The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 3517-3522

Assessment of the Functional Significance of the Intermediate Coronary Lesions with Intravascular Ultrasound (IVUS) and it's Correlation with Fractional Flow Reserve (FFR)

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ABSTRACT

Background: Worldwide, coronary artery disease (CAD) continues to be a leading cause of morbidity and mortality. Myocardial ischemia symptoms will be present in a large proportion of patients with obstructive CAD; hence it is important for doctors to make informed judgements about revascularization.

Objectives: The aim of the current work was to employ two independent minimally invasive modalities, fractional flow reserve (FFR) and intravascular ultrasound (IVUS), to evaluate the functional relevance of intermediate coronary artery lesions identified by visual evaluation by coronary angiography.

Patients and methods: This study comprised a total of 40 patients, hospitalized at the National Heart Institute and other facilities who underwent elective coronary angiography (40% to 70% by visual evaluation) for moderate non-left main coronary artery disease at one or more major epicardial coronary arteries. Patients were assessed by FFR, IVUS.

Results: The optimum minimum lumen area (MLA) cutoff value that compatible with ischemic FFR readings was 3 mm^2, which had a sensitivity of 78.92%, a specificity of 53%, and predictive values of 46.5% and 81%. Additionally, evaluation of the coronary artery lesions in accordance with the locations of the lesions in the primary epicardial vessels and the correlation between the MLA gathered by IVUS and the FFR values for these lesions were detected to determine the best cutoff value for each vessel individually.

Conclusion: It could be concluded that there is no statistical relevance between the target vessel and FFR. The FFR score and the presence or absence of diabetes were statistically significantly correlated.

Keywords: Fractional Flow Reserve**,** Intermediate coronary lesions and Intravascular Ultrasound.

INTRODUCTION

Worldwide, coronary artery disease (CAD) continues to be a leading cause of morbidity and mortality. Myocardial ischemia symptoms are present in a large proportion of patients with obstructive CAD, hence it is important for doctors to make informed judgements about revascularization. Invasive coronary angiography has historically been the gold standard test to determine the severity and scope of CAD. Yet, angiography has its limitations since it depicts a more intricate three-dimensional structure in two dimensions. Vessel foreshortening or overlay can also make it difficult to interpret pictures, and it can be difficult to accurately determine the degree of stenosis in extremely eccentric lesions. Previous investigations have shown the fallibility of stenosis severity on angiography, showing a 15–45% inter-observer variation in diameter stenosis. Hence, it is imprecise to estimate the degree of stenosis visually, with up to 30% of angiographic assessments being shown to be inaccurate [(1)].

Patients frequently fall into the category of "moderate" stenosis severity because of the inherent challenges in accurately assessing stenosis on angiography. An angiographic stenosis of between 30% and 70% is referred to as intermediate stenosis, and it poses a unique therapeutic problem with uncertainties regarding the best method of evaluation and treatment [(2)]. Registry data indicates that it may be present in up to 25% of patients having coronary angiography, even though the frequency of the condition in the general population is unknown [(3)].

A catheter-based imaging technique called intravascular ultrasonography (IVUS) produces cross-sectional pictures of the coronary artery that allow for measurements of the luminal and vessel regions [(4)]. When IVUS was first created in the 1970s, its primary use was to assess plaques in atherosclerotic coronary arteries [(5)]. However, with the advent of automatic lesion analysis software and improved imaging of metallic stent struts, the application of IVUS was expanded to include the successful implantation of coronary stents [(5)]. At this time, IVUS can reliably determine the load, morphology, and features of plaques. When angiographic diameter stenosis is deemed uncertain or inaccurate, IVUS quantification of coronary stenosis can be very helpful since it has less anatomic restrictions than angiography [(6)]. Yet, conducting Percutaneous Coronary Intervention (PCI) may be the most crucial use of IVUS in contemporary clinical practice. For the examination of lesions prior to PCI in difficult instances such left main (LM) stenosis, calcified lesions, or bifurcations, IVUS is a highly helpful tool [(7)].

To assess stent size, expansion, apposition, and edge dissection during PCI, IVUS is also beneficial [(5)]. It can be utilized to identify the factors leading to stent failure during PCI, including as in-stent restenosis and stent thrombosis (ST) [(8)].

Most specialists concur that IVUS advice enhances the effectiveness and results of PCI. Compared to angiography-guided PCI, IVUS-guided PCI has been demonstrated in several trials to be linked with decreased incidence of adverse clinical events [(9-12)].

Received: 22/10/2022
Accepted: 25/12/2022

The gold standard for determining the functional importance of angiographically intermediate lesions is fractional flow reserve (FFR) [13]. There have been several attempts to link IVUS data with the functional relevance of stenotic lesions, even though the positive predictive values of IVUS measurements were unsatisfactory for the detection of ischemia [14]. The information that is currently available on the connection between anatomic IVUS parameters and functional FFR outcomes has come from retrospective data analysis and is inconsistent. Moreover, the ideal minimum lumen area (MLA) cutoff value using IVUS for FFR & Lt.; 0.80 has not been well established [15, 16, 17], and it is still debatable whether IVUS MLA can be a trustworthy substitute to FFR in identifying the functional state of intermediate lesions. As a result, this study's goal was to assess the functional significance of intermediate coronary artery lesions discovered through visual assessment using coronary angiography by using two different minimally invasive modalities, fractional flow reserve (FFR) and intravascular ultrasound (IVUS).

PATIENTS AND METHODS

This study comprised a total of 40 patients, hospitalized at the National Heart Institute and other facilities who underwent elective coronary angiography (40% to 70% by visual evaluation) for moderate non-left main coronary artery disease at one or more major epicardial coronary arteries. Patients were assessed by using FFR, IVUS.

Exclusion criteria: Patients who had a prior coronary artery bypass graft (CABG), patients with chronic complete blockage of a left main coronary lesion, or those who were not eligible to receive adenosine.

Each patient was subjected to complete history taking. A thorough medical history was gathered, with an emphasis on coronary artery disease risk factors (hypertension, smoking, dyslipidemia, and diabetes mellitus), serum urea and creatinine levels, a 12-lead electrocardiogram taken while resting, a transthoracic echocardiogram (TTE) with a focus on left ventricular ejection fraction (LVEF) by both eyeballing and standard M-mode, and resting segmental wall motion abnormalities (RWMA). Also, coronary angiography using the authorized technique was carried out to examine any potential borderline lesions that may be included in our study as well as to get a complete morphological and accurate imaging of the coronary arteries. Adenosine infusion-induced hyperemia was emphasized by the estimation of coronary fractional flow reserve (FFR), and lesions with FFR less than 0.80 were considered functionally significant. At the site of the intermediate lesion, the reference lumen area (RLA), stenosis lumen area, and minimum lumen area were all be measured and calculated (MLA).

Ethical consideration:

This study was ethically approved by Menoufia University Hospitals' Ethical Scientific Committee. Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

Using technologies that are considered industry standards, such as Microsoft Excel 2019 and SPSS V.25, the data were tabulated and statistically evaluated. Quantitative data were expressed using the mean () SD, whereas qualitative data were expressed using frequency and percentage. To find the mean, divide the total number of observations by the total number of observations. The standard deviation calculates how much different kinds vary from their mean. Analytical statistics include the ROC (receiver operating characteristic) curve, Fisher's exact test, Mann-Whitney test, Chi-Squared (2), and correlation coefficient test (Person test). The definition of a significant level is p0.05.

RESULTS

Patients average age was (58.55 ± 7.89) ranged from 34 to 76 years. Regarding gender, (70%) of the population were males while (30%) were females. Also, 77.5% of cases had diabetes mellitus. While 22.5% were nondiabetics. Moreover, 47.5% of the total population were hypertensive, while (52.5%) of the total population were non hypertensive. Also, (72.5%) of the total population were dyslipidemic, while (27.5%) of the total population were non dyslipidaemic. the mean Ejection fraction was (62.03 ± 5.88) %. The mean creatinine level was (0.96 ± 0.19) mg/dL. Also, coronary angiography done to the patients revealed that 85% showed intermediate stenosis in only one vessel and 10 % showed stenotic lesions affecting two different vessels and 5 % had lesion affecting three vessels. Analysis of the patients' coronary angiographies showed that 40 patients had 48 different lesions, and 6 of them had multiple lesions in the coronary vasculature. These lesions were divided into three groups based on their anatomical locations: the left circumflex artery (LCX), which contained 15 lesions, the left anterior descending artery (LAD), which contained 23 lesions, and the right coronary artery (RCA), which contained 10 lesions. Also, the various measurements taken from the research group, such as the percentage of stenosis discovered by ocular evaluation, minimum luminal areas (MLA), FFR score obtained by IVUS and are tabulated in the following table demonstrating that the minimum and maximum visual degree of stenosis ranged from 50% to 70% with mean standard deviation (60.25 ±6.79 %) and FFR measurement ranged from 0.7 to 0.96 with mean standard deviation (0.82± 0.06) the minimum luminal regions (MLA) obtained by IVUS ranged from 2.40 to 4.80 cm^2 with mean standard deviation (3.38± 0.56) **(Tables 1).**

Table (1): Summarizes the patient's risk factors for coronary artery disease, the location of the lesion, the PCI that was performed on the vessel, the presence of visual stenosis, FFR, and MLA.

Variables	**Count**		**%**
Age/year	Mean± SD	58.55±7.89	
	Range	34.00-76.00	
Sex	Female	12	30.0%
	Male	28	70.0%
Diabetes Mellitus (DM)	Yes	31	77.5%
	No	9	22.5%
Hypertension (HTN)	Yes	19	47.5%
	No	21	52.5%
Smoking	Yes	24	60.0%
	No	16	40.0%
Dyslipidemia	Yes	29	72.5%
	No	11	27.5%
Ejection fraction (EF) %	Mean ± SD Range	62.03±5.88 (50.00-76.00)	
Creatinine (mg/dl)	Mean ± SD Range	0.96±0.19 (0.60-1.50)	
Number of diseased vessels	One	34	85.0%
	Two	4	10.0%
	Three	2	5.0%
Site of Lesion	LAD	23	48%
	LCX	15	31%
	RCA	10	21%
		Mean± SD	**Range**
Visual degree of stenosis (%)		60.25±6.79	50.00-70
FFR measurement		0.82±0.06	0.70-0.96
Minimal lumen area by IVUS (cm^2)		3.38±0.56	2.40-4.80
PCI done to the vessel.	Yes	16	40%
	No	24	60%

Patients were divided into two categories according to FFR value either more than or less than 0.8. The study demonstrated no significant correlation between FFR value and the study group demographic data. Also, there was statistically significant relation between presence or absence of diabetes and FFR value p= 0.006 in this study 16 lesions (out of 16 patients with FFR value < 0.80) their patients found to be diabetic and only 15 patients (out of 24 patients) with FFR value > 0.80. In addition, it is evident that there no statistical significance between target vessel and FFR **(Tables 2).**

Table (2): Relation between FFR value and coronary risk factors, ejection fraction, creatinine level and site of lesion.

		FFR				
		>0.8		**<0.8**		**P value**
		Count	**%**	**Count**	**%**	
Age	Mean±SD	58.29±10.06		57.13±7.02		0.690
Sex	Female	9	37.5%	3	18.8%	0.297
	Male	15	62.5%	13	81.3%	
DM	Yes	15	48.4%	16	51.6%	**0.006***
	No	9	100.0%	0	0.0%	
HTN	Yes	12	63.2%	7	36.8%	0.698
	No	12	57.1%	9	42.9%	
Smoking	Yes	14	58.3%	10	41.7%	0.792
	No	10	62.5%	6	37.5%	
Dyslipidemia	Yes	20	69.0%	9	31.0%	0.080
	No	4	36.4%	7	63.6%	
Ejection fraction (EF)	Mean ±SD	63.25±5.56		61.63±6.27		0.395
Creatinine (mg/dl)	Mean ±SD	1.01±0.22		0.91±0.18		0.128
Site of Lesion	LAD	14	60.9%	9	39.1%	1.00
	LCX	10	66.7%	5	33.3%	
	RCA	8	80%	2	40%	

To maintain consistency with ischemic FFR readings, the optimal cut-off value for MLA is 3 mm^2, which has a sensitivity of 78.92%, a specificity of 53%, and predictive values of 46.5% and 81%. The position of the coronary artery lesions in relation to the major epicardial vessels and the relationship between the MLA obtained by IVUS and the FFR values for these lesions were also taken into consideration to calculate the appropriate cutoff value for each vessel separately. With specificity and sensitivity of 87.50% and 40%, respectively, and predictive values of PPV=53.8% and NPV=80%, the optimal cutoff MLA for LAD vessel lesions were 3.2mm^2 (Table 3).

Table (3): The relationship between FFR readings and the sensitivity, specificity, and predictive value of various minimum luminal area (MLA) cut-off values acquired by IVUS.

Cut off points	Sensitivity	Specificity	+PV	-PV
≤ 2.5 mm^2	23.1	95.80	75.0	69.7
≤3 * mm^2	78.92	53.00	46.5	81.0
≤3.2 mm^2	76.92	41.67	41.7	76.9
≤3.4 mm^2	84.62	41.67	44.0	83.3
≤3.9 mm^2	84.62	33.33	40.7	80.0
≤4 mm^2	92.31	4.17	34.3	50.0

The optimum cutoff for LCX detection was 3 mm^2, which also had sensitivity and specificity values of 33.33% and 100%, respectively, as well as anticipating values of 100% and 66.7 percent. Moreover, the sensitivity, specificity, and predictive values for RCA were 50,0 %, 100 %, and 2.8 mm2, respectively (Figure 1; Tables 4).

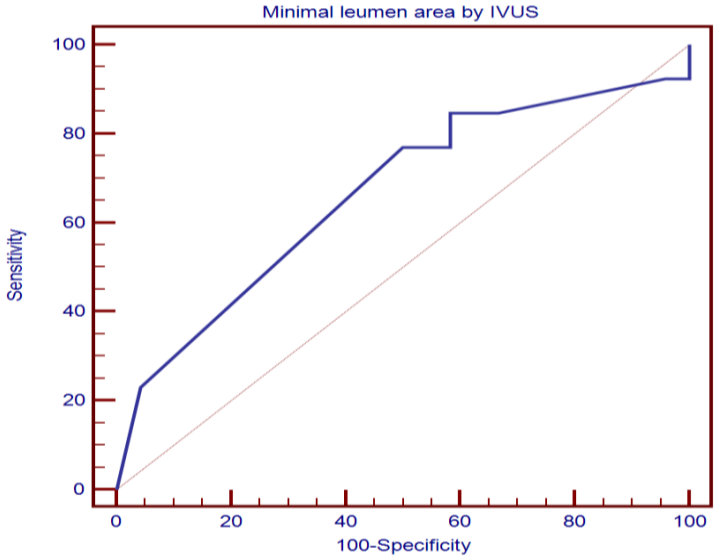

Figure (1): ROC curve for determining the optimal MLA cut-off value *(3 mm^2)* in relation to FFR value.

Table (4): The FFR in LAD, LCX, and RCA in relation to the sensitivity, specificity, and predictive value of different cut-off values for minimum luminal area (MLA) acquired by IVUS.

Cut off points	Sensitivity	Specificity	+PV	-PV
≤ 2mm^2	25.00	90.00	66.7	60.0
≤ 3.2 mm^2	87.50	40.00	53.8	80.0
≤ 5 mm^2	87.50	0.00	41.2	0.0
	MLA determined by IVUS in relation to FFR in LCX			
≤ 2.5 mm^2	33.33	100.00	100.0	66.7
≤ 3 mm^2	33.33	100.00	100.0	66.7
≤ 3.2 mm^2	66.67	50.00	50.0	66.7
	MLA determined by IVUS in relation to FFR in RCA			
< 2.8 mm^2	0.00	100.00		75.0
≤2.8 mm^2	50.00	100.00	100.0	85.7
≤3 mm^2	100.00	33.33	33.3	100.0

DISCUSSION

Coronary angiography is a poor method for detecting ischemia-producing stenosis in individuals with multivessel CAD, as shown by the FFR. In addition, in the category 50% to 70% stenosis (intermediate coronary lesions), and in the category 71% to 90% stenosis also exhibits this difference between angiographic and functional stenosis severity [(18)]. Coronary stenosis has been extensively evaluated using intravascular ultrasonography (IVUS), either objectively or subjectively. Compared to PCI guided by angiography alone, IVUS has reportedly been shown to enhance clinical results [(19)]. Therefore, the goal of our study was to further assess the relationship between quantitative coronary angiography (QCA), FFR, quantitative and qualitative IVUS to ascertain whether MLA obtained from IVUS can be used as an indicator in the diagnosis of functionally significant coronary artery stenosis in the presence of intermediate coronary lesions.

Lotfi *et al.* [(6)] produced an expert consensus declaration. It was shown that in cases with SIHD, FFR should be utilized to evaluate the functional importance of intermediate coronary stenosis (50-70%) and more severe stenosis (90%). This is because noninvasive stress imaging is sometimes contraindicated, inconsistent, non-diagnostic, or unavailable. As compared to PCI guided by angiography alone, PCI guided by FFR measurement improves outcomes and conserves costs in patients with multivessel coronary disease. Measuring FFR in patients with three-vessel coronary disease may enable reclassification of the number of diseased vessels and/or SYNTAX score, guiding choices between CABG and PCI. As compared to medical treatment alone, PCI of lesions with FFR 0.80 in SIHD improves symptom management and reduces the requirement for hospitalization necessitating urgent revascularization.

In the present study, 48 intermediate non-left main coronary lesions in major coronary arteries with RVD were analyzed (3-5 mm). Most of the targeted lesions were situated in the proximal and mid coronary segments of the vessels in order to prevent any lesion in the small branches, such as the diagonal and small obtuse marginal branches, from influencing the outcome regarding the ideal MLA that could anticipate the functional relevance of any intermediate coronary artery lesion impacting the main coronary vessels. There were no statistically significant differences in the population's demographics or coronary risk factors, except for diabetes mellitus, where 16 out of 16 patients with FFR values less than 0.8 had the disease. Additionally, there was a strong relationship between FFR value and DM, highlighting the influence of glycemic state on FFR value. This is aligned with clinical evidence demonstrating the validity of FFR assessment as a diagnostic tool [(20)]**.** Moreover, in both diabetics and individuals without diabetes, LL had the greatest influence on the FFR-derived estimate of hemodynamic significance. These results are true for all diabetic individuals with moderate grade coronary stenosis, regardless of how well their blood sugar is controlled.

Nonetheless, there is still some controversy around the usage of IVUS to assess the functional relevance of coronary artery abnormalities. Regarding the IVUS data from our investigation, which included both the minimal luminal area and the degree of stenosis, the optimum cut-off for MLA, which corresponds to the findings FFR values, is shown to have sensitivity and specificity of 78.92% and 53% for MLA3 mm^2, respectively, and predictive values of 46.5% and 81% for MLA3 mm^2.

Waksman *et al.* [(8)] presented the findings of the first research (Fractional Flow Reserve and Intravascular Ultrasound Relationship Study) to determine the IVUS predictors of ischemic FFR (defined as FFR0.80) and to assess the link between FFR and IVUS characteristics. The FIRST's key conclusions were: The most accurate threshold value for ischemia FFR diagnosis is an MLA 3.07 mm, and a reference vessel-specific study can improve the precision. The FFR values and anatomic measures obtained by IVUS show a satisfactory relationship. Our study only included 40 patients, whereas FIRST registry had 350 individuals with 367 lesions. This was one of the main disparities between our study and FIRST registry. Second: In contrast to First, the most of targeted lesions in our investigation were found in the proximal and mid portions of the main coronary veins rather than the distant segments or side branches.

The first's findings undoubtedly confirmed that the FFR measures and the anatomic evaluations of intermediate coronary lesions acquired by IVUS had a reasonable association. In vessels with a wider diameter, the association between MLA cutoff and FFR values was more favorable. For different vessel sizes, different MLA cutoffs had to be utilized. For the diagnosis of ischemia in intermediate lesions, defined as 40% to 80%, plaque composition as determined by virtual histology IVUS did not correlate with FFR. IVUS MLA may not be as accurate as FFR as a guidance for intervention in intermediate lesions, hence this should be validated clinically.

In their study, **Ben-Dor *et al.*** [(21)] found that the diagnostic accuracy of MLA was extremely different depending on the site of lesions. In our investigation, the optimal cut off MLA for LAD vascular lesions was 3.2 mm^2, for LCX it was 3 mm^2, and for RCA it was 2.8 mm^2. For proximal left anterior descending artery (LAD) lesions and mid-LAD lesions that were found before the second diagonal branch, 3.0 mm and 2.75 mm, respectively, were the optimal cutoff values of MLA to identify the functional relevance. They concluded that IVUS and

FFR are complementing procedures that have both been employed in the catheterization lab to deliver vital anatomical and functional information on stenoses of moderate severity. However, the appropriate MLA to predict the functional significance of lesions could not be found in other segments.

CONCLUSIONS

It could be concluded that there is no statistical relevance between the target vessel and FFR. The FFR score and the presence or absence of diabetes were statistically significantly correlated. A 3 mm^2 cutoff with sensitivity and specificity of 33.33% and 100%, respectively, was the best for LCX. Also, the RCA had a 2.8 mm^2 area, a sensitivity and specificity of 50% and 100%, respectively, and predictive values of 100% and 85.7 percent. In our investigation, the optimal cutoff MLA for LAD vessel lesions was 3.2 mm^2, 3 mm^2 for LCX, and 2.8 mm2 for RCA.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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