Multi-modality diagnostic assessment in interventional cardiology

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Chapter 3

Quantitative angiography and optical coherence tomography for the functional assessment of non-obstructive coronary stenoses: comparison with fractional flow reserve

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Quantitative angiography and optical coherence tomography for the functional assessment of non-obstructive coronary stenoses: comparison with fractional flow reserve
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ABSTRACT

Background. The purpose was to compare 3-dimensional quantitative coronary angiography (3D-QCA) with optical coherence tomography (OCT) for the functional assessment of non-obstructive coronary stenoses, as evaluated by fractional flow reserve (FFR).

Methods. Fifty-five non-obstructive coronary stenoses (30-50% diameter stenosis by visual estimation) were assessed in 36 patients using FFR, 2-dimensional QCA (2D-QCA), 3D-QCA, and OCT.

Results. Angiographic stenosis severity by 2D-QCA was 34±13% diameter stenosis and minimal lumen diameter (MLD) was 1.77±0.58 mm. Fractional flow reserve values were 0.85±0.10. Correlation coefficients between FFR and MLD or minimal lumen area (MLA) were highly significant for both 2D- and 3D-QCA (all $p<0.001$), but higher R^2 values were observed for 3D-QCA measurements. Although significant, correlation coefficients between OCT and FFR data were weak ($R^2=0.28$, $p=0.001$ for MLD; and $R^2=0.23$, $p=0.003$ for MLA). Correlation coefficients with FFR were significantly higher for 3D-QCA than for OCT (p values for MLD and MLA = 0.043 and 0.042, respectively). Non-obstructive stenoses with MLD>1.53 mm or MLA>2.43 mm^2 are unlikely to be hemodynamically significant.

Conclusions. In non-obstructive coronary stenoses, anatomical parameters derived from 3D-QCA can best identify lesions with preserved FFR values.

INTRODUCTION

Physiological assessment of coronary stenoses is essential for identifying patients with myocardial ischemia who benefit from mechanical revascularization in addition to best medical care (1,2). The estimation of stenosis severity by visual inspection of coronary angiograms notoriously fails to relate to its functional significance. Attempts at refining the information content provided by angiography using 2-dimensional quantitative angiography (2D-QCA) have shown modest correlation with pressure-derived fractional flow reserve (FFR) measurements (3). Still, up to one fourth of angiographically non-obstructive coronary stenoses are inappropriately deferred, while responsible for ischemic FFR values <0.80 (4,5).

Two recently developed advanced tools, namely 3-dimensional QCA (3D-QCA) and optical coherence tomography (OCT) have been assessed separately with respect to their capacity to predict functional significance of coronary stenoses (6-10). However, these 2 novel anatomical imaging modalities have never been compared in the same patient; and it remains unknown whether 3D-QCA and/or OCT have the potential to correctly identify non-obstructive stenoses that are indeed hemodynamically non-significant.

METHODS

Patient Population

Patients undergoing elective or urgent angiography showing one or more coronary stenoses qualitatively assessed as non-obstructive (30-50% diameter stenosis by visual estimation) were prospectively enrolled. Imaging data were acquired in the context of approved trials that included protocol-mandated OCT imaging. Exclusion criteria were hemodynamic instability, renal insufficiency, contraindications to intravenous adenosine administration, and anatomical characteristics such as extreme vessel tortuosity and severe calcification that might prevent the advancement of the OCT catheter. Post-hoc off-line analysis of the previously acquired dataset was retrospectively performed. Three-dimensional QCA is obtainable from the analysis of clinically-driven good quality coronary angiograms. Distal moderate disease was not an exclusion criterion, and the vessel segment was reconstructed from the proximal marker of the pressure wire, located downstream to the lesion of interest. Included vessels were free of critical stenoses elsewhere and did not supply collaterals. All studies were approved by the Ethics Committee of our institution and patients signed an informed consent. No complication resulted from the study. No extramural funding was used to support this work.

FFR measurement

In keeping with European Society of Cardiology guidelines, FFR is an integral part of treatment strategy (11). Myocardial FFR was measured using a 0.014-inch miniaturized pressure monitoring guide wire system (RADI PressureWire, St Jude Medical Systems, St Paul, MN) to record the distal coronary pressure. The wire was introduced through either a 6F or 7F guiding catheter; calibrated; advanced into the coronary artery; and, after equalization, positioned distal to the stenosis as previously described (3,12). Adenosine was administered to induce maximum hyperemia using either (1) intravenous adenosine at 140 µg/kg per minute infusion or (2) intracoronary adenosine (using a 50-µg bolus at the minimum). With FFR values close to 0.80, we used incremental doses of intracoronary adenosine up to 150 µg, provided the patient tolerated the lower dose, to ensure that maximum hyperemia was achieved. Fractional flow reserve was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter (Pd/Pa). Pullback was systematically performed to confirm that the FFR value in the guiding catheter was back to 1.00. An FFR threshold $\leq$0.80 was used to detect functionally significant lesions (e.g., ischemia-inducing stenosis) (12,13).

Quantitative coronary angiography analysis

Angiographic images were acquired at 15 frames per second (Innova 4100, GE, USA and Axiom Artis, Siemens, Forchheim, Germany). Two-dimensional QCA was performed using dedicated QCA software packages (QAngio XA 7.3, Medis medical imaging systems bv, Leiden, the Netherlands). Angiographic views with the least foreshortening and yielding the best depiction of the stenotic coronary segments were analyzed.

Three-dimensional QCA was performed offline using dedicated software packages (QAngio XA 3D Research Edition 1.0, Medis Specials bv, Leiden, the Netherlands) as previously described (14). Briefly, the software allows the volumetric reconstruction of the luminal and reference diameters of the analyzed segments, that is, the estimated vessel dimensions as if no obstruction was present, from two different projections at least 25° apart. Automated calibration was used in the 3D angiographic reconstruction. The analyses were performed on the electrocardiogram-gated end-diastolic frame. For the standard export of 512×512 angiographic images, the sample resolution is in the order of 0.2 mm. The entire target vessel was reconstructed in 3D, and all the cross-sections perpendicular to the vessel centerline were quantified. From these data, the minimal lumen area (MLA) was identified as the cross-section with the minimum area. Lumen diameters were automatically detected and reference diameters reconstructed by linear regression algorithms. Minimum luminal area, percentage area stenosis, minimum luminal diameter (MLD) and percentage diameter stenosis were measured using both 3D-QCA and 2D-QCA. Minimum luminal area by 2D-QCA is derived from MLD assuming a circular cross-section.

The eccentricity index was calculated as (maximal distance–minimal distance)/maximal distance (15). All measurements were performed by an experienced operator and evaluated by a second independent QCA analyst blinded to the FFR and OCT results. All coronary angiograms and FFR measurements were carried out after intracoronary nitrates administration.

Optical coherence tomography analysis

OCT pullbacks were performed at 20 mm/s by non-occlusive flushing technique using a 2.7 F imaging catheter with a dedicated workstation (C7-XRTM OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota, USA). Blood was cleared during the pullback by injection of contrast medium at 3-4 ml/sec over a period of 3-4 sec. OCT images were recorded at 100 frames/sec and converted to DICOM format at a resolution of 512 × 512 pixels. Z-offset calibration was performed before converting to DICOM format for the subsequent analysis.

Off-line analysis was performed using QIvus 2.1 (Medis medical imaging systems bv, Leiden, the Netherlands) and the corresponding segments between X-ray angiography and OCT was established using a co-registration software (QAngioOCT Research Edition 1.0, Medis Specials bv, Leiden, the Netherlands) previously described and validated (14,16). This software automatically performs precise anatomic overlap between angiography and OCT. Accordingly, longitudinal and transversal reconstructions of the coronary segment were obtained. After longitudinal delineation of the OCT segment, the smallest luminal area was identified automatically; both MLA and MLD were measured at that level. Eccentricity index was reported as maximum lumen diameter minus minimum lumen diameter divided by maximum lumen diameter (17).

Statistical Analysis

Statistical analysis was performed with IBM SPSS version 20 (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean±SD. Categorical variables are expressed as percentages. Data were analyzed on a per-patient basis for the clinical characteristics and on a per-vessel basis for the remaining calculations. Continuous variables were compared with t test. Quadratic and cubic regression analyses were used to identify "best fit" regressions and to determine the coefficients of determination between FFR and 2D-QCA, 3D-QCA, and OCT measurements. Correlation coefficients were compared using the Fisher Z-transformation. Comparative analysis of 2D-QCA, 3D-QCA and OCT measurements included estimation of area under the receiver-operating characteristic curve; identification of optimal cutoff value to predict the FFR cut-off of 0.80; and corresponding sensitivity, specificity and diagnostic accuracy metrics. Optimal cutoff value identification was based on statistical methods (highest sum of sensitivity and specificity). A modification of the classification by Swets (18) was used to classify diagnostic efficiency of OCT and 3D-QCA according to the values of the area under the curve (AUC) as low (<0.70), moderate (0.70 to 0.90), and high (>0.90). Inter-

and intra-observer variability for 3D-QCA and OCT-derived MLD and MLA are reported as average differences±standard deviation between paired data. Differences between luminal measurements obtained with 3D-QCA and OCT in the same stenoses were compared using Bland-Altman plots.

The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper.

RESULTS

Clinical demographics and coronary stenoses characteristics

Thirty-six patients with 55 non-obstructive lesions by visual inspection have been enrolled (Tables 1 and 2). Two-thirds of the patients had stable coronary artery disease, and the remainder had either non-ST-segment or ST-segment myocardial infarction. Fifty percent of the lesions involved the left anterior descending coronary artery. Quantitative stenosis severity

Table 1. Clinical characteristics of the study population

	n=36
Age (years)	61±12
Male gender, n (%)	24 (67)
Hypertension[1], n (%)	18 (50)
Diabetes[2], n (%)	3 (8)
Dyslipidemia[3], n (%)	23 (64)
Active smoker[4], n (%)	14 (39)
Family history of coronary disease[5], n (%)	6 (17)
Creatinine clearance (ml/min/1.73 m^2)	83±10
Left Ventricular Ejection Fraction (%)	69±10
Previous STEMI, n (%)	7 (19)
Previous NSTEMI, n (%)	7 (19)
Clinical presentation	
• *STEMI, n (%)*	3 (8)
• *NSTEMI/UA, n (%)*	5 (14)
• *Stable CAD, n (%)*	28 (78)

CAD, coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

[1] Defined as known systolic blood pressure values > 140 mmHg

[2] Defined as known diabetes mellitus requiring treatment other than diet

[3] Defined as total cholesterol values of > 200 mg/dl

[4] Defined as known smoking habit at the time of study inclusion

[5] Defined by the presence of at least one first-grade relative with known ischemic heart disease (diagnosis made before 60 years of age for males, before 65 years of age for females)

by angiography was 34±13% diameter stenosis by 2D-QCA evaluation and 38±14% by 3D-QCA. Mean FFR values were 0.85±0.10, while 14 (26%) out of 55 had an FFR≤0.80. MLA was significantly different (p=0.047) between imaging techniques, largest when measured by OCT (Table 2).

Table 2. Characteristics of coronary stenoses

				p	*FFR*
Lesions (all) Number of stenoses assessed in each patient	n=55				0.85±0.10 1.5±0.7
Vessel (n)					
• LAD	32				0.84±0.01
• LCx	10				0.87±0.14
• RCA	13				0.86±0.13
Anatomic Measurements	***2D-QCA***	***3D-QCA***	***OCT***		
• Diameter Stenosis (%)					34±12
• RVD (mm)	2.67±0.56	2.82±0.48	N/A	-	
• MLD (mm)	1.77±0.58	1.75±0.55	1.79 ±0.57	0.934	
• MLA (mm^2)	2.72±1.81	3.30±1.90	3.62±2.03	0.047	
• Diameter Stenosis (%)	34±13	38±14	N/A	-	
• Lesion Length (mm)	11±8	16±10	N/A	-	
• Eccentricity Index	0.27±0.18	0.18±0.11	0.24±0.13	0.004	

2D-QCA, two-dimensional quantitative coronary angiography; 3D-QCA, three-dimensional quantitative coronary angiography; FFR, fractional flow reserve; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; MLA, minimal lumen area; MLD, minimal lumen diameter; OCT, optical coherence tomography; RCA, right coronary artery; RVD, reference vessel diameter.

Correlation between 2D- and 3D-QCA measurements and FFR

Correlation coefficients between FFR and MLD or MLA were highly significant for both 2D- and 3D-QCA (all p<0.001), but higher R^2 values were observed for 3D-QCA measurements (figures 1 and 2). Receiver operating curve analysis showed an AUC>0.8 for both 2D-QCA and 3D-QCA derived measurements. The 95%CIs of AUC were 0.78 to 0.96 for 2D-QCA-MLD, 0.78 to 0.96 for 2D-QCA-MLA, 0.79 to 0.98 for 3D-QCA-MLD, and 0.78-0.99 for 3D-QCA-MLA. Best cut-off values for 2D-QCA-derived measurements were 1.54 mm for MLD (sensitivity 78%, specificity 93%, accuracy 86%) and 1.85 mm^2 for MLA (sensitivity 78%, specificity 93%, accuracy 86%). Best cut-off values for 3D-QCA-derived measurements were similar at 1.53 mm for MLD (sensitivity 80%, specificity 79%, accuracy 80%), but higher at 2.43 mm^2 for MLA (sensitivity 88%, specificity 86%, accuracy 87%).

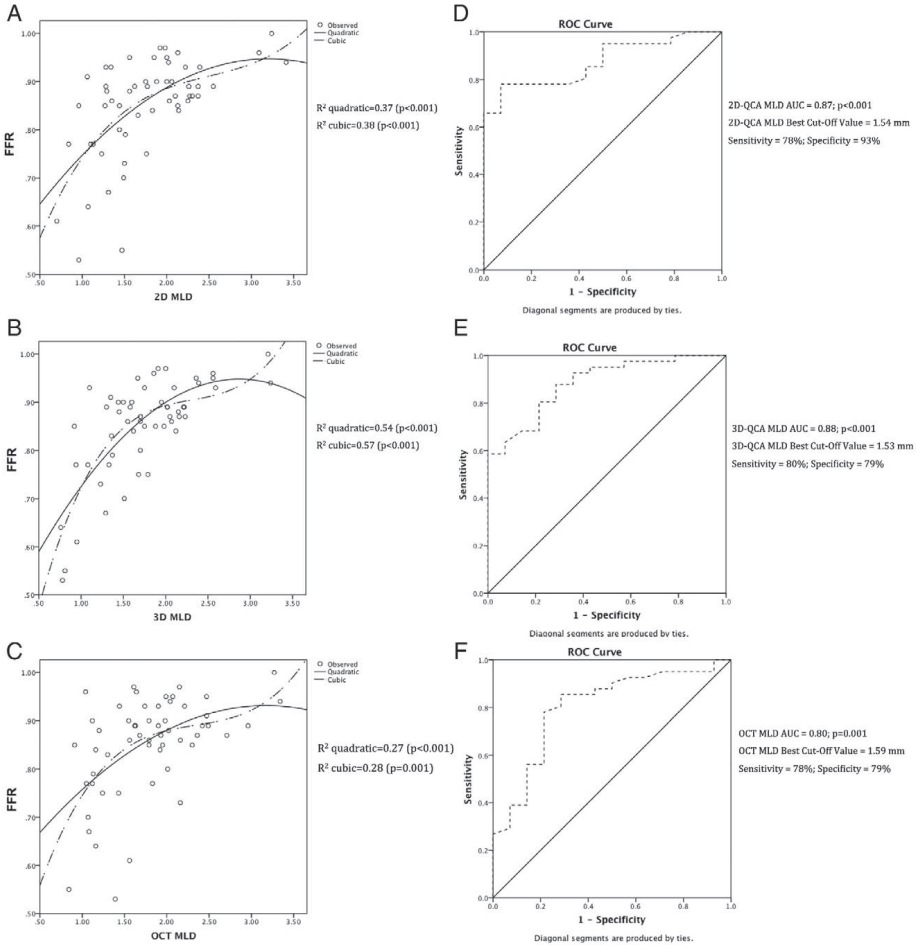

Figure 1. Best-fit regression curves analysis for 2D-QCA (A), 3D-QCA (B) and OCT (C) – derived MLD and their predictive accuracy with respect to normal FFR (> 0.80) (D, E and F) (Lesions n=55)
2D-QCA, two-dimensional quantitative coronary angiography; 3D-QCA, three-dimensional quantitative coronary angiography; AUC, area under the curve; FFR, fractional flow reserve; MLD, minimal lumen diameter; ROC, receiver-operating characteristics

Correlation between OCT measurements and FFR

Although significant, correlation coefficients between OCT and FFR data were weak: R^2=0.28, p=0.001 for MLD and R^2=0.23, p=0.003 for MLA (figures 1 and 2). Both MLD (AUC=0.80 95% CI 0.67-0.94; p=0.001) and MLA (AUC=0.78; 95% CI 0.64-0.92; p=0.002) had a moderate accuracy on predicting FFR>0.80. Best cut-off values of OCT-derived measurements to identify stenoses with FFR>0.80 were 1.59 mm for MLD (sensitivity 78%, specificity 79%, accuracy 79%) and 2.88 mm^2 for MLA (sensitivity 73%, specificity 71%, accuracy 72%).

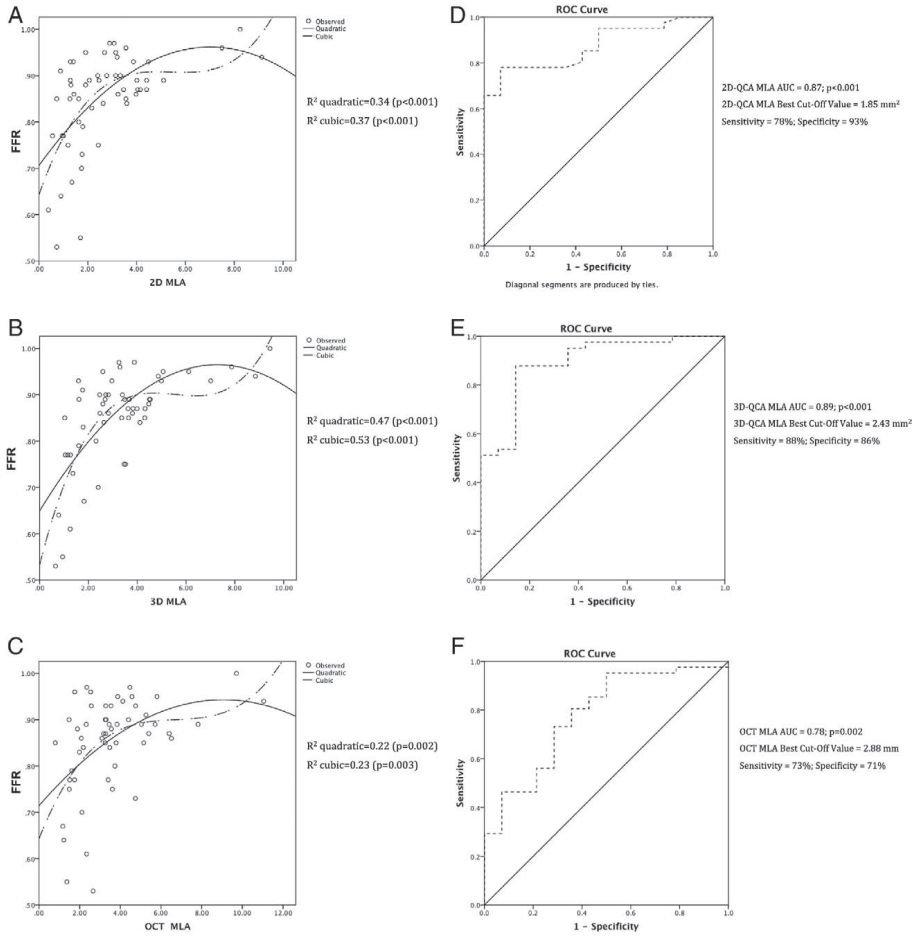

Figure 2. Best-fit regression curves analysis for 2D-QCA (A), 3D-QCA (B) and OCT (C) – derived MLA and their predictive accuracy with respect to FFR (> 0.80) (D, E and F) (Lesions n=55)
2D-QCA, two-dimensional quantitative coronary angiography; 3D-QCA, three-dimensional quantitative coronary angiography; AUC, area under the curve; FFR, fractional flow reserve; MLA, minimal lumen area; ROC, receiver-operating characteristics

3D-QCA versus OCT and measurement reliability

Correlation coefficients with FFR were significantly higher for 3D-QCA than for OCT (p values for MLD and MLA = 0.043 and 0.042, respectively) (figure 3). According to the Swets classification, 3D-QCA derived dimensions had a high predictive accuracy with respect to FFR values, as compared with the moderate accuracy for OCT derived estimates. Eccentricity index was significantly higher when assessed by OCT versus 3D-QCA (0.24±0.13 vs 0.18±0.11; p=0.009).

By Bland-Altman and regression analysis (figure 3), the mean difference in MLD between 3D-QCA and OCT was 0.04±0.46 mm (limits of agreement from –0.86 to 0.94 mm). For the MLA, the mean difference between 3D-QCA and OCT was 0.31±1.66 mm^2 (limits of agreement between –2.94 and 3.56 mm^2). Inter- and intraobserver variability for 3D-QCA and OCT measurements is shown in the online Appendix Supplementary Table 1.

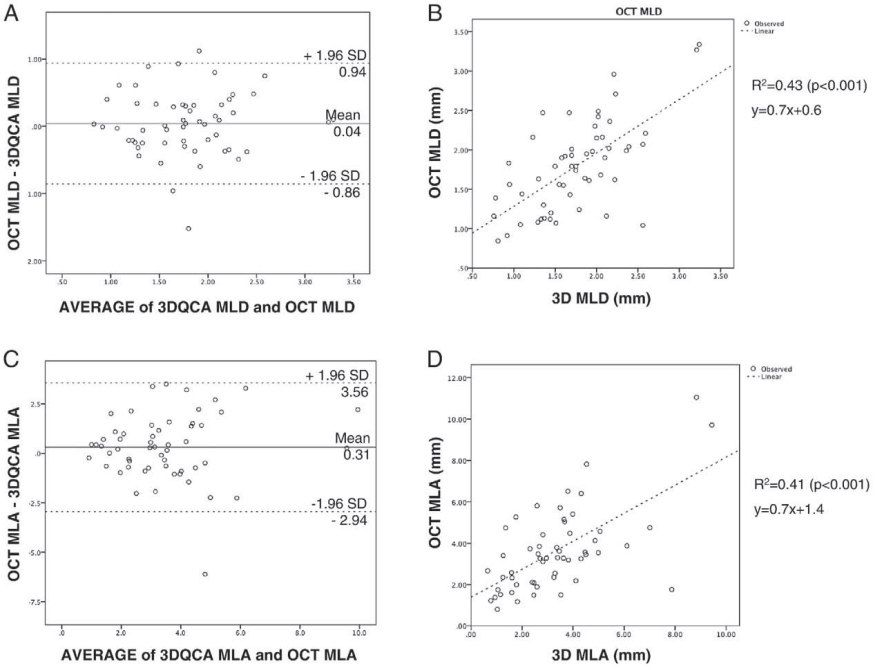

Figure 3. Differences in MLD and MLA between 3D-QCA and OCT (Lesions n=55)
For abbreviations see figures 1 and 2.

DISCUSSION

Main findings were as follows: although significant correlations with FFR were found for 2D-QCA, 3D-QCA, and OCT, best results were found for 3D-QCA.

This study represents the first direct comparison between 3D-QCA and OCT in assessing the functional significance of coronary stenoses. Two-dimensional QCA was also performed to place the 2 novel anatomic diagnostic methods (i.e. 3D-QCA and OCT) in context with a well-established tool. A recently developed co-registration software was applied (14).

In this study we demonstrate that a cubic regression model showed the best fit for assessing the correlation of 3D-QCA and OCT measurements with FFR, confirming previous findings in animal models (19). Whereas the trans-stenotic pressure loss is a quadratic function of pressure loss (ΔP) due to flow (Q) separation (s) and viscous forces friction (f) [($\Delta P = fQ + sQ^2$)]

(20), landmark studies in canine models used a cubic equation that best fitted the composite data in the form $\Delta P=aQ+bQ^2+cQ^3$ (19). This cubic, curve-fitting algorithm equation was used to estimate the single pressure gradient at any particular flow rate for that stenosis and has no physiologic significance but was used to determine a single pressure gradient falling within the range of pressure gradients measured experimentally at any given flow (19).

The stronger correlation between FFR and 3D-QCA, as opposed to OCT, can be explained by a combination of different factors. The vessel bending angle can affect dimensional measurements, especially when the imaging catheter is not positioned centrally during pullback (16). In this case, there is an overestimation of the true lumen dimensions due to the fact that the transversal plane as retrieved by the OCT catheter is not parallel to the vessel centerline (16). This overestimation is absent –by definition– in the 3D-QCA diagnostic assessment that does not interfere with the natural vessel curvature.

Both OCT and 3D-QCA have been previously compared separately to FFR (Table 3). Gonzalo et al. reported a moderate correlation –at best– between OCT and FFR, as assessed by linear and quadratic regression models (6). The diagnostic accuracy of OCT-derived dimensional variables, mainly MLA and MLD, in identifying hemodynamically significant coronary stenoses, was found to be moderate. In addition, Shiono et al. (9) assessed intermediate-to-significant stenoses, with higher diameter stenosis, and FFR values that were overall below the ischemic

Table 3. Studies comparing FFR to different anatomical imaging modalities (Panel A: 2D-QCA; Panel B: 3D-QCA; Panel C: OCT).

Author	Number of lesions assessed	%DS	FFR	Cut-off	AUC	Diagnostic Accuracy
Yong et al. †	63	51±14	0.74±0.18	MLD: 1.25 mm	MLD: 0.80	MLD: 71%
Pyxaras et al.	55	34±13	0.85±0.10	MLD: 1.54 mm MLA: 1.85 mm^2	MLD: 0.87 MLA: 0.87	MLD: 86% MLA: 86%
Saad et al. †	41	36±11	0.84±0.09	DS: 45% CSS: 57%	DS: 0.93 CSS: 0.93	DS: 90% CSS: 89%
Yong et al. †	63	51±14	0.74±0.18	MLA: 1.60 mm^2	MLA: 0.86	MLA: 80%
Pyxaras et al.	55	34±13	0.85±0.10	MLD: 1.53 mm MLA: 2.43 mm^2	MLD: 0.88 MLA: 0.89	MLD: 80% MLA: 87%
Shiono et al. †	62	58±17	0.72±0.14	MLD: 1.35 mm MLA: 1.91 mm^2 AS: 70%	MLD: 0.917 MLA: 0.904 AS: 0.940	MLD: 85.5% MLA: 85.4% AS: 90.3%
Gonzalo et al.	61	51±8	0.80±0.11	MLD: 1.34 MLA: 1.95 mm^2	MLD: 0.74 MLA: 0.73	MLD: 73% MLA: 72%
Pyxaras et al.	55	34±13	0.85±0.10	MLD: 1.53 mm MLA: 2.43 mm^2	MLD: 0.88 MLA: 0.89	MLD: 80% MLA: 87%

2D-QCA, two-dimensional quantitative coronary angiography; 3D-QCA, three-dimensional quantitative coronary angiography; AUC, area under the curve; CSS, cross-sectional stenosis; DS, percentage diameter stenosis; FFR, fractional flow reserve; MLA, minimal lumen area; MLD, minimal lumen diameter; OCT, optical coherence tomography.

† In these studies the cut-off of (ab)normality was 0.75, instead of 0.80.

threshold (at 0.75 in that study). Previously, Yong and colleagues (9) showed a moderate correlation of 2D and 3D-QCA with FFR, by linear regression analysis, and concluded that the accuracy of both methods in predicting pathological FFR is limited. The observed correlation was dependent on the FFR cut-off value used and on the lesion severity, with a trend towards less accurate assessment in moderate lesions (7). Similar were the findings by Saad et al. (8), suggesting significant, yet moderate predictive accuracy of 3D-QCA with respect to FFR as assessed by simple linear regression comparison models.

Higher cutoff values for hemodynamically significant minimal diameter and area were found in the present study as compared with previous ones (Table 3). Of note, 3D-QCA and OCT-derived values were similar; yet, the threshold value associated with pathological FFR was best identified by 3D-QCA. We found higher MLA cut-off value primarily because we assess the accuracy of 3D-QCA and OCT to determine the functional significance of presumably non-critical (i.e. with an FFR > 0.80) stenoses, while the proportion of hemodynamically significant lesions was higher in all previous studies.

Clinical implications

The functional interrogation of intermediate coronary stenoses (50-70% diameter stenosis by visual estimation) is currently assessment domain of FFR; and this led us to assess only non-obstructive stenoses, which are not considered at all for FFR measurement or intracoronary imaging. In fact, a sizable proportion of patients with non-obstructive coronary stenoses (30-50% diameter stenosis by visual assessment) may benefit from FFR assessment. Muller et al. (5) demonstrated that among 166 patients with isolated LAD stenosis and significant (≤0.80) FFR, 23.6% had only non-obstructive stenosis. In the present study, quantitative 3D assessment of coronary anatomy identified 14 out of 55 coronary stenoses deemed as lesions that "do not need further evaluation" by eyeballing while having an abnormal FFR<0.80. On the basis of visual estimation of stenosis severity, appropriate revascularization would have been deferred.

The data show that MLD and MLA measured by 3D-QCA are more accurate than the corresponding OCT metrics on identifying which lesions should not undergo FFR measurements. Instead of performing FFR in this entire lesion subset, 3D-QCA assessment provides useful information by ruling out hemodynamic significance in ¾ of lesions confirmed not to require additional FFR. Of note, 3D-QCA is readily available and less laborious than OCT because it does not require intracoronary manipulation of a microcatheter or additional contrast medium injections.

Study Limitations

We have not studied high-grade stenoses or long lesions and data span over a narrow range; the sample size was limited. Nevertheless, tight correlations were found and it was our intention to focus on non-obstructive lesions.

We found more accurate correlations between anatomy and FFR than previous studies, which can be due to any of the following: use of specific software packages, cubic regression models, or different threshold for ischemic FFR (0.80 instead of 0.75). We cannot exclude that volumetric OCT indexes, such as vascular resistance ratio recently reported by Guagliumi et al. (10) can enhance the accuracy of OCT in predicting FFR. We acknowledge that 3D-QCA and potentially 3D-OCT can provide integrated estimates of stenosis flow resistance, but only MLA and MLD assessment was included in the present analysis to allow direct comparison of all three imaging techniques with FFR. These simple metrics are well understood and easily available in clinical practice.

Loss of image quality can occur while exporting OCT images to DICOM format. However, previous validation studies using the same OCT software package showed high reproducibility of DICOM data analysis (21). The 3D-QCA software packages used in this study have been validated in phantoms (22) and in-vivo studies (14).

The inclusion of ACS patients might have been a source of measurement variability, due to possible vasomotor phenomena that may modify the correlation between the stenosis hemodynamic significance and anatomically-derived measurements. However, included lesions were non culprit; nor were they located in the culprit vessel. Ntalianis et al (23) have previously shown that FFR values in non-culprit vessels do not change significantly from acute phase to later follow up. We do not think that the presence of intracoronary thrombotic material affected our results, since it was detected by OCT in only one out of 55 lesions.

Likewise, previously infarcted myocardial areas may bare non-pathological FFR values despite upstream anatomically critical stenosis, as recently shown by Leone et al (24). However, in our study only 6 out of 55 lesions were upstream to a previously infarcted territory. Additionally, all lesions were assessed more than 2 months after the acute event (range 64-365 days).

Lastly, the current sample size does not allow to perform a meaningful per-vessel analysis.

CONCLUSIONS

In non-obstructive coronary stenoses, the 3D-QCA assessment showed stronger coefficients of determination with FFR than 2D-QCA and OCT, whereas the 2D- and 3D-QCA had higher accuracy than OCT with respect to the corresponding FFR values. We verified that a cubic regression model fits better the correlation between anatomical (i.e. 2D-QCA, 3D-QCA and OCT–derived MLD and MLA measurements) and functional (FFR) indices. These findings suggest that a diagnostic algorithm that integrates characterization of lesion severity by 3D-QCA may be helpful for treatment guidance.

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APPENDIX

Appendix Table 1. Inter- and intra-observer variability analysis.

Variable	Inter-observer Variability		Intra-observer variability	
	Mean Difference	SD	Mean Difference	SD
3D-QCA MLD (mm)	0.03	0.05	0.04	0.04
OCT MLD (mm)	0.02	0.08	0.02	0.02
3D-QCA MLA (mm^2)	0.04	0.02	0.01	0.05
OCT MLA (mm^2)	0.02	0.08	0.08	0.15

3D-QCA: three-dimensional quantitative coronary angiography; MLA: minimal lumen area; MLD: minimal lumen diameter; OCT: optical coherence tomography; SD: standard deviation