Original Article

The association between intravascular ultrasound-derived echo-attenuation and quantitative flow ratio in intermediate coronary lesions

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Background: The clinical relevance of moderate coronary stenosis is determined by its morphological characteristics and physiological significance. We investigated the relationship between high-risk plaque characteristics detected by intravascular ultrasound and functional significance assessed with quantitative flow ratio (QFR) in intermediate coronary lesions.

Methods: QFR was retrospectively analyzed in 352 intermediate lesions from 330 patients undergoing intravascular ultrasound examination. The functional significance was defined as QFR ≤0.8. High-risk plaque morphologies including plaque rupture, echo-lucent, echo-attenuation, and spotty calcification were identified, and attenuation indices including maximum angle, attenuation length, and superficial attenuation were determined. Clinically relevant echo-attenuation was defined as an attenuation with a minimum lumen area ≤4.0 mm^2 and plaque burden ≥70%.

Results: The prevalence of echo-attenuation was higher (63.0% *vs.* 37.6%, P=0.001) and attenuation length was longer (12.8±10.3 *vs.* 8.0±5.8 mm, P=0.015) in lesions with QFR ≤0.8 compared to those with QFR >0.8, associated with a higher rate of clinically relevant echo-attenuation (35.2% *vs.* 10.4%, P<0.001). On multivariable analysis, the presence of echo-attenuation was an independent predictor of QFR ≤0.8 [odds ratio (OR) 3.162, 95% confidence interval (CI): 1.263–7.917, P=0.014], whereas attenuation length was weakly correlated with QFR value (β=–0.185, B=–0.002, 95% CI: –0.004 to –0.001, P=0.001). Receiver-operating characteristic curve analysis revealed that the best cutoff of QFR in predicting clinically relevant echo-attenuation was 0.82 [area under the curve (AUC) =0.696, 95% CI: 0.616–0.775, P<0.001].

Conclusions: The presence of intravascular ultrasound-derived echo-attenuation confers an increased risk of QFR-defined functional significance in intermediate coronary lesions.

Keywords: Coronary artery disease; intermediate coronary lesion; quantitative flow ratio (QFR); intravascular ultrasound (IVUS); echo-attenuation

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Introduction

Numerous studies have demonstrated that physiologic-guided percutaneous coronary intervention (PCI) is associated with better clinical outcomes, especially for intermediate lesions, which comprise a high prevalence of anatomical-functional mismatch (1,2). Nevertheless, physiology is not the sole prognostic determinant, as previous intravascular ultrasound (IVUS) studies have shown that high-risk plaque morphologies, such as echo-attenuation, echo-lucent and spotty calcification, were additional prognostic indicators (3-5). Therefore, a rationale combining both physiological and morphological features would be of great clinical importance in decision making and risk assessment of intermediate coronary lesions (6).

Quantitative flow ratio (QFR) has been proved to have an excellent diagnostic performance compared with fractional flow reserve (FFR) (7). Furthermore, QFR may outweigh FFR regarding the feasibility of multi-modality assessment because of several advantages, including non-invasiveness, swiftness, and adenosine-free assessment (8,9). While recent studies have shown that QFR has clinical value in predicting hard cardiac events such as myocardial infarction (10,11), it remains less clear as to whether its prognostic implication is related to the ability of identifying the vulnerable plaque. The current study aimed to test the hypothesis that IVUS-derived high-risk plaque morphologies are associated with QFR-defined functional severity. We presented the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/cdt-21-402).

Methods

Study design and populations

The current study is a retrospective analysis of patients with susceptible coronary artery disease referred for coronary angiography between January 2015 and December 2018. A total of 448 patients with 482 intermediate *de novo* lesions [visual estimation of diameter stenosis (DS) of 50–75% and reference diameter ≥2.5 mm] examined with IVUS were consecutively enrolled. Subjects were excluded because of poor IVUS imaging quality (n=12), ostial lesions (n=3), tandem lesions (n=12), collateral flow supplying from the interrogated vessel (n=3), target lesions compressed by myocardial bridge (n=5), left main disease (n=6), vessel without 2 different projections (>25°) (n=2), severe vessel overlap (n=5), atrial fibrillation during angiography (n=5), incomplete auto-calibrated data for QFR examination (n=77). Therefore, 330 patients with 352 intermediate lesions were included in the final analysis (*Figure 1*). Patient clinical characteristics were retrospectively acquired from a dedicated PCI database.

The study protocol was applied in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board of Shanghai East Hospital (research project number: 2020/007). Individual consent for this retrospective analysis was waived.

IVUS examination and quantitative measurements

IVUS examination was performed after intracoronary administration of 200 μg of nitroglycerin using the iLab system (Boston Scientific, Natick, Massachusetts, USA). A 40 MHz ultrasound catheter was inserted into the interrogated vessel, then the transducer was advanced 10 mm distal to the target lesion and automatically pulled back at 0.5 mm/s to the ostium. All runs were recorded for subsequent off-line analysis.

IVUS imaging analysis was made by two experienced physicians who are blinded to QFR data using a validated planimetry software (Image viewer, Boston Scientific, Natick, Massachusetts, USA). The quantitative IVUS measurements were performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of IVUS Studies (12). Briefly, external elastic membrane (EEM) cross-sectional area (CSA), lumen CSA, and plaque plus media (P + M) CSA were automatically traced at the lesion site and 5 mm proximal and distal reference sites. The lesion site was defined as the site with the minimum lumen area (MLA). The reference site was defined as the site with the largest lumen and smallest plaque burden (PB) without any intervening side branch. Area stenosis (AS, %) was calculated as (mean reference lumen CSA – MLA)/mean reference lumen CSA. PB (%) was derived from following formula: PB = (P + M) CSA/EEM CSA. Remodeling index (RI) was calculated as the EEM CSA at the lesion site divided by the average of the proximal and distal reference segment EEM CSAs. Plaque eccentricity was calculated as (maximum – minimum plaque thickness)/maximum plaque thickness.

IVUS-derived high-risk plaque morphologies

The following IVUS-derived high-risk plaque morphologies which have been associated with plaque vulnerability and

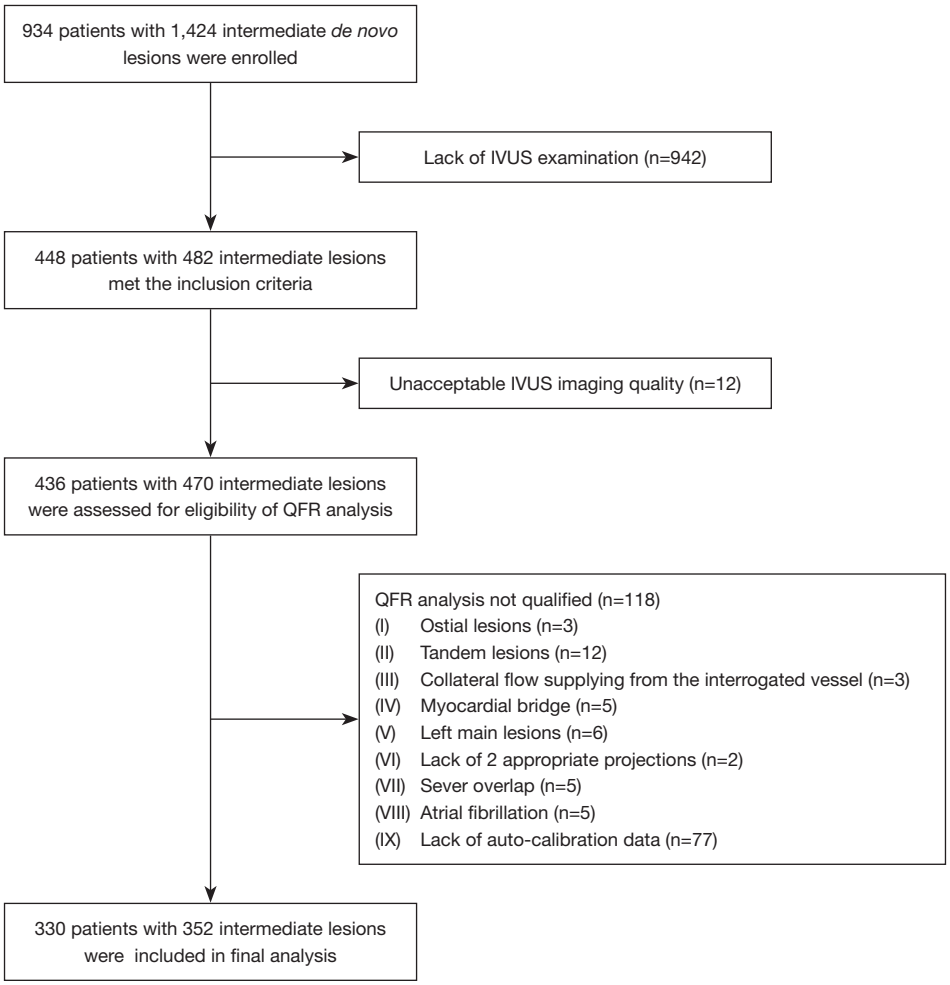


Figure 1 Flowchart of patient enrollment. N, lesion number; QFR, quantitative flow ratio; IVUS, intravascular ultrasound.

worse clinical outcomes were assessed (4,5,13): plaque rupture was defined as the presence of a cavity that communicated with the lumen. Positive remodeling was defined as a RI of >1.05. Echo-attenuation was defined as the loss of ultrasound signal behind plaque in the absence of calcification (3). The maximum attenuation angle was measured in degrees with a protractor centered on the lumen. The attenuation length was measured on the longitudinal view. The location of echo-attenuation was defined as superficial or deep as previously described (3). The echo-attenuation with an MLA ≤4 mm^2 and with a PB ≥70% was considered clinically relevant (14). Echo-lucent was defined as the absence of ultrasound signal within the plaque (3). Spotty calcification was defined as the plaque with calcium deposits within arcs of <90° (3). Discordance between the two investigators regarding the qualitative assessment was resolved by a consensus reading.

The inter- and intra- observer coefficient κ indices for echo-attenuation, echo-lucent and spotty calcification were 0.932, 0.772, and 0.880, and 0.966, 0.870 and 0.920, respectively.

QFR assessment

QFR was retrospectively analyzed by two qualified investigators who were blinded to the IVUS data using the validated QFR system (AngioPlus, Pulse Medical Imaging Technology, Shanghai Co., Ltd., Shanghai, China). The QFR calculation process was performed as previously validated algorithm (7). Briefly, three-dimensional model was reconstructed by automatically delineating the lumen contour in two appropriate projections with different angles (≥25°) of interrogated vessel. Manual correction was limited

and only permitted in case of side-branch or sub-optimal image quality. Contrast flow model using the frame count method was introduced to derive the final QFR value. QFR ≤0.8 was considered as functionally significant. Three-dimensional quantitative coronary angiography (3D-QCA) parameters, including reference vessel diameter (RVD), DS (%), minimal lumen diameter (MLD), and lesion length were automatically derived from the final QFR report.

Statistical analysis

The statistical analyses were performed with R software, version 4.0.4. (R foundation for Statistical Computing, Vienna, Austria), SPSS version 22.0 (SPSS institute, Chicago, Illinois, USA) and GraphPad prism 7.00 (GraphPad Software, Inc., La Jolla, California, USA). Continuous variables are expressed as mean ± standard deviation and were compared using Student's *t*-test. Categorical variables are expressed as frequencies (percentages) and were compared using chi-square test. Intra-observer and inter-observer differences were evaluated using Cohen's κ coefficient. The correlations between continuous parameters were assessed using Pearson correlation analysis. The independent correlation between continuous QFR value and IVUS parameters were assessed using multivariable liner regression analysis. Independent predictors of QFR ≤0.8 were evaluated using multivariable logistic regression which was performed after forward selection of clinical risk factors, QCA and IVUS parameters, with significance for addition to the model set at P≤0.15. Variables with significance levels of P<0.1 in univariable analysis were considered for multivariable analysis. Receiver operating characteristic (ROC) curves were introduced to identify the optimal cutoff value of IVUS parameters to predict the functional significance and to determine the best cutoff of QFR to predict the presence of echo-attenuation with clinical relevance. The comparisons of area under the curve (AUC) were performed using the Delong method (15). A two-sided P value <0.05 was considered statistically significant.

Results

Baseline characteristics

Overall, 276 patients had QFR >0.8 and 54 had QFR ≤0.8. The two groups did not differ with respect to demographics, clinical characteristics, and risk factors for coronary artery disease, except for a higher incidence of multi-vessel disease and higher triglyceride levels in patients with QFR ≤0.8 (*Table 1*).

Lesion characteristics

Compared to lesions with QFR >0.8 (n=298), those with QFR ≤0.8 (n=54) were more frequently located in left anterior descending artery, had higher DS, longer lesion length and smaller MLD and MLA. Furthermore, AS, PB and eccentricity were higher in lesions with QFR ≤0.8, but RVD and RI were similar between the two groups (*Table 2*).

The prevalence of echo-attenuation (63.0% *vs.* 37.6%, P=0.001) and clinically relevant echo-attenuation (35.2% *vs.* 10.4%, P<0.001) were higher in lesions with QFR ≤0.8 versus those with QFR >0.8. When the attenuation indices were compared according to QFR, only attenuation length was significantly different between the two lesion groups (12.8±10.3 *vs.* 8.0±5.8 mm, P=0.015). On the contrary, there were no significant differences between the two groups in plaque rupture, positive remodeling, echo-lucent and spotty calcification (*Table 2*).

Association between echo-attenuation and QFR

A representative illustration of echo-attenuation with QFR ≤0.8 is demonstrated in *Figure 2*. There was a significant albeit weak correlation between the maximum attenuation angle and QFR (r=–0.181, P=0.029) (*Figure 3A*), and a moderate correlation between attenuation length and QFR (r=–0.316, P<0.001) (*Figure 3B*). The comparisons of AUCs between attenuation indices and anatomical references (MLA and AS) for predicting QFR ≤0.8 are shown in *Figure 4*. The differences between attenuation length (AUC =0.639) and anatomical references (AUC =0.698 for MLA, P=0.429; AUC =0.634 for AS, P=0.946) were not statistically significant. Similar results were observed between attenuation angle (AUC =0.591) and anatomical references (P=0.129 for MLA; P=0.536 for AS).

When adjusting for IVUS parameters and other anatomical confounders, only attenuation length was correlated independently with QFR [β=–0.185, B=–0.002, 95% confidence interval (CI): –0.004 to –0.001, P=0.001] (*Table 3*). Echo-attenuation [odds ratio (OR) 3.162, 95% CI: 1.263–7.917, P=0.014], MLA (OR 1.749, 95% CI: 1.099–2.784, P=0.018) and DS (OR 1.357, 95% CI: 1.236–1.489, P<0.001), were identified as the independent predictors of QFR-defined functional significance (*Table 4*). ROC analysis showed that the best cutoff of QFR in predicting clinically

Table 1 Clinical characteristics as stratified by QFR =0.8

Characteristics	QFR >0.8 (n=276)	QFR ≤0.8 (n=54)	P value
Age, years	65.1±9.2	66.1±10.1	0.494
Male, n (%)	160 (58.0)	33 (61.1)	0.663
Hypertension, n (%)	184 (66.7)	38 (70.4)	0.596
Hypercholesterolemia, n (%)	11 (4.0)	5 (9.3)	0.099
Diabetes, n (%)	79 (28.6)	14 (25.9)	0.687
Current Smoker, n (%)	100 (36.2)	16 (29.6)	0.353
Acute coronary syndrome, n (%)	11 (4.0)	4 (7.4)	0.270
Multi-vessel disease, n (%)	153 (55.4)	38 (70.4)	0.045
Prior PCI history, n (%)	37 (13.4)	10 (18.5)	0.326
Prior CABG history, n (%)	1 (0.4)	0	0.658
Prior MI, n (%)	10 (3.6)	3 (5.6)	0.504
LVEF (%)	62.7±4.2	62.7±3.5	0.950
BMI, kg/m^2	24.2±3.9	24.0±2.7	0.830
Laboratory			
Creatinine, μmol/L	72.9±17.8	73.9±20.0	0.720
LDL-C, mmol/L	2.5±0.9	2.6±1.0	0.543
TG, mmol/L	1.4±0.8	1.7±1.0	0.045
HBA1c, %	6.2±1.3	6.5±1.4	0.299
Prior statin treatment, n (%)	42 (15.2)	11 (20.4)	0.417

Values are mean ± standard deviation or number (percentage). QFR, quantitative flow ratio; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; LVEF, left ventricular eject fraction; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HBA1c, hemoglobin A1c.

relevant echo-attenuation was 0.82 (AUC =0.696, 95% CI: 0.616–0.775, P<0.001) (*Figure 5*).

Discussion

The results of this study showed that in intermediate coronary lesions, presence of echo-attenuation was an independent morphological determinant of QFR-defined functional significance. QFR ≤0.82 was useful in predicting clinically relevant echo-attenuation.

Plaque morphologies and physiological significance

Classic anatomical parameters, from plain angiography-derived DS to IVUS-derived MLA and PB, have long been considered as the main determinants of functional significance of coronary stenotic lesions (16,17). In contrast, the relationships between plaque morphology and functional significance were less investigated and varied greatly among different imaging or relevant hemodynamic modalities. Previous virtual histology (VH)-IVUS studies failed to establish the association between plaque morphology and functional significance (18,19), mainly because of limited reproducibility of this technique (20). On the other hand, coronary computed tomography angiography (CCTA)-derived adverse plaque characteristics were independently correlated with FFR but not with positron emission tomography-derived myocardial blood flow or instantaneous wave-free ratio (21,22).

The major finding of the current study was that there existed a significant correlation between echo-attenuation and QFR-defined functional significance. It has been demonstrated that 91.4% of echo-attenuation detected by IVUS and near-infrared spectroscopy (NIRS)

Table 2 Lesion characteristics as stratified by QFR =0.8

Characteristics	QFR >0.8 (n=298)	QFR ≤0.8 (n=54)	P value
PCI after IVUS examination, n (%)	32 (10.7)	16 (29.6)	<0.001
Non-culprit lesions, n (%)	12 (4.0)	4 (7.4)	0.272
3D-QCA parameters, n (%)			
LAD lesions	207 (69.5)	50 (92.6)	<0.001
Proximal lesions	146 (49.0)	30 (55.6)	0.375
RVD, mm	3.2±0.6	3.3±0.6	0.422
DS, %	38.9±7.5	51.0±5.7	<0.001
Lesion length, mm	23.3±12.2	31.7±13.6	<0.001
MLD, mm	1.9±0.5	1.6±0.3	<0.001
IVUS parameters			
MLA, mm^2	4.4±1.7	3.3±0.8	<0.001
AS, %	57.8±11.5	64.8±10.3	<0.001
PB, %	65.3±8.8	70.0±9.1	<0.001
Eccentricity	0.76±0.17	0.81±0.15	0.026
RI	0.86±0.20	0.83±0.20	0.250
High risk IVUS features, n (%)			
Plaque rupture	20 (6.7)	2 (3.7)	0.398
Positive remodeling	51 (17.1)	6 (11.1)	0.271
Echo-lucent	108 (36.2)	20 (37.0)	0.775
Spotty calcification	116 (38.9)	26 (48.1)	0.211
Echo-attenuation	112 (37.6)	34 (63.0)	0.001
Clinically relevant echo-attenuation, n (%)[†]	31 (10.4)	19 (35.2)	<0.001
Attenuation indices	(n=112)	(n=34)	
Maximum attenuation angle, °	122.4±58.2	139.9±60.3	0.130
Attenuation length, mm	8.0±5.8	12.8±10.3	0.015
Superficial attenuation, n (%)	86 (76.8)	27 (79.4)	0.748

Values are mean ± standard deviation or number (percentage). [†], echo-attenuation with an MLA ≤4.0 mm^2 and with a PB ≥70%. QFR, quantitative flow ratio; PCI, percutaneous coronary intervention; 3D-QCA, 3-dimensional quantitative coronary angiography; LAD, left anterior descending; RVD, reference vessel diameter; DS, diameter stenosis; MLD, Minimum lumen diameter; IVUS, intravascular ultrasound; MLA, minimum lumen area; AS, area stenosis; PB, plaque burden; RI, remodeling index.

are histo-pathologically related to lipid-rich necrotic core or lipid pool (3,23). Hence, the inherent lipid-rich nature underscores the vulnerable characteristic of echo-attenuation. Consistent with our finding, recent optical coherence tomography (OCT) studies showed that OCT-derived thin-cap fibroatheroma (TCFA) was correlated with lower FFR and QFR (24,25). In contrast, previous *in-vitro* computational flow dynamics study showed that lipid-rich plaque was related to higher FFR value, owing to the greater deformation of the lumen under the stress (26). Therefore, computational FFR value may be underestimated in the lipid-rich lesion as the rigid vessel walls are universally assumed in all lesions during the angiography-based geometry reconstruction (27). On the other hand, recent

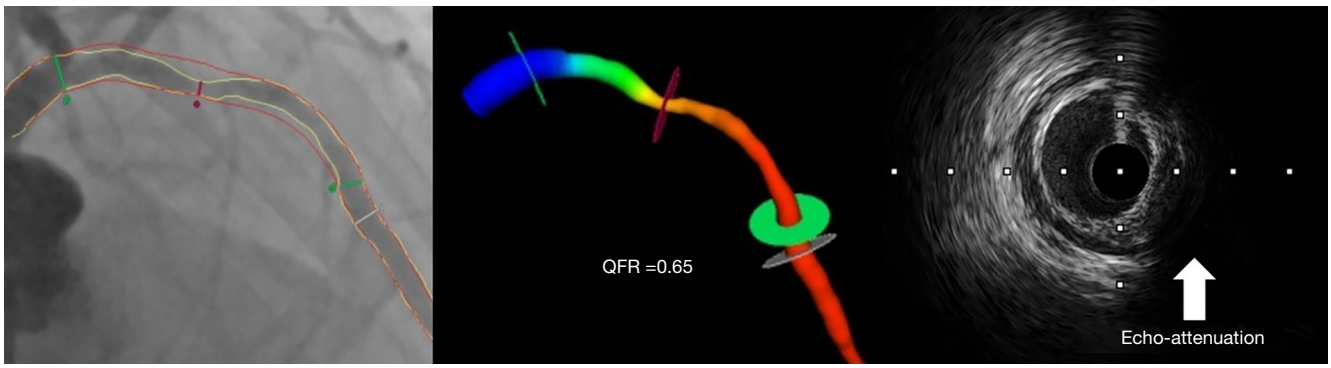


Figure 2 Representative illustration of an echo-attenuation with QFR-defined functional significance. QFR, quantitative flow ratio.

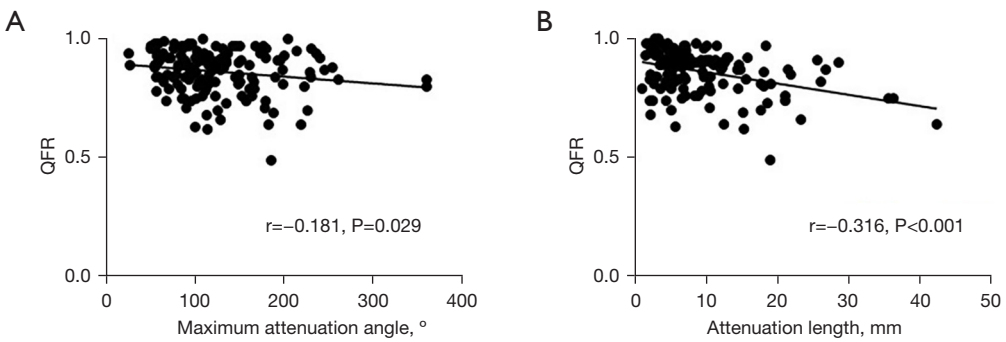


Figure 3 Negative correlations between attenuation indices and QFR. (A) Maximum attenuation angle; (B) attenuation length. QFR, quantitative flow ratio.

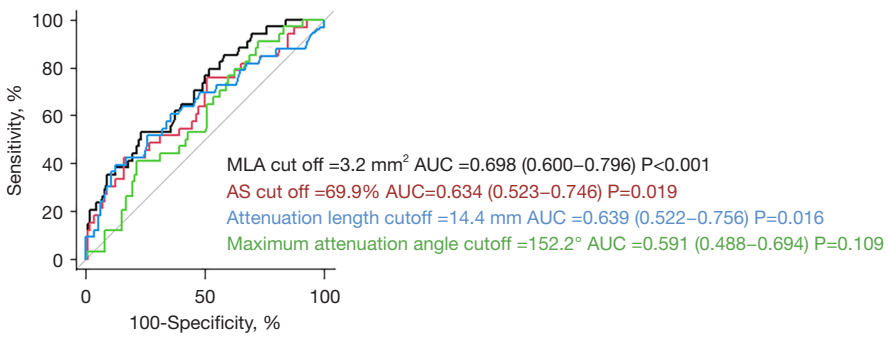


Figure 4 The ROC curve analysis of IVUS parameters for predicting QFR ≤0.8. AS, area stenosis; AUC, area under the curve; MLA, minimum lumen area; ROC, receiver operating characteristic; IVUS, intravascular ultrasound; QFR, quantitative flow ratio.

NIRS study has shown that lipidic plaques may negatively affect the FFR value through hampering the hyperemia-induced vasoreactivity (28). Further studies incorporating computational flow dynamics analysis, resistance/flow measurements and intravascular imaging are warranted to further explore the mechanism explaining the physiologic relevance of lipidic plaque component.

In this study, maximum attenuation angle and attenuation length were correlated weakly with QFR, and the diagnostic performance of attenuation indices in predicting the functional significance was not superior to that of classical IVUS-derived anatomical parameters. Furthermore, only

Table 3 Association between QFR and attenuation indices in multiple liner regression analysis

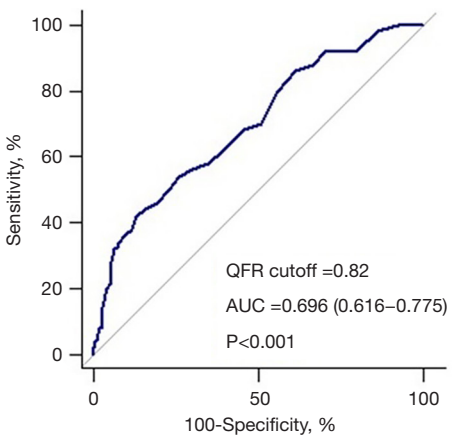
Variables	β	B	95% CI	P value
MLA	−0.001	0.000	−0.007 to 0.007	0.983
AS, %	−0.082	−0.065	−0.167 to 0.036	0.203
PB, %	−0.045	−0.001	−0.002 to 0.001	0.451
DS, %	−0.555	−0.006	−0.007 to −0.005	<0.001
Eccentricity	−0.028	−0.017	−0.076 to 0.042	0.580
Lesion length	−0.187	−0.001	−0.002 to −0.001	<0.001
LAD lesions	−0.282	−0.061	−0.083 to −0.038	<0.001
Multi-vessel disease	−0.064	−0.012	−0.033 to 0.008	0.228
Superficial attenuation	0.033	0.007	−0.015 to 0.029	0.513
Maximum attenuation angle	0.055	0.000	0.000 to 0.000	0.291
Attenuation length	−0.185	−0.002	−0.004 to −0.001	0.001

QFR, quantitative flow ratio; CI, confidence interval; MLA, minimum lumen area; AS, area stenosis; PB, plaque burden; DS, diameter stenosis; LAD, left anterior descending.

Table 4 Multivariable logistic regression for the prediction of QFR ≤0.8

Variables	Odds ratio (95% CI)	P value
Multi-vessel disease	0.469 (0.178–1.235)	0.126
LAD lesions	3.228 (0.837–12.450)	0.089
Eccentricity, per 0.1 increase	1.276 (0.992–1.641)	0.058
MLA, per 0.1 mm^2 decrease	1.749 (1.099–2.784)	0.018
Lesion length, per 1 mm increase	1.027 (0.993–1.062)	0.121
Diameter stenosis, per 1% increase	1.357 (1.236–1.489)	<0.001
Echo-attenuation	3.162 (1.263–7.917)	0.014

QFR, quantitative flow ratio; CI, confidence interval; LAD, left anterior descending; MLA, minimum lumen area.



Accuracy, %	80.7
Sensitivity, %	42.0
Specificity, %	87.1
Positive predictive value, %	35.0
Negative predictive value, %	90.1

Figure 5 The ROC Curve analysis of QFR for predicting clinically relevant echo-attenuation. AUC, area under the curve; QFR, quantitative flow ratio; ROC, receiver operating characteristic.

attenuation length was independently correlated with QFR in the multivariable liner regression analysis, suggesting that the size of echo-attenuation may be not the main contributor of functional significance. Further studies are needed to prove this issue.

In the current study, no other high-risk plaque morphologies were found to be correlated with QFR ≤0.8 except for echo-attenuation. In contrast, previous CCTA studies have demonstrated that positive remodeling and spotty calcification were associated with abnormal FFR (21,22). The explanations of this discrepancy are more likely multifactorial. First, different imaging modalities were used in previous studies. Second, positive remodeling, as a compensatory response to prevent lumen loss caused by plaque, may exert a positive impact on QFR value. Third, spotty calcification is correlated with a lower grade of lumen stenosis (29), which could decrease its effect on functional severity. Finally, compared with echo-attenuation, both spotty calcification and echo-lucent have limited accuracy in identifying lipid-rich plaque and, thus, may also have limitations in predicting functionally significant lesions (3).

Potential clinical implication

Initially, echo-attenuation was considered as a predictor of periprocedural myocardial injury and no-reflow phenomenon during PCI (30,31). A longitudinal IVUS study demonstrated that presence and progression of echo-attenuation were predictors of long-term cardiovascular events (5). The present study provides an additional insight into the clinical importance of echo-attenuation by linking physiological stenosis severity to this high-risk IVUS signature.

Notably, our study showed that despite the significant p-value, QFR ≤0.82 predicted clinically relevant echo-attenuation in intermediate coronary lesions, with a moderate AUC of 0.696. Likewise, although the negative predictive value of QFR >0.82 to preclude the clinically relevant echo-attenuation was high (90.1%), IVUS and QFR may complement each other in certain clinical scenarios with relatively higher prevalence of vulnerable plaque, such as diabetes mellitus and acute coronary syndrome (32). The upcoming large-scale prospective FAVOR III China trial may further elucidate the prognostic implications of QFR-guided PCI (33).

Limitation

There are some limitations in the current study. First, the selection bias may exist due to the retrospective nature of this single-center study. Second, acoustic shadow of calcification may prevent the deep attenuation from detecting by IVUS. Third, although the prognostic value of echo-attenuation has been demonstrated in the post-hoc analysis of previous IVUS trials, prospective outcome data are still lacking (5). Additionally, QFR should also be validated against other intravascular imaging modalities including NIRS and OCT. Fourth, the invasive physiological references, as well as the accuracy and feasibility of QFR computation were limited because of the retrospective nature. Finally, despite being one of the most well investigated virtual functional index, the commercially availability of QFR machine remains limited worldwide, which may limit the generalizability of the findings of the current study (34).

Conclusions

In intermediate coronary lesions, presence of IVUS-derived echo-attenuation is associated with increased risk of QFR-defined functional significance. Further studies are warranted to determine if QFR assessment could be used to detect vulnerable plaque that could potentially benefit from PCI.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/cdt-21-402). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was applied in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board of Shanghai East Hospital (research project number: 2020/No.007). Individual consent for this retrospective analysis was waived.

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