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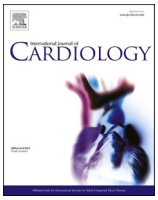

Head-to-head comparison of two angiography-derived fractional flow reserve techniques in patients with high-risk acute coronary syndrome: A multicenter prospective study

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ABSTRACT

Background: FFRangio and QFR are angiography-based technologies that have been validated in patients with stable coronary artery disease. No head-to-head comparison to invasive fractional flow reserve (FFR) has been reported to date in patients with acute coronary syndromes (ACS).

Methods: This study is a subset of a larger prospective multicenter, single-arm study that involved patients diagnosed with high-risk ACS in whom 30–70% stenosis was evaluated by FFR. FFRangio and QFR – both calculated offline by 2 different and blinded operators – were calculated and compared to FFR. The two co-primary endpoints were the comparison of the Pearson correlation coefficient between FFRangio and QFR with FFR and the comparison of their inter-observer variability.

Results: Among 134 high-risk ACS screened patients, 59 patients with 84 vessels underwent FFR measurements and were included in this study. The mean FFR value was 0.82 ± 0.40 with 32 (38%) being ≤0.80. The mean FFRangio was 0.82 ± 0.20 and the mean QFR was 0.82 ± 0.30, with 27 (32%) and 25 (29%) being ≤0.80, respectively. The Pearson correlation coefficient was significantly better for FFRangio compared to QFR, with R values of 0.76 and 0.61, respectively ($p = 0.01$). The inter-observer agreement was also significantly better for FFRangio compared to QFR (0.86 vs 0.79, $p < 0.05$). FFRangio had 91% sensitivity, 100% specificity, and 96.8% accuracy, while QFR exhibited 86.4% sensitivity, 98.4% specificity, and 93.7% accuracy.

Conclusion: In patients with high-risk ACS, FFRangio and QFR demonstrated excellent diagnostic performance. FFRangio seems to have better correlation to invasive FFR compared to QFR but further larger validation studies are required.

1. Introduction

Invasive physiological assessment has become a fundamental aspect of clinical decision-making in the management of coronary artery disease (CAD). It is indeed well-established that angiographic evaluation of lesion severity does not correlate well with functional significance [1,2] and that even mild angiographic stenoses, in vessels supplying a large myocardial territory can be associated with ischemia and future adverse vascular events [3]. Fractional Flow Reserve (FFR) has been validated to assess the functional significance of coronary stenosis and select the most adequate revascularization strategy, thus improving patient outcomes [1,2]. Despite the clinical evidence, FFR remains however underutilized [4]. This may be related to several factors, such as the additional time needed to perform the measurements, technical issues and risks associated with wiring of the coronary artery, or the potential side effects related to the use of some hyperemic agents.

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Recently, novel angiographic methods have emerged to estimate the invasive FFR ($FFR_{invasive}$) without the use of a pressure wire. The development of those angiography-derived FFR methods has garnered attention, as those tools could overcome the aforementioned limitations. Among the commercially available software, QFR (Medis Medical Imaging System, Leiden, the Netherlands) has been the most studied, followed by FFRangio (Cathworks Ltd., Kfar Saba, Israel) [5,6,7,8,9,10]. Both methods generate a 3D reconstruction of the coronary artery tree, but with a different mechanistic approach of the vessel properties. QFR calculates the pressure drop using the stenosis geometry via a 3D QCA model and models the hyperemic flow velocity based on the TIMI frame count analysis [11]. FFRangio uses a 3D reconstruction of the coronary artery tree, models it as an electric circuit with each segment acting as a resistor and estimates the resistance and the flow across the stenosis [8].

A meta-analysis found a sensitivity of 84% and a specificity of 88% for QFR as compared to $FFR_{invasive}$ [6] which appears to be potentially inferior to the performance of FFRangio observed in the FAST-FFR trial where the per-vessel sensitivity and specificity were 94% and 91%. However, a systematic review and meta-analysis, which included approximately 1800 vessels, observed similar diagnostic performances, without pronounced differences, between various computational approaches or software packages. It's important to note that the studies included in the analysis enrolled different populations and patients, and there was no direct comparison in the same vessels [12].

Non-ST-Elevation Myocardial Infarction (HIGH-RISK ACS) is of particular interest for angiography-derived FFR methods. Indeed, patients often present with a clear culprit lesion that requires intervention but also with additional lesions of uncertain hemodynamic significance and in which many physicians might be reluctant to perform $FFR_{invasive}$ in an acute setting, even if it has been proven to be reliable in this context [13]. In these patients, angiography-derived FFR has demonstrated excellent correlations with $FFR_{invasive}$, both for QFR or FFRangio [14]. Recently, a study evaluated the diagnostic accuracy of 5 different software/methods in a prospective cohort of 390 vessels [15]. However, it is important to highlight that FFRangio was not included in this analysis. Consequently, a direct comparison between FFRangio and the most extensively studied method in the literature (QFR) has not been reported to date.

We thus sought to perform a comparative assessment of the performance of QFR and FFRangio in this population where the ability to perform offline estimations of FFR could provide benefit for both patients and healthcare providers in terms of clinical decision-making and resource optimization.

2. Methods

2.1. Study design and study population

We performed a prospective, multicenter (Lausanne University Hospital, Switzerland and OLV Aalst, Belgium), single-arm, double-blinded study. The present work is a post-hoc analysis of a study whose design has been previously published [16], aiming to evaluate the diagnostic performance of computed tomography-derived FFR (FFR-CT) in high-risk ACS patients. In brief, the main study enrolled adult patients admitted with a suspicion of high-risk ACS with positive cardiac biomarkers and symptoms of ischemia. Main exclusion criteria were STEMI, severe renal failure, pregnant and breast-feeding women, patients with prior coronary artery bypass grafting (CABG) or previous stenting, or known severely reduced left ventricular ejection fraction. Importantly, patients with one or more very high-risk criteria as defined by current European and American high-risk ACS guidelines were excluded [17,18]. The present sub-study included only patients with at least one stenosis 30%–70% by visual estimation. All patients provided written informed consent prior to enrollment. Detailed inclusion/exclusion criteria of the study are reported in the **Supplemental Material.**

2.2. Study procedure

The standard procedure for diagnostic coronary angiography was carried out in accordance with local guidelines. The cine frame rate was set at a minimum of 10 frames per second. To ensure accuracy, operators were advised to capture three different projections with a minimum 30-degree separation for a stenosis ranging between 30 and 70% before proceeding with $FFR_{invasive}$. The C-arm's exact angle was left to the operator's discretion. $FFR_{invasive}$ was measured in the respective lesions by an interventional cardiologist according to standard practice. The PressureWire™ X Guidewire (Abbott, Chicago, Illinois, USA) was used to measure $FFR_{invasive}$ in each lesion with a visual diameter stenosis between 30%–70%. Prior to all measurements, the pressure wire and aortic pressure were equalized at the guide catheter's tip. Afterward, the pressure wire was advanced distal to the stenosis, and hyperemia was induced using intracoronary adenosine (150 μg for the right coronary artery and 200 μg for the left descending or the circumflex coronary arteries).

2.3. FFRangio measurement

The DICOM (Digital Imaging and Communications in Medicine) files were transferred directly via internal PACs system to the FFRangio console. The FFRangio was measured offline for all patients twice (by two physician operators who were blinded to the $FFR_{invasive}$ results and blinded to the results of each other). More specifically, the operators entered the mean aortic pressure of the patient, which was specifically the one recorded immediately prior to the administration of intracoronary adenosine for the invasive FFR measurement, selected the artery of interest by designating the responsible lesion and identified the three most optimal frames of each DICOM according to cardiac phase synchronization and visibility of the lesion. The FFRangio system then automatically created a 3D reconstruction of the coronary arteries designated by the operator based on the previous parameters.

2.4. QFR measurement

The DICOM angiograms were transferred directly via internal PACs system to the software package QAngio XA 3D. The QFR was measured offline for all patients twice (by the same two physician operators who were blinded to the $FFR_{invasive}$ results and to the results each other). Two angiographic projections at least 25 degrees apart were selected according to each target vessel. The investigators identified 1 or 2 anatomic landmarks (e.g., bifurcations) as reference points for matching location information in the 2 frames and subsequently indicated the most proximal site and the most distal site of the vessel. Vessel contours were automatically detected and manually corrected if needed. The software reconstructed a 3D anatomic vessel model without its side branches for the 3D quantitative coronary angiographic analysis and for the QFR computation. Final QFR values were obtained computing 3D-QCA and TIMI frame counting.

2.5. Definitions

FFRangio and QFR were measured in the same position as $FFR_{invasive}$ using the recorded position of the pressure wire. FFRangio and QFR values were defined as the average value measured offline by the two blinded operators (that had equal experience in using both software) and were then compared to the $FFR_{invasive}$ result for each lesion. A hemodynamically significant lesion was defined as a lesion with an FFR value of $\leq$0.80.

2.6. Endpoints

The two co-primary endpoints were the comparison of the Pearson correlation coefficient between FFRangio and QFR with FFRinvasive

and well as the comparison of their inter-observer variability.

The usual key performance indicators (accuracy, sensitivity, specificity, positive and negative predictive value) of FFRangio and QFR compared to $FFR_{invasive}$ were also reported and the diagnostic performance of FFRangio and QFR in the "grey zone" of $FFR_{invasive}$ values [0.75–0.85] was also investigated.

2.7. Statistical methods

Continuous variables were expressed as mean ± SD, and continuous variables were expressed as absolute numbers and percentages. Categorical patient characteristics were presented as percent frequency, and continuous characteristics were presented as mean mean ± SD or median with interquartile range. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of FFRangio and QFR were calculated, using $FFR_{invasive}$ as the gold standard. The FFRangio and QFR results for each lesion were classified as true/false positive or true/false negative (using $FFR_{invasive}$ as the reference standard and a value of ≤0.80 as the threshold for functionally significant lesions for both modalities). To explore the agreement between FFRangio QFR and $FFR_{invasive}$, Bland–Altman analyses were plotted, and the 95% limits (1.96 * SD) of agreements were calculated. A Pearson correlation coefficient between $FFR_{invasive}$, FFRangio and QFR was reported and values were compared using the Fisher's r to z transformation, a statistical method widely used for the purpose of comparing correlation coefficients.

A p value <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS Statistics (version 28.0.1, SPSS Inc., Chicago, Illinois, United States).

3. Results

Between August 2019 and March 2022, a total of 134 HIGH-RISK ACS patients were included in the main study and were screened for inclusion in the current study. Of the 134 patients screened, 59 patients had one or more intermediate coronary lesion (diameter stenosis of 30–70%) evaluated using $FFR_{invasive}$. The baseline clinical characteristics of these patients are displayed in Table 1. The mean age was 64 ± 9.3, 68% were male, and the mean body mass index was 28 ± 4.3 kg/m^2.

Among the 59 patients included in the study, a total of 84 lesions underwent physiological assessment ($FFR_{invasive}$). The same 84 lesions were also functionally evaluated with FFRangio and QFR. $FFR_{invasive}$ was measured in 1.4 vessels per patient and 23 patients had $FFR_{invasive}$ measured in more than one vessel. The artery most frequently evaluated was the left anterior descending (41%), followed by the right coronary artery (33%) and the left circumflex artery (26%). The procedural characteristics of the vessels are reported in Table 2.

3.1. $FFR_{invasive}$ values

The physiological assessment summary of the vessels is displayed in Table 3. Of the 84 lesions included, the mean value of $FFR_{invasive}$ was 0.82 ± 0.40. Out of the total of 32 lesions (38%) with pathological $FFR_{invasive}$ values (FFR ≤ 0.80), 17 (53%) were found in the LAD, 7 (22%) in the LCX and 8 (25%) in the RCA. In addition, 20 $FFR_{invasive}$ values were inside the grey zone of 0.75–0.85.

Table 1
Baseline characteristics. Data are presented as n (%) where appropriate.

Characteristic	n (%)
Age, y	64 ± 9.3
Male gender, n (%)	40 (67.7)
Body mass index, kg/m2	28 ± 4.3
Hypertension, n (%)	33 (55.9)
Hypercholesterolemia, n (%)	39 (66.1)
Smoking (current or former), n (%)	43 (72.8)
Diabetes mellitus (Type I or Type II), n (%)	14 (23.7)
Dyslipidemia, n (%)	40 (67.7)

Table 2
Angiographic characteristics. Data are presented as n (%) where appropriate. FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Angiographic findings	n (%)
Lesions per patient	1.4 ± 0.16
Target vessel	
LAD	34 (41)
RCA	28 (33)
LCX	22 (26)
% Diameter stenosis range	30–70

Table 3
Physiological assessment. Data are presented as n (%) where appropriate. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRangio device; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; QFR, fractional flow reserve measured by quantitative flow ratio.

Method used	n (%)
Invasive FFR	
Mean invasive FFR	0.82 ± 0.4
FFR ≤0.80	32 (38)
LAD	17 (53)
LCX	7 (22)
RCA	8 (25)
InvasiveFFR = [0.75–0.85]	20 (24)
FFRangio	
Mean FFRangio	0.82 ± 0.2
FFRangio ≤0.80	27 (32)
LAD	15 (56)
LCX	6 (22)
RCA	6 (22)
FFRangio = [0.75–0.85]	19 (22)
QFR	
Mean QFR	0.82 ± 0.3
QFR ≤0.80	25 (36)
LAD	13 (52)
LCX	6 (24)
RCA	6 (24)
QFR = [0.75–0.85]	16 (19)

3.2. FFRangio values

The mean FFRangio value was 0.82 ± 0.2 and 27 vessels (32%) had pathological FFRangio values (≤ 0.80). Pathological FFRangio values were found most frequently in the LAD (56%), followed by the RCA and the LCX (22% each). In addition, 19 FFRangio values were inside the grey zone of 0.75–0.85.

3.3. FFRangio diagnostic performances

The performance of FFRangio per vessel was the following: sensitivity of 84.4% (95% confidence interval [CI]: 67.2% to 94.7%), specificity of 100% (95% CI: 93.2% to 100%) and diagnostic accuracy of 94.1% (95% CI: 86.7% to 98.1%) (Table 4). The positive predictive value was 100% (95% CI: 87.2% to 100%) and the negative predictive value was 91.2% (95% CI: 80.7% to 97.1%). The Pearson correlation coefficient between $FFR_{invasive}$ and FFRangio was 0.76 (Fig. 1A). Additionally, the Bland–Altman plot demonstrated 95% confidence limits between −0.13 and 0.11 for the absolute differences (Fig. 2A). In total, 5 (5.9%) lesions were misclassified and all of them were false negative (positive $FFR_{invasive}$ but negative FFRangio), 3 of them belonging to the grey zone of FFRinvasive.

Table 4
Diagnostic performance. Per lesion and per coronary artery analysis for the total of sample size as well as analysis of the grey zone of FFRangio = [0.75–0.85] Results are % and 95% CI. FFR, fractional flow reserve measured by pressure guidewire; FFRangio, fractional flow reserve measured by FFRangio device; QFR, fractional flow reserve measured by quantitative flow ratio, LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery, QFR, fractional flow reserve measured by quantitative flow ratio.

Performance parameter	FFRangio	QFR
Per lesion analysis % (95% CI)		
Sensitivity	84.4 (67.2 to 94.7)	75 (56.6 to 88.5)
Specificity	100 (93.2 to 100)	98.1 (89.7 to 99.9)
Diagnostic Accuracy	94.1 (86.7 to 98.1)	82.3 (80.6 to 94.9)
Positive Predictive Value	100 (87.2 to 100)	96 (79.7 to 99.9)
Negative Predictive Value	91.2 (80.7 to 97.1)	86.4 (75.1 to 93.9)
Grey zone of FFR = [0.75–0.85]		
Sensitivity	72.7 (39.1 to 93.9)	63.64 (30.8 to 89.1)
Specificity	100 (66.4 to 100)	100 (63.1 to 100)
Diagnostic Accuracy	85 (62.1 to 96.8)	78.9 (54.4 to 93.9)

3.4. FFRangio diagnostic performances in grey zone of FFR values [0.75–0.85]

Within the grey zone, FFRangio had a sensitivity of 72.7% (95% [CI]: 39.1% to 93.9%), a specificity of 100% (95% [CI]: 66.4% to 100%) and a diagnostic accuracy of 85% (95% [CI]: 62.1% to 96.8%) **(**Table 4**)**.

3.5. QFR values

The mean QFR value was 0.82 ± 0.2 and 27 vessels (32%) had pathological QFR values (≤ 0.80). Positive QFR values were found most frequently in the LAD (52%), followed by the RCA and the LCX (24% each). Moreover, 16 QFR values were inside the grey zone of 0.75–0.85.

3.6. QFR diagnostic performances

The performance of QFR per vessel was the following: sensitivity of 75% (95% confidence interval [CI]: 56.6% to 88.5%), specificity of 98.1% (95% CI: 89.7% to 99.9%) and diagnostic accuracy of 94.1% (95% CI: 86.7% to 98.1%) **(**Table 4**)**. The positive predictive value was 96% (95% CI: 79.7% to 99.9%) and the negative predictive value was 89.4% (95% CI: 75.1% to 93.9%). The Pearson correlation coefficient between invasive FFR and QFR was 0.61 ($p < 0.001$). (Fig. 1B). Additionally, the Bland–Altman plot demonstrated 95% confidence limits between −0.14 and 0.12 for the absolute differences **(**Fig. 2**B)**. In total, 9 lesions (10.7%) were misclassified. Out of them, 8 were false negative (positive $FFR_{invasive}$) with 7 of them belonging to the grey zone of $FFR_{invasive}$.

3.7. QFR diagnostic performances in grey zone of FFR values [0.75–0.85]

Within the grey zone, QFR had a sensitivity of 63.6% (95% [CI]: 30.8% to 89.1%), a specificity of 100% (95% [CI]: 66.4% to 100%) and a diagnostic accuracy of 78.9% (95% [CI]: 54.4% to 93.9%) **(**Table 4**)**.

3.8. Comparison between FFRangio and QFR correlation

The Pearson correlation coefficient demonstrated a significantly higher value for FFRangio compared to QFR (0.76 vs 0.61, $p < 0.001$). The inter-observer agreement was also significantly better for FFRangio compared to QFR (0.86 vs 0.79, $p < 0.05$).

4. Discussion

This is the first study comparing these 2 different angiography-derived FFR modalities. FFRangio and QFR have been evaluated in a growing number of studies assessing their performance in various context including high-risk ACS. In this context, prior studies demonstrated good diagnostic performance for both modalities, but no head-to-head comparison has been reported to date. In this prospective, multi center, double blinded validation study, the 2 most studied angiography-derived FFR techniques, showcased high diagnostic performance and even demonstrated higher specificity compared to previous studies in the literature. Here, interestingly, FFRangio showed a

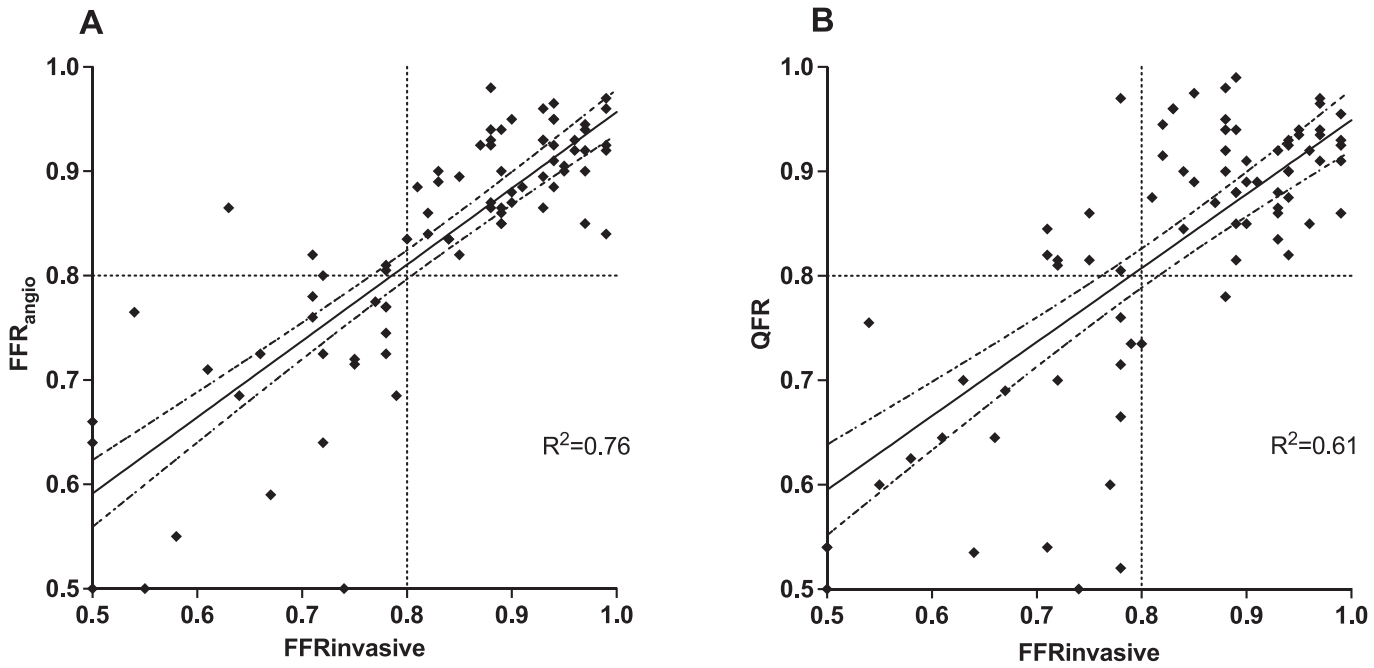

Fig. 1. Correlation between $FFR_{invasive}$ and FFRangio (A) and correlation between $FFR_{invasive}$ and QFR (B). Fig. 1A and B display the correlation scatter plot with a linear regression and 95% CI, the Pearson coefficient is reported. FFRangio; fractional flow reserve measured by FFRangio device; QFR, fractional flow reserve measured by quantitative flow ratio.

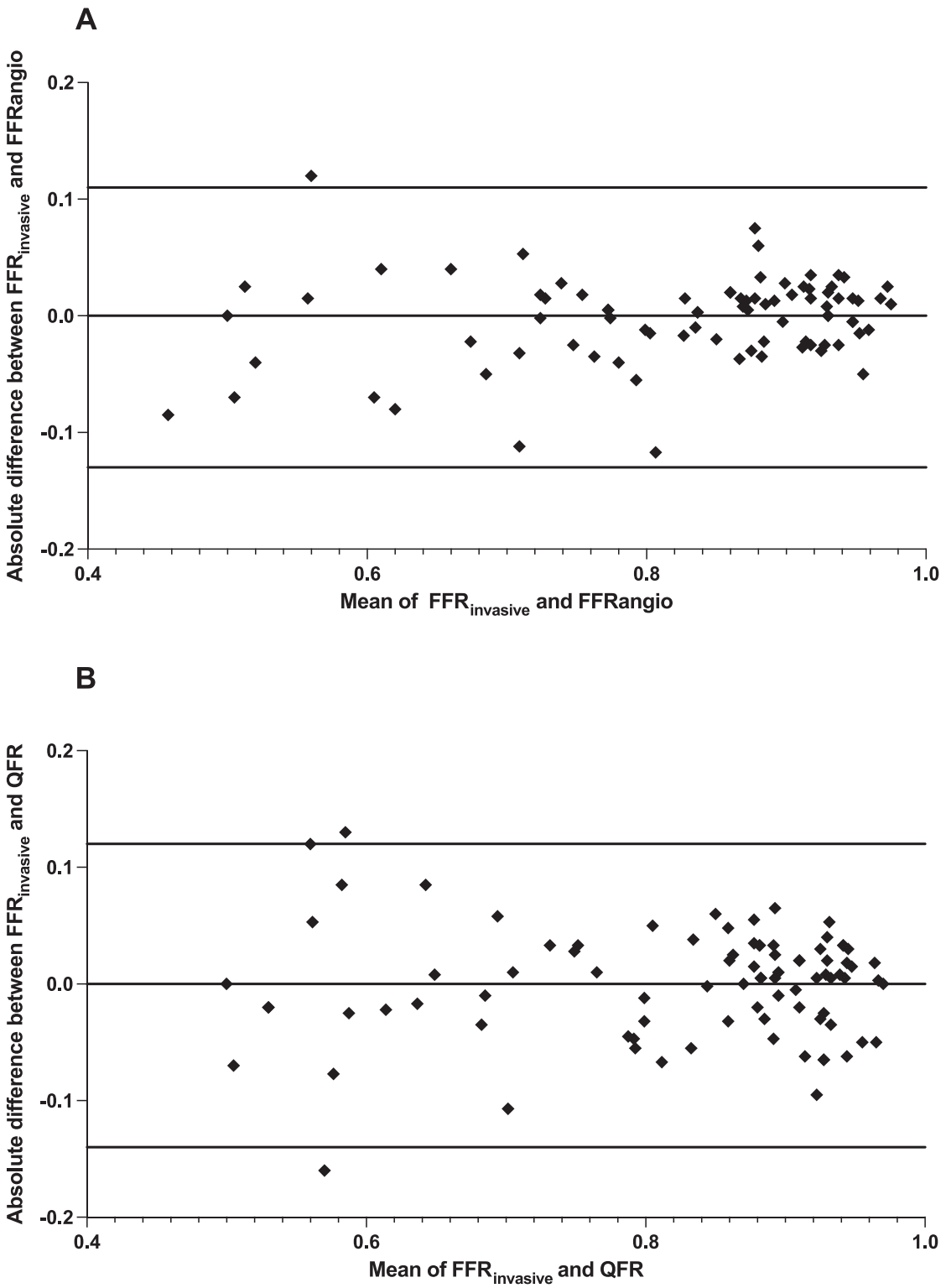

Fig. 2. Bland–Altman plot for FFR$_{invasive}$ and FFRangio (A) and for FFR$_{invasive}$ and QFR (B). Bland–Altman plot with 95% confidence limits between for the absolute differences. FFRangio; fractional flow reserve measured by FFRangio device; QFR, fractional flow reserve measured by quantitative flow ratio.

significantly better correlation to invasive FFR in comparison to the one of QFR with a better inter-observer agreement, even if the number of misclassified stenoses appears to be comparable.

The high specificity observed in this study has implications for clinical practice. By reducing the likelihood of unnecessary invasive procedures in patients without hemodynamically significant lesions, these angiography-derived FFR tools can contribute to improved patient safety and resource allocation. Unnecessary invasive procedures not only pose potential risks and complications to patients but also increase healthcare costs.

Regarding the misclassification of lesions, it is noteworthy that almost all the misclassified lesions were false negatives, indicating a failure to identify hemodynamically significant lesions. However, it is important to consider that most of these misclassified lesions were

within the grey zone of FFR values (0.75–0.85), where the decision to proceed with revascularization or adopt a conservative treatment approach is less clear-cut. In these cases, a conservative treatment strategy could still be considered. Finally, while our study design does not allow us to definitively determine why one technique outperforms the other, we can offer plausible explanations based on the technical aspects of each method. It is important to note that FFRangio and QFR employ fundamentally different approaches to calculate non-invasive FFR, which might contribute to the observed performance differences.

A key technical distinction is that FFRangio requires three diagnostic coronary angiography projections for its calculation, whereas QFR typically uses only two. This additional projection in FFRangio allows for a more comprehensive vessel analysis, including detailed assessment of de novo lesions, ostium localization, and thorough contouring of the lesion as well as the proximal and distal segments of the analyzed vessel. This approach, by incorporating more measurements, potentially offers a more robust analysis, minimizing the margin of error and enhancing the accuracy of the FFR estimation.

4.1. Limitations

The current study has a certain number of limitations. Importantly, the sample size was limited since these patients represent a subset of a larger study. The main reasons for exclusion from the study were previous stents, CABG, renal insufficiency, and elevated heart rate (>60 beats per second), which affected the feasibility and quality of the CT scan (main study). This rigorous patient selection however strengthens the findings these patients come from a homogenous population systematically selected according to a previously published research protocol. Further studies including a larger number of ACS patients will be reassuring and would more confidently support a potential superiority of FFRangio vs QFR in this setting. As this study was designed with the specific intent of conducting FFRangio and QFR measurements, coronary angiography was performed accordingly. It's important to acknowledge that our results may not readily apply to measurements conducted offline or retrospectively, especially when coronary angiography was not initially planned for non-invasive FFR assessment. This potential limitation stems from variations in measurement conditions and procedural objectives, impacting the generalizability of our results. It must also be noted that the time required to complete the QFR and FFRangio measurement, from the start of the image transfer to the final result was not recorded. Moreover, unlike QFR, FFRangio requires a mean arterial pressure value, which can fluctuate during the procedure, especially with nitroglycerine administration. The optimal pressure for routine FFRangio measurements remains undefined and could potentially affect the result. Furthermore, possible limitation stems from the microvascular involvement in ACS, which is not accounted for by FFrangio. It would be expected to result in positive invasive FFR but negative FFRangio. While theoretical expectations align with our study's 100% PPV and 91% NPV, this specific scenario occurred only five times (resulting in five false negatives), making it challenging to extrapolate general conclusions from this limited dataset. Finally, it would be of interest to compare the potentially different learning curves between the two modalities among different operators in order to evaluate the level of user-dependency and familiarity.

5. Conclusions

In this head-to-head comparison of the diagnostic performance of QFR and FFRangio, both demonstrated excellent diagnostic performance among patients presenting with high-risk ACS compared to invasive FFR. There was a significant difference in the correlation coefficient in favor of FFRangio. The current study reinforces the existing evidence regarding the diagnostic performance of angiography-derived FFR. This might foster the application of physiological evaluation in angiographically intermediate coronary artery lesions among high-risk ACS patients.

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Ethical approval regarding research involving human participants

All procedures performed during the study are in accordance with the ethical standards of the CHUV (Lausanne University Hospital) and the national research committee and with the 1964 Helsinki declaration and its later amendments. The Ethical committee from canton de Vaud, Switzerland (CER-VD) has approved the present protocol in June 2019 (protocol reference 2019–00392).

Informed consent

Written informed consent has been obtained from all individual participants included in the study.

CRediT authorship contribution statement

Ioannis Skalidis: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Nathalie Noirclerc:** Methodology, Investigation, Data curation. **David Meier:** Writing – original draft, Visualization, Supervision. **Wongsakorn Luangphiphat:** Writing – original draft, Software, Investigation. **Aurelien Cagnina:** Writing – original draft, Visualization, Formal analysis, Data curation. **Sarah Mauler-Wittwer:** Writing – review & editing, Software, Resources, Data curation. **Thabo Mahendiran:** Writing – original draft, Formal analysis, Data curation. **Bernard De Bruyne:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Alessandro Candreva:** Writing – review & editing, Data curation, Conceptualization. **Carlos Collet:** Writing – review & editing, Methodology, Investigation. **Jeroen Sonck:** Writing – review & editing, Formal analysis, Conceptualization. **Olivier Muller:** Writing – review & editing, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Stephane Fournier:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

Dr. David Meier is supported by the Swiss National Science Foundation (grant P2LAP3_199561). Dr. Stephane Fournier reports an institutional consultancy for Bayer and Cathworks. Professor Bernard De Bruyne reports an institutional consultancy for St.Jude Medical, Opsens, and Boston Scientific and institutional research grant support from Boston Scientific, Abbott, Medtronic, and Biotronik. All the other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131663.

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