Original Article

Diagnostic performance of quantitative flow ratio, non-hyperaemic pressure indices and fractional flow reserve for the assessment of coronary lesions in severe aortic stenosis

Cameron Dowling[1]^, Michael Michail[2,3], Jun Michael Zhang[1], Andrea Comella[1], Udit Thakur[1], Robert Gooley[1], Liam McCormick[1], Adam J. Brown[1], Dennis T. L. Wong[1]

[1]MonashHeart, Monash Health and Monash Cardiovascular Research Centre, Monash University, Melbourne, Australia; [2]Sussex Cardiac Centre, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; [3]Institute of Cardiovascular Science, University College London, London, UK
Contributions: (I) Conception and design: M Michail, AJ Brown, DTL Wong; (II) Administrative support: M Michail, AJ Brown, DTL Wong; (III) Provision of study materials or patients: M Michail, AJ Brown, DTL Wong; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
Correspondence to: Dr. Cameron Dowling, MBBS, PhD. MonashHeart, Monash Health and Monash Cardiovascular Research Centre, Monash University, 246 Clayton Rd, Clayton VIC 3168, Melbourne, Australia. Email: cameron.dowling@monashhealth.org.

Background: Quantitative flow ratio (QFR) may be used to assess the functional significance of coronary lesions. Only limited validation exists for this technology in the setting of severe aortic stenosis.
Methods: A prospective study was performed on patients who were being considered for transcatheter aortic valve implantation. QFR analysis was performed (Medis Medical Imaging System, Leiden, The Netherlands) and compared to invasive measurements of haemodynamic assessment [fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), diastolic pressure ratio during the wave-free period (dPR) and distal arterial pressure/arterial pressure (Pd/Pa)].
Results: A total of 35 patients were included in the study. Mean age was 75.5±6.5 and mean aortic valve gradient was 44.3±11.8 mmHg. There were 57 vessels analysed. The mean FFR was 0.83±0.10 and 22 vessels (39%) had a functionally significant FFR ≤0.80. QFR demonstrated a discriminatory power to predict functionally significant FFR [area under the receiver operating characteristic curve (AUC), 0.92; 95% confidence interval (CI): 0.84 to 1.00], representing a sensitivity of 73%, specificity of 91%, positive predictive value of 84%, negative predictive value of 84% and an accuracy of 84%. QFR also demonstrated a discriminatory power to predict functionally significant iFR ≤0.89 (AUC =0.92; 95% CI: 0.85 to 0.99), dPR ≤0.89 (AUC =0.90; 95% CI: 0.83 to 0.98) and Pd/Pa ≤0.92 (AUC =0.89; 95% CI: 0.80 to 0.97).
Conclusions: QFR demonstrates acceptable diagnostic performance in patients with severe aortic stenosis when both FFR and non-hyperaemic pressure indices are used as reference standards.

Keywords: Quantitative flow ratio (QFR); fractional flow reserve (FFR); instantaneous wave-free ratio (iFR); aortic stenosis; computed tomography (CT)

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^ ORCID: 0000-0003-3191-5361.

Introduction

Evaluation of coronary artery disease is an important consideration when assessing patients for transcatheter aortic valve replacement (TAVR). Fractional flow reserve (FFR) may be used to assess the physiological significance of coronary stenoses in the setting of severe aortic stenosis, and its usage to guide myocardial revascularisation has been associated with improved clinical outcomes when compared to angiographic guidance (1).

However, it would be desirable to avoid the administration of vasoactive medications in this vulnerable patient cohort (2). Furthermore, while non-hyperaemic indices are an alternative tool for physiological assessment in the setting of aortic stenosis (3,4), it would be advantageous to assess coronary lesions without the usage of wire-based tools.

One emerging technology for the physiological assessment of coronary stenoses is quantitative flow ratio (QFR), which is derived using complex mathematical methods built upon the principles of computational fluid dynamics (CFD) (5). QFR is computed using a modelled hyperaemic flow velocity, derived from thrombolysis in myocardial infarction frame count analysis, without pharmacologically-induced hyperaemia.

In this study we wished to compare the diagnostic performance of QFR against FFR and non-hyperaemic indices in the setting of severe aortic stenosis. We present the following article in accordance with the STARD reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-574/rc).

Methods

A single centre prospective study was performed at Monash Medical Centre, Melbourne between November 2018 and November 2019 on consecutive patients with symptomatic severe aortic stenosis who were being considered for TAVR. Full inclusion and exclusion criteria and flow of participants have been reported in the CAST-FFR study (6). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed by Monash Health Human Research Ethics Committee (HREC/43524/MonH-2018-67705v1) and all participants provided informed consent for inclusion in the study.

Pressure wire assessment

Coronary angiography was performed using standard protocols. Angiography was acquired at 15 frames per second. Pressure wire assessment (PressureWire X, Abbott Laboratories, Abbott Park, IL) was performed on coronary lesions of 30–90% severity in vessels with ≥2 mm diameter. Intracoronary glyceryl trinitrate (100 µg) was administered. The pressure wire was equalised with aortic pressure and then positioned in the distal third of the artery, at least 20 mm beyond the coronary lesion. Measurements was recorded (QUANTIEN, Abbott Laboratories) at rest and then hyperaemia was induced with intravenous adenosine (140 µg/kg/min). Measurements were repeated if there was >0.02 drift in the distal arterial pressure/arterial pressure (Pd/Pa) at the guiding catheter tip. Haemodynamic recordings were exported to Python v3.8 (Python Software Foundation, Wilmington, DE) to calculate FFR, instantaneous wave-free ratio (iFR), diastolic pressure ratio during the wave-free period (dPR) and Pd/Pa, using previously described methods (7).

Quantitate flow ratio analysis

QFR analysis was performed using QAngio XA3D v3.1.1 (Medis Medical Imaging System, Leiden, The Netherlands) by an independent core laboratory, using previously described methods (8). Analysis was performed on two angiographic acquisitions that were separated by ≥25°, ensuring that the angiographic projections had minimal foreshortening of the stenosis, and only minimal overlap of the main vessel and the side branches. Two-dimensional quantitative coronary angiography (QCA) was performed, and percentage diameter stenosis and lesion length recorded. The pressure wire recordings and angiographic information which was used to perform the QFR modelling were undertaken contemporaneously.

Statistical analysis

Statistical analysis was performed using SPSS v26.0 (IBM Corporation, Armonk, New York, USA). Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies (percentage). Correlation was assessed using a Pearson correlation coefficient (r). Agreement was assessed using a Bland-Altman technique. Discriminatory power was tested using the area under the receiver operating characteristic curve (AUC). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated. We calculated that with a functionally significant

Table 1 Baseline characteristics

Characteristic	Values (total n=35)
Age, years	75.5±6.5
Male, n (%)	25 [71]
Body mass index (kg/m^2)	28.7±7.1
STS score (%)	2.8±2.0
Cardiovascular risk factors, n (%)	
Diabetes mellitus	20 [57]
Hypertension	24 [69]
Hyperlipidaemia	23 [66]
Smoking history	16 [46]
Family history of IHD	9 [26]
Previous MI, n (%)	4 [11]
Previous CVA or TIA, n (%)	4 [11]
Peripheral vascular disease, n (%)	1 [3]
Atrial fibrillation, n (%)	4 [11]
Chronic kidney disease, n (%)	3 [9]
Echocardiographic parameters	
Left ventricular ejection fraction (%)	64.1±8.7
Peak aortic valve velocity (m/s)	4.3±0.5
Mean aortic valve gradient (mmHg)	44.3±11.8
Aortic valve area (cm^2)	0.91±0.22

CVA, denotes cerebrovascular accident; IHD, ischaemic heart disease; MI, myocardial infarction; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack.

FFR prevalence of 33%, 68 vessels would be required to provide an 80% power to demonstrate an AUC of 0.70, with a type I error rate of 5%. Assuming that most patients would have two evaluable vessels, we calculated that 34 patients would be required for study inclusion. A two-sided P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 35 patients were included in the study. Baseline characteristics demonstrated an elderly population with a high prevalence of traditional cardiovascular risk factors (*Table 1*). Echocardiographic parameters demonstrated a mean aortic valve gradient of 44.3±11.8 mmHg and a mean aortic valve area of 0.91±0.22 cm^2.

Table 2 Vessel distribution

Coronary artery	N (%) (N=57)
Left anterior descending artery	31 [54]
Diagonal artery	5 [9]
Ramus intermedius artery	1 [2]
Left circumflex artery	5 [9]
Obtuse marginal artery	9 [16]
Right coronary artery	3 [5]
Posterior descending artery	3 [5]

Pressure wire assessment

The mean FFR was 0.83±0.10 and 22 vessels (39%) had a functionally significant FFR ≤0.80. The mean iFR and dPR were 0.83±0.12 and 0.86±0.11, respectively and 51% and 49% had functionally significant values ≤0.89. The mean Pd/PA was 0.91±0.06 and 54% had significant lesions ≤0.92. No adverse events were recorded during pressure wire assessment.

Quantitate flow ratio analysis

A total of 68 vessels were considered for QFR analysis, but 11 vessels were excluded as there were inadequate orthogonal views, leaving a total of 57 vessels for inclusion. The most commonly assessed vessel was the left anterior descending artery (54%) (*Table 2*). The mean QFR was 0.83±0.12 and 33% of lesions had a functionally significant QFR ≤0.80. The mean QCA diameter stenosis was 33.6%±11.8% and QCA lesion length 9.5±6.6 mm.

Diagnostic performance of QFR

There was strong correlation between QFR and FFR [r=0.86; 95% confidence interval (CI): 0.78 to 0.92; P<0.001], iFR (r=0.80; 95% CI: 0.69 to 0.88; P<0.001), dPR (r=0.81; 95% CI: 0.69 to 0.88; P<0.001) and Pd/Pa (r=0.83; 95% CI: 0.72 to 0.89; P<0.001) (*Figure 1*). Bland-Altman analysis demonstrated agreement amongst QFR and FFR and non-hyperaemic indices (*Figure 2*).

QFR demonstrated an excellent discriminatory power to predict functionally significant FFR (AUC =0.92; 95% CI: 0.84 to 1.00; P<0.001) (*Figure 3A*) with good diagnostic

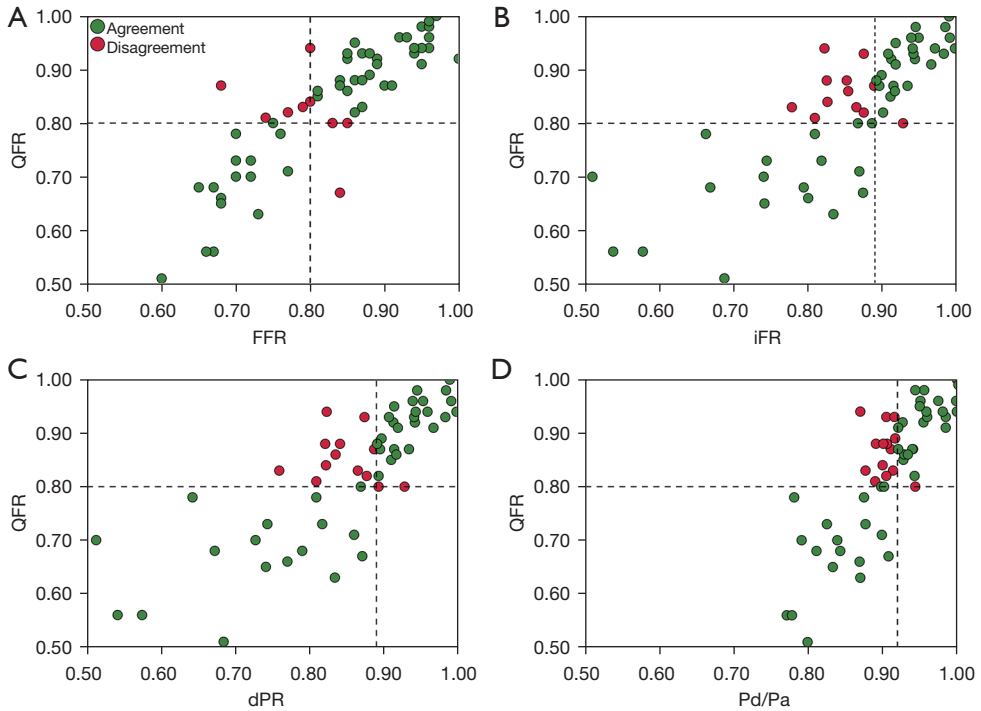

Figure 1 Correlation between QFR, FFR and non-hyperaemic indices. QFR demonstrated strong correlation with (A) FFR, (B) iFR, (C) dPR and (D) Pd/Pa. QFR, quantitative flow ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; dPR, diastolic pressure ratio during the wave-free period; Pd/Pa, distal arterial pressure/arterial pressure.

performance [sensitivity, 73%, specificity 91%, positive predictive value (PPV) 84%, negative predictive value (NPV) 84%, accuracy 84%] (*Tables 3,4*). QFR demonstrated similar diagnostic performance to iFR (difference in AUC =0.04; 95% CI: −0.04 to 0.12; P=0.31), dPR (difference in AUC =0.04; 95% CI: −0.04 to 0.12; P=0.35) and Pd/Pa (difference in AUC =0.06; 95% CI: −0.01 to 0.14; P=0.11). QFR demonstrated superior diagnostic performance to QCA diameter stenosis (difference in AUC =0.24; 95% CI: 0.08 to 0.39; P=0.003) and lesion length (difference in AUC =0.37; 95% CI: 0.20 to 0.54; P<0.001).

QFR demonstrated an excellent discriminatory power to predict functionally significant iFR (AUC =0.92; 95% CI: 0.85 to 0.99; P<0.001) (*Figure 3B*) with acceptable diagnostic performance (sensitivity 62%, specificity 96%, PPV 95%, NPV 71%, accuracy 79%). QFR demonstrated an excellent discriminatory power to predict functionally significant dPR (AUC =0.90; 95% CI: 0.83 to 0.98; P<0.001) (*Figure 3C*) with acceptable diagnostic performance (sensitivity 61%, specificity 93%, PPV 89%, NPV 71%, accuracy 77%). QFR demonstrated a good discriminatory power to predict functionally significant Pd/Pa (AUC =0.89; 95% CI: 0.80 to 0.97; P<0.001) (*Figure 3D*) with acceptable diagnostic performance (sensitivity 58%, specificity 96%, PPV 95%, NPV 66%, accuracy 75%).

A total of 45 lesions (79%) had a QFR outside the borderline zone of 0.75 to 0.85 and for these lesions, QFR demonstrated an excellent discriminatory power to predict functionally significant FFR (AUC =0.93, 97% CI, 0.94 to 1.00; P<0.001), with excellent diagnostic performance (sensitivity 87%, specificity 97%, PPV 93%, NPV 94%, accuracy 93%). For lesion within the borderline zone, QFR did not demonstrate discriminatory power to predict functionally significant FFR (AUC =0.77; 95% CI: 0.53 to 1.00; P=0.08) and there was poor diagnostic performance (sensitivity 43%, specificity 60%, PPV 60%, NPV 43%, accuracy 50%).

Discussion

The key findings of this study are (I) QFR demonstrates excellent discriminatory power and good diagnostic performance for predicting functionally significant FFR in the setting of severe aortic stenosis; (II) QFR demonstrates

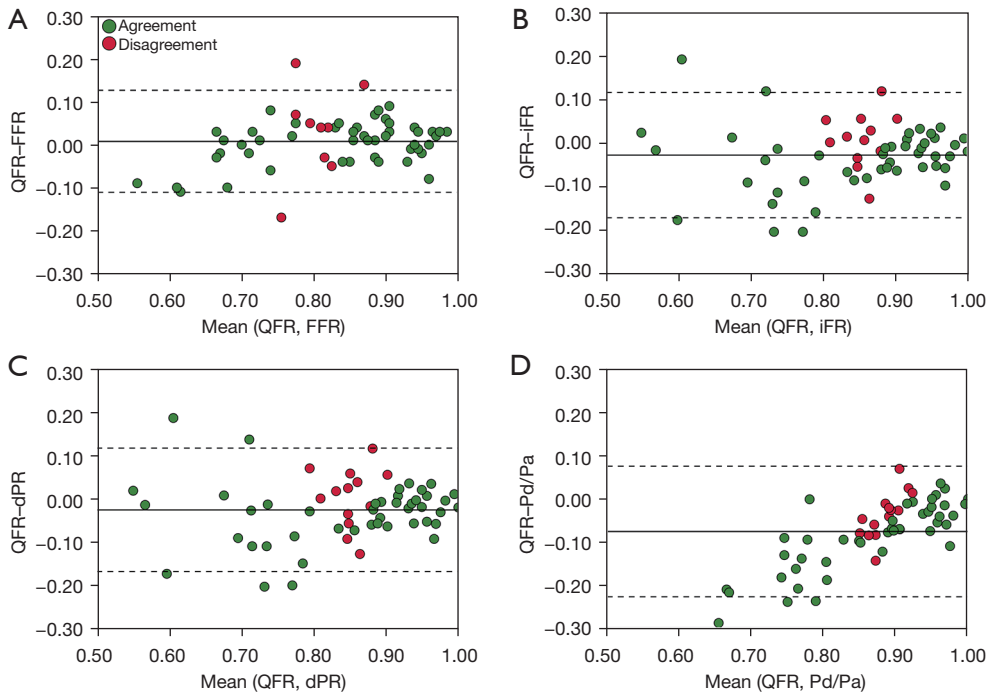

Figure 2 Bland-Altman plots of QFR, FFR and non-hyperaemic indices. QFR demonstrated agreement with (A) FFR, (B) iFR, (C) dPR and (D) Pd/Pa. QFR, quantitative flow ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; dPR, diastolic pressure ratio during the wave-free period; Pd/Pa, distal arterial pressure/arterial pressure.

an acceptable diagnostic performance for predicting functionally significant non-hyperaemic indices (iFR, dPR and Pd/PA); and (III) QFR demonstrates excellent diagnostic performance for predicting functionally significant FFR when QFR values are outside the borderline zone of 0.75 to 0.85.

Coronary artery disease is common in patients undergoing TAVR (9), but whether to revascularize these patients remains controversial and at present major society guidelines only recommend revascularisation for patients with significant (≥70%) proximal coronary artery disease or significant (≥50%) left main coronary artery disease (10).

Whilst there is a clear relationship between the severity of coronary artery disease and long-term clinical outcomes amongst TAVI patients (11), randomised trials have failed to demonstrate any improvement in clinical outcomes with angiographically-guided percutaneous coronary intervention (12). These findings are not surprising, however, as angiographically-guided PCI does not improve clinical outcomes for patients with stable coronary artery disease without aortic stenosis (13), and only FFR-guided PCI has been demonstrated to improve clinical outcomes (14,15).

FFR-guided PCI has been demonstrated in observational studies to be associated with improved clinical outcomes amongst TAVI patients (1) and a number of randomised clinical studies are currently evaluating the role of FFR-guided revascularisation, including the Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation (NOTION-3; NCT03058627) and Functional Assessment in TAVI (FAITAVI; NCT03360591) clinical studies.

Whilst FFR has for many years been considered the gold-standard for physiological assessment of coronary stenoses, equivalent clinical outcomes may also be achieved when PCI is guided by non-hyperaemic indices (16,17). This is a particularly attractive options for patients with severe aortic stenosis, in whom hyperaemia may be associated with significant hypotension. A number of studies have addressed the validity of non-hyperaemic indices in the setting of severe aortic stenosis (3,4,7,18), however their validity at long-term follow-up remains to be established (19).

Though non-hyperaemic indices are an attractive solution for assessing physiological significance, a less

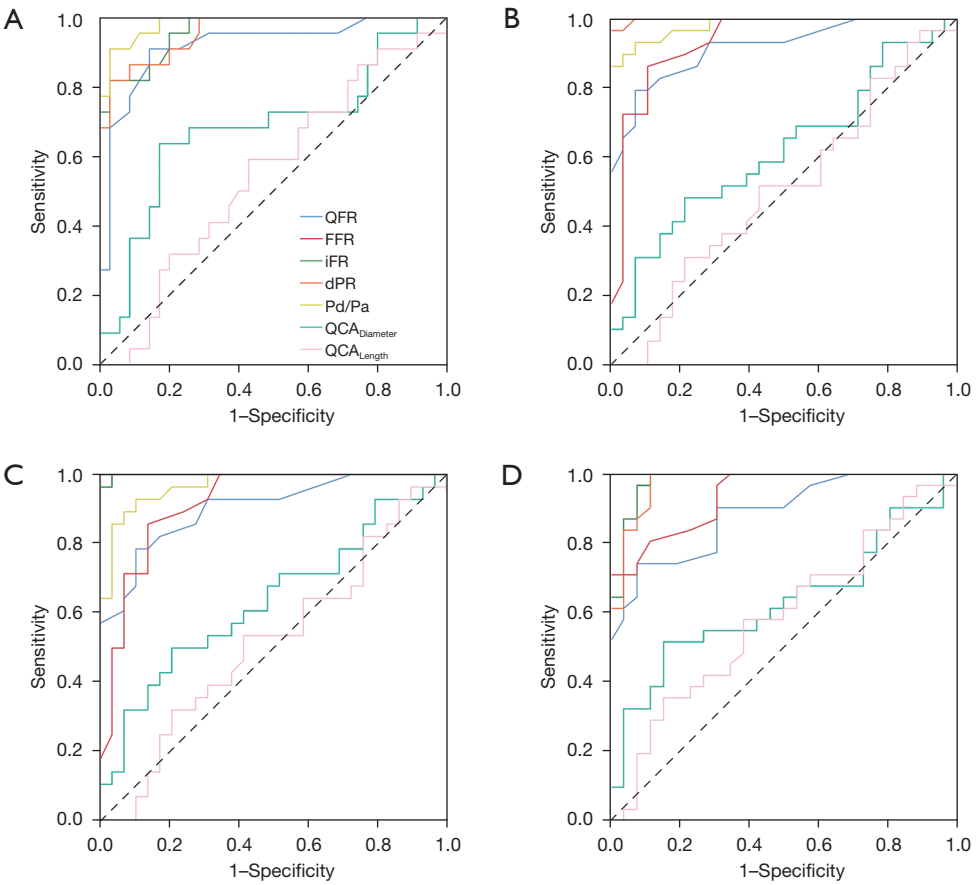

Figure 3 Discriminatory power of QFR, FFR, non-hyperaemic indices and QCA parameters. Reference standards are (A) FFR, (B) iFR, (C) dPR and (D) Pd/Pa. Diagonal segments are produced by ties. dPR, denotes diastolic pressure ratio during the wave-free period; iFR, instantaneous wave-free ratio; FFR, fractional flow reserve; Pd/Pa, distal arterial pressure/arterial pressure; QCA, quantitative coronary angiography; QFR, quantitative flow ratio.

invasive option would be the avoidance of wire-based techniques and QFR has emerged as one potential technology to address this problem. The technology is well-validated in patients without aortic stenosis (20-24), including in patients with myocardial infarction (24-26), and growing evidence is building for its validation in aortic stenosis (27,28).

With this as a background, the present compared the diagnostic performance of QFR against not only FFR, but also multiple non-hyperaemic indices (iFR, dPR and Pd/Pa) in the setting of severe aortic stenosis. We confirmed that QFR demonstrated an excellent diagnostic performance against an FFR reference standard, with a diagnostic accuracy of 84%. Furthermore, QFR demonstrated an acceptable diagnostic performance against iFR, dPR and Pd/Pa reference standards, with a diagnostic accuracy of 79%, 77% and 75%, respectively.

Physiological assessment of coronary stenoses in the setting of severe aortic stenosis is challenging (29). Aortic stenosis is associated with blunting of systolic flow because of obstruction of ventricular emptying by the stenosed aortic valve and compression of the microcirculation by the contracting myocardium, elevating intraventricular pressure (3). Furthermore, the presence of left ventricular hypertrophy, elevated intraventricular pressure and microvascular dysfunction may attenuate the response of the microcirculation to hyperaemic agents. For these reasons, non-hyperaemic indices, in particular those that do not include the systolic phase of the cardiac cycle, may be more reliable in the setting of severe aortic stenosis. Adding to this complexity, FFR was originally validated against positron emission tomography in patients without severe

Table 3 Diagnostic performance of FFR, non-hyperaemic indices and QCA parameters

References	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
FFR						
QFR	0.92 (0.84 to 1.00)	73	91	84	84	84
iFR	0.96 (0.92 to 1.00)	95	77	72	96	84
dPR	0.96 (0.91 to 1.00)	91	77	71	93	82
Pd/Pa	0.98 (0.96 to 1.00)	100	74	71	100	84
$QCA_{diameter}$	0.68 (0.53 to 0.83)	14	94	60	63	63
QCA_{length}	0.55 (0.40 to 0.70)	36	69	42	63	56
iFR						
QFR	0.92 (0.85 to 0.99)	62	96	95	71	79
FFR	0.93 (0.86 to 1.00)	72	96	95	77	84
dPR	1.00 (0.99 to 1.00)	97	100	100	97	98
Pd/Pa	0.98 (0.96 to 1.00)	93	86	87	92	89
$QCA_{diameter}$	0.62 (0.47 to 0.77)	86	4	48	20	46
QCA_{length}	0.51 (o.35 to 0.66)	66	32	50	47	49
dPR						
QFR	0.90 (0.83 to 0.98)	61	93	89	71	77
FFR	0.92 (0.84 to 0.99)	71	93	91	77	82
iFR	1.00 (0.99 to 1.00)	100	97	97	100	98
Pd/Pa	0.97 (0.93 to 1.00)	93	83	84	92	88
$QCA_{diameter}$	0.64 (0.49 to 0.78)	14	97	80	54	56
QCA_{length}	0.52 (0.36 to 0.67)	36	69	53	53	53
Pd/Pa						
QFR	0.89 (0.80 to 0.97)	58	96	95	66	75
FFR	0.94 (0.88 to 0.99)	71	100	100	74	84
iFR	0.98 (0.95 to 1.00)	87	92	93	86	89
dPR	0.98 (0.94 to 1.00)	84	92	93	83	88
$QCA_{diameter}$	0.63 (0.48 to 0.77)	13	96	80	48	51
QCA_{length}	0.58 (0.43 to 0.73)	39	73	63	50	54

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; FFR, fractional flow reserve; QCA, quantitative coronary angiography; QFR, quantitative flow ratio; iFR, instantaneous wave-free ratio; dPR, diastolic pressure ratio during the wave-free period; Pd/Pa, distal arterial pressure/arterial pressure.

aortic stenosis (30), and this work has not been replicated in patients with severe aortic stenosis, although validation of FFR and non-hyperaemic indices has been undertaken against single positron emission computed tomography (31).

In this study, we demonstrated that whilst QFR technology has been developed to predict FFR, QFR nonetheless demonstrated a discriminatory power to predict functionally significant lesions and an acceptable diagnostic accuracy when using a variety of non-hyperaemic indices (iFR, dPR and Pd/Pa) as reference standards.

Table 4 Cross tabulation of index test results by reference standards

Reference standard	QFR		Total
	≤0.80	>0.80	
FFR			
≤0.80	16	6	22
>0.80	3	32	35
Total	19	38	57
iFR			
≤0.89	18	11	29
>0.89	1	27	28
Total	19	38	57
dPR			
≤0.89	17	11	28
>0.89	2	27	29
Total	19	38	57
Pd/Pa			
≤0.92	18	13	31
>0.92	1	25	26
Total	19	38	57

QFR, quantitative flow ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; dPR, diastolic pressure ratio during the wave-free period; Pd/Pa, distal arterial pressure/arterial pressure.

These results differ from a previous study which had demonstrated poor diagnostic accuracy (61%) when using pre-TAVI iFR as a reference standard (28). Lesion severity in our study (34%±12%) was less than what was reported in the prior work (52%±12%) and aortic valve area was greater (0.91±0.22 cm^2) than what was previously reported (0.54±0.20 cm^2) and this could potentially explain the discrepancy in diagnostic accuracy between these two studies. However, other groups have demonstrated that QFR has good agreement with iFR (32), consistent with our study findings.

In this study we demonstrated that QFR had excellent diagnostic performance (accuracy 93%) when QFR values were outside the borderline zone (0.75 to 0.85) but poor diagnostic performance (accuracy 50%) when QFR values were within the borderline zone. These results are consistent with recently published findings in patients without aortic stenosis (24) and highlight how a tool such as QFR could be incorporated into routine TAVI assessment. We would suggest that for patients with coronary stenoses of 30 90% that real-time QFR could be calculated at the time of diagnostic angiography. For patients whose QFR values lie within the borderline zone of 0.75 to 0.85, further invasive assessment of coronary stenoses could be undertaken, potentially using a hybrid iFR/FFR strategy as has previously been proposed (33), noting that optimal iFR/FFR thresholds for identifying functional significance may be different in the setting of severe aortic stenosis (18). This information could then be used by the Heart Team to help guide patient treatment decisions.

In this study, QCA diameter stenosis demonstrated poor discriminatory power to predict functionally significant FFR and furthermore, QCA lesion length demonstrated no discriminatory power to predict functionally significant FFR. These findings are consistent with studies performed in patients without severe aortic stenosis and stresses the importance of physiological assessment of coronary artery disease (34).

Moving forward, the role of QFR-guided revascularisation of patients will need to be assessed prospectively and the FAVOR4-QVAS (NCT03977129) randomised study will be addressing the role of QFR-guided revascularisation in patients undergoing primary valve surgery.

Limitations

It is important to acknowledge the significant limitations of this study. Our sample size is small and further validation is required across larger patient cohorts. In this study, the QFR calculations were performed offline by a core laboratory and our work would be strengthened through online analysis, which has previously been demonstrated to be feasible with QFR technology (21,23). A significant proportion of vessels (16%) were not suitable for QFR analysis, which may limit the clinical applicability of this technology, although this limitation could potentially be overcome through online analysis. While core laboratory measurements of QFR generally demonstrate good reproducibility (35), the inter- and intra-observer reproducibility of QFR is dependent on observer experience, angiographic quality and coronary artery stenosis severity, and our study would have been strengthened through formal assessment of inter- and intra-observer variability (36). Our study only analysed pre-TAVI indices and would be strengthened through the measurement of post-TAVI values, as QFR has superior diagnostic performance to predict post-TAVI FFR

values (28). Our study did not report clinical outcomes and would be strengthened with this information, as low QFR values have been associated with worse clinical outcomes, (25,37-39). Resting full cycle ratio was not assessed in this study, and our study would have been strengthened through addition of this non-hyperaemic index. Computed tomography-derived FFR (CT_{FFR}) has recently been demonstrated to yield reasonable diagnostic accuracy to an FFR reference standard (6) and this study would be strengthened through a comparison of the diagnostic performance of QFR and CT_{FFR}. Our study excluded patients with significant left main coronary artery disease, and further validation is required within this patient cohort.

Conclusions

QFR demonstrates acceptable diagnostic performance when both FFR and non-hyperaemic pressure indices are used as reference standards in patients with severe aortic stenosis. If validated in future larger studies, QFR may be considered as an alternative to both FFR and non-hyperaemic indices for the physiological assessment of coronary lesions in patients with severe aortic stenosis.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-574/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-574/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-574/coif). RG reports personal fees from Boston Scientific, outside the submitted work. LM reports personal fees from Boston Scientific, outside the submitted work. AJB reports personal fees from Abbott Laboratories and Boston Scientific, outside the submitted work. DTLW currently serves as an unpaid editorial board member of *Cardiovascular Diagnosis and Therapy* from February 2021 to January 2023. The other authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed by a Monash Health Human Research Ethics Committee (HREC/43524/MonH-2018-67705v1) and all participants provided informed consent for inclusion in the study.

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