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Ahmed Zayed
National Heart Institute, a.zayed67@yahoo.com

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Invasive versus noninvasive assessment of functional significance of intermediate coronary artery lesions

Ahmed Zayed
Department of Cardiology, National Heart Institute, Cairo, Egypt

Abstract

Background
Myocardial perfusion imaging (MPI) is noninvasive test used for evaluation of functional significance of borderline coronary artery lesions. Moreover, instantaneous wave-free ratio (IFR) is a well-validated invasive method used for the same purpose.

Objectives
To compare the results of MPI and IFR in detection of ischemia in patients with single intermediate coronary artery lesion.

Patients and methods
A total of 60 patients with single intermediate coronary artery stenosis, visually judged as angiographic stenosis more than or equal to 50% and less than 70% during coronary angiography, were included. After coronary angiography, all patients were subjected to MPI and IFR at National Heart Institute between February 2018 and February 2020. IFR value less than or equal to 0.89 was considered significant, indicating functionally significant lesion, and IFR value more than or equal to 0.89 was considered insignificant, indicating functionally insignificant lesion. MPI results were considered positive when the defect size more than or equal to 10% in the territory of the affected vessel.

Results
Among 60 patients, 37 (61.7%) patients showed significant IFR value and 23 (38.3%) patients showed insignificant IFR value. Of 37 patients with significant IFR value, 30 (81.1%) patients showed positive MPI results and seven (18.9%) patients showed negative MPI results. Of 23 patients with insignificant IFR value, 19 (82.6%) patients showed negative MPI results, and four (17.4%) patients showed positive MPI results. So, there was good (kappa = 0.62), significant ($P = 0.001$) agreement between the MPI and IFR results. The sensitivity was 81.1%, the specificity was 82.6%, positive predictive value was 88.2%, the negative predictive value was 73.1%, and the accuracy was 81.7%.

Conclusions
MPI may be a valid alternative, noninvasive, less-expensive test than IFR for evaluation of functional significance of intermediate coronary artery lesions.

Keywords: Instantaneous wave-free ratio, myocardial perfusion imaging, coronary artery lesion

Introduction

Coronary angiography is an invasive imaging modality that is commonly used in diagnosis of coronary artery disease (CAD). However, the visual evaluation of severity of coronary artery lesion is subjective and may be poorly correlated with the physiological significance of the lesion [1]. Moreover, it may be fallacious in setting of diffuse disease and eccentric lesions [2]. In addition, percutaneous coronary intervention (PCI) of intermediate coronary artery lesion with unknown physiological significance is always debatable. So, assessment of severity of coronary artery stenosis and its physiological significance is an important issue for decision making either PCI or medical follow-up [3]. Myocardial perfusion imaging (MPI) and invasive measurement of pressure and flow are commonly used modalities for assessment of physiological significance of

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Correspondence to: Ahmed Zayed, MD,
Department of Cardiology, National Heart Institute, Cairo, Egypt.
Tel: +20 122 745 9212;
E-mail: a.zayed67@yahoo.com

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coronary artery stenosis. MPI is noninvasive test that can give an important information for the diagnosis of CAD as well as assessment of disease prognosis and guiding the revascularization decision. Diminished uptake of the radiopharmaceutical agent reflects the presence of significant CAD in the affected segment. The differences in the segmental myocardial perfusion can be assessed visually or quantitatively by exercise or pharmacologically induced vasodilatation. The role of MPI in evaluation of intermediate coronary artery lesions for PCI has been approved [4]. However, MPI may be of limited value for assessment of lesion severity in case of presence of multivessel disease, microvascular disease, and in case of multiple lesions [5]. On the contrary, instantaneous wave-free ratio (IFR) is an invasive technique calculated from the mean distal to mean aortic pressure ratio during free-period of diastole at which lowest resistance allows ideal assessment of physiological significance of the coronary artery lesion. So, it has an important role guiding the PCI decision in intermediate coronary artery lesions with unknown functional significance [6].

Aim

The aim of this study was to compare the results of noninvasive MPI and invasive IFR, which is considered as the gold standard test for ischemia, in assessment of functional significance of intermediate coronary artery stenosis.

Patients and methods

This prospective study included 60 patients with CAD who underwent coronary angiography at National Heart Institute between February 2018 and February 2020 and showed single intermediate degree of coronary artery stenosis, visually judged as angiographic stenosis more than or equal to 50% and less than or equal to 70%, during coronary angiography assessed by at least two expert operators. After coronary angiography, all patients were subjected to noninvasive assessment by MPI followed later by invasive assessment by IFR.

Patients with history of previous CABG, PCI, previous myocardial infarction, acute coronary syndrome, multivessel disease, left main disease, severe left ventricular hypertrophy, severe valvular lesions, severe pulmonary hypertension, uncontrolled cardiac arrhythmia, or congestive heart failure were excluded from the study.

Local ethics committee approved the study, and informed consent was obtained for each patient.

All patients were subjected to the following:

(1) History and clinical examination: including age, sex, NYHA functional classification, history of ischemic heart disease, history of diabetes mellitus, blood pressure and cardiac examination.
(2) 12-lead ECG: to detect any baseline abnormalities.
(3) Routine laboratory investigation: including CK-MB, troponin, serum creatinine, lipid profile, and random blood sugar.
(4) Doppler echocardiography: to assess left ventricular dimensions and systolic function.
(5) MPI: stress and rest Tc99m sestaMIBI myocardial perfusion SPECT 2-day protocol was performed. Patients were exercised on treadmill according to standard Bruce protocol. Technetium-99m sestmibi 20 mci was injected at peak exercise, and imaging acquisition was started after 30–60 min. After 24 h, the patients were reinjected with 20 mci Tc99m sestaMIBI and reimaged 30–60 min later [7]. Analysis of images was done by using previously validated automated program, and MPI results were considered positive when the defect size was more than or equal to 10% in the territory of the affected vessel.
(6) IFR: through transfemoral approach, 6-Fr guiding catheter was introduced with intracoronary injection of 100 μg of nitroglycerine. The pressure wire was calibrated and introduced into the guiding catheter. The wire was advanced to the tip of the guiding catheter, and pressure was equalized against the pressure measured through the guiding catheter. The wire is then advanced across the target lesion and trans-stenotic pressure measurement had been done. The IFR was calculated as the ratio of mean distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter. IFR value less than or equal to 0.89 was considered significant, indicating functionally significant lesion and IFR value more than or equal to 0.89 was considered insignificant, indicating functionally insignificant lesion [8]. The IFR is considered as the gold standard test for ischemia.

Statistical analysis

The categorized variables were expressed as *n* (%). Continuous variables were presented as mean ± SD. Comparison between categorical data was performed using χ^2 test or Fisher exact test instead if cell count was less than 5. Agreement between the two techniques was done using kappa statistic (poor agreement=<0.20; fair agreement = 0.20–0.40; moderate agreement = 0.40–0.60; good agreement = 0.60–0.80; and very good agreement = 0.80–1.00). Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV) (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.), negative predictive value (NPV) and accuracy were calculated. Statistical Package for the Social Sciences (SPSS) computer program (version 19 Windows) was used for data analysis. *P* value less than or equal to 0.05 was considered significant.

Results

This study included 60 patients with ischemic heart disease and single intermediate coronary artery lesion during coronary angiography. They underwent assessment of functional significance of the lesion by noninvasive single-photon emission tomography (SPECT-MPI) and invasive assessment by IFR. The mean age of the patients was 55 ± 4 years. A total of 36 (60%) patients were male and 24 (40%) patients were female. Smoking was present in 30 (50%) patients. Diabetes

mellitus was the risk factor in 39 (65%) patients. Hypertension was the risk factor in 32 (53.3%) patients. Dyslipidemia was present in in 42 (70%) patients. Family history of CAD was present in 15 (25%) patients. The main symptom was typical chest pain in all patients (Table 1).

Left anterior descending (LAD) artery was the target vessel in 23 (38.3%) patients. Left circumflex artery was the target vessel in 20 (33.3%) patients. Right coronary artery (RCA) was the target vessel in 17 (28.3%) patients.

Among 60 patients, 37 (61.7%) patients showed significant IFR value and 23 (38.3%) patients showed insignificant IFR value. Of 37 patients with significant IFR value, 30 (81.1%) patients showed positive MPI results and seven (18.9%) patients showed negative MPI results. Of 23 patients with insignificant IFR value, 19 (82.6%) patients showed negative MPI results and four (17.4%) patients showed positive MPI results. So, there was good (kappa = 0.62), significant ($P = 0.001$) agreement between the MPI and IFR results. The sensitivity was 81.1%, the specificity was 82.6%, PPV was 88.2%, the NPV was 73.1%, and the accuracy was 81.7% (Table 2).

Among 23 patients with LAD lesion, 16 (69.6%) patients showed significant IFR value and seven (30.4%) patients showed insignificant IFR value. Of 16 patients with significant IFR value, 13 (81.2%) patients showed positive MPI results and three (18.8%) patients showed negative MPI results. Of seven patients with insignificant IFR value, six (85.7%) patients showed negative MPI results and one (14.3%) patient showed positive MPI results. So, there was good (kappa = 0.62), significant ($P = 0.002$) agreement between the MPI and IFR results. The sensitivity was 81.2%, the specificity was 85.7%, PPV was 92.9%, the NPV was 66.7%, and the accuracy was 82.6% (Table 3).

Among 20 patients with left circumflex artery lesion, 11 (55%) patients showed significant IFR value and nine (45%) patients showed insignificant IFR value. Of 11 patients with significant IFR value, nine (81.8%) patients showed positive MPI results and two (18.2%) patients showed negative MPI results. Of nine patients with insignificant IFR value, eight (88.9%) patients showed negative MPI results and one (11.1%) patient showed positive MPI results. So, there was good (kappa = 0.7), significant ($P = 0.002$) agreement between the MPI and IFR results. The sensitivity was 81.8%, the specificity was 88.9%, PPV was 90%, the NPV was 80%, and the accuracy was 85% (Table 4).

Among 17 patients with right coronary artery lesion, 10 (58.8%) patients showed significant IFR value and seven (41.2%) patients showed insignificant IFR value. Of 10 patients with significant IFR value, eight (80%) patients showed positive MPI results and two (20%) patients showed negative MPI results. Of seven patients with insignificant IFR value, six (85.7%) patients showed negative MPI results and one patient showed positive MPI results. So, there was good (kappa = 0.64), significant ($P = 0.008$) agreement between the MPI and IFR results. The sensitivity was 80%,

Table 1: Demographic and clinical data of the patients

	n=40 [*n* (%)]
Male	36 (60)
Female	24 (40)
Smoking	30 (50)
Diabetes mellitus	39 (65)
Hypertension	32 (53.3)
Dyslipidemia	42 (70)
Family history	15 (25)

Table 2: Association between instantaneous wave-free ratio and myocardial perfusion imaging in all patients

	IFR [*n* (%)]		Kappa coefficient	*P*
	Significant (*n*=37)	Insignificant (*n*=23)		
MPI				
Positive (*n*=34)	30 (81.1)	4 (17.4)	0.622	0.001*
Negative (*n*=26)	7 (18.9)	19 (82.6)		

IFR, instantaneous wave-free ratio; MPI, myocardial perfusion imaging; NPV, negative predictive value; PPV, positive predictive value.
**P* value less than or equal to 0.05=significant, sensitivity=81.1%, specificity=82.6%, PPV=88.2%, NPV=73.1%, accuracy=81.7%.

Table 3: Association between instantaneous wave-free ratio and myocardial perfusion imaging in left anterior descending territory

	IFR [*n* (%)]		Kappa coefficient	*P*
	Significant (*n*=16)	Insignificant (*n*=7)		
MPI				
Positive (*n*=15)	13 (81.2)	1 (14.3)	0.62	0.002*
Negative (*n*=8)	3 (18.8)	6 (85.7)		

IFR, instantaneous wave-free ratio; MPI, myocardial perfusion imaging; NPV, negative predictive value; PPV, positive predictive value.
**P* value less than or equal to 0.05=significant, sensitivity=81.2%, specificity=85.7%, PPV=92.9%, NPV=66.7%, accuracy=82.6%.

Table 4: Association between instantaneous wave-free ratio and myocardial perfusion imaging in left circumflex artery territory

	IFR [*n* (%)]		Kappa coefficient	*P*
	Significant (*n*=11)	Insignificant (*n*=9)		
MPI				
Positive (*n*=10)	9 (81.8)	1 (11.1)	0.700	0.002*
Negative (*n*=10)	2 (18.2)	8 (88.9)		

IFR, instantaneous wave-free ratio; MPI, myocardial perfusion imaging; NPV, negative predictive value; PPV, positive predictive value.
**P* value less than or equal to 0.05=significant, sensitivity=81.8%, specificity=88.9%, PPV=90%, NPV=80%, accuracy=85%.

Table 5: Association between instantaneous wave-free ratio and myocardial perfusion imaging in right coronary artery territory

	IFR [*n* (%)]		Kappa coefficient	*P*
	Significant (*n*=10)	Insignificant (*n*=7)		
MPI				
Positive (*n*=9)	8 (80.0)	1 (14.3)	0.643	0.008*
Negative (*n*=8)	2 (20.0)	6 (85.7)		

IFR, instantaneous wave-free ratio; MPI, myocardial perfusion imaging; NPV, negative predictive value; PPV, positive predictive value. **P* value less than or equal to 0.05=significant, sensitivity=80%, specificity=85.7%, PPV=88.9%, NPV=75%, accuracy=82.4%.

the specificity was 85.7%, PPV was 88.9%, the NPV was 75%, and the accuracy was 82.4% (Table 5).

Discussion

In this study, we used IFR as the gold standard reference test for ischemia depending on data from the previous studies. In CLARIFY study, the IFR showed good agreement with functional flow reserve (FFR) when compared in 50 patients. Moreover, among the more than 100 patients with LAD lesions who underwent FFR, IFR, and resting Pd/Pa using PET-derived coronary flow reserve, the overall diagnostic accuracy was not different (70% for FFR, 74% for IFR, and 70% for resting Pd/Pa) [9]. In addition, this agreement was observed in large studies conducted on both techniques like DEFINE-FLAIR [10] and IFR SWEDE-HEART [11]. Furthermore, IFR accuracy was assessed in more than 100 patients with borderline coronary artery lesion. The IFR showed strong concordance with FFR (r = 0.81 and $P < 0.0001$), with sensitivity and specificity of 80 and 86%, respectively [12]. Moreover, a meta-analysis evaluated 6000 lesions, and there was a significant correlation between the FFR and IFR (r = 0.79 and $P < 0.001$) [13]. The sensitivity and specificity were 78 and 83%, respectively, positive and negative likelihood ratio were 4.5 and 0.28, respectively, and the overall accuracy was 81% [14]. Our study showed good agreement between MPI and IFR in evaluation of functional significance of borderline coronary artery lesion. MPI was shown to have high overall sensitivity and specificity (81.1 and 82.6%, respectively). Moreover, it showed high PPV and NPV (88.2 and 73.1%, respectively), and the accuracy was 81.7%. Our results are consistent with the results of Erhard *et al.* [15] who concluded that SPECT-MPI was carried out and sensitivity and specificity were 83% and 77%, respectively, when used to evaluate the results of FFR. Another study evaluated 40 patients using the pressure wire during coronary angiography and compared the results with MPI using thallium-201, and the study concluded that FFR can accurately assess the presence of ischemia on SPECT in patients with stable CAD [16]. Moreover, Sahiner *et al*. [17] showed that MPI-SPECT had overall sensitivity and specificity of 85 and 84%, respectively, and it was more accurate than visual analysis. In addition, a meta-analysis, involving 110 patients, compared the results of MPI-SPECT with the gold standard FFR, and the sensitivity and specificity were 70 and 78%, respectively for MPI and positive and negative likelihood ratios were 3.4 and 0.4, respectively [18]. Furthermore, Dai *et al.* [19] compared MPI with FFR results and showed overall sensitivity and specificity of 78 and 79% respectively, and positive and negative likelihood ratios were 3.7 and 0.28, respectively. Moreover, other study showed MPI-SPECT overall sensitivity and specificity were 73 and 83%, respectively, with positive and negative likelihood ratios were 4.2 and 0.3, respectively [20]. In our study, we excluded patients with multivessel and left main disease to overcome limitations in MPI as some studies showed poor association between MPI and IFR, particularly in patients with multivessel disease, as MPI usually assesses the difference in blood flow between the different vessels, and so, the possibility of balanced ischemia in case of multivessel disease may be a great obstacle for precise assessment. A study evaluated 60 patients with multivessel disease and they underwent MPI and FFR. The MPI results were in agreement with FFR in 42% of patients. MPI results were underestimated in 36% of patients and overestimated in 22% of patients compared with FFR, and there was inaccurate concordance between the two methods in detection of significant ischemia. The sensitivity and specificity of MPI were 76 and 38%, respectively. The PPV and NPV of MPI were 66 and 50%, respectively, compared with FFR [21]. Moreover, Zhou *et al.* [22] stated that multivessel and left main disease were a major obstacle to MPI in assessment of functional significance of coronary artery lesion.

Conclusions

This study demonstrates that noninvasive MPI-SPECT showed significant concordance, as well as high sensitivity, specificity, PPV, and NPV when compared with invasive IFR, which is considered the gold standard test for ischemia, in assessment of functional significance of intermediate coronary artery lesion in patients with single vessel disease. So, MPI can be used as an alternative nonexpensive, noninvasive test for assessment of functional significance of borderline coronary artery lesion in this group of patients.

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Conflicts of interest

There are no conflicts of interest.

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