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REVIEW

Impact of fractional flow reserve on decision-making in daily clinical practice: A single center experience in Egypt

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ABSTRACT

Background: Fractional flow reserve (FFR) is the reference standard for the assessment of the functional significance of coronary artery stenoses, but remains underutilized. Our aims were to study whether FFR changed the decision for treatment of intermediate coronary lesions and to assess the clinical outcome in the deferred and intervention groups.

Methods: In this retrospective study, coronary angiograms of patients with moderately stenotic lesions (40–70%) for which FFR was performed were re-analyzed by three experienced interventional cardiologists (blinded to FFR results) to determine its angiographic significance and whether to defer or perform an intervention.

Results: We revised 156 equivocal lesions of 151 patients. The clinical presentation were stable angina (65.6%) and acute coronary syndrome in (34.4%). All reviewers had concordant agreement to do PCI in 59 (37.8%) lesions based on angiographic assessment. Interestingly 23 (39%) of these lesions were functionally non-significant by FFR. The reviewers agreed to defer 97 (62.2%) lesions, however, 32 (33%) of these lesions were functionally significant by FFR and necessitated PCI. MACE were similar in both groups (1.5% vs 2.4%, p = 1.0).

Conclusion: Mismatches between visually- and FFR- estimated significance of intermediate coronary stenosis are frequently encountered across a wide spectrum of clinical presentations. FFR leads to a change in decision for coronary intervention. The clinical and cost implications of such changes-in areas with limited resources- needs further evaluation.

Contents

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; FFR, fractional flow reserve; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non ST segment elevation myocardial infarction; OPD, outpatient department; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiographic; STEMI, ST segment elevation myocardial infarction; TLR, target lesion revascularization.

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1. Introduction

Fractional flow reserve (FFR) is currently considered the gold standard for assessment of functional significance of coronary stenosis and the expected benefit from revascularization.[1,2] The FFR provides a well-defined cut-off value for deciding whether to revascularize immediately or to defer intervention.

Several studies have investigated methods for identifying patients that might benefit from FFR-guided percutaneous coronary angiography (PCI) including stable patients with single or multi-vessel coronary artery disease,[3,4] equivocal left main lesions, and bifurcation lesions.[5,6] In addition, FFR has been validated for patients with acute coronary syndrome.[7]

FFR guided PCI has been associated with significantly better long term clinical outcome in several large randomized trials.[8]

Interestingly, despite these apparent benefits, less than 10% of coronary procedures use adjunctive intracoronary imaging or use FFR to guide management.[9] This is due to various practical limitations such as the added time and extra cost associated with the use of a coronary pressure wire and the need for intracoronary or intravenous administration of adenosine.

In daily clinical practice, many patients undergo coronary angiography without objective evidence of ischemia. Traditionally cardiologists trained to assess lesion severity with angiogram and quantitative coronary angiographic (QCA) measurement, and their clinical judgment. However, several studies showed significant inter-observer and even intra-observer variability.[4,10] No reliable solid data showed that whether multiple observers could yield results that are more consistent with FFR.

The aims of the study were to (1) study whether FFR changed the decision for treatment of intermediate coronary artery lesions (2) To assess the clinical outcome in the deferred and intervention groups in the real-world.

2. Materials and methods

2.1. Study design

This was an observational, retrospective cohort study that included 151 patients who underwent functional assessment of intermediate coronary lesions (156 lesions) by FFR during coronary angiography for patients with stable coronary disease, or acute coronary syndrome (non-culprit vessel) in the interval between January 2013 and December 2015 in Aswan Heart Center. Ethics Committee's approval was obtained for the study protocol.

For all patients who were enrolled in the study; age, gender, traditional risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking history), history of coronary artery disease (CAD) (previous PCI or coronary artery bypass graft surgery (CABG), clinical status at time of presentation (stable angina pectoris, unstable angina pectoris, non-ST elevation myocardial infarction (NSTEMI) or STEMI, estimated ejection fraction by echocardiography was recorded and analyzed.

Each coronary angiography for these patients was re-analyzed by three expert interventional cardiologists (>200 PCI/year), independently from each other, to determine the angiographic significance of these lesions and the need for revascularization based on visual assessment and blinded to the previous FFR values. Concordant agreement was considered when at least two operators had the same decision.

2.2. Coronary angiography and FFR protocol

Coronary angiographic imaging was performed in accordance with conventional standard techniques. FFR assessment were performed for all lesions that had been judged equivocal by the operator at the time of coronary angiography. After intravenous administration of heparin at a dose of 70 IU/kg, evaluation was performed with a 0.014-inch intracoronary pressure wire (Pressure Wire, Certus or Aeris, Radi Medical Systems; (St Jude Medical, Minneapolis, MN, USA) as described previously.[11,12] First, intracoronary 200 micrograms isosorbide dinitrate was injected then reactive hyperemia was induced using intracoronary adenosine (200 micograms for left coronary and 100 micograms for right coronary), FFR $\leq$ 0.80 was used as the cut-off to indicate functionally significant coronary artery lesions. PCI was performed for lesions $\leq$ 0.80 (intervention group), while those with FFR > 0.8, optimal medical treatment (deferred group) was achieve using clinician judgment. PCI was performed with the use of standard techniques from either the femoral or radial artery.[13]

Table 1
Demographic, clinical and angiographic characteristics of the study population.

Characteristics	N = 151
Age (years ± SD)	55.9 ± 8.7
Male	107 (70.9)
Cardiovascular risk factors	
Smoking	98 (64.9)
DM	79 (52.3)
HTN	87 (57.6)
Dyslipidemia	101 (66.9)
Family history	33 (21.8)
Cardiovascular history	
Prior PCI	53 (35)
Prior CABG	6 (4)
Prior non-invasive study	25(16.5)
LV systolic dysfunction (EF < 50%)	26 (17.2)
Clinical presentation	
Stable angina pectoris	99 (65.6)
Unstable angina	29 (19.2)
NSTEMI	4 (2.6)
STEMI (non-infarct related artery)	19 (12.6)
Procedural access	
Femoral access	118 (78.2)
Radial access	33 (21.8)
Lesion characteristics	
Location	
LAD	81 (51.9)
LCx	27 (17.3)
RCA	48 (30.8)
No of diseased vessels	
One vessel disease	111 (73.5)
Two vessel disease	36 (23.8)
Three vessel disease	4 (2.7)

Values are presented as number [%] or mean ± standard deviation.

2.3. Follow-up and clinical events

Clinical course was analyzed on the basis of follow-up visits in the outpatient department (OPD) (135 patients), together with telephone contact in cases who were not able to attend OPD (13 patients). Major adverse cardiac events (MACE), cardiac mortality, myocardial infarction (MI), and composite end points that comprised cardiovascular death, non-fatal acute coronary syndrome (ACS), target lesion revascularization (TLR) were determined.

2.4. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences, version 16 (SPSS 16). Firstly, all variables were tested for normality using Kolmogrov-Smirnov test. Quantitative data were presented as mean (±standard deviation). Qualitative data were presented as number (percentage). Categorical variables were compared using Chi-square analysis (χ^2). P < .05 was considered statistically significant.

3. Results

We revised data of 151 patients who underwent FFR measurements for equivocal lesions during coronary angiography between (January 2013-December 2015). Data on clinical outcome was completed in 148 patients (mean age 55.9 ± 8.7 years) (three patients could not be reached). The median follow up period was 22 months (range, 12–53 months).

3.1. Baseline clinical and angiographic characteristics

In this study, 70.9% of patients who underwent FFR analysis were male with mean age of 55.9 ± 8.7 years. Smoking and dyslipidemia were the most prevalent traditional risk factors. The clinical presentation were diverse including stable angina (65.6%), unstable angina (19.2%), NSTEMI (2.6%) and STEMI (12.6%). Angiographically, 111 (73.7%) patients of the study population had single vessel disease and majority of the studied lesions were in the left anterior descending artery 81 (51.9%), Table 1.

Non-significant FFRs (>0.8) were found in 83 (56.1%) patients and were managed conservatively with the guidelines directed medical treatment, and significant FFRs (≤0.8) were found in 65 patients (43.9%), for all of them PCI was performed.

Table 2
Clinical and angiographic characteristics between both groups.

	Deferred n = 83 (56.1%)	Intervention n = 65 (43.9%)	P
Male Gender	56 (67.5)	49 (75.4)	0.29
Smoking	50 (60.3)	46 (70.8)	0.12
DM	40 (48.2)	38 (58.5)	0.2
HTN	45 (54.2)	40 (61.5)	0.37
Dyslipidemia	47 (56.6)	52 (80)	0.003
Family History	18 (21.7)	15 (23.1)	0.84
Prior PCI	28 (33.7)	24 (36.9)	0.68
Prior CABG	3 (3.6)	4 (4.6)	1.0
LV systolic dysfunction	15 (18.1)	11 (16.9)	0.85
Stable angina	55 (66.3)	43 (66.2)	0.98
Unstable angina	14 (16.9)	13 (20)	0.6
NSTEMI	3 (3.6)	1 (1.5)	0.6
STEMI	12 (14.5)	7 (10.8)	0.5
Femoral access	67 (80.7)	49 (75.4)	0.43
Number of disease vessels			
One vessel disease	65 (78.3)	45 (69.2)	0.45
Two vessel disease	16 (19.3)	18 (27.7)	
Three vessel disease	2 (2.4)	2 (3.1)	

Values are presented as number [%].

Table 3
Major adverse cardiovascular events during follow-up.

	Deferred n = 83 (56.1%)	Intervention n = 65 (43.9%)	P
Death	2 (2.4)	1 (1.5)	1.0
Non-fatal ACS	8 (9.6)	6 (9.2)	0.9
TLR	5 (6)	4 (6.2)	1.0
CABG referral	0 (0)	1 (1.5)	0.4
Composite of death, ACS, TLR	11 (13.3)	10 (15.4)	0.7

Values are presented as number [%].

There was no significant difference in clinical and angiographic characteristics between deferred and intervention groups except for dyslipidemia that was more prevalent in the intervention group, Table 2.

3.2. Analysis and decision blinded to FFR

All reviewers had concordant agreement to do PCI to 59 (37.8%) lesions based on angiographic assessment. Interestingly 23 (39%) of these lesions were functionally non-significant by FFR.

On the other hand, the reviewers agreed to defer 97 (62.2%) lesions, however, 32 (33%) of these lesions were functionally significant by FFR and necessitated PCI. Of note, complete agreement (the three reviewers had the same decision) was achieved in only 76%

3.3. Clinical outcome

MACE were similar in patients who underwent PCI immediately and those in whom PCI was deferred based on FFR values, death (1.5% vs 2.4%, p = 1.0), MI (9.2% vs 9.6%, p = .9), TLR (6.2% vs 6%, p = 1.0) and composite end points (15.4% vs 13.3%, p = .7), Table 3.

4. Discussion

FFR is currently the "gold standard" for assessing the functional significance of coronary artery lesions by determination of the characteristics of blood flow proximal and distal to a coronary stenosis during pharmacologically-mediated microvascular hyperemia.[14]

Over the last decade, several studies have investigated methods for identifying patients that might benefit from FFR-guided PCI including wide range of clinical presentations. The results of the FAME study[15] – supported by the 5 years follow up of the DEFER study-[16] demonstrated a lower rates of adverse events and lower healthcare costs with FFR guided PCI. In contrast, no clinical benefit was noticed from revascularization of angiographically obstructive lesions (>50% stenosis) which were hemodynamically insignificant according to FFR.

Despite the well stablished FFR benefits, less than 10% of coronary procedures use adjunctive intracoronary imaging or employ FFR to guide management.[9] This is due to various practical limitations related to the measurement of FFR such as the added time and expense associated with the use of a coronary pressure wire and the need for intracoronary or intravenous administration of adenosine. Consequently, revascularization is frequently performed in patients with functionally non-significant lesions, who may not benefit from the intervention.

The current study is the first study to assess the effect of FFR on the clinical decision to manage intermediate coronary artery stenosis in a cohort of Egyptian patients. This study had the following main findings, first, significant FFR (≤0.8) was found in approximately 43.9% of patients with intermediate lesions, and of those, 33.7% presented with acute coronary syndrome. Second, when

experts revise the severity of moderately severe coronary lesions there was concordant agreement to do PCI to 59 (37.8%) lesions based on angiographic assessment. In spite that 23 (39%) of these lesions were functionally non-significant by FFR.

Also, the reviewers agreed to defer 97 (62.2%) lesions, however, 32 (33%) of these lesions were functionally significant by FFR and necessitated PCI. Third, there was no significant difference in outcome between groups treated with or without revascularization, whether the treatment was in concordance or discordance with FFR-based recommendations.

Our study cohort included a variety of clinical presentations, which ranged from stable coronary disease to acute coronary syndrome MI. previous study found that FFR was useful in improving diagnostic efficiency in patients with non-STEMIs.[17]

Non-significant FFRs (> 0.8) were found in 83 (56.1%) patients and were managed conservatively with the recommended medical treatment, and significant FFRs ($\leqslant 0.8$) were found in 65 patients (43.9%), for all of them PCI was performed. This is different from data derived from Orvin et al.[18] who retrospectively studied cohort of patient similar to ours, the author found only 29.1% of patients had functionally significant stenosis (FFR ≤ 0.8) and (70.9%) had non-significant FFRs (>0.8). In the same study, in angiographic visual assessment, nearly half the patients (49.7%) had intermediate stenosis; 12.7% had significant stenosis (>70%) and 37.6% had non-significant stenosis (<50% stenosis).

Assessment of intermediate coronary lesions is challenging, and the use of angiographic visual assessment may lead to incorrect management. Tonini et al.[19] demonstrated a significant miscorrelation (only 65% concordance) between the severity of intermediate lesions assessed with the angiogram and that assessed with FFR measurements. Similarly, miscorrelation was also reported between QCA assessments and FFR measurements.[20]

Even experienced interventionists perform inexpertly when asked to visually assess coronary lesion on angiography when taking intracoronary pressure measurements as gold standard for the detection of hemodynamically significant disease.

Several studies consistently prove the poor correlation between visual assessment and the FFR results. In concordance with our results, Bo Xu et al.[10] studied the inter-observer differences (between six interventional cardiologists) in visually-guided treatment decisions for coronary artery lesions to assess the clinical impact of FFR in the real-world cohort of patients. There were significant inter-observer variations in visually-guided treatment decisions for coronary artery lesions (P = .026), the cardiologists decided to stent on average 41% of the lesions, and to medically manage 59% of the lesions.

Similarly, in a study conducted by Bilge et al.[21] to determine whether results similar to FFR can be obtained with visual assessment conducted with 3 observers independent from each other, interestingly, there was statistically significant differences exist between the individual results of observers and the FFR result.

In another study, Brueren and colleagues[22] found that the agreement between eyeball assessment and FFR existed in (69.2%) of the cases and that visual assessment of lesion severity alone would have resulted in a wrong decision in 30.7% of the cases, they concluded that treatment decisions should not be based on visual lesion assessment even when performed by experienced cardiologists.

In reality, many factors may influence the physician's decision whether to perform revascularization including patient preference, compliance with medication, the lesion complexity and the procedure cost which may all lead to a decision which can be discordant with the FFR result.

Despite its well established clinical value, the regular use of FFR in daily practice is not consistently cost effective, so, it's important to determine the lesion group in which the FFR procedure can yield to actually important results, recently, Wong et al.,[23] conducted a new rating score system, depended on using minimal lumen diameter obtained by quantitative angiography, lesion length, myocardium at risk (Bypass Angioplasty Revascularization Investigation [BARI] and Myocardial Jeopardy Index [MJI]) variables, and they concluded Combined angiographic assessment (DILEMMA score) have incremental predictive value over these individual indices alone for detecting functionally significant coronary artery stenoses.

The clinical outcome results in our study were similar to those reported by Miller et al.[24] and Katia et al.[25] both evaluated long-term outcomes (death, MI, and revascularization) in patients managed with FFR-guided revascularization strategy. They demonstrated no statistical difference in long-term clinical outcomes for patients deferred and those that underwent PCI.

5. Conclusion

Mismatches between visually- and FFR- estimated significance of intermediate coronary stenosis are frequently encountered. FFR leads to a change in decision in more than one third of instances. The clinical and cost implications of such change in decision-making – particularly in areas with limited resources – needs further evaluation in larger studies.

6. Limitations

Our results represent a retrospective, single center experience involving small number of patients and, hence, need confirmation with larger multicenter studies. Lesions severity were assessed by visual rather than quantitative coronary angiography, this may have led to over- or underestimation.

Conflicts of interest

None.

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