Coronary flow velocity reserve in three major coronary arteries by transthoracic echocardiography for the functional assessment of coronary artery disease: a comparison with fractional flow reserve

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Aims
Coronary flow velocity reserve (CFVR) measurement in three major coronary arteries by transthoracic echocardiography is a promising and non-invasive method for detecting myocardial ischaemia. Its value when compared with fractional flow reserve (FFR) is unknown. Our aim was to determine the diagnostic accuracy of CFVR in three major coronary arteries for detecting ischaemia compared with FFR.

Methods
This is a prospective study in 172 vessels of 140 patients with at least one ≥50% stenosis in a major epicardial artery as determined by visual assessment on computed tomography coronary angiography. We performed CFVR measurement by transthoracic echocardiography within 48 h before coronary angiography and FFR measurement. The cut-off value of CFVR was estimated by the receiver operating characteristic (ROC) curve based on that of FFR ≤0.75.

Results
The CFVR was 1.86 ± 0.36 in coronary arteries with FFR ≤0.75 (n = 79) and 2.54 ± 0.48 in those with FFR > 0.75 (n = 93, P < 0.0001). CFVR with cut-off of 2.2, determined by the ROC curve, was 85% sensitive and 79% specific in predicting the stenotic condition of the coronary artery with FFR ≤0.75 in three major vessels. In each vessel, the sensitivity and specificity were 85 and 78% (left anterior descending coronary artery), 94 and 83% (right coronary artery), and 88 and 88% (left circumflex coronary artery). CFVR was indirect proportional to FFR (r = 0.56, P < 0.0001) and to per cent diameter stenosis (r = 0.26, P = 0.0008).

Conclusions
The non-invasive CFVR measurement could be a reliable stenosis-specific method for determining the haemodynamic significance of three major coronary arteries.

Keywords
Coronary flow velocity reserve • Fractional flow reserve • Coronary artery disease

Introduction
The pressure-derived fractional flow reserve (FFR) is an accurate stenosis-specific method to evaluate the haemodynamic significance of coronary artery disease (CAD)1–3 and has become to be routinely applied to determine the severity of coronary artery stenosis4,5 in the catheter laboratory. However, the patients who do not need coronary intervention should be kept from any invasive imaging technique. Therefore, non-invasive alternative imaging technique has been required.

Coronary flow velocity reserve (CFVR) is an established physiological marker of coronary circulation and has been employed to

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determine functionally significant coronary stenosis. However, the clinical utility of CFVR by transthoracic Doppler echocardiography (TTDE) has been limited to diagnosing the left anterior descending artery (LAD) stenosis because of relatively low feasibility of detecting other coronary arteries, although CFVR by TTDE in itself is considered as an easy and valuable method for coronary flow assessment. Recently, the success rates to measure CFVR of right coronary artery (RCA) and left circumflex coronary artery (LCX) have been increasing owing to the advancement in ultrasonic technology, accordingly CFVR measurement in three major coronary arteries may contribute to non-invasive detection of functional significance of coronary stenosis. However, the accuracy of CFVR in three major coronary arteries when compared with FFR is not determined.

Thus, this study was sought to estimate the diagnostic ability of CFVR by TTDE to predict functional significance of coronary stenosis in major three coronary arteries, using FFR as the reference method.

Methods

Study population

Between January 2009 and July 2012, 348 patients with chest pain underwent computed tomography coronary angiography (CTA) who were considered for non-urgent revascularization. Among 348 CTA examinations, 179 patients had at least one ≥50% stenosis in a major epicardial artery as determined by visual assessment on CTA. Thirty-two patients were excluded because of not meeting inclusion criteria, and 147 patients underwent TTDE within 48 h before FFR measurement (Figures 1 and 2).

Exclusion criteria included myocardial infarction within 3 months, need for urgent revascularization, history of coronary artery bypass grafting, advanced atrioventricular block, atrial fibrillation, left ventricular dysfunction, severe left main disease, presence of chronic total occlusion, critical aortic stenosis, contraindications to iodinated contrast, bronchospastic lung disease requiring long-term steroid therapy, and renal insufficiency (eGFR < 60 mL/min/1.73 m²).

The study was approved by our institutional Ethics Committee and all participants gave written informed consent.

Doppler echocardiographic studies

All enrolled patients were fasted overnight and abstained from any beverage containing significant amount of flavonoids and caffeine for 48 h to avoid any effect of them in affecting coronary endothelial function. CFVR was significantly decreased by smoking cigarettes, accordingly, all patients abstained from smoking for 48 h. Doppler echocardiography was performed with Vivid E9 (GE Healthcare, Horten, Norway) using a broadband transducer of 3.0 MHz for the LAD and with 2.4 MHz for the RCA and LCX. For colour Doppler flow mapping, the velocity ranged from 12 to 25 cm/s. The colour gain was adjusted to provide optimal images.

To measure LAD flow velocity, we located an acoustic window in the mid-clavicular line in the fourth or fifth intercostal space in the left lateral decubitus position. After the lower portion of the interventricular sulcus had been located in a long-axis cross-section, the ultrasound beam was inclined laterally. Next, coronary blood flow in the LAD (middle to distal) was measured using colour Doppler flow mapping. After a sample volume (length, 1.5 mm) was positioned on the colour signal in the LAD, coronary flow velocity was recorded by pulsed-wave Doppler echocardiography. We tried to make the ultrasound beam as parallel to the LAD flow as possible. To measure RCA flow, we selected distal part of the RCA for colour Doppler identification and flow velocity measurement. After an optimal two-dimensional image had been obtained in the apical two-chamber view, the transducer was rotated in a counterclockwise manner until the posterior interventricular sulcus was clearly visualized. Next, the linear colour signal, which persisted throughout the diastole, was searched carefully in the posterior interventricular sulcus under the guidance of Doppler colour flow mapping. A sample volume (1.5–2.0 mm) was positioned on the colour signal and the coronary flow velocity was recorded by pulsed-wave Doppler echocardiography. To measure LCX flow, we searched Doppler flow signals in the LCX as the linear colour signal persisted during diastole at the basal to the mid-portion of the left ventricular lateral region in the apical four-chamber view, avoiding the far apical portion, where a signal recorded could belong to a diagonal artery coming from the LAD. The reference structure was the lateral wall itself, where obtuse marginal arteries (distal LCX) run. Next, Doppler spectral tracings of the circumflex flow velocities were recorded with a sample volume positioned on the visualized colour signal. First, we recorded the baseline spectral Doppler signals in >5 cardiac cycles at end-expiration by TTDE. Then, we intravenously administered adenosine triphosphate (0.14 mg/kg body weight/min) for 2 min to record spectral Doppler signals. This allowed us to obtain the peak flow response induced by coronary microvesSEL dilatation. Heart rate was monitored, and electrocardiography was performed continuously in all patients. Blood pressure was recorded at the baseline and every minute during adenosine triphosphate infusion. Experienced investigators, who were blinded to all other data, measured coronary flow velocities offline by tracing the contour of the spectral Doppler signal (EchoPAC, GE Healthcare, Horten, Norway). Mean diastolic velocities were measured at the baseline and during hyperaemia. Measurements were averaged over five cardiac cycles. CFVR was defined as the ratio of mean diastolic velocity during hyperaemia to that at the baseline. CFVR can be determined using both peak and mean diastolic coronary flow velocities. However, in the previous study, the mean diastolic velocity showed a greater specificity than peak diastolic velocity, while the sensitivity was same. Therefore, we used the mean diastolic velocity in the present study.

Coronary angiography

Coronary angiography was performed using standard techniques via the femoral or radial approach. The severity of coronary stenosis was evaluated by multiple projections and was determined by experienced investigators with commercially available quantitative coronary angiographic (QCA) software program. Using the guiding catheter as a scaling device, reference diameter, minimal luminal diameter, and percentage diameter stenosis (DS) were calculated.

Fractional flow reserve

Aortic pressure (Pa) was measured through the guiding catheter. Coronary pressure (Pd) was measured with a commercially 0.014-inch pressure monitoring guidewire (PressureWire™, Certus, St Jude Medical St Paul, MN). After the wire was calibrated, advanced through the catheter, and equalised with the Pa in the catheter, it was placed at least 3 to 4 cm distal to the stenosis and manipulated until an optimal and stable velocity signal was obtained. The position of the tip of the wire was confirmed by fluoroscopy and angiography. The Pa, Pd, instantaneous peak velocity, and electrocardiogram were obtained online at baseline and after induction of maximal hyperaemia with 0.14 mg/kg/min of i.v. adenosine triphosphate for 2 min. An abnormal value of FFR was defined as ≤0.75 and ≤0.8. Heart rate, distal pressure, and aortic pressure were continuously recorded and digitally stored during the procedure.
Statistical analysis
Continuous variables are expressed as means ± standard deviations. Categorical variables are expressed as counts and percentages. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to predict the ability of each imaging modality to identify coronary stenosis. The receiver-operating characteristic (ROC) curve was determined to evaluate the predictive performance of CFVR to FFR on invasive coronary angiography. Statistical significance was assessed as \( P < 0.05 \). Data were analysed using SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA).

Results
Adequate spectral Doppler recordings of coronary flow were obtained in 172 of 183 angiographic lesions (94% feasibility) in 140 out of 147 patients. FFR was successfully evaluated at the all 140 lesions. A total of 172 coronary arteries in 140 patients were thus obtained in 140 patients. FFR was successfully evaluated in the all 140 patients. CTA, computed tomography coronary angiography; TTDE, trans-thoracic Doppler echocardiography; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve.

Figure 1  Patient flow diagram. In the 348 patients who were underwent CTA examinations, 179 patients had at least one ≥50% stenosis in a major epicardial artery as determined by visual assessment on CTA. One hundred and forty-seven patients underwent TTDE and CFVR was adequately obtained in 140 patients. FFR was successfully evaluated in the all 140 patients. CTA, computed tomography coronary angiography; TTDE, trans-thoracic Doppler echocardiography; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve.
Figure 2  (A) A representative case of the LAD lesion. The LAD flow by colour Doppler imaging (arrow). (B and C) Basal and hyperaemic flow velocities of the LAD. Estimated CFVR was 2.0. (D) CAG. %DS of the stenosis of the LAD (arrow) was 65%. (E) The FFR of the LAD was 0.69. It was below the ischaemic threshold of 0.75, indicating a functionally significant stenosis. LAD, left anterior descending coronary artery; CFVR, coronary flow velocity reserve; CAG, coronary angiography; DS, diameter stenosis; FFR, fractional flow reserve. (B) A representative case of the RCA lesion. (A) The RCA flow by colour Doppler imaging (red arrow). (B and C) Basal and hyperaemic flow velocities of the RCA. Estimated CFVR was 1.4. (D) CAG. %DS of the stenosis of the RCA (arrow) was 53%. (E) The FFR of the RCA was 0.70. It was below the ischaemic threshold of 0.75, indicating a functionally significant stenosis. RCA, right coronary artery; CFVR, coronary flow velocity reserve; CAG, coronary angiography; DS, diameter stenosis; FFR, fractional flow reserve. (C) A representative case of the LCX lesion. (A) The LCX flow by colour Doppler imaging (arrow). (B and C) Basal and hyperaemic flow velocities of the LCX. Estimated CFVR was 1.6. (D) CAG. %DS of the stenosis of the LCX (arrow) was 66%. (E) The FFR of the LCX was 0.64. It was below the ischaemic threshold of 0.75, indicating a functionally significant stenosis. LCX, left circumflex coronary artery; CFVR, coronary flow velocity reserve; CAG, coronary angiography; DS, diameter stenosis; FFR, fractional flow reserve.
feasibility). Inter-observer and intra-observer variability in CFVR measurements were determined in 15 randomly selected vessels by repeated coronary flow recordings. Inter-observer variability was calculated as the standard deviation of the differences between the measurements made by two independent observers who were unaware of the other patient data and was expressed as a percentage of the average value. Intra-observer variability was calculated as the standard deviation of the differences between the first and second measurements (2-week interval) for a single observer and was expressed as a percentage of the average value. The mean absolute differences in CFVR measurements were $4.7\pm 2.1\%$ (inter-observer) and $4.5\pm 2.0\%$ (intra-observer).

**Coronary angiography**

Data are shown in Table 1. Of 140 patients analysed, there were 72 (51%) patients with one-vessel disease, 46 (33%) with two-vessel disease, and 22 (16%) with three-vessel disease. There were 132 ($>50\%$) with $\leq50\%$ DS and 40 (23%) with $\leq50\%$ DS. Moreover, vessels with $\leq0.75$ FFR ($n = 79$, $0.65\pm 0.07$) revealed to have greater $\%$DS than those with $>0.75$ FFR ($n = 93$, $0.83\pm 0.06$). FFR is good proportional to QCA ($r = 0.40$, $P < 0.0001$).

**CFVR by TTDE vs. FFR**

Of 172 analysed vessels, there was no significant difference in coronary flow velocity at baseline between FFR under and over 0.75. However, during hyperaemia, coronary flow velocity increased greater in vessels with FFR $>0.75$, resulting in higher CFVR. The CFVR was $1.86\pm 0.36$ in coronary arteries with FFR $\leq0.75$ ($n = 79$) and $2.54\pm 0.48$ in those with FFR $>0.75$ ($n = 93$, $P < 0.0001$). In addition, correlation studies revealed that CFVR was indirectly proportional to FFR ($r = 0.56$, $P < 0.0001$) (Figure 3). A cut-off value of CFVR to detect FFR $\leq0.75$ was determined as 2.2 by the ROC curve for three coronary vessels (area under the curve: AUC = 0.89, 95% confidence interval: CI = 0.84–0.94) (Figure 4). CFVR with cut-off of 2.2 was 85% sensitive and 79% specific in predicting the stenotic condition of coronary artery with FFR $\leq0.75$ in three major vessels. Furthermore, regarding LAD, a cut-off value was also 2.2 (AUC = 0.89, 95% CI = 0.81–0.96). Likewise, RCA gave a cut-off value with 2.1 (AUC = 0.92, 95% CI = 0.84–0.99), LCX with 2.2 (AUC = 0.90, 95% CI = 0.77–1.00), and RCA and LCX with 2.2 (AUC = 0.92, 95% CI = 0.85–0.98) (Table 3 and Figure 5).

Sixty-seven vessels demonstrated CFVR $\leq2.2$ with FFR $\leq0.75$ (true positive). There were 20 vessels with CFVR $\leq2.2$ and FFR $>0.75$ (false positive). On the other hand, 73 vessels showed CFVR $>2.2$ and FFR $>0.75$ (true negative). The remaining 12 vessels showed CFVR $>2.2$ but FFR $\leq0.75$ (false negative). The sensitivity, specificity, PPV, NPV, and accuracy of CFVR compared with FFR (cut-off of 0.75) were 85, 79, 77, 86, 81%, respectively.

Table 4 also presents the data using an FFR 0.8 cut-off. A cut-off value of CFVR to detect FFR $\leq0.8$ was determined as 2.3 by the ROC curve for three coronary vessels (AUC = 0.80, 95% CI = 0.73–0.86). CFVR with cut-off of 2.3 was 75% sensitive and 71% specific in predicting the stenotic condition of coronary artery in three major vessels.
Impaired CFVR was shown in vessels with a DS ≥ 50% compared with those ≤ 50%. There were 73 vessels with CFVR ≤ 2.2 and DS ≥ 50%. Fourteen vessels had CFVR ≤ 2.2 and DS < 50%. There were 26 vessels with CFVR > 2.2 and DS < 50%; however, 59 vessels had CFVR > 2.2 with DS ≥ 50%. In addition, CFVR was proportional to %DS ($r = 0.26$, $P = 0.0008$).

### CFVR vs. QCA analysis

The relationship between CFVR and QCA (DS ≤ 40%, 40% < DS < 70%, 70% < DS ≤ 90%, DS > 90%) is summarized in Figure 6. The median CFVR was 2.36, 2.22, 2.09, 1.57, respectively. The CFVR in vessels with DS ≤ 40% was significantly greater than that with 70% < DS ≤ 90% ($P = 0.039$).
Discussion

The standard method/index for diagnosing significant coronary stenosis has been changing. Exercise-electrocardiogram was replaced by exercise or pharmacological stress-scintigram and echocardiography because of relatively low diagnostic accuracy. Moreover, myocardial perfusion and flow reserve by contrast enhanced MR and Doppler echocardiography have demonstrated relatively high diagnostic potential. The appropriate cut-off values of these imaging techniques have mostly decided in reference to morphological significance of coronary stenosis. Patient prognosis, however, is proved to be more closely related to the functional significance of the disease. In this regard, FFR has become to be a reliable measure of functional stenotic significance. Therefore, an optimal cut-off value of CFVR by TTDE towards FFR is deemed to be determined. Several studies have compared invasively measured CFVR with FFR, however, there was a single published study to compare CFVR by TTDE with FFR, in which the LAD was solely assessed in a small number of patients, and moreover, an optimal cut-off value of CFVR towards FFR was not assessed. Therefore, comparison of CFVR with FFR in three major coronary arteries could be clinically useful.

Conceptual and pathophysiological differences between FFR and CFVR

Discordant result between CFVR and FFR was found in 32 arteries (19%) in the present study using an FFR cut-off of 0.75 and a CFVR cut-off of 2.2. This is rather low compared with the previous study with invasively measured CFVR (cut-off 2.0) and FFR (27%). An alteration in cut-off value (2.0–2.2) may increase cases with false positive and decrease false negative, however, 12 and 7% in this study would be comparable with 10 and 17% in the invasive study. The relatively lower rate of false positive could be attributed by the patient characteristics with low frequency of coronary risk factors. The characteristics of 20 false positive cases were found to be relatively higher incidence of hypertension (90%) than those with true negative (73%). On the other hand, the false negatives were 12 cases (7%) in this study. There might be possible explanations for this discrepancy (false negative). According to the ischaemic threshold, patients have different 'normal CFVR'. Some patients with healthy coronary artery could have higher 'normal CFVR'. Relative CFVR may also give a reason for this discrepancy, however, no case with false negative was determined CFVR in the non-stenotic...
coronary artery in the current study. Three patients, who could be performed follow-up CFVR study after coronary intervention, improved their CFVR $>3.0$. Another hypothesis might aid to explain.

Microvascular resistance exercises an influence on the haemodynamic parameters used in the evaluation of the stenosis of the interrogated vessels, especially in the case with coronary stenosis. In anatomically
fixed stenosis, decrease in hyperaemic microvascular resistance will decrease CFVR, while FFR will increase.

Concerning cut-off value of FFR, the use of 0.75 as reflecting a significant lesion is debatable given that previous studies in a variety of clinical and angiographic conditions with FFR cut-off values of 0.75–0.8. Therefore, we added the data analysis for FFR cut-off values of 0.8 in addition to 0.75. Increasing the FFR cut-off to the upper limit of the ‘grey zone’ (0.8) could lead to a reduction in the number of false positives with an increase in false negatives. In our findings, the number of false positives decreased from 20 (12%) to 18 (10%), while those of false negatives increased from 12 (7%) to 28 (16%) as a result of increasing cut-off value from 0.75 to 0.8.

FFR measurements within the grey zone (0.75–0.8) may put the operator in a dilemma as to how to proceed with therapy in the best interest of patients. Lindstaedt et al. demonstrated that patients with coronary lesions in the grey zone FFR range can be deferred from revascularization without putting them at an increased risk for major adverse events in single-centre study. To determine an optimal FFR cut-off value, a large and randomized trial would be desirable.

In the present study, we underwent FFR measurements only in 172 vessels with suspicion to have at least one ≥50% stenosis in a major coronary artery as determined on CTA. Therefore, it is difficult that we compare the diagnostic value of combined CTA/CFVR to CTA alone by using the data of our study, but both of the specificity and PPV of combined CTA/CFVR in our study (79 and 77%) were greater than those of CTA alone in the previous study (66 and 64%).

CFVR vs. QCA
We highlight the well-known limitations of QCA in assessing the functional significance of CAD. Table 1 shows that a large number of arteries have physiologically significant disease (FFR ≤0.75 or ≤0.80); however, the DS by QCA was ≤70%. The length of disease within these arteries may have a larger role in the severity of flow reduction. The sensitivity and NPV with QCA are excellent, but the specificity and PPV are poor. Figure 6 shows the relationship between CFVR and QCA. The CFVR in vessels with DS ≤40% was significantly greater than that with 70% < DS ≤90% (P = 0.039); however, there is no significant difference among other groups.

Regarding the correlation between CFVR and FFR, our result (r = 0.56) was similar to previous studies, including invasive (r = 0.60) and non-invasive by TTDE on the LAD (r = 0.59).

Limitations
Consistent with clinical practice, CFVR, and FFR was only measured in vessels which were suspect of coronary stenosis by CT coronary angiography before admission. Therefore, in order to assess feasibility of this method, CFVR and FFR measurement in all three major arteries should be warranted. Adenosine is not administered to all the patients, contraindicated in asthmatics and patients with high-degree atioventricular block, and two patients were excluded because of asthma. The relatively small number of vessels, especially in RCA and LCX, is also a limitation of this study. CFVR of six RCA and four LCX could not be determined because of a technical error. Indeed, ~6% of vessels were not determined of this study. To provide accurate diagnosis to all the patients, further improvement in TTDE imaging techniques and ultrasound machine upgrade is required. In addition, we cannot be certain that we have correctly measured the flow velocity of the appropriate coronary artery; for example, patients with co-dominant circulation, it can be difficult to know which vessel provides the majority of the blood supply to the inferior wall.

Conclusions
The non-invasive CFVR measurement by TTDE could be a reliable stenosis-specific alternative for determining the haemodynamic significance of three major coronary arteries.

In routine clinical practice, CFVR is suitable for the assessment of functional severity of intermediate coronary lesions and the follow-up of those treated medically, with the advantages of being non-invasive, easily available at bedside, at low cost, with no radiation exposure.

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