Diagnostic agreement of quantitative flow ratio with fractional flow reserve in a Latin-American population

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Abstract
Quantitative flow ratio (QFR) is a recently proposed angiographic index that allows to assess the pressure loss in coronary arteries in a similar fashion as the fractional flow reserve (FFR). The purpose of this study was to evaluate the diagnostic performance of QFR as compared to FFR, in a Latin-American population of patients with suspected ischaemic heart disease. QFR was retrospectively derived from coronary angiograms. The association, diagnostic performance, and continuous agreement of fixed-flow QFR (fQFR) and contrast-flow QFR (cQFR) with FFR was assessed by continuous and dichotomous methods. 90 vessels from 66 patients were finally included. The study comprised coronary stenoses of intermediate severity, both angiographically (diameter stenosis: 46.6 ± 12.8%) and physiologically [median FFR = 0.83 (quartile 1–3, 0.76–0.89)]. The correlation of FFR with both fQFR [ρ = 0.841, (95% CI 0.767 to 0.893), p < 0.001] and cQFR [ρ = 0.833, (95% CI 0.755 to 0.887), p < 0.001] was strong. The diagnostic performance of cQFR was good [area under the ROC curve of 0.92 (95% CI 0.86 to 0.97, p < 0.001)], with 0.80 as the optimal cQFR cut-off against FFR ≤ 0.80. This 0.80 cQFR cut-off classified correctly 83.3% of total stenoses, with a sensitivity of 85.2% and specificity of 80.6%. QFR was strongly associated with FFR and exhibited a high diagnostic performance in this Latin-American population.

Keywords Quantitative flow ratio · Fractional flow reserve · Ischaemic heart disease · Percutaneous coronary intervention

Introduction
In patients with symptoms compatible with ischaemic heart disease (IHD), clinical guidelines recommend invasive coronary angiography (ICA) complemented by physiological guidance with pressure wire-derived fractional flow reserve (FFR), particularly if symptoms are responding poorly to medical treatment and revascularization is being considered [1]. The worldwide use of coronary physiology indices like FFR, however, remains low [2], particularly in developing regions, like Latin-America.

Quantitative flow ratio (QFR®; QAngio XA 3D, Medis Medical Imaging Systems, Leiden, The Netherlands) is a novel computational software that allows to calculate FFR from ICA without the need of pressure wires [3]. QFR has been extensively investigated and has exhibited robust diagnostic features in European, Asian, and US- populations [4]. In order to correctly frame results of ongoing QFR-clinical trials, a multicultural evaluation is important, because ethnicity has been suggested as a potential source of heterogeneity in QFR diagnostic performance [5, 6].

The purpose of this study was to evaluate the diagnostic performance of QFR as compared to FFR, in a Latin-American population of patients with suspected IHD.
Methods

Study population

Patients with a clinical indication for FFR interrogation of ≥ 1 intermediate coronary stenosis (> 30% by visual assessment) investigated at Hospital General del Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) de Queretaro, Mexico, were prospectively studied. Patients with myocardial infarction <5 days, contraindications to adenosine, left main disease, as well as vessels supplying previously known infarcted territories, with serial stenoses, marked diffuse narrowings or with surgical grafts were excluded. Approval from the Institutional Review Board was obtained, and all patients gave informed consent.

Cardiac catheterization and haemodynamic measurements

Invasive coronary angiography was performed according to best local practice in a prospective fashion aiming for future QFR retrospective analyses. Coronary angiographies were obtained via the radial or femoral approach with 6 or 7 french guiding catheters. Optimal angiographic views, aimed to avoid vessel foreshortening and overlapping, were obtained following the administration of intracoronary nitrates (0.2 mg). Angiographies were obtained at fifteen frames per second. After diagnostic angiography, pressure sensor-equipped guidewires (Verrata pressure-wire, Koninklijke Philips N.V.) were used to measure intracoronary pressure using described methodologies [7]. First, the pressure wire was zeroed and equalized. Afterwards, the pressure sensor was positioned at least 3 cm distal to the index stenosis and the guiding catheter was flushed with saline. Hyperaemia was induced with intracoronary adenosine, using 100 to 200 mcgrs in the right coronary artery and 200 to 400 mcgr in the left main. FFR was calculated as the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) at peak hyperemia. Pressure wire pullback maneuver to check for pressure drift was always performed. If pressure drift was significant (> 3 mmHg) pressure recordings were repeated. FFR ≤ 0.80 and was used as cut-off.

Computation of QFR

Three-dimensional quantitative coronary angiography (QCA) and QFR analyses were retrospectively performed by a single operator using dedicated software (QFR 2.0 by Medis, Leiden, the Netherlands) (Fig. 1). Briefly, end-diastolic frames of two optimal angiography projections, separated by at least 25° degrees, were selected, and used for three-dimensional (3D) model reconstruction [3]. The 3D contour model of the segment of interest and its reference vessel were constructed in an automated manner, and manual correction of the contours was performed, if required. Afterwards, 2D and 3D-QCA variables and the fixed-flow QFR (fQFR) were automatically calculated by the software. Coronary flow velocity was estimated using the Thrombolysis in Myocardial Infarction (TIMI) frame-count, indicating the frames where contrast entered and exited the segment of interest of the vessel. With this information, the software automatically calculated the contrast corrected-QFR (cQFR) value. Since cQFR is the one used in clinical trials, agreement analyses are only provided for this variable [8].

Statistical analysis

Continuous variables are presented as mean ± SD or median [quartile 1 and quartile 3 (Q1-3)] and categorical variables as counts and percentages. Normality and homogeneity of the variances were tested using Shapiro–Wilk and Levene tests. Data was analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of calculations. For dichotomization of QFR values, receiver-operating characteristic (ROC) analyses were used to determine its optimal cut-off against FFR ≤ 0.80, defined as that maximizing correct classification, with the highest sensitivity and specificity. Continuous agreement was assessed with parametric (Bland–Altman) and robust (Passing-Bablok) methods as well as with Lin’s concordance correlation coefficient. On the basis of the formula proposed by Buderer et al. [9], given a prevalence of positive FFR values of 40%, and an expected sensitivity of 0.90, specificity of 0.85 [4] and precision of ± 10%, 87 vessels are required to estimate, with a clinically acceptable degree of precision, the sensitivity and specificity of QFR against FFR. The STATA 12.1 statistical software package was used for all calculations.

Results

Baseline characteristics

A total of 153 vessels were screened for inclusion. From these, 63 were excluded, because of incomplete clinical data (n = 12), significant artifacts and pressure-drift in pressure recordings (n = 15) and angiographies of insufficient quality (n = 36). The final study population consisted of 90 vessels from 66 patients. Clinical, angiographic, and physiological characteristics of the study population are shown in Tables 1 and 2. Most patients were male, had stable symptoms, and the most prevalent risk factors were hypertension and diabetes. The study comprised coronary stenoses of intermediate
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severity, both angiographically (diameter stenosis (DS%): 46.6 ± 12.8%) and physiologically [median FFR = 0.83 (Q1-3, 0.76–0.89)]. 36 vessels (40%) had a positive FFR (< 0.80) value.

Correlations of FFR with QFR and anatomical severity of the stenosis

The correlation of FFR with both fQFR [ρ = 0.841, (95% CI 0.767 to 0.893), p < 0.001] and cQFR [ρ = 0.833, (95% CI 0.755 to 0.887), p < 0.001] was strong. These variables scatterplots are provided in Fig. 2 (panels A and C). Regression analyses identified a linear relationship, with a coefficient of determination (R2) of 0.75 for cQFR, and 0.69 for fixed QFR (p < 0.001 for both). The relationship of DS% with FFR, fixed- and cQFR is provided provided in Fig. 3. DS% was modestly correlated with FFR [ρ = −0.561, (95% CI −0.692 to −0.397), p < 0.001], fQFR [ρ = −0.657, (95% CI −0.763 to −0.512), p < 0.001] and cQFR [ρ = −0.663, (95% CI −0.767 to −0.524), p < 0.001].

Fig. 1 Coronary angiography and QFR computation. A moderate stenosis in the left circumflex was evaluated with FFR and QFR. Panels B and C exhibits two angiographies with superimposed diameters functions, which is further described in Panel D. The lesion characteristics and QFR value is shown in Panel A. In this example the FFR value was 0.79.

Table 1 General characteristics of patients included in study n = 66

| Baseline demographics |       |
|-----------------------|-------|
| Age (years)           | 66.1 ± 8.8 |
| Gender (Male)         | 71.2 (47) |
| Medical history       |       |
| Prior myocardial infarction | 33.8 (22) |
| Prior PCI             | 29.2 (19) |
| Hypertension          | 84.6 (55) |
| Diabetes              | 47.7 (31) |
| Current smoker (< 6 Month) | 18.7 (12) |
| History of other vascular disease | 2.6 (1) |
| Renal dysfunction (serum creatinine > 2.0) | 6.2 (4) |
| Clinical presentation |       |
| Stable symptoms       | 56.1 (37) |
| Unstable angina       | 21.2 (14) |
| NSTEMI (> 5 days before enrollment) | 3.0 (2) |
| STEMI (> 5 days before enrollment) | 19.7 (13) |

Numbers are percentages (N) or mean ± standard deviation
Diagnostic performance of QFR against FFR

ROC analyses (Fig. 2 and 4) identified 0.78 as the optimal fQFR cut-off against FFR ≤ 0.80, with an area under the ROC curve (c-statistic) of 0.90 (95% CI 0.86 to 0.97, p < 0.001). This 0.78 fQFR cut-off classified correctly 82.2% of total stenoses, with a sensitivity of 83.3% and specificity of 80.6% (Fig. 2, panel D). The diagnostic performance of cQFR was numerically better, with 0.80 as the optimal cQFR cut-off against FFR ≤ 0.80, and an area under the ROC curve (c-statistic) of 0.92 (95% CI 0.86 to 0.97, p < 0.001). This 0.80 cQFR cut-off classified correctly 83.3% of total stenoses, with a sensitivity of 85.2% and specificity of 80.6% (Fig. 2, panel B). Figure 4 shows the ROC curves of DS%, fQFR and cQFR against FFR ≤ 0.80. No significant difference between the areas under the ROC fQFR and cQFR curves was documented [difference in c-statistics 0.00 (95% CI − 0.01 to 0.00), p = 0.684]. The area under the DS% ROC curve against FFR was significant, yet smaller, 0.72 (95% CI 0.61 to 0.83, p < 0.001), and statistically inferior to that of both fQFR and cQFR values.

Agreement of QFR with FFR

Since cQFR is the one that is currently been tested in clinical trials, agreement analyses are only provided for it. Figure 5 provides the continuous agreement between cQFR and FFR. A high concordance between these variables was observed and demonstrated by a Lin’s correlation coefficient of 0.819. Panel A of Fig. 5 shows their Passing-Bablok regression line, that revealed constant (A = 0.23, 95% CI 0.22 to 0.33) and proportional (B = 0.67, 95% CI 0.58 to 0.75) differences between the indices. Their Bland–Altman plot (Fig. 5, panel B) demonstrated some heteroscedasticity and proportional error, a very small systematic bias (0.00); and significant imprecision on individual basis, as the 95% limits of agreement were wide (− 0.15 to 0.16).

Discussion

This study addressed the relationship of FFR with QFR in a Latin-American population of patients with suspected IHD. Our results support the diagnostic value of QFR in establishing the hemodynamic severity of coronary stenosis and supports the incorporation of QFR in the clinical decision-making process of IHD in Latin-America. This is important at a time, when clinical guidelines clearly support the use of intracoronary physiology in the catheterization laboratory, and ongoing clinical trials are providing encouraging results for QFR. In the following paragraphs, these aspects will be discussed in detail.

Clinical value of FFR

Over the last decades, vast clinical data has demonstrated that FFR is one of the few diagnostic tests that not only improves patient outcome but also, at the same time, is cost-effective and cost-saving in developed countries [1, 2]. Supported by several randomized clinical trials, FFR has achieved the highest class (I) and level (A) of recommendation in clinical guidelines following the demonstration that physiological rather than anatomical revascularization results in better patients’ outcome [1]. Moreover, in a recent metanalysis of the available randomized controlled trials, FFR-guided percutaneous coronary intervention resulted in a reduction of the composite of cardiac death or myocardial infarction compared with lone optimal medical therapy, which was driven by a decreased risk of myocardial infarction [10]. Still however, the worldwide use of coronary physiology in the catheterization laboratory remains low. This is particularly true in developing regions like Latin-America. Several explanations for these have been proposed [2]. FFR certainly adds some complexity and time to the procedure. FFR carries a small but
inherent risk due to coronary artery instrumentation and use of vasodilators. Additionally, there exists some amount of hesitation on the degree of hyperaemia that is achieved with vasodilators (which is not an issue for non-hyperemic pressure ratios assessment). However, one of the most relevant factors contributing to the low use of intracoronary physiology is the incremental cost of pressurewires and vasodilators. It can be hypothesized that the economical constrains experienced in developing regions like Latin-America can further lead to a decreased use of physiology guidance. By allowing to estimate an angiography-derived proxy of FFR without the use of a pressurewire and hyperaemic agents, QFR becomes a particularly attractive adjuvant tool for Latin-America and other developing regions.

Fig. 2  Relationship of FFR with fQFR and cQFR. Panels A and C exhibit the scatterplots and lineal regressions. Panel B and D show the sensitivity, specificity and correctly classified lines across the QFR values.
Clinical value of QFR

QFR is a computational software that computes from 2 high quality angiograms a surrogate of FFR. For these, QFR constructs a 3D model of the stenotic and normal segments of the coronary artery and then estimates the pressure loss produced by the atherosclerotic plaque following fundamental physiological principles [3]. QFR has been extensively investigated and previous studies from China, Europe and Japan demonstrated both feasibility and accuracy of online QFR assessment [11, 12]. A recent meta-analysis that included thirty-nine studies involving 5440 patients observed that QFR had a good diagnostic accuracy to predict FFR < 0.80, with a meta-analytic sensitivity and specificity of 85% and 91%, respectively [4]. Our results are supportive and incremental because we observed very similar diagnostic characteristics for QFR in our Latin-American population. This information is relevant because ethnicity has been suggested as a potential source of heterogeneity in QFR diagnostic performance [5].

Very recently, the FAVOR III China (Angiographic quantitative flow ratio-guided coronary intervention) trial was published [8]. This landmark QFR study is the first large, multicentre, blinded, sham-controlled trial designed to test the clinical usefulness of a QFR-guided revascularization strategy in terms of clinical events. Here, 3847 patients were randomly assigned to a QFR-guided or an angiography-guided PCI strategy. The primary endpoint was the 1-year rate of major adverse cardiac events, defined as the composite of death from any cause, myocardial infarction, or ischaemia-driven revascularization. Importantly, the 1-year primary endpoint occurred less frequently in the QFR-guided group [110 (5.8%) patients] as compared to the angiography-guided group [167 (8.8%) patients] and the difference was clinically relevant and statistically significant: − 3.0% [95% CI − 4.7 to − 1.4]; hazard ratio 0.65 [95% CI 0.51 to 0.83]; p = 0.0004). Moreover, QFR lead to a significantly lower use of coronary stents (1.45 vs 1.58; p < 0.001) and procedural times (44.6 vs 49.5 min; p < 0.001), and a significantly increased rate of deferral of PCI (19.6% vs 5.2%; p < 0.001). Finally, the lower rate of events observed in the QFR-guided group was driven by fewer myocardial infarctions (3.4% vs 5.7%; p < 0.001) and ischaemia-driven revascularizations (2.0% vs 3.1%; p < 0.001) as compared to the angiography-guided group. The study was hence

![Fig. 3 Scatterplots of the relationship between anatomical stenosis severity as assessed by 2D diameter stenosis (%) with FFR (Panel A), cQFR (Panel B) and fQFR (Panel C)](image)

![Fig. 4 Receiver operator characteristics (ROC) curves illustrating the diagnostic performance of fQFR, cQFR and DS% against FFR < 0.80)](image)
able to show that QFR can safely translate to patients the benefits of physiology guidance observed in randomized FFR trials and provides robust support to the incorporation of QFR in routine clinical practice.

Limitations

This study has several limitations. First, the sample size is small, albeit the largest available from Latin-America [6]. However, our sample size is sufficient to calculate, with reasonable clinical precision, the sensitivity and specificity of QFR against FFR [9]. Second and in spite that all physiology traces and angiographies were obtained by a single experienced operator (MEP), a significant proportion of patients were excluded because of angiographies of insufficient quality. This fact exhibits a described limitation of the QFR technique, the requirement of high quality angiographies, and also reflects the real world angiographic and QFR-analyses learning curve. Third, included stenosis were of intermediate severity both functionally and angiographically. This limits the translation of our findings to other populations of stenosis. Still, pressurewires are mostly used for intermediate stenosis assessment. Finally, this was a single-center experience. Hence, the external reproducibility of our findings must be challenged. Nonetheless, we believe the gathered observations contribute to increase the adoption of QFR and physiology guidance in Latin-America.

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The authors have not disclosed any funding.

Declarations

Conflict of interest

MEP, TPH, HGG have served as speakers in educational events organized Boston Scientific and Abbot, developers of pressure wires.

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