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Factors influencing the functional significance in intermediate coronary stenosis

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Abstract

    Objective   To analyze the influencing factors of the functional significance determined by fractional flow reserve (FFR) in intermediate coronary artery stenosis. **Methods**   The study enrolled 143 patients with 203 intermediate coronary lesions. Pressure-derived FFR of these lesions was gained at maximal hyperemia induced by intravenous adenosine infusion. An FFR < 0.80 was considered as abnormal functional significance. Anatomic parameters at the lesion sites were obtained by off-line quantitative coronary angiography analysis (QCA). The predictive value of the demographic characteristics and anatomic parameters for FFR in these intermediate lesions was assessed using multiple linear and binary logistic regression analysis. **Results**   Overall, FFR < 0.8 was found in 70 (34%) of the total 203 intermediate coronary lesions. FFR values were positively correlated with QCA-measured minimum lumen diameters (MLD, $r = 0.372$, $P = 0.000$) and the reference vessel diameters (RVD, $r = 0.217$, $P = 0.002$) were negatively correlated with percent area stenosis (AS, $r = -0.251$, $P = 0.000$) and percent diameter stenosis (DS, $r = -0.210$, $P = 0.000$). Age, MLD and the lesion location in different coronary arteries were the independent determinants of FFR < 0.8. **Conclusions**   MLD can predict the functional significance of intermediate coronary stenosis, while age and the lesion location in different coronary arteries should be taken into account as important influencing factors of FFR values.

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1   Introduction

    Accurate functional assessment of lesion severity is crucial for clinical decision making in patients with intermediate coronary stenosis. Fractional flow reserve (FFR) is determined by the ratio of pressure distal to the lesion (Pd)/pressure proximal to the lesion (Pa) under maximal hyperemia. The pressure gradient across the stenosis becomes greater as blood flow across the lesion increases during hyperemia induction. FFR proves its value in diagnosing functionally significant stenosis,[1] which is defined as an FFR threshold < 0.80 under maximal hyperemia.[2] In Europe, class IA recommendation is currently employed by FFR for the assessment of stable coronary stenosis ahead of revascularization when functional information is lacking.[3]

    The utility of the pressure wire remains under low level due to several limitations in measuring FFR, including the high cost, laboriousness of the manual procedure and possible adverse systemic effects of adenosine administration, such as bradycardia, chest pain and bronchospasm. Consequently, numerous research investigations have been carried out to evaluate the predictive value of the anatomic characteristics by intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) to the functional significance by FFR. Previous studies have showed moderate correlation between coronary stenosis severity assessed by QCA/IVUS and FFR. However, functional significance of a coronary stenosis may not be determined by the severity of a stenosis alone, because in theory, maximal arteriolar vasodilatation is essential for minimal myocardial resistance in a given arterial territory, which FFR applies as a physiologic index of coronary artery stenosis. FFR measurement is theoretically impossible when there are diabetes mellitus (DM), hypertension, hyperlipidemia and other potential factors present, including smoking status, age and sex, etc., since associated functional and/or structural abnormalities in the coronary microvasculature could be caused by such factors. When the functional significance of a lesion is assessed by

QCA or IVUS, physicians should take demographic and anatomical variations of coronary artery into concern. Therefore, we performed this study to evaluate these factors that could influence FFR value.

2 Methods

2.1 Patient population

The study enrolled 143 consecutive patients (203 lesions) from December 2008 to April 2013 at Peking University Third Hospital, which was approved by the Peking University Third Hospital Ethics Committee in accordance with the Declaration of Helsinki, with informed consent waived due to the retrospective nature of the study. All patients underwent anatomic and physiological assessment by off-line QCA, FFR, respectively.

The 143 consecutive patients (203 lesions) were referred to coronary angiography and found to have intermediate coronary lesions (40% to 70% stenosis by angiographic visual assessment). Exclusion criteria included: significant left main disease (diameter stenosis > 50%), multiple lesions in the same vessel, myocardial infarction in the territory of the target coronary artery, angiographic evidence of collateral flow distally to the assessed lesion, significant valvular disease, bypass graft lesions, or left coronary dominant type.

2.2 QCA analysis

QCA was performed offline by two experienced interventional cardiologists blinded to the FFR results. Calibration of quantification was carried out with the guide catheter full of contrast. Reference segment and percent stenosis were measured in end-diastole in the projection where maximal narrowing was observed. Reference vessel diameter (RVD) was defined as the mean of diameters within the 5-mm proximal and distal non-affected segments in absence of collateral branches. Lesion length was determined in the projection with less fore-shortening. The following measurements were obtained by the QCA software: lesion length (LL), proximal and distal reference diameters (acquired in the 5 mm non-affected segments next to the proximal and distal edge of the lesion), and minimum lumen diameter (MLD) of the lesion. Average of proximal and distal RVD and percent diameter stenosis [DS: (RVD-MLD)/RVD] were obtained, and QAngio XA software version 7.1.43.0 (Medis Medical Imaging Systems, Leiden, the Netherlands) was introduced for measurement. Lesion location was determined according to the American Heart Association classification.[4] Minor modification was made to reflect the amount of myocardium supplied by the target coronary segment. Proximal left anterior descending coronary artery

(LAD) was defined as the segment between the branching point of the left main stem and the first major branch (septal or diagonal branch), and proximal left circumflex coronary artery (LCX) defined as the segment between the branching point of the left main stem and the first obtuse marginal branches. Proximal right coronary artery (RCA) was defined as the segment between the origin of RCA and the first major right ventricular branch. The other part of the coronary artery was defined as distal coronary artery.

2.3 FFR measurement

FFR methodology was employed in a standard fashion, and adenosine or adenosine triphosphate (ATP: 140 μg/kg per minute by intravenous infusion) was for maximum hyperemia. FFR was calculated as the ratio of the coronary pressure distal to the lesion measured by the pressure wire and the mean aortic pressure measured by the guiding catheter under maximum hyperemia. Stenosis was considered functionally significant when FFR < 0.80.

2.4 Statistical analysis

Data were presented as mean ± SD or frequency for continuous and categorical variables. Student *t*-test was used for compare of continuous variables, and chi-square test used for analysis of discrete variables. In order to investigate independent predictors of FFR < 0.8, clinical variables were examined using multivariate analysis in a binary regression and linear regression analysis. Backward selection was introduced, and 0.05 was the significant level when entering an explanatory variable into the model. The final model only included significant variables at $P < 0.05$ using the Wald test.

Receiver operating characteristic (ROC) curve analysis was used to compare the diagnostic performance of MLD and resting Pd/Pa with FFR, and the area under the curve (AUC) was calculated (SPSS, version 17.0). The AUC summarizes the accuracy of a diagnostic test. An area of 1 represents a perfect test, while an area of 0.5 represents a bad test. Accuracy of the MLD and resting Pd/Pa to correctly predict the outcomes of FFR was calculated for predefined and clinically used cut-off values (FFR = 0.80). The characteristics among different coronary artery trees were analyzed for statistically significant differences using the one-way ANOVA, followed by Tukey *post-hoc* test. The difference was deemed statistically significant at $P < 0.05$.

3 Results

3.1 Baseline characteristics

The baseline demographic, angiographic, and QCA characteristics are summarized in Table 1. FFR < 0.80 at

maximum hyperemia was found in 71 (35%) lesions. There was no significant difference in baseline clinical characteristics between patients with FFR < 0.8 and those with FFR ≥ 0.8, except that patients with FFR < 0.8 were younger (P = 0.001). Coronary lesions with FFR < 0.8 had greater DS and AS, less RVD, MLD and resting Pd/Pa in contrast to FFR ≥ 0.8. There was a trend towards higher frequency of lesion location in LAD when FFR < 0.8 (P = 0.09).

3.2   Determinants for FFR

FFR at maximum hyperemia was significantly correlated with QCA-measured AS (r = –0.251, P = 0.000), MLD (r = 0.372, P = 0.000), and showed a weak correlation with DS% (r = –0.210, P = 0.000) and RVD (r = 0.217, P = 0.002).

Table 1.   The baseline clinical, angiographic, and QCA characteristics between FFR < 0.8 and ≥ 0.8.

Characteristics	Total	FFR < 0.8 (n = 71)	FFR ≥ 0.8 (n = 132)	P-value
Age, yrs	65.0 ± 11.3	61.4 ± 12.2	66.9 ± 10.4	0.001
Male, %	67.0	70.4	65.2	0.446
Hypertension, %	70.4	72.0	67.6	0.516
Hyperlipidemia, %	53.2	50.6	54.9	0.554
Diabetes, %	33.0	35.2	31.8	0.624
Current smoker, %	37.9	42.3	35.6	0.352
Family history, %	25.6	28.2	24.2	0.488
Angiographic lesions location				
LAD, %	64	71	60	0.090
LCX, %	15	9	17	0.109
RCA, %	21	20	23	0.546
Proximal segment, %	51.2	45.1	54.5	0.198
QCA parameters				
MLD, mm	1.65 ± 0.39	1.47 ± 0.29	1.75 ± 0.40	0.000
RVD, mm	2.69 ± 0.56	2.53 ± 0.59	2.78 ± 0.52	0.002
DS, %	37.8 ± 11.9	40.2 ± 11.4	36.5 ± 12.1	0.034
LL, mm	11.45 ± 5.77	12.2 ± 6.7	11.1 ± 5.2	0.201
AS, %	54.7 ± 18.1	59.1 ± 17.3	52.4 ± 17.8	0.007
Functional				
Resting Pd/Pa	0.93 ± 0.05	0.90 ± 0.05	0.96 ± 0.03	0.000
FFR	0.82 ± 0.09	0.72 ± 0.07	0.88 ± 0.05	0.000

Data are presented as mean ± SD or %. AS: area stenosis; DS: diameter stenosis; FFR: fractional flow reserve; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LL: lesion length; MLD: minimum lumen diameter; Pd/Pa: ratio of the pressures distal and proximal; QCA: quantitative coronary angiography; RCA: right coronary artery; RVD: reference vascular diameter.

Multiple linear and binary logistic regression analyses included age, male sex, hypertension, diabetes, hyperlipidemia, current smoker, family history of CHD, different coronary lesion location, AS, DS, RVD, LL, and MLD. In the overall cohort of 203 lesions, MLD, DS and different lesion location were predictors for FFR as continuous variables independent of possible confounding variables (P < 0.05), and the independent determinants of FFR < 0.80 were age, MLD and different lesion location. As shown in Table 2. The cutoff value of MLD to predict FFR < 0.80 was 1.565 (63.4% sensitivity, 62.1% specificity, AUC = 0.703; 95% CI: 0.630–0.776; P = 0.000).

The resting Pd/Pa is the pressure gradient over coronary stenosis before the adenosine stress, which is surely correlated to FFR, thus was not listed as a variable in the predictive model of FFR. We found that the resting Pd/Pa was positively correlated with FFR (r = 0.723, P = 0.000), and the AUC of resting Pd/Pa to predict FFR < 0.8 was 0.858. When we analyzed the independent factors that influenced resting Pd/Pa with a linear regression model, it was found that coronary artery and MLD were still the predictors, and DS (%) and AS (%) were the other two predictive factors (data were not shown here). The resting Pd/Pa value, similar to the FFR value, tended to be lower in LAD compared to RCA or LCX.

3.3   Influence of lesion location on FFR value

The functional significance of stenosis was different for lesions at different coronary artery locations, and there were 51 lesions (39%) with FFR < 0.8 among the 130 intermediate lesions located in LAD, 14 (32.6%) in RCA lesions and five (16.7%) in LCX lesions. Although there was no statistical significance (P = 0.09), the FFR value in 130 LAD lesions was significantly lower compared with LCX lesions (0.81 ± 0.09 *vs*. 0.87 ± 0.08, P = 0.004), and tended to be lower than that in RCA lesions (0.81 ± 0.09 *vs*. 0.84 ± 0.10, P = 0.172).There were no significant differences in the demographic characteristics among these three groups, and the

Table 2.   Determinants of functionally significant coronary artery stenosis (FFR < 0.8).

	B	Wals	P	Exp (B)	CI
Time, 1 year	−.047	9.682	0.002	0.954	0.926–0.983
MLD, 1 mm	−7.329	7.117	0.008	0.001	0.000–0.143
Different coronary artery (LAD)	−0.574	5.136	0.023	0.563	0.343–0.925

FFR: fractional flow reserve; LAD: left anterior descending coronary artery; MLD: minimum lumen diameter.

differences in anatomic and functional characteristics are shown in Table 3.

As to the lesion location of different coronary arteries, there was no difference either in FFR value or percentage of FFR < 0.8 between proximal and distal lesion locations, as shown in Table 4.

Table 3. The clinical, angiographic, QCA and functional characteristics of different coronary arteries.

Characteristics	LAD (*n* = 130)	RCA (*n* = 43)	LCX (*n* = 30)
Demographic			
Age, years	64.5 ± 11.4	63.8 ± 11.0	68.7 ± 11.2
Male, %	66.2	69.8	66.7
Hypertension, %	56.9	44.2	50.0
Hyperlipidemia, %	56.9	46.6	0.156
Diabetes, %	32.3	37.2	30.0
Current smoker, %	35.4	44.2	40.0
Family history, %	28.5	16.3	26.7
Anatomic			
MLD, mm	1.63 ± 0.40	1.70 ± 0.31	1.69 ± 0.45
RVD, mm	2.68 ± 0.54	2.90 ± 0.61*	2.47 ± 0.47[#]
RVD ≥ 2.8 mm, %	59.2	53.5	76.7
DS, %	38.6 ± 11.5	39.9 ± 11.5	31.3 ± 12.5*,[#]
> 60%, %	33.1	30.2	63.3
50%−60%, %	37.7	32.6	16.7
40%−50%, %	29.2	37.2	20.0
LL, mm	11.9 ± 5.8	11.9 ± 6.0	8.6 ± 4.4*,[#]
LL ≥ 10 mm, %	63.8	55.8	30.0*,[#]
AS, %	54.7 ± 17.4	59.8 ± 19.0	47.5 ± 20.4*,[#]
Functional			
Resting Pd/Pa	0.92 ± 0.05	0.95 ± 0.04*	0.97 ± 0.04*
FFR	0.81 ± 0.09	0.84 ± 0.10	0.87 ± 0.08*
FFR < 0.8, %	39.2	32.6	16.7

*$P < 0.05$ *vs*.LAD; [#]$P < 0.05$ *vs*. RCA. AS: area stenosis; DS: diameter stenosis; FFR: Fractional flow reserve; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LL: Lesion length; MLD: minimum lumen diameter; Pd/Pa: ratio of the pressures distal and proximal; RCA: right coronary artery; RVD: reference vascular diameter.

4 Discussion

The present study revealed that: (1) the functional significance of moderate coronary stenosis was influenced by many other factors except lesion severity; (2) the different coronary artery tree of the lesion location did influence the FFR value, although the lesion location in the artery tree had no effect on the FFR value; and (3) age of the patients should be taken into consideration when the functional significance of a lesion was evaluated by QCA-measured anatomic parameters.

The relation between anatomic characteristics by QCA and functional significance by FFR has been extensively studied. It is suggested that lesion length, DS and minimum lumen diameter may be correlated with FFR.[5–7] Nevertheless, the correlation between stenosis severity and pressure-derived physiological parameters is either moderate or weak, but there is a large dispersion of FFR values for a similar angiographic degree of stenosis, consistent with our study. We found that FFR at maximum hyperemia was significantly correlated with QCA-measured AS, MLD, lesion length, DS, and the RVD, but the correlation was moderate or weak.

The Hagen-Poiseuille equation states that flow in a tube is determined by $^{\Delta}P\pi r^4/8\eta L$, where 'L' and 'r' are the length and radius of the tube, respectively, $^{\Delta}P$ refers to the pressure gradient across the tube, and η means the viscosity. Thus, there are also many other factors that may affect coronary blood flow except the intravascular-derived severity of a lesion. According to Hagen-Poiseulle equation, radius was much more powerful than length for the impact of flow in a tube. This was consistent with our finding that MLD was an independent factor in the multiple variable regression analysis, while length was not so powerful.

In our study, it was also found that a different coronary artery tree could influence the FFR value, which was an independent predictor of FFR < 0.8. The FFR value seemed higher in LCX lesions, lower in the RCA lesions and lowest in LAD lesions. And the percentage of LAD location in FFR < 0.8 appeared higher compared to non-LAD location.

Table 4. Influence of lesion location on FFR value and percentage of FFR < 0.8 in different coronary arteries.

	FFR value				FFR < 0.8, %			
	LAD (*n* = 130)	RCA (*n* = 43)	LCX (*n* = 30)	Total (*n* = 203)	LAD (*n* = 130)	RCA (*n* = 43)	LCX (*n* = 30)	Total (*n* = 203)
Proximal	0.81 ± 0.09	0.86 ± 0.07	0.88 ± 0.07	0.83 ± 0.09	39.4	30.0	13.0	30.5
Distal	0.82 ± 0.09	0.85 ± 0.10	0.86 ± 0.09	0.82 ± 0.09	39.0	34.8	27.0	39.8
P value	0.515	0.361	0.336	0.574	0.958	0.896	0.336	0.198

FFR: Fractional flow reserve; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery.

We also found the age was much younger in the FFR < 0.8 group. The two independent factors of FFR value were also found by Park, *et al*.[8] In their study, it was revealed that the independent predictors for mismatch (DS ≥ 50% and FFR > 0.80) were advanced age, non-left anterior descending artery location, and other anatomic characteristics, and conversely, reverse mismatch (DS < 50% and FFR < 0.80) was independently associated with younger age, LAD location, and other factors.

The importance of LAD in the functional significance of a lesion has recently been reported by other investigators.[9,10] They found that an intermediate lesion was 3.4–4.4 times more likely to be functionally significant if it was located at the LAD instead of any other arteries, attributed to the presence of myocardial ischemia which was determined by both the lesion severity and the amount of myocardium supplied,[11,12] as a much larger myocardial mass was supplied by LAD compared with other coronary arteries. But there was no difference in FFR value, or FFR < 0.8 between the proximal and distal stenosis along the same coronary artery tree in the present study, although Koo, *et al*.[9] found that the probability of a functionally significant intermediate lesion was further increased [odds ratio (OR): 2.97] if the lesion was proximal.

Furthermore, it was recently reported that the resting baseline Pd/Pa was linearly related to FFR in intermediate lesions,[13] whereby a certain range of the resting baseline Pd/Pa values strongly predicted functional significance with excellent NPV and high sensitivity, or excellent PPV and high specificity,[14] similar to our study. The AUC of resting Pd/Pa to predict FFR < 0.8 was 0.858. When we analyzed the independent factors that influenced resting Pd/Pa with a linear regression model, it was found that coronary artery and MLD were still the predictors and the DS and AS were the other two predictive factors (data not shown here). The resting Pd/Pa value, similar to the FFR value, tended to be lower in LAD than in RCA or LCX.

We saw the accordance of MLD and the lesion location in different coronary arteries, which influenced the ratio of distal coronary pressure to aortic pressure under pre- or post-hyperemia. It was implied that the MLD and the lesion location in different coronary arteries were two of the most important factors related to the functional significance of an intermediate stenosis. While the discrepancy of age, DS and AS maybe linked to the hyperemia. The effect of DS and AS on the ratio of distal to proximal coronary pressure can be deleted by that of vascular dilation by adenosine. With regard to age, it is different. Adenosine is an important cardio-protective agent that works via several adenosine receptor subtypes to regulate cardiovascular activity. It is well established that functional responses to adenosine decline with age. Jenner, *et al*.[15] have already found that, in rat heart, adenosine A1 and A2 receptor expression decreases with age. Therefore, we speculate that the decreased adenosine receptor may weaken the effect of hyperemia induced by adenosine at the same dosage, as may explain the ΔP across the lesion decreased and FFR value tended to be higher.

4.1 Limitations

There are several limitations of the present study. First, this was a retrospective study with limitations inherent to this type of investigation. Second, it was a single-center study with a relatively smaller sample size and hence our findings might not be applicable to other study populations. The lower prevalence of FFR < 0.80 (n = 71, 35%), RCA (n = 43, 21%) and LCX (n = 30, 17%) in the study group may also affect statistical analysis. Third, the morphological assessment of lesions was exclusively QCA. During the process of atherosclerosis, fluid dynamic conditions may "mold" stenosis, making them progressively longer, or changed in shape in both inward and outward remodelling. Assessment of anatomic characteristics by QCA may not be as accurate as that by IVUS, and even IVUS can't reliably evaluate the anatomic characteristics.

4.2 Conclusions

In intermediate coronary artery stenosis, functional significance is related to many factors, including anatomic and demographic characteristics. The correlation between anatomical and functional severity of coronary artery disease defined by QCA and FFR is poor. Age and the lesion location in different coronary arteries can influence the functional significance, and therefore such factors should be taken into account when judging the benefit of revascularization, or performing functional assessment that overcomes limitations of simple stenosis quantification in making clinical decisions.

Acknowledgments

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