Original Article

Are baseline conditions of coronary arteries sufficient for calculating angio-based index of microcirculatory resistance and fractional flow reserve?

Chenguang Li[1,2#], Yumeng Hu[3#^], Jingpu Wang[1,2#], Congcong Pan[1,2], Hao Lu[1,2], Yizhe Wu[1,2], Zhangwei Chen[1,2], Zhiqiang Pei[1,2], Li Shen[1,2], Jingsong He[3], Xiaochang Leng[3], Jianping Xiang[3], Junbo Ge[1,2]

[1]Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]National Clinical Research Center for Interventional Medicine, Shanghai, China; [3]ArteryFlow Technology Co., Ltd., Hangzhou, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: J Ge, J Xiang, C Li; (III) Provision of study materials or patients: C Li, J Wang; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: Y Hu, J Wang, C Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Junbo Ge, MD. Department of Cardiology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China; National Clinical Research Center for Interventional Medicine, Shanghai, China. Email: jbge@zs-hospital.sh.cn; Jianping Xiang, PhD. ArteryFlow Technology Co., Ltd., 459 Qianmo Road, Hangzhou 310051, China. Email: jianping.xiang@arteryflow.com.

Background: Angio-based index of microcirculatory resistance (IMR) and fractional flow reserve (FFR) have been developed, however, the differences between baseline and hyperemic data and their effects on their computation have not yet been discussed. This study aimed to compare the diagnostic performance of a novel method for calculating IMR and FFR from coronary angiography under baseline and hyperemic conditions.

Methods: We performed a retrospective study to investigate the diagnostic performance of angiography-derived IMR (AccuIMR) and FFR (AccuFFRangio) computed from the hyperemic condition ($AccuIMR_{hyp}$, $AccuFFRangio_{hyp}$) and baseline condition ($AccuIMR_{base}$, $AccuFFRangio_{base}$) in 101 consecutive patients with chronic coronary syndrome (CCS) who underwent measurements of IMR and FFR at a single center, using wire-based IMR and FFR as the reference standard.

Results: $AccuIMR_{hyp}$ showed much better correlation with IMR than $AccuIMR_{base}$ (r=0.77 *vs.* 0.47, P<0.001). The diagnostic accuracy and area under the curve (AUC) for identifying significant microvascular dysfunction was higher for $AccuIMR_{hyp}$ than $AccuIMR_{base}$ [92.1% (95% CI: 85.0–96.5%) *vs.* 83.2% (95% CI: 74.4–89.9%), P=0.012; 0.942 (95% CI: 0.877–0.979) *vs.* 0.815 (95% CI: 0.726–0.886), P=0.003]. The computed AccuFFRangio showed good correlations with FFR and good diagnostic performance under both hyperemic and baseline conditions [r=0.68 *vs.* 0.68, P>0.99; diagnostic accuracy =95.9% (95% CI: 89.8–98.9%) *vs.* 94.9% (95% CI: 88.4–98.3%), P=0.728; AUC =0.989 (95% CI: 0.942–1.000) *vs.* 0.973 (95% CI: 0.919–0.995), P=0.381]. The net reclassification index (NRI) demonstrated that hyperemic group had improved reclassification ability compared to the baseline group in identification of IMR >25 (NRI =0.20, P<0.001) and FFR ≤0.8 (NRI =0.11, P<0.001).

Conclusions: By comparing the calculated angio-derived IMR and FFR under the baseline and hyperemic conditions, this study demonstrates that AccuIMR calculation is more accurate using the hyperemic condition, while AccuFFRangio calculation is accurate under both conditions.

^ ORCID: 0000-0002-0779-9172.

Keywords: Fractional flow reserve; invasive coronary angiography; index of microcirculatory resistance (IMR); coronary artery disease

Submitted Jan 15, 2023. Accepted for publication Jun 18, 2023. Published online Aug 09, 2023.
doi: 10.21037/qims-23-72
View this article at: https://dx.doi.org/10.21037/qims-23-72

Introduction

A common clinical scenario is that the patients with coronary vascular disease underwent successful percutaneous coronary intervention (PCI), yet continued to have angina, the value of the index of microcirculatory resistance (IMR) remained high, indicating no significant improvement in microcirculatory perfusion and poor recovery of cardiac function (1,2). From previous studies, after successful angioplasty for acute myocardial infarction, up to one-third of patients cannot benefit from intervention due to the accompanying microvascular occlusion, this is because coronary microcirculation plays a crucial role in metabolic regulation of coronary blood flow (3). Microvascular occlusion hinders the recovery of myocardial blood flow (4), and this cannot be identified by fractional flow reserve (FFR) measurement except IMR test (5). Another common scenario for considering IMR is the patient who has symptoms of angina but no significant epicardial coronary stenosis is detected, about 20% of patients are in this type (2,6). However, the traditional measurement of IMR requires the use of pressure wire and vasodilator, along with multiple injections of normal saline, resulting in increased complexity and extended measurement time (2,3), which limited its utility. Doppler-flow-velocity is an alternative technique to measure microvascular resistance without the need of saline injection, while Doppler malalignment and variability in velocity envelopes also hampered its clinical applicability (3,7). Angiography-based FFR derived from computational fluid dynamics and three-dimensional (3D) reconstruction technique was a novel approach for the functional evaluation of coronary artery disease without the need of pressure wire (8-10). It has been widely validated and showed great diagnostic performance in predicting ischemia (11-14). Based on the foundation of angiography-based FFR, a pressure wire-free calculation approach of IMR has been developed (15,16), which could be a promising tool for the assessment of coronary microcirculation.

It is noteworthy that FFR and IMR are both defined at hyperemia. When it comes to the computation of these indexes using the angiographic data, are baseline conditions of coronary arteries good enough for calculating angio-based FFR or IMR? When the state of coronary arteries changes from baseline to maximum hyperemia with the full dilation of the distal bed, blood flow changes, for example, there is usually a significant increase in the coronary blood flow rate and a slight decrease in the pressure at the coronary ostium; the information contained in the image data changes accordingly, which could affect the computation of angio-based indexes. The aim of this study was to investigate and compare the diagnostic performance of angio-based FFR and IMR computed from both baseline and hyperemic states. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-72/rc).

Methods

Study population

Between May 2020 and November 2021, consecutive patients with chronic coronary syndrome (CCS), who had undergone coronary angiography and wire-based IMR and FFR measurements within three months at Zhongshan Hospital, Fudan University (Shanghai, China) were eligible for this retrospective validation study. Patients were excluded from this study due to significant overlap of vessels, fuzzy coronary angiography images and angiographic projection angles <25° apart. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2016-018), and individual consent for this retrospective analysis was waived according to *Measures for the Ethical Review of Biomedical Research Involving Humans* published by the National Health Commission of the PRC (CLI.4.282697).

FFR and IMR

Clinically, FFR and IMR are two important physiological indexes. FFR is used to evaluate epicardial coronary arteries,

whereas IMR is used to assess coronary microcirculation. FFR is defined as the ratio of the distal pressure to the proximal pressure of the stenosis at hyperemia (17,18). The proximal pressure is usually replaced by the aortic pressure available by physiological monitoring instruments in the operation. In general, FFR can be defined as the following formula:

$$FFR = Pd/Pa = 1 - \Delta P/Pa \quad [1]$$

Pa is the available aortic pressure, Pd is the distal pressure of the stenosis and ΔP is the pressure drop across the stenosis.

IMR, first described in 2003 (19), is usually obtained by the thermodilution method (20). In this manner, IMR is defined as the product of the distal pressure and the mean transit time at hyperemia (2). The mean transit time of room-temperature saline injected into a coronary artery is acquired by a temperature sensor, whereas a pressure sensor measures the distal pressure. IMR is defined as the following formula:

$$IMR = Pd \times Tmn \quad [2]$$

Pd is the distal pressure of the stenosis, and Tmn is the mean transit time.

In this study, invasive coronary angiography, including the wire-based FFR and IMR measurement, was performed according to best local practice. Two angiographic projections were acquired during the measurement.

Angio-based FFR and IMR calculation

The angio-based FFR and IMR analysis was performed by two well-trained investigators who were blinded to the IMR and FFR results using the AccuFFRangio (Version 1.0, ArteryFlow Technology, Hangzhou, China) and AccuIMR (Version 1.0, ArteryFlow Technology, Hangzhou, China) software.

The computation of AccuFFRangio includes 2 main steps: first, 2 angiographic projections, at least 25° apart, were selected for the 3D reconstruction of the vessel of interest. Then, as previously described (10,14), pressure drop from proximal to distal is in general caused by two factors, viscous loss and expansion loss. The first one is related to friction, and the other is mainly related to the rapid change of vessel radius (21). Based on hemodynamics, the calculation of pressure drop is related to vessel geometry and flow velocity. As the 3D model of interrogated vessel was achieved, the thrombolysis in myocardial infarction (TIMI) frame count method (22) was a relatively feasible solution to estimate the mean blood flow velocity. If the X-ray angiographic images are hyperemic, the calculated velocity can be directly available; if at baseline condition, a velocity conversion relationship from a rest state to hyperemic would be necessary (8). With the vessel geometry and flow velocity obtained from angiographic images, the calculation of AccuFFRangio is quite straightforward.

AccuIMR was calculated on the basis of AccuFFRangio, starting from the formula of IMR.

$$AccuIMR = Pd \times Tmn = Pa \times AccuFFRangio \times L/V \quad [3]$$

Where L is the length of the target vessel, and V is the mean flow velocity. Vessel length was obtained from the 3D reconstructed model, and the velocity was measured by angiographic images. Thus, with the computed AccuFFRangio, AccuIMR was subsequently derived, as previously described (23,24).

AccuIMR and AccuFFRangio were computed under the hyperemic condition (hyperemic group) and baseline condition (baseline group) in all 101 patients. AccuIMR and AccuFFRangio were measured at the same position where IMR and FFR were obtained. *Figure 1* demonstrates the computation of AccuFFRangio and AccuIMR by coronary angiography on a left anterior descending artery (LAD) under both conditions.

Statistical analysis

Continuous variables with mean ± SD and binary variables were presented as percentages. Continuous variables were compared using Mann-Whitney's test or Kruskall-Wallis' test, as appropriate. Wilcoxon test were used for paired samples. Correlation between angio-based IMR (or FFR) and invasive IMR (or FFR) was assessed by the Pearson or Spearman correlation analysis. Bland-Altman plot was used to quantify the agreement between angio-based IMR (or FFR) and corresponding wire-based indexes. Using wire-based IMR and FFR as the reference standard, the diagnostic performances [including diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)] of angio-based IMR (or FFR) to predict microvascular dysfunction (IMR >25 U) [or ischemia (FFR ≤0.8)] were calculated (5). The area under the receiver-operating characteristic curve (AUC) of angio-based IMR (or angio-based FFR) was used to evaluate the discriminatory ability. Based on a preliminary study, where the accuracy of $AccuIMR_{hyp}$ was 90%, 100 patients would yield >85% power to allow the margin of non-inferiority

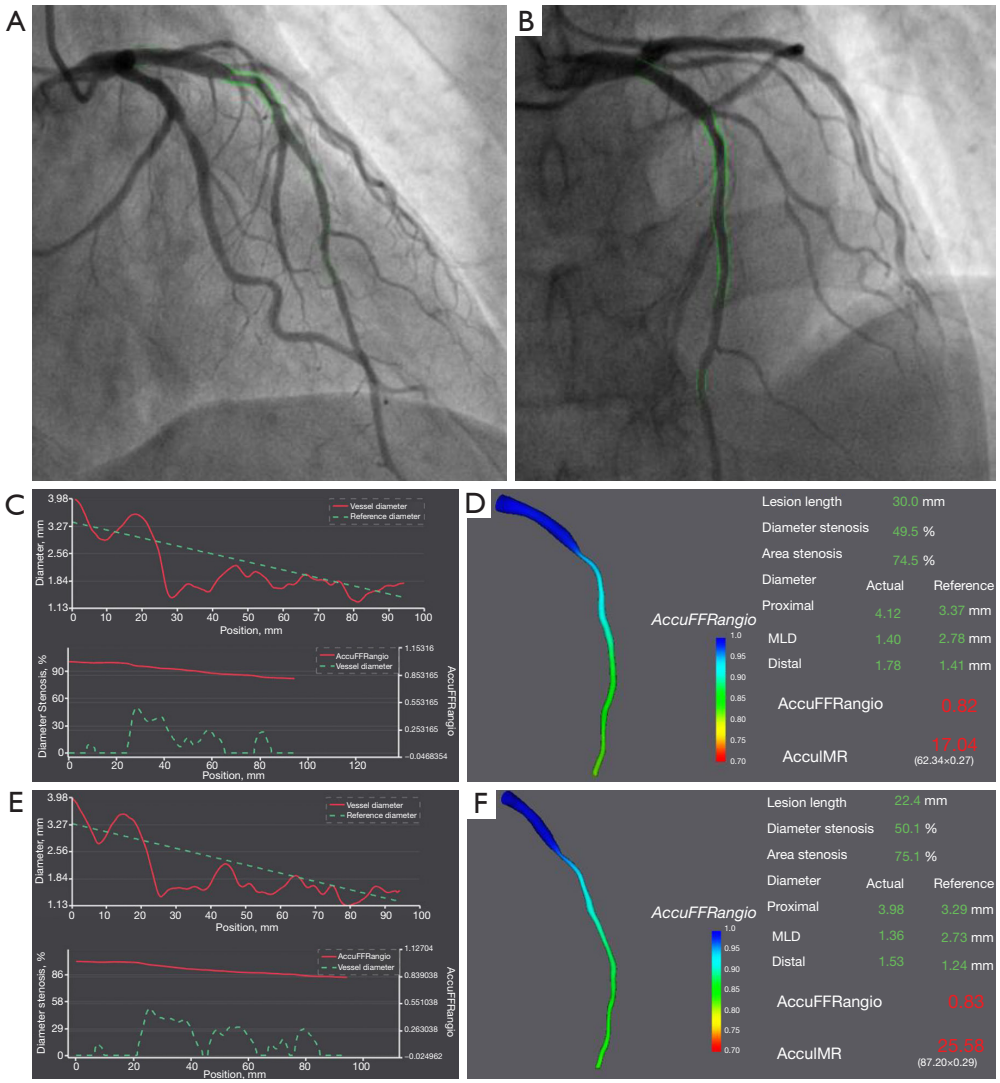

Figure 1 Computation of FFR and IMR by coronary angiography on LAD with physiologically severe stenosis. Two sets of baseline, end-diastolic angiography with angle difference of projection ≥25° (A,B); the vessel diameter-position curve and diameter-stenosis of AccuFFRangio and vessel diameter curve at baseline (C) and hyperemic (E) conditions; 3D vessel model with AccuFFRangio value distribution at baseline (D) and hyperemic (F) conditions with AccuFFRangio and AccuIMR values and other morphological parameters of the vessel at baseline and hyperemic conditions. FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; MLD, minimal lumen diameter; AccuFFRangio, angiography-derived FFR; AccuIMR, angiography-derived IMR.

of 10% between two measurements with a 2-sided type I error of 0.05. Further, reclassification performance of baseline and hyperemic group was compared using net reclassification index (NRI). The intraobserver and interobserver variabilities in Angio-based IMR and FFR analysis was performed on randomly selected 50 cases using Bland-Altman analysis and the analyses were blinded to each other. A two-sided P value (<0.05) was regarded as statistically significant. All the statistical analyses were conducted by using MedCalc (version 19.0, MedCalc Software Inc., Belgium).

Results

Study characteristics

Figure 2 presents the study flow. A total of 101 patients

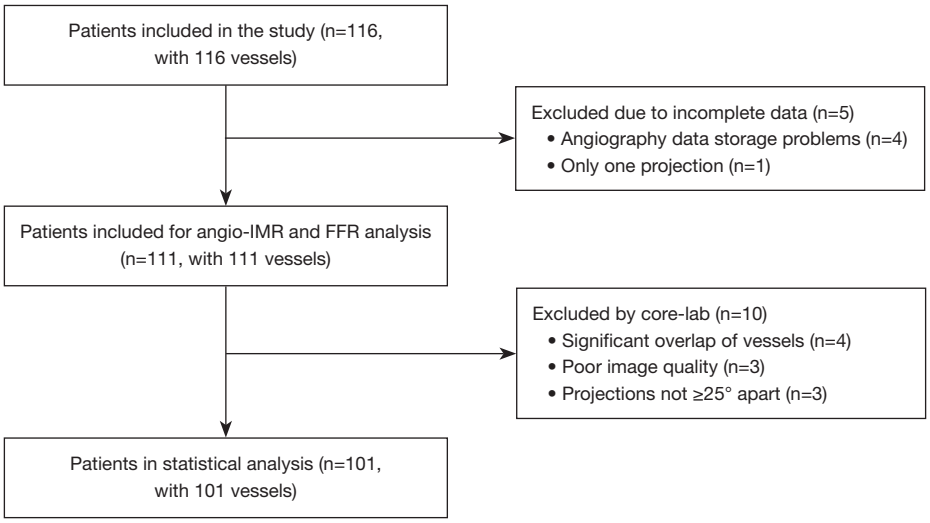

Figure 2 Patients flow chart. FFR, fractional flow reserve; IMR, index of microcirculatory resistance.

with 101 vessels were included in the current analysis. Comparisons of the AccuFFRangio and AccuIMR under baseline condition and hyperemic condition were made successfully in all 101 patients. The lesions for the algorithm validation were from 72 LAD, 2 left circumflex arteries (LCX), 26 right coronary arteries (RCA) and 1 posterior descending artery (PDA). No significant difference in FFR or IMR were found between LAD and RCA (IMR, P=0.618; $AccuIMR_{hyp}$, P=0.974; $AccuIMR_{base}$, P=0.573; FFR, P=0.200; $AccuFFRangio_{hyp}$, P=0.506; $AccuFFRangio_{base}$, P=0.500). The average invasive FFR and IMR were 0.90±0.06 and 23.0±15.2 U, respectively. Clinical characteristics for the whole cohort are presented in *Table 1*.

Correlation and agreement between angio-based computations and invasive measurements

The calculations of IMR and FFR were based on X-ray angiographic images, which were either under the baseline or hyperemic conditions. The results of AccuFFRangio and AccuIMR were compared between the baseline group and hyperemic group. The FFR and IMR measured by guidewire were used as the gold standard.

The mean results of FFR were 0.90±0.06 for pressure wire measurement, 0.89±0.09 for baseline group *vs.* 0.89±0.09 for hyperemic group. Both the results under the baseline and hyperemic states show good correlation (r=0.68 *vs.* 0.68, P>0.99) with FFR. The mean results of IMR were 23.0±15.2 U for pressure wire measurement, 22.2±7.5 U for baseline group *vs.* 23.7±12.3 U for hyperemic group, the results of hyperemic condition showed better correlation and agreement (r=0.77 *vs.* 0.47, P<0.001; mean differences: –0.7±9.8 *vs.* 0.8±13.5 U), as shown in *Figures 3*,*4*.

Diagnostic performance of AccuFFRangio and AccuIMR

Using the cut-off value of FFR ≤0.80 for identifying ischemia-causing stenosis and IMR >25 U for detecting microvascular dysfunction, the diagnostic accuracy, sensitivity, specificity of AccuFFRangio were 94.9% (95% CI: 88.4–98.3%), 77.8% (95% CI: 40.0–97.2%), 96.6% (95% CI: 90.4–99.3%), respectively, using baseline data; and those of AccuFFRangio using hyperemic data were 95.9% (95% CI: 89.8–98.9%), 88.9% (95% CI: 51.8–99.7%), 96.6% (95% CI: 90.4–99.3%), respectively; the diagnostic accuracy, sensitivity, specificity of $AccuIMR_{base}$ were 83.2% (95% CI: 74.4–89.9%), 75.0% (95% CI: 57.8–87.9%), 87.7% (95% CI: 77.2–94.5%), respectively, and those of $AccuIMR_{hyp}$ were 92.1% (95% CI: 85.0–96.5%), 88.9% (95% CI: 73.9–96.9%), 93.9% (95% CI: 85.0–98.3%), respectively (*Table 2*). $AccuIMR_{hyp}$ demonstrated much better diagnostic accuracy and sensitivity than $AccuIMR_{base}$ (P=0.012 and 0.011, respectively), while there was no significant difference in accuracy between $AccuFFRangio_{hyp}$ and $AccuFFRangio_{base}$ (P=0.728) though hyperemic calculation improved sensitivity (P=0.035).

The AUC for diagnosis of significant microvascular dysfunction was higher for $AccuIMR_{hyp}$ than $AccuIMR_{base}$

Table 1 Patients clinical characteristics

Parameter	Values (N=101)
Age (years)	61±10
Male	78 [79]
Weight (kg)	72±10
Height (cm)	169±8
Body mass index (kg/m^2)	25±3
Cardiovascular risk factors	
Systolic blood pressure (mmHg)	123±13
Diastolic blood pressure (mmHg)	73±7
LVEF (%)	65±5
CKD	3 [3]
Diabetes	22 [22]
Hypertension	63 [64]
Hyperlipidemia	24 [24]
Current smoker	20 [20]
Previous PCI	34 [34]
Previous myocardial infarction	13 [13]
Family CAD history	3 [3]
Vessel location	
LAD	71 [72]
LCX	2 [2]
RCA	26 [26]
PDA	1 [1]
QCA, FFR and IMR	
DS%	41±14
MLD (mm)	2±2
FFR ≤0.8	9 [9]
IMR >25 U	36 [36]

Data are presented as mean ± SD or % [n]. LVEF, left ventricular ejection fraction; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; PDA, posterior descending artery; QCA, quantitative coronary angiography; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; DS, diameter stenosis; MLD, minimal lumen diameter.

[0.942 (95% CI: 0.877–0.979) *vs.* 0.815 (95% CI: 0.726–0.886), P=0.003], while AccuFFRangio calculated from both conditions showed similar AUCs (P=0.381), as shown in *Figure 5*. For reclassification ability, the hyperemic group showed improved reclassification indexes compared to the baseline group in the identification of IMR >25 (NRI =0.20, P<0.001) and FFR ≤0.8 (NRI =0.11, P<0.001).

Variability analysis

The mean time for AccuIMR assessment (including three-dimensional reconstruction based on angiographic images and frame count analysis) was 5.65±2.57 min. Intraobserver and interobserver variability in AccuIMR analysis were 0.1±0.2 and 0.2±0.2, respectively; and those for AccuFFRangio were 0.00±0.03 and 0.01±0.02, respectively.

AccuIMR across the spectrum of clinical characteristics

AccuIMR did not differ significantly between clinical characteristics (hypertension, diabetes, hyperlipidemia and smoking) or computation conditions (baseline and hyperemic) (Figure S1). Kruskal-Wallis' tests showed the P value of 0.674 and 0.747 for AccuIMR$_{base}$ and AccuIMR$_{hyp}$, respectively. The smallest P value obtained by Mann-Whitney tests and were 0.225 between hypertension and diabetes group for AccuIMR$_{base}$ and 0.350 between diabetes and hyperlipidemia group for AccuIMR$_{hyp}$ group. Notably, the medians were similar between AccuIMR$_{base}$ and AccuIMR$_{hyp}$ while the mean values of AccuIMR were generally higher for hyperemic group in all clinical characteristic subgroups. Patients with diabetes showed the highest AccuIMR value, though the differences were not significant.

Table 3 shows comparison of correlation coefficients between IMR and AccuIMR. Using the cutoff of 0.8, FFR classified the patients into two subgroups (ischemic or non-ischemic), it is noteworthy that the difference between the baseline group and hyperemic group was significant in both subgroups. Considering patients with or without microvascular dysfunction (IMR >25 or ≤25), AccuIMR$_{hyp}$ showed much better correlation with IMR than AccuIMR$_{base}$, especially in the cohort of patients with microvascular dysfunction (P=0.028).

Discussion

IMR computed from coronary angiography has been documented with good performance in assessing the coronary microvascular function, IMR computations derived from coronary angiography under baseline condition or hyperemic condition have been investigated (16,25,26). However, the differences between baseline and hyperemic data and their effects on IMR computation

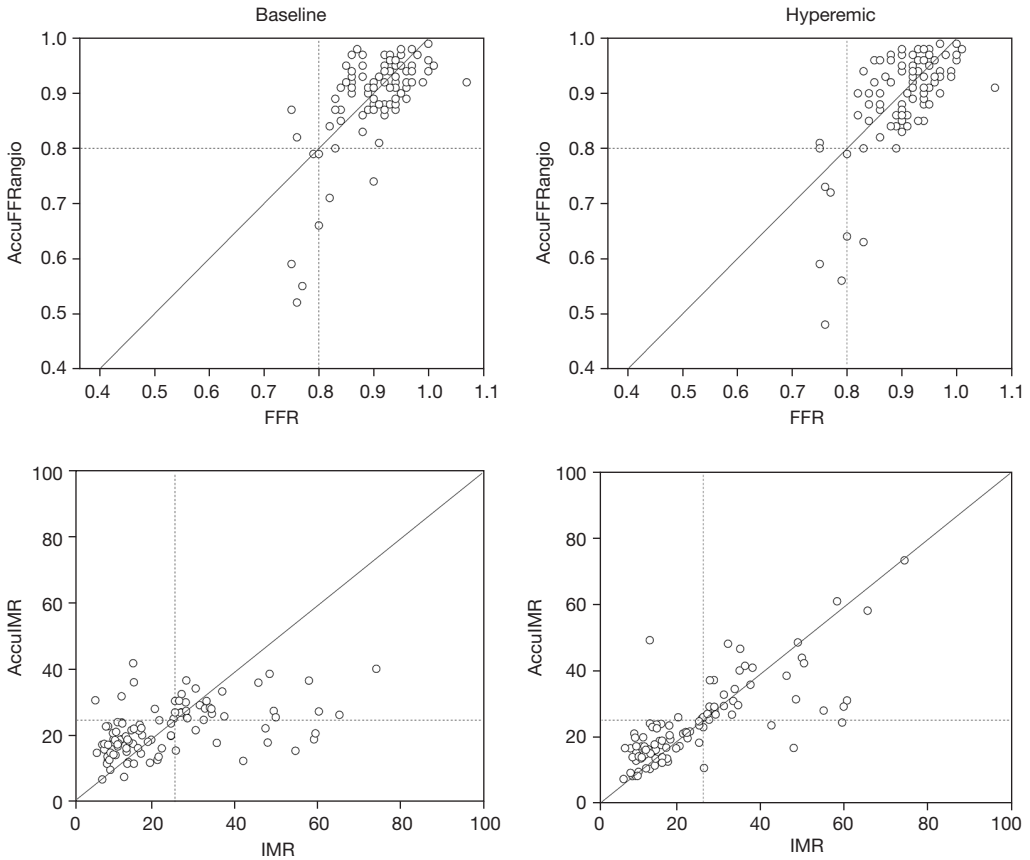

Figure 3 Correlations between AccuFFRangio and FFR, AccuIMR and IMR under baseline condition (left) and hyperemic condition (right). FFR, fractional flow reserve; IMR, index of microcirculatory resistance AccuFFRangio, angiography-derived FFR; AccuIMR, angiography-derived IMR.

have not yet been discussed. In this retrospective study, we evaluated the angio-based IMR computation approach in 101 patients at both baseline state and hyperemic state, using wire-derived IMR as the reference standard. AccuIMR at hyperemic state showed a very good correlation with IMR (correlation coefficient r=0.77) and with the receiver-operating characteristic AUC of 0.942, which validated its potential to be a pressure-wire-free alternative to IMR for the diagnosis of coronary microcirculation.

Impact of clinical characteristics on angio-IMR

In this study, clinical factors like hypertension, diabetes, hyperlipidemia and smoking had very limited influence on the computation of AccuIMR under both conditions. AccuIMR maintained a good stability regarding different kinds of patients, which means the protential of a wide range of clinical utility. In the subgroups of patients with FFR ≤0.8 or >0.8, AccuIMR showed statistically significant difference between the baseline and hyperemic group, $AccuIMR_{hyp}$ correlated much better with IMR than $AccuIMR_{base}$ in all severity of stenoses. This is partially in line with previous study that IMR is independent of epicardial coronary stenoses (27).

Angio-IMR under baseline and hyperemic conditions

Comparing the AccuIMR results, $AccuIMR_{base}$ showed much worse results (correlation coefficient r=0.47 and AUC =0.815) than those of $AccuIMR_{hyp}$ (correlation coefficient r=0.77 and AUC =0.942). On the other hand, AccuFFRangio, which was computed using the same set of angiographic data at both states, showed very similar diagnostic performance in predicting FFR ≤0.8 at either baseline state or hyperemic state (AccuFFRangio value: 0.89±0.09 *vs.* 0.89±0.09). The evident error

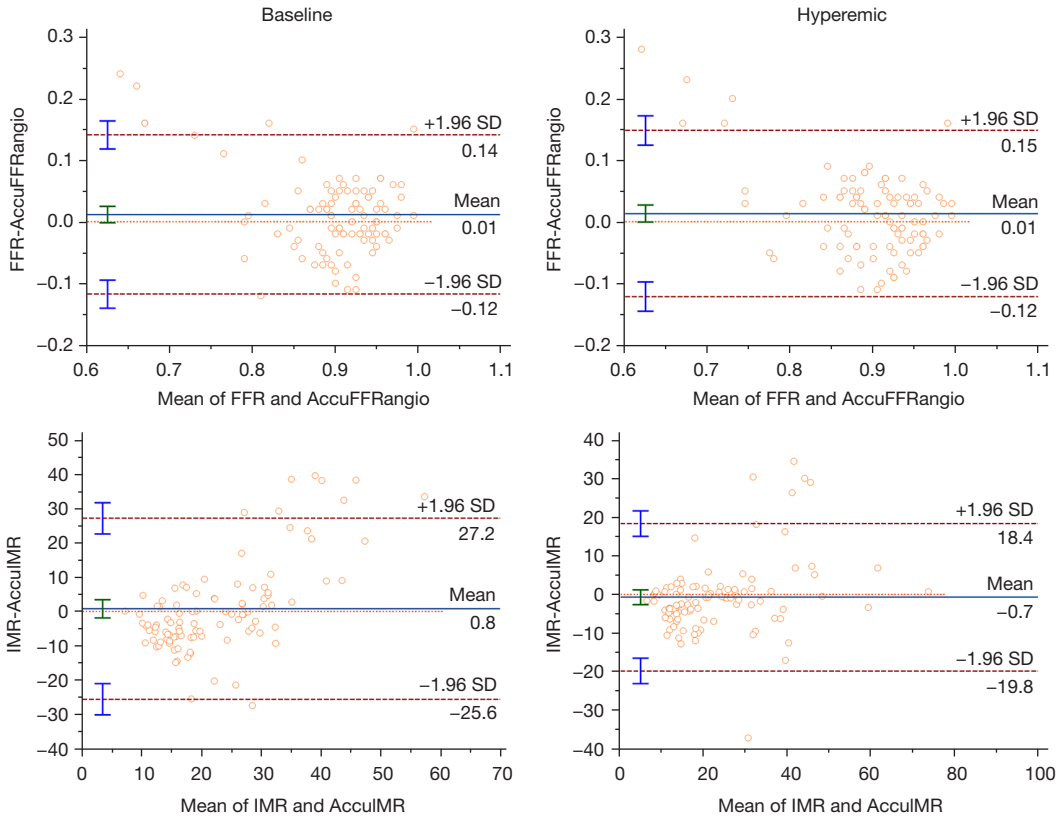

Figure 4 Bland-Altman plot for the differences between AccuFFRangio and FFR, AccuIMR and IMR under baseline condition (left) and hyperemic condition (right). FFR, fractional flow reserve; IMR, index of microcirculatory resistance; SD, standard deviation; AccuFFRangio, angiography-derived FFR; AccuIMR, angiography-derived IMR.

Table 2 Diagnostic performance of AccuIMR and AccuFFRangio at baseline and hyperemic conditions

Performance	AccuIMR			AccuFFRangio		
	Baseline (95% CI)	Hyperemic (95% CI)	P value	Baseline (95% CI)	Hyperemic (95% CI)	P value
Accuracy	83.2% (74.4–89.9%)	92.1% (85.0–96.5%)	0.012	94.9% (88.4–98.3%)	95.9% (89.8–98.9%)	0.728
Sensitivity	75.0% (57.8–87.9%)	88.9% (73.9–96.9%)	0.011	77.8% (40.0–97.2%)	88.9% (51.8–99.7%)	0.035
Specificity	87.7% (77.2–94.5%)	93.9% (85.0–98.3%)	0.131	96.6% (90.4–99.3%)	96.6% (90.4–99.3%)	1.000
PPV	77.1% (63.2–86.9%)	88.9% (75.5–95.4%)	–	70.0% (42.1–88.2%)	72.7% (46.1–89.3%)	–
NPV	86.4% (78.1–91.8%)	93.9% (85.8–97.5%)	–	97.7% (92.6–99.3%)	98.8% (93.1–99.8%)	–
AUC	0.815 (0.726–0.886)	0.942 (0.877–0.979)	0.003	0.973 (0.919–0.995)	0.989 (0.942–1.000)	0.381

AccuIMR, angiography-derived index of microcirculatory resistance; AccuFFRangio, angiography-derived fractional flow reserve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

between $AccuIMR_{hyp}$ and $AccuIMR_{base}$ might arise from the conversion of Pa and Tmn at baseline state to the hyperemic state. As the input of the method, if the state of angiographic images are hyperemic, the accurate hyperemic coronary ostial pressure can be directly used, including the transit time estimated by TIMI frame count method which directly corresponds to the measured wire transit time. If baseline data were used in the computation of angio-based

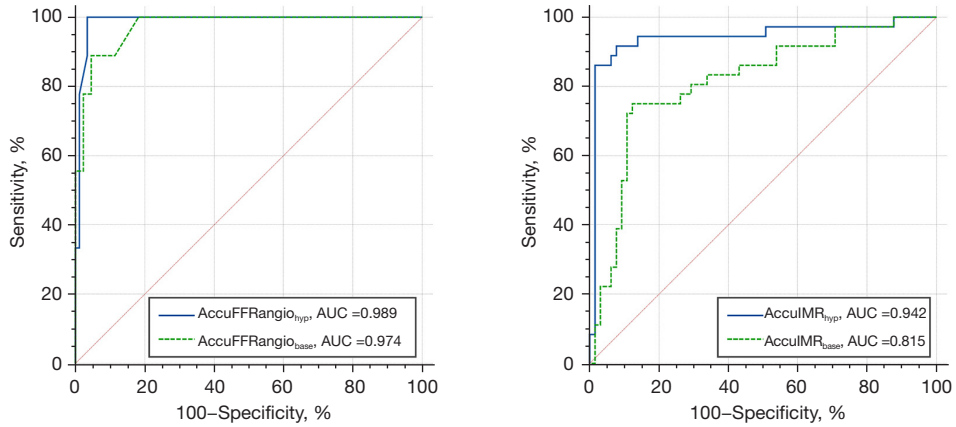

Figure 5 ROC curves of AccuFFRangio and AccuIMR under baseline and hyperemic conditions. AUC, area under the curve; ROC, receiver operating characteristic; AccuIMR, angiography-derived index of microcirculatory resistance; AccuFFRangio, angiography-derived fractional flow reserve.

Table 3 Comparison of correlation coefficients between IMR and AccuIMR

Index	Correlation coefficient, r		P value
	Baseline	Hyperemic	
FFR >0.8	0.48	0.75	0.003
FFR ≤0.8	0.19	0.71	0.048
IMR >25	0.02	0.66	0.028
IMR ≤25	0.27	0.69	0.063

IMR, index of microcirculatory resistance; AccuIMR, angiography-derived IMR; FFR, fractional flow reserve.

IMR and FFR, characteristics at baseline state should be converted to the values of hyperemic state. There could be errors between converted values and the real results from hyperemic conditions, resulting in a relatively bad outcome. One can see that the influence of conversion error was only significant on AccuIMR, while the impact on AccuFFRangio was not obvious. To figure it out, we should focus on the computation nature of these two indexes. FFR is defined as Pd/Pa, which can also be expressed as (Pa–ΔP)/Pa, where ΔP was calculated by computational fluid dynamics. Pa was directly obtained from hyperemic data or converted from data at baseline state. The conversion error only occurred in Pa, and the total error of FFR could be small considering the magnitude of ΔP and Pa because of the division relationship. As for AccuIMR, it can be expressed as (Pa–ΔP)×Tmn, if data of baseline condition were used, conversion error occurred in both parts of Pa and Tmn, the total error of IMR could be significant from the multiplication relationship.

Regarding the ability of AccuIMR to correlate with IMR in the setting of presence and absence of microvascular dysfunction, AccuIMR$_{hyp}$ showed much better correlation with IMR than AccuIMR$_{base}$ in the cohort of patients with microvascular dysfunction, which means hyperemic state cloud be quite important when assessing patients' microcirculation using angio-IMR approach due to the poor correlation of angio-IMR computed from baseline state with IMR as observed in this study. Thus, we suggest that data of hyperemic state should be used to estimate AccuIMR for coronary microcirculation, which can provide better results. Conversely, diagnostic accuracy cannot be guaranteed due to the nature of data from baseline state.

Angio-IMR across different coronary syndromes

De Maria *et al.* (16) presented and validated an angiography–derived IMR approach (IMR$_{angio}$) for the assessment of coronary microcirculation in 45 ST elevation myocardial infarction (STEMI) patients. IMR$_{angio}$ showed good correlation with IMR in both infarct related artery (IRA) and non-IRA of STEMI patients. Furthermore, Scarsini *et al.* (28) investigated the diagnostic performance of IMR$_{angio}$ across different kinds of patients [STEMI, non-ST elevation acute coronary syndrome (NSTE-ACS) and CCS]. IMR$_{angio}$ was correlated with IMR across the whole spectrum of coronary syndromes with good diagnostic performance, showing the potential of angio-derived IMR

for the assessment of coronary physiology itself without the limitation of coronary syndromes-related condition. In addition, they evaluated the influence of non-hyperemic (NH) parameters, which was similar to the baseline group in this study. The results demonstrated that NH-IMR$_{angio}$ only significantly related with IMR in IRA of STEMI but not in NSTE-ACS and CCS. In this study with the cohort of CCS patients, AccuIMR$_{hyp}$ also showed much better correlation with IMR than the non-hyperemic group. The results supported each other. However, why non-hyperemic and hyperemic angio-IMR showed no significant difference regarding IRA in STEMI patients? This could be the outcome of the depleted microvascular vasodilatory capacity of the IRA which could not respond to a vasodilatory agent like other microvessels. Moreover, microvascular obstruction (MVO) is more likely to be linked with STEMI patients (29) which means vasodilatory agents might be ineffective. While most microvascular dysfunctions were caused by functional disorders, there could be noteworthy differences between baseline and hyperemic state. In this case, we could suggest a hybrid model of using angio-IMR to assess coronary microvascular dysfunction: In general, hyperemic angio-IMR could be a better choice for its better diagnostic performance across different coronary syndromes, while for STEMI patients, non-hyperemic/baseline computation of angio-IMR could broaden the utility of angio-derived IMR approaches.

Potential of angio-IMR

The coronary artery system can be divided into large epicardial vessels and endocardial microvascular. Only large vessels are visible in coronary angiography and the FFR and IMR are important indexes in evaluating coronary blood flow. FFR is often used to assess the hemodynamic influence of coronary stenosis on blood supply, which is a review of large coronary vessels. IMR, on the other side, is the assessment of coronary microcirculation.

FFR has already been proved to be the best tool for improving patient's diagnostic outcomes and saving resources (30). The development of angio-FFR, with their excellent diagnostic performance (11,14,31,32), has removed the restriction of the need for pressure wire and promoted the application of non-invasive FFR assessment. Thousands of patients have taken the benefits of the low-cost, convenient AccuFFRangio technique. However, some problems cannot be detected by FFR assessment only. For example, some patients had abnormal stress and angina, but no severe coronary stenosis was found, whereas some patients had undergone PCI but their coronary syndromes continued. IMR is a useful physiological index for quantitative assessment of coronary microvasculature (19), providing supplemental information to help decision-making in the cath lab, but its extended cost limited its utility. AccuIMR, which can be easily obtained from coronary angiography only, could be a useful assessment approach.

Study limitations

Beyond the retrospective nature, the investigation was mainly limited by its relatively small sample size. Only 101 CCS patients were involved, so the findings of this study may include an element of serendipity and patients with acute coronary syndrome were not included. Due to the current guideline of CCS, IMR was only measured in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved FFR, thus the conclusions derived from this study were limited by selection bias and may have been underpowered by the limited number of positive FFR cases included (Figure S2). However, the results are still encouraging to warrant a larger and a more in-depth study.

Perspectives

Clinical competencies

Among patients with stable chronic coronary syndrome, angio-based IMR computed at hyperemic condition provides more accurate diagnosis of significant microcirculatory dysfunction than that computed at baseline. It requires a short processing time and can be completed at point-of-care with its excellent diagnostic performance.

Translational outlook

Further clinical trials are needed to validate the prognostic value of this novel AccuIMR in patients with ischemic heart disease and to compare the probability of potential outcomes of patients with other IMR techniques.

Conclusions

By comparing the calculated IMR and FFR under the baseline and hyperemic conditions, this study demonstrates that AccuIMR calculation is more accurate under the hyperemic condition, while AccuFFRangio calculation is accurate under both baseline and hyperemic conditions.

Baseline conditions of coronary arteries are sufficient for calculating angio-based FFR, but not for IMR.

Acknowledgments

Funding: This work was supported by National Natural Science Foundation of China (No. 81900305 to JG), National Key Research and Development Program of China (No. 2018YFE0103000 to JG), Shanghai Clinical Research Center for Interventional Medicine (No. 19MC1910300 to JG), Shanghai Municipal Key Clinical Specialty (No. shslczdzk01701 to JG), Clinical Research Plan of Shanghai Hospital Development Center (No. SHDC2020CR5009 to JG), and Hangzhou Leading Innovation and Entrepreneurship Team Project (No. TD2022007 to JX).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-72/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-72/coif). JG receives grants from National Natural Science Foundation of China (No. 81900305), National Key Research and Development Program of China (No. 2018YFE0103000), Shanghai Clinical Research Center for Interventional Medicine (No. 19MC1910300), Shanghai Municipal Key Clinical Specialty (No. shslczdzk01701), and Clinical Research Plan of Shanghai Hospital Development Center (No. SHDC2020CR5009); YH and JH are employees of ArteryFlow; X Leng is a co-founder of ArteryFlow; JX receives grant from Hangzhou Leading Innovation and Entrepreneurship Team Project (No. TD2022007) and is the CEO of ArteryFlow. 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). This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2016-018), and individual consent for this retrospective analysis was waived according to *Measures for the Ethical Review of Biomedical Research Involving Humans* published by the National Health Commission of the PRC (CLI.4.282697).

References

1. Yong AS, Layland J, Fearon WF, Ho M, Shah MG, Daniels D, Whitbourn R, Macisaac A, Kritharides L, Wilson A, Ng MK. Calculation of the index of microcirculatory resistance without coronary wedge pressure measurement in the presence of epicardial stenosis. JACC Cardiovasc Interv 2013;6:53-8.
2. Fearon WF, Kobayashi Y. Invasive Assessment of the Coronary Microvasculature: The Index of Microcirculatory Resistance. Circ Cardiovasc Interv 2017;10:e005361.
3. Martínez GJ, Yong AS, Fearon WF, et al. The index of microcirculatory resistance in the physiologic assessment of the coronary microcirculation. Coron Artery Dis 2015;26 Suppl 1:e15-26.
4. Rochitte CE, Lima JA, Bluemke DA, et al. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. Circulation 1998;98:1006-14.
5. Nishi T, Murai T, Ciccarelli G, Shah SV, Kobayashi Y, Derimay F, Waseda K, Moonen A, Hoshino M, Hirohata A, Yong ASC, Ng MKC, Amano T, Barbato E, Kakuta T, Fearon WF. Prognostic Value of Coronary Microvascular Function Measured Immediately After Percutaneous Coronary Intervention in Stable Coronary Artery Disease: An International Multicenter Study. Circ Cardiovasc Interv 2019;12:e007889.
6. Panza JA. Myocardial ischemia and the pains of the heart. N Engl J Med 2002;346:1934-5.
7. Teunissen PF, de Waard GA, Hollander MR, et al. Doppler-derived intracoronary physiology indices predict the occurrence of microvascular injury and microvascular perfusion deficits after angiographically successful primary percutaneous coronary intervention. Circ Cardiovasc

Interv 2015;8:e001786.
8. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JHC, Holm NR, Wijns W; FAVOR Pilot Trial Study Group. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv 2016;9:2024-35.
9. Pellicano M, Lavi I, De Bruyne B, et al. Validation Study of Image-Based Fractional Flow Reserve During Coronary Angiography. Circ Cardiovasc Interv 2017;10:e005259.
10. Jiang J, Tang L, Du C, Leng X, He J, Hu Y, Dong L, Sun Y, Li C, Xiang J, Wang J. Diagnostic performance of AccuFFRangio in the functional assessment of coronary stenosis compared with pressure wire-derived fractional flow reserve. Quant Imaging Med Surg 2022;12:949-58.
11. Westra J, Andersen BK, Campo G, et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc 2018;7:e009603.
12. Fearon WF, Achenbach S, Engstrom T, et al. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. Circulation 2019;139:477-84.
13. Li J, Gong Y, Wang W, et al. Accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR. Cardiovasc Res 2020;116:1349-56.
14. Li C, Leng X, He J, et al. Diagnostic Performance of Angiography-Based Fractional Flow Reserve for Functional Evaluation of Coronary Artery Stenosis. Front Cardiovasc Med 2021;8:714077.
15. Tebaldi M, Biscaglia S, Di Girolamo D, et al. Angio-Based Index of Microcirculatory Resistance for the Assessment of the Coronary Resistance: A Proof of Concept Study. J Interv Cardiol 2020;2020:8887369.
16. De Maria GL, Scarsini R, Shanmuganathan M, Kotronias RA, Terentes-Printzios D, Borlotti A, Langrish JP, Lucking AJ, Choudhury RP, Kharbanda R, Ferreira VM; Oxford Acute Myocardial Infarction (OXAMI) Study Investigators; Channon KM, Garcia-Garcia HM, Banning AP. Angiography-derived index of microcirculatory resistance as a novel, pressure-wire-free tool to assess coronary microcirculation in ST elevation myocardial infarction. Int J Cardiovasc Imaging 2020;36:1395-406.
17. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177-84.
18. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991-1001. Erratum in: N Engl J Med 2012;367:1768.
19. Fearon WF, Balsam LB, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, Yock PG, Yeung AC. Novel index for invasively assessing the coronary microcirculation. Circulation 2003;107:3129-32. Erratum in: Circulation 2003;108:3165.
20. Pijls NH, De Bruyne B, Smith L, et al. Coronary thermodilution to assess flow reserve: validation in humans. Circulation 2002;105:2482-6.
21. Kirkeeide RL. Coronary obstructions, morphology and physiologic significance. In: Reiber JHC, Serruys PW, editors. Quantitative Coronary Arteriography. Developments in Cardiovascular Medicine. vol 117. Dordrecht: Springer; 1991:229-44.
22. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879-88.
23. Jiang J, Li C, Hu Y, et al. A novel CFD-based computed index of microcirculatory resistance (IMR) derived from coronary angiography to assess coronary microcirculation. Comput Methods Programs Biomed 2022;221:106897.
24. Fan Y, Li C, Hu Y, Hu X, Wang S, He J, Leng X, Xiang J, Lu Z. Angiography-based index of microcirculatory resistance (AccuIMR) for the assessment of microvascular dysfunction in acute coronary syndrome and chronic coronary syndrome. Quant Imaging Med Surg 2023;13:3556-68.
25. Ai H, Feng Y, Gong Y, et al. Coronary Angiography-Derived Index of Microvascular Resistance. Front Physiol 2020;11:605356.
26. Mejia-Renteria H, Lee JM, Choi KH, Lee SH, Wang L, Kakuta T, Koo BK, Escaned J. Coronary microcirculation assessment using functional angiography: Development of a wire-free method applicable to conventional coronary angiograms. Catheter Cardiovasc Interv 2021;98:1027-37.
27. Fearon WF, Aarnoudse W, Pijls NH, De Bruyne B, Balsam

LB, Cooke DT, Robbins RC, Fitzgerald PJ, Yeung AC, Yock PG. Microvascular resistance is not influenced by epicardial coronary artery stenosis severity: experimental validation. Circulation 2004;109:2269-72.
28. Scarsini R, Shanmuganathan M, Kotronias RA, Terentes-Printzios D, Borlotti A, Langrish JP, Lucking AJ; OxAMI Study Investigators; Ribichini F, Ferreira VM, Channon KM, Garcia-Garcia HM, Banning AP, De Maria GL. Angiography-derived index of microcirculatory resistance (IMRangio) as a novel pressure-wire-free tool to assess coronary microvascular dysfunction in acute coronary syndromes and stable coronary artery disease. Int J Cardiovasc Imaging 2021;37:1801-13.
29. McGeoch R, Watkins S, Berry C, Steedman T, Davie A, Byrne J, Hillis S, Lindsay M, Robb S, Dargie H, Oldroyd K. The index of microcirculatory resistance measured acutely predicts the extent and severity of myocardial infarction in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2010;3:715-22.
30. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation 2010;122:2545-50.
31. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. Lancet 2021;398:2149-59.
32. Witberg G, De Bruyne B, Fearon WF, et al. Diagnostic Performance of Angiogram-Derived Fractional Flow Reserve: A Pooled Analysis of 5 Prospective Cohort Studies. JACC Cardiovasc Interv 2020;13:488-97.

Cite this article as: Li C, Hu Y, Wang J, Pan C, Lu H, Wu Y, Chen Z, Pei Z, Shen L, He J, Leng X, Xiang J, Ge J. Are baseline conditions of coronary arteries sufficient for calculating angio-based index of microcirculatory resistance and fractional flow reserve? Quant Imaging Med Surg 2023;13(9):6215-6227. doi: 10.21037/qims-23-72

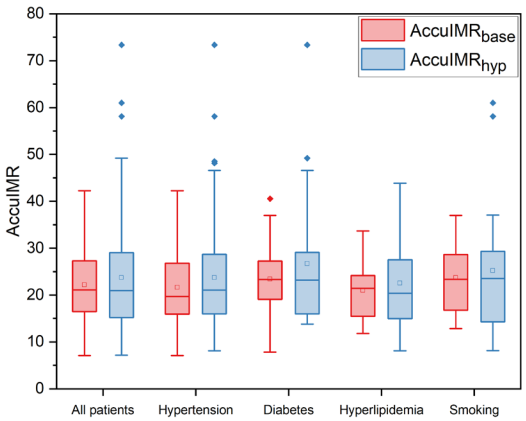

Figure S1 AccuIMR across the spectrum of patient characteristics. Box plots depict AccuIMR median values in patients with hypertension, diabetes, hyperlipidemia and smoking. No statistically significant differences were observed among these groups. AccuIMR, angiography-derived index of microcirculatory resistance.

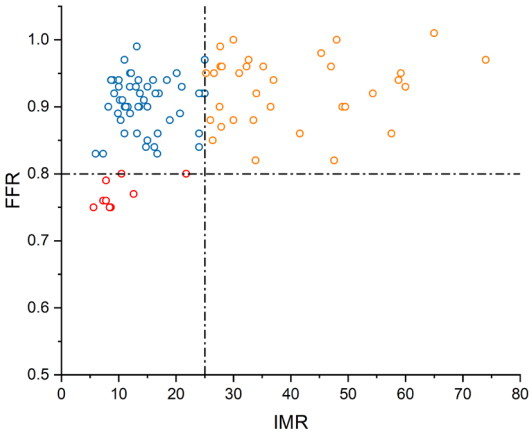

Figure S2 Classification of patients according to FFR and IMR. FFR, fractional flow reserve; IMR, index of microcirculatory resistance.

https://dx.doi.org/10.21037/qims-23-72