Visual-Functional Mismatch Between Coronary Angiography, Fractional Flow Reserve, and Quantitative Coronary Angiography

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Abstract

Anatomical and functional mismatches are not uncommon in the assessment of coronary lesions. The aim of this study was to identify clinical and lesion-specific factors affecting angiographic, anatomical, and functional mismatch in intermediate coronary lesions. In patients who underwent coronary angiography for clinical reasons, fractional flow reserve (FFR), and quantitative coronary angiography (QCA) analyses for intermediate stenotic lesions were performed simultaneously. Mismatches between the measured values were analyzed. A total of 95 intermediate lesions were assessed simultaneously by visual angiography, FFR, and QCA. The visual-FFR mismatch was found in 40% of the lesions while reverse visual-FFR mismatch was determined in nearly 14% of the lesions. Mismatch and reverse mismatch between FFR and QCA parameters were observed in 10 and 23% of the lesions. FFR value was significant in 32% of the lesions while visually significant stenosis was shown in 61% of the lesions. Among the visual-FFR reverse mismatch group, the prevalence of culprit lesions within the left anterior descending (LAD) was significantly higher than other vessels (p value < 0.02). There were high frequencies of angiographic, QCA, and functional mismatches in analyses of intermediate coronary lesions. LAD lesions showed the highest mismatch. Angiographic or QCA estimation of lesion severity has consistently resulted in inappropriate stenting of functionally nonsignificant lesions or undertreatment of significant lesions based on FFR.

Keywords

- angiography
- ischemia
- QCA
- FFR
- coronary imaging
- stenosis
- coronary intervention

Patients with symptomatic ischemia have the most benefit from percutaneous coronary intervention (PCI). An intermediate coronary lesion seen on angiography can be under- or overestimated using visual estimation. Intermediate lesions are defined as a luminal narrowing area between 40 and 70% diameter stenosis (DS). Assessment of a coronary lesion with intermediate severity continues to be a challenge for the cardiologists.¹ Unfortunately, noninvasive imaging techniques, as

well as coronary angiography are flawed with inaccuracy particularly in obese patients or in patients with multivessel coronary artery disease. This has resulted in inappropriate stenting of functionally nonsignificant lesions, and in some cases, inappropriate deferral of PCI of significant lesions.

Due to coronary arteriography limitation using visual estimation, quantitative coronary angiography (QCA) has been used to improve accuracy. The greatest advantage of

QCA is its theoretical observer independence minimizing significant potential intraobserver and interobserver variability. In prospective studies, the potential for observer error with visual analysis from a coronary angiogram has been estimated to exceed 35%. Perhaps the single greatest drawback of QCA is the lack of correlation between the functional predictions of angiographic disease severity and directly measured physiologic variables, as they relate to coronary flow and fractional flow reserve (FFR).²⁻⁴ Because of the numerous other factors contributing to resistance to blood flow, differences between the anatomic and physiologic data can be expected, most often in the assessment of disease severity, especially in the lesions with intermediate stenosis. To overcome this limitation, physiologic testing is often performed before proceeding with coronary interventions. The functional significance of coronary stenotic lesions is determined not only by the degree of stenosis, but also by viability of myocardial tissue supplied by the lesion, collaterals, and vasomotor tone among others. These physical constraints and resultant flow characteristics contribute to the disparity between the angiographic and corresponding physiologic assessment of disease severity.⁵ An intermediate stenosis, defined as a 40 to 70% diameter narrowing is encountered in almost 50% of the patients undergoing coronary arteriography. FFR measurements are consistent with stress testing results and can identify important lesions, thereby assisting in immediate decision-making at the time of cardiac catheterization. The accuracy of FFR for assessment of the functional significance of a coronary stenosis has been well established.⁶ In the DEFER study, nonsignificant stenosis (as indicated by a $\text{FFR} > 0.75$) was randomized to be treated either medically or by stenting. After a follow-up of 5 years, the prognosis of those lesions with $\text{FFR} > 0.75$ treated medically was excellent with a mortality and myocardial infarction (MI) rate of $< 1\%$ per year and was not improved by stenting. In the FFR-guided arm of the fractional flow reserve versus angiography for multi vessel evaluation (FAME) study, lesions with an $\text{FFR} < 0.80$ were stented, while PCI was deferred in lesions with $\text{FFR} > 0.80$. After a follow-up of 2 years, outcome of the deferred lesions was excellent with medical treatment yielding a $< 1\%$ rate of MI or death.⁷ FFR-guided PCI reduces the need for revascularization for many intermediate lesions.⁸ Moreover, FFR-guided coronary artery bypass grafting (CABG) was associated with a lower number of graft anastomoses and lower rate of on-pump surgery compared with angiography-guided CABG without a higher event rate during follow-up.⁹

Coronary angiography often underestimates or overestimates lesion's functional severity.³⁻¹¹ A subanalysis of the FAME trial demonstrated that two-thirds of coronary lesions with a $\text{DS} > 50\%$ were not ischemia-producing. Conversely, for left main lesions, approximately one-fifth of the lesions with a $\text{DS} < 50\%$ were ischemia-producing. Although such a "visual-functional mismatch" is frequently encountered, the mechanism of this phenomenon is poorly understood.¹⁰ The aim of this study was to identify clinical and lesion-specific factors affecting angiographic, anatomical, and functional mismatch in intermediate coronary lesions.

Methods

This study was a prospective single-center observational study. This study was approved by the institutional review board. All patients enrolled provided written informed consent. All patients in this study underwent routine coronary angiography due to clinical indications. To evaluate physiologically significant intermediate coronary stenosis (defined between 40 and 70% by visual estimation), FFR study was performed and QCA was measured. Visual estimation of the lesion severity was compared with FFR and QCA data. Factors affecting their mismatch were analyzed. Exclusion criteria included multiple stenosis ($\text{DS} > 40\%$ on visual estimation) within a single target vessel (lesions were considered separate if they were more than three reference vessel diameters apart), bypass graft lesions, left main lesions, side branch lesions, in-stent restenosis, previous PCI in the target vessel, culprit vessels in the setting of a MI, history of MI in target vessel territory, thrombolysis in MI flow grade < 3 and angiographic thrombi-containing lesions. Angiographic visual, FFR "mismatch" was defined as angiographic visual $\text{DS} > 50\%$ coupled with $\text{FFR} > 0.80$, whereas "reverse mismatch" was defined as angiographic visual $\text{DS} \leq 50\%$ coupled with $\text{FFR} \leq 0.80$. For QCA-FFR analysis, minimum luminal diameter (MLD) $\% \geq 50\%$ was considered significant and mismatch and reverse mismatch between their results were also evaluated. Treatment strategies were determined based on the operator's decision.

Fractional Flow Reserve

"Equalizing" was performed with the guide wire sensor positioned at the guiding catheter tip. The 0.014-in pressure guide wire (Radi, St. Jude Medical, Uppsala, Sweden) was then advanced distal to the stenosis. FFR was measured at the maximal hyperemia induced by intracoronary administration of 200 μg of nitroglycerin, and infusion of intra coronary adenosine (200 μg for right coronary artery and 300 μg for left anterior descending [LAD] or left circumflex artery). Stenosis was considered significant when FFR was < 0.80 .

Quantitative Coronary Angiography

Patients initially underwent routine coronary angiography. Angiographic cine images were acquired at 15 frames per second (Axiom Artis II, Siemens, Germany). Two-dimensional (2D)-QCA was performed offline using standard commercial software, Syngo, Siemens. All analyses were performed during the electrocardiographic-gated end-diastolic frame. Angiographic views with the least foreshortening and yielding the best depiction of the stenosis were used. Edge detection correction was performed if required. Minimum luminal area, percentage area stenosis, MLD, percentage DS, and lesion length were measured using 2D-QCA. All measurements were performed twice and averaged by a single experienced cardiologist blinded to the FFR results. Interobserver error was determined by a second cardiologist.

Results

In this study, 95 lesions among 72 eligible patients who underwent coronary angiography were assessed. The baseline characteristics of patients are provided in ►Table 1. The average age was 59.7 years. Overall, 53 (56%) of patients were males and 42 (44%) were females. A total of 34% of patients had a history of diabetes. Acute coronary syndrome comprising non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina was the presenting clinical symptom in 43% of patients. Visual-FFR mismatch was found in 40% of the lesions while reverse visual-FFR mismatch was determined in nearly 14% of the lesions (►Table 2). In addition, mismatch and reverse mismatch between FFR and QCA parameters were observed in 10 lesions (10%) and 22 lesions (23%), respectively (►Table 3). The age of patients in the significant FFR group was higher than the nonsignificant group, but their

difference did not show any statistical significance (►Tables 2 and 3). The differences in coronary risk factor prevalence and ejection fractions of patients in subgroup analyses were not significant. LAD was the most common culprit vessel evaluated in this study (58 cases, 61%). Distribution of culprit stenosis is shown in ►Table 4. FFR value was significant in 31 lesions (32%), while visually significant stenosis was shown in 58 lesions (61%). Moreover, anatomically significant stenosis based on QCA parameters (defined as MLD ≥ 50) was only found in 22% of the lesions. Analysis of culprit vessels showed that in visual-FFR mismatch and reverse mismatch groups, LAD was the most commonly involved vessel with 57.9 and 71.4%, respectively. Prevalence in QCA-FFR mismatch and reverse mismatch groups was 40 and 66%, respectively. Among the visual-FFR reverse mismatch group, the prevalence of culprit lesions within the LAD was significantly higher than other vessels (p value < 0.02). In the QCA-FFR mismatch group, the LAD was significantly more involved than the other vessels (p value < 0.04). Acute coronary syndrome was a significantly more common clinical presentation in patients with visual-FFR reverse mismatch group (p value < 0.004), while there was no significant difference in the clinical presentation of the visual-FFR mismatch group (p value = 0.44). The correlations between FFR data and QCA parameters showed positive modest correlations between MLD and reference diameter with FFR (p value < 0.01 , ►Figs. 1 and 2).

Table 1 Baseline characteristics of patients

Patients characteristics	N (%)
Age (y) (mean $\pm$ SD)	59.7 $\pm$ 8.9 (range, 41–86)
Sex	
Male (%)	53 (56%)
Female (%)	42 (44%)
Risk factors	
Diabetes mellitus (%)	36 (37.9)
HTN (%)	43 (45.3)
Dyslipidemia (%)	40 (42.1)
Smoking (%)	21 (22.1)
Symptom on admission	
Stable angina	54 (56.8)
Unstable angina	40 (42.10)
NSTEMI	1 (1.1)
Vessel	
LAD	58 (61.1)
LCX	17 (17.9)
RCA	20 (22)

Abbreviations: HTN, hypertension; LAD, left anterior descending; LCX, left circumflex artery; NSTEMI, non-ST segment elevation myocardial infarction; RCA, right coronary artery; SD, standard deviation.

Discussion

Earlier studies showed that FFR < 0.75 is an accurate predictor of ischemia while more recent studies have used FFR ≤ 0.80 as a cutoff to guide revascularization; thus, we used 0.80 as a cut-off value for significant FFR in our analysis.^{11,12} In this prospective study, our data demonstrated that visual-functional mismatch between coronary angiography and FFR was frequently encountered (as high as 53%) and mismatch between QCA parameters and FFR was also as high as 34% which is in agreement with results of previous studies by Park et al that showed 40% mismatch.¹³ The DS by visual estimation was significantly greater compared with DS calculated by QCA analysis which was consistent with findings of multiple trials.¹³ The physiological effect of stenosis depends on clinical and local factors. FFR reflects the sum of all these factors and the reliability of FFR results for decision making has been

Table 2 Vessel and lesion distribution

		Stenosis site				Total
		Origin	Proximal	Mid	Distal	
Vessel	LAD	10 (17.2%)	28 (48.3%)	20 (34.5%)	0	58
	LCX	2 (11.8%)	4 (23.5%)	11 (64.7%)	0	17
	RCA	0	7 (35%)	9 (45%)	4 (20%)	20
Total		12	39	40	4	95

Abbreviations: LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery.

Table 3 Demographic, angiographic, and visual stenosis values parameters

	Visual stenosis values $\leq$ 50% (n = 37)			Visual stenosis values $>$ 50% (n = 58)		
	FFR value			FFR value		
	Significant-stenosis ¹³ (Reverse mismatch group)	Nonsignificant-stenosis (24)	p Value	Significant-stenosis (20)	Nonsignificant-stenosis (38) (Mismatch group)	p Value
Age	61.92 $\pm$ 9.88	60.15 $\pm$ 8.77	0.8	64.17 $\pm$ 7.12	56.8 $\pm$ 10.65	0.1
Sex (M/F)	3/4 (42.9/57.1)	13/11 (54.2/45.8)	0.62	10/10 (50/50)	26/12 (68.4/31.6)	0.16
DM (%)	5 (38.5)	12 (50)	0.52	4 (20)	15 (39.5)	0.12
HTN (%)	6 (46.2)	15 (62.5)	0.33	8 (40)	14 (36.8)	0.81
Dyslipidemia (%)	5 (71.4)	7 (53.8)	0.65	7 (35)	15 (39.5)	0.72
Smoking (%)	1 (7.7)	6 (25)	0.38	4 (20)	10 (26.3)	0.59
MLD (%)	40.30 $\pm$ 14.39	39.54 $\pm$ 10.27	0.85	47.85 $\pm$ 13.84	42.86 $\pm$ 11.56	0.51
Symptom			0.004 ^a			0.44
1 stable angina	4 (30.8)	19 (79.2)		9 (45)	22 (57.9)	
2 unstable angina	9 (69.2)	5 (20.8)		11 (55)	15 (39.5)	
3 NSTEMI	0 (0)	0 (0)		0 (0)	1 (2.6)	
EF	47.69 $\pm$ 10.12	45.82 $\pm$ 10.39	0.6	49 $\pm$ 10.46	48.42 $\pm$ 6.74	0.4
LAD	11 (84.6)	11 (45.8)	0.02 ^a	14 (70)	22 (57.9)	0.52
LCX	2 (15.4)	3 (12.5)		4 (20)	8 (21.1)	
RCA	0 (0)	10 (41.7)		2 (10)	8 (21.1)	
Original	2 (15.4)	6 (25)	0.59	2 (10)	2 (5.3)	0.41
Proximal	7 (53.8)	9 (37.5)		10 (50)	13 (34.2)	
Mid	4 (30.8)	7 (29.2)		7 (35)	22 (57.9)	
Distal	0 (0)	2 (8.3)		1 (5)	1 (2.6)	
FH	1 (7.7)	4 (16.7)	0.63	4 (20)	4 (10.5)	0.32

Abbreviations: DM, diabetes mellitus; EF, ejection fraction; F, female; HTN, hypertension; LAD, left anterior descending; LCX, left circumflex artery; M, male; MLD, minimum luminal diameter; NSTEMI, non-ST segment elevation myocardial infarction; RCA, right coronary artery.

^ap Value < 0.05 significant.

documented in previous studies.¹⁴ Our study showed that in the visual-FFR reverse mismatch subgroup, the LAD was the most common culprit vessel which was similar to findings of other studies.¹³ This finding suggests that underestimation of stenosis by visual assessment in the LAD may be due to the larger perfusion area supplied by the LAD compared with other coronary vessels which directly affects the physiological significance of the stenosis expressed in FFR results.

In the visual reverse mismatch group, like other studies, our results also showed that acute coronary syndrome (NSTEMI, unstable angina [UA]) was more common than stable angina (p value < 0.04). This finding maybe related to the shape of plaques in ACS patients that directly influence FFR and make its results significant compared with a similar degree of stenosis in stable plaques. This study showed that in the visual-FFR mismatch group, the LAD was the most common culprit vessel, which was consistent with other researchers. FFR-guided coronary intervention was shown to be superior to 2D-QCA driven coronary intervention in preventing MI, revascularization or death.¹² Our Study

showed that correlation of 2D-QCA parameters with FFR results were weakly positive in this regard and our data were similar to previous reports.¹⁵⁻¹⁸ This weak correlation could have been related to limitations of 2D-QCA, because it only allows characterization of lesion severity in a single plane while physiologic effects of stenosis represented by FFR were not only related to degree of stenosis but also to features such as myocardial viability and presence of collaterals.

Conclusion

Our study revealed that relying only on angiographic or noninvasive evaluation or QCA has resulted in inappropriate stenting of functionally nonsignificant lesions and, in some cases, inappropriate deferral of PCI of significant lesions. Mismatch was largest in the LAD lesions suggesting that evaluating intermittent lesions in the LAD territory using visual estimation or QCA alone is inaccurate and FFR should be considered for better assessment.

Table 4 Demographic, angiographic, and quantitative coronary angiography parameters in patients

	QCA ≤ 50% (n = 74)			QCA > 50% (n = 21)		
	FFR Value			FFR Value		
	Significant-stenosis (22) (Reverse mismatch)	Nonsignificant-stenosis (52)	p Value	Significant-stenosis ¹¹	Nonsignificant-stenosis ¹⁰ (Mismatch)	p Value
Age	58.48 ± 8.45	59.67 ± 8.59	0.54	65.72 ± 8.1	56.8 ± 10.65	0.04 ^a
Sex (M/F)	9/13 (40.9/59.9)	32/20 (61.5/38.5)	0.16	4/4 (50/50)	7/3 (70/30)	0.6
DM (%)	8 (36.4)	20 (38.5)	0.86	1 (9.1)	7 (70)	0.004
HTN (%)	10 (45.5)	24 (46.2)	0.94	4 (36.4)	5 (50)	0.52
Dyslipidemia (%)	10 (45.5)	21 (40.4)	0.8	3 (36.4)	5 (50)	0.52
Smoking (%)	4 (18.2)	11 (21.2)	0.7	1 (9.1)	5 (50)	0.03
Symptom			0.09			0.03
1 stable angina	8 (36.4)	32 (61.5)		5 (45.5)	9 (90)	
2 unstable angina	32 (61.5)	19 (36.5)		6 (54.5)	1 (10)	
3 NSTEMI	0 (0)	1 (1.9)				
MLD %	38.81 ± 9.1	38.32 ± 8.73	0.53	61 ± 7.52	58.5 ± 5.11	0.3
EF	50.41 ± 9.87	46.82 ± 8.51	0.28	46.81 ± 13.65	50.50 ± 7.24	0.45
LAD	17 (77.3)	29 (55.8)	0.04	8 (72.7)	4 (40)	0.28
LCX	4 (18.2)	8 (15.4)		2 (18.2)	3 (30)	
RCA	1 (4.5)	15 (28.8)		1 (9.1)	3 (30)	
Original	3 (13.6)	8 (15.4)	0.34	1 (9.1)	0 (0)	0.67
Proximal	12 (54.5)	17 (32.7)		5 (45.5)	5 (50)	
Mid	6 (27.3)	24 (46.2)		5 (45.5)	5 (50)	
Distal	1 (4.5)	3 (5.8)		0 (0)	0 (0)	

^ap Value <0.05 significant. **Fig. 1** Correlation between FFR and MLD. FFR, fractional flow reserve; MLD; minimum luminal diameter. **Fig. 2** Correlation between FFR and REFD. FFR, fractional flow reserve; REFD, reference diameter.

Limitation

The number of patients might not be large enough limiting our results. We confined our study to patients without left main disease. Furthermore, we excluded patients with history of MI and serial stenosis, which complicated FFR measurements limiting our data to simple lesions.

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