Coronary angiography-derived index for assessing microcirculatory resistance in patients with non-obstructed vessels: The FLASH IMR study

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Background Assessing index of microcirculatory resistance (IMR) is customarily performed using intracoronary wires fitted with sensors by at least 3 intracoronary injections of 3 to 4 mL of room-temperature saline during sustained hyperemia, which is time- and cost-consuming.

Methods The FLASH IMR study is a prospective, multicenter, randomized study to assess the diagnostic performance of coronary angiography-derived IMR (caIMR) in patients with suspected myocardial ischemia with nonobstructive coronary arteries using wire-based IMR as a reference. The caIMR was calculated by an optimized computational fluid dynamics model simulating hemodynamics during diastole based on coronary angiograms. TIMI frame count and aortic pressure were included in computation. caIMR was determined onsite in real time and compared blind to wire-based IMR by an independent core laboratory, using wire-based IMR ≥25 units as indicative of abnormal coronary microcirculatory resistance. The primary endpoint was the diagnostic accuracy of caIMR, using wire-based IMR as a reference, with a pre-specified performance goal of 82%.

Results A total of 113 patients underwent paired caIMR and wire-based IMR measurements. Order of performance of tests was based on randomization. Diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of caIMR were 93.8% (95% CI: 87.7%-97.5%), 95.1% (95% CI: 83.5%- 99.4%), 93.1% (95% CI: 84.5%-97.7%), 88.6% (95% CI: 75.4%-96.2%) and 97.1% (95% CI: 89.9%-99.7%). The receiver-operating curve for caIMR to diagnose abnormal coronary microcirculatory resistance had area under the curve of 0.963 (95% CI: 0.928-0.999).

Conclusions Angiography-based caIMR has a good diagnostic yield with wire-based IMR.

ClinicalTrials.gov identifier NCT05009667. (Am Heart J 2023;263:56–63.)

The microvascular domain of coronary circulation plays a key role in supply and regulation of blood flow to myocardium.[1,2] Structural derangements in microvasculature, like arteriolar stiffening and thickening and capillary rarefaction, as well as functional abnormalities of the microcirculation may increase vascular resistance and limit myocardial blood supply and cause ischemia in the absence of epicardial vessel obstructions.[3] Clinical practice guidelines and scientific consensus documents recommend measurement of microcirculatory resistance in cases of myocardial ischemia with a suspected microvascular origin.[4-8] The index of microcirculatory resistance (IMR), based on the thermodilution principle, was introduced nearly 20 years ago to investigate microvascular hemodynamics in patients with ischemic heart disease (IHD).[9-11] More recently, we have proposed a novel wire-free coronary angiography-derived index of microcirculatory resistance (caIMR), based on an optimized computational fluid dynamics (CFD) model and aortic pressure

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Submitted February 5, 2023; accepted March 31, 2023

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0002-8703

https://doi.org/10.1016/j.ahj.2023.03.016

waves,[12-17] to assess abnormal coronary microcirculatory resistance in patients with different coronary syndromes.

The caIMR is computed under the premise that the values of resting microcirculatory resistance at the diastolic state approximates those based on whole-cycle measurements during hyperemia.[18,19] We have validated the accuracy of caIMR retrospectively in 56 patients of suspected myocardial ischemia with nonobstructive epicardial coronary arteries.[14] The objective of this prospective and multicenter clinical study is to evaluate diagnostic performance of caIMR in patients with suspected myocardial ischemia, using wire-based IMR as a reference.

Methods

Study design

The prospective, multicenter, and randomized FLASH IMR (also defined as FLASH III) study was conducted at 3 centers in China to assess feasibility and performance of the FlashAngio IMR system (including FlashAngio IMR console, FlashAngio IMR software, and FlashPressure IMR pressure transducer; Rainmed Ltd., Suzhou, China), using wire-based IMR as the reference standard. To avoid biasing the trial by the order of measurements, patients who met trial inclusion and angiographic criteria were randomized by a central randomization system. Patients were equally randomized to IMR-first or caIMR-first measurement groups. All patients provided written informed consent before screening, and the study protocol was approved by the ethics committee of each participating center. The study was performed in accordance with the declaration of Helsinki and Good Clinical Practice Guidelines of the China Food and Drug Administration and registered at Clinicaltrials.gov (Identifier: NCT05009667).

This study was supported by Shanghai Clinical Research Center for Interventional Medicine (No. 19MC1910300), Shanghai Municipal Key Clinical Specialty (No. shslczdzk06201), National Natural Science Foundation (No. 82170458) and Rainmed Ltd., Suzhou, China. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

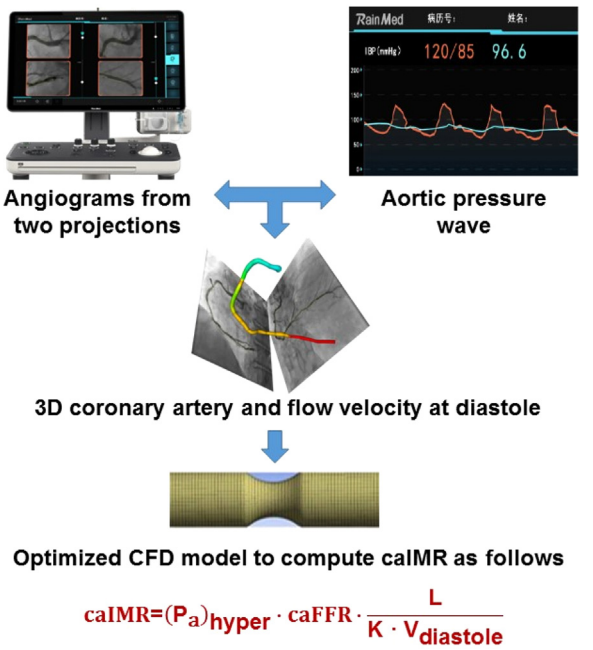
Theory

Based on aortic pressure waves and coronary angiograms from 2 projections, a novel physiological parameter, caIMR (unit: mm H g · s/mm),[14] is proposed as follows:

$$\text{caIMR} = (P_a)_{hyp} \cdot \text{caFFR} \cdot \frac{L}{K \cdot V_{diastole}} \quad (1)$$

where L is a constant (non-dimensional L = 75, mimicking 75 mm downstream from the inlet of coronary arterial tree), caFFR is the coronary angiography-derived fractional flow reserve,[20] $(P_a)_{hyp}$ and $(P_d)_{hyp} = (P_a)_{hyp} \cdot \text{caFFR}$ is the mean pressure (unit: mm Hg) at the aorta and the distal position at the maximal hyperemia respectively, $V_{diastole}$ is the mean flow velocity (unit: mm/s) at the distal position at diastole, and K is a constant (K = 2.1) obtained from a previous literature[21] and $V_{hyp} = K \cdot V_{diastole}$ refers to the mean flow velocity (unit: mm/s) at the distal position at the maximal hyperemia, as shown in Figure 1. Here, caIMR characterizes the microcirculatory resistance in unit volume of myocardium distal to the L position. The detailed theoretical derivation is described in Appendix A.

Figure 1



Schematic representative performance of caIMR.

Participants

Patients between 18 and 80 years of age, who presented with angina pectoris or chest discomfort with lumen diameter stenosis of all epicardial coronary arteries <50% by visual estimate based on coronary angiograms, were eligible for enrolment. Exclusion criteria included clinical presentation as acute myocardial infarction, pre-existing myocardial infarction, secondary heart valve disease, cardiomyopathies, severe cardiac insufficiency and LVEF ≤35%, renal insufficiency (eGFR <60 mL/min (1.73) or undergoing dialysis), life expectancy ≤24 months, allergy to iodine contrast agents, contraindications for administration of adenosine or ATP, and current or recent (<1 month) participation in another clinical trial. Angiographic exclusion criteria included severe myocardial bridges, ostial or proximal (≤3 mm from the aorta) lesions, and angiographic features pre-

cluding adequate contour detection by the FlashAngio IMR software (poor vessel opacification, severe branch overlap, distortion or poor angiographic image quality). In patients with suspected ischemia with non-obstructed coronary arteries (INOCA), experts consensus like the EAPCI document recommend the left anterior descending (LAD) artery as the pre-specified target vessel reflecting its subtended myocardial mass and coronary dominance.[6] The right coronary artery (RCA) or left circumflex (LCx) artery is also chosen if it provides blood to a relatively large area of myocardium by visual estimate from cardiologists.

caIMR measurement

Patients were randomized to receive caIMR or wire-based IMR first. Coronary angiography was performed via radial access in most patients. Similar to previous studies,[14,20] coronary angiography was carried out using the manual contrast injection and recorded at 15 frames per second. At least 2 angiographic projections, separated by $\geq 30^{o}$ to avoid vessel overlap, without table movement, were performed for 3-dimensional (3D) reconstruction of coronary arteries. Digital Imaging and Communications in Medicine (DICOM) angiography images were input to the FlashAngio IMR console, based on which 3D mesh reconstruction of coronary arteries was generated along the vessel path from the inlet to the most distal position automatically. The FlashPressure IMR pressure transducer (Rainmed Ltd., Suzhou, China) was connected to the guiding catheter to record the aortic pressure waveform over the entire procedure. Mean aortic pressure (MAP) was computed by averaging over the third to eighth cycles following angiography, based on which the maximal hyperemic mean aortic pressure, $(P_a)_{hyp}$, equals to MAP-MAP*0.2 when MAP $\geq$ 95 mm Hg and MAP-MAP*0.15 when MAP $<$ 95 mm Hg.[20]

The diastolic flow velocity ($V_{diastole}$) was determined automatically by the FlashAngio IMR software, similar to a previous study.[22] Briefly, systolic and diastolic periods are identified without the need of concomitant EKG acquisition based on the movement of the tip of the guiding catheter engaged in the coronary artery, with the shorter catheter tip movement time interval corresponding to the systolic period, and the longer time interval to the diastolic period. We compute the diastolic flow velocity by the thrombolysis in myocardial infarction (TIMI) Frame Count method, i.e., diastolic flow velocity = (contrast passing length)/(diastolic time interval), where contrast passing length is the distance that contrast moves in 3D reconstructed coronary arteries during the period of diastole. The maximal hyperemic flow velocity, V_{hyp}, is assumed equal to $2.1 \times V_{diastole}$ [21] (see the detail in Appendix A).

We have developed a specially-designed CFD model to carry out the steady-state laminar flow simulation across the stenotic blood vessel in 10 to 30 seconds,[20] which is described in Appendix B. The CFD method with the inlet velocity of V_{hyp} was used to solve Navier-Stokes and continuity equations in the FlashAngio software and compute the pressure drop ($(\Delta P)_{hyp}$) along meshed coronary arteries from the inlet to the distal position (75 mm downstream from the inlet of coronary arterial tree) and $(P_d)_{hyp} = (P_a)_{hyp} - (\Delta P)_{hyp}$ and caFFR$= \frac{(P_d)_{hyp}}{(P_a)_{hyp}}$. The caIMR was computed from equation. Onsite caIMR computation was performed by an independent technician who was blinded to the wire-based IMR measurement. Offline caIMR was performed by an independent core laboratory (Clinical Consultancy Research Center, Shanghai, China) blinded to both wire-based IMR measurement and onsite caIMR computation.

Wire-based IMR and CFR measurements

A Certus thermodilution-pressure wire was inserted to the distal position by interventional cardiologists, similar to a previous study.[14] Intracoronary nitrate (100 μg) was administered before IMR measurements. Thermodilution curves were obtained by at least 3 intracoronary injections of 3 to 4 mL of room-temperature saline at baseline to determine the mean transit time (T_{mn}'). Hyperemic blood flow was induced by intravenous administration of adenosine-5'-triphosphate (ATP) at $\geq$140 μg/kg/min. Thermodilution curves were obtained by at least 3 intracoronary injections of 3 to 4 mL of room-temperature saline during sustained hyperemia to determine the mean transit time (T_{mn}). Performance of wire-based IMR measurements was according to the standard procedure suggested by the RadiAnalyzer Xpress instrument (St. Jude Medical, St. Paul, MN). Wire-based coronary flow reserve (CFR, equals to Tmn'/ Tmn) was measured simultaneously. Examination of pressure drift was carried out through a pull-out of the pressure wire to the guiding catheter tip, where the ratio of (wire-based mean pressure)/MAP should be between 0.97 and 1.03. It is needed to repeat the process if pressure drift exceeded these limits.

Endpoints

The primary endpoint was the diagnostic accuracy (DA) of wire-free and CFD-derived caIMR, using wire-based IMR as the reference standard with a clinical significance cutoff value of 25 units. The target goal for diagnostic accuracy was 82% with a 2-sided significance level of 0.05, based on previously published reports of a retrospective caIMR study.[14] Secondary endpoints included the agreement, correlations, sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and receiver operated characteristics area under the curve (AUC) of caIMR compared to wire-based IMR.

Statistical analysis

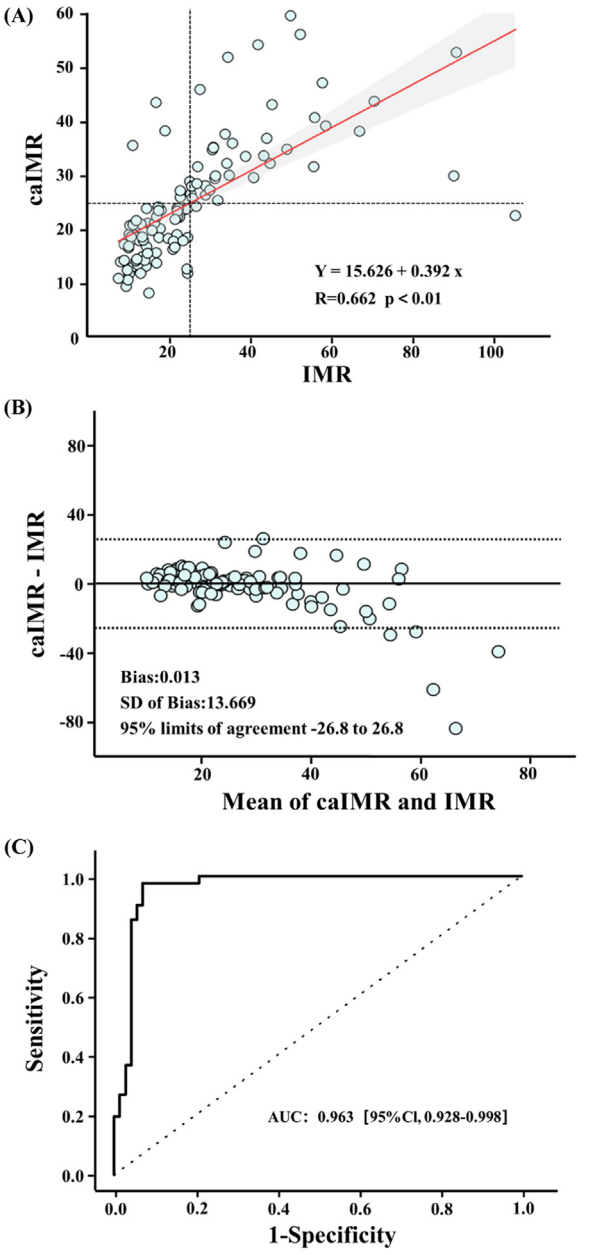
Based on a type I error (α) = 0.025 (2-sided), projected 10% data loss, and statistical power (1 – β) of 80%, a total of 116 patients were required for the study.[23] Categorical variables are presented as counts and percentages. Continuous patients and procedural characteristics are presented as mean and standard deviation (SD) and compared using the student's t-test or Mann-Whitney U test. Correlations are summarized by the linear regression model. Systematic differences are assessed by the Bland–Altman analysis. Two-sided 95% confidence intervals (CIs) were added using the Clopper-Pearson exact method where applicable. Statistical analysis was performed by the Proc Genmod with the repeated statement and the adjusted center effect. Receiver-operating curves of caIMR, were generated using a logistic regression model. An intention-to-treat (ITT) analysis was performed with a test significance level of 0.05 using the SAS version 9.4 (SAS Institute, Inc., Cary, NC) by The Peking University Clinical Research Institute, Beijing, China.

Results

Between October and December, 2021, 116 patients were enrolled in 3 centers. In 3 patients wire-based IMR measurements could not be obtained (1 case of vasospasm, 1 of vascular dissection and 1 of device failure). Paired caIMR and wire-based IMR as well as CFR were successfully obtained in 113 patients (1 targeted vessel was considered per patient). The baseline patient and vessel characteristics are presented inTable I. The LAD arterial system (47.8%) is the most commonly assessed vessel followed by the RCA (38.9%) and circumflex artery (13.3%), with the mild stenosis (23.8%). The onsite mean values of caIMR and wire-based IMR have the similar value of about 25.7 units with the SD of 10.7 and 18.1, respectively. The rates of patients with wire-based IMR and caIMR ≥25 units, that is, abnormal coronary microcirculatory resistances, are 36.3% and 38.9%, respectively. The rate of patients with CFR ≤2.5 and CFR ≤2.0 is 40.7% and 18.6%, respectively.

The diagnostic accuracy of onsite caIMR was 93.8%, using wire-derived IMR as the standard reference with a cutoff value of 25 units, exceeding the prespecified performance goal of 82%, meeting the primary endpoint of the study (Table II). Figure 2A shows the linear relationship between caIMR and wire-based IMR (caIMR = 0.392 · IMR + 15.6, R = 0.662, P< .05). The Bland-Altman analysis did not identify systematic differences between caIMR and IMR, with a mean difference of 0.013 (Figure 2B). Although there was a modest correlation coefficient between IMR and caIMR (R = 0.662), caIMR demonstrated the high diagnostic sensitivity, specificity, PPV, and NPV (95.1%, 93.1%, 88.6% and 97.1% respectively) against wire-based IMR (Table II), with a receiver-operating characteristic AUC of 0.963 (Figure 2C). Anal-

Figure 2



Correlation and agreement between wire-based IMR and caIMR. (A) A least-squares fit shows a relationship: caIMR = 0.392 · IMR + 15.6 (R = 0.662; P < .05) (Vessel Number: n = 113) and (B) Bland-Altman plots for pairwise comparisons (mean difference: 0.013; SD: 13.7; 95% limits of agreement -26.8 to 26.8) (Vessel Number: n = 113) and (C) Receiver-operating curve for wire-based IMR and caIMR (a cutoff of 25), where AUC (area under the curve) is 0.963 (95% limits of agreement: 0.928-0.998) (Vessel Number: n = 113).

Table I. Population Characteristics ($n = 113$)

Demographics	
Age (y) (mean ± SD)	62.9 ± 8.0
Male	64 (56.6 %)
Body mass index (kg/m^2) (mean ± SD)	25.2 ± 3.2
Medical history	
Hypertension	72 (66.1 %)
Hyperlipidemia	47 (43.1 %)
Diabetes mellitus	28 (25.7%)
Current smoking	37 (33.9 %)
Previous PCI	15 (13.3%)
Hemodynamic measures and blood results	
Systolic BP, mm Hg (mean ± SD)	134.2 ± 20.7
Diastolic BP, mm Hg (mean ± SD)	76.1 ± 11.9
Creatinine, µmol/L (mean ± SD)	74.4 ± 14.4
Hemoglobin, g/L (mean ± SD)	133.7 ± 13.4
Platelet count, 10^9/L (mean ± SD)	219.1 ± 69.3
LVEF, % (mean ± SD)	65.8 ± 5.5
Procedural and lesion characteristics	
Radial access (%)	112 (99.1 %)
Target vessel	
LAD	54 (47.8 %)
LCX	15 (13.3 %)
RCA	44 (38.9 %)
Percent stenosis, % (mean ± SD)	23.8 ± 17.1
Coronary artery fistula	1 (0.88 %)
Onsite caIMR (unit: mm Hg·sec)	113 (100 %)
Mean caIMR (mean ± SD)	25.7 ± 10.7
Positive rate	44 (38.9 %)
Wire-based IMR (unit: mm Hg·sec)	113 (100 %)
Mean IMR (mean ± SD)	25.7 ± 18.1
Positive rate	41 (36.3 %)
Wire-based CFR	113 (100 %)
Mean CFR (mean ± SD)	3.49 ± 1.58
Positive rate with CFR ≤ 2.5	46 (40.7 %)
Positive rate with CFR ≤ 2.0	21 (18.6 %)

Table II. Diagnostic performance of caIMR

Accuracy	93.8 (87.7-97.5)
Sensitivity	95.1 (83.5-99.4)
Specificity	93.1(84.5-97.7)
PPV	88.6 (75.4-96.2)
NPV	97.1 (89.9-99.7)
AUC 0.963 (0.928-0.999)	

Values are n% (95% CI).
AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

ysis of DA, Sn, Sp, PPV, NPV and AUC between caIMR and wire-based IMR in the offline core laboratory was consistent with the onsite analysis (Supplementary Table SI and Figure S1). Figure S2 shows representative cases with both caIMR and wire-based IMR measurements in patients with preserved and elevated microcirculatory resistances.

Discussion

Herein we demonstrate good diagnostic performance of wire-free and CFD-derived caIMR compared to invasive wire-based IMR. The present study is the first prospective, multicenter study for evaluation of wire-free IMR with respect to wire-based IMR. The main findings of the study are; (1) the overall diagnostic accuracy of 93.8% for computed caIMR exceeded the prespecified performance goal, thus the primary endpoint of the study was met; (2) the documented high sensitivity and specificity (95.1% and 93.1% respectively) of caIMR supports the potential applicability of this technology in the clinical arena.

Assessment of elevated microcirculatory resistance is recommended as part of the work-up of patients with myocardial ischemia, particularly in those with nonobstructive coronary artery disease.[6-8] Like CFR,[24] microcirculatory resistance has been proposed to identify abnormal hemodynamics in patients with chronic and acute coronary syndromes, as well as in other contexts, for example, cardiac transplant patients.[25-28] However, widespread implementation of IMR in clinical practice is hampered by the fact of requiring a specific intracoronary wire and by requiring at least 3 intracoronary injections of 3 to 4 mL of room-temperature saline during sustained hyperemia, which is time- and cost-consuming.

To circumvent the above-discussed obstacles in adoption of IMR measurements, several investigators have reported angiography-derived IMR methods based on quantitative flow ratio (QFR, Medis, Leiden, Netherlands).[29] De Maria et al.[30] proposed the IMR_{angio} index, intended mainly for assessment based on coronary angiograms obtained during adenosine-induced hyperemia, which was further evaluated in a slightly larger cohort of 145 patients, with 246 pressure-wire IMR measurements in 189 coronary vessels.[31] Mejia-Renteria et al.[32] validated an alternative approach using resting angiograms in patients with intermediate stenoses, showing a good agreement of angio IMR with invasive IMR. In our study we proposed caIMR,[14] a CFD-derived index that performs selective assessment of diastolic microvascular resistance. Since the whole-cycle microcirculatory resistance during hyperemia approximates the resting value over the wave-free period,[18,19] equivalent resistance measurements as those obtained with wire-based IMR during adenosine infusion can be demonstrated with caIMR from resting coronary angiograms. In the first retrospective clinical validation study in 56 patients, caIMR has shown a correlation with wire-based IMR with an accuracy of 84.2% and an AUC of 0.919 for predicting an invasive IMR ≥25 units in patients with angina pectoris and no obstructive coronary arteries,[14] which was further confirmed by a study performed in a slightly larger cohort of 138 patients and 187 vessels.[12] On the other hand, prognostic thresholds of the IMR for abnormal hemodynamics after PCI in acute ST elevation myocardial infarction (STEMI) have been reported as higher values because of different etiology.[27] Lee's group suggested that measurements of microcirculatory resistance with caIMR (a high cutoff

value of 40 units) have a good prognostic value after PCI in acute STEMI.[13,15]

In this study we focused on the applicability of caIMR to assess microcirculatory resistance in patients with suspected ischemia without obstructed coronary vessels. We used a cutoff value of 25 units for both CFD-computed caIMR and wire-based IMR. This is the IMR cutoff value currently recommended to identify abnormal microcirculatory conductance in patients with INOCA, according to a recently published ESC/EAPCI Expert Consensus Document on this topic.[6] The caIMR has a high onsite diagnostic accuracy of 93.8%, consistent with the offline analysis in the core laboratory. The high diagnostic accuracy and short computational time of less than 1 minute with total operation time less than 5 minutes may establish caIMR as a viable alternative to wire-based IMR to determine abnormal coronary microcirculatory conductance.

The caIMR holds potential advantages compared to invasive wire-based IMR: (1) the risk for manipulation of thermodilution-pressure-wire related complications is eliminated; (2) intravenous infusion of hyperemic drugs, which is mandatory for invasive IMR measurement, is not needed; (3) repeated injections of 3 to 4 mL of saline during hyperemia are omitted; (4) technical pitfalls related to wire-based physiological assessments, such as waveform distortion, ventricularization and signal drift, are eliminated[33]; (5) measurements in several vessels can be easily performed; (6) assessment of caIMR can be easily performed pre and post PCI to assess pre-existing or procedure-related abnormal coronary microcirculatory resistance; and (7) a combination of caFFR and caIMR could enhance physiological assessment of macro- and microvascular diseases in patients with IHDs.[20]

Wire-based IMR $\geq$25 units or CFR $<$2.0 has been recommended to demonstrate coronary microcirculatory dysfunctions according to the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.[4] CFR $<$2.5 was also assumed to identify coronary microcirculatory dysfunctions in a previous study.[34] Here, diagnostic accuracies of IMR were 69.9% and 67.3% and diagnostic accuracies of caIMR were 63.7% and 61.1% in reference to CFR with a cutoff value of 2.0 and 2.5, respectively. In a coronary arterial tree, CFR is defined as the ratio of the maximal hyperemic blood flow to the resting blood flow while IMR is the ratio of the inlet pressure to the maximal hyperemic blood flow. CFR characterizes coronary microvascular responses to hyperemic drugs and IMR features microvascular resistance at hyperemia. The 2 parameters show different physiological phenomena, for example, a patient with severe coronary arteriolar rarefaction has high IMR, but could have high CFR given strong coronary microvascular responses to adenosine, which might explain the diagnostic inconsistency of low CFR and high IMR (or high caIMR). A combination of CFR and caIMR (or IMR) could improve imaging based physiological assessment. Since the aim of the study is to evaluate diagnostic performance of caIMR using wire-based IMR as a reference, the following studies to investigate the different clinical outcomes in patients with abnormal CFR, IMR and caIMR are needed.

Finally, it has to be emphasized that assessment of INOCA also includes interrogation of the endothelium-dependent pathway, which is accomplished with intracoronary acetylcholine infusion. Our study has focus strictly in providing measurements of microcirculatory resistance, which explores the endothelium-independent pathway. As the acetylcholine tests do not require the use of an intracoronary wire, we anticipate that the combination of caIMR and acetylcholine infusion through the guiding catheter may contribute to a faster and more efficient assessment of INOCA avoiding intracoronary instrumentation.

Limitations

Our study has some limitations. First, caIMR is derived from angiography-derived diastolic flow velocity in the contrast-induced sub-hyperemia, which is different from wire-based IMR in the maximal hyperemia. This caused a moderate correlation coefficient of 0.662 despite very high values of DA, Sn, Sp, and AUC (all $>$93%). Although caIMR performs well at lower IMR values, the Bland-Altman plot shows higher differences between IMR and caIMR in 3 patients with IMR $>$90, which may be caused by suboptimal response to infusion of hyperemic drugs and needs further investigation. Second, most of patients in the study didn't receive functional noninvasive stress test for myocardial ischemia before coronary angiography. The study to evaluate the correlation of caIMR and radionuclide myocardial perfusion image is ongoing. Third, the study only demonstrated the diagnostic performance of caIMR in patients with suspected ischemia or chronic coronary syndromes. The diagnostic accuracy and cutoff value of caIMR in the other conditions, including acute coronary syndromes, cardiomyopathy and heart transplantation, should be evaluated prospectively. Fourth, the study evaluated IMR and caIMR in only 1 vessel per patient. Future studies are needed to evaluate the diagnostic performance of caIMR in multiple vessels. Finally, the present study is at an early stage of caIMR development. The studies to investigate the clinical outcomes in patients with microcirculatory dysfunctions diagnosed on the basis of caIMR are needed.

Conclusions

The prospective, multicenter, randomized study has shown the high accuracy, sensitivity and specificity of wire-free caIMR using wire-based IMR as the reference standard. The caIMR can potentially increase the clini-

cal use of physiological assessment of abnormal coronary microcirculatory resistance.

Funding

This work was supported by Shanghai Clinical Research Center for Interventional Medicine (No. 19MC1910300), Shanghai Municipal Key Clinical Specialty (No. shslczdzk06201), National Natural Science Foundation (No. 82170458) and Rainmed Ltd., Suzhou, China.

Conflicts of interest

Yunlong Huo holds stocks of Rainmed Ltd., Suzhou, China and there is nothing to disclose for others.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.03.016.

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