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Assessment of Cases with Intermediate Coronary Artery Stenosis Using Instantaneous Wave Free Ratio versus Myocardial Perfusion Imaging by Single Photon Emission Tomography

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Abstract:

Background: Coronary artery disease (CAD) continues to be a major global health burden. Accurately evaluating coronary severity is essential for deciding whether revascularization is necessary. Intermediate coronary artery stenosis presents a diagnostic challenge as anatomical severity does not always correlate with functional significance. This study aimed to use myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) with the instantaneous wave-free ratio (iFR) for assessing the functional relevance of intermediate coronary lesions. **Methods:** This was a prospective observational study including 50 cases diagnosed with intermediate coronary disease. It was conducted in the National Heart Institute in Cairo, and Benha University Hospitals, Egypt, during the period from January 2022 to Mars 2024. **Results:** MPI results in 22 of the participants, or 44%, have positive myocardial perfusion defects. The majority, comprising 28 participants or 56%, showed negative MPI results. Also, the IFR has a mean value of 0.90 with a standard deviation of 0.03 with values spanning from 0.84 to 0.96. Regarding the agreement between MPI and IFR tests, a kappa value of 0.878, with a p-value of less than 0.001, indicates a very strong agreement between these two diagnostic methods. Specifically, 20 cases (40%) were positively identified by both MPI and IFR, while 27 cases (54%) were negative in both tests, underscoring a high level of consistency. **Conclusion:** The SPECT, with its high level of diagnostic agreement with iFR, is considered a reliable, non-invasive alternative that avoids the complexities and risks associated with invasive intervention and radiation exposure.

Keywords: Instantaneous wave-free ratio, Intermediate coronary artery stenosis, Single-photon emission computed tomography, Myocardial perfusion imaging.

Introduction

Coronary artery disease (CAD) involves a spectrum of clinical manifestations whose classification evolves with advancements in understanding pathophysiology, symptomatology (onset and duration), biochemical changes, and effects on left ventricular function [1].

A major clinical challenge in CAD management is the precise evaluation of intermediate coronary artery lesions, which frequently complicate decision-making due to their ambiguous physiological significance. These lesions, commonly characterized by 40–70% luminal narrowing on coronary angiography, demand thorough assessment to inform appropriate therapeutic strategies [2].

An intermediate lesion, as visualized on angiography, is defined by a diameter stenosis ranging from ≥40% to ≤70%. Despite advancements in interventional cardiology, particularly with the use of drug-eluting stents (DES), which offer high procedural success, minimal complications, and durable outcomes, the temptation persists to stent all ambiguous lesions. Nevertheless, discerning which lesions are functionally significant remains a critical concern [3].

Myocardial perfusion imaging (MPI) using Single Photon Emission Computed Tomography (SPECT) has long served as a dependable non-invasive modality for detecting myocardial ischemia. By evaluating myocardial perfusion under stress conditions, SPECT MPI aids in estimating the functional repercussions of coronary artery stenoses. However, its use is limited by factors such as radiation exposure, lengthy protocols, and the potential need for pharmacologic stress agents [4].

MPI–SPECT has proven valuable in identifying reversible ischemia, determining the extent of perfusion defects, and supporting decisions regarding revascularization [5].

Historically, it has even been employed to validate invasive physiological assessments such as fractional flow reserve (FFR). However, robust outcomes research has elevated FFR to the status of a gold standard for evaluating the hemodynamic significance of coronary lesions, offering a strong evidence base for its clinical utility [6].

More recently, the instantaneous wave-free ratio (iFR) has emerged as a novel physiological index that circumvents the need for pharmacologic stress agents. iFR quantifies the pressure gradient across coronary stenoses during a diastolic phase when resistance is at its lowest and most stable. Its simplicity, safety, and integration into routine coronary angiography workflows position it as an attractive alternative to both FFR and MPI–SPECT for lesion assessment [7,8].

This study aimed to evaluate and compare the efficacy of MPI–SPECT, as a non-invasive functional test, with iFR, an invasive physiological index, in determining the functional relevance of intermediate coronary artery stenoses.

Patients and methods:

Patients:

This prospective research enrolled 50 cases diagnosed with ischemic heart disease and intermediate single-vessel coronary artery lesions at the National Heart Institute and Benha University Hospitals during the period from January 2022 to Mars 2024. All cases were further evaluated using iFR measurement and SPECT MPI within two weeks of angiography. The agreement and diagnostic accuracy between the two modalities were analyzed statistically.

Informed written consent was obtained from all cases after providing a clear explanation of the study's objectives. Each case was assigned a confidential identification code to ensure anonymity. The study protocol received approval from the local Ethics Committee (MD 11-4-

2021) of the Faculty of Medicine, Benha University, prior to its initiation.

Inclusion criteria were cases complaining of chest pain and diagnosed with ischemic heart disease based on non-invasive tests. Scheduled for coronary angiography which revealed an intermediate lesion (40-70% stenosis) in a single vessel.

Exclusion criteria were participants presented with cardiogenic shock, chronic total occlusion (CTO) of a coronary artery, or surgical candidates due to conditions such as severe valvular heart disease. Additional exclusions included patients with end-stage renal or hepatic failure, left main or multivessel coronary artery disease, and those experiencing acute coronary syndromes (both STEMI and Non-ST-Elevation ACS). Individuals with pronounced left ventricular hypertrophy were also excluded, as associated microvascular dysfunction could potentially compromise the accuracy of iFR measurements

Methods

All cases included in this study underwent a comprehensive and systematic clinical evaluation protocol designed to ensure accurate baseline characterization and assessment of cardiovascular status. The process began with detailed history taking, during which essential demographic data were collected, including the patient's name, age, gender, and body mass index (BMI). In addition, a thorough investigation into the presence of CAD risk factors was carried out. This included inquiries into lifestyle and medical history, such as cigarette smoking, a known contributor to atherosclerosis, and chronic illnesses like diabetes mellitus, dyslipidemia, and hypertension. A detailed family history was also obtained to identify any hereditary predisposition to coronary heart disease. **Full clinical examination: Clinical examination including [**thorough physical examination including complete general examination and local cardiac examination was performed for every patient: 12 leads ECG: to exclude dynamic ST-T changes, Vital signs: pulse, blood pressure, capillary filling time, respiratory rate and temperature]. **Routine laboratory investigations [**CBC, PT, PTT, urea, creatinine, ALT, AST cardiac enzymes (CKMB, and Troponin), fasting blood sugar, HbA1c and lipid profile.

Transthoracic echocardiography

To further assess cardiac function, all patients underwent two-dimensional transthoracic echocardiography (TTE). This non-invasive imaging modality was employed to evaluate left ventricular systolic function and screen for significant valvular heart disease that might confound the study outcomes. Echocardiographic imaging and measurements were performed in accordance with the standardized protocols and recommendations of both the European Association of Echocardiography (EAE) and the American Society of Echocardiography (ASE), ensuring consistency and diagnostic accuracy across all cases. The evaluation of left ventricular ejection fraction (LVEF), a key indicator of systolic function, was performed using the Modified Simpson's Biplane Method, also known as the Biplane Method of Disks. This technique is particularly reliable for assessing global left ventricular performance, especially when high-quality apical views (typically the apical 2-chamber and 4-chamber views) are available. During the procedure, the endocardial borders of the left ventricle were manually traced at the end of diastole and systole. The echo software then automatically calculated the left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV), from which the ejection fraction was derived using the following formula: $EV = [(EDV - ESV) \times 100$ [9].

Coronary angiography

The procedure begins with thorough pre-assessment, focusing on identifying any contraindications to contrast or arterial access and optimizing hemodynamic stability. The patient is positioned in the catheterization suite, and aseptic techniques are rigorously followed. Radial access is preferred due to its lower complication rate, though femoral access may be necessary in certain cases, such as complex radial courses or severe radial spasm. After achieving local anesthesia, the artery is cannulated, and a vascular sheath is introduced to secure stable access. A guidewire is then advanced under fluoroscopy, followed by catheterization of the coronary ostium. The choice of catheter—often Judkins for diagnostic purposes—depends on vessel anatomy and operator preference.

IFR Protocol

The iFR measurement is undertaken following the identification of an intermediate coronary artery stenosis—typically defined as a 40–70% narrowing—on initial diagnostic coronary angiography, where further physiological evaluation is warranted. Once the target lesion has been delineated, a pressure-sensing guidewire (PHILIPS OmniWire) is prepared by calibrating and zeroing it outside the patient's body to establish reliable baseline pressure. With the guiding catheter securely engaged at the coronary artery's ostium, the pressure wire is carefully advanced through the catheter and positioned within the aortic root. This strategic placement allows for pressure equalization between the guidewire and the guiding catheter, a critical step that confirms accurate alignment of pressure readings prior to navigating the wire across the coronary lesion for iFR assessment

MPI (SPECT) Protocol

A two-day imaging protocol utilizing Tc-99m sestamibi myocardial perfusion SPECT was conducted under both stress and rest conditions. Patients capable of physical exertion performed a treadmill exercise following the standard Bruce protocol, while those with contraindications underwent pharmacologic stress testing using dobutamine. At peak stress, a body weight-adjusted dose of Tc-99m sestamibi was administered intravenously. To minimize hepatic uptake and enhance image clarity, patients were instructed to consume a fat-rich meal immediately after injection. Imaging was then performed 30 to 60 minutes later with the patient positioned supine. On the second day, a second injection of 20 mCi Tc-99m sestamibi was given, and rest imaging followed using the same acquisition protocol. All image reconstruction and processing steps were performed according to the American Society of Nuclear Cardiology (ASNC) standards [10].

Statistical analysis:

Data were analyzed using SPSS software, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means ± standard deviations (SD) and comparisons between groups were performed using the unpaired Student's t-test or one-way ANOVA (F-test), as appropriate. Categorical variables were summarized as frequencies and percentages, and associations were evaluated using the Chi-square test or Fisher's exact test when expected cell counts were low. A two-tailed $P < 0.05$ was considered indicative of statistical significance.

Results

The mean age of the cases was 55.12 years (SD = 8.44), with a median age of 54 years and an age range of 41 to 69 years. The gender distribution included 18 females (36%) and 32 males (64%). The mean BMI was 28.31 kg/m² (SD = 2.53), with a median of 27.90 kg/m² and a range of 24.10 to 32.70 kg/m². Comorbidities were prevalent, with 18 cases (36%) having hypertension, 13 cases (26%) with diabetes mellitus, and 32 cases (64%) with dyslipidemia. Additionally, 35 cases (70%) had a family history of relevant medical conditions, and 20 cases (40%) were smokers. **Table 1**

The mean ejection fraction (EF) among the cases was 66.58% with a standard deviation of 3.73%, and the median EF was 67.0%, ranging from 60% to 72%. **Table 2**

The data from myocardial perfusion imaging (MPI) across the 50 study participants indicates a balanced distribution of results, reflective of coronary perfusion status. MPI results in 22 of the participants, or 44%, have positive myocardial perfusion defects. The majority, comprising 28 participants or 56%, showed negative MPI results. Also, the IFR has a mean value of 0.90 with a standard deviation of 0.03 with values spanning from 0.84 to 0.96. **Table 3**

Regarding the agreement between MPI and IFR tests among studied cases. A kappa value of 0.878, with a p-value of less than 0.001, indicates a very strong agreement between these two diagnostic methods. Specifically, 20 cases (40%) were positively identified by both MPI and IFR, while 27 cases (54%) were negative in both tests, underscoring a high level of consistency. Only 3 cases (6%) showed discordant results between the two tests, with 1 case positive on MPI but negative on IFR, and 2 cases negative on MPI but positive on IFR. **Table 4**

Regarding validity of MPI to predict IFR results, it showed high AUC of 0.997, indicating nearly perfect diagnostic accuracy. Best cut off value and performance characteristics. **Table 5**

Table 1: Demographics of study subjects.

		Cases n=50
Age (years)	Mean ± SD	55.12 ± 8.44
	Median (Min-Max)	54.00 (41.00-69.00)
Gender	Female	18(36.0%)
	Male	32(64.0%)
BMI (kg/m2)	Mean ± SD	28.31 ± 2.53
	Median (Min-Max)	27.90 (24.10-32.70)
Comorbidities and risk factors	Hypertension	18(36.0%)
	DM	13(26.0%)
	Dyslipidemia	32(64.0%)
	Family history	35(70.0%)
	Smoking	20(40.0%)

Table 2: Echocardiography examination in studied cases.

		Cases n=50
Ejection fraction %	Mean ± SD	66.58 ± 3.73
	Median (Min-Max)	67.0 (60-72)

Table 3: Distribution of the studied cases according to MPI and IFR.

		Cases n=50
IFR	Mean ± SD	0.90 ± 0.03
	Median (Min-Max)	0.90 (0.84-0.96)
	Positive (iFR </= 0.89)	22 (44.0%)
	Negative (iFR > 0.89)	28 (56.0%)
		Cases n=50
MPI	Positive	22(44.0%)
	Negative	28(56.0%)

Table 4: Agreement between MPI and IFR.

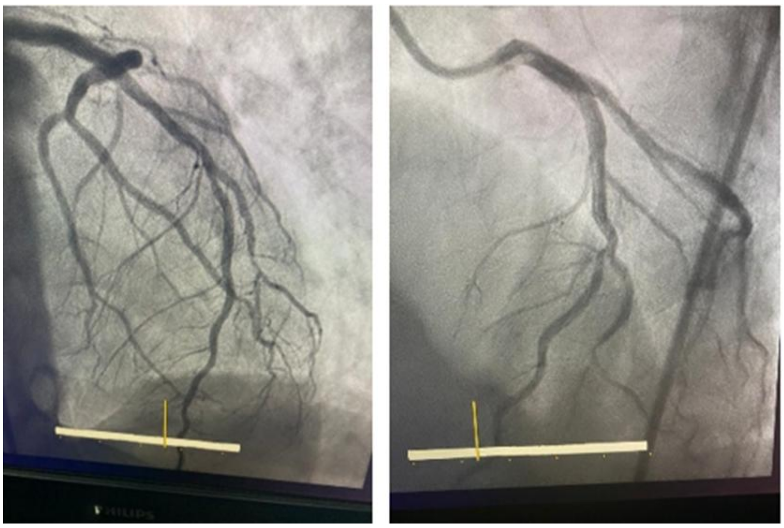
		IFR				K	p
		Positive		**Negative**			
		N	**%**	**N**	**%**		
MPI	**Positive**	20	40.0%	1	2.0%	0.878	<0.001*
	Negative	2	4.0%	27	54.0%		

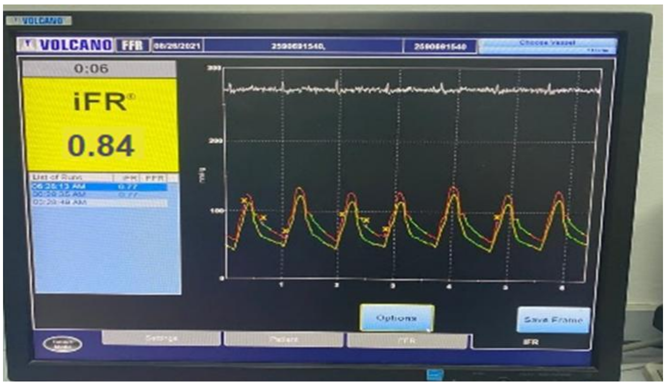
K: kappa agreement

Table 5: Validity of MPI to predict IFR results.

IFR					
AUC	**95% CI**	**p**	**Cut off**	**Sensitivity (%)**	**Specificity (%)**
0.997	0.923 to 1.000	<0.001*	0.84	95.45	100

AUC, area under ROC curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value, *: Significant ≤0.05





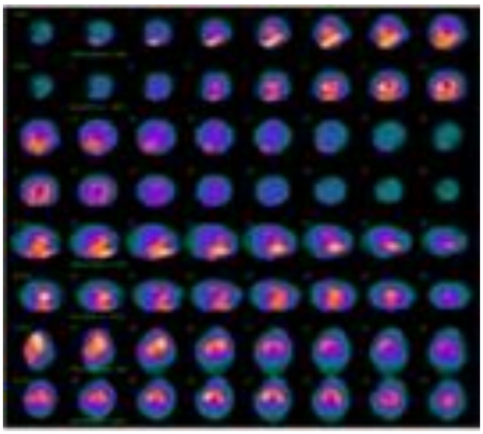


Fig (1) A sample of study case showed intermediate LAD mid segment stenosis, where iFR was 0.84 and stress thallium showed moderate reversible hypoperfusion defect in anterolateral wall.

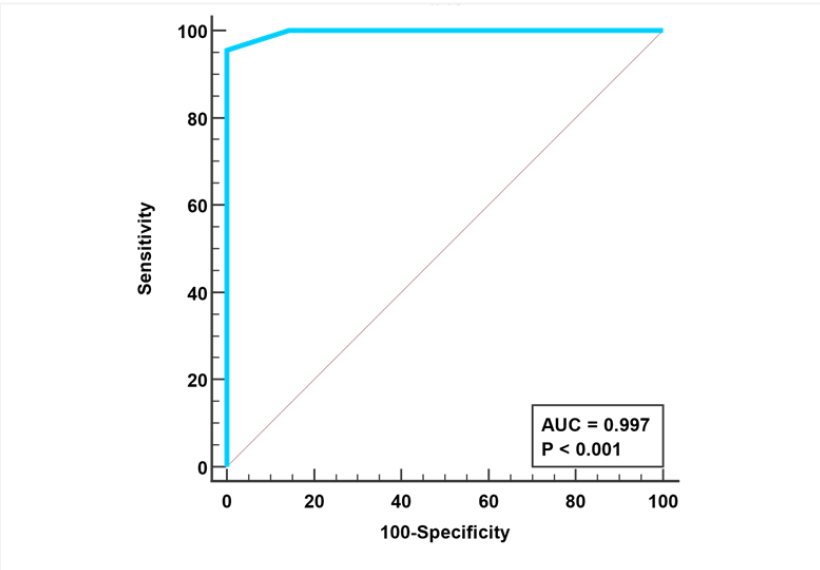


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Fig (2) ROC curve of MPI in prediction of IFR results

Discussion:

MPI using SPECT has long been established as a reliable non-invasive method for assessing myocardial ischemia[11].

SPECT MPI presents valuable insights into the perfusion status of the myocardium under stress conditions, helping clinicians evaluate the physiological impact of coronary artery stenosis[12].

According to demographic data, the mean age of the studied cases was 55.12 ± 8.44 years. The median age was 54 years, ranging from 41 to 69 years. Regarding gender distribution among the 50 cases studied, 18 (36%) participants were female and 32 (64%) were male. Concerning the Body Mass Index (BMI), the mean BMI was 28.31 ± 2.53kg/m². Regarding the prevalence of specific comorbidities, 18 (36%) had hypertension, 13 (26%) had diabetes mellitus (DM), and 32 (64%) had dyslipidemia. The data from the 50 cases reveal that 35 participants (70%) report a positive family medical history. Additionally, 40% of the participants were smokers.

Consistently, Zayed and colleagues[13]., compared MPI and IFR in cases with single intermediate coronary artery lesions. They reported a mean age of 55 years for their study participants, which is quite like the mean age of 55.12 years in our study. The gender distribution in their study, with 60% males and 40% females, also aligns closely with our findings, which showed 64% male and 36% female participants. However, there are notable differences in the prevalence of risk factors. They found that 50% of their cases were smokers, compared to 40% in our study. The prevalence of DM was significantly higher in their study at 65%, as opposed to 26% in ours. Similarly, hypertension and dyslipidemia were reported in 53.3% and 70% of their cases, respectively, both higher than the 36% and 64% noted in our cohort. They also reported a lower prevalence of a family history of coronary artery disease at 25%, whereas 70% of our participants had a relevant family history[13].

The data from myocardial perfusion imaging (MPI) across the 50 study participants indicates a balanced distribution of results, reflective of coronary perfusion status. MPI results indicate that 22 of the participants, or 44%, have positive myocardial perfusion defects. The majority, comprising 28 participants or 56%, showed negative MPI results.

The findings from Amin and colleagues, regarding MPI defect sizes and MPI results contrast with ours. They reported a mean defect size of 15.6% with a SD of 4.5%, ranging from 10% to 22%, and a median of 14%. Additionally, their study showed that 40% of the MPI results were positive, while 60% were negative. These differences might stem from variations in patient demographics, the severity of coronary lesions, or differences in imaging techniques, which could influence the detection and interpretation of perfusion defects[11].

In the present study, the iFR has a mean value of 0.90 with a standard deviation of 0.03, with values spanning from 0.84 to 0.96.

In consistent with our findings, Amin reported a mean IFR value of 0.89 with a standard deviation of 0.094, and values ranging from 0.65 to 1.05. The median value is 0.92. The distribution of IFR results in their study is 40% positive and 60% negative[11].

Regarding the agreement between myocardial perfusion imaging (MPI) and iFR tests among the studied cases, a kappa value of 0.878 with a p-value of less than 0.001 was recorded. Specifically, 20 cases (40%) were positively identified by both MPI and IFR, while 27 cases (54%) were negative in both tests. Only 3 cases (6%) showed discordant results between the two tests, with 1 case positive on MPI but negative on IFR, and 2 cases negative on MPI but positive on IFR.

Regarding validity of IFR to predict MPI results, the IFR demonstrates excellent diagnostic accuracy with AUC of 0.997, indicating near-perfect discrimination between positive and negative MPI results. The 95% confidence interval ranges from 0.923 to 1.000, underscoring the robustness of the IFR as a predictive tool. The statistical significance is highlighted by a p-value of less than 0.001, indicating a highly significant predictive ability. The optimal cut-off value for IFR is identified at 0.84, with a high sensitivity of 95.45% and a specificity of 100%, suggesting that the IFR is exceptionally effective in identifying true positive and true negative cases of myocardial perfusion defects.

In their analysis of IFR and MPI results, Zayed found that 61.7% of cases showed significant IFR values, with a good kappa agreement of 0.62 between IFR and MPI results, indicative of reliable diagnostic concordance. They also reported high sensitivity and specificity for MPI, which closely mirrors the strong agreement and diagnostic reliability we observed in our study[13].

In harmony with our findings, Amin reported a strong and statistically significant concordance between iFR and FFR, with $\kappa = 0.918$ ($P < 0.001$) and 96% agreement, and $\kappa = 0.754$ ($P < 0.001$) with 88% agreement, respectively. The diagnostic metrics for iFR included SN 90.9%, SP 100%, PPV 100%, NPV 93.3%, and LR– 0.09. For MPI, these were SN 81.8%, SP 92.9%, PPV 90%, NPV 86.7%, LR+ 11.45, and LR– 0.20, respectively [11].

Supporting our findings, Hwang and colleagues., evaluated over 100 patients with LAD stenosis using both PET imaging and invasive physiological indices, including FFR, iFR, and resting Pd/Pa. The study aimed to establish optimal diagnostic thresholds using PET-derived CFR and RFR as reference standards. Results demonstrated comparable overall accuracy across indices for CFR < 2.0, with iFR achieving 74% accuracy. For RFR < 0.75, iFR showed a diagnostic accuracy of 71%, suggesting that iFR correlates well with PET-based assessments in detecting flow-limiting CAD [14].

Moreover, van de Hoef reported that using a composite reference standard (myocardial perfusion scintigraphy + HSR index), the AUC for ischemia detection was similar for iFR and FFR (0.84 vs. 0.88, P = 0.20, respectively), concluding that both indices offer equivalent diagnostic performance in identifying ischemia-inducing lesions [15].

In a prospective study by Härle, involving over 100 cases with borderline stenoses, a strong correlation was observed between iFR and FFR ($r_s = 0.81$, $P < 0.0001$). ROC analysis yielded an AUC of 0.9106, underscoring the high diagnostic value of iFR. Moreover, applying an iFR-only strategy with a treatment threshold of ≤ 0.89 showed diagnostic concordance with FFR-only decisions in ~83% of over 120 lesions, with SN 80% and SP 86%, respectively [16].

These findings are consistent with our study results, which also demonstrated the effectiveness of IFR in assessing the severity of coronary lesions. The strong correlation and high diagnostic agreement with FFR found in the Härle and colleagues' study reinforce the validity of using IFR as a dependable non-invasive diagnostic tool in the clinical evaluation of coronary artery disease[16]. This is further supported by studies from Fede and colleagues., and Raja and colleagues., who reported close agreement between FFR and IFR, and found that IFR reliably correlates with FFR across various subgroups and vascular territories without being affected by heart rate or blood pressure[17][18].

This study has some limitations. First, the study was conducted at only two hospitals with a relatively small sample size which might limit the generalizability of the findings to a larger population. Second, the study didn't use FFR in conjunction to iFR for assessment of intermediate coronary lesions and finally the study focused on the immediate diagnostic agreement between SPECT MPI and iFR without assessing long-term clinical outcomes.

Conclusion:

From our findings we can conclude that the MPI using SPECT aligns strongly with the iFR in evaluating the clinical significance of intermediate coronary artery lesions. The SPECT, with its high level of diagnostic agreement with iFR, is considered a reliable, non-invasive alternative that avoids the complexities and risks associated with invasive intervention and radiation exposure. This makes SPECT an attractive tool for clinicians in the routine assessment of coronary artery disease, offering both safety and efficacy in the clinical setting.

Conflict of interest

None declared any conflict of interest

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