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# Computational quantitative flow ratio to assess functional severity of coronary artery stenosis

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ABSTRACT

*Background:* Computational quantitative flow ratio (QFR) based on 3-dimensional quantitative coronary angiography (3D QCA) analysis offers the opportunity to assess the significance of coronary artery disease (CAD) without using an invasive pressure wire or inducing hyperemia. This study aimed to evaluate the diagnostic performance of QFR compared to wire-based fractional flow reserve (FFR) and to validate the previously reported QFR cut-off value of >0.90 to safely rule out functionally significant CAD.

*Methods:* QFR was retrospectively derived from standard-care coronary angiograms. Correlation and agreement of fixed-flow QFR (fQFR) and contrast-flow QFR (cQFR) models with invasive wire-based FFR was calculated. Diagnostic performance of QFR was evaluated at different QFR cut-off values defining significant CAD (FFR ≤ 0.80).

*Results:* 101 vessels in 96 patients who underwent FFR were studied. Mean FFR was 0.87 ± 0.08 and 21 of 101 (21%) vessels had an FFR ≤ 0.80. Correlation of fQFR and cQFR with FFR was $r = 0.71$ ($p < 0.001$) and $r = 0.70$ ($p < 0.001$), respectively. Sensitivity and specificity were 57% and 93% for fQFR and 67% and 96% for cQFR at a QFR cut-off value >0.80 defining non-significant CAD, respectively. fQFR > 0.90 was present in 34 (34%) and cQFR > 0.90 in 39 (39%) vessels. For both QFR models, none of the vessels with QFR > 0.90 had an FFR ≤ 0.80.

*Conclusions:* QFR appears to be a safe and effective gatekeeper to wire-based FFR when applying a QFR threshold of >0.90 to rule out significant CAD. Further prospective research is required to establish QFR in the real-life setting of functional CAD assessment in the catheterization laboratory.



## 1. Introduction

Coronary artery disease (CAD) is the most common cause of death globally, resulting in 8.9 million deaths annually worldwide [1]. The clinical relevance of CAD can be assessed by visual inspection of the anatomical stenosis on the coronary angiogram [2] or by measuring its functional consequence using fractional flow reserve (FFR) [3] or instantaneous wave-free ratio (iFR) [4,5]. Functional assessment of CAD by FFR was shown to be superior to visual assessment for therapy decision-making [6]. To determine FFR, the introduction of an invasive pressure wire and induction of hyperemia is required, increasing patient discomfort, complication risk and costs associated with the catheterization procedure. Tu et al. developed fast quantitative flow ratio (QFR) computation models based on 3-dimensional quantitative coronary angiography (3D QCA) to calculate FFR from angiographic images without introducing an invasive pressure wire in the coronary artery or inducing hyperemia, and showed good agreement of QFR computation models with wire-based FFR [7]. Validation of these first results on QFR analysis is essential in order to prevent inappropriate adjustment of diagnostic strategies based on results of unreproducible studies (Baker, Nature 2016). Our study will explore the diagnostic accuracy of QFR and the potential of QFR to safely rule out haemodynamic relevant coronary artery stenosis by evaluation of various QFR rule-out thresholds. We aim to validate the previously reported QFR cut-off value of >0.90 to safely rule out functionally significant CAD [7].

## 2. Methods

### 2.1. Study design

This is a retrospective, single-centre observational study performed in the University Medical Center Groningen, The Netherlands. QFR is compared to the reference standard of FFR. The medical ethics review board of the University Medical Center Groningen reviewed the protocol (METc 2016/455). None of the patients objected to the use of their medical data for scientific research.

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### 2.2. Study population

Coronary angiograms of all patients in whom FFR was performed in the UMCG as part of routine clinical care in the period between January 2015 and July 2015 were screened for further analysis by dedicated QFR software (QAngio XA 3D/QFR research version 1.0.28.0, Medis Medical Imaging Systems, Leiden, The Netherlands). In- and exclusion criteria of angiograms were based on practical requirements of QFR software. Inclusion criteria were: 1) documentation of the exact wire-based FFR values, 2) availability of two angiogram acquisitions of the interrogated vessel, 3) an angle ≥25° between the two angiogram acquisitions of one vessel and 4) perpendicularity of both acquisitions towards the interrogated vessel. Exclusion criteria were: 1) no documented nitroglycerine administration prior to the recording of acquisitions, 2) image acquisition speed of <10 frames/s, 3) prior coronary artery bypass grafting (CABG) on the interrogated vessel 4) true bifurcation lesion (1-1-1 according to Medina classification), 5) ostial left main or ostial right coronary artery lesion, 6) retrograde filling of the interrogated vessel, 7) hyperdynamic heart.

### 2.3. Enrolment of cases

QFR was retrospectively derived from standard-care coronary angiograms. Although acquisitions were of sufficient quality for clinical decision making, not all acquisitions met the software requirements for standardized views and adequate contrast injection. Four known analysis-complicating factors were scored: degree of vessel overlap (0 = none, 1 = moderate, 2 = severe), degree of foreshortening (0 = none, 1 = moderate, 2 = severe), general image quality/brightness (0 = none, 1 = moderate, 2 = bad) and quality of contrast agent injection (0 = fast/brisk, 1 = slow/stagnating). An Image Quality Score (IQS) was calculated on a per-vessel basis by summing up the scores per factor for the two acquisitions separately. Vessels with IQS ≥3 for one of the two acquisitions were considered inappropriate for QFR calculation and excluded from further analysis.

### 2.4. Image collection

Coronary angiogram acquisitions of patients were collected from the Picture Archiving and Communication System (PACS). All patients received an individual study-specific code. When the inclusion criteria were met, the appropriate acquisitions were selected and stored separately from the rest of the acquisitions. Final QFR analysis was performed on these separately stored acquisitions one week later to ensure readers were blinded for possibly performed interventions visible on acquisitions encountered during the selection process. Coronary angiogram acquisitions were recorded with a frame acquisition speed of 10 or 15 frames per second.

### 2.5. QFR analysis

Offline QFR analysis was performed by a trained (Level 2 Certification, Medis Medical Imaging Systems) reader. A second trained reader was consulted in case execution of QFR analysis was troublesome. All readers were blinded to the wire-based FFR values. The vessel in which FFR was performed was known to the reader. To avoid excessive compression of the interrogated vessel, end-diastolic frames were selected. End-diastolic phase was defined by the presence of maximal myocardial relaxation on the acquisition frame in combination with end of P-wave on the electrocardiographic signal, when available. Setpoints for segment selection were placed at the ostium of the interrogated vessel proximally and at the location of the proximal tip of the FFR pressure sensor distally in order to conduct QFR analysis in accordance with the original FFR procedure. To match vessel contours, side branches were indicated as corresponding anatomical landmarks on both acquisitions. Vessel contours were automatically detected on the two acquisitions and manually adjusted in case of erroneous registration or side branch disturbance. Based on the corresponding 2D acquisitions, a 3D reconstruction of the single coronary vessel was generated by the QFR software. Bifurcation lesions were analysed as single vessels without side branches. 3D QCA percent diameter stenosis (DS) and percent area stenosis (AS) were derived from the 3D model of the vessel and calibration data saved in the DICOM files of acquisitions. Fixed-flow QFR (fQFR) and contrast-flow QFR (cQFR) were calculated by the software, as previously described [7,8]. In brief, pressure drop is calculated using a quadratic equitation incorporating vessel geometry and hyperemic flow velocity (HFV). fQFR is calculated using a fixed experiential HFV of 0.35 m/s, based on a previous study [8]. cQFR is calculated using a modelled HFV, derived from frame counting on contrast-enhanced images acquired at rest. Frame counting is manually performed by indicating the acquisition frame at which the contrast bolus reaches proximal and distal limits of the analysed segment. Fig. S1 shows an overview of the practical execution of QFR analysis.

### 2.6. FFR

Blood pressures were measured at the catheter tip and distally from the stenosis using PressureWire Aeris (St. Jude Medical Systems, Saint Paul, Minnesota, United States). A bolus of 200–400 μg nitroglycerin was administered intracoronary prior to measurements. A dose of 120 μg adenosine was administered intracoronary to induce hyperaemia. In case of sequential lesions adenosine was administered intravenously (140 μg/kg/min). After reaching minimal FFR value distally, the pressure wire was pulled back across the vessel to assess pressure drop across single lesions. To calculate FFR, mean distal coronary pressure was divided by mean aortic pressure.

### 2.7. Statistical analysis

Categorical variables are shown as a number and percentage. Continuous variables are described by mean ± SD or median (interquartile range) in case of non-normal distribution. Wire-based FFR was defined as the reference standard. An FFR threshold of ≤0.80 was used to define significant CAD. Pearson correlation coefficient ($r$) was calculated to quantify the correlation of QFR models with wire-based FFR and Spearman correlation coefficient ($\rho$) was calculated to quantify correlation of 3D QCA parameters with FFR. Bland Altman analysis was used to determine agreement of QFR models with FFR. The diagnostic performance of QFR and 3D QCA was evaluated by describing diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A common 3D QCA DS cut-off value of ≥50% and optimal Youden Index AS cut-off value of ≥63.5% was used to define significant coronary stenosis. To evaluate the potential use of QFR as a gatekeeper to FFR, we determined the diagnostic performance of both the optimal QFR cut-off value in our study population (as determined by the Youden Index) and the previously reported QFR cut-off value of >0.90 defining non-significant CAD. [7] The area under the receiver operating characteristic curves (AUC) were compared using the DeLong method. Statistical significance was defined as a two-sided $p$-value of <0.05. Statistical analysis was performed using SPSS (IBM SPSS Statistics version 23.0, Chicago, United States). Receiver operating characteristic curve analysis was performed using Stata (StataCorp LP, StataMP version 13.0, College Station, United States).

## 3. Results

### 3.1. Patient and lesion characteristics

274 patients with 333 vessels were screened for inclusion. A total of 128 patients with 133 vessels met basic in- and exclusion criteria. Seventeen vessels had IQS ≥3 and were excluded. Fifteen additional vessels were excluded after 2 readers reached consensus about inadequateness of acquisitions caused by factors not reflected by the IQS. The final study population consisted of 96 patients and 101 coronary vessels. Fig. 1 shows an overview of patient and vessel selection. Patient characteristics are shown in Table 1. Lesion characteristics are shown in Table S1. The mean FFR was 0.87 ± 0.08. In 21 of 101 vessels, the lesion caused an FFR ≤ 0.80.

### 3.2. Correlation and agreement of QFR and 3D QCA with FFR

The correlation of fQFR and cQFR with wire-based FFR was $r = 0.71$ ($p < 0.001$) and $r = 0.70$ ($p < 0.001$), respectively (Fig. S2). For 3D QCA DS and AS, correlation with wire-based FFR was $\rho = -0.47$ ($p < 0.001$) and $\rho = -0.37$ ($p < 0.001$), respectively (Fig. S3). The mean difference with wire-based FFR was 0.003 ± 0.06 ($p = 0.39$) for fQFR and − 0.001 ± 0.06 ($p = 0.64$) for cQFR (Fig. S2).

### 3.3. Diagnostic performance of QFR compared to 3D QCA

Accuracy, sensitivity, specificity, PPV and NPV were 85%, 57%, 93%, 67%, and 89% for fQFR and 90%, 67%, 96%, 82%, and 92% for cQFR at a QFR cut-off value of >0.80, respectively. Accuracy, sensitivity, specificity, PPV and NPV were 75%, 43%, 84%, 41%, and 85% for DS and 74%, 67%, 76%, 42%, and 90% for AS, respectively. AUC was significantly larger for fQFR (AUC 0.92) compared to 3D QCA DS (AUC 0.79, difference; 0.13, $p < 0.001$) and AS (AUC 0.74, difference; 0.18, $p < 0.001$) and significantly larger for cQFR (AUC 0.92) compared to 3D QCA DS (AUC 0.79, difference; 0.13, $p < 0.001$) and AS (AUC 0.74, difference; 0.18, $p < 0.001$) (Fig. 2).

### 3.4. Diagnostic performance of QFR at optimal QFR thresholds

The optimal QFR cut-off was >0.83 for fQFR and >0.82 for cQFR in our study population. At optimal QFR cut-offs, 2 and 5 vessels were falsely indicated as non-obstructive by fQFR and cQFR, respectively. Accuracy, sensitivity, specificity, PPV and NPV were 80%, 90%, 78%, 51% and 97% for fQFR and 87%, 76%, 90%, 67% and 94% for cQFR at these QFR cut-offs, respectively, as shown in Table 2.