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ORIGINAL PAPER

Applicability of quantitative flow ratio for rapid evaluation of intermediate coronary stenosis: comparison with instantaneous wave-free ratio in clinical practice

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Abstract

Quantitative flow ratio (QFR) is an image-based fractional flow reserve (FFR) computed by three-dimensional quantitative coronary angiography and estimated flow velocity. Several studies have reported that QFR was rapidly computed within approximately 5 min and had a good diagnostic performance as compared with FFR. However, studies comparing QFR with instantaneous wave-free ratio (iFR) as an index with a prognostic value comparable to that of FFR are limited. Thus, we investigated the applicability of QFR with respect to iFR, both being easy-to-measure indices not requiring pharmacological hyperaemic induction. We computed QFR in prospectively enrolled 150 coronary lesions (including 50 lesions for onsite QFR analysis) in consecutive patients with intermediate stenosis evaluated by iFR. The correlation and diagnostic performance of QFR were compared using iFR as a reference. The mean QFR and iFR were 0.81 ± 0.12 and 0.89 ± 0.11, respectively. QFR and iFR exhibited a good correlation in all subjects ($R = 0.70$, $p < 0.0001$) and the onsite-analysed vessels ($R = 0.74$, $p < 0.0001$). In the receiver-operating characteristics analysis, the area under the curve of QFR predicting iFR ≤ 0.89 was 0.91. Applying the cut-off value of QFR ≤ 0.80 and iFR ≤ 0.89, the sensitivity, specificity, positive and negative predictive values were 85%, 83%, 72%, and 91%, respectively, in all subjects, and 82%, 82%, 78%, and 85%, respectively, in the onsite-analysed vessels. QFR including onsite analysis demonstrated a good correlation with iFR and a diagnostic performance comparable to that of iFR in consecutive patients with intermediate coronary stenosis, suggesting its potential as a rapidly derived index for evaluating myocardial ischaemia in clinical settings.

Keywords Quantitative flow ratio · Coronary angiography · Instantaneous wave-free ratio · Fractional flow reserve

Abbreviations

3D	3-Dimensional
DS%	Percent diameter stenosis
FFR	Fractional flow reserve
FFR-CT	Computed tomography-derived FFR
iFR	Instantaneous wave-free ratio
MLD	Minimum lumen diameter
QCA	Quantitative coronary angiography
QFR	Quantitative flow ratio
TIMI	Thrombolysis in myocardial infarction

Introduction

In clinical practice for the diagnosis of coronary artery diseases, the physiological evaluation of coronary lesions, especially intermediate stenosis, is important for estimating myocardial ischaemia and for decision-making in revascularisation [1, 2]. Ischaemia-driven coronary revascularisation with the aid of guidewire-based indices such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) has been associated with improved clinical outcome in several studies [3–6]. However, guidewire-based measurement is associated with several problems due to its invasive nature.

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Quantitative flow ratio (QFR) is an image-based virtual FFR index computed by three-dimensional (3D) quantitative coronary angiography (QCA) and flow velocity estimated by thrombolysis in myocardial infarction (TIMI) frame count using dedicated software. Several studies have reported a good correlation, agreement between QFR and FFR, favourable diagnostic performance of QFR compared to guidewire-based indices [7–14], and reproducibility [15]. Notably, the average time for QFR computation was short, at approximately 5 min [9, 16, 17]. However, studies comparing QFR with iFR as a simply measurable approved resting index with a prognostic value comparable to that of FFR are limited [10, 13].

To assess if QFR could serve as a useful index in clinical practice, we compared QFR and iFR, which are both simply measurable indices not requiring pharmacological hyperaemic induction. The aim of this study was (1) to confirm the relationship between QFR and iFR, and to determine the diagnostic accuracy of QFR using iFR as a reference in prospectively enrolled consecutive patients, and (2) to investigate the applicability of onsite QFR analysis by the in-procedure comparison to iFR during invasive coronary angiography.

Material and methods

Subjects

Consecutive patients who underwent coronary angiography and iFR measurement for the evaluation of intermediate coronary stenosis were prospectively enrolled between December 2017 and January 2019 at our centre. Patients lacking two optimal angiographic projections at least 25° apart, such as overlapping interrogated vessels, without preferred references in proximal or distal vessels, and with incomplete pressure-wire measurements were excluded.

Coronary angiography and iFR measurement

Coronary angiography was performed using the monoplane or biplane X-ray system (Infinix Celeve-i INFX-8000V/8000C; Canon Medical Systems, Ohtawara, Japan). Angiographic images were recorded at 15 frames/s. Two angiographic projections at least 25° apart, which clearly depicted the objective lesion/vessel, were acquired for the QFR analysis. For iFR measurement, a coronary pressure wire (Verrata®; Philips, Amsterdam, The Netherlands) was used. After calibration and equalization, the pressure wire was advanced and the sensor of the wire was placed distal to the lesion. Coronary pressure at the both proximal and distal side was recorded simultaneously. The pressure sensor was pulled back to the catheter tip to check the pressure drift.

3D-QCA and QFR calculation

The 3D coronary image reconstruction and QCA analysis with QFR calculation were performed using validated software (QAngio® XA 3D/QFR; Medis, Leiden, The Netherlands) by selected certified investigators who were blinded to the iFR values. Initially, two optimal angiographic projections at least 25° apart were selected for fundamental resources. Adequately contrast-filled end-diastolic images were loaded. Subsequently, proximal and distal points were registered as the regions of interest. The 3D QCA was automatically reconstructed with the proposed analytic model, which was based on geometrical features derived from the entrance angle of the coronary stenosis, angularity of the centre line, and reference points of the lumen diameter. Lumen contours and the proximal or distal reference points were manually adjusted if needed. Thereafter, percent diameter stenosis (DS%), lesion length, minimum lumen diameter (MLD), and reference proximal and distal vessel diameters were calculated automatically using the 3D QCA.

The detailed theory and algorithm of QFR computation has been described previously [7, 8]. In the present study, contrast-flow QFR was applied using frame count analysis from non-hyperaemic angiographic images to model hyperaemic flow velocity. The TIMI frame count of the contrast bolus from the proximal to the distal portion of the analysed segment of the vessel was used as an estimation of coronary flow velocity. Finally, QFR was computed (Fig. 1). The QFR value at the position matched the location of the pressure sensor on the pressure wire was used for comparison with the iFR.

Onsite QFR analysis

The QFR analysis system was placed in the control room of the catheterization laboratory. If possible in the clinical setting, the selected investigators analysed QFR during the catheterization procedure, just after angiographic image acquisition and prior to iFR measurement, for the in-procedure comparison to iFR as onsite QFR analysis. In other cases, QFR was computed after angiography and iFR examination by investigators who were blinded to the iFR values.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (IQR). Data were analysed on a per-patient basis for clinical characteristics and on a per-vessel basis for lesion characteristics. Pearson's correlation coefficient was calculated to quantify the correlation between iFR and QFR. Bland–Altman plot was used to visualize and compare iFR and QFR.

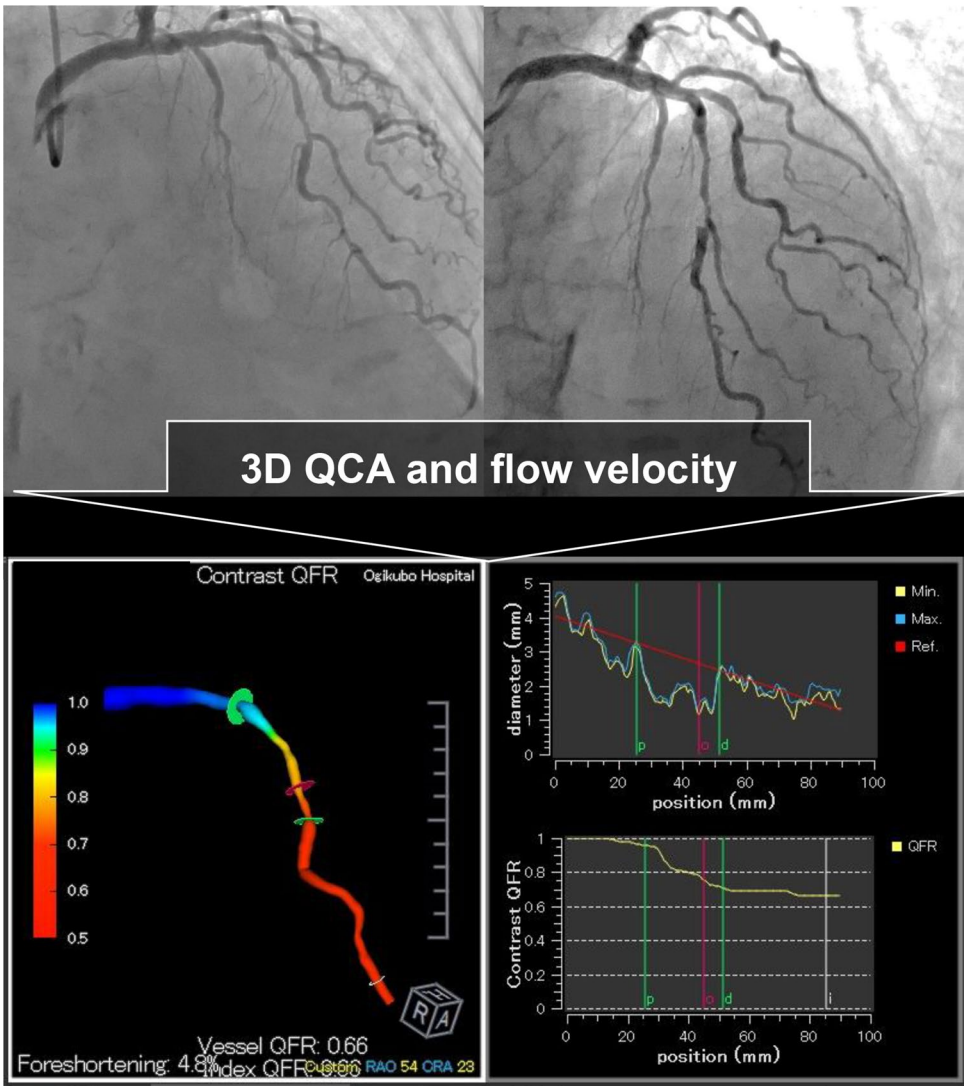

Fig. 1 Example of QFR analysis of intermediate stenosis of the left anterior descending coronary artery

The performance of QFR for predicting functionally significant stenosis was assessed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The area under the curve (AUC) in the receiver operating characteristic (ROC) analysis was used to assess the diagnostic accuracy of QFR and 3D QCA. All statistical analyses were performed with JMP® version 13.0 (SAS Institute, Cary, NC, USA). A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics and QFR computation feasibility

Among consecutive 161 vessels in 128 patients with intermediate stenosis evaluated by coronary angiography and iFR measurement, 11 vessels (7%) were totally excluded because of non-optimal angiographic projections for QFR analysis (n = 9) or incomplete pressure-wire measurement (n = 2). The remaining 150 vessels (93%) in 121 patients underwent QFR analysis. Patient and lesion characteristics are shown in Tables 1 and 2, respectively. In a total of 50 vessels (33%), QFR was computed during the catheterization procedure for the in-procedure comparison to iFR as onsite QFR analysis.

Correlation between QFR and iFR

The mean QFR and iFR were 0.81 ± 0.12 and 0.89 ± 0.11, respectively. QFR and iFR were well correlated ($R = 0.70$, $p < 0.0001$) and the mean difference was 0.078 ± 0.089 (Fig. 2). In the onsite QFR analysis, the correlation was also good ($R = 0.74$, $p < 0.0001$) and the mean difference was 0.085 ± 0.080 (Fig. 3).

Table 1 Baseline patient characteristics (n = 121)

Age, years	71 ± 11
Male	82 (68)
BMI, kg/m^2	24.1 ± 4.1
Hypertension	83 (69)
Dyslipidaemia	77 (64)
Diabetes	43 (36)
Cardiovascular history	
Prior myocardial infarction	26 (21)
Prior PCI	43 (36)
Prior CABG	3 (2)
CAD type	
UA/NSTEMI	4 (3)
Stable angina	42 (35)
Other stable CAD	75 (62)

Values are presented as mean ± SD or n (%)

BMI body mass index, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *NSTEMI* non-ST-elevated myocardial infarction, *PCI* percutaneous coronary intervention, *UA* unstable angina

Table 2 Baseline lesion characteristics (n = 150)

Index coronary artery	
Left anterior descending artery	96 (64)
Left circumflex artery	20 (13)
Right coronary artery	34 (23)
Prior infarct-related artery	10 (7)
Stent-related lesions	13 (9)
Bifurcation lesions	69 (46)
Diffuse/tandem lesions	63 (42)
iFR	
Mean ± SD	0.89 ± 0.11
Median (IQR)	0.92 (0.86–0.95)
FFR (n = 69)	0.82 ± 0.08
Percent diameter stenosis	49 ± 9
Minimum lumen diameter, mm	1.4 ± 0.4
Reference vessel diameter	
Proximal, mm	2.9 ± 0.6
Distal, mm	2.5 ± 0.5

Values are presented as n (%), mean ± SD or median (IQR)

Diagnostic accuracy of QFR

Applying the iFR cut-off of ≤ 0.89 (n = 52) and the QFR cut-off of ≤ 0.8 (n = 61) resulted in 44 true-positive, 81 true-negative, 17 false-positive, and 8 false-negative results. The sensitivity, specificity, PPV, and NPV of QFR were 85%, 83%, 72%, and 91%, respectively, in all subjects, and 82%, 82%, 78%, and 85%, respectively, in the onsite QFR analysis. For the ROC analysis for the diagnosis of iFR ≤ 0.89, QFR had a greater AUC of 0.91 than MLD (AUC 0.71) and DS% (AUC 0.68) (Fig. 4).

Discussion

The present study of consecutive patients with intermediate coronary stenosis who were prospectively evaluated via QFR and iFR showed that QFR demonstrated a good correlation with iFR and had a diagnostic performance comparable to that of iFR. Moreover, the favourable diagnostic accuracy was also maintained in onsite QFR analysis.

Several studies including our previous report [9] showed that QFR had good correlation, agreement, and diagnostic performance compared to wire-based FFR as the standard [7–14]. However, reports which compared QFR with iFR as a simply measurable approved resting index with comparable prognostic value to FFR are limited. A few retrospective studies reported the correlation between QFR and iFR with R of 0.71 and 0.74 that was similar to that in the present study [10, 13].

The notable feature of QFR measurement is its short duration. In our previous analysis the average time to calculate QFR was 266 s (IQR 181–332s, n = 151) [9], and was reported as approximately 5 min in the other multicentre trials [16, 17]. This is one of the major differences between QFR and computed tomography-derived FFR (FFR-CT), which is another image-based virtual FFR tool that requires several hours for computation using a dedicated supercomputer employing complex algorithms. Based on its non-invasive nature, FFR-CT has the advantage of detecting or evaluating ischaemia-inducible coronary vessels in elective patients suspected of having coronary artery disease. Several studies have reported the diagnostic utility of FFR-CT, especially as a gatekeeper of invasive testing [18–20]. In contrast, QFR has the potential to become a rapidly analysable index in patients undergoing invasive coronary angiography. For instance, in the multicentre trials of FAVOR II Europe-Japan [16], FAVOR II China [17] and a meta-analysis of diagnostic performance of QFR in prospectively enrolled patients [14], the feasibility of online QFR analysis was reported. Spitaleri et al. reported the utility of QFR analysis in the identification of non-culprit coronary lesions requiring revascularisation in patients with ST-segment-elevation myocardial infarction and multi-vessel disease [21]. Asano et al. investigated the prognostic value of the functional SYNTAX score derived from QFR in patients with three-vessel coronary disease [22]. All these studies indicate the feasibility and utility of QFR analysis as a rapid method not requiring a pressure guidewire or drug-induced hyperaemia. Furthermore, the promising results of the present study confirm the applicability of QFR for the rapid evaluation of intermediate coronary artery disease in daily clinical practice.

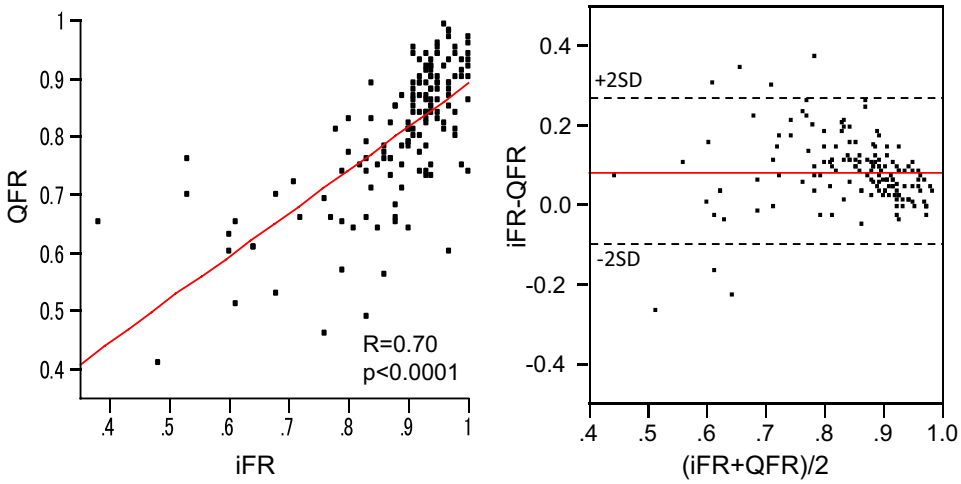

Fig. 2 Correlation and Bland–Altman plot between QFR and iFR

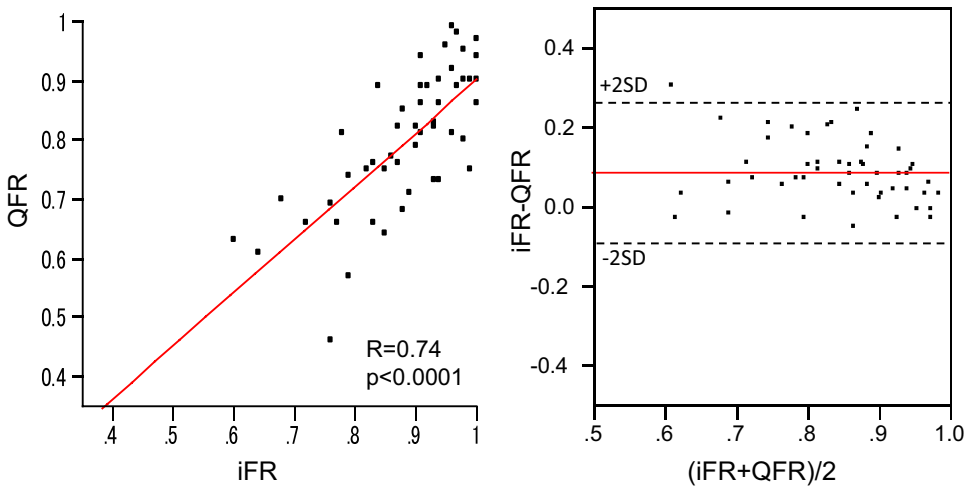

Fig. 3 Correlation and Bland–Altman plot between QFR and iFR in onsite-analysed vessels

However, the non-negligible number of discordant cases, such as the 25 out of 150 (17%) false-negative and false-positive results of QFR compared with iFR, which resulted in the suboptimal PPV of 72%, needs to be considered. The cause of the discordance between FFR and iFR is thought to originate from the differences in the patients' conditions with or without maximal hyperaemia during the measurement and coronary flow reserve [23]. It is unclear whether the same explanation can be applied to the comparison between the image-based virtual FFR based on the modelled hyperaemic flow velocity and iFR as a resting index. Mejía-Rentería et al. reported on the influence of coronary microcirculatory dysfunction on the diagnostic performance of QFR [24]. Further investigation will be needed to establish the proper use of QFR and to distinguish the meanings of the measurements of each modality.

Limitations

First, the small sample size, especially for the onsite QFR analysis, and the single-centre design are major limitations of the current study. Second, because we enrolled consecutive patients who underwent iFR measurement and QFR computation, various targets including bifurcation, diffuse/tandem, stented, or prior infarction-related lesions should have been candidates for analysis. Nevertheless, a new advanced software with the algorithm adapted for bifurcation was not used. Moreover, QFR in previous infarction-related arteries was reportedly assessed with reduced accuracy in functional severity [25]. Third, among cases excluded because of the lack of optimal angiographic projections, there were a few with left main trunk or ostial lesions, which are clinically important for evaluating disease severity. Finally, all QFR computations in this study were

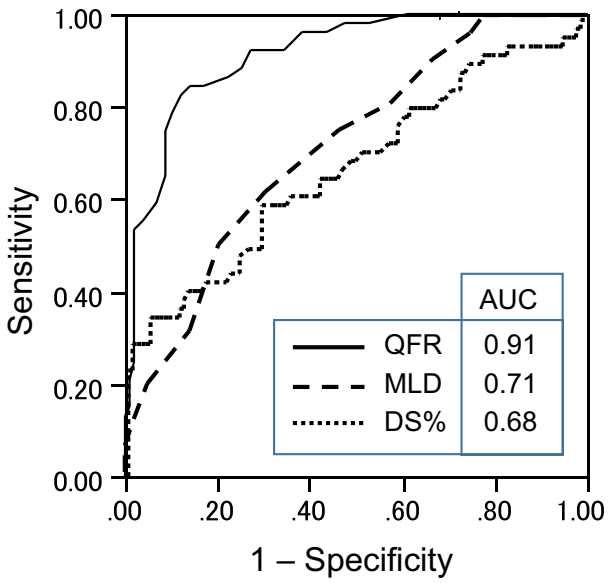

Fig. 4 Receiver operating characteristic (ROC) curves for the diagnosis of iFR ≤ 0.89. *AUC* area under the curve, *DS%* percent diameter stenosis, *MLD* minimum lumen diameter

performed by selected investigators who were trained and certified as expert users. This may be a limitation in terms of the general use of QFR in daily clinical practice.

Conclusions

QFR, including onsite analysis, exhibited a good correlation with iFR and a diagnostic performance comparable to that of iFR in consecutive patients with intermediate coronary stenosis, suggesting its potential for the rapid evaluation of myocardial ischaemia in various clinical settings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the institutional ethical review board. All patients provided written informed consent before enrolment.

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