Functional Significance of Intermediate Coronary Lesions

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Abstract

Background: The significance of coronary artery stenosis of intermediate severity (diameter stenosis of > 40% to < 70%) was difficult to be determined. The 2-dimensional representation of the arterial lesion provided by angiography is limited in distinguishing intermediate lesions that require stenting from those simply need appropriate medical therapy. This study aims to assess the functional significance of intermediate coronary lesions in coronary angiography invasively and non–invasively.

Methods: 30 patients with intermediate coronary stenosis in coronary angiography were subjected to non-invasive stress imaging either exercise myocardial perfusion imaging (MPI) or dobutamine stress echocardiography and the results were compared with results of Intravascular Ultrasound and Fractional Flow Reserve.

Results: In our study we found that among 14 patients with FFR value < 0.8; 12 patients had reversible ischemia in stress test. Additionally among 16 patients with FFR value > 0.8; 14 patients had negative stress test. FFR value had sensitivity and specificity 85.7% & 87.5% respectively to predict result of non-invasive stress test with a predictive value PPV & NPV 85.7% & 87.5% respectively with accuracy 86.7%. On the contrary by comparing minimal luminal area measured by IVUS with the results of non-invasive stress test there was no statistically significant difference between two groups. However the best cut-off value for minimal luminal area (MLA) measured by IVUS which was concordant with ischemic FFR value (< 0.8) was < 4.5 mm² with sensitivity and specificity 57.1% &56.3% respectively and predictive values PPV = 53.3% and NPV = 60%.

Conclusion: In patients with intermediate coronary lesions, FFR is a useful index for functional assessment of severity of coronary artery stenosis in comparison to non-invasive stress test and can be used as a guide before coronary revascularization. The best cut-off value for minimal luminal area measured by IVUS was < 4.5 mm²

ABBREVIATIONS

CAD: Coronary Artery Disease; DES: Drug Eluting Stent; DM: Diabetes Mellitus; ECG: Electrocardiography; EEM: External Elastic Membrane; EF: Ejection Fraction; FFR: Fractional Flow Reserve; HTN: Hypertension; IVUS: Intravascular Ultrasound; LAD: Left Anterior Descending; MLA: Minimal Luminal Area; MPI: Myocardial Perfusion Imaging; NPV: Negative Predictive Value; Pa: Mean Arterial Pressure; Pd: Mean Distal Coronary (transstenotic) Pressure; PCI: Percutaneous Coronary Intervention; PPV: Positive Predictive Value; RLA: Reference Lumen Area; SPECT: Single Photon Emission Computerized Tomography

INTRODUCTION

An intermediate coronary lesion on coronary angiography is defined as a luminal narrowing with a diameter stenosis > 40% but < 70%. Assessment of a coronary lesion with intermediate severity continues to be a challenge for cardiologists [1]. In the current era of drug-eluting stents (DES), when percutaneous coronary revascularization is achieved with high success, a low complication rate, and excellent long-term patency, it might be tempting to treat all suspected lesions with implantation of a DES. However, there are still procedural complications associated with angioplasty, the inherent risk of restenosis, and late stent thrombosis [2].

Selective coronary angiography is accepted as the standard for determining the presence and extent of epicardial coronary artery disease (CAD) [3]. However, there is significant interobserver and intra-observer variability in interpretation of the severity of stenosis on coronary angiography. In addition, cross-sectional...
anatomic imaging obtained from histopathological specimens and intravascular ultrasound (IVUS) has highlighted limitations of coronary angiography [4].

Owing to the increased sensitivity of IVUS in identifying disease and its close correlation with pathology, IVUS had become the more accurate standard for defining the anatomy of atherosclerosis in vivo. Intravascular ultrasound is a catheter-based technique that provides tomographic images perpendicular to the length of the coronary arteries [5].

FFR is an invasive modality which is helpful to overcome the limitations of coronary angiography in assessment of the functional significance of a coronary stenosis. FFR is defined as the ratio of maximal blood flow achievable in stenotic coronary artery relative to maximal flow in the same vessel if it were normal. The normal FFR value should be equal to 1.0 FFR value of < 0.75 was considered a significant value for obstructive CAD which correlated with ischemia on noninvasive stress tests [6]. However several studies have demonstrated that in patients with an intermediate coronary lesion and an FFR 0.8, percutaneous coronary intervention (PCI) can safely be deferred [6].

PATIENTS AND METHODS

Thirty patients with intermediate coronary lesions underwent both invasive and non-invasive functional assessment of severity of coronary stenosis from May 2011 to January 2014 in Wady El-Neel Hospital. Five of them were females and twenty five were males, their mean age was (57.57 ± 10.30).

This study included patients who have anginal symptoms and those who are eligible to do coronary angiography and possible intracoronary stenting. Patients with in-stent restenosis, chronic total occlusion, acute coronary syndrome, more than two vessel disease and those with left main coronary artery disease were excluded.

All patients were subjected to the following: detailed medical history including risk factors of coronary artery disease (Diabetes mellitus, hypertension, smoking and dyslipidemia), through clinical examination, 12-leads resting ECG, laboratory investigations including fasting blood sugar, glycated haemoglobin, complete lipid profile and serum creatinine. Resting Trans-Thoracic Echocardiography to assess left ventricular function (EF) and resting wall motion abnormalities.

Stress Imaging Test

Pharmacological stress echocardiography: The test is performed using dobutamine as a stressor and the dose is gradually up titrated according to the standard protocols. Interpretation is usually by visual assessment based on analysis of thickening and inward systolic motion before, during and after stress. The heart is typically divided into a 17 segment model and a score assigned to each segment at baseline and during stress based on the degree of thickening. The presence of a new or worsening regional wall motion abnormality in 1 or more segments identifies an ischemic response. The site of this response gives a clue as to the artery affected. The extent of ischemia is based on the number of affected segments, the occurrence of ischemia at an early stage of the test, the wall motion score index at rest and peak stress, and a slow recovery time [7].

SPECT MPI (TC 99m sestamibi scintigraphy): Exercise SPECT MPI imaging protocol used: With the same-day rest-stress protocol using a Tc99m-labeled perfusion agent, a first injection at rest is followed by imaging roughly 30 minutes later. A second injection with 2 to 3 times the activity is administered during peak exercise to overcome the background signal from the rest images, and repeat imaging is performed. Ischemia is suspected when there is reduced tracer uptake on the stress acquisition which is reversible on the rest acquisition. A fixed defect, i.e. a defect present on both stress and rest acquisitions, is suggestive of an infarct provided attenuation artifacts are ruled out. Also the surface area of ischemic zone can be calculated in order to assess extent and severity of ischemia considering an area more than 10% represents a significant ischemia [6].

Coronary angiography: Selective coronary angiography by standard Judkins technique was performed on all subjects with the right femoral approach. Evaluation of all coronary angiograms was made by two observers who were blinded to the clinical and laboratory data to detect the angiographically intermediate coronary lesions which are defined as a luminal narrowing with a diameter stenosis > 40% and < 70% [8,9].

Intravascular coronary ultrasound (IVUS) measurements: In this study we used a rotational mechanical probe (Atlantis SR Pro-Boston Scientific) which uses a driving cable to rotate at 1800 rpm (30 images per second). The probe emits an ultrasound beam typically at a frequency 40 MHz which is perpendicular to the catheter and vessel and the signal is reflected from surrounding tissue and reconstructed into a real-time tomographic gray-scale image. In this system, the imaging transducer is protected in a transparent sheath, which facilitates smooth and uniform pullback [10].

Once the index artery is cannulated by guiding catheter the IVUS probe is advanced over a 0.014 guide wire and pushed beyond the lesion; the ultrasound catheter is then pulled back slowly at a constant speed within the sheath either manually or motorized (usually 0.5 mm/s) which permits volumetric evaluation of the lesion and plaque dimensions after longitudinal or 3-dimensional reconstruction [10].

Ultrasound waves are reflected at the interface of two different tissues. In coronary arteries, there are two clear borders which can be defined: the lumen-intimal border and the media-external elastic membrane (EEM) border. Blood speckle in the lumen reflects more weakly than the echo signal from the intima, allowing for a clear lumen-intimal border next to the IVUS catheter. At the same time, the media is echolucent (faint echo signal), which is manifest on the gray-scale image as a dark ring outside the intima. The other clear border, the media-EEM border, is between the dark media and echo dense (bright echo signal) adventitia. Manual or computer-assisted planimetry of these two borders allows precise measurements of the lumen area, intima-media area, and EEM area [10].

MEASUREMENTS OBTAINED FROM IVUS IMAGE

By using direct manual planimetry the reference lumen area (RLA) at the site of intermediate lesion was planimetered and calculated then the stenosis lumen area (minimal lumen area MLA) is measured also by the same technique (direct planimetry).
By using the following equation the percent of stenotic area in comparison to the reference lumen area can be obtained [10].

\[
\text{Area stenosis} = \frac{\text{RLA} - \text{MLA}}{\text{RLA}} \times 100
\]

Measurement of coronary fractional flow reserve (FFR)

The use of diagnostic catheters is technically feasible. However, due to the higher risk of friction hampering wire manipulation, the smaller internal caliber prejudicing pressure measurements and the inability to perform ad hoc PCI using diagnostic catheters, the use of guiding catheters was recommended [11].

The pressure wire system used in this study to measure intracoronary pressure, namely the Pressure Wire Certus (Saint Jude Medical Systems Inc., Uppsala, Sweden). It is a 0.014 inch wires have similar handling characteristics to most standard angioplasty guide wires. The sensor is located 30 mm from the tip, at the junction between the radiopaque and radiolucent portions.

In this study we applied an analyzer termed RadiAnalyzerXpress. The artery of the interest was cannulated using guiding catheter to be ready for ad hoc PCI if indicated. Once the cables were connected to the analyzer, we switched analyzer on and thus the analyzer performed a system check and an auto setup was enabled. Then Equalization of the pressure was done before measuring FFR. [11].

Recording and calculation of FFR

Sensor element was advanced distal to the stenosis of interest. Then we waited for stable baseline pressure values. FFR value was calculated using the following equation: \( \text{FFR}_{\text{myo}} = P_d / P_a \) (where \( \text{FFR}_{\text{myo}} \) is myocardial FFR, \( P_d \) is mean distal coronary (transstenotic) pressure and \( P_a \) is mean arterial pressure) [11] (Figure 1).

In this study intracoronary injection of 150 µ adenosine for left system and 120 µ for right coronary artery was applied to achieve maximum hyperemia. Then FFR was measured again at maximum hyperemia. Coronary Stenosis with FFR value < 0.8 is considered significant [11].

STATISTICAL ANALYSIS

Statistics were done by computer using SPSS. Software, version 20. A word processing, database and statistics program. Descriptive statistics were done using X mean, SD standard deviation to measure the central tendency of data and the distribution of data around their mean value. Student’s t- test: for testing statistical significant difference between mean values of two samples. \( X^2 \) tests (Chi square test) to test for statistical significant relation between different variable or grades in qualitative data. Pearson correlation coefficient test: \( r \) to test for linear relation between two numeric variables. Mann Whitney test: non parametric test for comparing two groups of data not normally distributed or for small sample size. Fisher exact test: for comparing two independent proportions when the expected observation in any cell of the table is below 5. Significant result is considered if \( P \) value < 0.05, highly significant result is considered if \( P \) value < 0.001 and non-significant result is considered if \( P \) value > 0.05.

RESULTS

Thirty patients with intermediate coronary lesions as visualized by traditional coronary angiography were subjected to both invasive and non-invasive assessment of lesion functional significance and ad hoc percutaneous coronary intervention (PCI) if indicated. The mean age of the patients was (57.57 ± 10.30), 25 cases (83.3%) were males and 5 cases (16.7%) were females.

The studied patients were classified into 2 groups: group I included patients with FFR value < 0.8 (14 patients) and group II included patients with FFR value ≥ 0.8 (14 patients). There was statistically no difference between the two groups as regard age and sex (\( P \) value > 0.05).

Regarding cardiovascular risk factors 15 patients (50%) were hypertensive, 17 patients (56.7%) were diabetic, 15 patients (50%) have dyslipidemia and 18 patients (60%) were smokers. There was no significant difference between the studied groups as regard these risk factors except for diabetes mellitus which was significantly more prevalent in patients with FFR value < 0.8 (\( P \) value < 0.05) (Table 1).

LV EF % was significantly lower in patients with FFR value < 0.8 (\( P \) value < 0.05). Moreover the percent of luminal stenosis was significantly higher in the same group (\( P \) value < 0.05). As shown in (Table 1).

According to result of non-invasive stress imaging our patients were further classified into two groups: group A included patients with negative results (53.3%) and group B included patients with positive results for ischemia (46.7%). There was no statistically significant difference between the two groups as regard age, sex and risk factors (\( P \) value > 0.05), however LV EF % was significantly lower in the patients with positive stress tests (\( P \) value < 0.05). Moreover the percent of luminal stenosis was significantly higher in the same group (\( P \) value < 0.05) (Table 2).

By comparing the results of FFR and non-invasive stress imaging we found that among 14 patients with FFR value < 0.8; 12 patients had reversible ischemia in stress test. Additionally among 16 patients with FFR value > 0.8; 14 patients had negative stress test. FFR value had sensitivity and specificity 85.7% &
87.5% respectively to predict result of non-invasive stress test with a predictive value PPV & NPV 85.7% & 87.5% respectively with accuracy 86.7% (Table 3,4) demonstrated the correlation between FFR value and different variables and revealed that there was a significant positive correlation between EF and FFR value on the other hand there was a significant negative correlation between FFR value and blood sugar as well as percent of stenosis as detected by IVUS.

In this study the mean FFR value was (0.805 ± 0.185), the mean luminal area obtained by IVUS was (5.6 ± 2.8) and mean percent of stenosis measured by IVUS was (46 ± 25).

In our study the best cut-off value for MLA measured by IVUS which was concordant with ischemic FFR values was < 4.5 mm² with a sensitivity and specificity 57.1% & 56.3% respectively and a predictive values PPV=53.3% and NPV=60% (Table 5) (Figure 2). Additionally the best cut-off value for MLA which was concordant with the results of non-invasive stress test was 4.5 mm² with sensitivity and specificity 64.3% & 62.5% respectively and a predictive values PPV=60% and NPV=66.7% (Table 6).

**DISCUSSION**

Decisions regarding coronary intervention should be based on objective evidence of myocardial ischemia. Even in the drug-eluting stent era, every coronary intervention carries the risk of procedural-associated complications, late stent thrombosis, and restenosis [12].

Angiography is inaccurate in assessing the functional significance of a coronary stenosis if it is compared with fractional flow reserve FFR especially in intermediate lesions (40% to 70%); this study supports the concept that FFR reliably indicates functionally significant coronary stenosis when compared with non-invasive stress tests [12].

In our study there was no significant difference between the studied groups as regard these risk factors except for diabetes.

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### Table 1: Comparison between different variables in relation to the values of FFR in studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>FFR &lt; 0.80 (no:14)</th>
<th>FFR ≥ 0.80 (no:16)</th>
<th>Test of sign.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.04 ± 10.70</td>
<td>56.75 ± 10.18</td>
<td>T : 0.49</td>
<td>0.625</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>13</td>
<td>X2 : 0.11</td>
<td>0.743</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>3</td>
<td>X2 : 5.13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DM</td>
<td>11</td>
<td>6</td>
<td>X2 : 2.14</td>
<td>0.143</td>
</tr>
<tr>
<td>HTN</td>
<td>5</td>
<td>10</td>
<td>X2 : 0.54</td>
<td>0.464</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>8</td>
<td>7</td>
<td>X2 : 0.20</td>
<td>0.654</td>
</tr>
<tr>
<td>Smoking</td>
<td>9</td>
<td>9</td>
<td>X2 : 0.20</td>
<td>0.654</td>
</tr>
<tr>
<td>EF%</td>
<td>55.7 ± 4.1</td>
<td>64.9 ± 5.9</td>
<td>T : 2.74</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RLA</td>
<td>9.39 ± 2.23</td>
<td>9.39 ± 3.09</td>
<td>T : 0</td>
<td>1</td>
</tr>
<tr>
<td>MLA</td>
<td>4.33 ± 1.10</td>
<td>4.73 ± 1.48</td>
<td>X2 : 0.82</td>
<td>0.417</td>
</tr>
<tr>
<td>% of stenosis</td>
<td>55.5 ± 4.45</td>
<td>46.44 ± 11.62</td>
<td>T : 2.74</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PCI</td>
<td>14</td>
<td>0</td>
<td>X2 : 30</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Abbreviations:** DM: Diabetes Mellitus; HTN: Hypertension; EF: Ejection Fraction; FFR: Fractional Flow Reserve; PCI: Percutaneous Coronary Intervention; RLA: Reference Luminal Area; MLA: Minimal Luminal Area

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### Table 2: Comparison between different variables in relation to the results of non-invasive stress test in studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A Negative stress test (no : 16)</th>
<th>Group B Positive stress test (no : 14)</th>
<th>Test of sign.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.88 ± 10.67</td>
<td>57.30 ± 10.30</td>
<td>T : 0.14</td>
<td>0.894</td>
</tr>
<tr>
<td>Male</td>
<td>12 (75%)</td>
<td>13 (92.8%)</td>
<td>X2 : 1.71</td>
<td>0.1900</td>
</tr>
<tr>
<td>Female</td>
<td>4 (25%)</td>
<td>7 (1.7%)</td>
<td>X2 : 0.62</td>
<td>0.431</td>
</tr>
<tr>
<td>DM</td>
<td>10 (62.5%)</td>
<td>11 (95.8%)</td>
<td>X2 : 2.14</td>
<td>0.143</td>
</tr>
<tr>
<td>HTN</td>
<td>6 (37.5%)</td>
<td>9 (64.2%)</td>
<td>X2 : 2.14</td>
<td>0.143</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6 (37.5%)</td>
<td>9 (64.2%)</td>
<td>X2 : 0.09</td>
<td>0.765</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (62.5%)</td>
<td>8</td>
<td>X2 : 1.71</td>
<td>0.1900</td>
</tr>
<tr>
<td>EF%</td>
<td>64.31 ± 5.58</td>
<td>60.36 ± 5.19</td>
<td>T : 2.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RLA</td>
<td>9.81 ± 3.05</td>
<td>8.93 ± 2.19</td>
<td>T : 0.89</td>
<td>0.378</td>
</tr>
<tr>
<td>MLA</td>
<td>4.91 ± 1.45</td>
<td>4.13 ± 1.03</td>
<td>T : 1.67</td>
<td>0.107</td>
</tr>
<tr>
<td>% of Stenosis</td>
<td>46.63 ± 11.7</td>
<td>55.29 ± 4.65</td>
<td>T : 2.59</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PCI (Yes)</td>
<td>2</td>
<td>12</td>
<td>X2 : 16.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Abbreviations:** DM: Diabetes Mellitus; HTN: Hypertension; EF: Ejection fraction; PCI: Percutaneous Coronary Intervention; RLA: Reference Luminal Area; MLA: Minimal Luminal Area.
Table 3: Sensitivity, Specificity and Predictive values of FFR in relation to stress test.

<table>
<thead>
<tr>
<th></th>
<th>Positive stress test</th>
<th>Negative stress test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FFR &lt; 0.8</strong></td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td><strong>FFR ≥ 0.8</strong></td>
<td>2</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>

Sensitivity of FFR : 12/14 : 85.7%, Specificity : 14/16 : 87.5%, PPV : 12/14 : 85.7%, NPV : 14/16 : 87.5% Accuracy : 26/30 : 86.7%.

Table 4: Correlation between FFR value and other variables.

<table>
<thead>
<tr>
<th>Relation</th>
<th>R</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR and age</td>
<td>-0.07</td>
<td>0.7051</td>
</tr>
<tr>
<td>FFR and EF</td>
<td>0.44</td>
<td>0.0150</td>
</tr>
<tr>
<td>FFR and RLA</td>
<td>0.08</td>
<td>0.6810</td>
</tr>
<tr>
<td>FFR and MLA</td>
<td>0.30</td>
<td>0.1060</td>
</tr>
<tr>
<td>FFR and % of Stenosis</td>
<td>-0.54</td>
<td>0.002</td>
</tr>
<tr>
<td>FFR and Blood Sugar</td>
<td>-0.65</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** FFR: Fractional Flow Reserve, EF: Ejection Fraction, RLA: Reference Luminal Area; MLA: Minimal Luminal Area

Table 5: The best cut-off level of MLA in relation to FFR value.

<table>
<thead>
<tr>
<th>Cut-off level of MLA</th>
<th>Sensitivity%</th>
<th>Specificity%</th>
<th>PPV %</th>
<th>NPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8 mm²</td>
<td>28.6</td>
<td>68.8</td>
<td>44.4</td>
<td>5.24</td>
</tr>
<tr>
<td>4 mm²</td>
<td>35.7</td>
<td>56.3</td>
<td>41.7</td>
<td>50</td>
</tr>
<tr>
<td>4.5 mm²</td>
<td>57.1</td>
<td>56.3</td>
<td>53.3</td>
<td>60</td>
</tr>
<tr>
<td>5 mm²</td>
<td>71.4</td>
<td>37.5</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

**Abbreviations:** MLA: Minimal Luminal Area; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Table 6: The best cut-off level of MLA in relation to stress test.

<table>
<thead>
<tr>
<th>Cut-off level of MLA</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8 mm²</td>
<td>35.7</td>
<td>75</td>
<td>55.6</td>
<td>57.1</td>
</tr>
<tr>
<td>4 mm²</td>
<td>50</td>
<td>68.8</td>
<td>58.3</td>
<td>61.1</td>
</tr>
<tr>
<td>4.5 mm²</td>
<td>64.3</td>
<td>62.5</td>
<td>60</td>
<td>66.7</td>
</tr>
<tr>
<td>5 mm²</td>
<td>78.6</td>
<td>43.8</td>
<td>55</td>
<td>70</td>
</tr>
</tbody>
</table>

**Abbreviations:** MLA: Minimal Luminal Area; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Figure 2 ROC Curve for detection of the best cut-off value of MLA in relation to FFR value.

mellitus which was significantly more prevalent in patients with FFR value < 0.8 (P value < 0.05). also there was a highly significant negative correlation between FFR value and DM (P value < 0.001) reflecting the impact of glycemic state on FFR value and this agreed with a clinical research done by Sebastian Reith et al., who found that intermediate coronary lesions differed significantly in diabetics versus non diabetics in both hemodynamic relevance (FFR < 0.80, 37.7% vs 24.2% respectively P< 0.05) and lesion
length (10.91 ± 5.79 mm vs 9.23 ± 3.85 mm respectively P<0.05) [13].

In our study we compared the results of FFR and non-invasive stress imaging and found that among patients with FFR value < 0.8; 12 patients had reversible ischemia in stress test and only two patients had a negative stress test, it may be attributed to the fact that non-invasive stress test in some patients may be inconclusive as the sensitivity and specificity of SPECT for the diagnosis of coronary stenosis (defined as > 50% stenosis) is 86% and 74%, respectively [14]. A false negative study may be a feature of three-vessel and left main stem disease. It is due to balanced ischemia phenomenon as in those with multivessel disease. False positive tests due to attenuation artifacts lower the specificity [15].

It was evident in our study that there was statistically significant relation between FFR value and results of non-invasive stress test as FFR has a sensitivity and specificity 85.7% & 87.5% respectively to predict the result of non-invasive stress test whether positive or negative with a predictive value PPV & NPV 85.7% & 87.5% respectively and a diagnostic accuracy 86.7%.

The high both positive and negative predictive value of FFR in relation to non-invasive stress test made it a powerful diagnostic tool for diagnosis of functionally significant coronary artery stenosis that can induce myocardial ischemia. In agreement with our study Jagdish H et al., who studied 20 patients with angiographically intermediate coronary stenosis and compared the stress test results with the results of FFR, in all 13 patients with an FFR of < 0.75, reversible myocardial ischemia was demonstrated. In contrast, 5 of 7 patients with an FFR of > 0.75 showed a negative non-invasive stress test for reversible myocardial ischemia. No revascularization procedures (PCI) were performed in 7 (35%) patients who already had FFR value > 0.75 [16].

Our study showed a statistically highly significant relation (p < 0.0001) between FFR value and PCI, as all cases with FFR value < 0.80 (14 cases) already performed PCI and those with a FFR value ≥ 0.80 did not, there was also a statistically highly significant relation (p < 0.0001) between results of non-invasive stress test and doing PCI as 12 cases (out of 14 cases with positive stress test) already performed PCI and on the other hand only 2 cases (out of 16 cases with negative stress test) who did PCI thus patients with coronary stenosis of intermediate severity, FFR appears to be a useful diagnostic index equivalent to objective non-invasive stress imaging tests to assess the functional severity of coronary stenosis and thus the eligibility for coronary revascularization.

According to an expert consensus statement published recently by Amir Lotfi et al., it revealed that FFR was first validated using a cutoff value of 0.75. With further experience with the technique, investigators appreciated that by extending the cutoff value to 0.80, the sensitivity of FFR could be improved without greatly compromising the specificity [17].

For this reason, a cutoff value of < 0.80 was used in FAME 1 [9] and FAME 2 studies as well as our study and shown to be clinically valid. It is now the recommended ischemic reference standard for the invasive functional assessment of myocardial ischemia [15].

The use of IVUS to determine the functional significance of coronary artery lesions remains a matter for debate. As regard IVUS measurements obtained from this study including minimal luminal area and percent of stenosis, there was no statistically significant difference among the studied groups as regard minimal luminal area. On the contrary the percent of luminal stenosis was significantly higher in the patients with FFR value <0.8 and those with positive stress test (P value <0.05). Moreover there was a significant negative correlation between FFR value and percent of stenosis detected by IVUS.

According to our study, it is demonstrated that the best cutoff value for MLA which is corresponding to the results of non-invasive stress test and may be able to discriminate functionally significant coronary artery stenosis was an MLA < 4.5 mm² showing sensitivity and specificity 64.3% &62.5% respectively and a predictive values PPV=60% and NPV=66.7%. In the current study the suggested MLA cutoff value had a low PPV & NPV for clinical decision making. In addition, the agreement of the result between MLA and myocardial SPECT was poor. So MLA < 4.5 mm² is considered a weak diagnostic tool in relation to non-invasive stress test for diagnosis of functionally significant myocardial ischemia.

Despite lack of data in this concern, Jung-Min Ahn et al., published a paper that evaluated the ability of minimal luminal area (MLA) measured by intravascular ultrasound (IVUS) to assess the functional significance of coronary stenosis. The best cutoff value of MLA was ≤ 2.1 mm² with 86.7% sensitivity, 50.4% specificity, 38.6% positive predictive value, and 91.3% negative predictive value versus lesions with a positive SPECT [18].

A previous study evaluated 300 patients with 357 de novo intermediate native coronary lesions and confirmed the clinical usefulness of IVUS when intervention was deferred based on MLA > 4 mm², with event rate of 4.4% and target lesion revascularization rate of 2.8% during a mean follow-up of 13 months [19].

Although MLA is an important factor to determine the coronary blood flow, other anatomical factors measured by IVUS also act as the resistance to the flow. Therefore, a single parameter such as IVUS MLA may have limitations for predicting the result of myocardial SPECT. In our study it is demonstrated that a MLA < 4.5 mm² has a sensitivity 57.1% and specificity 56.3% in relation to FFR value < 0.8, so MLA <4.5 mm² is considered a weak diagnostic tool in relation to FFR for diagnosis of functional myocardial ischemia.

The results of the FIRST study (Fractional Flow Reserve and Intravascular Ultrasound Relationship Study) are presented by Waksman et al., to evaluate the correlation between FFR and IVUS parameters and try to identify IVUS predictors of ischemic FFR (defined as FFR < 0.80). The main findings of the FIRST are: 1) anatomic measurements by IVUS show a moderate correlation with the FFR values; 2) an MLA < 3.07 mm² is the best overall threshold value for identifying ischemic FFR and 3) the accuracy can be improved by a reference vessel-specific analysis [20].
Although a very high negative predictive value for IVUS-MLA > 3.07 mm² may basically rule out functionally significant stenosis. However, Magni V et al., concluded that the issue of superiority between these 2 modalities might be irrelevant because IVUS and FFR should be complementary techniques to be used in the catheterization laboratory to provide critical anatomic and functional data that permit more accurate decisions in the management of the patient [21].

The major differences between our study and FIRST registry were related to First: number of patients included in both studies being only 30 patients in our study and 350 patients (367 lesions) in FIRST registry. Second: our study is unicenter research on the other hand FIRST trial was a multicenter registry. Third: the accuracy of FIRST study improved by a reference vessel-specific analysis unlike our study that were performed only on the large epicardial vessels and this made the best cutoff value obtained in our study was larger than in FIRST registry 4.5 mm² and 3.07 mm² respectively. The results of the FIRST will certainly reinforce the view that IVUS is not a reliable alternative for FFR in functional assessment of angiographically intermediate stenoses. FFR is superior for physiology and IVUS is superior for anatomy [20].

Bon-Kwon Koo et al., published a study aimed to determine the optimal MLA obtained by intravascular ultrasound (IVUS) and its diagnostic accuracy for defining the functional significance of intermediate coronary stenoses in different locations of the coronary tree among patients with already FFR value less than 0.80. The best cutoff value of MLA to define the functional significance was 3.0 mm² for proximal left anterior descending artery (LAD) lesions and 2.75 mm² for mid-LAD lesions. So when IVUS parameters are used to determine the functional significance of lesions in patients with intermediate coronary artery stenoses, different criteria should be used according to lesion location. In segments or vessels with anatomic variations, IVUS cannot be used for functional assessment of a stenosis [22].

Furthermore Ben-Dor I et al., studied 92 intermediate lesions from 84 patients and concluded that MLA of < 2.8 mm² and < 3.2 mm² best correlated with an FFR < 0.75 and < 0.80, respectively [23].

Taken together, these studies mentioned above suggested that an MLA ≥ 4.0 mm² can accurately identify non-ischemic lesions for which PCI can be safely deferred. By contrast, an MLA < 4.0 mm² does not accurately predict a haemodynamically significant lesion and should not be used to justify revascularization. The significance of an MLA < 4.0 mm² should be considered in the context of reference vessel size, lesion length, area stenosis, plaque burden, and area of myocardium at risk. Whereas FFR is the preferred tool for intermediate lesion assessment, an algorithm for contemporary IVUS guided PCI of non–left main lesions is proposed in [24].

In practical terms, IVUS has a limited role in the functional assessment of intermediate stenosis to accurately identify ischemia-inducible lesions and ascertain the indication for revascularization, but is a valuable and established tool to guide a percutaneous coronary intervention.

**STUDY LIMITATIONS**

**First**

The major limitation of this study is the number of patients included in this study which is too small to make definitive conclusions and this issue was obvious as regard cutoff value of MLA corresponding to functional myocardial ischemia.

**Second**

The study performed mainly on large epicardial vessels and did not include small branches eg diagonal and obtuse marginal branches. This made the cutoff value of MLA proposed by our study not sufficient and larger than other studies.

**Third**

The possibility of catheter-induced spasm during introduction of IVUS probe could not be completely excluded particularly in small caliber vessels. Fifth: The cutoff points of minimum lumen diameter suggested in our study cannot be applied to lesions with multiple stenoses.

**Fourth**

The cutoff points of minimal luminal area proposed in our study cannot be applied alone as an accurate diagnostic tool for assessment of severity of coronary artery stenosis in relation to FFR value and non-invasive stress test as other parameters such as lesion length and plaque burden should be incorporated in order to improve diagnostic accuracy.

**Finally**

Clinical outcomes could not be evaluated in this study. The outcomes of FFR-guided versus IVUS-guided revascularization strategy need to be evaluated in future randomized trials.

**CONCLUSION**

Measuring FFR during coronary angiography is useful in determining whether intermediate stenosis is functionally important and may therefore be responsible for reversible myocardial ischemia. In this study, the accuracy of FFR for this purpose was equivalent to that of the information provided by the non-invasive tests. Therefore it is believed that FFR may be useful in clinical decisions about revascularization in patients with intermediate stenosis when objective evidence of reversible ischemia is lacking.

**REFERENCES**


