



# Evaluation of the Advantages of Myocardial Blood Flow Index in the Diagnosis of Chronic Obstructive Coronary Artery Disease Versus Coronary Computed Tomography Angiography: A Feasibility Study

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## Abstract

**Background:** There is a hidden relationship between the degree of coronary artery stenosis and downstream myocardial remodeling. The mutual influence in myocardial ischemia and myocardial remodeling provides an index for quantifying the myocardial blood flow based on the principles of physics.

**Objectives:** This study aimed to evaluate the advantages of myocardial blood flow index (MBFI) in the diagnosis of chronic obstructive coronary artery disease (CAD).

**Patients and Methods:** The data of 68 patients (39 males; mean age:  $57.0 \pm 10.20$  years) with suspected CAD were analyzed retrospectively, including the imaging findings of coronary computed tomography angiography (CCTA) and invasive coronary angiography (ICA) within one week. The MBFI was also calculated for the patients. After determining the optimal cut-off value based on ICA (stenosis  $\geq 70\%$ ) as the gold standard test, the diagnostic performance of MBFI and CCTA was compared. The diagnostic accuracy was examined by the receiver operating characteristic (ROC) curve. For statistical analysis, chi-square test was performed to analyze influence data, and a P-value less than 0.05 was considered statistically significant.

**Results:** In 68 cases evaluated in this study, the average scan dose of CCTA was  $3.02 \pm 1.15$  millisievert (mSv). There were 28 cases with stenosis  $\geq 70\%$ . The optimal cutoff value of MBFI and CCTA was 0.111 and 70%, respectively. Also, the area under the curve (AUC) for MBFI and CCTA was 0.857 and 0.621 ( $Z = 2.091$ ,  $P = 0.0365$ ), respectively. The sensitivity, specificity, positive predictive value, and negative predictive value were 92.31%, 92.86%, 88.89%, and 95.12% for MBFI and 61.54%, 78.57%, 64.00%, and 76.74% for CCTA, respectively. The diagnostic accuracy was also estimated at 92.65% for MBFI and 72.06% for CCTA ( $\chi^2 = 9.844$ ,  $P = 0.0017$ ).

**Conclusion:** In this study, MBFI performed better than CCTA in identifying lesions with stenosis  $\geq 70\%$ . A lower MBFI indicated the need for an upcoming active intervention, while a higher MBFI suggested avoiding unnecessary invasive testing.

**Keywords:** Coronary Artery Disease, Invasive Coronary Angiography, Myocardial Blood Flow Index, Functional Assessment, Diagnostic Test

## 1. Background

Recently, there has been a renewed interest in the functional evaluation of coronary lesions. Multiple studies have described the value of functional indicators in the accurate diagnosis of coronary artery disease (CAD). Some research has been conducted on the fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) (1), myocardial microcirculation resistance index (2), and myocardial blood flow (3). The results of these studies suggested a hidden relationship between the degree of coro-

nary artery stenosis and downstream myocardial remodeling (4, 5). In CAD, myocardial ischemia is the primary indication for PCI and also a prominent factor in myocardial remodeling (6, 7). On the other hand, myocardial remodeling aggravates myocardial ischemia (8). Therefore, there is a mutual increase in myocardial ischemia and myocardial remodeling, which may aid in quantifying the myocardial blood flow (9).

## 2. Objectives

The present study aimed to evaluate the advantages of myocardial blood flow index (MBFI) in the diagnosis of chronic obstructive CAD compared to coronary computed tomography angiography (CCTA).

## 3. Patients and Methods

### 3.1. Clinical Protocols

#### 3.1.1. Consecutive Collection of Medical Records

The clinical medical follow-up data of 920 patients suspected of CAD were collected continuously, including the imaging data of CCTA and invasive coronary angiography (ICA) from February 2018 to September 2018. Finally, 68 cases were selected for this study. This research was approved by the ethics committee (No. 2022-B009) and implemented according to the tenets of the Declaration of Helsinki ([www.wma.net/e/policy/](http://www.wma.net/e/policy/)). All patients signed a written informed consent form. The exclusion criteria are listed in [Figure 1](#).

### 3.2. Coronary Computed Tomography Angiography Protocol

#### 3.2.1. Scanning Parameters

Using CCTA (Dual-Source CT Somatom Definition, Siemens, Germany) with prospective electrocardiogram (ECG) triggering (Adaptive Sequential, Siemens Healthcare, Germany), the scanning parameters were as follows using a CareDose 4D automatic exposure control system:  $2 \times 64 \times 0.6$  mm collimation with a Z-flying focal spot; gantry rotation time, 330 ms; pitch, 0.2 - 0.43; and voltage/tube product, 100 - 120 kV. The tube current was set automatically according to the weight of each patient.

Image acquisition was triggered at 35 - 75% of R-R interval. The Hounsfield unit (HU) of the descending aorta was dynamically detected 10 seconds after the contrast agent injection with the tracer technique. If the threshold was 120 HU, the triggering started four seconds later. The total dosage was 50 - 70 mL (contrast agent: 370 mgI/mL of iopromide, Ultravist, Bayer, Germany) followed by 30 mL of saline. The injection rate (3.8 - 4.2 mL/s) was adjusted according to the patient's heart rate, body mass index (BMI), and cardiac function. Reconstruction was also performed with a medium smooth convolution kernel (B26f) at a slice thickness of 0.75 mm in 0.3-mm increments.

#### 3.2.2. Computed Tomography Image Reconstruction

An offline commercial Siemens Syngo platform (Siemens Medical Solutions, Erlangen, Germany) was used for computed tomography (CT) image reconstruction. The severest lesion was selected for analysis using

the semi-automatic software. It was calculated according to the minimal lumen diameter and the corresponding reference diameter. The stenosis degree was categorized as: Normal (0%), mild (1 - 49%), moderate (50 - 69%), severe (70 - 99%) and total occlusion.

#### 3.2.3. Image Quality Assessment

The image quality was evaluated by two prominent experts with 10 years of experience in CCTA, who reached consensus through consultation. The fine images were selected for this study ([10](#)).

### 3.3. Myocardial Blood Flow Index

#### 3.3.1. Myocardial Blood Flow Model

As current is equal to the ratio of voltage to resistance, myocardial blood flow is equal to the ratio of myocardial perfusion pressure to myocardial resistance. Based on the lumped parameter network (LPN) ([11](#)), as a parallel characteristic impedance model ([12](#)), the myocardial blood flow is primarily equal to the ratio of myocardial perfusion pressure to the myocardial mass ([13](#)). Blood circulation in the myocardium was completed within five cardiac cycles ([14](#)); in other words, after five cardiac cycles, the blood flow volume can distribute throughout the myocardium. Additionally, the right atrial pressure is about 0 mmHg at rest ([15](#)); consequently, the patient's diastolic blood pressure (DP) can be regarded as the myocardial perfusion pressure. Therefore, the ratio of DP multiplied by five cardiac cycles to the mass represents the myocardial blood flow. As the BMI ([16](#)), sex ([17](#)), and age ([18](#)) are all associated with the myocardial blood flow, the myocardium blood flow model ([Figure 2](#)) should integrate these factors, which differs from the hyperemic myocardial blood flow index ([19](#)).

#### 3.3.2. Calculation of Myocardial Blood Flow Index

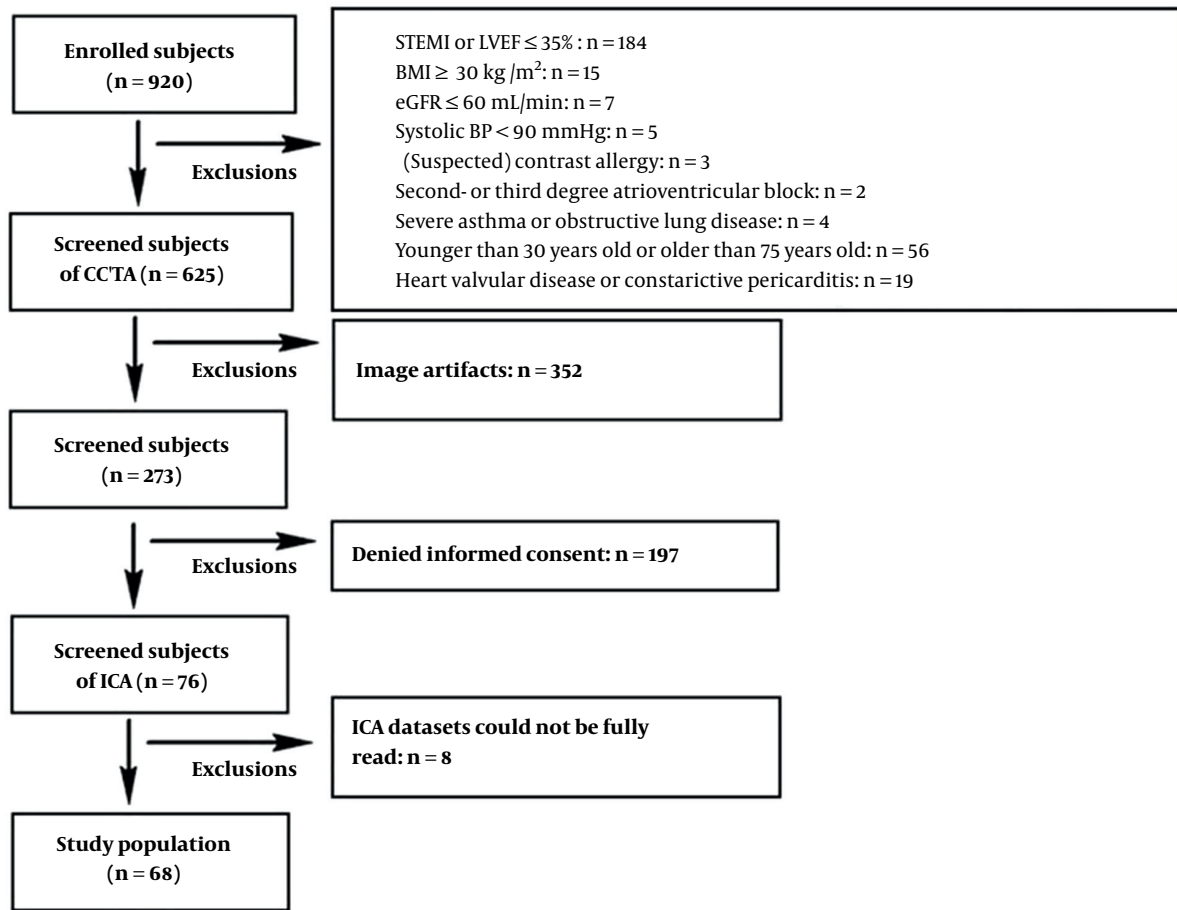
The MBFI was calculated and adjusted according to the literature ([9](#), [12](#), [14](#), [20](#)). The MBFI formula is as follows:

$$MBFI = \frac{5 \times 60}{HR} \times \frac{DP}{M \times BMI} - 0.015 \times n \quad (1)$$

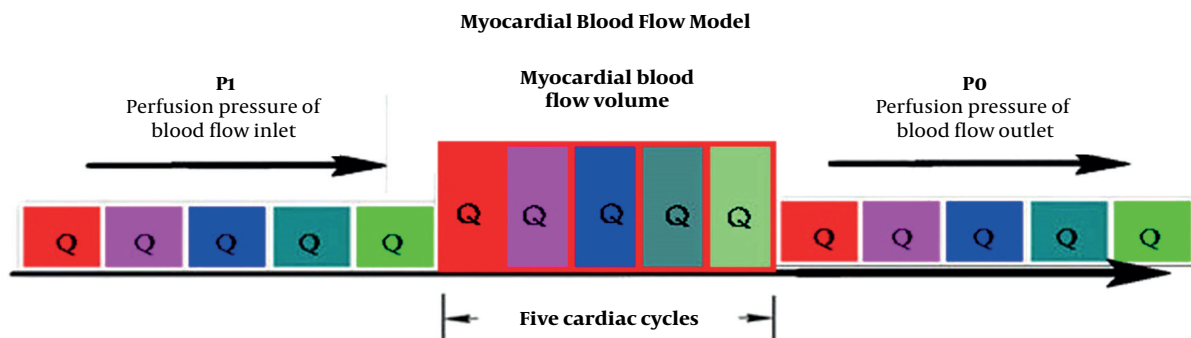
Where n represents the age interval, M represent myocardial mass and HR represent heart rates.

#### 3.4. Invasive Coronary Angiography Protocol

Basic ICA was performed within one week after the CCTA protocol. The coronary arteries were divided into 15 segments according to the standards of the American Heart Association. The results were reported by two experts with 20 years of experience in cardiac intervention, who was unaware of the results of CCTA. They reached consensus through consultation. The stenosis degree was categorized as normal (no stenosis), mild (< 50% stenosis),



**Figure 1.** The flowchart of patient enrollment; STEMI, ST segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; BMI, body mass index; eGFR, estimated glomerular filtration rate; BP, blood pressure; CCTA, coronary computed tomography angiography; and ICA, invasive coronary angiography.



**Figure 2.** The myocardial blood flow model

moderate (50 - 69% stenosis), severe ( $\geq 70\%$  stenosis), and total occlusion. The stenosis degree was categorized as: normal (0%), mild (1 - 49%), moderate (50 - 69%), severe (70 - 99%) and total occlusion.

### 3.5. Diagnostic Analysis

By using ICA as the gold standard ( $\geq 70\%$  stenosis), the diagnostic performance of MBFI and CCTA was investigated. If the value of MBFI was less than or equal to the optimal cutoff value, the more obvious lesion was considered as severe. Similarly, if the result of CCTA was more than or equal to 70% (diameter narrowing), the lesion was considered severe.

### 3.6. Statistical Analysis

Continuous variables are expressed as mean  $\pm$  standard deviation (SD), while categorical variables are presented as frequency or percentage. The diagnostic power of MBFI and CCTA was evaluated using the receiver operating characteristic (ROC) curve. The area under the curve (AUC) of MBFI was compared with that of CCTA by DeLong's test. Chi-square test was also used for enumeration data, and  $P < 0.05$  was considered statistically significant.

## 4. Results

The baseline data of the enrolled patients are summarized in Table 1. In 68 cases, the average scan dose of CCTA was  $3.02 \pm 1.15$  millisievert (mSv). There were 28 cases with  $\geq 70\%$  stenosis. The optimal cutoff values for MBFI and CCTA were 0.111 and 70%, respectively. The AUC was 0.857 for MBFI and 0.621 for CCTA, showing a significant difference ( $Z = 2.091$ ,  $P = 0.0365$ ) (Figure 3). The sensitivity, specificity, positive predictive value, and negative predictive value were 92.31%, 92.86%, 88.89%, and 95.12% for MBFI versus 61.54%, 78.57%, 64.00%, and 76.74% for CCTA, respectively. The diagnostic accuracy was also estimated at 92.65% for MBFI and 72.06% for CCTA ( $\chi^2 = 9.844$ ,  $P = 0.0017$ ) (Table 2 and Figures 4 and 5).

## 5. Discussion

Due to its high temporal and spatial resolution, CCTA can provide the anatomical information of lesions, including the features, extent, and severity of stenosis. This method enjoys a reputation as an accurate noninvasive first-line method in the guidelines to evaluate patients with a low-to-intermediate risk of CAD due to its high sensitivity, specificity, and negative predictive value (21). However, its diagnostic accuracy may reduce because of respiratory artifacts and calcified plaques; besides, it cannot

**Table 1.** The Baseline Characteristics of the Patients (n = 68)<sup>a</sup>

Characteristics	Total (n = 68)
Gender	
Male	39
Female	29
Age (y)	57 $\pm$ 10.2
History of risk factors	
Hypertension <sup>b</sup>	21
Diabetes mellitus <sup>c</sup>	24
Dyslipidemia <sup>d</sup>	38
Smoking (n)	17
Family history of CAD	5
Average heart rate (time/min)	73 $\pm$ 11.7
Average diastolic blood pressure (mmHg)	83 $\pm$ 11.9
Average serum creatinine ( $\mu\text{mol/L}$ )	82
Average body mass index ( $\text{kg/m}^2$ )	23 $\pm$ 3.5
Results of ICA	
One-vessel stenosis	33
Two-vessel stenosis	21
Multi-vessel stenosis	14
A left main lesion with three-vessel stenosis <sup>e</sup>	1
Average radiation dose (mSv)	3.02 $\pm$ 1.15

Abbreviations: CAD, coronary artery disease; ICA, invasive coronary angiography; mSv, millisievert.

<sup>a</sup> Values are presented as mean  $\pm$  SD or frequency (percentage).

<sup>b</sup> Blood pressure  $\geq 140/90$  mmHg or treatment for hypertension.

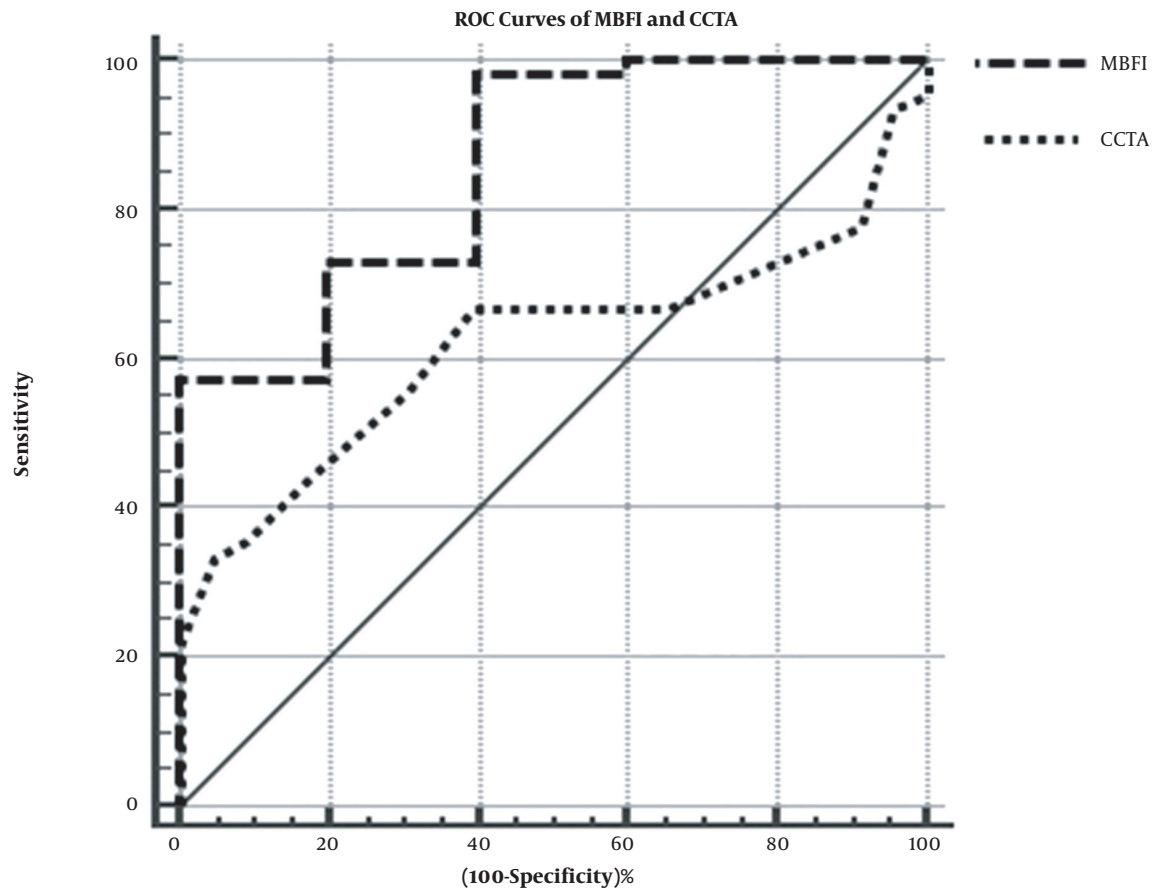
<sup>c</sup> Fasting blood glucose is above 7.0 mmol/L, or the glucose tolerance test is above 11.1 mmol/L two hours after a meal.

<sup>d</sup> Total cholesterol  $> 180$  mg/dL or treatment for hypercholesterolaemia.

<sup>e</sup> There were only 2 patients with left main coronary artery disease combined with two-vessel stenosis.

show whether coronary artery lesions have any hemodynamic significance (22). Nevertheless, it has the potential to screen patients with ischemic heart disease (IHD) (23).

Noninvasive methods, such as stress echocardiography, cardiovascular magnetic resonance, CCTA combined with myocardial perfusion imaging, and FFR derived from CCTA, can play an important role in evaluating IHD (24, 25). Radionuclide myocardial perfusion, echocardiography, and cardiac magnetic resonance imaging are accurate methods for evaluating myocardial ischemia and are also suitable for the follow-up of IHD cases. Nevertheless, it is difficult to diagnose IHD using these techniques, as they cannot clearly show the coronary arteries. Computed tomography-derived FFR (CT-FFR) has been employed to evaluate functional lesions, resulting in improved prognosis (19), although this method is limited by massive calcifications and image quality (25).



**Figure 3.** The receiver operating characteristic curves for the myocardial blood flow index (MBFI) and computed coronary tomography angiography (CCTA)

**Table 2.** The Receiver Operating Characteristic Curve Analysis of Myocardial Blood Flow Index and Coronary Computed Tomography Angiography

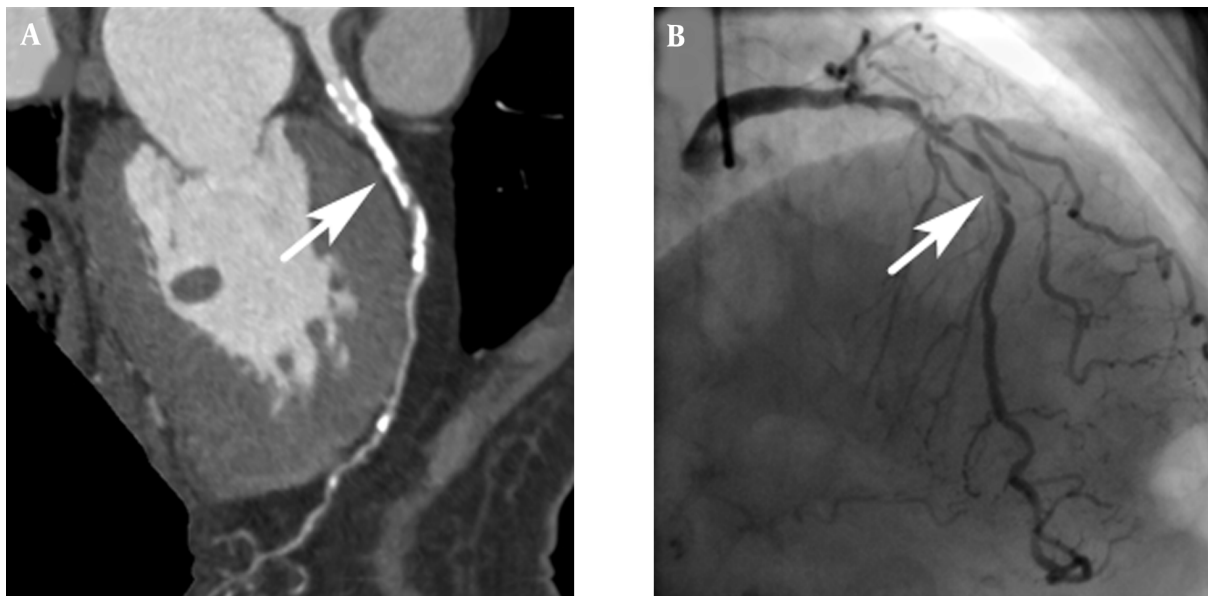
Method	COV	Sensibility (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	DA	P Value
MBFI	0.111	92.31% (0.734 - 0.987)	92.86% (0.794 - 0.981)	88.89% (0.697 - 0.971)	95.12% (0.822 - 0.992)	0.857 (0.751 - 0.930)	92.65%	0.0001
CCTA	70%	61.54% (0.407 - 0.791)	78.57% (0.628 - 0.892)	64.00% (0.426 - 0.813)	76.74% (0.610 - 0.877)	0.621 (0.495 - 0.736)	72.06%	0.0710

Abbreviations: COV, cutoff value; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; DA, diagnostic accuracy; CI, confidence interval; MBFI, myocardial blood flow index; CCTA, coronary computed tomography angiography.

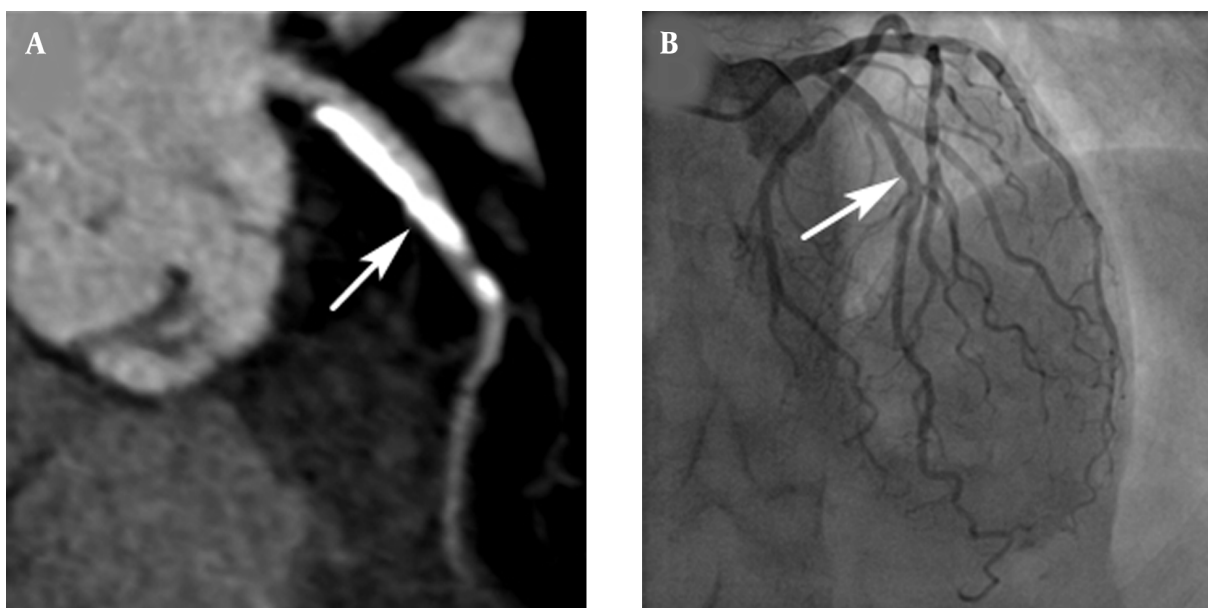
In the present study, MBFI demonstrated a larger AUC than CCTA in the diagnosis of chronic obstructive CAD, with a significant difference ( $Z = 2.091$ ,  $P < 0.05$ ). By considering ICA stenosis  $\geq 70\%$  as the gold standard for the diagnosis of severe lesions, the sensitivity, specificity, positive predictive value, and negative predictive value of MBFI were estimated at 92.31%, 92.86%, 88.89%, and 95.12%, respectively, which exceeded those of CCTA (61.54%, 78.57%, 64.00%, and 76.74%, respectively). Besides, the diagnostic accuracy of MBFI was significantly higher than that of CCTA ( $\chi^2 = 9.844$ ,  $P < 0.01$ ). Similar to other functional parameters

(26), this model, which was composed of cardiac physiological parameters, yielded better diagnostic results compared to the conventional diagnostic method of CCTA and made the diagnosis more accurate.

Although previous studies, using stenosis  $\geq 50\%$  as the gold standard, have reported that CCTA has high sensitivity and specificity in the diagnosis of CAD (27, 28), there is little information in the literature to confirm the ability of CCTA in diagnosing CAD, with stenosis  $\geq 70\%$  as the gold standard. If stenosis was  $\geq 70\%$ , it commonly suggested the possibility of ischemic myocardium. To confirm this possi-



**Figure 4.** A 68-year-old male patient with unstable angina. The imaging findings of the left anterior descending (LAD) artery. A, The computed coronary tomography angiography (CCTA) image shows suspected stenosis in the LAD (arrow). The myocardial blood flow index (MBFI) is 0.082, which indicates a suspected lesion with severe stenosis; B, The invasive coronary angiography (ICA) image shows the severe lesion with 95% stenosis (arrow).



**Figure 5.** The imaging findings of the left anterior descending (LAD) artery in a 71-year-old male patient with unstable angina. A, Computed coronary tomography angiography (CCTA) image shows a suspected severe stenosis (arrow) in the LAD (arrow); B, The invasive coronary angiography images show a gentle lesion with 10% stenosis. Myocardial blood flow index is 0.128, which suggests a lesion with no severe stenosis.

bility, CCTA should be preferably combined with other indices (19, 29). Accordingly, the use of functional parameters is becoming more common to improve diagnostic accuracy, and MBFI may have potential applications in the diagnosis or screening of CAD.

The current study had some limitations. This was a retrospective study, while a prospective study with a larger sample size is suggested to demonstrate the MBFI advantages. Besides, further experimental information is needed to determine whether diabetes plays a role in the model.

In conclusion, the diagnostic ability of MBFI was superior to that of CCTA in identifying lesions with stenosis  $\geq$  70%. A lower MBFI indicated the need for an upcoming active intervention, while a higher MBFI suggested avoiding unnecessary invasive testing.

## Footnotes

**Authors' Contributions:** Study concept and design: Q. X.; analysis and interpretation of data: Q. X. and G. W.; drafting of the manuscript: X. F. and D. Z.; critical revision of the manuscript for important intellectual content: Q. X., X. F., and G.W.; statistical analysis: Q. X. and S. G.

**Clinical Trial Registration Code:** The clinical trial code of this study is chict180018376 (link: [www.chict180018376.org.cn/historyversionpub.aspx?regno=ChiCTR1800018376](http://www.chict180018376.org.cn/historyversionpub.aspx?regno=ChiCTR1800018376)).

**Conflict of Interests:** The authors declare that there is no conflict of interests regarding the publication of this paper.

**Data Reproducibility:** The dataset presented in this study is available on request from the corresponding author during submission or after publication.

**Ethical Approval:** This study was approved under the ethical approval code, 2022-B009 (link: [wahh.com.cn/Sites/Uploaded/File/2022/04/016378440106395344618430067.pdf](http://wahh.com.cn/Sites/Uploaded/File/2022/04/016378440106395344618430067.pdf)).

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**Informed Consent:** All patients signed a written consent form.

## References

- De Backer O, Biasco L, Lonborg J, Pedersen F, Holmvang L, Kelbaek H, et al. Long-term outcome of FFR-guided PCI for stable coronary artery disease in daily clinical practice: a propensity score-matched landmark analysis. *EuroIntervention*. 2016;**11**(11):e1257-66. [PubMed ID: 26865443]. <https://doi.org/10.4244/EIJV11I11A247>.
- Jin X, Yoon MH, Seo KW, Tahk SJ, Lim HS, Yang HM, et al. Usefulness of Hyperemic Microvascular Resistance Index as a Predictor of Clinical Outcomes in Patients with ST-Segment Elevation Myocardial Infarction. *Korean Circ J*. 2015;**45**(3):194-201. [PubMed ID: 26023307]. [PubMed Central ID: PMC4446813]. <https://doi.org/10.4070/kcj.2015.45.3.194>.
- Pelletier-Galarneau M, Ferro P, Patterson S, Ruddy TD, Beanlands RS, deKemp RA. Comparison of myocardial blood flow and flow reserve with dobutamine and dipyridamole stress using rubidium-82 positron emission tomography. *J Nucl Cardiol*. 2021;**28**(1):34-45. [PubMed ID: 32449001]. <https://doi.org/10.1007/s12350-020-02186-1>.
- Murai T, Lee T, Yonetsu T, Iwai T, Takagi T, Hishikari K, et al. Variability of microcirculatory resistance index and its relationship with fractional flow reserve in patients with intermediate coronary artery lesions. *Circ J*. 2013;**77**(7):1769-76. [PubMed ID: 23535218]. <https://doi.org/10.1253/circj.cj-12-1442>.
- Kitabata H, Kubo T, Ishibashi K, Komukai K, Tanimoto T, Ino Y, et al. Prognostic value of microvascular resistance index immediately after primary percutaneous coronary intervention on left ventricular remodeling in patients with reperfused anterior acute ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2013;**6**(10):1046-54. [PubMed ID: 24156965]. <https://doi.org/10.1016/j.jcin.2013.05.014>.
- Liu J, Meng Q, Liang X, Zhuang R, Yuan D, Ge X, et al. A novel small molecule compound VCP979 improves ventricular remodeling in murine models of myocardial ischemia/reperfusion injury. *Int J Mol Med*. 2020;**45**(2):353-64. [PubMed ID: 31789413]. [PubMed Central ID: PMC6984775]. <https://doi.org/10.3892/ijmm.2019.4413>.
- Xue X, Luo L. lncRNA HIF1A-AS1 contributes to ventricular remodeling after myocardial ischemia/reperfusion injury by adsorption of microRNA-204 to regulating SOCS2 expression. *Cell Cycle*. 2019;**18**(19):2465-80. [PubMed ID: 31354024]. [PubMed Central ID: PMC6739046]. <https://doi.org/10.1080/15384101.2019.1648960>.
- Jiang M, Xie X, Cao F, Wang Y. Mitochondrial Metabolism in Myocardial Remodeling and Mechanical Unloading: Implications for Ischemic Heart Disease. *Front Cardiovasc Med*. 2021;**8**:789267. [PubMed ID: 34957264]. [PubMed Central ID: PMC8695728]. <https://doi.org/10.3389/fcvm.2021.789267>.
- Xiong QF, Fu XR, Xu J, Wu GY. Analyzing the Application of Myocardial Blood Flow Index in the Diagnosis of In-Stent Stenosis. *Iran J Radiol*. 2021;**18**(1). <https://doi.org/10.5812/iranjradiol.107251>.
- Liu Y, Li J, Zhao H, Jia Y, Ren J, Xu J, et al. Image quality and radiation dose of dual-source CT cardiac angiography using prospective ECG-triggering technique in pediatric patients with congenital heart disease. *J Cardiothorac Surg*. 2016;**11**:47. [PubMed ID: 27059600]. [PubMed Central ID: PMC4826524]. <https://doi.org/10.1186/s13019-016-0460-9>.
- Sinclair MD, Lee J, Cookson AN, Rivolo S, Hyde ER, Smith NP. Measurement and modeling of coronary blood flow. *Wiley Interdiscip Rev Syst Biol Med*. 2015;**7**(6):335-56. [PubMed ID: 26123867]. <https://doi.org/10.1002/wsbm.1309>.
- Westerhof N, Bosman F, De Vries CJ, Noordergraaf A. Analog studies of the human systemic arterial tree. *J Biomech*. 1969;**2**(2):121-43. [PubMed ID: 16335097]. [https://doi.org/10.1016/0021-9290\(69\)90024-4](https://doi.org/10.1016/0021-9290(69)90024-4).
- Hamada M, Kuwahara T, Shigematsu Y, Kodama K, Hara Y, Hashida H, et al. Relation between coronary blood flow and left ventricular mass in hypertension: noninvasive quantification of coronary blood flow by thallium-201 myocardial scintigraphy. *Hypertens Res*. 1998;**21**(4):227-34. [PubMed ID: 9877515]. <https://doi.org/10.1291/hypr.21.227>.
- Lindner JR, Villanueva FS, Dent JM, Wei K, Sklenar J, Kaul S. Assessment of resting perfusion with myocardial contrast echocardiography: theoretical and practical considerations. *Am Heart J*. 2000;**139**(2 Pt 1):231-40. [PubMed ID: 10650295].
- Berlin DA, Bakker J. Understanding venous return. *Intensive Care Med*. 2014;**40**(10):1564-6. [PubMed ID: 24966066]. <https://doi.org/10.1007/s00134-014-3379-4>.

16. Dore H, de Araujo Goncalves P, Carvalho MS, Sousa PJ, Ferreira A, Cardim N, et al. Body mass index as a predictor of the presence but not the severity of coronary artery disease evaluated by cardiac computed tomography. *Eur J Prev Cardiol*. 2014;**21**(11):1387–93. [PubMed ID: 23774273]. <https://doi.org/10.1177/2047487313494291>.
17. Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. *Atherosclerosis*. 2015;**239**(1):260–7. [PubMed ID: 25634157]. <https://doi.org/10.1016/j.atherosclerosis.2015.01.017>.
18. Gurel NZ, Carek AM, Inan OT, Levantsevych O, Abdelhadi N, Hammadah M, et al. Comparison of autonomic stress reactivity in young healthy versus aging subjects with heart disease. *PLoS One*. 2019;**14**(5). e0216278. [PubMed ID: 31067240]. [PubMed Central ID: PMC6505888]. <https://doi.org/10.1371/journal.pone.0216278>.
19. Rossi A, Dharampal A, Wragg A, Davies LC, van Geuns RJ, Anagnostopoulos C, et al. Diagnostic performance of hyperaemic myocardial blood flow index obtained by dynamic computed tomography: does it predict functionally significant coronary lesions? *Eur Heart J Cardiovasc Imaging*. 2014;**15**(1):85–94. [PubMed ID: 23935153]. <https://doi.org/10.1093/ehjci/et133>.
20. Artru AA, Katz RA, Colley PS. Autoregulation of cerebral blood flow during normocapnia and hypocapnia in dogs. *Anesthesiology*. 1989;**70**(2):288–92. [PubMed ID: 2492410]. <https://doi.org/10.1097/00000542-198902000-00018>.
21. Mansour HH, Alajerami YS, Najim AA. Coronary computed tomography angiography versus invasive coronary angiography: medical staff perceptions and diagnostic interest in Gaza-Palestine. *Ir J Med Sci*. 2021;**190**(2):567–75. [PubMed ID: 32978639]. <https://doi.org/10.1007/s11845-020-02376-3>.
22. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med*. 2018;**379**(3):250–9. [PubMed ID: 29785878]. <https://doi.org/10.1056/NEJMoa1803538>.
23. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;**130**(19):1749–67. [PubMed ID: 25070666]. <https://doi.org/10.1161/CIR.0000000000000095>.
24. Balfour PC, Gonzalez JA, Kramer CM. Non-invasive assessment of low- and intermediate-risk patients with chest pain. *Trends Cardiovasc Med*. 2017;**27**(3):182–9. [PubMed ID: 27717538]. [PubMed Central ID: PMC5346457]. <https://doi.org/10.1016/j.tcm.2016.08.006>.
25. Chen J, Wetzel LH, Pope KL, Meek LJ, Rosamond T, Walker CM. FFRCT: Current Status. *AJR Am J Roentgenol*. 2021;**216**(3):640–8. [PubMed ID: 33377794]. <https://doi.org/10.2214/AJR.20.23332>.
26. von Knebel Doeberitz PL, De Cecco CN, Schoepf UJ, Albrecht MH, van Assen M, De Santis D, et al. Impact of Coronary Computerized Tomography Angiography-Derived Plaque Quantification and Machine-Learning Computerized Tomography Fractional Flow Reserve on Adverse Cardiac Outcome. *Am J Cardiol*. 2019;**124**(9):1340–8. [PubMed ID: 31481177]. <https://doi.org/10.1016/j.amjcard.2019.07.061>.
27. Maffei E, Palumbo A, Martini C, Notarangelo F, Sacco C, Ugo F, et al. Predictive value of computed tomography coronary angiography for the evaluation of acute chest pain: single center preliminary experience. *Acta Biomed*. 2010;**81**(3):157–64. [PubMed ID: 22530452].
28. Xie D, Na J, Zhang M, Dong S, Xiao X. CT angiography of the lower extremity and coronary arteries using 256-section CT: a preliminary study. *Clin Radiol*. 2015;**70**(11):1281–8. [PubMed ID: 26275584]. <https://doi.org/10.1016/j.crad.2015.07.003>.
29. Anagnostopoulos CD, Siogkas PK, Liga R, Benetos G, Maaniitty T, Sakellarios AI, et al. Characterization of functionally significant coronary artery disease by a coronary computed tomography angiography-based index: a comparison with positron emission tomography. *Eur Heart J Cardiovasc Imaging*. 2019;**20**(8):897–905. [PubMed ID: 30629151]. <https://doi.org/10.1093/ehjci/jey199>.