



# Comparison of three-dimensional quantitative coronary angiography and intravascular ultrasound for detecting functionally significant coronary lesions

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**Background:** Three-dimensional quantitative coronary angiography (3D-QCA) can provide more accurate measurement of true vessel size and may be comparable to intravascular ultrasound (IVUS) in identifying functionally significant coronary stenosis, as determined by fractional flow reserve (FFR). This study aimed to evaluate the diagnostic accuracy of 3D-QCA for predicting FFR <0.8.

**Methods:** We assessed 175 lesions in 175 patients by FFR, IVUS, and 3D-QCA. Correlations between 3D-QCA values, IVUS values, and FFR values were analyzed. Receiver operating characteristic (ROC) curves were used to evaluate diagnostic accuracy of 3D-QCA for predicting FFR <0.8 and to determine the appropriate cut-off value.

**Results:** Upon evaluating 3D-QCA values, minimum lumen area (MLA) correlated with FFR value ( $r=0.48$ ,  $P<0.001$ ). Considering IVUS values, MLA correlated with FFR value ( $r=0.43$ ,  $P<0.001$ ). Also, 3D-QCA MLA was well correlated with IVUS MLA ( $r=0.61$ ,  $P<0.001$ ). The area under the ROC curve (AUC) for 3D-QCA MLA was 0.77, and the best cut-off value was 2.37 (sensitivity: 73%, specificity: 71%). The AUC for IVUS MLA was 0.73, and the best cut-off value was 3.01 (sensitivity: 71%, specificity: 65%). There was no significant difference in AUC for 3D-MLA and IVUS-MLA ( $P=0.27$ ).

**Conclusions:** 3D-QCA is not inferior to IVUS for functional assessment of intermediate coronary lesions. We can consider 3D-QCA as a suitable substitute for IVUS or FFR in determining coronary intervention.

**Keywords:** Coronary artery disease; fractional flow reserve (FFR); quantitative coronary angiography; intravascular ultrasound (IVUS)

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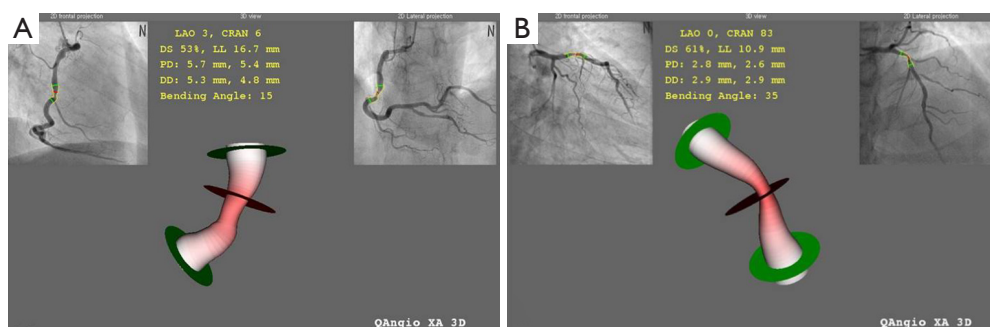
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## Introduction

Fractional flow reserve (FFR) can identify ischemia-producing lesions with a cut-off value of FFR <0.80 and is regarded as the standard of reference for evaluation of functionally significant coronary lesions (1,2). Intravascular ultrasound (IVUS) can provide more detailed assessment

of lumen morphology and lesion severity than visual estimation on two-dimensional quantitative coronary angiography (2D-QCA). Recent studies have suggested the optimal IVUS criteria for predicting ischemic FFR value <0.80. FFR and IVUS provide additional information for physiological and anatomical lesion significance but require



**Figure 1** Examples of 3D-QCA of right coronary artery (A) and left anterior descending artery (B) using two projections. QCA, quantitative coronary angiography.

a wiring procedure and time (3-7). Three-dimensional quantitative coronary angiography (3D-QCA) derived from routine 2D angiography has been developed and offers a reasonable alternative to FFR or IVUS (8-13). The purpose of this study was to compare the diagnostic efficacy of 3D-QCA, and IVUS for detecting functionally significant coronary lesions determined by FFR <0.80. We present the following article in accordance with the STARD reporting checklist (available at <http://dx.doi.org/10.21037/cdt-20-560>).

## Methods

### Study population

Between April 2011 and August 2014, we included 175 patients with stable ischemic heart disease who underwent coronary angiography and revealed intermediate severity (50–70% on visual estimation) at Ajou university hospital. All patients had both FFR and IVUS examination. 175 lesions in 175 patients were assessed retrospectively by FFR, IVUS, 2D-, and 3D-QCA. Exclusion criteria were tandem lesion in the target vessel (stenosis >50% of diameter on visual estimation), prior myocardial infarction, prior coronary artery bypass surgery, prior implanted stent in the target vessel, and acute coronary syndrome. We also excluded myocardial bridge defined by difference of diameter stenosis (DS)% higher than 20% between cardiac cycles by visual estimation. The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by Ajou University Hospital Institutional Review Board (AJIRB-MED-MDB-20). Because of the retrospective

nature of the research, the requirement for informed consent was waived.

### FFR measurement

The 0.014-inch pressure guide wire (Radi, St Jude Medical, Uppsala, Sweden) was externally calibrated, and “equalizing” was performed at the guiding catheter tip. The pressure guide wire was positioned distal to the lesion. FFR was measured at maximal hyperemia induced by intravenous adenosine infusion (140 µg/kg/min) or intracoronary adenosine bolus infusion (60–80 µg). An FFR value <0.80 was considered functionally significant. On operator discretion, the lesion was treated by percutaneous coronary intervention.

### Quantitative coronary angiography

2D-QCA analysis was performed with standard automated edge-detection function (CASS-5, Pie Medical, Maastricht, Netherlands). 3D-QCA analysis was performed blinded to the FFR and IVUS data using QAngio XA 3D (Medis Medical Imaging Systems, Leiden, Netherlands). For 3D-QCA analysis, two angiographic images at least 25° apart were selected. Lumen contours were delineated for each projection using the automated edge-detection function as used in 2D-QCA. After processing lumen contours, coronary lumen and reference vessel were reconstructed as shown in *Figure 1*.

### IVUS imaging and analysis

IVUS studies was performed after administration of 0.2 mg intracoronary nitroglycerin using motorized

**Table 1** Baseline clinical characteristics of 175 patients

Characteristics	Data
Age (years)	66±15
Male	110 (63%)
Cardiac risk factors	
Hypertension	98 (56%)
Dyslipidemia	31 (18%)
Diabetes mellitus	45 (26%)
Current smoker	40 (23%)
Family history	13 (7%)

transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, MN) consisting of a rotating 40-MHz transducer within a 3.2F imaging sheath. IVUS images were analyzed by 2 trained cardiologists in our center blinded to the FFR results using computerized planimetry (EchoPlaque 3.0, Indec Systems, Mountain View, CA). The proximal and distal reference segments were selected within 10 mm proximal and distal to the lesion without any side branches. Minimum lumen area (MLA) was measured by tracing the border of echo-dense plaque at the site of the smallest lumen, and plaque burden (PB) at the MLA site was calculated as [external elastic membrane (EEM) area – lumen area]/EEM area ×100 (%). Lesion length was measured from the most proximal to the most distal site of stenosis.

### Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL) and MedCalc version 14.8 (MedCalc Software, Ostend, Belgium). All values were expressed as mean ± standard deviation (continuous variables) or as number and percentage (categorical variables). Receiver operating characteristic (ROC) curve analysis was used to establish the cut-off values of IVUS and QCA parameters for predicting FFR <0.8. The best cut-off values were calculated using the Youden index. The area under the ROC curve (AUC) was compared by using the DeLong test.

### Results

The baseline clinical characteristics and the angiographic

and IVUS measurements in 175 patients with 175 lesions are summarized in *Tables 1,2*. The mean FFR value at hyperemia was 0.81, and 70 vessels (40%) showed FFR <0.8. The mean difference of 3D-QCA MLA and IVUS MLA was 0.66 [95% confidence interval (CI), 0.47 to 0.86] (*Figure 2*). The MLA of 3D-QCA correlated with FFR value ( $r=0.48$ ,  $P<0.001$ ) (*Figure 3*). Of IVUS values, MLA correlated with FFR value ( $r=0.43$ ,  $P<0.001$ ) (*Figure 4*). Also, 3D-QCA MLA was well correlated with IVUS MLA ( $r=0.61$ ,  $P<0.001$ ) (*Figure 5*). The ROCs analysis for predicting FFR <0.8 is shown in *Table 3*. The area under the ROC curve (AUC) for 3D-QCA DS% was 0.72, and the best cut-off value was 51.3 (sensitivity: 67%, specificity: 65%, accuracy: 66%). The AUC for 3D-QCA MLA was 0.77, and the best cut-off value was 2.37 (sensitivity: 73%, specificity: 71%, accuracy: 73%). The AUC for IVUS MLA was 0.73, and the best cut-off value was 3.01 (sensitivity: 71%, specificity: 65%, accuracy: 68%) (*Figure 6*). There was no significant difference in AUC for 3D-QCA DS%, and 3D-QCA MLA with IVUS-MLA ( $P=0.89$  and  $P=0.27$ , respectively).

### Discussion

This study aimed to directly compare the 3D-QCA and IVUS for predicting functionally significant coronary lesions determined by FFR <0.80. We demonstrate that 3D-QCA offers comparable diagnostic efficacy to IVUS for detecting FFR <0.80.

#### IVUS and FFR in assessment of coronary stenosis

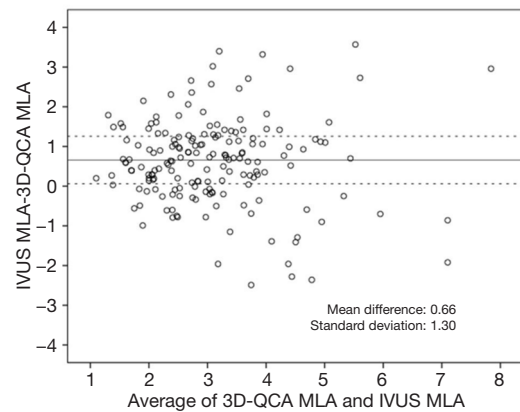
Visual estimation and conventional 2D-QCA have been routinely used for assessing coronary disease for a long time (8). However, it is difficult to depict true vascular structures of coronary arteries due to limited spatial and temporal resolutions, inability to reflect extraluminal irregularities, lesion asymmetry, and tortuosity. Intracoronary imaging modality like IVUS has been widely used to overcome anatomical pitfalls of visual estimation and 2D-QCA (9,11,12,14). In addition to the anatomical significance obtained by IVUS, FFR may confer additional information of the physiological significance of coronary stenosis. Although it is not possible to determine the exact ischemic potential of epicardial stenosis only based upon vessel geometry, some correlation between FFR and stenosis geometry exists (4,5,7,10,15-18). Several studies identified IVUS cut-off values of 4 and 6 mm<sup>2</sup> for a MLA when

**Table 2** QCA, IVUS, and FFR measurements in 175 lesions

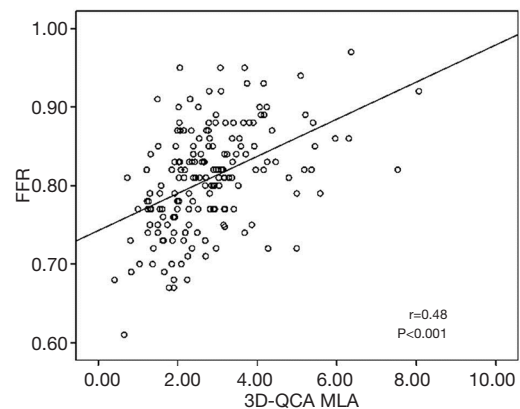
Measurements	Data
<b>Vessel</b>	
Left anterior descending artery	150 (86%)
Left circumflex artery	7 (4%)
Right coronary artery	18 (10%)
<b>2D-QCA</b>	
Diameter stenosis, %	53.5±13.30
Minimum lumen diameter, mm	1.5±0.5
Reference vessel diameter, mm	3.2±0.6
Lesion length, mm	21.9±11.1
<b>3D-QCA</b>	
Minimum lumen area, mm <sup>2</sup>	2.78±1.23
Reference vessel area, mm <sup>2</sup>	8.04±3.72
Lesion length, mm	18.08±8.13
Diameter stenosis, %	47.6±12.50
Percent area stenosis, %	55.56±14
<b>IVUS</b>	
Minimum lumen area, mm <sup>2</sup>	3.44±1.4
EEM area at MLA site, mm <sup>2</sup>	11.81±3.77
Plaque burden, %	69±11
Proximal reference lumen area, mm <sup>2</sup>	12.19±11.12
Proximal reference EEM area, mm <sup>2</sup>	16.21±3.67
Distal reference lumen area, mm <sup>2</sup>	8.49±3.41
Distal reference EEM area, mm <sup>2</sup>	11.83±4.25
Lesion length, mm	23.42±11.23
<b>FFR</b>	
Pre-adenosine	0.92±0.05
Post-adenosine	0.81±0.07

QCA, quantitative coronary angiography; MLA, minimum lumen area; IVUS, intravascular ultrasound; FFR, fractional flow reserve.

differentiating functionally significant coronary lesions in non-left main coronary artery and left main coronary artery, respectively (4-6,18-20). In a study by Kang *et al.*, the best cut-off value of the MLA to predict FFR <0.80 was 2.4 mm<sup>2</sup> with a diagnostic accuracy of 68% (3). Koo *et al.* raised the importance of reference vessel size by reporting the segment-specific cut-off value of 3.0 mm<sup>2</sup> for proximal



**Figure 2** Difference between 3D-QCA MLA and IVUS MLA. QCA, quantitative coronary angiography; MLA, minimum lumen area; IVUS, intravascular ultrasound.



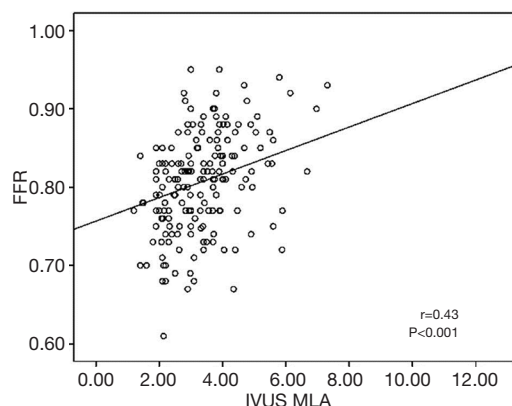
**Figure 3** Linear correlation analysis of MLA by 3D-QCA and FFR. QCA, quantitative coronary angiography; MLA, minimum lumen area; FFR, fractional flow reserve.

LAD lesions and 2.75 mm<sup>2</sup> for mid LAD lesions (21).

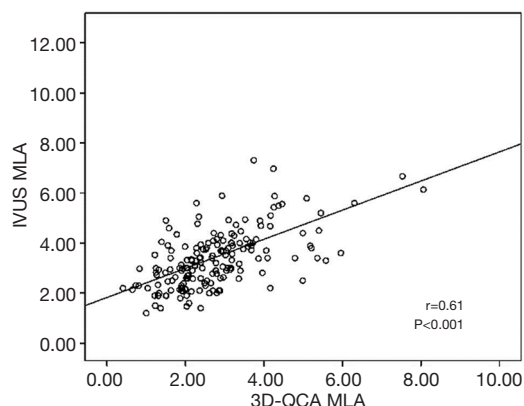
**Utility of 3D-QCA**

3D-QCA has been recently developed to compensate for the limitations of conventional 2D-QCA and allows accurate delineation of true vessel structure by fusion of two angiographic views (8,12-14,22). Even though 3D-QCA is derived from incomplete 2D luminography and cannot fully overcome the limitations of 2D-QCA, it may be able to better reflect vessel tortuosity and lesion eccentricity in the assessment of coronary lesions. 3D-QCA can be more easily obtained from preexisting orthogonal 2D images than

can FFR or IVUS. Nishi *et al.* have reported that 3D-QCA parameters have better predictive value for reduced FFR compared with 2D-QCA. In that study, 3D-QCA MLA and MLD utilized for reduced FFR were comparable to IVUS MLA of 42 lesions (11).



**Figure 4** Linear correlation analysis of MLA by IVUS and FFR. MLA, minimum lumen area; IVUS, intravascular ultrasound; FFR, fractional flow reserve.



**Figure 5** Linear correlation analysis of MLA by 3D-QCA and MLA by IVUS. QCA, quantitative coronary angiography; MLA, minimum lumen area; IVUS, intravascular ultrasound.

### Comparison of 3D-QCA and IVUS for reduced FFR

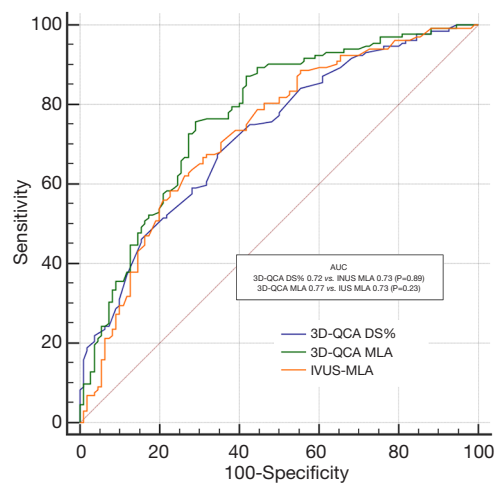
The present study aimed to reinforce T. Nishi's results with enrollment of many more coronary lesions. Anatomical value of 3D-QCA MLA, and IVUS MLA was correlated with physiologic value of FFR. 3D-QCA MLA and IVUS MLA showed linear correlation with each other. Nishi *et al.* suggested that the diagnostic accuracy of 3D-QCA MLA for reduced FFR using ROC analysis was comparable to that of IVUS MLA (11). Huang *et al.* reported that diagnostic accuracy of 3D-QCA derived DS% for reduced FFR was 75% (23). Similarly, in our study, the diagnostic accuracy of 3D-QCA DS%, 3D-QCA MLA, and IVUS MLA for ischemic FFR was 66%, 73%, and 68%. Diagnostic accuracy of 3D-QCA DS% is slightly lower than that of 3D-QCA MLA and IVUS MLA. The area parameter may reflect much truer vessel geometry than diameter parameter. The best cut-off value of 3D-QCA DS%, 3D-QCA MLA, and IVUS MLA for ischemic FFR was 51.3%, 2.37 mm<sup>2</sup> and 3.01 mm<sup>2</sup>, respectively. In other IVUS studies, 2D-QCA derived MLA that was calculated from MLD showed a mean difference of 1–1.5 mm<sup>2</sup> from IVUS MLA (4,9,19,21). The mean difference of 3D-QCA MLA and IVUS MLA in our study was 0.66 mm<sup>2</sup>, and this smaller difference may be due to correction effect by 3D-QCA. AUC of 3D-QCA MLA and IVUS MLA for predicting FFR <0.80 showed no statistically significant difference, implicating similar diagnostic efficacy. In the study of Huang *et al.*, optical coherence tomography (OCT) based FFR showed superiority in predicting ischemic FFR than 3D-QCA derived parameters, integrating both anatomical and physiologic significance. We also integrated both anatomical and physiologic parameter by validating the optimal cut off value (23). In real world practice, FFR and IVUS are relatively expensive tools and require additional procedure and time, though they have many advantages. If FFR or IVUS are not available, 3D-QCA may be a good substitute in assessment of intermediate coronary stenosis without extra procedures (8).

**Table 3** Receiver operating characteristics curve analysis for predicting FFR <0.8

	Best cut-off	Sensitivity	Specificity	AUC	Accuracy
3D-QCA DS%	51.3%	67%	65%	0.72	66%
3D-QCA MLA	2.37 mm <sup>2</sup>	73%	71%	0.77	73%
IVUS MLA	3.01 mm <sup>2</sup>	71%	65%	0.73	68%

FFR, fractional flow reserve, QCA, quantitative coronary angiography; MLA, minimum lumen area; IVUS, intravascular ultrasound.





**Figure 6** Comparison of ROC curves of 3D-QCA DS%, 3D-QCA MLA and IVUS MLA for predicting FFR <0.80. QCA, quantitative coronary angiography; MLA, minimum lumen area; IVUS, intravascular ultrasound; FFR, fractional flow reserve.

### Limitations

There are several limitations in our study. First, though more patients and lesions were enrolled in this study than by T. Nishi's, the present study is a retrospective, observational study with a small number of individuals. Second, patients and clinical factors were not taken into account for analysis. Third, functional ischemia is determined by not only anatomical stenosis, but also location of lesion, burden of myocardial mass, microvascular resistance, and clinical situation (24,25). However, this study did not reflect the above factors. This may be why the correlation between anatomic value of 3D-QCA MLA and IVUS MLA was slightly better than that with the physiologic value of FFR.

### Conclusions

3D-QCA is useful and comparable to IVUS in assessment of functionally significant coronary lesions. When IVUS or FFR are not available or are contraindicated, 3D-QCA may be a good alternative to facilitate decision making.

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### Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at <http://dx.doi.org/10.21037/cdt-20-560>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/cdt-20-560>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/cdt-20-560>). 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 was conducted in accordance with the Declaration of Helsinki (as was revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by Ajou University Hospital Institutional Review Board (AJIRB-MED-MDB-20). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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