Original Article

Noninvasive transthoracic doppler flow velocity and invasive thermodilution to assess coronary flow reserve

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Background: Coronary flow reserve (CFR) provides prognostication and coronary physiological information, including epicardial coronary stenosis and microvascular function. The relationship between stress transthoracic Doppler echocardiography (TDE)-derived coronary flow velocity reserve ($CFR_{S\text{-}TDE}$) and thermodilution-derived coronary flow reserve (CFR_{thermo}) before and after elective percutaneous coronary intervention (PCI) remains unclear.

Methods: This single-center prospective registry study evaluated patients who underwent fractional flow reserve (FFR)-guided elective PCI for left anterior descending artery (LAD) lesions with wire-based invasive physiological measurements and pre- and post-PCI stress TDE examinations.

Results: A total of 174 LAD lesions from 174 patients were included in the final analysis. A modest correlation was detected between the pre-PCI $CFR_{S\text{-}TDE}$ and the pre-PCI CFR_{thermo} (r=0.383, P<0.001). The frequently used $CFR_{S\text{-}TDE}$ threshold of 2.0 corresponded to a pre-PCI CFR_{thermo} of 2.18. Pre-PCI $CFR_{S\text{-}TDE}$ underestimated pre-PCI CFR_{thermo} [1.89 (1.44–2.31) *vs.* 2.05 (1.38–2.93), P<0.001]. Both $CFR_{S\text{-}TDE}$ and CFR_{thermo} increased significantly post-PCI [pre-PCI $CFR_{S\text{-}TDE}$ 1.89 *vs.* post-PCI $CFR_{S\text{-}TDE}$ 2.33, P<0.001; pre-PCI CFR_{thermo} 2.05 (1.38–2.93) *vs.* post-PCI CFR_{thermo} 2.59 (1.63–3.55), P<0.001]. In contrast, there was no significant relationship between changes in $CFR_{S\text{-}TDE}$ and changes in CFR_{thermo} after PCI (r=0.008, P=0.915) or between post-PCI $CFR_{S\text{-}TDE}$ and post-PCI CFR_{thermo} (r=0.054, P=0.482).

Conclusions: Pre-PCI $CFR_{S\text{-}TDE}$ and CFR_{thermo} are modestly correlated, but post-PCI $CFR_{S\text{-}TDE}$ and CFR_{thermo} have no correlation. $CFR_{S\text{-}TDE}$ and CFR_{thermo} are not interchangeable, particularly post-PCI, suggesting that the two metrics represent different coronary physiologies after PCI.

Keywords: Coronary flow reserve (CFR); fractional flow reserve (FFR); chronic coronary syndrome (CCS); microvascular dysfunction

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Introduction

The coronary flow reserve (CFR) is a well-validated index that can be used to assess coronary circulation and functional impairment. The CFR also provides prognostication in various patient subsets (1). CFR reflects the integrated coronary disease burden, including epicardial functional stenosis severity and microvascular dysfunction (1,2). Given the limited availability of pressure-velocity wires such as ComboWire (Phillips Volcano, San Diego, California, USA), thermodilution-derived coronary flow reserve (CFR_{thermo}) has become an increasingly used invasive method to measure CFR and evaluate coronary circulation in catheter laboratories because of its wide availability and ease of performance. Stress transthoracic Doppler echocardiography (S-TDE) of the left anterior descending artery (LAD) is a non-invasive method for assessing CFR based on flow velocity. $CFR_{S\text{-}TDE}$ is a low-cost, widely available, and efficiently performed method that does not require radiation or contrast, and the results have good agreement with intracoronary Doppler wire-derived CFR and positron emission tomography (PET)-derived myocardial flow reserve (3-7). However, data on the association between $CFR_{S\text{-}TDE}$ and CFR_{thermo} are currently limited. CFR, similar to the microcirculatory resistance (IMR) index, may reflect microvascular function after the successful modification of functionally significant epicardial stenosis by percutaneous coronary intervention (PCI). The aim of this study was to compare $CFR_{S\text{-}TDE}$ and CFR_{thermo} in the LAD with functionally significant proximal lesions before and after PCI. Further, we evaluated the correlation of IMR with $CFR_{S\text{-}TDE}$ and CFR_{thermo} before and after PCI.

Methods

Study design and patient population

This is a prospective study including patients with chronic coronary syndrome (CCS) who were planned to undergo elective PCI for *de novo*, single, hemodynamically significant lesions in proximal LAD at Tsuchiura Kyodo General Hospital, a single tertiary-care hospital in Japan between April 1, 2019 and November 30, 2022. All patients suffered from anginal symptoms (Canadian Cardiovascular Society class 1–3) and LAD lesions with fractional flow reserve (FFR) ≤0.80. Eligible patients were enrolled from our regular clinical population. The exclusion criteria were (I) acute coronary syndrome or total occlusion, (II) LAD lesions exhibiting angiographically visible collateral flow, (III) inability to provide consent to the study protocol, (IV) previous LAD PCI or myocardial infarction, (V) coronary artery bypass graft surgery, (VI) left main significant disease, (VII) chronic renal disease having baseline serum creatinine level >1.5 mg/dL, (VIII) decompensated heart failure, (IX) cardiomyopathy, (X) atrial fibrillation, and (XI) contraindications to adenosine administration. The patient selection flowchart is shown in *Figure 1*.

Guideline-directed medical therapy including high-dose statins, dual antiplatelets, β-blockers, and antihypertensives was started before or immediately after diagnostic angiography in all the patients. In accord with the study protocol, ad hoc PCI was not performed. After PCI, we further excluded patients with periprocedural myocardial infarction [as defined by the Fourth Universal Definition of Myocardial Infarction (8) based on a blood sample collected on average of 20–24 hours post PCI], ischemic symptoms, electrocardiogram (ECG) findings, and other newly detected imaging abnormalities after PCI completion because it had been reported that such events affect post-PCI physiological parameters (9). In the final analysis, we included the patients with minor cardiac troponin elevation without other manifestations required by the abovementioned definition.

This study was approved by the Institutional Ethics Committee of Tsuchiura Kyodo General Hospital (approval No. 809) and was performed in compliance with the tenets of the Declaration of Helsinki (as revised in 2013) for human studies. Written informed consent for the study and future anonymous data utilization was taken from all the patients.

Invasive diagnostic coronary angiography

Each patient initially underwent standard diagnostic coronary angiography via the radial artery using a 5F system for assessment of the coronary anatomy and functional stenosis severity by FFR measurements. The CMS-MEDIS system (Medis Medical Imaging Systems, Leiden, The Netherlands) was used for quantitative coronary angiography analyses. All patients received a bolus injection of heparin (5,000 IU) before the procedure. We administered intracoronary bolus injections of nitroglycerin (0.2 mg) at the beginning of the procedure and before functional assessments. Patients with LAD lesions showing

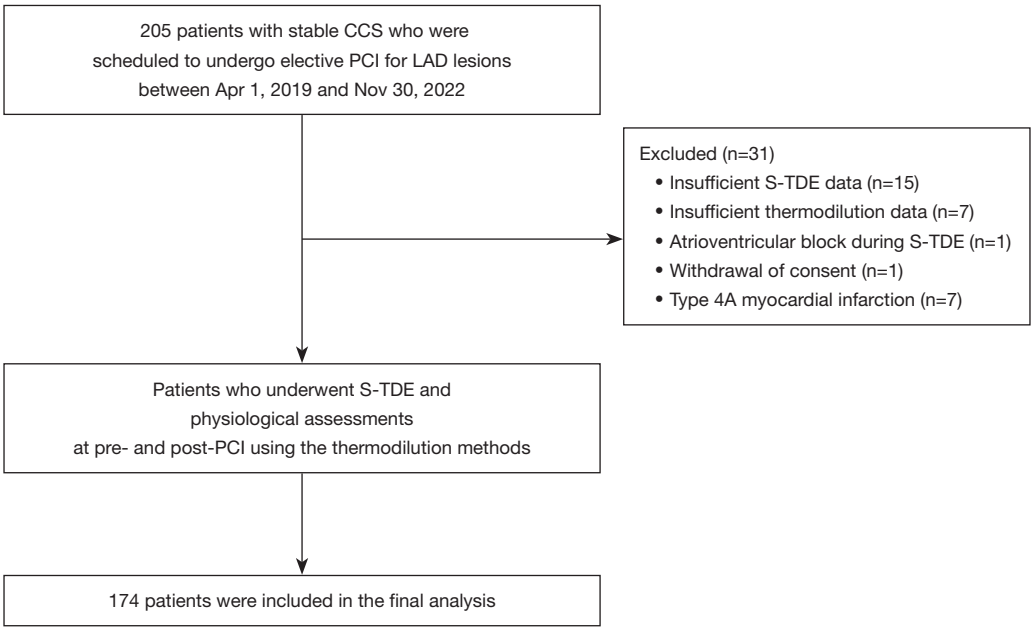

Figure 1 Study flowchart. A total of 174 patients were included in the final analysis. CCS, chronic coronary syndrome; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; S-TDE, stress transthoracic Doppler echocardiography.

FFR ≤0.80 were eligible and subsequently enrolled.

PCI and physiological assessments

All patients underwent FFR-guided PCI according to guidelines (10,11). Pre- and post-PCI physiological assessments were performed with a temperature-sensitive pressure sensor-equipped guidewire (Abbott Vascular, St. Paul, MN, USA) using routine techniques (12,13). Briefly, a bolus injection of intracoronary nitroglycerin (0.2 mg) was administered, and then the wire sensor was advanced and positioned in the far distant of the target vessel. FFR value was defined as the ratio of the mean distal coronary pressure to the mean aortic pressure during stable maximum hyperemia, which was induced by the intravenous adenosine administration (140 μg/kg/min through a central venous route). After the FFR measurement, when the sensor window reached the tip of the guiding catheter during hyperemia via a pull-back maneuver, a mean pressure drift of ≤2 mmHg was confirmed. A repeat assessment was performed when the pressure drift was >2 mmHg, as mandated by institutional standard protocol. All patients were ensured that they had not consumed caffeine-containing beverages for at least 24 hours prior to catheterization. CFR was calculated as the ratio of the resting mean transit time (T_{mn}) to the hyperemic T_{mn} using a thermodilution technique. The IMR was calculated as the distal coronary pressure at maximum hyperemia divided by the inverse of the hyperemic T_{mn}. Post-PCI physiological assessments were performed in a similar way after post-stenting high-pressure dilatation with a noncompliant balloon and/or additional stenting guided by physiology and intracoronary imaging at the operators' discretion and when the operator considered the final PCI procedure.

PCI techniques and the use of imaging devices, such as intravascular ultrasound or optical coherence tomography, and type of stent (drug-eluting stent) were left to the discretion of the interventionalists.

Measurement of coronary flow velocity using stress TDE

We performed coronary flow measurements in LAD using S-TDE before (1 day) and after (3 days) PCI for all eligible patients. Echocardiographic studies were conducted based on the guideline from the American Society of Echocardiography, using a commercially available digital ultrasound system (GE Vivid E95; GE Vingmed Ultrasound, Horten, Norway) with a multifrequency transducer and second-harmonic technology (12). Briefly, after the standard examination, coronary flow in the mid-distal portion of the LAD was evaluated in a modified 3-chamber view. For the color flow mapping, the velocity range was set to

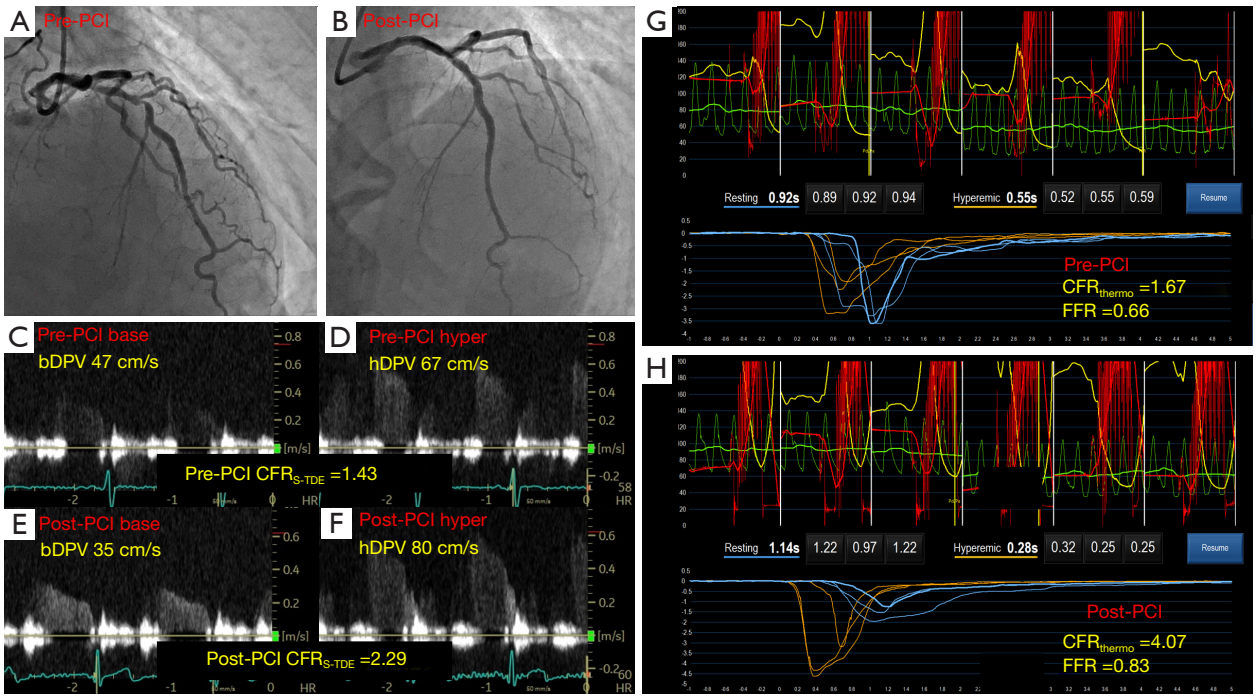

Figure 2 Representative images of coronary flow velocity measurements. A representative case of an LAD lesion that underwent S-TDE and thermodilution examinations before and after successful PCI. (A) Pre-PCI angiography. (B) Post-PCI angiography. (C) Pre-PCI bDPV. (D) pre-PCI hDPV. (E) Post-PCI bDPV. (F) Post-PCI hDPV. (G) Pre-PCI CFR_{thermo}. (H) Post-PCI CFR_{thermo}. LAD, left anterior descending artery; S-TDE, stress transthoracic Doppler echocardiography; PCI, percutaneous coronary intervention; bDPV, base diastolic peak velocity; hDPV, hyper diastolic peak velocity; CFR_{thermo}, thermodilution-derived coronary flow reserve; CFR_{S-TDE}, stress transthoracic Doppler echocardiography-derived coronary flow velocity reserve; FFR, functional flow reserve.

16–24 cm/s. A sample volume (3–5 mm wide) was pointed at the distal LAD segment to measure coronary flow velocity. Peak diastolic coronary flow velocity was measured under basal resting conditions (bDPV) and during maximum hyperemia (hDPV) induced by intravenous adenosine administration (140 μg/kg/min through a central venous route). All the data were digitally stored for repeated offline reviews and analyses. Three appropriate flow signal profiles at rest and during hyperemia were collected from the recorded data.

The CFR_{S-TDE} was obtained as the ratio of the hDPV to the bDPV using the software package of the ultrasound system. All stored data were separately analyzed twice at 1-week intervals by two experts, who were blinded to the clinical data, in order to evaluate the intra-observer reproducibility of the TTE-derived data. To evaluate the effect of measurement variability on the measurement of diastolic peak velocity by S-TDE, two independent observers (YH and TN), who were blinded to the patients' physiological results, analyzed 50 randomly selected Doppler velocity tracing records. Each observer had no access to the readings of the other observer or CFR_{thermo} data. Inter-observer variability was evaluated as the standard deviation of the differences between the two observers, defined as a percentage of the average value. Intra-observer reproducibility was repeated by one observer 5 min apart in 30 patients who underwent S-TDE measurements twice. All patients were instructed to avoid caffeine consumption for at least 24 hours before S-TDE. *Figure 2* shows a representative case of the CFR_{S-TDE} recording and measurements in the LAD before and after LAD PCI.

Statistical analysis

Categorical data were expressed as the number and percentage and compared using the chi-square or Fisher's exact test, as appropriate. The normality of the distributed values was assessed using Shapiro-Wilk tests. Continuous variables were showed as the mean ± standard deviation for normally distributed variables or as the median (25^{th}–75^{th}

Table 1 Baseline characteristics

Parameter	Total (n=174)
Age, years	68 (60–77)
Male	132 (75.9%)
Hypertension	143 (82.1%)
Diabetes mellitus	81 (46.6%)
Dyslipidemia	97 (55.7%)
Smoker	111 (63.8%)
eGFR (mL/min/1.73 m^2)	64.6 (50.7–75.2)
LDL-cho (mg/dL)	78 (65–103)
NT-proBNP (pg/mL)	209 (72–740)
HbA1c (%)	6.2 (5.8–6.9)
hs-troponin I (ng/L)	11 (5–41)
QCA analysis	
QCA MLD	1.11 (0.82–1.39)
QCA RD	2.49 (2.14–2.91)
QCA %stenosis	54.7 (43.4–64.8)
QCA lesion length	22.5 (15.3–33.1)

Values are presented as n (%), or median (interquartile range). eGFR, estimated glomerular filtration rate; LDL-cho, low density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; HbA1c, Hemoglobin A1c; hs-troponin, high sense-troponin I; QCA, quantitative coronary angiography; MLD, minimal lumen diameter; RD, reference lumen diameter; %stenosis, percent diameter stenosis.

Table 2 Baseline echocardiography parameters

Parameter	Total (n=174)
LVDd (mm)	46 [42–50]
LVDs (mm)	29 [26–34]
IVS (mm)	12 [10–13]
PW (mm)	12 [10–13]
LVEF (%)	64 [54–69]
LA diameter (mm)	39 [35–42]
E/A ratio	0.8 [0.6–1.0]

Values are presented as median [interquartile range]. LVDd, left ventricular end-diastolic diameter; LVDs left ventricular end-systolic diameter; IVS, interventricular septum thickness; PW posterior wall thickness; LVEF, left ventricular ejection fraction; LA diameter, left atrial diameter.

percentile) for non-normally distributed variables and were compared using Student's *t*-tests and the Mann-Whitney *U*-test, respectively. Associations were evaluated by analyzing Pearson's correlation for normally distributed data and Spearman's correlation for non-normally distributed data. Bland-Altman analyses were used to test for agreement. The kappa statistic was used to test the inter-rater reliability of CFR values before and after PCI. Receiver-operating characteristic (ROC) curves were analyzed to assess the best cutoff value of pre-PCI CFR_{thermo} values corresponding to the $CFR_{S\text{-}TDE}$ cutoff value. The optimal cutoff value was determined using the Youden index. All statistical analyses were performed using R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$.

Results

Baseline patient characteristics and angiographical and physiological findings

Among the 205 patients who were initially enrolled and underwent PCI, 24 patients were excluded due to incomplete S-TDE data acquisition (n=15), incomplete thermodilution data (n=7), termination of S-TDE testing because of the appearance of atrioventricular block (n=1), and withdrawal of consent (n=1). Additionally, 7 patients who showed type 4A myocardial infarction were also excluded from the final analysis. Finally, 174 patients who had successful FFR-guided LAD PCI with complete pre- and post-PCI S-TDE and wire-based physiological data were included in the analysis. *Tables 1,2* summarize the characteristics of the 174 patients. *Tables 3,4* show the pre- and post-PCI angiographic and physiological data respectively. The median pre-PCI FFR, CFR_{thermo}, $CFR_{S\text{-}TDE}$ were 0.70, 2.05, 1.89, respectively, while the median post-PCI FFR, CFR_{thermo}, and $CFR_{S\text{-}TDE}$ were 0.83, 2.59, and 2.33, respectively. In all cases, FFR significantly improved after PCI, from 0.70 (0.62–0.74) before PCI to 0.83 (0.80–0.87) after PCI ($P<0.001$). Both CFR_{thermo} and $CFR_{S\text{-}TDE}$ were also significantly increased after PCI ($P<0.001$ and $P<0.001$ respectively, *Tables 3,4*), although the CFR_{thermo} and $CFR_{S\text{-}TDE}$ are decreased in 42% and 23% of the patients, respectively. The hyperemic diastolic peak velocity detected by S-TDE significantly increased from 51 to 69 cm/s ($P<0.001$). $CFR_{S\text{-}TDE}$ similarly increased after PCI, although

Table 3 Pre-PCI physiological indices

Parameter	Total (n=174)
FFR	0.70 (0.62–0.74)
CFR_{thermo}	2.05 (1.38–2.93)
$CFR_{S\text{-}TDE}$	1.89 (1.44–2.31)
IMR	23.4 (18.2–34.6)
Base T_{mn} (s)	0.97 (0.68–1.31)
Hyper T_{mn} (s)	0.44 (0.32–0.63)
Base DPV (cm/s)	26.0 (20.5–32.5)
Hyper DPV (cm/s)	51.0 (38.0–66.5)

Values are presented as median (interquartile range). PCI, percutaneous coronary intervention; FFR, functional flow reserve; CFR_{thermo}, thermodilution-derived coronary flow reserve; $CFR_{S\text{-}TDE}$, stress transthoracic Doppler echocardiography-derived coronary flow velocity reserve; IMR index of microcirculatory resistance; T_{mn}, mean transit time; DPV, diastolic peak velocity.

Table 4 Post-PCI physiological indices

Parameter	Total (n=174)
FFR	0.83 (0.80–0.87)
CFR_{thermo}	2.59 (1.63–3.55)
$CFR_{S\text{-}TDE}$	2.33 (1.91–2.90)
IMR	21.0 (15.5–30.4)
Base T_{mn} (s)	0.89 (0.53–1.20)
Hyper T_{mn} (s)	0.32 (0.23–0.45)
Base DPV (cm/s)	29.0 (24.0–35.0)
Hyper DPV (cm/s)	69.0 (53.5–84.0)

Values are presented as median (interquartile range). PCI, percutaneous coronary intervention; FFR, functional flow reserve; CFR_{thermo}, thermodilution-derived coronary flow reserve; $CFR_{S\text{-}TDE}$, stress transthoracic Doppler echocardiography-derived coronary flow velocity reserve; IMR index of microcirculatory resistance; T_{mn}, mean transit time; DPV, diastolic peak velocity.

41 (23%) patients showed a decrease in post-PCI $CFR_{S\text{-}TDE}$. Both CFR_{thermo} and $CFR_{S\text{-}TDE}$ showed a modest correlation with the pre-PCI FFR (r=0.383 and r=0.366, respectively; Figure S1A,S1B).

Agreement between pre-PCI CFRthermo and CFRS-TDE

The median pre-PCI CFR_{thermo} was significantly higher than the pre-PCI $CFR_{S\text{-}TDE}$ [2.05 (1.38–2.93) *vs.* 1.89 (1.44–2.31), P<0.001]. The commonly used $CFR_{S\text{-}TDE}$ cutoff value of 2.0 corresponded to 2.18 of CFR_{thermo} as determined by ROC analysis [AUC: 0.710 (0.633–0.787)]. Pre-PCI CFR_{thermo} and $CFR_{S\text{-}TDE}$ had a moderate correlation (r=0.379, P<0.001, *Figure 3A*). The corresponding Bland-Altman plot indicated a bias of 8.3% (*Figure 3B*), and the intraclass correlation coefficient was 0.534 (P<0.001). The concordance rate for diagnosing decreased pre-PCI CFR using a cutoff value of 2.0 for $CFR_{S\text{-}TDE}$ and the corresponding CFR_{thermo} of 2.18 obtained by ROC analysis was 0.317 by kappa value.

Agreement between post-PCI CFRthermo and CFRS-TDE

The median (interquartile range) post-PCI CFR_{thermo} and $CFR_{S\text{-}TDE}$ values were 2.59 (1.63–3.55) and 2.33 (1.91–2.90), respectively. Notably, no significant correlation was found between post-PCI CFR values obtained by two methods (*Figure 4*). Furthermore, no significant correlation was detected between delta CFR_{thermo} and delta $CFR_{S\text{-}TDE}$ (r=0.008, P=0.915). After PCI, the concordance rate of diagnosing decreased post-PCI CFR using 2.0 as the unified cutoff value for both $CFR_{S\text{-}TDE}$ and CFR_{thermo} was 0.078 by kappa value.

Relationship between microvascular function and CFR

There was a modest correlation between pre-PCI CFR_{thermo} and pre-PCI IMR (r=–0.393, P<0.001), while a very weak but significant relationship was found between pre-PCI $CFR_{S\text{-}TDE}$ and pre-PCI IMR (r=–0.155, P=0.041). Post-PCI IMR showed a statistically significant moderate correlation with post-PCI CFR_{thermo} (r=–0.343, P<0.001), whereas no significant correlation was found between post-PCI IMR and post-PCI $CFR_{S\text{-}TDE}$ (r=–0.109, P=0.151). Association between IMR and CFR_{thermo}, IMR and $CFR_{S\text{-}TDE}$ are shown in Figure S2.

Interobserver variability and reproducibility of S-TDE measurements

Good agreement was observed between the two independent observers' measurements of diastolic peak velocity (r=0.92). The interobserver variability for diastolic peak velocity was 3.8%, and the intraclass correlation coefficient was 93% for accredited readers. The reproducibility of diastolic peak velocity was 3.2% between first and second (5 min apart) S-TDE measurements.

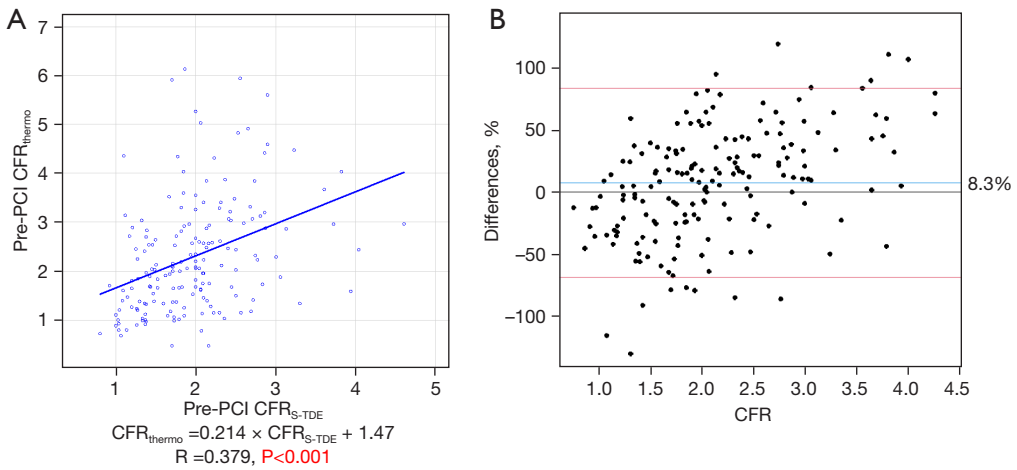

Figure 3 Comparison between pre-PCI CFR_{thermo} and CFR_{S-TDE}. (A) Correlation between pre-PCI CFR_{thermo} and CFR_{S-TDE}. (B) Corresponding Bland-Altman plot of CFR_{thermo} and CFR_{S-TDE}. PCI, percutaneous coronary intervention; CFR_{thermo}, thermodilution-derived coronary flow reserve; CFR_{S-TDE}, stress transthoracic Doppler echocardiography-derived coronary flow velocity reserve.

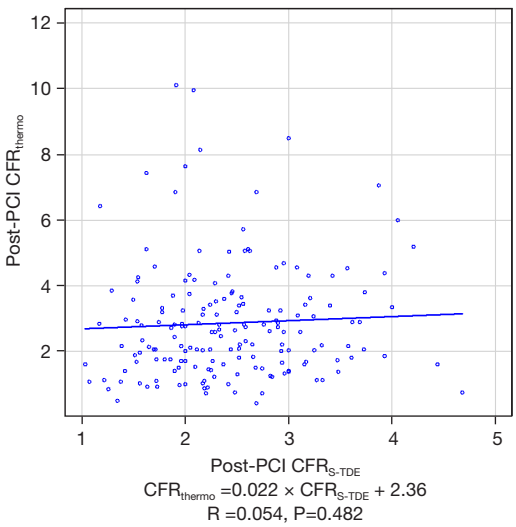

Figure 4 Comparison between post-PCI CFR_{thermo} and CFR_{S-TDE}. Correlation between post-PCI CFR_{thermo} and CFR_{S-TDE} values. PCI, percutaneous coronary intervention; CFR_{thermo}, thermodilution-derived coronary flow reserve; CFR_{S-TDE}, stress transthoracic Doppler echocardiography-derived coronary flow velocity reserve.

Discussion

The association between CFR_{S-TDE} and CFR_{thermo} has not been clarified yet. The main findings of this study are as follows. First, there is a moderate correlation between CFR_{thermo} and CFR_{S-TDE} before PCI, while they are not associated after PCI. Second, both CFR_{thermo} and CFR_{S-TDE} are increased after PCI in a total cohort, although the CFR_{thermo} and CFR_{S-TDE} are decreased in 42% and 23% of the patients, respectively. Third, the CFR_{thermo} is significantly higher than CFR_{S-TDE} both pre- and post-PCI. Fourth, the pre-PCI CFR_{thermo} has a modest correlation with pre-PCI IMR, while pre-PCI CFR_{S-TDE} has a very weak but borderline significant relationship with pre-PCI IMR. Fifth, post-PCI IMR has a significant correlation with post-PCI CFR_{thermo}, while there is no significant correlation between post-PCI IMR and post-PCI CFR_{S-TDE}. Sixth, the concordant rate of diagnosing decreased CFR using a cutoff value of 2.0 for pre-PCI CFR_{S-TDE} and the corresponding pre-PCI CFR_{thermo} of 2.18 is 0.317 by kappa value and 0.078 for post-PCI CFR when applying the unified cutoff value of 2.0. To our best knowledge, the present study is the first to compare non-invasive transthoracic Doppler echocardiography (TDE)-derived flow velocity and invasive thermodilution-derived physiological measures for the assessment of pre- and post-PCI CFR before and after elective PCI, although the examination time window was different.

Correlation between pre-PCI CFRS-TDE and pre-PCI CFRthermo measurements

Previous studies reported that noninvasive measurements of coronary flow velocity and CFR by S-TDE in the LAD accurately reflected the invasive measurement of coronary flow velocity and CFR using a Doppler flow velocity wire

and the noninvasive standard reference method by PET (4,5). Our results are consistent with those of Demir *et al.* (7) who demonstrated that CFR_{thermo} overestimated invasively measured velocity-derived CFR, while both parameters showed a modest correlation before PCI. The observed systemic bias was not uniform from low to high CFR values. Further, compared to $CFR_{S\text{-}TDE}$, CFR_{thermo} introduced higher overestimation, as indicated by higher CFR values (*Figure 3B*). Our results are consistent with previous studies comparing CFR_{thermo} with invasive velocity wire-derived CFR values. However, to our best knowledge, we are the first to use noninvasive S-TDE data for comparison with CFR_{thermo} in patients treated with PCI (7,13). In contrast to CFR_{thermo}, S-TDE-derived or invasive wire-derived CFR provides theoretically and clinically more robust reference markers for coronary flow volume, as reported in previous studies (4,5,13). Notably, invasive wire-derived Doppler flow velocity method is challenging for obtaining optimal signal data (14), whereas $CFR_{S\text{-}TDE}$ is widely available and has good reproducibility with a high level of sufficient signal tracing, as shown in this study (190/205, 92.7%). Considering these circumstances, $CFR_{S\text{-}TDE}$ may be more feasible and robust than invasive Doppler wire-derived CFR and CFR_{thermo} as routine assessments of CFR in clinical practice.

The exact mechanism of the overestimation of CFR_{thermo} remains undetermined. When using CFR for the assessment of coronary physiology, differences in the cutoff values for stratification or diagnosis according to the methodology of measuring CFR values should be noted.

Correlation between post-PCI CFRS-TDE and post-PCI CFRthermo measurements

In contrast to the results of the pre-PCI comparison of $CFR_{S\text{-}TDE}$ and CFR_{thermo}, post-PCI CFR_{thermo} showed no significant correlation with $CFR_{S\text{-}TDE}$, which has not been reported previously. Notably, the discordant rate between post-PCI CFR_{thermo} and post-PCI $CFR_{S\text{-}TDE}$ was 41%, using 2.0 as the cutoff value for both post-PCI $CFR_{S\text{-}TDE}$ and post-PCI CFR_{thermo}. This could be explained as follows. First, the measurement window for CFR from the completion of PCI by each method was different [CFR_{thermo}, immediately after PCI completion; $CFR_{S\text{-}TDE}$, 3 days (median) after PCI completion]. Compared with CFR_{thermo}, $CFR_{S\text{-}TDE}$ is more likely to represent stable post-PCI coronary circulation (15,16). Second, post-PCI variability of transit time or inconsistent surrogate marker of coronary flow by transit time compared with S-TDE derived flow velocity (7). Further studies are needed to elucidate the clinical significance of the differences between these two post-PCI CFR metrics and their clinical relevance. The invasive CFR measurement by wire-derived flow velocity depends on the technical expertise of the operator, and suboptimal signal quality of Doppler traces has been reported to occur in as high as 30% of measurements (14). In contrast, both CFR_{thermo} and noninvasive $CFR_{S\text{-}TDE}$ provide very high level of signal tracing performance for obtaining CFR (198/205, 96.6% and 190/205, 92.7%, respectively in this study). It is unlikely that the population bias might have caused the discordant results between these two post-PCI metrics in the present study because the subjects were prospectively enrolled following an all-comers design according to the study protocol in routine clinical practice. The relationships between pre- and post-PCI inverse of resting and hyperemic T_{mn} and TDE-derived velocity, both proposed as surrogate markers of coronary flow, is shown in Figure S3. In contrast to the pre-PCI relationship, no significant relationship was found between post-PCI hyperemic flow velocity and post-PCI inverse of hyperemic T_{mn}. This observation may at least partially explain the discordant results of the CFR values between the two methods after PCI.

Microvascular resistance by IMR or CFR after PCI

Microvascular dysfunction is increasingly noted to be a cause of myocardial ischemia (17,18). Coronary microvascular disease and its significance in cardiac events among patients without significant obstructive disease have also been reported (1,19). Recent studies have reported the coexistence of coronary microvascular dysfunction and epicardial obstructive disease (20,21). In the present study, residual microvascular dysfunction after epicardial stenosis removal by PCI may be relevant to myocardial ischemia or cardiac events possibly caused by microvascular dysfunction after PCI. In the absence of obstructive epicardial disease, the current ESC guidelines recommend the measurement of CFR or IMR for the assessment of microvascular function in clinical practice, without referring to which modality is the best for the CFR measurements (22). Given that no significant relationship was observed between post-PCI $CFR_{S\text{-}TDE}$ and IMR or between post-PCI $CFR_{S\text{-}TDE}$ and CFR_{thermo}, the modality to obtain or the metric to represent post-PCI microvascular function should be chosen or interpreted considering the results of this study. Our results

are consistent with those of a previous report showing no correlation between thermodilution-derived IMR and Doppler-derived microvascular resistance (7). A clinically applicable reference measure of microvascular resistance remains inconclusive, limiting the ability to compare the diagnostic accuracy of these two indices. Further studies are needed to elucidate which index accurately reflects microvascular function after PCI or if the combination of these metrics could predict worse future outcomes.

Limitations

This was a single-center retrospective analysis of prospectively registered patient data and relevant to an observational nature; thus, inherent limitations exist. The number of study patients was limited by rigorous inclusion and exclusion criteria, possibly leading to a certain level of selection bias, although all patients were prospectively included in routine clinical practice. The present study was conducted in a group of patients with epicardial functional stenosis and future studies are needed to investigate the relationship between $CFR_{S\text{-}TDE}$ and CFR_{thermo} and their prognostic efficacy in non-flow-limiting lesions or patients with ischemia and non-obstructive coronary artery. In the Doppler echocardiographic interrogation of coronary flow in the LAD, LAD flow data before and after PCI were comparable only at identical guidewire positions and fixed vessel diameters under similar hemodynamic conditions. However, a change in the LAD diameter after PCI or a difference in the guidewire position cannot be ruled out. The measurement window of CFR by each approach was different (CFR_{thermo}, immediately after PCI completion; $CFR_{S\text{-}TDE}$, 3 days after PCI completion) and this difference could have affected the results. The absolute coronary flow volume, such as in PET studies as a reference, was not assessed in this study. Importantly, hyperemic conditions in the present study were achieved by intravenous infusion of adenosine, indicating the hyperemia could be induced in pancoronary territories. Given microvascular function is affected by collateral flows from non-LAD territories, intracoronary adenosine infusion might better induce hyperemia only in the LAD territory. Finally, this study used the thermodilution method for the CFR_{thermo} and IMR. Currently, neither RayFlow® catheters (HEXACATH, Paris, France) nor a 0.014" dual pressure and Doppler velocity sensor-tipped guidewire (ComboWire XT, Philips Volcano, San Diego, CA, USA) are commercially accessible in Japan. These methods may provide different wire-based CFR and hyperemic absolute microvascular resistance when commercially available worldwide, thus further investigations are warranted.

Conclusions

Pre-PCI CFR_{thermo} and $CFR_{S\text{-}TDE}$ have modest correlation, whereas post-PCI CFR_{thermo} and $CFR_{S\text{-}TDE}$ have no significant correlation. There is a modest correlation between CFR_{thermo} and IMR before and after PCI, whereas there is no significant correlation between post-PCI $CFR_{S\text{-}TDE}$ and post-PCI IMR. $CFR_{S\text{-}TDE}$ and CFR_{thermo} are not interchangeable, particularly post-PCI. This suggests that the two metrics represent different post-PCI coronary physiology.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-416/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Ethics Committee of Tsuchiura Kyodo General Hospital (approval No. 809) and was performed in compliance with the tenets of the Declaration of Helsinki (as revised in 2013) for human studies. Written informed consent for the study and future anonymous data utilization was taken from all the patients.

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