Journal of the American College of Cardiology
Published by Elsevier Inc.
Vol. 59, No. 12, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.09.078

Morphometric Assessment of Coronary Stenosis Relevance With Optical Coherence Tomography

A Comparison With Fractional Flow Reserve and Intravascular Ultrasound

Nieve Gonzalo, MD, PhD, Javier Escaned, MD, PhD, Fernando Alfonso, MD, PhD, Christian Nolte, MD, Vera Rodriguez, BSc, Pilar Jimenez-Quevedo, MD, PhD, Camino Bañuelos, MD, Antonia Fernández-Ortiz, MD, PhD, Eulogio Garcia, MD, Rosana Hernandez-Antolin, MD, PhD, Carlos Macaya, MD, PhD

Madrid, Spain

Objectives The study sought to assess the diagnostic efficiency of optical coherence tomography (OCT) in identifying hemodynamically severe coronary stenoses as determined by fractional flow reserve (FFR). Concomitant OCT and intravascular ultrasound (IVUS) area measurements were performed in a subgroup of patients to compare the diagnostic efficiency of both techniques.

Background The value of OCT to determine stenosis severity remains unsettled.

Methods Sixty-one stenoses with intermediate angiographic severity were studied in 56 patients. Stenoses were labeled as severe if FFR ≤0.80. OCT interrogation was performed in all cases, with concomitant IVUS imaging in 47 cases.

Results Angiographic stenosis severity was 50.9 ± 8% diameter stenosis with 1.28 ± 0.3 mm minimal lumen diameter. FFR was ≤0.80 in 28 (45.9%) stenoses. An overall moderate diagnostic efficiency of OCT was found (area under the curve [AUC]: 0.74; 95% confidence interval [CI]: 0.61 to 0.84), with sensitivity/specificity of 82%/63% associated with an optimal cutoff value of 1.95 mm^2. Comparison of the results in patients with simultaneous IVUS and OCT imaging revealed no significant differences in the diagnostic efficiency of OCT (AUC: 0.70; 95% CI: 0.55 to 0.83) and IVUS (AUC. 0.63; 95% CI: 0.47 to 0.77; p = 0.19). Sensitivity/specificity for IVUS was 67%/65% for an optimal cutoff value of 2.36 mm^2. In the subgroup of small vessels (reference diameter <3 mm) OCT showed a significantly better diagnostic efficiency (AUC: 0.77; 95% CI: 0.60 to 0.89) than IVUS (AUC: 0.63; 95% CI: 0.46 to 0.78) to identify functionally significant stenoses (p = 0.04).

Conclusions OCT has a moderate diagnostic efficiency in identifying hemodynamically severe coronary stenoses. Although OCT seems slightly superior to IVUS for this purpose (particularly in vessels <3 mm), its low specificity precludes its use as a substitute of FFR for functional stenosis assessment. (J Am Coll Cardiol 2012;59:1080–9) © 2012 by the American College of Cardiology Foundation

Although the limitations inherent to coronary angiography to depict atheromatous involvement and functional stenosis significance have been repeatedly highlighted (1), decision making on coronary revascularization is largely based on the interpretation of the coronary angiogram at the light of available clinical data. This attitude is particularly suitable in case of a single, severe (>70% diameter) stenosis, but does not address the problem of intermediate severity or multiple coronary stenoses. In these cases use of additional diagnostic methods is recommended to determine the clinical impact of specific stenoses. Fractional flow reserve (FFR) is the intracoronary physiology standard to evaluate functional relevance of coronary stenosis in the catheterization lab (2–4). Intravascular ultrasound (IVUS) is an intracoronary imaging method able to provide information about lumen area, vessel area, and plaque burden that can be used for the guidance of percutaneous revascularization procedures. Several studies have investigated on an expanded use of IVUS to identify hemodynamically severe stenoses using FFR as a

See page 1090

From the Department of Interventional Cardiology, Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 2, 2011; revised manuscript received September 22, 2011, accepted September 27, 2011.

standard of reference (5,6). Over the last years it has been customary to use the cutoff minimum lumen area (MLA) value of <4 mm^2 as indicative of hemodynamic severity. Optical coherence tomography (OCT) is a recently developed intracoronary imaging modality that uses light instead of sound to obtain cross-sectional images of the artery (7). OCT offers a resolution 10 times higher than IVUS, offering a much clearer delimitation of the intima-luminal limit and therefore allowing automatic measurement of the lumen area with excellent reproducibility (8–10). However, very little data are available regarding the potential of OCT to depict the hemodynamic relevance of a stenosis (11).

The primary objective of the present study was to assess the diagnostic efficiency of OCT in identifying hemodynamically severe coronary stenoses as determined by FFR. A secondary objective was to compare diagnostic efficiency of OCT and IVUS for this purpose.

Methods

Study population. Patients scheduled for coronary angiography in whom 1 or more coronary stenoses with intermediate angiographic severity (40% to 70% diameter stenosis by quantitative coronary angiography [QCA]) were documented were prospectively included in the study. Only intermediate stenoses were included in order to respect the conditions in which FFR was validated as a surrogate method for the detection of ischemia (2). Stenoses located in culprit vessels of acute coronary syndromes, serial stenoses, or diffuse coronary narrowings were excluded. Vessels providing circulation to previously infarct regions were also excluded. Other exclusion criteria were left main stenosis, graft stenosis, contraindications to adenosine administration, hemodynamic instability, renal insufficiency, and anatomical characteristics such as vessel tortuosity and severe calcification that do not allow the advancement of OCT and IVUS catheters. The study was approved by the Ethics Committee of our institution and the patients gave informed consent.

Angiographic analysis. Angiographic views (without superimposition or shortening) were obtained after intracoronary nitrates (0.2 mg). Analysis (minimum lumen diameter [MLD], percent diameter stenosis, and reference lumen diameter) was performed by experience personnel blinded to FFR and imaging analyses using validated QCA software (CASS II, Pie Medical, Maastricht, the Netherlands).

FFR measurements. FFR was measured with a coronary pressure guidewire (St. Jude Medical, St. Paul, Minnesota, or Volcano Corporation, San Diego, California) at maximal hyperemia induced by intravenous adenosine, administered at 140 μg/kg/min through a central vein. Calculation of FFR, on the basis of the ratio between intracoronary and aortic pressure during hyperemia, was performed automatically by the corresponding interface, and verified by the operator to rule out any source of error. Stenoses were labeled as hemodynamically severe if FFR ≤0.80 (4).

Abbreviations and Acronyms

%AS = percent area stenosis

AUC = area under the curve

CI = confidence interval

FFR = fractional flow reserve

IVUS = intravascular ultrasound

MLA = minimum lumen area

MLD = minimum lumen diameter

NPV = negative predictive value

OCT = optical coherence tomography

PPV = positive predictive value

QCA = quantitative coronary angiography

ROC = receiver-operating characteristic

OCT acquisition. OCT imaging of the target stenosis was obtained using the commercially available FD-OCT C7XR system and the DragonFly catheter (SJM, Lightlab Imaging Inc., Westford, Massachusetts). The automated pullback was performed at 20 mm/s while the blood was removed by a short injection of iso-osmolar contrast (Iopamidol 370, Iopamiro, Bracco, Italy) at 37°C through the guiding catheter. The images were digitally stored for offline analysis.

OCT analysis. OCT measurements were performed using the proprietary software for offline analysis (LightLab Imaging). The sites selected for analysis were: 1) the cross section with the smallest lumen area; and 2) the reference cross section (defined as the frame with the largest lumen within 10 mm proximal or distal to the MLA and before any side branch). At the site with the smallest lumen area we measured the MLA, the MLD, and the maximum lumen diameter. At the reference cross section we measured the reference lumen area. Percent area stenosis (%AS) was calculated as: (reference lumen − MLA)/reference lumen · 100. The eccentricity lumen index at the MLA site was calculated as: (maximum lumen diameter − MLD)/maximum lumen diameter. Stenosis length was defined as the region around the MLA where the lumen area was <50% of the reference lumen area.

IVUS acquisition. Per protocol, IVUS imaging of the stenosis imaged with OCT was also attempted unless any concurrent circumstances recommended the limiting of intracoronary imaging to OCT. IVUS images of the target stenosis were obtained with ILab system (Boston Scientific, Natick, Massachusetts) and the Atlantis Pro Imaging catheter (40 MHz, Boston Scientific) during automated motorized pullback at 0.5 mm/s. Images were digitally stored for offline analysis.

IVUS analysis. IVUS analysis was performed using validated software (QIVUS, Medis, Leiden, the Netherlands). In a similar way as previously described for OCT, we selected the MLA site and the reference site (defined as the frame with the largest lumen within 10 mm proximal or distal to the MLA and before any side branch). To make sure that the same stenosis was measured with both techniques, matching of the OCT and IVUS pullbacks was performed using landmarks such as side branches and other anatomical features (Fig. 1). After selecting the MLA site and the reference, IVUS analysis was performed by an experienced analyst blinded to the OCT results. At the

JACC Vol. 59, No. 12, 2012
March 20, 2012:1080–9

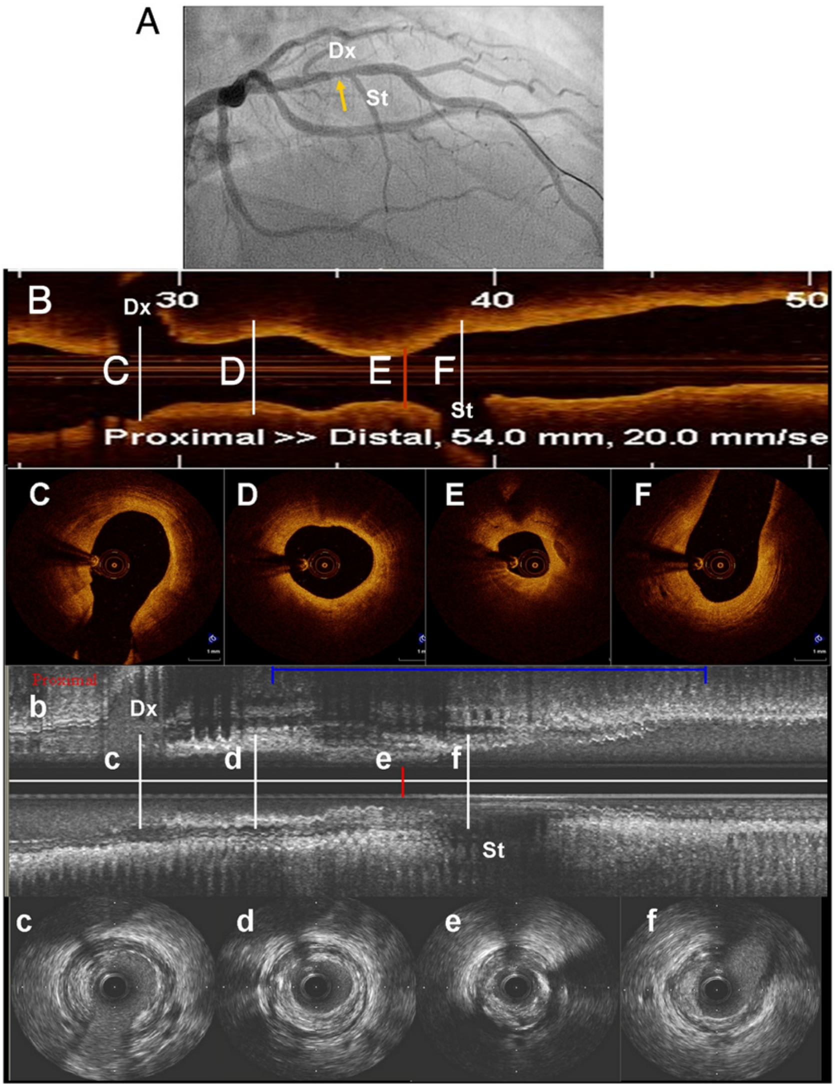

Figure 1 **Matching of Optical Coherence Tomography and Intravascular Ultrasound Pullbacks**

(A) Angiographic view showing an intermediate stenosis in the mid left anterior descending coronary artery **(yellow arrow)**. Distal to the lesion there is a septal branch (St) and proximal there is a diagonal branch (Dx). **(B, b)** Longitudinal optical coherence tomography and intravascular ultrasound reconstructions showing the 2 side branches (St and Dx) and the stenosis. **(C, c; D, d; E, e; F, f)** Corresponding cross-sectional optical coherence tomography and intravascular ultrasound images. **(C, c)** Diagonal branch. **(D, d)** Reference cross section. **(E, e)** Minimum lumen area. **(F, f)** Septal branch.

MLA site the following measurements were performed: 1) MLA; 2) MLD; 3) vessel area; 4) maximum plaque thickness; and 5) minimum plaque thickness. At the reference site we measured lumen and vessel area. Plaque area, plaque burden, stenosis length, %AS, and remodeling index were calculated at previously published. We calculated a plaque eccentricity index at the MLA as maximum plaque thickness divided by minimum plaque thickness.

Statistical analysis. Statistical analysis was performed with SPSS version 13 (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percents. Data were analyzed on a per-patient basis for the clinical characteristics and on a per-stenosis basis for the rest of calculations. Continuous variables were compared with *t* test. Linear regression analysis was used to determine the correlation coefficients between FFR and OCT and IVUS measurements. Bayesian analysis of OCT and IVUS measurements included estimation of area under the receiver-operating characteristic (ROC) curve, identification of optimal cutoff value to predict an FFR ≤0.80, and associated sensitivity and specificity. Optimal cutoff value identification was based on statistical methods (highest sum of sensitivity and specificity) and clinical criteria. A modification of the classification by Swets was used to classify diagnostic efficiency of OCT and IVUS according to the values of the area under the curve (AUC) as low (<0.70), moderate (0.70 to 0.90), and

Table 1 **Clinical Data and Stenosis Characteristics by Angiography, OCT, and IVUS**

Clinical characteristics (n = 56)	
Age, yrs	62 ± 11
Male, %	47 (83.9)
HTN, %	40 (71.4)
DM, %	19 (33.9)
Dyslipidemia, %	41 (73.2)
Smoking, %	25 (44.6)
Family history of coronary disease, %	3 (5.4)
Clinical presentation, %	
Stable angina	22 (39.3)
Unstable angina	7 (12.5)
Asymptomatic control	14 (25.0)
Second vessel	13 (23.2)
Angiographic stenosis characteristics (n = 61)	
Vessel, %	
LAD	30 (49.2)
LCX	15 (24.6)
RCA	16 (26.2)
Diameter stenosis, %	50.9 ± 7.7
MLD, %	1.28 ± 0.3
Reference diameter, mm	2.60 ± 0.6
Lesion length, mm	7.1 ± 3.0
OCT stenosis characteristics (n = 61)	
MLA, mm^2	1.96 ± 0.84
MLD, mm	1.36 ± 0.31
Lesion length, mm	3.58 ± 2.37
Reference lumen area, mm^2	6.47 ± 2.72
Eccentricity lumen index	0.21 ± 0.13
Percent area stenosis	69 ± 10
IVUS stenosis characteristics (n = 47)	
MLA, mm^2	2.61 ± 0.89
MLD, mm	1.63 ± 0.25
Vessel area, mm^2	12.04 ± 4.57
Plaque area, mm^2	8.69 ± 4.67
Plaque burden, %	76.52 ± 7.91
Lesion length, mm	3.18 ± 2.02
Reference lumen area, mm^2	7.08 ± 3.45
Reference vessel area, mm^2	12.74 ± 5.74
Remodeling index	1.02 ± 0.32
Percent area stenosis	59 ± 16
Plaque eccentricity index	4.45 ± 3.35

Values are mean ± SD or n (%).
DM = diabetes mellitus; HTN = hypertension; IVUS = intravascular ultrasound; 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.

high (>0.90) (12). Comparison of ROC curves was performed using the DeLong method. Differences between lumen measurements obtained with IVUS and OCT in the same stenosis were calculated and expressed in Bland-Altman plots.

Results

Clinical and angiographic characteristics. A total of 56 patients presenting 61 intermediate stenoses were included in the study. There were no complications associated to the use of intracoronary diagnostic techniques. In 12 patients the operator decided to limit intracoronary imaging to OCT interrogation on the basis of anatomical characteristics, length of the procedure, or patient discomfort. Thus, 61 stenoses were studied with FFR and OCT, and 47 stenoses (77%) were also studied with IVUS. Clinical data and stenosis characteristics by angiography, OCT, and IVUS are shown in Table 1.

FFR measurements. FFR measurements were performed in all study patients without complications. Mean FFR was 0.80 ± 0.11 (range 0.43 to 0.97). A balanced number of hemodynamically significant (n = 28, 46%) and nonsignificant (n = 33, 54%) stenoses, as judged by the FFR cutoff value, was documented in the study population

Relation between OCT measurements and FFR. Table 2 shows the differences in OCT measurements between stenosis with FFR ≤0.80 and those with FFR >0.80. Regression analysis showed a significant but poor correlation between lumen measurements by OCT and the FFR value (Figs. 2A to 2C). The sensitivity and specificity and ROC curves for MLA and MLD as measured by OCT are shown in Figure 3. In the overall group, the diagnostic efficiency of OCT-measured MLA and MLD to identify significant stenoses was moderate. The AUC was 0.74 (95% confidence interval [CI]: 0.61 to 0.84) for MLA and 0.73 (95% CI: 0.60 to 0.83) for MLD. Best cutoff values of OCT-derived measurements to identify stenoses with FFR ≤0.80 were 1.95 mm^2 for MLA (82% sensitivity, 63% specificity, positive predictive value [PPV] 66%, negative predictive value [NPV] 80%, accuracy 72%) and 1.34 mm for MLD (82% sensitivity, 67% specificity, PPV 68%, NPV 81%, accuracy 73%). On the contrary, the diagnostic efficiency of OCT-derived %AS was low (AUC: 0.61; 95% CI: 0.47 to 0.76), with its best cutoff value being 70%AS (61% sensitivity, 55% specificity, PPV 53%, NPV 62%, accuracy 57%).

Relation between IVUS measurements and FFR. Differences in IVUS measurements between stenosis with FFR ≤0.80 and FFR >0.80 are shown in Table 3. Regression analysis showed no significant correlation between FFR value and IVUS measurements (MLA, MLD, %AS, stenosis length, remodeling index, plaque burden, and plaque eccentricity) (Figs. 2D to 2F). The sensitivity specificity and ROC curves for MLA and MLD in relation with FFR value are shown in Figure 4. The diagnostic efficiency of

Table 2 **Differences in OCT Measurements Between Stenoses With FFR >0.80 or ≤0.80**

	FFR ≤0.80	FFR >0.80	p Value
MLA	1.64 ± 0.80	2.2 ± 0.7	0.005
MLD	1.23 ± 0.30	1.46 ± 0.30	0.004
Lesion length	4.1 ± 3.0	3.1 ± 1.5	0.10
Reference lumen	5.7 ± 2.2	7.1 ± 2.9	0.03
Eccentricity lumen index	0.21 ± 0.12	0.20 ± 0.10	0.80
Percent area stenosis	70 ± 10	67 ± 10	0.10

Values are mean ± SD.
FFR = fractional flow reserve; MLA = minimal lumen area; MLD = minimal lumen diameter.

JACC Vol. 59, No. 12, 2012
March 20, 2012:1080–9

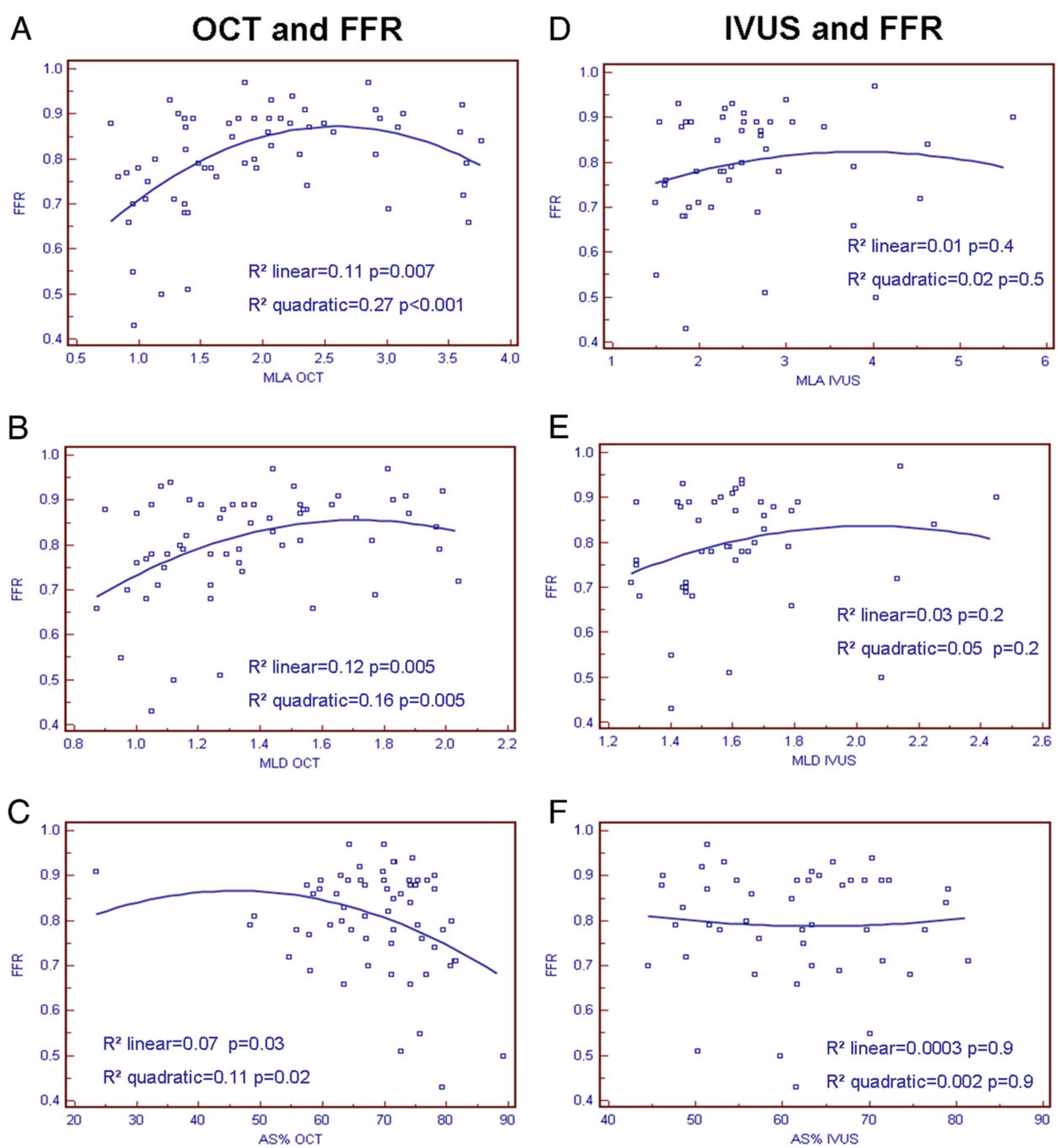

Figure 2 **Relation Between FFR and OCT and IVUS Measurements**

(A, B, C) Fractional flow reserve (FFR) and optical coherence tomography (OCT) measurements. **(D, E, F)** FFR and intravascular ultrasound (IVUS) measurements. AS% = percent area stenosis; MLA = minimum lumen area; MLD = minimum lumen diameter.

IVUS as a method to assess hemodynamic stenotic relevance was low. The AUC for IVUS-derived measurements in identifying stenoses with FFR ≤0.80 was 0.63 for MLA (95% CI: 0.47 to 0.77), 0.67 for MLD (95% CI: 0.51 to 0.79), and 0.48 for %AS (95% CI: 0.31 to 0.65). Optimal cutoff values for IVUS parameters were 2.36 mm^2 for MLA (67% sensitivity, 65% specificity, PPV 67%, NPV 65%, accuracy 66%), 1.59 mm for MLD (67% sensitivity, 65% specificity, PPV 67%, NPV 65%, accuracy 66%), and 61% for %AS (54% sensitivity, 43% specificity, PPV 50%, NPV 47%, accuracy 49%).

Comparison of MLA and MLD measurements with OCT and IVUS. Figure 5 shows the Bland-Altman and regression analysis for MLA and MLD measurements with IVUS and OCT. Mean relative and absolute differences in MLA measured with IVUS and OCT were 32.3 ± 26%

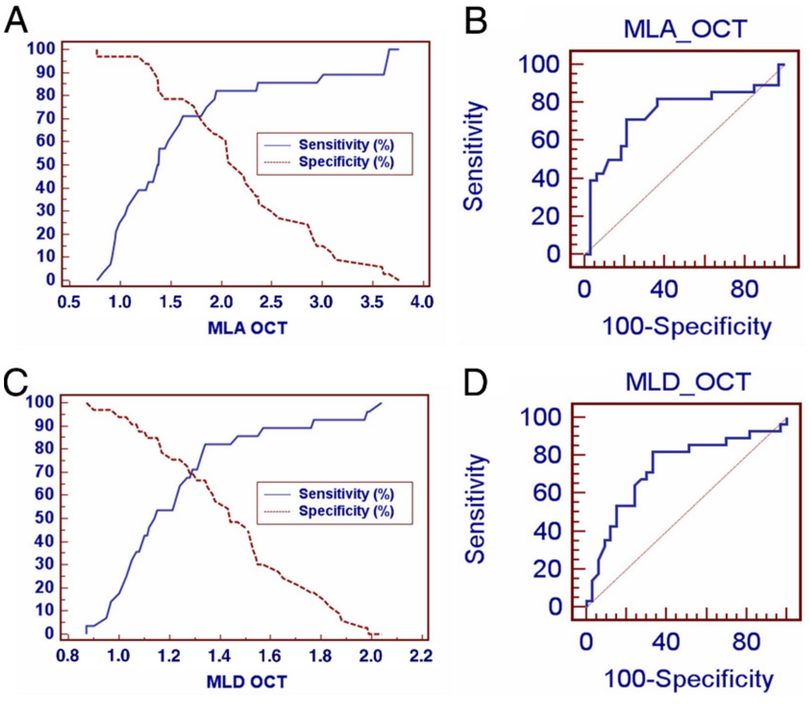

Figure 3 **OCT-Derived Lumen Measurements and FFR**

(A) Sensitivity and specificity curve for OCT-derived MLA to predict FFR ≤0.80. **(B)** Receiver-operating characteristic curve for OCT-derived MLA to predict FFR ≤0.80. **(C)** Sensitivity and specificity curve for OCT-derived MLD to predict FFR ≤0.80. **(D)** Receiver-operating characteristic curve for OCT-derived MLD to predict FFR ≤0.80. Abbreviations as in Figure 2.

and 0.65 ± 0.62 mm^2 (limits of agreement of −0.57 to 1.87 mm^2), respectively. For the MLD, the mean relative and absolute differences between IVUS and OCT were 19.5 ± 16% and 0.27 ± 0.23 mm^2 (limits of agreement of −0.20 to 0.74 mm^2), respectively.

Diagnostic efficiency of OCT and IVUS. ROC curves showing the sensitivity and specificity of the MLA measured by OCT and IVUS to identify functionally significant stenosis were compared (Fig. 6). OCT showed a better diagnostic efficiency (AUC: 0.70; 95% CI: 0.55 to 0.83) than IVUS (AUC: 0.63; 95% CI: 0.47 to 0.77) but the differences between the curves were not statistically significant ($p = 0.19$).

Diagnostic efficiency of OCT and IVUS in small vessels. To evaluate the influence of vessel size on the ability of IVUS and OCT to identify hemodynamically significant stenoses, we analyzed the subgroup of stenoses located in vessels with a reference diameter <3 mm as measured by QCA. OCT was performed in 49 stenoses with reference diameter <3 mm and IVUS was performed in 38 stenoses with reference diameter <3 mm. The ROC curves for both techniques are shown in Figures 7A and 7B. The AUC of the MLA measured by OCT to predict and FFR ≤0.80 in vessels <3 mm was 0.81 (95% CI: 0.67 to 0.90), associated with a best cutoff point of 1.62 mm^2 (80% sensitivity, 83% specificity, PPV 83%, NPV 80%, accuracy 82%). The AUC of the IVUS-derived MLA to predict and FFR ≤0.80 in vessels <3 mm was 0.63 (95% CI: 0.46 to 0.78), with a best cutoff point of 2.36 mm^2 (72% sensitivity, 62% specificity, PPV 73%, NPV 62%, accuracy 68%). Comparison of the ROC curves of IVUS and OCT in vessels <3 mm with both measurements revealed a better diagnostic efficiency of OCT (AUC: 0.77; 95% CI: 0.60 to 0.89) than IVUS (AUC: 0.63; 95% CI: 0.46 to 0.78) to identify functionally significant stenoses ($p = 0.04$) (Fig. 7C).

Table 3 **Differences in IVUS Measurements Between Stenoses With FFR >0.80 or ≤0.80**

	FFR ≤0.80	FFR >0.80	p Value
MLA, mm^2	2.42 ± 0.8	2.73 ± 0.9	0.20
MLD, mm	1.55 ± 0.2	1.69 ± 0.3	0.08
Vessel area, mm^2	11.8 ± 4.0	12.3 ± 5.2	0.70
Plaque area, mm^2	9.0 ± 4.0	8.4 ± 5.3	0.60
Plaque burden, %	78.5 ± 6.6	75.4 ± 8.2	0.10
Lesion length, mm	3.6 ± 2.5	2.6 ± 1.1	0.08
Reference lumen area, mm^2	6.4 ± 2.1	7.8 ± 4.3	0.10
Reference vessel area, mm^2	12.3 ± 5.1	13.3 ± 6.3	0.50
Remodeling index	1.07 ± 0.4	0.96 ± 0.2	0.20
Percent area stenosis	61.1 ± 9.5	61.4 ± 9.9	0.90
Plaque eccentricity index	4.7 ± 3.4	4.1 ± 3.3	0.50

Values are mean ± SD.
IVUS = intravascular ultrasound; other abbreviations as in Table 2.

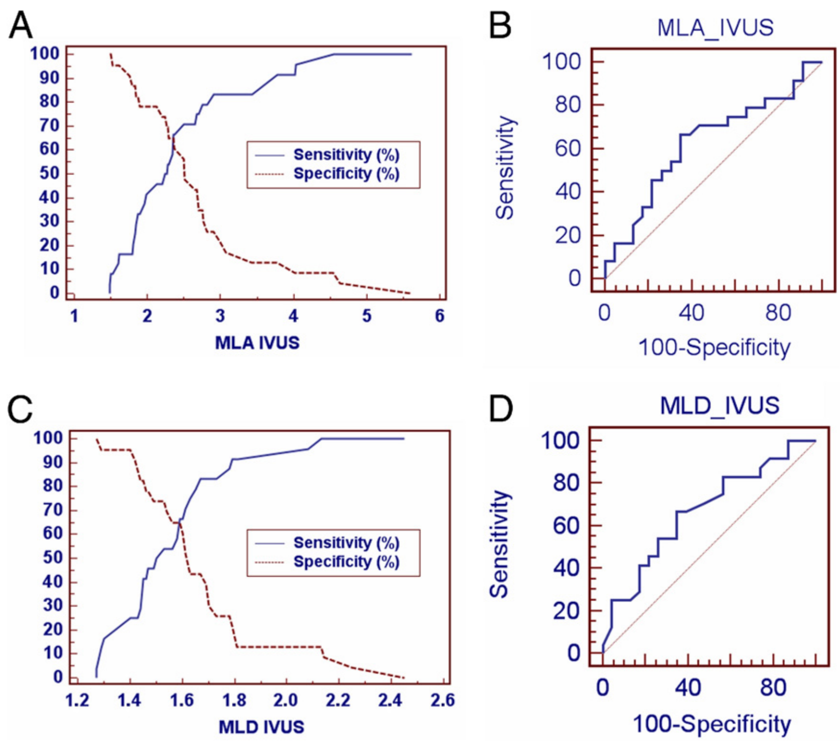

Figure 4 **IVUS-Derived Lumen Measurements and FFR**

(A) Sensitivity and specificity curve for IVUS-derived MLA to predict FFR ≤0.80. **(B)** Receiver-operating characteristic curve for IVUS-derived MLA to predict FFR ≤0.80. **(C)** Sensitivity and specificity curve for IVUS-derived MLD to predict FFR ≤0.80. **(D)** Receiver-operating characteristic curve for IVUS-derived MLD to predict FFR ≤0.80. Abbreviations as in Figure 2.

Discussion

The main findings of the present study are the following: 1) OCT has a moderate diagnostic efficiency in identifying coronary stenoses with an associated FFR <0.80; 2) OCT is slightly more efficient than IVUS in the assessment of functional stenosis severity, particularly in vessels <3 mm; and 3) the optimal geometrical cutoff values for using OCT and IVUS in functional stenosis assessment are much lower than the customarily applied 4 mm^2 IVUS-derived cutoff value.

Over the last 15 years there has been a continued discussion on the differences between anatomical and functional assessment of coronary stenosis. This debate had its roots in the overwhelming previous use of coronary angiography as the gold standard in assessing coronary artery disease, as well as in the accumulated evidence on the inherent limitations of angiography for this purpose (1). More recently, this criticism has extended to other coronary imaging techniques like IVUS. Although IVUS is certainly superior to coronary angiography in establishing intraluminal coronary dimensions, the obtained luminal measurements do not take into consideration major determinants of stenosis severity, like the size, viability, and microcirculatory status of the subtended myocardium, or the presence of collateral circulation, to name a few (2). These limitations are circumvented by FFR, an accepted surrogate of noninvasive ischemia detection tests. Notwithstanding that, like other noninvasive techniques, FFR is not free of limitations in assessing ischemia, given its high spatial resolution and its ability to perform, like OCT and IVUS, a per-stenosis assessment justified its use as a reference in this and other studies (5,6,13,14).

The present study evaluated the diagnostic efficiency of OCT in identifying hemodynamically severe coronary stenoses as determined by FFR. Currently available Fourier-domain OCT systems provide high-quality images obtained over long coronary segments during a short contrast injection (15). The potential of OCT to investigate different aspects of atherosclerosis, to optimize the result of stent deployment, and to evaluate the long-term effects of stent implantation anticipate a widespread use of the technique in an immediate future (9,16). Therefore, it is important to gain information on its potential as a tool to outline functional stenosis severity.

Among the different OCT parameters evaluated, the MLA was the best to predict functional significance. An OCT-derived MLA cutoff point of 1.95 mm^2 showed a moderate diagnostic efficiency with a sensibility of 82% and an NPV of 80%. OCT had therefore a moderate value to

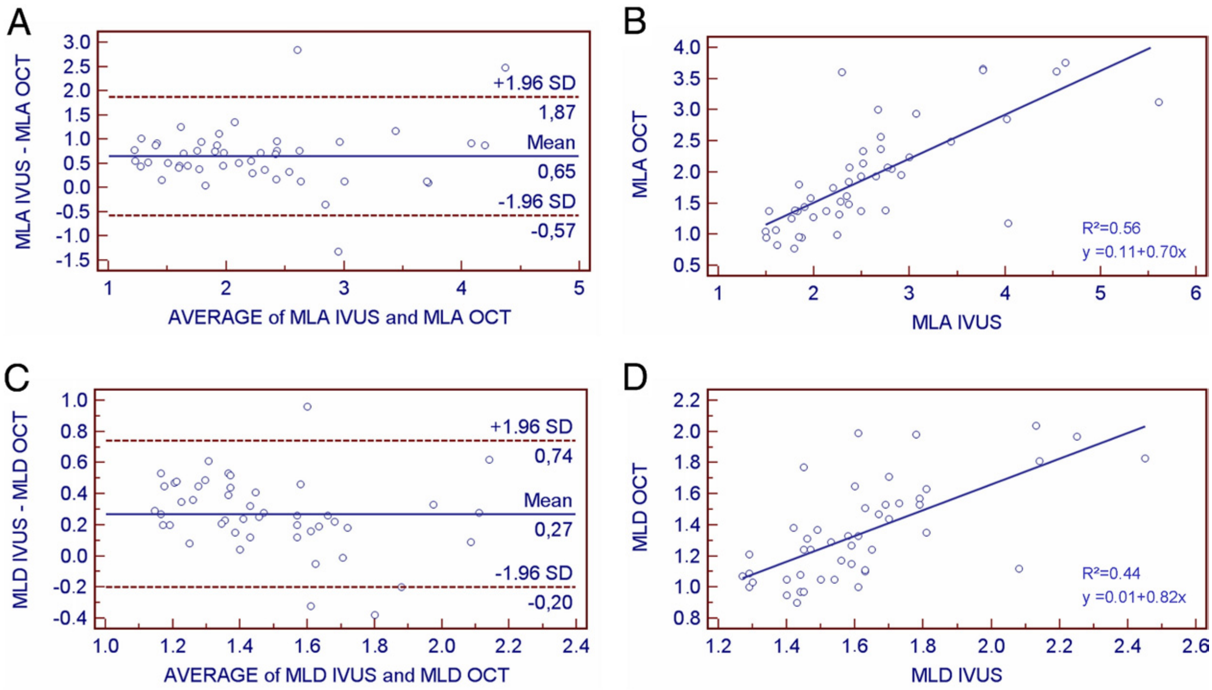

Figure 5 **Differences in Lumen Measurements Between OCT and IVUS**

Bland-Altman plots showing the differences in MLA **(A)** and MLD **(C)** measurements between OCT and IVUS. Correlation between MLA **(B)** and MLD **(D)** measurements with OCT and IVUS. Abbreviations as in Figure 2.

exclude functional impact when the MLA was >1.95 mm^2 (5 of 26 patients with MLA >1.95 mm^2 had an FFR ≤0.80; interestingly all of them were stenoses located on the left anterior descending coronary artery, emphasizing the concept of the relation between the optimal MLA and the myocardial mass served by the vessel). However the specificity and PPV were lower (63% and 66%, respectively) indicating the need of a more specific test to evaluate functional significance when the OCT-derived MLA is <1.95 mm^2, in order to avoid unnecessary interventions. OCT therefore should be used with caution as a tool to investigate functional stenosis severity, and restricted to selected cases not amenable for FFR interrogation. The more efficient way of using OCT for functional stenosis assessment would be ruling out stenosis severity on the grounds of an MLA >1.95 mm^2, but at the expense of almost 1 false negative in every 5 stenoses interrogated in this way.

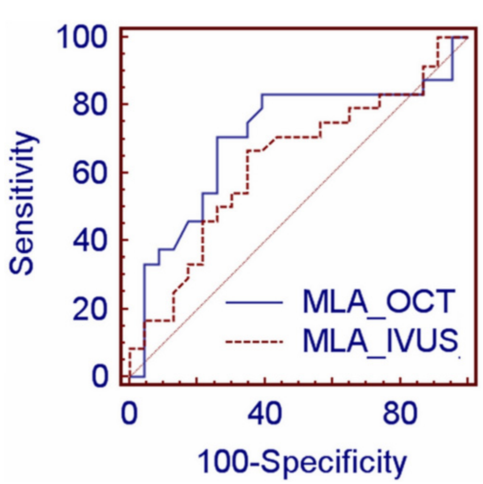

Figure 6 **Comparison of OCT and IVUS**

Comparison of receiver-operating characteristic curve for OCT- and IVUS-derived MLA to predict FFR ≤0.80. Abbreviations as in Figure 2.

This emphasizes again the fact that a single cross-sectional area in a vessel is only 1 of the multiple factors influencing the flow and it does not reflect the stenosis location, the amount and viability of the myocardium supplied by the vessel, or the presence of collateral circulation.

The optimal OCT-MLA cutoff point in our study is much lower than the customarily used 4 mm^2 IVUS optimal cutoff value. This IVUS cutoff value is based in several studies that have used FFR to assess the diagnostic efficiency of IVUS in identifying hemodynamically severe coronary stenoses (5,6). The safety of using this cutoff for clinical decision making was tested by Abizaid et al. (17). In their study, on the basis of a population of 300 patients, deferring percutaneous coronary intervention in intermediate stenoses

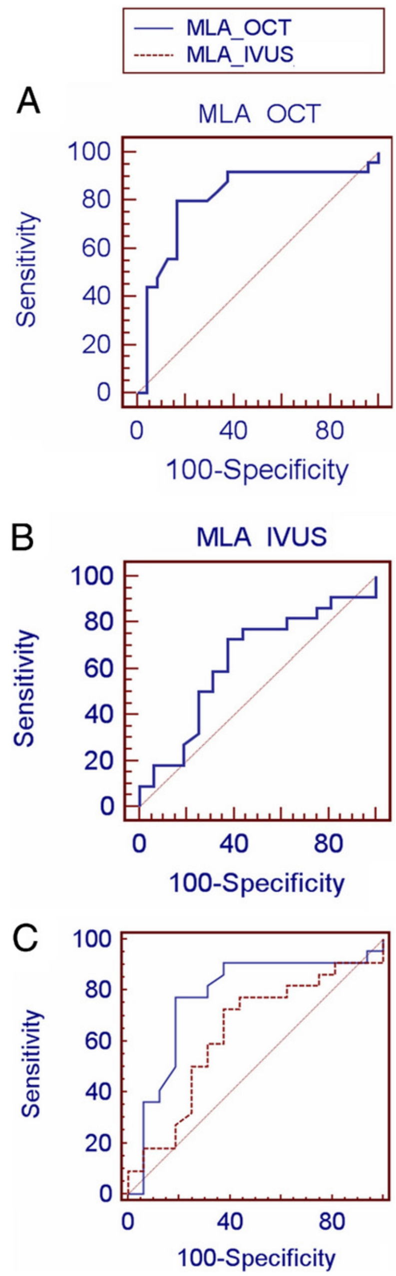

Figure 7 **Vessels <3 mm**

Receiver operating characteristic curves for **(A)** OCT- and **(B)** IVUS-derived MLA to predict FFR ≤0.80 in vessels with a reference diameter <3 mm. **(C)** Comparison of ROC curves for OCT- and IVUS-derived MLA to predict FFR ≤0.80 in vessels with a reference diameter <3 mm. Abbreviations as in Figure 2.

on the basis of an IVUS MLA >4 mm^2 criterion was safe, with a low event rate (2% death or myocardial infarction) at an average follow-up of 13 months (17). On the basis of this evidence the MLA <4.0 mm^2 cutoff has been the IVUS parameter more frequently applied in the clinical setting to determine the presence of severe stenosis. Despite this, the frequent discrepancies in the IVUS MLA <4 mm^2 and FFR <0.80 criteria of stenotic relevance noted by operators in their everyday practice led to a critical review of the customarily used cutoff of MLA in IVUS (18). Recently, Kang et al. (14) revisited the relationship between IVUS and FFR measurements in a population of 236 intermediate coronary stenoses, obtaining quite similar results to those presented in our study. Thus, in their study the best cutoff value of MLA to predict FFR <0.80 was <2.4 mm^2 (sensitivity 90%, specificity 60%; AUC: 0.8; 95% CI: 0.74 to 0.84), which is very close to the 2.36 mm^2 IVUS-derived MLA cutoff point identified in our study (14). The better diagnostic efficiency demonstrated by IVUS in their study may be related with some baseline differences in the vessels evaluated (in their sample only 11% of the vessels assessed had a reference diameter <2.5 mm, while in the present study almost half [49.2%] of the target vessels had a reference diameter <2.5 mm). A marked reduction of IVUS diagnostic efficiency when applied to vessels with a reference diameter <2.5 mm was reported by the same authors (14).

Regarding the comparison between the 2 imaging techniques, in the overall group OCT showed a slightly higher diagnostic efficiency than IVUS but the difference between the ROC curves was not statistically significant. However, OCT was significantly better when vessels <3 mm in diameter were selected. There is concern about the applicability of previously reported IVUS cutoff points in small vessels (19). A recent study assessed the value of IVUS to predict hemodynamic significance of stenosis in small vessels. The authors reported an IVUS-derived MLA <2.0 mm^2 as the best cutoff value to predict FFR <0.75 (sensitivity 82%, specificity 81%) in vessels with a reference diameter <3 mm (20). In our study the best cutoff point for small vessels was 1.62 mm^2 for OCT and 2.36 mm^2 for IVUS.

The slightly higher diagnostic efficiency of OCT over IVUS may be related to the better delimitation of the lumen-vessel boundary obtained with this technique, which facilitates automatic tracing and measurement of the lumen area with an excellent reproducibility (8,15,21). It is important to remember that the efficiency of IVUS measurements in the near field is hampered by a limited spatial resolution (>100 μm), which can be particularly relevant in situations where the stenotic lumen area is close to that of the IVUS probe. In addition to this, image distortion created by noncoaxial orientation of the catheter or lack of echoes ("dropout") and the blood speckle can limit a clear definition of the luminal border. Several studies have indicated the differences in lumen measurements with IVUS and OCT that we also found in the present study (22,23). In vessels <3 mm with small lumen where the catheter is almost occlusive, the difference in lumen delimitation with the 2 techniques may be even more important, explaining the significantly better diagnostic efficiency of OCT in this subgroup.

Management of angiographically intermediate stenosis remains a challenge for the interventional cardiologist. There is evidence about the safety of using FFR to define stenosis severity in stable patients but pressure wire measurements have limitations in other clinical contexts such as serial stenosis, where identifying the more severe one can be important to establish the revascularization strategy. Apart from lumen dimensions, OCT can provide morphological details (e.g., plaque rupture, presence of thrombus, calcification) that can be useful not only to decide whether treatment is needed but also to guide the procedure (11). The use of physiological and anatomical information may be therefore complementary to guide decision making in certain stenoses.

Study limitations. The present study included a limited sample size. Further investigation is needed to confirm the results. IVUS was not performed in all cases but there were no significant differences in target vessel, reference vessel diameter, MLA by OCT, FFR value, and percent of functionally significant stenosis between the groups with and without IVUS.

Although spatial matching of OCT and IVUS pullbacks was optimized by using landmarks such as side branches and other anatomical features, some error introduced by an inadequate coregistration between the 2 techniques cannot be excluded. The results of the present study would apply only to stable coronary stenoses as the use of FFR in unstable lesions, such as those found in the culprit vessel of acute coronary syndromes, remains controversial despite some published data in these settings. The impact of MLA on myocardial perfusion is related to the mass of viable perfused myocardium distal to the stenosis. However, this parameter was not quantified in our study.

Conclusions

OCT has a moderate diagnostic efficiency in identifying coronary stenoses with an associated FFR <0.80. OCT is slightly more efficient than IVUS in the assessment of functional stenosis severity, particularly in vessels <3 mm. The optimal geometrical cutoff values for using OCT and IVUS in functional stenosis assessment are much lower than the customarily applied 4 mm^2 IVUS cutoff value.

Reprint requests and correspondence: Dr. Nieves Gonzalo, Department of Interventional Cardiology, Hospital Clínico San Carlos, C/ Martín Lagos s/n, 28040 Madrid, Spain.E-mail: nieves_gonzalo@yahoo.es.

REFERENCES

1. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010;55:2816–21.
2. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–8.
3. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;49:2105–11.
4. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
5. Takagi A, Tsurumi Y, Ishii Y, Suzuki K, Kawana M, Kasanuki H. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. Circulation 1999;100:250–5.
6. Briguori C, Anzuini A, Airoldi F, et al. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. Am J Cardiol 2001;87:136–41.
7. Gonzalo N, Serruys PW, Regar E. Optical coherence tomography: clinical applications and the evaluation of DES. Minerva Cardioangiol 2008;56:511–25.
8. Gonzalo N, Garcia-Garcia HM, Serruys PW, et al. Reproducibility of quantitative optical coherence tomography for stent analysis. EuroIntervention 2009;5:224–32.
9. Gonzalo N, Garcia-Garcia HM, Regar E, et al. In vivo assessment of high-risk coronary plaques at bifurcations with combined intravascular ultrasound and optical coherence tomography. J Am Coll Cardiol Img 2009;2:473–82.
10. Guagliumi G, Musumeci G, Sirbu V, et al. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. J Am Coll Cardiol Intv 2010;3:531–9.
11. Stefano GT, Bezerra HG, Attizzani G, et al. Utilization of frequency domain optical coherence tomography and fractional flow reserve to assess intermediate coronary artery stenoses: conciliating anatomic and physiologic information. Int J Cardiovasc Imaging 2011;27:299–308.
12. Swets JA. Measuring the accuracy of diagnostic systems. Science 1988;240:1285–93.
13. Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. J Am Coll Cardiol Intv 2010;3:307–14.
14. Kang SJ, Lee JY, Ahn JM, et al. Validation of intravascular ultrasound-derived parameters with fractional flow reserve for assessment of coronary stenosis severity. Circ Cardiovasc Interv 2011;4:65–71.
15. Gonzalo N, Tearney GJ, Serruys PW, et al. Second-generation optical coherence tomography in clinical practice. High-speed data acquisition is highly reproducible in patients undergoing percutaneous coronary intervention. Rev Esp Cardiol 2010;63:893–903.
16. Gonzalo N, Serruys PW, Okamura T, et al. Optical coherence tomography assessment of the acute effects of stent implantation on the vessel wall: a systematic quantitative approach. Heart 2009;95:1913–9.
17. Abizaid AS, Mintz GS, Mehran R, et al. Long-term follow-up after percutaneous transluminal coronary angioplasty was not performed based on intravascular ultrasound findings: importance of lumen dimensions. Circulation 1999;100:256–61.
18. Magni V, Chieffo A, Colombo A. Evaluation of intermediate coronary stenosis with intravascular ultrasound and fractional flow reserve: Its use and abuse. Catheter Cardiovasc Interv 2009;73:441–8.
19. Costa MA, Sabate M, Staico R, et al. Anatomical and physiologic assessments in patients with small coronary artery disease: final results of the Physiologic and Anatomical Evaluation Prior to and After Stent Implantation in Small Coronary Vessels (PHANTOM) trial. Am Heart J 2007;153:296e1–7.
20. Lee CH, Tai BC, Soon CY, et al. New set of intravascular ultrasound-derived anatomic criteria for defining functionally significant stenoses in small coronary arteries (results from Intravascular Ultrasound Diagnostic Evaluation of Atherosclerosis in Singapore [IDEAS] study). Am J Cardiol 2010;105:1378–84.
21. Okamura T, Gonzalo N, Gutierrez-Chico JL, et al. Reproducibility of coronary Fourier domain optical coherence tomography: quantitative analysis of in vivo stented coronary arteries using three different software packages. EuroIntervention 2010;6:371–9.
22. Gonzalo N, Serruys PW, Garcia-Garcia HM, et al. Quantitative ex vivo and in vivo comparison of lumen dimensions measured by optical coherence tomography and intravascular ultrasound in human coronary arteries. Rev Esp Cardiol 2009;62:615–24.
23. Yamaguchi T, Terashima M, Akasaka T, et al. Safety and feasibility of an intravascular optical coherence tomography image wire system in the clinical setting. Am J Cardiol 2008;101:562–7.

Key Words: fractional flow reserve ▪ functional assessment ▪ intermediate coronary stenosis ▪ intravascular ultrasound ▪ optical coherence tomography.