Comparison of Diagnostic Performance of Quantitative Flow Ratio in Patients With Versus Without Diabetes Mellitus

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Quantitative flow ratio (QFR) is a novel technique to calculate fractional flow reserve (FFR), without hyperemia induction or a pressure wire, and has not yet been validated in patients with diabetes mellitus (DM), who are at increased risk of coronary microvascular dysfunction. The purpose of our study was to compare the diagnostic performance of QFR in diabetic and nondiabetic patients. Patients who underwent invasive coronary angiography and subsequent invasive FFR measurement within 6 months were included. QFR was determined in all coronary arteries in which invasive FFR was performed, using a dedicated software package. Diagnostic accuracy and the area under the receiver-operating characteristic curve (AUC) were determined for QFR, using an invasive FFR cut-off value of ≤0.80 as the reference standard. In total, 320 coronary arteries from 66 (25%) diabetic and 193 (75%) nondiabetic patients were analyzed. On a vessel-based analysis, diagnostic accuracy, sensitivity, and specificity showed no significant difference between diabetic and nondiabetic patients: 88% versus 85% (p = 0.47), 71% versus 69% (p = 0.72), and 95% versus 91% (p = 0.24). Moreover, the AUC was not significantly different between patients with and without DM, 0.91 versus 0.93 (p = 0.74). The per-vessel AUC was significantly higher for QFR compared with percent diameter stenosis in both diabetic and nondiabetic patients, 0.91 versus 0.76 (p <0.05) and 0.93 versus 0.77 (p <0.001), respectively. In conclusion, we showed a good diagnostic performance of QFR which was independent of the presence of DM. **(Am J Cardiol 2019;123:1722−1728)**

In patients who underwent invasive coronary angiography (ICA), the severity of coronary stenoses is often determined by either visual assessment or fractional flow reserve (FFR) measurement. FFR-guided revascularization of coronary stenoses has shown a favorable long-term outcome and a reduction in the number of stents implanted, compared with angiographic guidance.[1−4] Despite these advantages, the implementation of invasive FFR for guidance of coronary revascularization is limited.[5−7] Quantitative flow ratio (QFR) is a novel technique to assess the hemodynamic significance of coronary artery stenoses.[8−11] QFR computation is based on a 3-dimensional (3D) reconstruction of the coronary artery and computational fluid dynamics. As opposed to invasive FFR, QFR computation is performed on nonhyperemic angiographic projections without the use of a pressure wire. Although FFR could be affected by the presence of coronary microvascular dysfunction (CMD) when maximal blood flow during hyperemia is limited, QFR assumes fixed boundary conditions for the prediction of the hyperemic response.[12] QFR has not yet been validated in diabetic patients. Because CMD is highly frequent in diabetic patients, the diagnostic performance of QFR may be suboptimal in this patient population.[13,14] Accordingly, this study compares the diagnostic performance of QFR in diabetic and nondiabetic patients, and assesses the incremental value of QFR compared with 3D quantitative coronary angiography for the identification of functionally significant coronary narrowings in diabetic and nondiabetic patients.

Methods

The study population was derived from the QFR referral database cohort.[15] These were patients who underwent ICA in a hospital where FFR could not be performed, and underwent subsequent FFR measurement and percutaneous coronary intervention if needed in our hospital within the period 2011 to 2016. Patients were excluded if FFR measurement was performed >6 months after the initial ICA, or within 48 hours of the occurrence of a non-ST segment elevation myocardial infarction (NSTEMI). Patients with unstable angina or non-ST segment elevation myocardial infarction who were studied in a staged procedure later than 48 hours after the initial ICA were excluded from the study. Clinical data were prospectively entered in the electronic patient file

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and retrospectively analyzed. The Medical Ethical Committee of the Leiden University Medical Center, the Netherlands, approved this retrospective evaluation of clinically collected data and waived the need for written informed consent. A diagnosis of diabetes mellitus (DM) was based on the medical history recorded in the electronic patient file and use of antidiabetic medication, according to the American Diabetes Association.[16]

Clinically acquired mono- or biplane angiogram images from referring hospitals in patients who underwent FFR measurement were retrospectively collected for QFR analysis. FFR measurement was performed at the discretion of the operator, using a pressure wire (Brightwire 2; Volcano Corp, San Diego, California). FFR measurement was performed according to the manufacturer's guidelines and has been described in detail previously.[15] The exact anatomic position of the pressure sensor at the angiogram was recorded and stored for all patients.

QFR computation was performed for all coronary arteries in which invasive FFR was measured for clinical indications. QFR computation was performed in an offline fashion, using a dedicated software package (QAngio XA 3D/QFR, Medis Medical Imaging Systems B.V., Leiden, the Netherlands). The complete workflow of QFR computation has already been described previously.[17] In short, 2 angiographic views of a coronary artery were selected with projection angles ≥25° apart. Coronary arteries with excessive overlap and/or foreshortening were excluded from further analysis. Subsequently, the end-diastolic frame (defined by the frame with maximal left ventricular dimensions and absence of contrast inflow in the ascending aorta) was selected for both angiographic views. Hereafter, a semiautomatic detection of the lumen contours was performed, which was used to reconstruct a 3D model of the coronary artery. The thrombolysis in myocardial infarction frame counting method was used to determine the transport time of the injected contrast medium. Subsequently, the contrast-flow velocity was calculated, based on the length of the selected coronary artery segment and the transport time of the contrast medium in this segment. Finally, the hyperemic-flow velocity was calculated from the contrast-flow velocity, and QFR was computed based on the 3D model of the vessel and the flow velocity using computational fluid dynamics principles as described by Kirkeeide et al.[9,18] The QFR values on the coronary tree corresponded to the exact location of the pressure sensor at the angiogram. In addition to QFR, 3D quantitative coronary angiography parameters, including diameter stenosis (DS), lesion length, minimal lumen diameter, and area stenosis, were automatically derived. Coronary artery stenoses with a QFR value of ≤0.80 were considered significant, using an invasive FFR cut-off value of ≤0.80 as the reference standard.

Distribution of continuous variables was determined using histograms and normal Q-Q plots. Continuous variables are presented as mean ± standard deviation or as median and 25% to 75% interquartile range (IQR) as appropriate, and were compared with the independent sample Student's *t* test and Mann-Whitney U test, respectively. Categorical variables are presented as number and percentages, and were compared with the chi-square test. Per-vessel and per-patient diagnostic accuracy, sensitivity, specificity, and positive and negative predictive value for QFR were compared between diabetic and nondiabetic patients using the "N-1" chi-square test.[19,20] Receiver-operating characteristic curves were constructed for QFR and %DS in diabetic and nondiabetic patients, with invasive FFR as the reference standard. The area under the receiver-operating characteristic curve (AUC) was compared between diabetic and nondiabetic patients using the method of DeLong et al.[21] In addition, the correlation and agreement between QFR and invasive FFR were assessed with the Pearson's correlation coefficient and a Bland-Altman plot, respectively, in coronary vessels of both diabetic and nondiabetic patients. All statistical analyses were performed with the SPSS software package (IBM Corp Released 2015; IBM SPSS Statistics for Windows, Version 23.0; Armonk, New York: IBM Corp) and MedCalc for Windows, version 18.2.1 (MedCalc Software, Ostend, Belgium). Statistical tests were considered significant if the two-sided p value was <0.05.

Results

The data of 66 (25%) diabetic (all type 2 DM) and 193 (75%) nondiabetic patients were evaluated. A detailed overview of the baseline patient characteristics is displayed in Tables 1 and 2.

Median time between the initial ICA and FFR measurement was 18 (IQR 8 to 27) days. In total, 372 coronary arteries were analyzed. Fifty-two coronary arteries (14%)

Table 1
Baseline patient characteristics

		Diabetes mellitus		
Variables	Total (n = 259)	Yes (n = 66)	No (n = 193)	p Value
Age (years)	67 ± 9	67 ± 9	67 ± 9	0.71
Men	181 (70%)	47 (71%)	134 (69%)	0.78
Hypertension	190 (74%)	60 (91%)	130 (68%)	<0.001
Body mass index ≥30 kg/m^2	54 (21%)	21 (32%)	33 (17%)	<0.05
Prior myocardial infarction	41 (16%)	11 (17%)	30 (16%)	0.82
Prior percutaneous coronary intervention	83 (32%)	29 (44%)	54 (28%)	<0.05
Prior coronary bypass surgery	6 (2%)	3 (5%)	3 (2%)	0.18
Serum creatinine (μmol/L)	89 ± 26	87 ± 20	90 ± 28	0.52
Estimated glomerular filtration rate* (ml/min/1.73 m^2)	74 ± 17	75 ± 17	74 ± 17	0.75

Values are mean ± standard deviation or n (%).
* Calculated using the CKD-EPI formula.

Table 2
Diabetic patient characteristics

Variables	Total (n = 66)
Diabetes type 2	57 (100%)
Diabetes duration (years)	12 (7-15)
Diabetes complication*	12 (19%)
Stroke and/or transient ischemic attack	7 (11%)
Medication	
Oral antidiabetic medication	47 (72%)
Insulin use	21 (32%)
ACE-inhibitors/ARB	48 (74%)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Values are mean ± standard deviation, median (interquartile range), or n (%).

* Diabetes complication included peripheral vascular disease, nephropathy, neuropathy, and retinopathy according to the medical history.

Table 4
Per-vessel diagnostic performance of QFR

	Diabetes mellitus		
Variables	Yes (n = 82)	No (n = 238)	p Value
Accuracy	88% (79-94%)	85% (79-89%)	0.47
Sensitivity	71% (49-87%)	69% (56-79%)	0.72
Specificity	95% (86-99%)	91% (85-95%)	0.24
PPV	85% (65-95%)	74% (64-83%)	<0.05
NPV	89% (81-94%)	88% (84-91%)	0.88

NPV = negative predictive value; PPV = positive predictive value.
Values are mean (95% confidence interval).

were excluded due to excessive overlap and/or foreshortening (n = 18), insufficient image quality (n = 17), absence of angiographic views with projection angles ≥25° apart (n = 6), ostial stenosis (n = 5), presence of a coronary stent (n = 4), or aneurysm (n = 2). Of the analyzed 320 coronary arteries, mean DS was 43.2 ± 8.6% and median lesion length was 20.1 (IQR 12.4 to 29.6) mm (Table 3). Mean QFR and FFR were 0.86 ± 0.09 and 0.85 ± 0.08, respectively; in 26% and 28% of the vessels, QFR and FFR were ≤0.80, respectively. Mean QFR and FFR were not significantly different between diabetic and nondiabetic patients (0.86 ± 0.08 vs 0.86 ± 0.09, p = 0.73 and 0.85 ± 0.07 vs 0.85 ± 0.08, p = 0.92, respectively).

On a vessel-based analysis, diagnostic accuracy, sensitivity, and specificity for QFR showed no significant difference between diabetic and nondiabetic patients: 88% (95% confidence interval [CI] 79% to 94%) versus 85% (95% CI 79% to 89%; p = 0.47), 71% (95% CI 49% to 87%) versus 69% (95% CI 56% to 79%; p = 0.72), and 95% (95% CI 86% to 99%) versus 91% (95% CI 85% to 95%; p = 0.24; Table 4).

Moreover, on a patient-based analysis, diagnostic accuracy, sensitivity, and specificity for QFR also showed no significant difference between diabetic and nondiabetic patients: 88% (95% CI 78% to 95%) versus 82% (95% CI 76% to 87%; p = 0.26), 75% (95% CI 53% to 90%) versus 69% (95% CI 57% to 80%; p = 0.37), and 95% (95% CI 84% to 99%) versus 88% (95% CI 81% to 93%; p = 0.11; Table 5).

The per-vessel AUC for QFR was not significantly different between diabetic and nondiabetic patients, 0.91 (95% CI 0.84 to 0.99) versus 0.93 (95% CI 0.89 to 0.96; p = 0.74; Figure 1). In both diabetic and nondiabetic patients, the per-vessel AUC was significantly higher for QFR compared with %DS, diabetic patients: 0.91 (95% CI 0.84 to 0.99) versus 0.76 (95% CI 0.66 to 0.87; p <0.05; Figure 1) and nondiabetic patients: 0.93 (95% CI 0.89 to 0.96) versus 0.77 (95% CI 0.70 to 0.83; p <0.001; Figure 1). In addition, a good correlation between QFR and invasive FFR was found for coronary vessels of diabetic (r = 0.74, p <0.001) and nondiabetic patients (r = 0.83, p <0.001; Figure 2). The agreement between QFR and invasive FFR was high for both diabetic (mean difference 0.014 ± 0.053) and nondiabetic coronary vessels (mean difference 0.009 ± 0.051; Figure 2). In Figure 3, a case example is shown for a left anterior descending coronary artery, showing good agreement between FFR (0.77) and QFR (0.78), which was

Table 3
Baseline vessel characteristics

		Diabetes mellitus		
Variables	Total (n = 320)	Yes (n = 82)	No (n = 238)	p Value
Analyzed coronary artery				0.92
Left anterior descending	216 (68%)	55 (67%)	161 (68%)	
Left circumflex	46 (14%)	13 (16%)	33 (14%)	
Right	33 (10%)	9 (11%)	24 (10%)	
Coronary side branch	25 (8%)	5 (6%)	20 (8%)	
Diameter stenosis (%)	43.2 ± 8.6	42.7 ± 8.9	43.3 ± 8.5	0.60
Lesion length (mm)	20.1 (12.4-29.6)	20.8 (11.9-31.8)	20.0 (12.7-28.6)	0.61
Area stenosis (%)	55.4 ± 13.0	55.7 ± 14.3	55.3 ± 12.6	0.81
Minimal lumen diameter (mm)	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	0.70
Quantitative flow ratio	0.86 ± 0.09	0.86 ± 0.08	0.86 ± 0.09	0.73
Vessels with quantitative flow ratio ≤0.80	82 (26%)	20 (24%)	62 (26%)	0.77
Fractional flow reserve	0.85 ± 0.08	0.85 ± 0.07	0.85 ± 0.08	0.92
Vessels with fractional flow reserve ≤0.80	91 (28%)	24 (29%)	67 (28%)	0.85

Values are mean ± standard deviation, median (interquartile range), or n (%).

Table 5
Per-patient diagnostic performance of QFR

Variables	Diabetes mellitus Yes (n = 66)	No (n = 193)	p Value
Accuracy	88% (78-95%)	82% (76-87%)	0.26
Sensitivity	75% (53-90%)	69% (57-80%)	0.37
Specificity	95% (84-99%)	88% (81-93%)	0.11
PPV	90% (70-97%)	75% (64-83%)	<0.05
NPV	87% (77-93%)	85% (80-89%)	0.69

NPV = negative predictive value; PPV = positive predictive value.
Values are mean (95% confidence interval).

measured at the exact location of the pressure sensor at the angiogram.

Discussion

In our study, the diagnostic performance of QFR was assessed in diabetic and nondiabetic patients using invasive FFR as the reference standard. We showed a high diagnostic accuracy of QFR, which was independent of the presence of DM. Also, QFR had a significantly higher diagnostic accuracy than %DS in both diabetic and nondiabetic patients.

Our study is the first to demonstrate that QFR is highly accurate in patients with DM. DM is known to increase the risk of cardiovascular mortality and morbidity and is associated with macro- and microvascular complications.[13,14] Multiple studies have noted an increased prevalence of CMD among patients with DM, which is caused by both structural and functional coronary microvascular abnormalities.[13,14,22−24] Despite the increased risk of CMD among patients with DM, our study confirms that the use of QFR in these patients does not hamper diagnostic accuracy. Therefore, the current results indicate the practical use of QFR in daily clinics in patients with DM, which is not inferior compared with patients without DM.

The diagnostic accuracy of QFR was recently studied in patients with CMD. Mejía-Rentería et al[25] performed QFR analysis in 300 vessels from 248 patients who all underwent invasive evaluation of coronary microcirculatory function using the index of microcirculatory resistance (IMR). The diagnostic accuracy of QFR was significantly lower in patients with CMD (IMR ≥23 U) compared with patients with normal microvascular status (IMR <23 U; AUC 0.88 vs 0.96, p <0.05). However, the diagnostic accuracy of QFR remained superior to %DS in the presence of CMD (AUC 0.88 vs 0.72, p <0.001). The reduced diagnostic performance of QFR in patients with CMD may be explained from the fixed boundary conditions that are assumed for QFR computation. QFR analysis is based on the thrombolysis in myocardial infarction frame counting method, which is applied on 2 angiographic projections without induced hyperemia. The hyperemic-flow velocity is modeled using the contrast-flow velocity at baseline, and is therefore based on the assumption that the hyperemic response to adenosine is predictable. Because the hyperemic response could be impaired in the presence of CMD, this could possibly result in a reduced diagnostic ability of QFR to identify functionally significant stenoses.

Despite the increased risk of CMD in patients with DM, QFR was highly accurate in our diabetic patient population compared with invasive FFR. Several explanations may be given for the comparable diagnostic accuracy of QFR in diabetic and nondiabetic patients. First, the use of antidiabetic medication could have resulted in an improved hyperemic response in diabetic patients. In our study, the majority of diabetic patients (86%) used antidiabetic medication (72% oral medication and 32% insulin). A previous study demonstrated a significant improvement in myocardial blood flow (MBF) in patients with type 2 DM by treatment with glibenclamide and metformin.[26] Moreover, it was shown that insulin infusion improved MBF in patients with type 2 DM.[27] Second, patient-specific flow is incorporated in the QFR analysis by assessment of the contrast-flow velocity at baseline. Other authors have reported

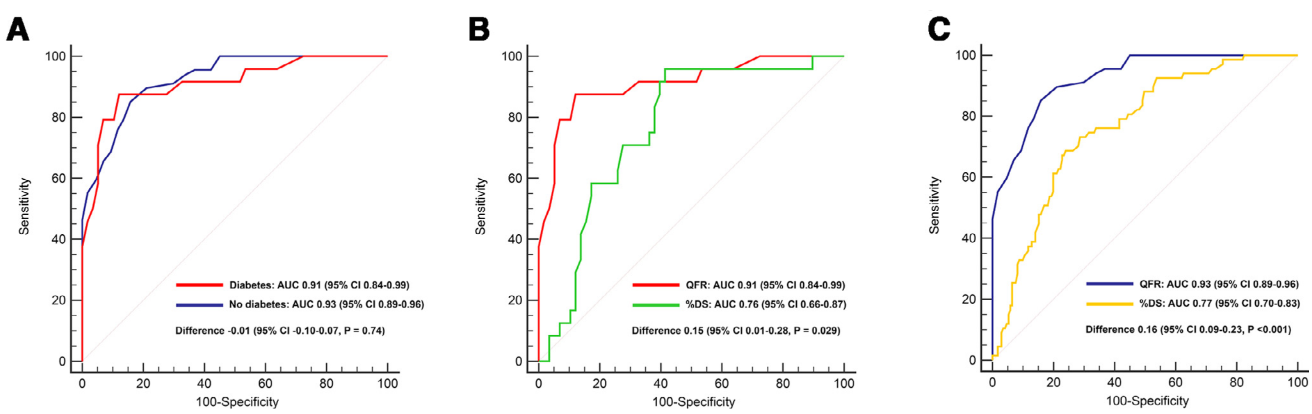

Figure 1. The per-vessel receiver-operating characteristic curves for QFR and %DS in diabetic and nondiabetic patients. (*A*) The per-vessel receiver-operating characteristic curves for QFR in diabetic and nondiabetic patients. The area under the curve was not significantly different between diabetic and nondiabetic patients, 0.91 (95% CI 0.84 to 0.99) versus 0.93 (95% CI 0.89 to 0.96; p = 0.74). (*B*) The per-vessel receiver-operating characteristic curves for QFR and %DS in diabetic patients. In diabetic patients, the area under the curve was significantly higher for QFR compared to %DS, 0.91 (95% CI 0.84 to 0.99) versus 0.76 (95% CI 0.66 to 0.87; p <0.05). (*C*) The per-vessel receiver-operating characteristic curves for QFR and %DS in nondiabetic patients. In nondiabetic patients, the area under the curve was significantly higher for QFR compared to %DS, 0.93 (95% CI 0.89 to 0.96) versus 0.77 (95% CI 0.70 to 0.83; p <0.001). AUC = area under the receiver-operating characteristic curve; CI = confidence interval; DS = diameter stenosis; QFR = quantitative flow ratio.

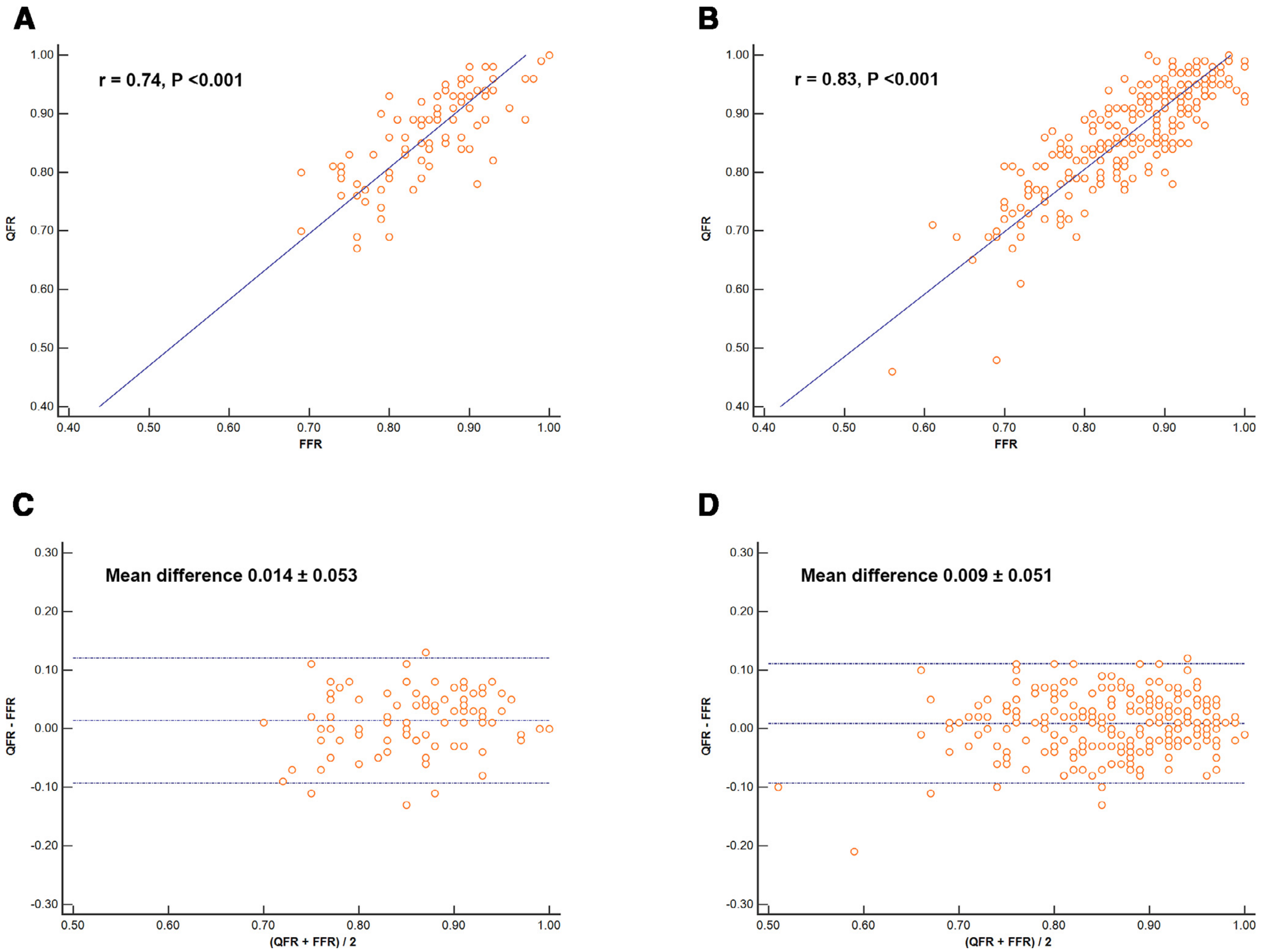

Figure 2. The correlation and agreement between QFR and invasive FFR in diabetic and nondiabetic patients. A good correlation between QFR and invasive FFR was found for coronary vessels of (*A*) diabetic (r = 0.74, p <0.001) and (*B*) nondiabetic patients (r = 0.83, p <0.001). Furthermore, the agreement between QFR and invasive FFR was high for both (*C*) diabetic (mean difference 0.014 ± 0.053) and (*D*) nondiabetic coronary vessels (mean difference 0.009 ± 0.051). FFR = fractional flow reserve; QFR = quantitative flow ratio.

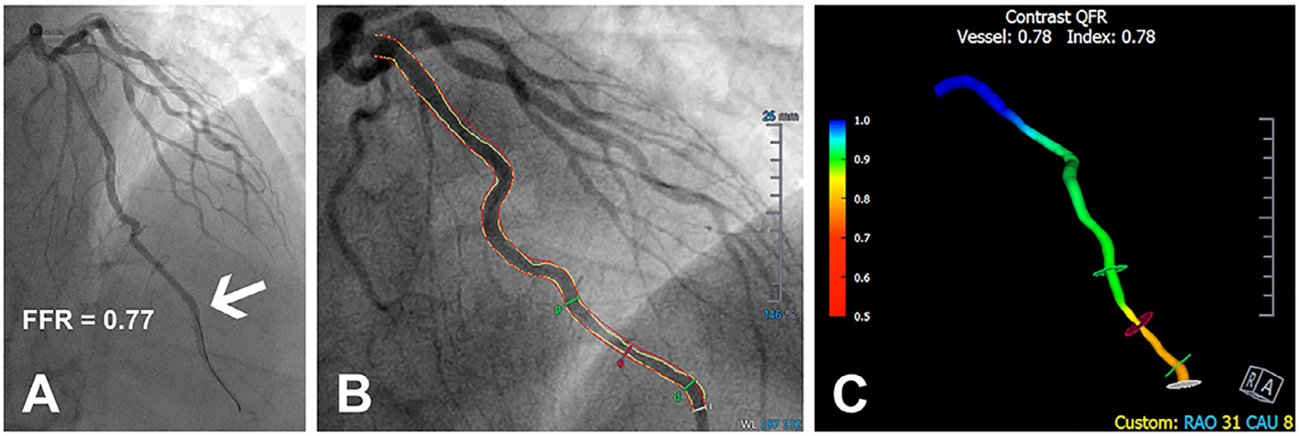

Figure 3. Example of QFR analysis in a left anterior descending coronary artery. (*A*) Example of a left anterior descending coronary artery with intermediate stenoses in the proximal and distal part of the vessel. FFR, which was measured at the location of the white arrow, was 0.77. (*B*) One of the 2 angiographic views that were used for QFR analysis, including the lumen and reference contours. (*C*) The 3D model of the coronary artery. QFR was computed based on the 3D model of the vessel and the flow velocity of the contrast medium using computational fluid dynamics principles. The QFR value on the coronary tree, which corresponded to the exact location of the pressure sensor at the angiogram, was 0.78. 3D = 3-dimensional; FFR = fractional flow reserve; QFR = quantitative flow ratio.

significantly lower coronary flow reserve in diabetic compared with nondiabetic patients, because of increased basal coronary flow, whereas hyperemic coronary flow was found to be similar.[28] This increased basal coronary flow could be reflected by a lower frame count during QFR analysis, without affecting the diagnostic performance of QFR. Third, the prevalence of CMD in our diabetic patient population could be relatively low or comparable to the nondiabetic patient population. This would be in accordance with a recent study that showed a low prevalence of DM (<10%) among patients with CMD.[29] Furthermore, Mejía-Rentería et al[25] showed a similar prevalence of DM in patients with CMD (IMR ≥23 U) compared with patients with normal microvascular status (IMR <23 U; 40% vs 37%, p = 0.78).

This study has several limitations that are inherent to its retrospective and single-center design. The prevalence of CMD among our patient population was unknown because measures of coronary microvascular function and noninvasive imaging tests were not systematically obtained. However, coronary microvascular status is often unknown in patients referred for ICA. Moreover, in the majority of diabetic patients, CMD is associated with normal myocardial perfusion.[22] Ideally, IMR could have further refined our results; however, the current results indicate the practical use of QFR in daily clinics in patients with DM, which is not inferior compared with patients without DM. Echocardiographic data were not available for all patients. Therefore, the effect of valvular heart disease on coronary microvascular function and the impact on left ventricular function and diagnostic accuracy of QFR could not be studied. Also, angiographic projections for QFR analysis were retrospectively evaluated. In-procedure selection of angiographic projections suitable for QFR analysis would probably have resulted in a higher diagnostic accuracy of QFR. Finally, we could not assess the influence of DM type on the diagnostic accuracy of QFR, as we only included patients with type 2 DM.

In conclusion, we showed a good diagnostic performance of QFR, which was independent of the presence of DM. Also, QFR demonstrated a superior diagnostic accuracy compared with %DS in both diabetic and nondiabetic patients.

Disclosures

The Department of Cardiology of the Leiden University Medical Center received research grants from Biotronik, Medtronic, Boston Scientific, and Edwards Lifesciences. Johan H.C. Reiber is the CEO of Medis and has a part-time appointment at LUMC as professor of medical imaging. Gerhard Koning is an employee of Medis. Arthur J. Scholte received consulting fees from Toshiba Medical Systems and GE Healthcare. All other authors have reported that they have no relationships relevant to the contents of this study to disclose.

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