post-PCI hyperemic coronary flow increase. Pre-PCI CFR, not post-PCI physiological indices, may help identify patients who require an adjunctive management strategy after successful PCI.

Disclosures

None.

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