Interindividual Variations in the Adenosine-Induced Hemodynamics During Fractional Flow Reserve Evaluation: Implications for the Use of Quantitative Flow Ratio in Assessing Intermediate Coronary Stenoses

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Background—Quantitative flow ratio (QFR), a novel functional angiography technique, computes fractional flow reserve (FFR) without pressure wires or adenosine. We investigated interindividual variations in the adenosine-induced hemodynamics during FFR assessment and their influence on QFR diagnostic performance.

Methods and Results—Patients with coronary stenoses who underwent intracoronary pressure and flow assessment were analyzed. Adenosine-induced hemodynamics during FFR measurement were determined by the percentage change in mean aortic pressure (%ΔPa) and the resistive reserve ratio (RRR). The diagnostic performance of QFR was evaluated and compared in each tertile of %ΔPa and RRR using FFR as reference. A total of 294 vessels (245 patients) were analyzed. Mean FFR was 0.80±0.11. Individuals showed a wide variation in the adenosine response in terms of %ΔPa (ranging from −75% to 43%; median, −9% [interquartile range, −3% to −17%]) and the RRR (ranging from 0.45 to 20.15; median, 3.1 [interquartile range, 2.1–4.9]). No significant differences for diagnostic efficiency of QFR were found between tertiles of %ΔPa (area under the curve for the receiver-operating characteristic analysis, 0.950 in tertile 1, 0.929 in tertile 2, and 0.910 in tertile 3; *P*=0.270) or between tertiles of the RRR (area under the curve for the receiver-operating characteristic analysis, 0.909 in tertile 1, 0.923 in tertile 2, and 0.959 in tertile 3; *P*=0.167). The classification agreement between QFR and FFR was not significantly modified by %ΔPa (tertile 1, 89%; tertile 2, 87%; and tertile 3, 86%; *P*=0.827) or by the RRR (tertile 1, 86%; tertile 2, 85%; and tertile 3, 91%; *P*=0.398).

Conclusions—Patients undergoing FFR assessment show large interindividual variations in the magnitude of adenosine-induced hemodynamics. However, such variations do not affect the diagnostic performance of QFR in assessing the functional relevance of observed stenoses. (*J Am Heart Assoc*. 2019;8:e012906. DOI: 10.1161/JAHA.119.012906.)

Fractional flow reserve (FFR), an invasive stenosis-specific measure of myocardial ischemia, has been shown to result in favorable clinical outcomes when used to guide coronary revascularization in intermediate stenoses.[1] Because of its large body of clinical evidence, further diagnostic tools assessing the physiological relevance of coronary stenoses have been tested using FFR as the reference standard. This is the case for quantitative flow ratio (QFR), a novel functional angiography method based on computational algorithms developed to evaluate, in a wire- and adenosine-free manner, the physiological significance of epicardial stenoses (Figure 1). By applying mathematical algorithms to coronary anatomical features in conventional angiography, combined with flow information derived from the TIMI (Thrombolysis in Myocardial Infarction) frame counting method, QFR allows fast computation of FFR.[2] This technique has been recently validated by 2

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large prospective multicenter clinical trials that have shown a high correlation and agreement between QFR and FFR.[3,4] One of the main benefits of incorporating functional angiography methods like QFR into clinical practice would be the reduction of procedural burden associated with the use of pressure wires and adenosine administration, which are the cornerstones of FFR measurement. However, an aspect that deserves attention is that, in calculating functional stenosis relevance, these techniques assume fixed boundary conditions that may not represent interindividual, heterogeneous hemodynamic and hyperemic responses to adenosine.

In this study, we first assess the interindividual variations in the hemodynamic responses to adenosine, and subsequently, we evaluate the effect of such variations on the diagnostic performance of QFR with respect to FFR in a large unselected clinical population.

Methods

Study Design and Patient Selection

This is an observational, multicenter, international study involving patients with coronary artery disease from 4 tertiary centers (Hospital Clinico Universitario San Carlos, Madrid, Spain; Samsung Medical Center, Seoul, South Korea; Seoul National University Hospital, Seoul, South Korea; and VU Medical Center, Amsterdam, the Netherlands) who underwent intracoronary thermodilution-derived flow and pressure measurements as part of their clinical assessment. QFR analysis was performed at a dedicated core laboratory in a blinded manner with respect to the invasive physiological results, and raw physiological studies were collected and independently analyzed. The influence of hemodynamic variations on the diagnostic performance of QFR was evaluated according to interindividual variations in the percentage change of mean aortic pressure (%ΔPa) and the resistive reserve ratio (RRR), both induced by adenosine during FFR assessment. Exclusion criteria were ostial stenosis in the left main stem or right coronary artery; previous coronary artery bypass surgery; significant valvular heart disease; severe tortuosity or overlapping of the target vessel, limiting the 3-dimensional reconstruction; poor angiography quality precluding QFR analysis; and lack of availability or suboptimal quality of the raw physiological studies. In case of acute myocardial infarction as the initial clinical presentation, we included patients with intermediate stenoses in non–infarct-related arteries evaluated with intracoronary pressure and flow measurements at a staged procedure (>48 hours) after successful revascularization of the culprit vessel. All patients provided written informed consent for the procedure, and the study protocol was in accordance with the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author on reasonable request.

Invasive Physiological Study

Intracoronary pressure and flow measurements were obtained with a pressure-temperature sensor fitted guidewire (Certus wire; St Jude Medical, St Paul, MN) by using the thermodilution technique, as described elsewhere.[5] Intracoronary nitroglycerin, usually at a dose of 200 μg, was administered before physiological measurements. At baseline conditions, mean aortic pressure, mean intracoronary pressure distal to the target stenosis, and mean transit time were measured. Maximal hyperemia was induced by adenosine infusion (140 μg/kg/minute) through a femoral or antecubital vein over a minimum of 2 minutes. During steady-state hyperemia, mean proximal aortic pressure, mean intracoronary pressure distal to the target stenosis, and mean transit time were measured. FFR was calculated as the lowest stable ratio of mean intracoronary pressure distal to the target stenosis divided by mean proximal aortic pressure during steady state hyperemia; the index of hyperemic microvascular resistance was calculated as the product between mean intracoronary
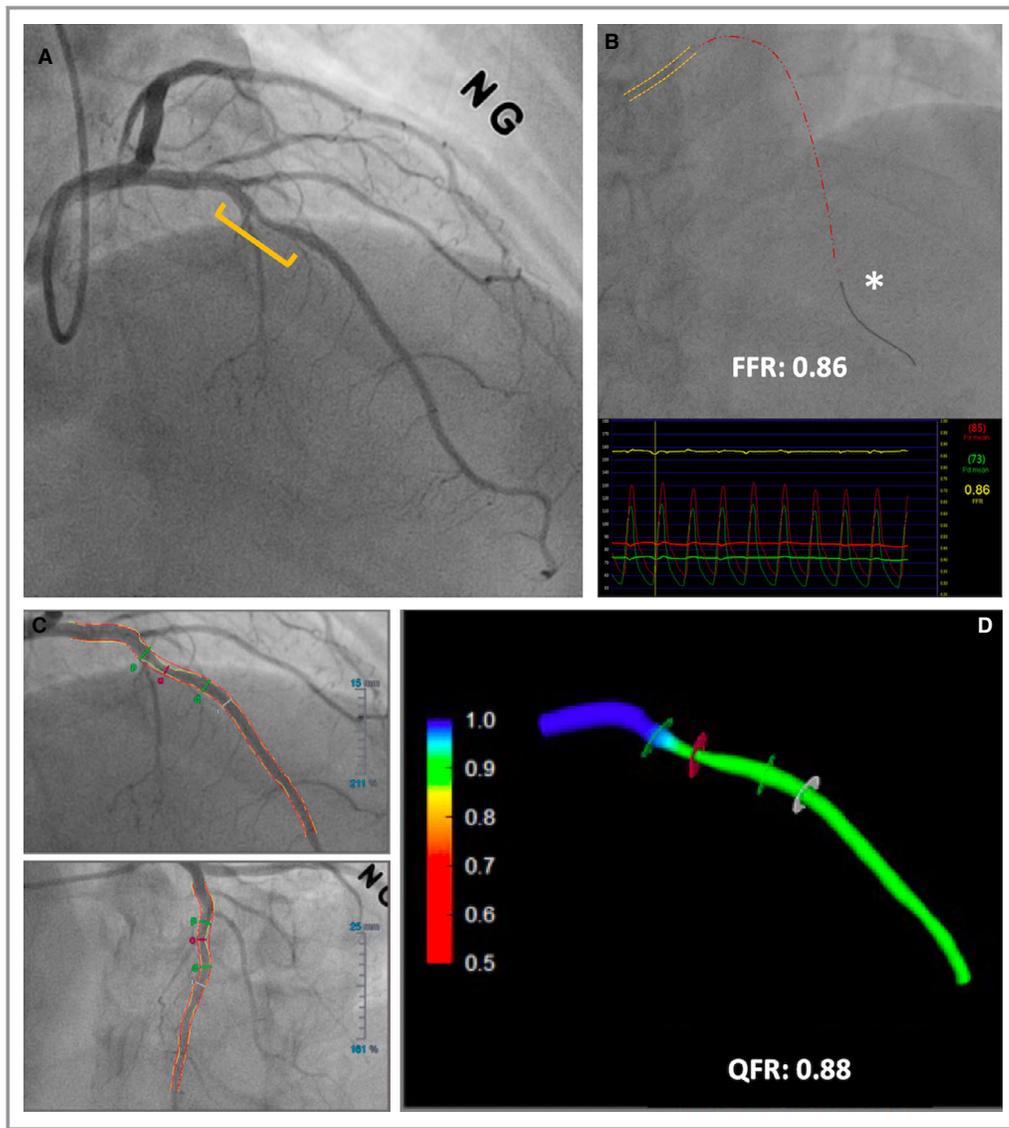
Figure 1. Example of physiological assessment of a coronary stenosis using wire: fractional flow reserve (FFR) and functional angiography. **A**, Moderate stenosis in the mid segment of the left anterior descending coronary artery. **B**, An invasive physiological assessment of such stenosis with wire–FFR (*) under adenosine infusion ruled out myocardial ischemia. **C**, From 2 angiographic projections separated by >25°, a 3-dimensional reconstruction of the target vessel was performed. **D**, Without pressure wires or adenosine, quantitative flow ratio (QFR)–based functional angiography estimated an FFR of 0.88, similar to the wire–FFR result.

pressure distal to the target stenosis and mean transit time during steady state hyperemia, and it was corrected by the formula of Yong et al.[6]

Assessment of Hemodynamic and Hyperemic Responses Induced by Adenosine

The magnitude of hemodynamic changes and hyperemic response achieved during FFR assessment was quantified by %ΔPa and the RRR. %ΔPa was calculated as follows: −[100−

(hyperemic aortic pressure×100/baseline aortic pressure)]. The RRR is an index that evaluates the capacity of the coronary microcirculation to change its vascular tone from baseline to hyperemic conditions and was calculated as the basal microvascular resistance divided by the hyperemic microvascular resistance, as described elsewhere.[7] The basal microvascular resistance, a measure of the resting vascular tone of the subtended microcirculation, was calculated by a simplified method [basal microvascular resistance=mean intracoronary pressure distal to the target stenosis (at baseline)×mean

transit time (at baseline)].[7] The overall population was categorized in tertiles of %ΔPa and tertiles of RRR values. Diagnostic performance of QFR with respect to FFR was evaluated in each resultant tertile group and compared between them.

QFR Analysis

From conventional index angiography, 2 angiographic projections separated by ≥25° were selected according to each target vessel. Three-dimensional QCA (quantitative coronary angiography) and QFR were calculated using the QAngio–XA 3-dimensional software (research edition, version 1.0; Medis, Leiden, the Netherlands), as described elsewhere.[2]

Statistical Analysis

Continuous variables are expressed as mean±SD or median (interquartile range), according to normal or nonnormal distribution of data, which was evaluated by the Kolmogorov-Smirnov test. Categorical variables are presented as numbers and percentages. Demographic and clinical data were analyzed on a per-patient basis. Because the study population included patients with multiple vessels evaluated, the remaining calculations were analyzed on a per-vessel basis using a generalized estimating equation model to adjust intrasubject variability among vessels from the same patient, applying an independent correlation structure with normal distribution and no transformation of dependent variable. The diagnostic efficiency of QFR was determined by the area under the curve (AUC) for the receiver-operating characteristic analysis with FFR as reference.

Table 1. Baseline Clinical Characteristics (N=245)

Characteristics	Value
Age, y	64±10
Men	186 (76)
Cardiovascular risk factors	
Hypertension	163 (67)
Diabetes mellitus	94 (38)
Dyslipidemia	143 (58)
Smoker	56 (23)
Obesity	43 (18)
Chronic renal failure	17 (7)
Previous myocardial infarction	33 (14)
Multivessel disease	157 (64)
Clinical presentation	
Stable angina	172 (70)
Acute coronary syndrome	73 (30)

Values are mean±SD or number (percentage).

Comparison of AUC between groups was performed by the DeLong method. The accuracy of QFR was calculated as the percentage of classification agreement with FFR using the cutoff ≤0.80 for both methods. The relationship between physiological indexes was assessed by Pearson correlation coefficient (r), and the agreement was assessed by the Bland–Altman method. Sensitivity, specificity, predictive values, and likelihood ratios of QFR were derived from the receiver-operating characteristic analysis. The statistical analysis was performed with SPSS statistics, version 23 (IBM Corp, Armonk, NY), and MedCalc software, version 17.6 (MedCalc Software bvba, Ostend, Belgium). $P<0.05$ was considered statistically significant.

Results

Baseline Clinical and Lesion Characteristics

A total of 294 coronary arteries from 245 patients were included in the final analysis after fulfilling participation

Table 2. Anatomic and Physiological Characteristics (N=294)

Characteristics	Value
Target vessel	
Left main	6 (2)
Left anterior descending artery	173 (59)
Diagonal branch	14 (5)
Left circumflex artery	38 (13)
Obtuse marginal branch	17 (6)
Right coronary artery	46 (16)
Three-dimensional quantitative angiography	
Reference diameter, mm	2.76±0.57
Minimum lumen diameter, mm	1.3 (1 to 1.6)
Diameter stenosis, %	52±12
Physiology measurements	
Rest Pd/Pa	0.93 (0.88 to 0.96)
FFR	0.82 (0.74 to 0.88)
Vessels with FFR ≤0.80	133 (45)
Patients with FFR measurement in >1 vessel	49 (20)
Quantitative flow ratio	0.81 (0.71 to 0.87)
Coronary flow reserve	2.3 (1.6 to 3.8)
Index of microcirculatory resistance	16 (12 to 23)
Resistive reserve ratio	3.1 (2.1 to 4.9)
%ΔPa, mm Hg	−9 (−3 to −17)
Pa decreases with adenosine	253 (86)
Pa increases with adenosine	41 (14)

Values are number (percentage), mean±SD, or median (interquartile range). %ΔPa indicates percentage change of mean aortic pressure induced by adenosine; FFR, fractional flow reserve; Pa, aortic pressure; Pd, intracoronary distal pressure.
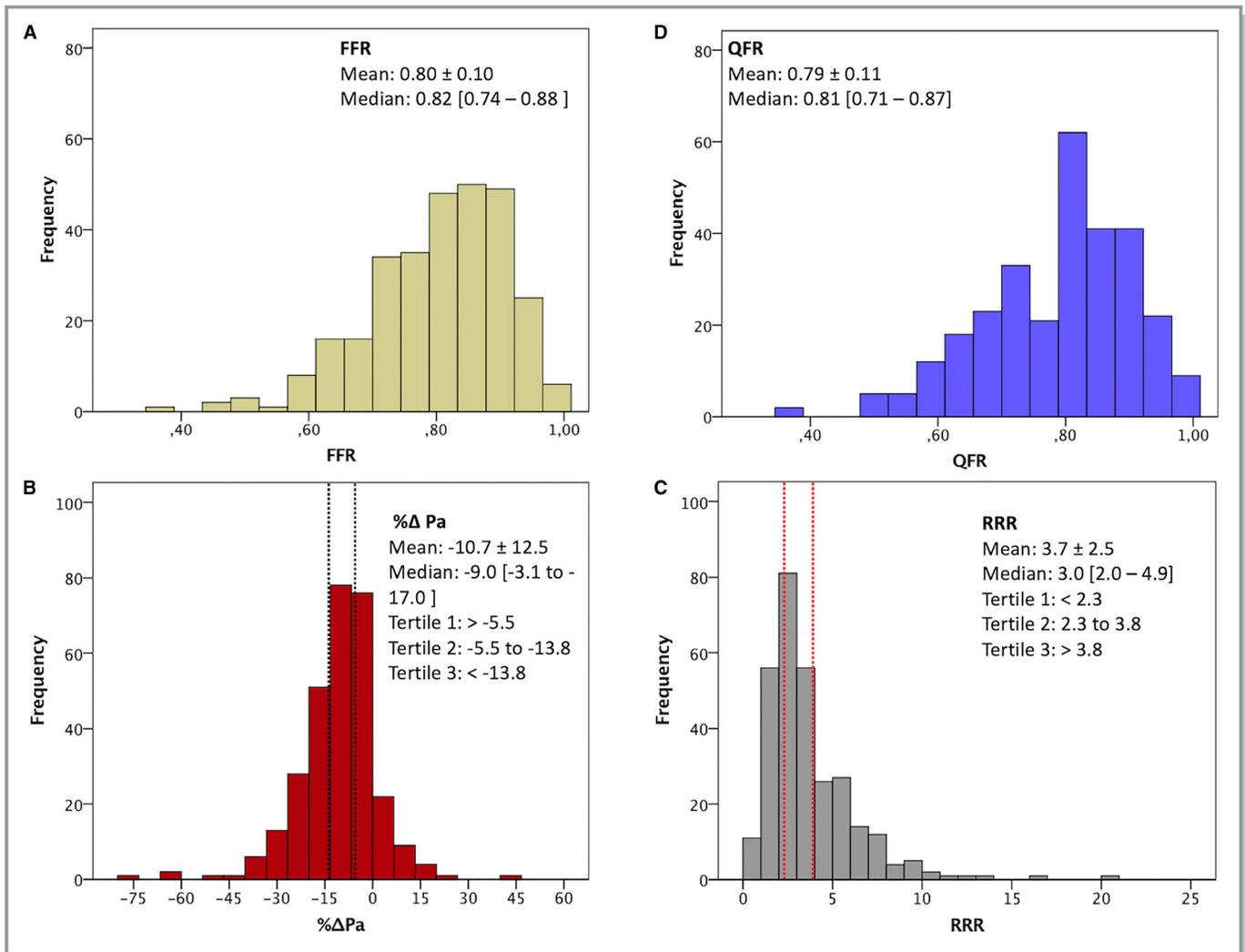
Figure 2. Distribution of fractional flow reserve (FFR; **A**), adenosine‐induced percentage change in mean aortic pressure (%ΔPa; **B**), resistive reserve ratio (RRR; **C**), and quantitative flow ratio (QFR; **D**) values in the total population (294 coronary arteries).

criteria (Table S1 depicts the excluded cases). Mean age was 64±10 years (men, 76%). Multivessel coronary disease was present in 64% of the population, and stable angina was the clinical presentation in most patients (70%) (Table 1). The left anterior descending coronary artery was the most common interrogated vessel (59%), and most of the lesions were of adequate size for revascularization (mean±SD reference diameter, 2.76±0.57 mm) (Table 2). Overall, the severity of the stenoses was moderate, as determined by the percentage diameter stenosis (52±12% derived from 3-dimensional QCA) and by FFR (mean±SD, 0.80±0.11; median, 0.82 [interquartile range, 0.74–0.88]) (Figure 2A).

Interindividual Variations in the Hemodynamic and Hyperemic Responses to Adenosine

The overall population showed a wide variation in the adenosine response in terms of the %ΔPa during FFR assessment, ranging from −75% to 43% (Figure 2B). A decrease in the aortic pressure in response to adenosine was observed in 253 vessels (86%), whereas an increase in aortic pressure was observed in 41 vessels (14%). The median %ΔPa was −9% (interquartile range, −3% to −17%). Categorization of the overall population according to tertiles of the %ΔPa resulted in the following groups: %ΔPa tertile 1, >−5.5; %ΔPa tertile 2, −5.5 to −13.8; and %ΔPa tertile 3, <−13.8.

In terms of the microcirculatory resistance shift from baseline to hyperemia, the overall population also showed a wide variation in the response to adenosine, with an RRR ranging from 0.45 to 20.15 (Figure 2C). The median RRR was 3.1 (interquartile range, 2.1–4.9). The resultant groups based on tertiles of the RRR were as follows: RRR tertile 1, <2.3; RRR tertile 2, 2.3 to 3.8; and RRR tertile 3, >3.8.

A low and inverse significant correlation was found between %ΔPa and the RRR (r=−0.18, P=0.002) (Figure 3).
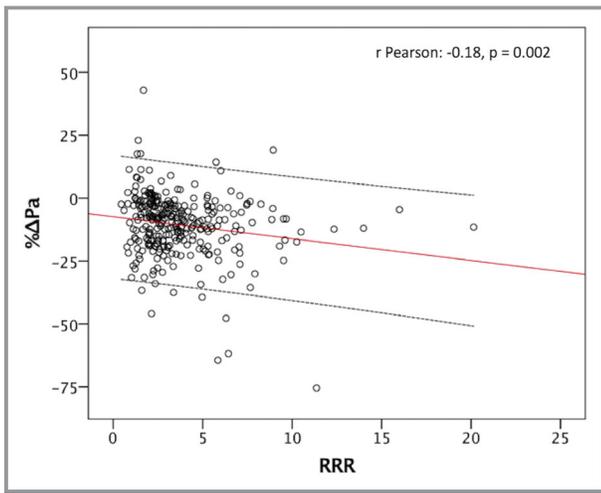
Figure 3. Relationship between adenosine-induced change in mean aortic pressure (%ΔPa) and the resistive reserve ratio (RRR).

Influence of Adenosine-Induced Aortic Pressure Changes on QFR Diagnostic Performance

The correlation between QFR and FFR tended to be lower in the group with the more profound adenosine-induced hypotensive response ($r=0.80$ in tertile 3 of %ΔPa versus $r=0.87$ in tertile 2 of %ΔPa versus $r=0.86$ in tertile 1 of %ΔPa), although such difference was not statistically significant (tertile 3 versus tertile 1, $P=0.180$; tertile 3 versus other tertiles, $P=0.120$) (Figure 4A). Similarly, the absolute difference between FFR and QFR values did not correlate with the degree of adenosine-induced changes in aortic pressure ([FFR−QFR] versus %ΔPa: $r=-0.074$, $P=0.205$) (Figure 5A). Furthermore, the Bland-Altman analysis (Figure 6A) depicts a similar agreement between QFR and FFR in each tertile of the %ΔPa (mean±SD difference: tertile 1, 0.017±0.057; tertile 2, 0.011±0.061; tertile 3, 0.014±0.073; $P=0.826$ for comparison between groups). The diagnostic efficiency as per AUC of QFR in determining the functional stenosis relevance was progressively lower as adenosine-induced hypotension increased (Figure 7A), but the difference did not reach statistical significance ($P=0.273$ for comparison of AUC between tertile 1 and tertile 3; $P=0.329$ for comparison of AUC between tertile 3 and the other tertiles). The accuracy of QFR was also numerically lower as adenosine-induced hypotension increased, but without significant difference between tertiles of %ΔPa (percentage of dichotomous agreement between QFR and FFR: tertile 1, 88.7%; tertile 2, 86.9%; tertile 3, 85.7%; $P=0.531$ [tertile 1
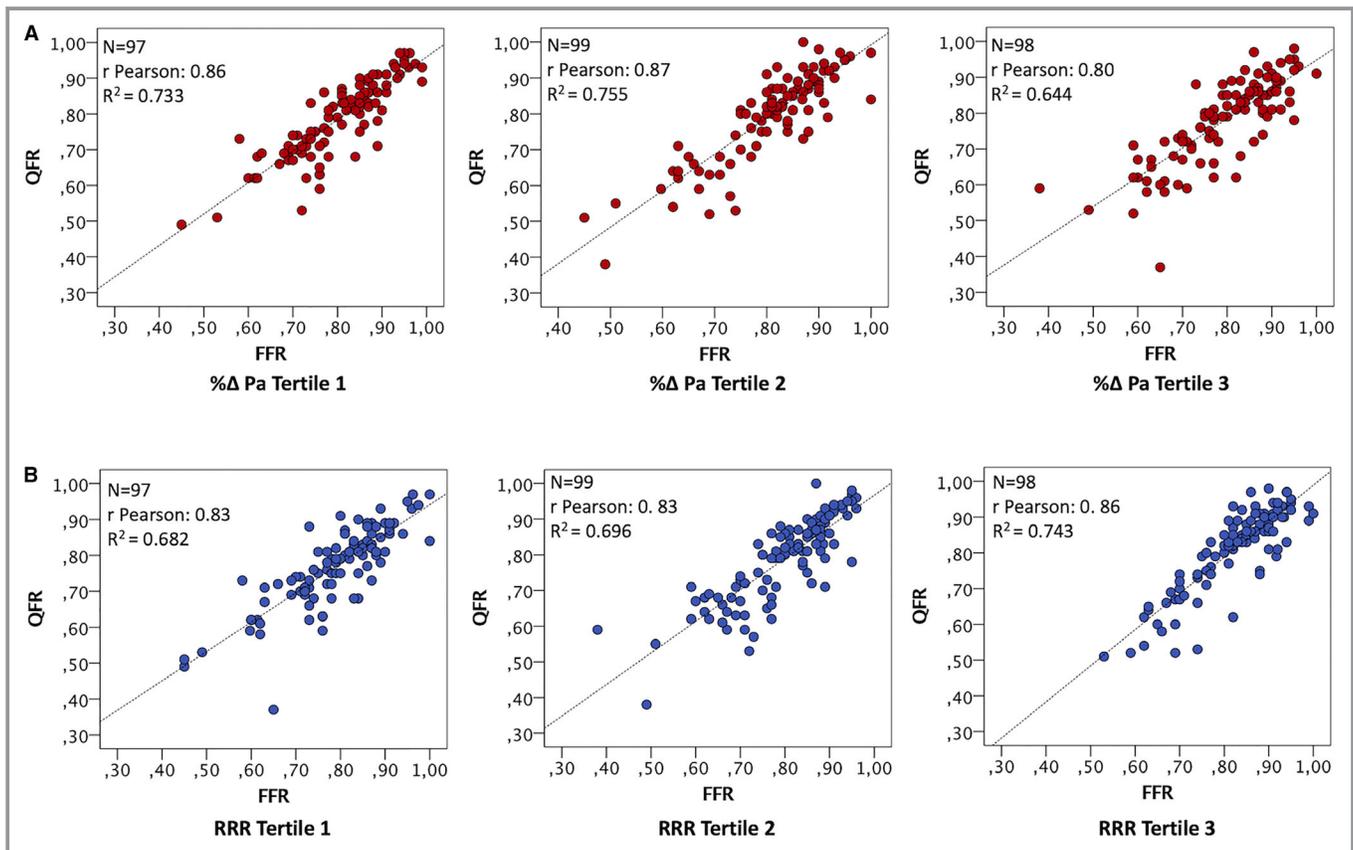
Figure 4. Correlation between quantitative flow ratio (QFR) and fractional flow reserve (FFR) in each tertile of adenosine-induced percentage change in mean aortic pressure (%ΔPa) (**A**) and in each tertile of the resistive reserve ratio (RRR) (**B**).
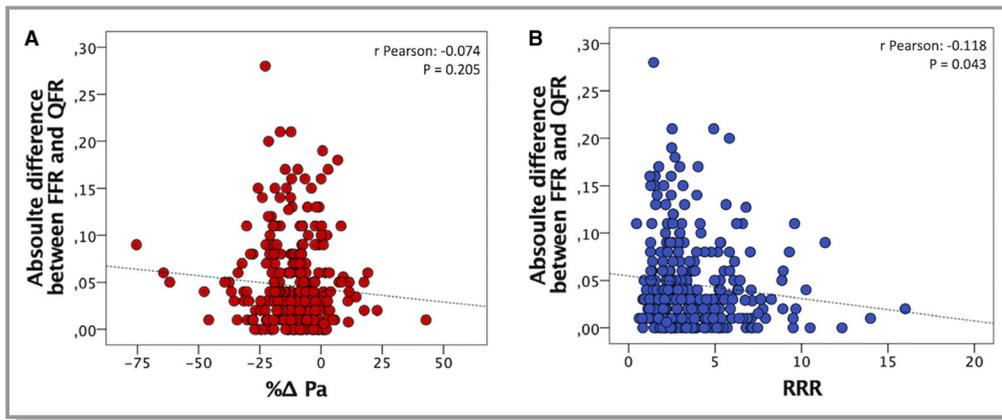
Figure 5. Effect of adenosine-induced percentage change in mean aortic pressure [%ΔPa] (**A**) and resistive reserve ratio [RRR] (**B**) in the absolute difference between quantitative flow ratio (QFR) and fractional flow reserve (FFR).

versus tertile 3]). When comparing hypotensive versus hypertensive response during adenosine infusion (ie, decrease versus increase in aortic pressure), the diagnostic efficiency of QFR was similar in both groups (AUC, 0.931 [0.900–0.962] versus 0.967 [0.916–0.998], respectively; P=0.238 for comparison of AUC) (Figure 8). Table 3 depicts a detailed comparison of the diagnostic performance of QFR between groups of %ΔPa tertiles.
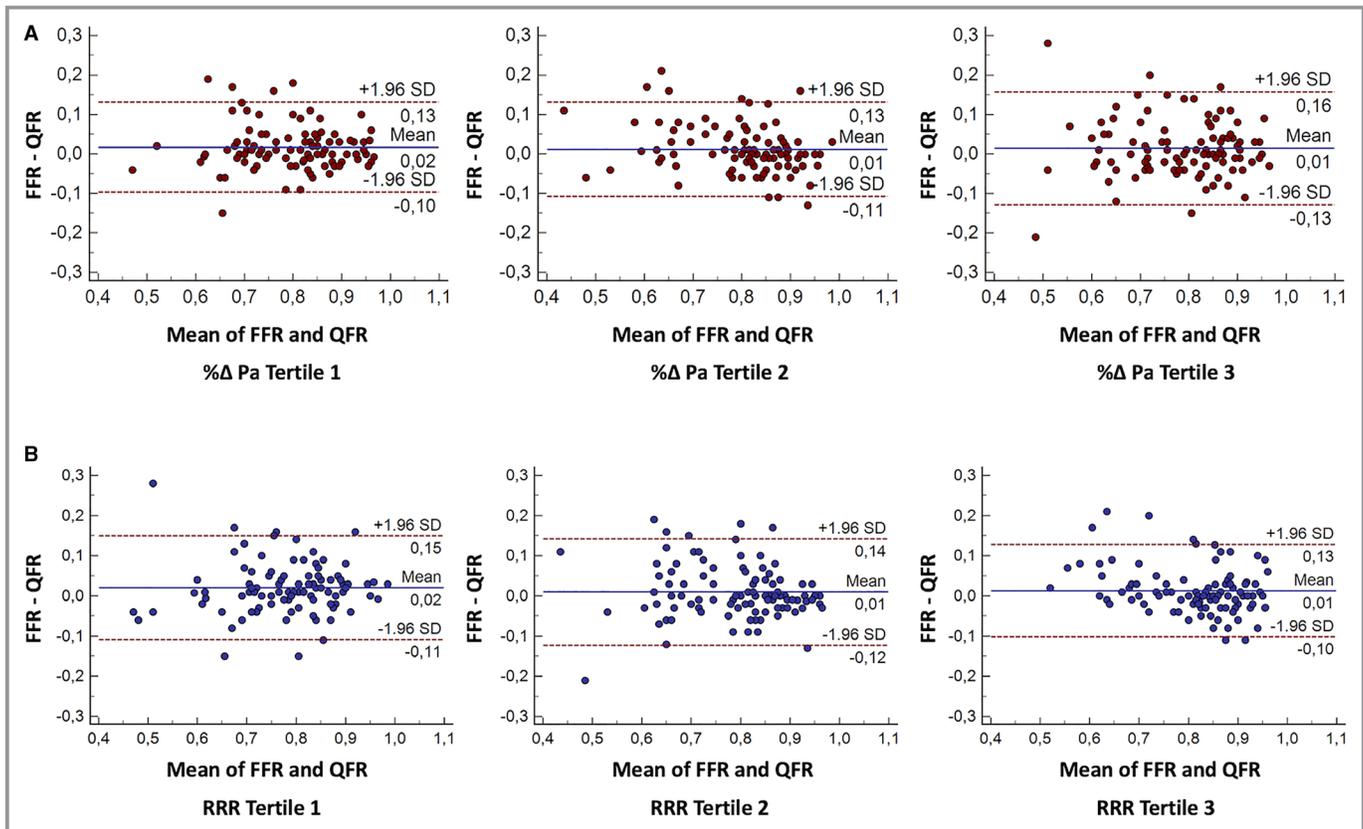
Figure 6. Bland-Altman plots illustrating the agreement between quantitative flow ratio (QFR) and fractional flow reserve (FFR), according to tertiles of adenosine-induced percentage change in mean aortic pressure (%ΔPa) and tertiles of resistive reserve ratio (RRR). In this picture, the differences between FFR and QFR are plotted against the averages of the 2 techniques. Horizontal lines represent the mean difference between both methods (continuous blue line) and the limits of agreement (red dashed lines). The figure reveals that agreement between both techniques is similar regardless of the magnitude of aortic pressure change (**A**) and the RRR (**B**) achieved during adenosine administration.
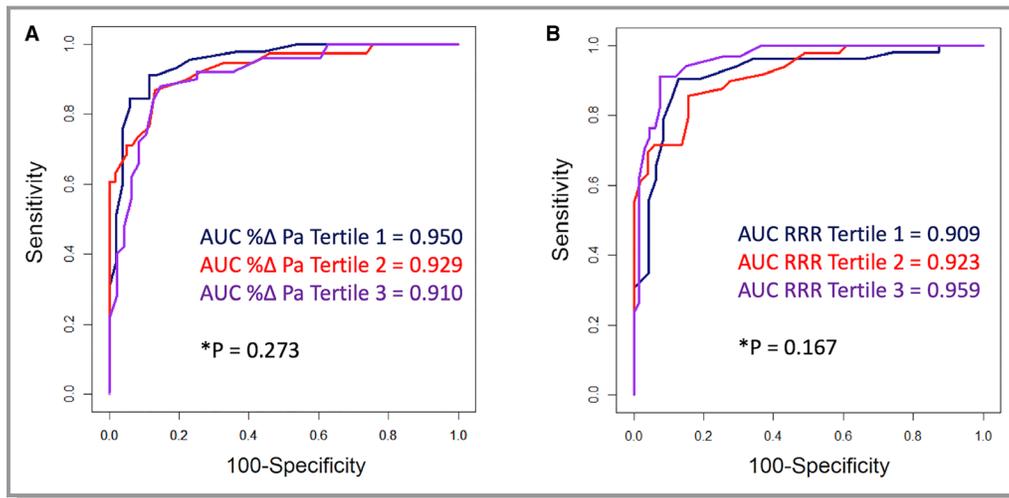
Figure 7. Interindividual variations in the adenosine-induced hemodynamics during fractional flow reserve (FFR) assessment do not significantly affect the diagnostic performance of quantitative flow ratio (QFR). In this study, adenosine-induced hemodynamics during FFR assessment were determined by adenosine-induced percentage change in mean aortic pressure (%ΔPa) and the resistive reserve ratio (RRR=baseline microvascular resistance divided by hyperemic microvascular resistance), which were categorized in tertiles across the overall study population. The figure shows the area under the curve (AUC) from the receiver-operating characteristic analysis for QFR in each tertile of %ΔPa (**A**) and in each tertile of the RRR (**B**) using FFR (≤0.80) as the reference standard. No significant differences were found between AUC across tertiles of %ΔPa and tertiles of the RRR. *P value for comparison of AUC between tertile 1 and tertile 3.

Influence of Myocardial Hyperemia Achieved During Adenosine Infusion on QFR Diagnostic Performance

The correlation between QFR and FFR was high in each tertile of the RRR and tended to be stronger in tertile 3 (r=0.83 in tertile 1 of RRR; r=0.83 in tertile 2 of RRR; r=0.86 in tertile 3 of

RRR; P=0.271 for comparison between group 3 and the others) (Figure 4B). A low significant association was found between the absolute difference of FFR and QFR values (FFR−QFR) and the RRR (r=−0.118, P=0.043) (Figure 5B). As depicted by Bland-Altman analysis (Figure 6B), the agreement between both methods was similar in each tertile of the RRR. The diagnostic efficiency of QFR in determining the functional
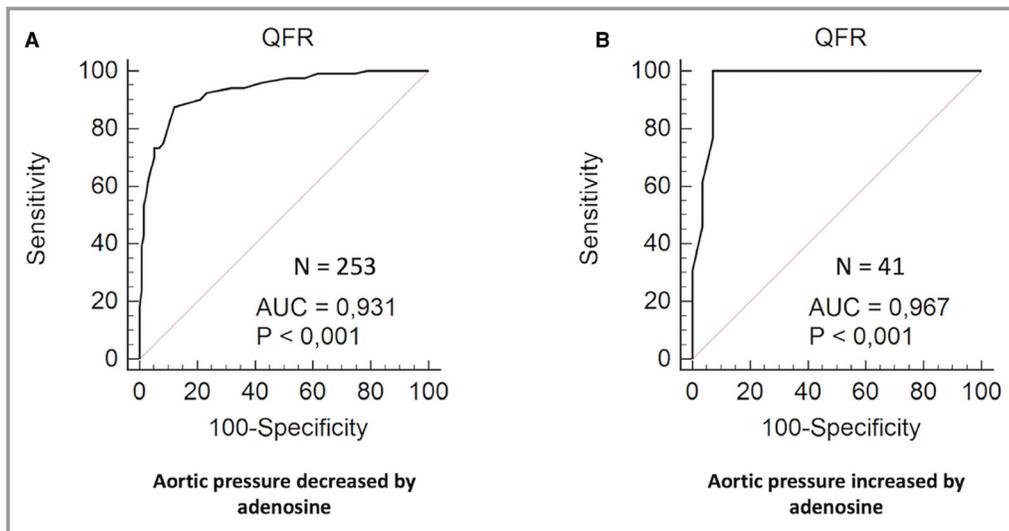
Figure 8. Diagnostic efficiency of quantitative flow ratio (QFR), according to the aortic pressure response during adenosine infusion. The area under the curve (AUC) derived from the receiver-operating characteristic analysis was high regardless of decrease (**A**) or increase (**B**) of mean aortic pressure during adenosine infusion when measuring fractional flow reserve.

Table 3. Influence of Adenosine-Induced %ΔPa on the Diagnostic Performance of QFR

Variable	Overall Population (N=294)	%ΔPa			P Value
		Tertile 1 (N=97)	Tertile 2 (N=99)	Tertile 3 (N=98)	
AUC	0.931 (0.896–0.957)	0.950 (0.886–0.984)	0.929 (0.860–0.971)	0.910 (0.835–0.958)	0.273* 0.329†
Accuracy	256 (87)	86 (88.7)	86 (86.9)	84 (85.7)	0.531* 0.622†
Correlation	0.84	0.86	0.87	0.80	0.180* 0.120†
Mean difference FFR−QFR	0.014±0.064	0.017±0.057	0.011±0.061	0.014±0.073	0.763* 0.998†
Sensitivity	89 (82–94)	91 (79–98)	87 (72–96)	88 (76–96)	0.496* 0.799†
Specificity	86 (80–91)	87 (74–94)	87 (76–94)	85 (72–94)	0.688* 0.638†
Negative predictive value	90 (85–94)	92 (81–97)	91 (82–96)	87 (76–94)	0.256* 0.226†
Positive predictive value	84 (78–89)	85 (75–92)	81 (68–89)	86 (76–93)	0.843* 0.509†
Likelihood ratio (+)	6.5 (4.4–9.6)	6.8 (3.4–13.6)	6.6 (3.4–12.8)	6.0 (3.0–12.1)	…
Likelihood ratio (−)	0.13 (0.08–0.2)	0.10 (0.04–0.3)	0.15 (0.07–0.3)	0.14 (0.07–0.3)	…

Values are percentage for accuracy, number±SD for mean difference, number (95% CI) for likelihood ratios, and percentage (95% CI) for all other parameters. %ΔPa indicates percentage change of mean aortic pressure induced by adenosine; AUC, area under the curve; FFR, fractional flow reserve; QFR, quantitative flow ratio.
*P value for comparison between tertile 1 and tertile 3.
†P value for comparison between tertile 3 and the other tertiles (1 and 2) together.

stenosis severity increased progressively in each tertile of the RRR, being numerically higher in tertile 3, although without reaching statistical significance in comparison with the other groups (AUC: tertile 1, 0.909 [0.834–0.958]; tertile 2, 0.923 [0.852–0.967]; tertile 3, 0.959 [0.898–0.989]; P=0.167 for comparison of AUC between tertile 1 and tertile 3) (Figure 7B). The accuracy of QFR (ie, dichotomous classification agreement with FFR) was also numerically higher in tertile 3 but not statistically different in comparison with the other groups (QFR accuracy: tertile 1, 86%; tertile 2, 85%; tertile 3, 91%; P=0.209 for comparison between tertile 3 and the others). The specificity (tertile 1, 78%; tertile 2, 87%; tertile 3, 92%; P=0.028) and the negative predictive value (tertile 1, 88%; tertile 2, 87%; tertile 3, 95%; P=0.043) were both significantly higher in tertile 3 in comparison with the other tertiles of RRR. Table 4 shows a detailed comparison of diagnostic parameters of QFR, according to tertiles of the RRR.

Discussion

In this study, we found a wide interindividual variability in the hemodynamic and myocardial hyperemic responses to adenosine during FFR interrogation of intermediate coronary stenoses. Interestingly, this large variability did not affect

the overall diagnostic performance of QFR, despite being a functional angiography method that assumes a homogeneous hyperemic response in its calculation. Next, we will discuss the potential reasons for the independence of QFR from these interindividual variations and the potential advantages for this technique over FFR in clinical scenarios in which transient modification of the hyperemic responses may occur.

Adenosine produces endothelium-independent microcirculatory vasodilation, a condition under which coronary microcirculatory resistance is minimal, myocardial blood flow is maximally increased, and the relationship between pressure and flow becomes near linear. This is considered a prerequisite for the FFR approach that enables using pressure measurements as a surrogate of coronary flow. On the other hand, adenosine also causes vasodilation in noncoronary vascular beds, and its administration typically produces a decrease in the systemic arterial pressure during stable myocardial hyperemia. Previous studies have shown a large interindividual variability in the blood pressure response to intravenous adenosine infusion, with most patients developing mild hypotension, others developing profound hypotension, and a minority developing a paradoxical increase in the systemic arterial pressure.[8]

Table 4. Influence of the RRR on the Diagnostic Performance of QFR

Variable	Overall Population (N=294)	RRR			P Value
		Tertile 1 (N=97)	Tertile 2 (N=99)	Tertile 3 (N=98)	
AUC	0.931 (0.896–0.957)	0.909 (0.834–0.958)	0.923 (0.852–0.967)	0.959 (0.898–0.989)	0.167* 0.119[†]
Accuracy	256 (87)	83 (86)	84 (85)	89 (91)	0.274* 0.209[†]
Correlation	0.84	0.83	0.83	0.86	0.469* 0.271[†]
Mean difference FFR−QFR	0.014±0.064	0.020±0.065	0.009±0.067	0.013±0.059	0.403* 0.798[†]
Sensitivity	89 (82–94)	90 (79–97)	85 (72–94)	91 (76–98)	0.812* 0.373[†]
Specificity	86 (80–91)	78 (63–89)	87 (74–94)	92 (83–97)	0.006* 0.028[†]
Negative predictive value	90 (85–94)	88 (75–94)	87 (76–93)	95 (87–98)	0.080* 0.043[†]
Positive predictive value	84 (78–89)	83 (73–89)	85 (74–92)	86 (73–94)	0.563* 0.654[†]
Likelihood ratio (+)	6.5 (4.4–9.6)	4.1 (2.3–7.1)	6.3 (3.1–12.7)	11.7 (5.0–27.3)	…
Likelihood ratio (−)	0.13 (0.08–0.2)	0.12 (0.05–0.3)	0.17 (0.09–0.3)	0.09 (0.03–0.3)	…

Values are percentage for accuracy, number±SD for mean difference, number (95% CI) for likelihood ratios, and percentage (95% CI) for all other parameters. AUC indicates area under the curve; FFR, fractional flow reserve; QFR, quantitative flow ratio; RRR, resistive reserve ratio.
*P value for comparison between tertile 1 and tertile 3.
[†]P value for comparison between tertile 3 and the other tertiles (1 and 2) together.

Because most of functional angiography techniques are based on assumptions of fixed boundary conditions,[2,9–11] it is essential to understand how patient-specific hemodynamic responses to adenosine in real practice can affect the diagnostic accuracy of these methods, which aim to predict FFR. In our study, on the basis of a large population of unselected individuals in whom FFR was used to guide coronary revascularization in a real-world setting, we have analyzed the interindividual variations in the adenosine response, considering its vasodilating properties in noncoronary vascular beds (quantified by aortic pressure variations, %ΔPa), its vasodilating properties in the coronary microcirculation (quantified by the RRR), and how such variations can affect the diagnostic performance of QFR.

As Figure 2 shows, the hemodynamic response to adenosine in our study population was variable between individuals. The %ΔPa ranged from −75% to 43%, the response to adenosine was paradoxical (increase in aortic pressure) in 14% of patients, and the RRR ranged from 0.45 to 20.15. The diagnostic efficiency of QFR showed a tendency to decrease as the hypotensive response increased (AUC, 0.950 in tertile 1 and 0.910 in tertile 3), but such a difference was not statistically significant. The impact of such a tendency could be possibly minor as far as the

classification agreement with FFR had only a minimal decrease from 88.7% in tertile 1 (the tertile of patients with milder hypotensive response) to 85.7% in tertile 3 (the tertile of patients with more profound hypotensive response). On the contrary, the diagnostic efficiency of QFR increased progressively in each tertile of the RRR, being numerically higher in tertile 3, although not statistically different in comparison with the other groups (AUC, 0.909 in tertile 1 and 0.959 in tertile 3; P=0.167 for comparison of AUC between tertile 1 and tertile 3). Interestingly, the specificity and the negative predictive value of QFR were significantly better in the higher tertile of the RRR, the group of patients in whom a higher myocardial hyperemia was achieved (Table 4). This could be clinically relevant because functional angiography may be used to defer further invasive procedures in patients with coronary artery disease. However, the dichotomous classification agreement between QFR and FFR had a low, nonstatistically significant increase from 86% in tertile 1 of RRR (the tertile of patients with suboptimal myocardial hyperemia) to 91% in tertile 3 of RRR (P=0.209 for comparison between tertile 3 and the others).

Why does the demonstrated large interindividual variability on hemodynamic shifts in response to adenosine have so little reflection in the performance of QFR? Although the
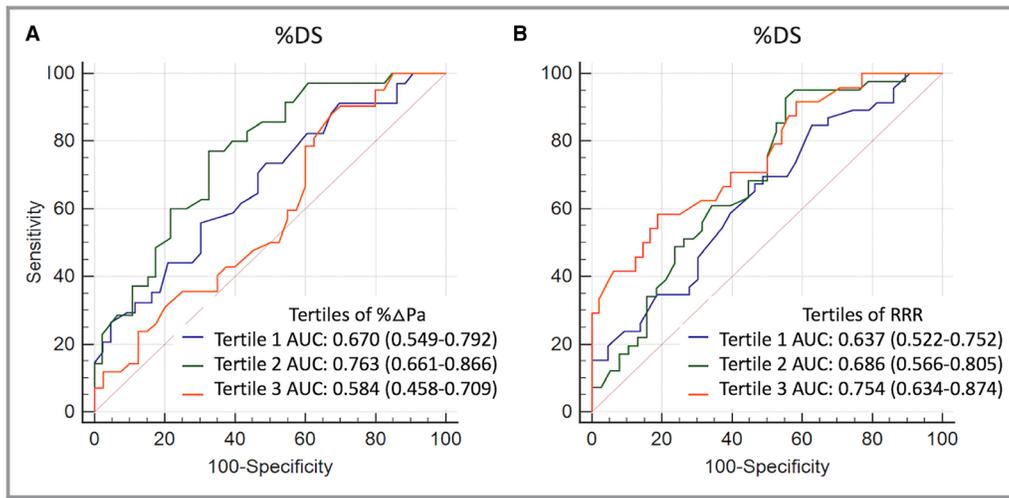
Figure 9. Diagnostic efficiency of angiography alone (percentage diameter stenosis [%DS]), according to interindividual variations in adenosine-induced hemodynamics. The figure shows the area under the curve (AUC) from the receiver-operating characteristic (ROC) analysis depicting the diagnostic efficiency of %DS in determining the fractional flow reserve–based (≤0.80) functional stenosis relevance according to variations (tertiles) in the mean aortic pressure (adenosine-induced percentage change in mean aortic pressure [%ΔPa]; **A**) and in the resistive reserve ratio (RRR; **B**) during adenosine infusion. **A**, Pairwise comparison of ROC curves: tertile 1 vs tertile 2, P=0.251; tertile 1 vs tertile 3, P=0.332; tertile 2 vs tertile 3, P=0.030. **B**, Pairwise comparison of ROC curves: tertile 1 vs tertile 2, P=0.564; tertile 1 vs tertile 3, P=0.168; tertile 2 vs tertile 3, P=0.430.

value of translesional pressure ratios, like FFR, experiences variations in magnitude, according to the extent of myocardial hyperemia,[12] the values of QFR depend much more on other determinants. Functional angiography models merge anatomical and physiological principles. Through complex mathematical equations, these data are used to simulate and predict distribution of flow and pressure across the entire segmented vessel. In the case of QFR, the algorithm computes the translesional pressure gradient by the sum of the pressure decrease across each individual vessel segment by applying a quadratic function on the meshed coronary model and the algorithm estimates the hyperemic flow velocity from the vessel-lumen volume and the TIMI frame count. In other words, functional angiography is based on merging 2 different visions of the coronary stenosis: on one hand, the vision is as a geometric model of vessel narrowing fully separated from the coronary circulation with clearly outlined characteristics, like changes in luminal area, inflow, and outflow angles; on the other hand, the vision is as a pressure gradient device once the stenosis is inserted in a complex hydraulic circuit under assumed boundary conditions, like aortic pressure and microcirculatory resistance. More important, QFR incorporates some patient-specific hemodynamic data, such as the resting contrast flow velocity (TIMI frame counting). From this, the algorithm estimates the hyperemic flow in each individual case, which has demonstrated in previous studies an improvement on the diagnostic

performance of QFR in predicting FFR compared with the fixed-QFR model (which uses a fixed empiric hyperemic flow velocity).[2] In our study, we have found that incorporating TIMI frame counting analysis attenuates some differences observed on fixed-QFR model diagnostic performance across tertiles of %ΔPa and RRR (Tables S2 and S3). In addition, initial QFR algorithms were tuned using real population-based invasive physiological parameters, so it could be possible that the final sophisticated algorithm, when applied to high image quality angiographies and accurate meshed coronary models, overcomes interindividual variations in the response to adenosine, such as changes in aortic pressure and variations in the myocardial hyperemia. Unlike other functional angiography methods, such as FFR$_{angio}$, the QFR algorithm does not incorporate blood pressure values.[13] Finally, in outlining the stenosis severity, the boundary conditions may play a lesser role than the hemodynamic effect derived from the complex stenosis geometry. In support of this hypothesis, we found that the diagnostic performance of angiography alone (percentage diameter stenosis) in determining the FFR-based functional stenosis relevance is substantially affected by interindividual variations in adenosine-induced hemodynamics, contrary to what we found with QFR (Figure 9).

The clinical implications of our findings are several: from a comprehensive physiological analysis using invasive measurements of pressure and flow, our findings support the current

QFR algorithm for predicting FFR without adenosine or additional patient-specific hemodynamic parameters. In addition, the findings of this study make QFR attractive in challenging scenarios for FFR use, such as clinical settings in which administration of adenosine or additional coronary instrumentation may increase procedural risks or patient discomfort or in which an adequate hyperemia for FFR assessment cannot be guaranteed. In the face of such challenges, our findings suggest that QFR may complement invasive physiological techniques or may allow expansion of physiology-based clinical decision-making pathways into everyday clinical practice. For the time being, and pending clinical outcome studies, it seems that functional angiography methods can effectively obviate patient-specific boundary conditions for an accurate assessment of functional stenosis severity.

Study Limitations

Our study has several limitations. As a consequence of the retrospective design of the study, some vessels had to be excluded from analysis because of insufficient angiographic image quality, making them unsuitable for QFR computation (Table S1). In addition, considering the registry and the retrospective nature of the study as well as the complexity of the invasive physiology technique used, power calculations to estimate sample size were not performed. However, we arbitrarily used all the population available from our international cooperative registry, resulting finally in a substantial size population. Furthermore, investigation of factors affecting the diagnostic performance of QFR beyond adenosine-induced hemodynamics is beyond the scope of the current study. For this, we cannot rule out the confounding effect for patient or vessel characteristics or the effect modification by participating centers. However, when all the statistical analyses were repeated, according to participating centers, no results were changed. Another limitation is that adenosine was administered through the peripheral vein in most of the cases, which can certainly limit the opportunity to achieve maximal hyperemia because adenosine action is rapidly inactivated in blood. In this regard, central intravenous administration of adenosine is considered the gold standard to achieve maximum coronary hyperemia. However, in real clinical practice, administration of adenosine through the peripheral vein is the most used method in measuring FFR, which makes it possible that our results can be translated to the real world. Another limitation is that this study was not designed to assess the effect of intraindividual FFR variations on the diagnostic performance of QFR, according to a different adenosine dose. Finally, no data on clinical follow-up are present in our study.

Conclusions

Patients undergoing FFR assessment show large interindividual variations in the magnitude of adenosine-induced hemodynamics. However, such variations do not affect the diagnostic performance of QFR in assessing the functional relevance of observed stenoses.

Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Cases excluded from analysis.

	No. of vessels
Initially available cases	395
Cases excluded from the final analysis	101 (25.5%)
Reason for exclusion	
Ostial stenosis in the LM or RCA	10
Surgically grafted target vessels	2
Inadequate projections for 3D reconstruction	28
Significant overlapping	17
Inadequate angiogram quality	19
Contrast filling precluding an accurate TIMI frame counting	19
Resting hemodynamic data not available	6

LM, left main stem; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction;

3D, three-dimensional.

Table S2. Incremental value of the TIMI frame counting analysis on the diagnostic

performance of QFR according to adenosine-induced percent change in aortic pressure.

	Overall population N = 294	Tertile 1 %ΔPa N = 97	Tertile 2 %ΔPa N = 99	Tertile 3 %ΔPa N = 98	P value
AUC					
f-QFR	0.893(0.857-0.929)	0.924(0.872-0.976)	0.908(0.844-0.971)	0.848(0.772-0.925)	† 0.107
c-QFR	0.931(0.896-0.957)	0.950(0.886-0.984)	0.929(0.860-0.971)	0.910(0.835-0.958)	‡ 0.273
	* 0.004	*0.339	* 0.421	*0.157	
Accuracy					
f-QFR	228(78)	83(86)	70(71)	74(76)	† 0.076
c-QFR	256(87)	86(89)	86(87)	84(86)	‡ 0.531
	*0.004	*0.565	*0.007	*0.086	
Correlation					
f-QFR	0.76	0.77	0.83	0.69	† 0.246
c-QFR	0.84	0.86	0.87	0.80	‡ 0.180
	*0.007	*0.061	*0.320	*0.084	
Mean difference FFR – QFR					
f-QFR	0.028±0.079	0.029±0.075	0.030±0.072	0.024±0.093	† 0.680
c-QFR	0.014±0.064	0.017±0.057	0.011±0.061	0.014±0.073	‡ 0.763
	*0.018	*0.211	*0.046	*0.403	
Sensitivity					
f-QFR	87(80-92)	98(88-99)	87(72-96)	78(63-88)	† 0.000
c-QFR	89(82-94)	91(79-98)	87(72-96)	88(76-96)	‡ 0.496
	*0.456	*0.033	*1.000	*0.063	
Specificity					

	f-QFR	70(62-77)	74(60-85)	62(48-74)	75(60-86)	† 0.873
	c-QFR	86(80-91)	87(74-94)	87(76-94)	85(72-94)	‡ 0.688
		*0.000	*0.023	*0.000	*0.081	
NPV						
	f-QFR	87(81-91)	98(85-99)	88(76-95)	77(66-85)	† 0.000
	c-QFR	90(85-94)	92(81-97)	91(82-96)	87(76-94)	‡ 0.256
		*0.254	*0.056	*0.492	*0.069	
PPV						
	f-QFR	70(65-75)	76(67-83)	59(50-67)	76(66-84)	† 1.000
	c-QFR	84(78-89)	85(75-92)	81(68-89)	86(76-93)	‡ 0.843
		*0.000	*0.114	*0.000	*0.075	
LH +						
	f-QFR	2.9(2.2-3.7)	3.7(2.4-5.8)	2.3(1.6-3.2)	3.1(1.9-5.2)	-
	c-QFR	6.5(4.4-9.6)	6.8(3.4-13.6)	6.6(3.4-12.8)	6.0(3.0-12.1)	-
		-	-	-	-	
LH -						
	f-QFR	0.18(0.10-0.30)	0.03(0.00-0.2)	0.21(0.09-0.50)	0.30(0.20-0.50)	-
	c-QFR	0.13(0.08-0.20)	0.10(0.04-0.3)	0.15(0.07-0.30)	0.14(0.07-0.30)	-
		-	-	-	-	

Whereas the f-QFR model assumes a fixed empiric flow velocity for calculating QFR, the c-QFR model estimates the hyperemic flow from the resting contrast flow velocity (TIMI frame counting). The table shows a comparison of diagnostic parameters for f-QFR and c-QFR across tertiles of %ΔPa. Values are n (95% confidence interval), n (%) or n ± standard deviation.
* P value for comparison between f-QFR and c-QFR within each tertile of %ΔPa; † P value for comparison of f-QFR between tertiles 1 and 3; ‡ P value for comparison of c-QFR between tertiles 1 and 3. AUC, area under the curve; c-QFR, contrast model of QFR; FFR, fractional flow reserve; f-QFR, fixed model of QFR; LH, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; QFR, quantitative flow ratio; TIMI, thrombolysis in myocardial infarction; %ΔPa, percent change in mean aortic pressure induced by adenosine.

Table S3. Incremental value of the TIMI frame counting analysis on the diagnostic

performance of QFR according to adenosine-induced myocardial hyperemia.

	Overall population N = 294	Tertile 1 RRR N = 97	Tertile 2 RRR N = 99	Tertile 3 RRR N = 98	P value
AUC					
f-QFR	0.893(0.857-0.929)	0.885(0.818-0.953)	0.870(0.803-0.937)	0.916(0.860-0.971)	† 0.465
c-QFR	0.931(0.896-0.957)	0.909(0.834-0.958)	0.923(0.852-0.967)	0.959(0.898-0.989)	‡ 0.167
	* 0.004	* 0.509	* 0.192	* 0.032	
Accuracy					
f-QFR	228(78)	76(78)	73(74)	78(80)	† 0.732
c-QFR	256(87)	83(86)	84(85)	89(91)	‡ 0.274
	* 0.004	* 0.148	* 0.060	* 0.039	
Correlation					
f-QFR	0.76	0.78	0.72	0.80	† 0.714
c-QFR	0.84	0.83	0.83	0.86	‡ 0.469
	* 0.007	* 0.328	* 0.052	* 0.179	
Mean difference FFR – QFR					
f-QFR	0.028±0.079	0.031±0.075	0.026±0.092	0.027±0.070	† 0.700
c-QFR	0.014±0.064	0.020±0.065	0.009±0.067	0.013±0.059	‡ 0.403
	* 0.018	* 0.276	* 0.139	* 0.132	
Sensitivity					
f-QFR	87(80-92)	90(79-97)	83(70-93)	88(72-97)	† 0.656
c-QFR	89(82-94)	90(79-97)	85(72-94)	91(76-98)	‡ 0.812
	* 0.456	* 1.000	* 0.701	* 0.494	
Specificity					

		Tertile 1	Tertile 2	Tertile 3	Tertile 4	P value
	f-QFR	70(62-77)	68(52-81)	65(50-78)	74(62-84)	† 0.357
	c-QFR	86(80-91)	78(63-89)	87(74-94)	92(83-97)	‡ 0.006
		* 0.000	* 0.118	* 0.000	* 0.000	
NPV						
	f-QFR	87(81-91)	86(72-93)	81(68-89)	93(83-97)	† 0.111
	c-QFR	90(85-94)	88(75-94)	87(76-93)	95(87-98)	‡ 0.080
		* 0.254	* 0.679	* 0.250	* 0.556	
PPV						
	f-QFR	70(65-75)	77(68-84)	69(60-77)	63(53-72)	† 0.033
	c-QFR	84(78-89)	83(73-89)	85(74-92)	86(73-94)	‡ 0.563
		* 0.000	* 0.297	* 0.007	* 0.000	
LH +						
	f-QFR	2.9(2.2-3.7)	2.8(1.8-4.4)	2.4(1.6-3.5)	3.4(2.2-5.2)	-
	c-QFR	6.5(4.4-9.6)	4.1(2.3-7.1)	6.3(3.1-12.7)	11.7(5.0-27.3)	-
		-	-	-	-	
LH -						
	f-QFR	0.18(0.10-0.30)	0.14(0.06-0.30)	0.26(0.10-0.50)	0.16(0.06 - 0.4)	-
	c-QFR	0.13(0.08-0.20)	0.12(0.05-0.30)	0.17(0.09-0.30)	0.09(0.03-0.3)	-
		-	-	-	-	

The table shows a comparison of diagnostic parameters for f-QFR and c-QFR across tertiles of the resistive reserve ratio (RRR). Values are n (95% confidence interval), n (%) or n ± standard deviation. * P value for comparison between f-QFR and c-QFR within each tertile of RRR; † P value for comparison of f-QFR between tertiles 1 and 3; ‡ P value for comparison of c-QFR between tertiles 1 and 3. LM, left main stem; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; 3D, three-dimensional.