Diagnostic Agreement of Quantitative Flow Ratio With Fractional Flow Reserve and Instantaneous Wave-Free Ratio

Doyeon Hwang, MD;* Ki Hong Choi, MD;* Joo Myung Lee, MD, MPH, PhD; Hernán Mejía-Rentería, MD; Jihoon Kim, MD; Jonghanne Park, MD; Tae-Min Rhee, MD; Ki-Hyun Jeon, MD; Hyun-Jong Lee, MD, PhD; Hyun Kuk Kim, MD, PhD; Taek Kyu Park, MD, PhD; Jeong Hoon Yang, MD; Young Bin Song, MD, PhD; Eun-Seok Shin, MD, PhD; Chang-Wook Nam, MD, PhD; Jae-Jin Kwak, MD; Joon-Hyung Doh, MD, PhD; Joo-Yong Hahn, MD, PhD; Jin-Ho Choi, MD, PhD; Seung-Hyuk Choi, MD, PhD; Javier Escaned, MD, PhD; Bon-Kwon Koo, MD, PhD; Hyeon-Cheol Gwon, MD, PhD

Background—Quantitative flow ratio (QFR) has a high diagnostic accuracy in assessing functional stenoses relevance, as judged by fractional flow reserve (FFR). However, its diagnostic performance has not been thoroughly evaluated using instantaneous wave-free ratio (iFR) or coronary flow reserve as the reference standard. This study sought to evaluate the diagnostic performance of QFR using other reference standards beyond FFR.

Methods and Results—We analyzed 182 patients (253 vessels) with stable ischemic heart disease and 82 patients (105 nonculprit vessels) with acute myocardial infarction in whom coronary stenoses were assessed with FFR, iFR, and coronary flow reserve. Contrast QFR analysis of interrogated vessels was performed in blinded fashion by a core laboratory, and its diagnostic performance was evaluated with respect to the other invasive physiological indices. Mean percentage diameter stenosis, FFR, iFR, coronary flow reserve, and QFR were $53.1\pm19.0\%$, 0.80 ± 0.13, 0.88 ± 0.12, 3.14 ± 1.30, and 0.81 ± 0.14, respectively. QFR showed higher correlation ($r=0.863$ with FFR versus 0.740 with iFR, $P<0.001$), diagnostic accuracy (90.8% versus 81.3%, $P<0.001$), and discriminant function (area under the curve$=0.953$ versus 0.880, $P<0.001$) when FFR was used as a reference standard than when iFR was used as the reference standard. However, when coronary flow reserve was used as an independent reference standard, FFR, iFR, and QFR showed modest discriminant function (area under the curve$=0.682$, 0.765, and 0.677, respectively) and there were no significant differences in diagnostic accuracy among FFR, iFR, and QFR (65.4%, 70.6%, and 64.9%; all P values in pairwise comparisons >0.05, overall comparison $P=0.061$).

Conclusions—QFR has a high correlation and agreement with respect to both FFR and iFR, although it is better when FFR is used as the comparator. As a pressure-derived index not depending on wire or adenosine, QFR might be a promising tool for improving the adoption rate of physiology-based revascularization in clinical practice. (***J Am Heart Assoc***. 2019;8:e011605. DOI: 10.1161/ JAHA.118.011605.)

Key Words: computational fluid dynamics • diagnostic agreement • fractional flow reserve • instantaneous wave-free ratio • quantitative flow ratio

The presence of inducible myocardial ischemia is the prerequisite indication for percutaneous coronary intervention. In this regard, a pressure-derived physiologic index, fractional flow reserve (FFR), has been the standard invasive method to evaluate the functional significance of epicardial coronary artery stenosis.[1,2] Recently, instantaneous wave-free

<div style="border: 2px solid red;">

Clinical Perspective

What Is New?

- Quantitative flow ratio (QFR) showed higher correlation and diagnostic performance for the prediction of fractional flow reserve than instantaneous wave-free ratio; however, the absolute efficacy of QFR to predict instantaneous wave-free ratio was also excellent. In addition, diagnostic performance of fractional flow reserve, instantaneous wave-free ratio, and QFR was comparable when coronary flow reserve was used as a reference method.

What Are the Clinical Implications?

- As QFR does not require additional interrogation with a pressure wire or administration of hyperemic agents, and shows significantly shorter measurement time than invasive physiologic assessment, this might represent a more simple, safe, and cost-effective method to guide revascularization.
- With excellent diagnostic agreement of QFR with both fractional flow reserve and instantaneous wave-free ratio, QFR-guided strategy might be a promising tool for improving the adoption rate of physiology-based revascularization.

</div>

ratio (iFR), which does not require hyperemia, was developed as an alternative for FFR,[3] and 2 randomized controlled trials demonstrated comparable clinical outcomes between iFR- and FFR-guided strategies with less use of revascularization after iFR-guided treatment.[4,5] On this ground, recent guidelines recommend the measurement of FFR or iFR in defining the functional significance of intermediate epicardial coronary stenoses as a class IA recommendation.[1]

However, the adoption rates of FFR- or iFR-guided percutaneous coronary intervention are still low in real-world practice.[6] As alternative methods to evaluate functional significance of epicardial coronary stenosis, functional coronary imaging has recently emerged, allowing wire-free functional assessment of stenosis severity based on a computational fluid dynamics model or mathematical assumptions of coronary flow. Quantitative flow ratio (QFR) is a 3-dimensional quantitative coronary angiography (QCA)–based computation of FFR, and previous studies have demonstrated excellent correlations and diagnostic agreements with FFR.[7–12] However, as QFR is calculated using simulated hyperemic status of coronary circulation,[7,8] this might show discrepancies with iFR-based treatment decision-making, as this latter index is measured during resting status.[13,14] Nevertheless, data for diagnostic performance of QFR compared with iFR as a reference standard are still limited.[15] In addition, as FFR and iFR are pressure-derived surrogates of coronary flow, and QFR uses simulated coronary flow, the comparison of diagnostic performance of these indices using other independent

reference tests, such as coronary flow reserve (CFR), would be more reasonable.[13,16]

For these reasons, we sought to evaluate the diagnostic performance and agreement of QFR using FFR or iFR as reference standards, and also evaluated these 3 physiologic indices using CFR as an independent reference standard.

Methods

Anonymized patient-level data will be made available by the corresponding author upon reasonable request.

Study Population

The study population was derived from previously published studies.[17] Briefly, between April 2016 and June 2018, a total of 118 consecutive patients with acute myocardial infarction (AMI) who underwent clinically indicated physiologic assessment for nonculprit stenosis with visual stenosis of 40% to 80% were included from the prospective Institutional Registry of Samsung Medical Center.[17] AMI was defined as the third universal definition of MI.[18] Data from 203 patients with stable ischemic heart disease (SIHD) were selected from the prospective multicenter registry of comprehensive physiologic assessment, which enrolled consecutive patients who underwent clinically indicated invasive coronary angiography and physiologic assessment from 5 university hospitals in Korea (Samsung Medical Center, Seoul National University Hospital, Inje University Ilsan Paik Hospital, Keimyung University Dongsan Medical Center, and Ulsan University Hospital) (clinicaltrials.gov: NCT02186093).[19]

Among these populations, 82 patients with AMI (105 nonculprit vessels) and 182 patients with SIHD (253 vessels) were included in the current analysis after excluding vessels without available QFR because of anatomical or angiographic limitations in QFR analysis (Figure 1). The excluded patients (57 patients, 17.8%) had limited coronary angiographic image quality for QFR analysis (calibration failure, ostial disease, insufficient projections, tortuous vessels, overlapping of vessels, or poor contrast filling). The study protocol was approved by the institutional review board of each participating center and was conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Invasive Angiography and Measurement of Physiologic Indices

Coronary angiography was performed with standard techniques. After administration of intracoronary nitrate (100 or 200 μg), angiographic views were obtained. QCA was
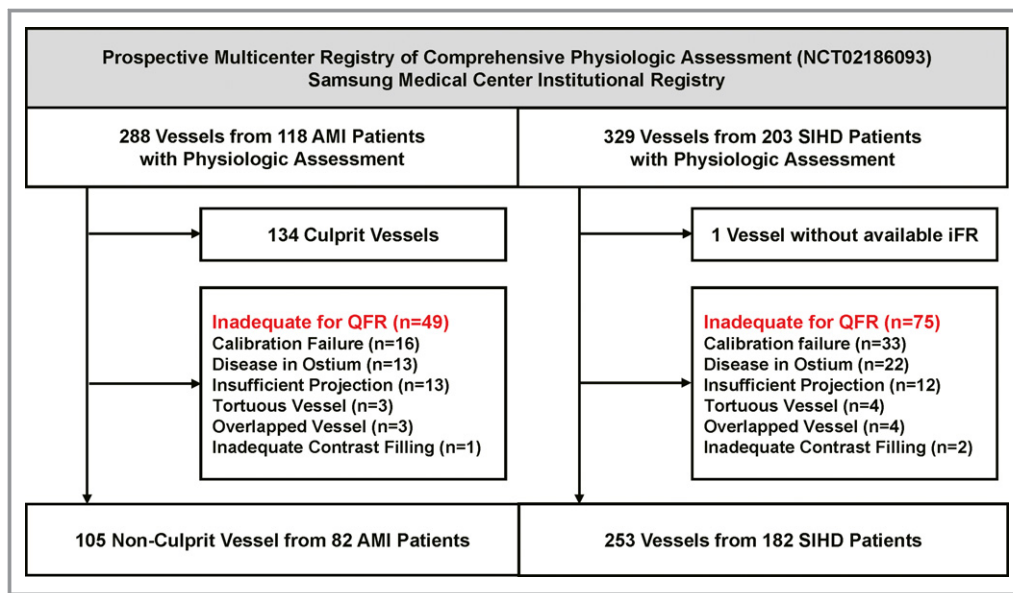
Figure 1. Study flow. Among these populations, 82 patients with acute myocardial infarction (AMI) (105 nonculprit vessels) and 182 patients with stable ischemic heart disease (SIHD) (253 vessels) were included in the current analysis after excluding vessels without available quantitative flow ratio (QFR) caused by anatomical or angiographic limitations in QFR analysis. iFR indicates instantaneous wave-free ratio.

performed with optimal projections using validated software (CAAS II, Pie Medical System). From QCA, minimal lumen diameter, reference vessel size, and lesion length were measured and percentage diameter stenosis was calculated.

After diagnostic angiography, coronary physiologic indices were obtained as previously described.[19] After engagement of a 5-7F guide catheter without side holes in the coronary artery, the pressure-temperature sensor guide wire (Abbott Vascular) was calibrated and equalized to aortic pressure. Then, it was placed at the distal segment of a target vessel. Before each physiologic measurement, intracoronary nitrate (100 or 200 µg) was administered. Intravenous infusion of adenosine (140 µg/kg per min through a peripheral vein) or intracoronary bolus injection of nicorandil (2 mg) was used to induce hyperemia.[20,21]

Resting distal to aortic coronary pressure (Pd/Pa) was calculated as the ratio of mean aortic pressure (Pa) to mean distal coronary arterial pressure (Pd). iFR was calculated as the mean Pd divided by the mean Pa during the diastolic wave-free period. The resting tracing data were extracted and the iFR was calculated using automated algorithms acting over the wave-free period during a minimum of 5 beats, as previously described.[14] FFR was acquired during maximal hyperemia and was defined as the lowest value of mean hyperemic Pd/Pa. CFR was calculated as resting mean transit time divided by hyperemic resting mean transit time. To derive resting mean transit time, a thermodilution curve was obtained by using 3 injections (4 mL each) of room-temperature saline in both resting and hyperemic states.

After every measurement, the pressure wire was pulled back to the guide catheter and the presence of pressure drift was checked. All coronary physiologic measurements were performed after diagnostic angiography in patients with SIHD or after percutaneous coronary intervention for the culprit vessel in the nonculprit vessel of patients with AMI. Coronary physiologic data were collected and validated at a core laboratory in a blinded fashion. The cutoff values of FFR ≤0.80, iFR ≤0.89, resting Pd/Pa ≤0.92, and CFR ≤2.0 were used in the current study.[13,14]

Computation of QFR

Three-dimensional QCA and analysis of QFR were performed by an independent core laboratory with dedicated software (QAngio-XA 3D, version 1.2, Medis) in a blinded fashion for clinical data or invasive FFR, iFR, resting Pd/Pa, or CFR values, as previously described.[8,9] Briefly, end-diastolic frames of 2 optimal angiography projections, which were separated with angles of at least 25°, were selected and used for 3-dimensional model reconstruction. The 3-dimensional contour model of the segment of interest and its reference vessel were constructed in an automated manner and manual correction of contour was performed, if necessary. After acquisition of fixed QFR, estimated contrast coronary flow was calculated using thrombolysis in myocardial infarction (TIMI) frame-count adjustment, which indicated the frames where contrast entered and exited the segmented part of the vessel.[8] With application of TIMI frame-count adjustment in

Table 1. Baseline Patient and Lesion Characteristics

Patient Characteristics (N=264)	
Demographics	
Age, y	60.6±13.3
Men	203 (76.9)
Body mass index, kg/m^2	24.1±3.2
Hypertension	133 (50.4)
Diabetes mellitus	87 (33.0)
Hypercholesterolemia	156 (59.1)
Current smoker	47 (17.8)
Family history of coronary artery disease	20 (17.4)
Prior myocardial infarction	16 (6.1)
Left ventricular ejection fraction, %	60.9±10.1
Clinical presentations	
SIHD	182 (68.9)
non–ST-segment–elevation myocardial infarction	55 (20.8)
ST-segment–elevation myocardial infarction	27 (10.2)
Lesion Characteristics (N=358)	
Lesion location	
LAD	223 (62.3)
LCX	68 (19.0)
RCA	67 (18.7)
Quantitative coronary angiography	
Reference vessel diameter, mm	3.14±0.61
Minimum lumen diameter, mm	1.50±0.72
Diameter stenosis, %	53.1±19.0
Lesion length, mm	15.6±10.0
Invasive physiologic indices	
Fractional flow reserve	0.80±0.13
Instantaneous wave-free ratio	0.88±0.12
Resting Pd/Pa	0.92±0.09
Quantitative flow ratio	0.81±0.14
Coronary flow reserve	3.14±1.30

Values are expressed as mean±SD or number (percentage). LAD indicates left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; Pd/Pa, distal to aortic coronary pressure; SIHD, stable ischemic heart disease.

the calculation method, the software automatically calculated the contrast QFR value. The cutoff value of contrast QFR ≤0.80 was used in the current study.[8,9]

Statistical Analysis

Categorical variables are presented as numbers and relative frequencies. Continuous variables are presented as mean and SD or median with interquartile range according to their distributions, which were checked by the Kolmogorov-Smirnov test. ANOVA was used for comparison of continuous variables among the groups. Repeated measure correlation coefficients (*r*) using linear mixed model were calculated to assess the correlations among FFR, iFR, CFR, and QFR for adjustment of multivessel measurements within a patient. The differences of correlation coefficients were tested by the Fisher r-to-z transformation. The agreement between QFR and FFR or between QFR and iFR was tested by Bland-Altman plots.

Diagnostic performances of QFR were presented with sensitivity, specificity, positive predictive value (PPV), negative predictive value, and diagnostic accuracy. Diagnostic performances were compared using McNemar test or weighted generalized score statistic. Discriminant function was evaluated using area under the curve (AUC) and 95% CIs in receiver operating curve analysis, and AUC was compared with the DeLong method. To evaluate interindividual variability in QFR assessment, 2 independent researchers analyzed 30 randomly selected cases. The paired measurements were compared using paired sample *t* test.

All probability values were 2-sided, and *P*<0.05 was considered statistically significant. The statistical package R, version 3.4.3 (R Foundation for Statistical Computing) was used for statistical analysis.

Results

Baseline Patient and Lesion Characteristics

Baseline patient and lesion characteristics are presented in Table 1. The mean age was 60.6±13.3 years and 203 patients (76.9%) were men. Mean percentage diameter stenosis, FFR, iFR, CFR, and QFR were 53.1±19.0%, 0.80±0.13, 0.88±0.12, 3.14±1.30, and 0.81±0.14, respectively. The proportions of FFR ≤0.80, iFR ≤0.89, and CFR ≤2.0 were 39.9%, 40.5%, and 23.4%, respectively. The distributions of FFR, iFR, and QFR according to clinical presentation are shown in Figure S1. Regarding interindividual variability in QFR assessment, the QFR values from 2 independent researchers were nearly the same without significant differences (0.792±0.107 versus 0.794±0.109, *P*=0.919).

Diagnostic Performance of QFR to Predict FFR or iFR

QFR was significantly correlated with FFR and iFR; nevertheless, QFR showed a significantly higher correlation coefficient with FFR than iFR (*r*=0.863 versus 0.740, *P*<0.001) (Figure S2 and Table 2). The higher correlation of QFR with FFR than with iFR

Table 2. Comparison of Diagnostic Performance of QFR to Predict FFR or iFR

	FFR as Reference	iFR as Reference	P Value
Total population			
Sample size	264 Patients with 358 vessels	264 Patients with 358 vessels	
Correlation coefficient	0.863 (0.800–0.907)	0.740 (0.631–0.820)	<0.001
Sensitivity, %	92.3 (87.9–96.7)	80.0 (73.5–86.5)	<0.001
Specificity, %	89.8 (85.7–93.8)	82.2 (77.0–87.3)	<0.001
PPV, %	85.7 (80.2–91.2)	75.3 (68.5–82.1)	0.002
NPV, %	94.6 (91.5–97.7)	85.8 (81.0–90.6)	0.004
Diagnostic accuracy, %	90.8 (90.7–90.8)	81.3 (81.2–81.4)	<0.001
SIHD			
Sample size	182 Patients with 253 vessels	182 Patients with 253 vessels	
Correlation coefficient	0.857 (0.779–0.909)	0.741 (0.612–0.831)	<0.001
Sensitivity, %	90.1 (84.0–96.2)	78.4 (69.8–87.0)	0.012
Specificity, %	89.5 (84.8–94.2)	81.8 (75.9–87.7)	<0.001
PPV, %	82.8 (75.4–90.3)	69.7 (60.6–78.7)	0.006
NPV, %	94.2 (90.5–97.9)	87.7 (82.5–92.9)	0.066
Diagnostic accuracy, %	89.7 (89.7–89.8)	80.6 (80.5–80.8)	<0.001
AMI (nonculprit)			
Sample size	182 Patients with 105 vessels	182 Patients with 105 vessels	
Correlation coefficient	0.884 (0.737–0.951)	0.739 (0.461–0.885)	0.002
Sensitivity, %	96.2 (90.9–101.4)	82.5 (72.6–92.3)	0.008
Specificity, %	90.6 (82.7–98.4)	83.3 (72.8–93.9)	0.067
PPV, %	90.9 (83.3–98.5)	85.5 (76.1–94.8)	0.371
NPV, %	96.0 (90.6–101.4)	80.0 (68.9–91.1)	0.027
Diagnostic accuracy, %	93.3 (93.2–93.4)	82.9 (82.6–83.1)	0.009

Values are expressed as estimates with 95% CIs. Correlation coefficient was calculated based on per-vessel analysis using mixed linear model for adjustment of multivessel measurements within a patient. The differences of correlation coefficients were tested by the Fisher r-to-z transformation. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated based on per-vessel analysis and compared using McNemar test or weighted generalized score statistic. AMI indicates acute myocardial infarction; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; QFR, quantitative flow ratio; SIHD, stable ischemic heart disease.

was similar in both AMI nonculprit and SIHD vessels ($r=0.857$ versus 0.741 in patients with SIHD, $P<0.001$; 0.884 versus 0.739 in patients with AMI, $P=0.002$) (Figure S2 and Table 2). The agreement between QFR and FFR was also higher than that between QFR and iFR in the total population (bias±SD: 0.002±0.140 versus −0.070±0.188, $P<0.001$), and the higher agreement of QFR with FFR than with iFR was also similarly observed in both AMI nonculprit and SIHD vessels (Figure S3).

Diagnostic performances of QFR to predict FFR ≤0.80 or iFR ≤0.89 are shown in Table 2. With FFR as a reference standard, the sensitivity, specificity, positive PPV, negative predictive value, and diagnostic accuracy of QFR were 92.3%, 89.8%, 85.7%, 94.6%, and 90.8%, respectively. With iFR as a reference, the sensitivity, specificity, PPV, negative predictive value, and diagnostic accuracy of QFR were 80.0%, 82.2%, 75.3%, 85.8%, and 81.3%. All indices of diagnostic performance of QFR were higher when FFR was used as a reference than iFR, regardless of clinical presentation (all $P<0.05$) (Table 2). The distributions of target vessels were not significantly different according to the concordance or discordance of QFR, compared with FFR or iFR ($P=0.692$ for QFR with FFR; 0.659 for QFR with iFR) (Table S1).

The discriminant functions of QFR to predict FFR ≤0.80 or iFR ≤0.89 are shown in Figure 2 and Table 3. The AUC values of QFR for FFR ≤0.80 or iFR ≤0.89 were 0.953 (95% CI, 0.932–0.974) and 0.880 (95% CI, 0.844–0.917), respectively (P for comparison<0.001). In both patients with SIHD and those with AMI, the AUC values of QFR for FFR ≤0.80 was significantly higher than those for iFR ≤0.89. However, there
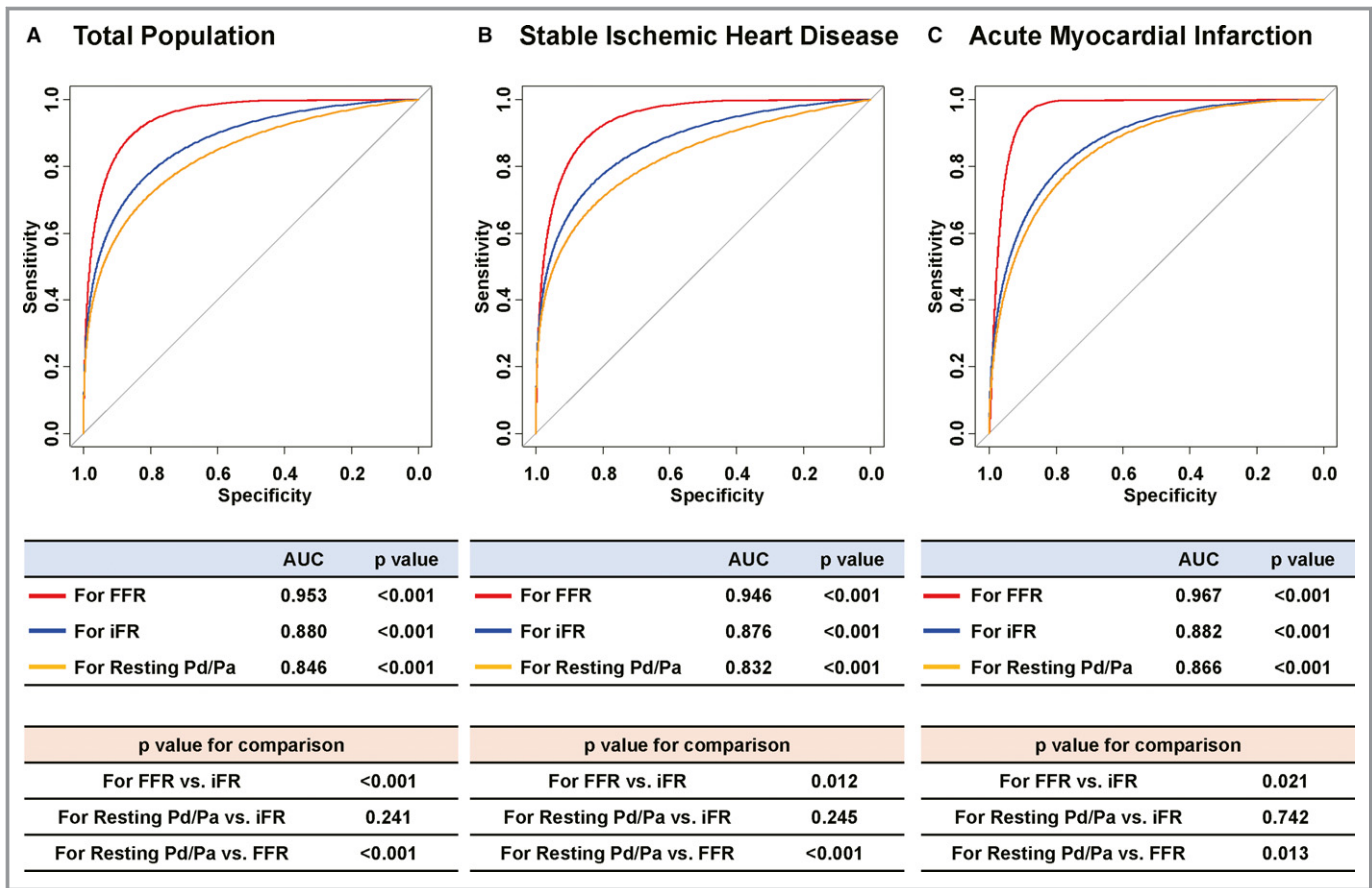
Figure 2. Discriminant function of quantitative flow ratio (QFR) to predict fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), and resting distal to aortic coronary pressure (Pd/Pa). Discriminant functions of QFR to predict FFR ≤0.80, iFR ≤0.89, or resting Pd/Pa ≤0.92 are presented in (**A**) total population, (**B**) vessels of stable ischemic heart disease, or (**C**) nonculprit vessels of acute myocardial infarction. AUC indicates area under the curve.

was no significant difference in AUC of QFR between the nonculprit vessel of patients with AMI and those with SIHD, regardless of the reference methods used (Table 3).

The discriminant function of QFR to predict resting Pd/Pa ≤0.92 was also evaluated and the AUC values of QFR for iFR ≤0.89 or resting Pd/Pa ≤0.92 were not significantly different (Figure 2). In comparison of discriminant functions among QFR, iFR, and resting Pd/Pa to predict FFR≤0.80 as a reference, QFR showed significantly higher AUC than iFR (0.953 versus 0.918, P=0.023) or resting Pd/Pa (0.953 versus 0.909, P=0.023); however, there was no significant difference between iFR and resting Pd/Pa (P=0.682) (Figure S4).

Comparison of FFR, iFR, and QFR Using CFR as an Independent Reference Standard

The discriminant functions of FFR, iFR, and QFR were modest with CFR as a reference standard, although iFR showed a significantly higher discriminant function than FFR or QFR

(Figure 3 and Table 4). However, when CFR ≤2.0 was used as a reference standard, the overall diagnostic accuracies of FFR, iFR, and QFR were not significantly different (65.4%, 70.6%, and 64.9%, respectively; all P values in pairwise comparisons >0.05, overall comparison P=0.061) as with sensitivity, specificity, PPV, and negative predictive value (Table 4).

Among the total population, QFR showed discordance mainly with iFR rather than FFR. QFR disagreed with iFR in 18.7% (67/358 vessels), including 38 vessels with QFR ≤0.80 and iFR >0.89 (10.6%), and 29 vessels with QFR >0.80 and iFR ≤0.89 (8.1%) (Figure 4 and Table 5). CFR was significantly higher in vessels with iFR >0.89 than with iFR <0.89, regardless of QFR values (QFR >0.80 group: CFR 3.48±1.19 for iFR >0.89 versus CFR 2.59±1.13 for iFR ≤0.89, P=0.016; QFR ≤0.80 group: CFR 3.66±1.46 for iFR >0.89 versus CFR 2.52±1.18 for iFR ≤0.89, P<0.001). However, CFR was comparable between the vessels with QFR >0.80 and QFR ≤0.80, in both the iFR >0.89 group (P=0.896) and the iFR ≤0.89 group (P=0.997) (Figure 4 and Table 5).

Table 3. Comparison of Discriminant Function of QFR to Ischemic Reference Standard

	FFR as Reference 264 Patients With 358 Vessels		iFR as Reference 264 Patients With 358 Vessels		
	AUC (95% CI)	P Value	AUC (95% CI)	P Value	P for Comparison*
Total population	0.953 (0.932–0.974)	<0.001	0.880 (0.844–0.917)	<0.001	<0.001
SIHD	0.946 (0.919–0.974)	<0.001	0.876 (0.828–0.923)	<0.001	0.011
AMI	0.967 (0.936–0.998)	<0.001	0.882 (0.817–0.947)	<0.001	0.021
P for comparison†	0.320	NA	0.876	NA	NA

Area under the curve (AUC) values were calculated based on per-vessel analysis and compared with the DeLong method. QFR indicates quantitative flow ratio.
*P value for comparison according to the reference tests (fractional flow reserve [FFR] or instantaneous wave-free ratio [iFR]).
†P value for comparison according to the clinical presentations (nonculprit of acute myocardial infarction [AMI] or stable ischemic heart disease [SIHD] vessels).

Discussion

The current study evaluated the diagnostic performance of QFR to define functionally significant epicardial coronary stenoses using FFR or iFR as reference standard methods. In addition, these physiologic indices were also evaluated using CFR as an independent reference standard. The main findings were as follows. First, QFR showed excellent correlation and diagnostic performance for both invasive pressure–derived physiologic indices (FFR and iFR), regardless of clinical presentation. Second, the correlation, diagnostic perfor-mance, and discriminant function of QFR were better for FFR than for iFR. Third, when CFR was used as a reference standard, iFR showed the highest discriminant function in comparison with FFR or QFR, and the discordance between

QFR and iFR was mainly driven by differences in the coronary flow (CFR). However, the diagnostic accuracies of FFR, iFR, and QFR were not statistically different using CFR as a reference standard.

Invasive Physiologic Indices in Contemporary Practice

As coronary revascularization is only beneficial when reversible myocardial ischemia is present, there have been numerous efforts to detect the presence of myocardial ischemia. Although many noninvasive tests to assess myocardial ischemia are available, a previous study reported a low diagnostic yield and limited PPV of these tests.[22] Currently, FFR, a pressure-derived physiologic index, has been validated

	AUC	p value
FFR	0.682	<0.001
iFR	0.765	<0.001
Resting Pd/Pa	0.764	<0.001
QFR	0.677	<0.001

p value for comparison	
FFR vs. iFR	0.002
FFR vs. Resting Pd/Pa	0.005
FFR vs. QFR	0.794
iFR vs. Resting Pd/Pa	0.979
iFR vs. QFR	0.004
Resting Pd/Pa vs. QFR	0.009

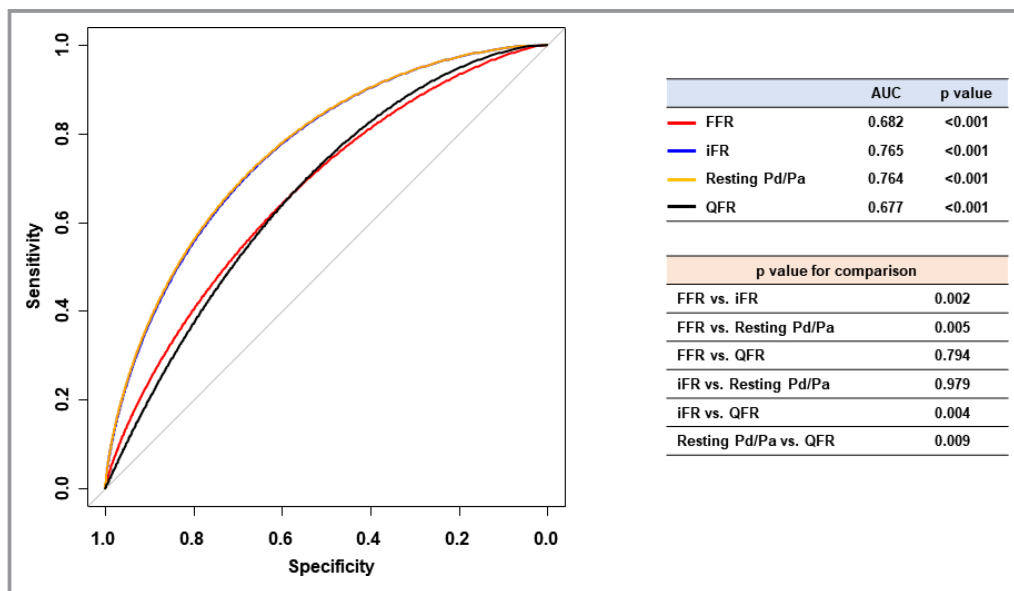**Figure 3.** Discriminant functions of fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), resting distal to aortic coronary pressure (Pd/Pa), and quantitative flow ratio (QFR) with coronary flow reserve (CFR) as a reference standard. Discriminant functions of FFR, iFR, resting Pd/Pa, and QFR with CFR ≤2.0 as a reference standard are presented. AUC indicates area under the curve.

Table 4. Comparison of Diagnostic Performance and Discriminant Function of FFR, iFR, and QFR With CFR as a Reference Standard

	FFR	iFR	QFR
AUC	0.682 (0.600–0.764)*	0.765 (0.691–0.838)[†,‡]	0.677 (0.596–0.758)*
Sensitivity, %	61.1 (48.1–74.1)	68.5 (56.1–80.9)	64.8 (52.1–77.6)
Specificity, %	66.7 (59.7–73.6)	71.2 (64.5–77.9)	65.0 (57.9–72.0)
PPV, %	35.9 (26.1–45.7)	42.0 (31.7–52.4)	36.1 (26.5–45.6)
NPV, %	84.9 (78.9–90.8)	88.1 (82.8–93.4)	85.8 (79.9–91.7)
Diagnostic accuracy, %	65.4 (65.2–65.6)	70.6 (70.4–70.7)	64.9 (64.7–65.1)

Values are expressed as estimates (95% CIs). Area under the curve (AUC) values were calculated based on per-vessel analysis and compared with the DeLong method. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated based on per-vessel analysis and compared using McNemar test or weighted generalized score statistic. CFR indicates coronary flow reserve.
*$P<0.05$ compared with instantaneous wave-free ratio (iFR).
[†]$P<0.05$ compared with fractional flow reserve (FFR).
[‡]$P<0.05$ compared with quantitative flow ratio (QFR).

in several large-scale randomized controlled trials and is considered a standard invasive method to define the functional significance of an epicardial coronary stenosis.[2] Recently, another invasive physiologic method, iFR, which can be measured in the resting state without induction of hyperemia, was introduced.[4,5] Previous studies reported about 10% to 30% disagreement between FFR and iFR in the classification of functional significance of coronary lesions[2]; however, recent large-scale randomized controlled trials reported comparable clinical outcomes between FFR- and iFR-guided revascularization strategies with less revascularization after the iFR-guided strategy.[4,5] Consequently, both FFR- and iFR-guided revascularization strategies are included in the recent guidelines with a class 1A recommendation.[1] Nevertheless, the adoption rate of FFR or iFR in real-world practice is still limited.[6,23]

Emerging Role of QFR as an Alternative to Invasive Physiologic Assessment

The low adoption rates of FFR- or iFR-guided revascularization strategies might be associated with additional coronary instrumentation and cost of drugs and devices, prolonged procedural time, possible patient discomfort with adenosine administration for FFR measurement, limited confidence with the results, experience, or personal beliefs.[24] To overcome these limitations, there have been several efforts to develop new techniques for assessing functional significance of coronary lesions from noninvasive tests[25] or without additional pressure wire interrogation. QFR is an angiography-derived method that provides functional assessment of coronary stenoses from computation of 3-dimensional QCA
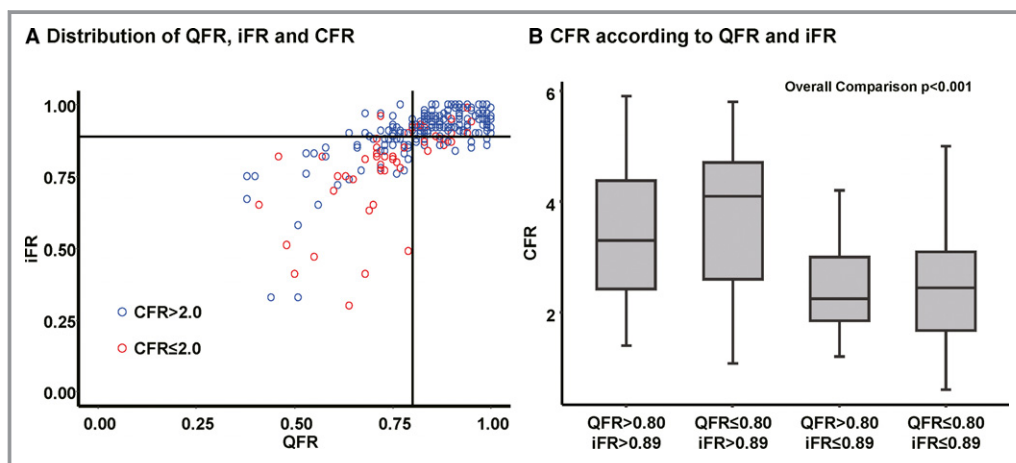

Figure 4. Distribution of coronary flow reserve (CFR) according to quantitative flow ratio (QFR) and instantaneous wave-free ratio (iFR). Scatter plot according to QFR and iFR values is shown (**A**). Black lines represent the cutoff values of 0.80 for fractional flow reserve (FFR) and 0.89 for iFR. Vessels with CFR ≤2.0 are in red, whereas vessels with CFR >2.0 are in blue. Box plot shows the CFR values according to the QFR and iFR agreement groups (**B**).

Table 5. Physiologic and Angiographic Differences in Vessels Among 4 QFR and iFR Agreement Groups

	QFR >0.80 and iFR >0.89 (n=175)	QFR ≤0.80 and iFR >0.89 (n=38)	QFR >0.80 and iFR ≤0.89 (n=29)	QFR ≤0.80 and iFR ≤0.89 (n=116)	*P* Value
Quantitative coronary angiography					
Reference vessel diameter, mm	3.20±0.62*	3.26±0.59*	2.77±0.56[†,‡,§]	3.12±0.59*	0.003
Minimal lumen diameter, mm	1.82±0.70[‡,§]	1.30±0.54[†*]	1.71±0.63[‡,§]	1.03±0.52[†*]	<0.001
Diameter stenosis, %	44.6±17.2[‡,§]	61.2±12.7[†,*]	40.1±17.5[‡,§]	66.6±13.8[†,*]	<0.001
Lesion length, mm	12.3±7.2[‡,§]	17.9±8.8[†]	12.1±7.2[§]	20.5±12.2[†,*]	<0.001
Invasive physiologic indices					
FFR	0.89±0.05[‡,*,§]	0.81±0.06[†,§]	0.84±0.04[†,§]	0.67±0.11[†,‡,*]	<0.001
QFR	0.91±0.06[‡,§]	0.74±0.05[†,*,§]	0.87±0.05[‡,§]	0.66±0.11[†,‡,*]	<0.001
iFR	0.95±0.03[*,§]	0.93±0.03[*,§]	0.86±0.03[†,‡,§]	0.75±0.13[†,‡,*]	<0.001
CFR	3.48±1.19[*,§]	3.66±1.46[*,§]	2.59±1.13[†,‡]	2.52±1.18[†,‡]	<0.001
Resting mean transit time	0.94±0.48*	0.97±0.40*	0.60±0.25[†,‡]	0.82±0.36	<0.001
Hyperemic mean transit time	0.29±0.18[§]	0.28±0.12	0.25±0.11	0.36±0.16[†]	0.007
IMR, U	21.5±13.3[§]	17.1±8.5	17.6±8.9	14.0±6.6[†]	<0.001
IMR >25U	23.7%	13.8%	10.0%	9.0%	0.055

CFR indicates coronary flow reserve; FFR, fractional flow reserve; IMR, index of microvascular resistance.

*$P<0.05$ compared with quantitative flow ratio (QFR) >0.80 and instantaneous wave-free ratio (iFR) ≤0.89.

[†]$P<0.05$ compared with QFR >0.80 and iFR >0.89.

[‡]$P<0.05$ compared with QFR ≤0.80 and iFR >0.89.

[§]$P<0.05$ compared with QFR ≤0.80 and iFR ≤0.89.

and TIMI frame count without additional pressure wire or induction of hyperemia. Previous studies reported excellent correlation and diagnostic agreement of QFR compared with FFR.[7–12] Furthermore, QFR analysis showed significantly lower measurement time than FFR.[11]

Nevertheless, QFR has not been thoroughly evaluated using other reference standards beyond FFR. As the current guideline also recommends the use of iFR-guided decision as class IA recommendation,[1] it is important to evaluate the diagnostic ability of QFR in defining functionally significant stenosis using iFR as a reference standard. In a previous study by Emori et al,[15] QFR showed good correlation with iFR as well as with FFR. Although diagnostic accuracy of QFR was numerically higher with FFR than with iFR (94% versus 74%), that difference was not statistically significant, probably because of insufficient sample size. The current study demonstrates the excellent correlation and diagnostic agreement of QFR not only with FFR but also with iFR. However, QFR was more strongly correlated with FFR than iFR, and diagnostic performance and discriminant function of QFR were better with FFR than with iFR. These results were consistently found in both SIHD and AMI nonculprit vessels. Considering that QFR is derived from the mathematical assumptions for hyperemic status of coronary circulation, the better correlation and diagnostic agreement of QFR with FFR than with iFR seems to be natural. As QFR was originally

designed to predict FFR, the current results show the features of QFR rather than which one is correct or which one is better. Furthermore, diagnostic accuracy (81.3%) and discriminant function (AUC=0.725) of QFR for iFR in the current study were also good. Therefore, the findings of this study support the clinical value of QFR in determining the functional significance of coronary stenoses from the iFR point of view.

It should be noted that QFR showed wider variance in lesions with a lower range of FFR and iFR (Figure S3). This might be related to the intrinsic limitation of any simulated indices including computed tomography–derived FFR, as these simulated indices cannot inherently reflect the collateral flow or combined microvascular dysfunction.[25–27]

Discrepancies Between QFR and Invasive Pressure–Derived Indices on the Basis of CFR

The current study also evaluated FFR, iFR, and QFR using CFR as an independent reference standard. As with previous studies, iFR showed better discriminant function for CFR compared with FFR or QFR. In addition, the discordance between QFR and iFR was mainly caused by differences in patient-specific CFR. In the algorithm of contrast-QFR model, the fixed-QFR value, which assumes an empiric coronary flow, is adjusted to the patient's specific coronary flow using TIMI frame count.[7] Although contrast QFR provided more accurate

prediction of invasive FFR than fixed QFR,[7,8] the correlation between TIMI frame-count–based volumetric flow rate reserve in the algorithm of contrast QFR[7] and actual Doppler-derived CFR was modest (r=0.62).[28] Current results imply that contrast QFR would have limited ability to reflect the actual patient-specific CFR, and the discordance between QFR and iFR might originate from the fundamental difference between the 2 indices. Furthermore, in the case of significant microvascular dysfunction, any types of computational or simulated methods including QFR might have limited diagnostic accuracy.[29] Nevertheless, the diagnostic accuracy of QFR was not significantly different from those of FFR or iFR with CFR as a reference standard. These results imply that FFR, iFR, and QFR might share similar limitations as a surrogate marker of coronary flow. In addition, it also implies that the fundamental difference of FFR, iFR, and QFR with CFR would not have substantial influence to a binary decision using those surrogate indices of coronary flow in routine clinical practice. However, considering the difference in revascularization rates between FFR- and iFR-guided treatment in the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) or iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) trials, where iFR guidance resulted in 5% fewer revascularizations than FFR guidance, it should be noted that QFR-guided decision-making might result in slightly higher revascularization rates than iFR-guided decision-making.

Clinical Implications

The current study evaluated the diagnostic performance of QFR using other reference standards beyond FFR. Although QFR showed higher correlation and diagnostic performance for prediction of FFR than iFR, the absolute efficacy of QFR to predict iFR was also good. In addition, the diagnostic accuracies of FFR, iFR, and QFR were not significantly different when CFR was used for a reference standard. As QFR does not require additional interrogation with a pressure wire or administration of hyperemic agents, and shows significantly shorter measurement time than invasive physiologic assessment,[11] this may represent a more simple, safe, and cost-effective method to guide revascularization. With excellent diagnostic agreement of QFR with both FFR and iFR, which are the current standard methods to define functional significance of epicardial coronary stenosis, a QFR-guided strategy might be a promising tool to improve the adoption rate of physiology-based revascularization. Ongoing randomized controlled trials evaluating superiority in clinical outcomes following a QFR-guided strategy compared with an angiography only–guided strategy (FAVOR III China, NCT03656848) would clarify the value of QFR in daily clinical practice.

Limitations

There are several limitations in this study. First, clinical outcome data were not evaluated; therefore, we could not evaluate the prognostic implications of QFR-guided treatment. Second, as QFR is an angiography-based method, its accuracy depends on the quality of images and optimal projection. Indeed, about 17% of patients and 26% of vessels were excluded from the QFR analysis based on improper quality of angiographic images. Although these rates were high in the current study, they might be lower with the use of recommended angiographic projections and simultaneous on-site real-time QFR analysis. Third, because the contrast QFR model computes TIMI frame count to adjust the simulation of coronary flow, the quality of contrast injection would have a potential influence on the accuracy of the contrast QFR model. However, there has been no standardization method of contrast injection technique and there was no direct evidence that evaluated the influence of contrast injection technique and the accuracy of contrast QFR. Fourth, various agents (intravenous adenosine or intracoronary nicorandil) were used for hyperemia induction in this study. However, it is reported that all of these agents have similar hyperemic efficacy without systemic bias in FFR measurement.[20,21] Fifth, CFR can be affected by microvascular function and does not essentially represent epicardial coronary stenosis alone. However, considering the relatively small proportion of vessels with high index of microvascular resistance as well as low CFR (5.7% of total vessels), the influence from the significant microvascular dysfunction might be minimal in the current analysis. Last, contrast FFR, which is another nonhyperemic pressure ratio, was not available in the current study.

Conclusions

QFR has a high correlation and agreement with respect to both invasive pressure–derived indices, FFR and iFR, although better when FFR is used as the comparator. The differences observed between QFR and iFR may be explained by CFR. As a pressure-derived index not depending on wire or adenosine, QFR might be a promising tool for improving the adoption rate of physiology-based revascularization.

Disclosures

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.

2. Lee JM, Doh JH, Nam CW, Shin ES, Koo BK. Functional approach for coronary artery disease: filling the gap between evidence and practice. *Korean Circ J*. 2018;48:179–190.

3. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol*. 2012;59:1392–1402.

4. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376:1824–1834.

5. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Todt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Frobert O. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376:1813–1823.

6. Dehmer GJ, Weaver D, Roe MT, Milford-Beland S, Fitzgerald S, Hermann A, Messenger J, Moussa I, Garratt K, Rumsfeld J, Brindis RG. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol*. 2012;60:2017–2031.

7. Tu S, Barbato E, Koszegi Z, Yang J, Sun Z, Holm NR, Tar B, Li Y, Rusinaru D, Wijns W, Reiber JH. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. *JACC Cardiovasc Interv*. 2014;7:768–777.

8. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JH, Holm NR, Wijns W; FAVOR Pilot Trial Study Group. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot Study. *JACC Cardiovasc Interv*. 2016;9:2024–2035.

9. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F, Fang W, Chen J, Li W, Guan C, Holm NR, Wijns W, Hu S. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70:3077–3087.

10. Collet C, Onuma Y, Sonck J, Asano T, Vandeloo B, Kornowski R, Tu S, Westra J, Holm NR, Xu B, de Winter RJ, Tijssen JG, Miyazaki Y, Katagiri Y, Tenekecioglu E, Modolo R, Chichareon P, Cosyns B, Schoors D, Roosens B, Lochy S, Argacha JF, van Rosendael A, Bax J, Reiber JHC, Escaned J, De Bruyne B, Wijns W, Serruys PW. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. *Eur Heart J*. 2018;39:3314–3321.

11. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, Nef H, Naber C, Barbierato M, Tu S, Neghabat O, Madsen M, Tebaldi M, Tanigaki T, Kochman J, Somi S, Esposito G, Mercone G, Mejia-Renteria H, Ronco F, Botker HE, Wijns W, Christiansen EH, Holm NR. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc*. 2018;7:e009603. DOI: 10.1161/jaha.118.009603

12. Westra J, Tu S, Winther S, Nissen L, Vestergaard MB, Andersen BK, Holck EN, Fox Maule C, Johansen JK, Andreasen LN, Simonsen JK, Zhang Y, Kristensen SD, Maeng M, Kaltoft A, Terkelsen CJ, Krusell LR, Jakobsen L, Reiber JHC, Lassen JF, Bottcher M, Botker HE, Christiansen EH, Holm NR. Evaluation of coronary artery stenosis by quantitative flow ratio during invasive coronary angiography: the WIFI II Study (Wire-Free Functional Imaging II). *Circ Cardiovasc Imaging*. 2018;11:e007107.

13. Hwang D, Jeon KH, Lee JM, Park J, Kim CH, Tong Y, Zhang J, Bang JI, Suh M, Paeng JC, Na SH, Cheon GJ, Cook CM, Davies JE, Koo BK. Diagnostic performance of resting and hyperemic invasive physiological indices to define myocardial ischemia: validation with (13)N-ammonia positron emission tomography. *JACC Cardiovasc Interv*. 2017;10:751–760.

14. Lee JM, Park J, Hwang D, Kim CH, Choi KH, Rhee TM, Tong Y, Park JJ, Shin ES, Nam CW, Doh JH, Koo BK. Similarity and difference of resting distal to aortic coronary pressure and instantaneous wave-free ratio. *J Am Coll Cardiol*. 2017;70:2114–2123.

15. Emori H, Kubo T, Kameyama T, Ino Y, Matsuo Y, Kitabata H, Terada K, Katayama Y, Taruya A, Shimamura K, Shiono Y, Tanaka A, Hozumi T, Akasaka T. Quantitative flow ratio and instantaneous wave-free ratio for the assessment of the functional severity of intermediate coronary artery stenosis. *Coron Artery Dis*. 2018;29:611–617.

16. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Foin N, Malik IS, Mikhail GW, Hughes AD, Francis DP, Mayet J, Di Mario C, Escaned J, Piek JJ, Davies JE. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv*. 2014;7:492–502.

17. Choi KH, Lee JM, Kim HK, Kim J, Park J, Hwang D, Rhee TM, Park TK, Yang JH, Song YB, Shin ES, Nam CW, Doh JH, Hahn JY, Choi JH, Choi SH, Koo BK, Gwon HC. Fractional flow reserve and instantaneous wave-free ratio for nonculprit stenosis in patients with acute myocardial infarction. *JACC Cardiovasc Interv*. 2018;11:1848–1858.

18. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.

19. Lee JM, Choi KH, Hwang D, Park J, Jung JH, Kim HY, Jung HW, Cho YK, Yoon HJ, Song YB, Hahn JY, Doh JH, Nam CW, Shin ES, Hur SH, Koo BK. Prognostic implication of thermodilution coronary flow reserve in patients undergoing fractional flow reserve measurement. *JACC Cardiovasc Interv*. 2018;11:1423–1433.

20. Toth GG, Johnson NP, Jeremias A, Pellicano M, Vranckx P, Fearon WF, Barbato E, Kern MJ, Pijls NH, De Bruyne B. Standardization of fractional flow reserve measurements. *J Am Coll Cardiol*. 2016;68:742–753.

21. Lee JM, Kato D, Oi M, Toyofuku T, Takashima H, Waseda K, Amano T, Kurita A, Ishihara H, Lim WH, Doh JH, Nam CW, Tanaka N, Koo BK, Tanaka N. Safety and efficacy of intracoronary nicorandil as hyperaemic agent for invasive physiological assessment: a patient-level pooled analysis. *EuroIntervention*. 2016;12:e208–e215.

22. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.

23. Tebaldi M, Biscaglia S, Fineschi M, Musumeci G, Marchese A, Leone AM, Rossi ML, Stefanini G, Maione A, Menozzi A, Tarantino F, Lodolini V, Gallo F, Barbato E, Tarantini G, Campo G. Evolving routine standards in invasive hemodynamic assessment of coronary stenosis: the nationwide Italian SICI-GISE Cross-Sectional ERIS Study. *JACC Cardiovasc Interv*. 2018;11:1482–1491.

24. Johnson NP, Koo BK. Coronary psychology: do you believe? *JACC Cardiovasc Interv*. 2018;11:1492–1494.

25. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DIS-COVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol*. 2011;58:1989–1997.

26. Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Botker HE, Achenbach S. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63:1145–1155.

27. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol*. 2013;61:2233–2241.

28. Stoel MG, Zijlstra F, Visser CA. Frame count reserve. *Circulation*. 2003;107:3034–3039.

29. Mejia-Renteria H, Lee JM, Lauri F, van der Hoeven NW, de Waard GA, Macaya F, Perez-Vizcayno MJ, Gonzalo N, Jimenez-Quevedo P, Nombela-Franco L, Salinas P, Nunez-Gil I, Del Trigo M, Goto S, Lee HJ, Liontou C, Fernandez-Ortiz A, Macaya C, van Royen N, Koo BK, Escaned J. Influence of microcirculatory dysfunction on angiography-based functional assessment of coronary stenoses. *JACC Cardiovasc Interv*. 2018;11:741–753.