Clinical Validation of Intravascular Ultrasound Imaging for Assessment of Coronary Stenosis Severity
Comparison With Stress Myocardial Perfusion Imaging
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OBJECTIVES
To validate intravascular ultrasound (IVUS) measurements for differentiating functionally significant from nonsignificant coronary stenosis.

BACKGROUND
To date, there are no validated criteria for the definition of a flow-limiting coronary artery stenosis by IVUS.

METHODS
Preinterventional IVUS imaging (30-MHz imaging catheter) of 70 de novo coronary lesions was performed. The lesion lumen area and three IVUS-derived stenosis indexes comparing lesion lumen area with the lesion external elastic lamina (EEL) area, the mean reference lumen area and the mean reference EEL area were compared with the results of stress myocardial perfusion imaging.

RESULTS
The lesion lumen area and three IVUS-derived stenosis indexes showed sensitivities and specificities ranging between 80% and 90% using stress myocardial perfusion imaging as the gold standard. The lesion lumen area ≤4 mm² is a simple and highly accurate criterion for significant coronary narrowing.

CONCLUSIONS
Quantitative IVUS indices can be reliably used for identifying significant epicardial coronary artery stenoses. (J Am Coll Cardiol 1999;33:1870–8) © 1999 by the American College of Cardiology

Determination of lesion severity in the coronary interventional laboratory is crucial. Underestimation of lesion severity will leave critical arterial stenoses untreated, and if luminal narrowings are overestimated, unnecessary coronary interventions will be performed, and coronary restenosis lesions might be unnecessarily induced owing to vessel injury (1,2). Coronary angiography has been used as the “gold standard” for the diagnosis of coronary narrowings and guiding coronary interventions. Using an animal coronary constriction model without atherosclerotic plaque, Gould (3) demonstrated that coronary flow reserve deteriorates when the lumen diameter stenosis exceeds 50%. This theory might also be applicable to human coronary lesions with focal plaque and nearly normal reference segments.

However, human coronary arteries are commonly diffusely diseased, and coronary angiography, which measures lumen-to-lumen diameters, underestimates the lesion severity within a vessel with diffuse atherosclerotic lesions (4). Coronary angiography has other limitations for evaluating lesion severity, these being lesion location, lesion morphology, and superimposition of arterial branches (5–13). Currently, one of the more frequent indications of intravascular ultrasound (IVUS) is for the assessment of angiographic lesions of uncertain severity. However, there are no validated criteria for the definition of a flow-limiting coronary artery stenosis by IVUS.

The IVUS imaging is a technique that provides two-dimensional imaging of the artery including vessel wall (intima and media) as well as luminal dimensions. This technique can provide not only absolute lesion lumen area but also unique stenosis indexes:

1. The comparison of the lesion lumen area with the reference lumen area corresponds to the angiographic method for calculation of percent stenosis. We define
this as the luminal percent cross-sectional area stenosis (luminal percent area stenosis).

2. Comparison of the lesion lumen area to the external elastic lamina (EEL) area at the stenosis site provides an assessment of percent stenosis that is analogous to the pathologist's histopathologic measurements. We use this to calculate the measured lesion percent cross-sectional area stenosis (lesion percent area stenosis).

3. Comparison of the lesion lumen area to the mean reference EEL yields a percent area stenosis that takes into account arterial remodeling. We define this as the corrected (for remodeling) lesion percent cross-sectional area stenosis (corrected percent area stenosis).

Accordingly, the aim of this clinical study was to validate the IVUS measurements that can be used to differentiate functionally significant from nonsignificant epicardial coronary stenoses. Because of the recognized limitation of angiography for the assessment of flow-limiting stenoses (4–21), IVUS parameters were compared with stress nuclear perfusion imaging.

METHODS

Patients, vessels and coronary lesions studied. The study group came from our database of preinterventional IVUS imaging, which was performed by the responsible interventional cardiologist as he or she believed indicated for the assessment of the stenosis severity, plaque morphology or for selection of interventional devices. There were 79 cases of preinterventional IVUS imaging of coronary arteries in which only one de novo lesion was identified by angiography, and stress myocardial single-photon emission computed tomography (SPECT) imaging was performed within two weeks of the IVUS imaging. The following vessels were excluded from the quantitative IVUS image analysis: four vessels in which IVUS images were suboptimal for quantitative measurements because of heavy intimal calcification or a technical problem with the IVUS system, and five vessels in which the proximal reference site could not be identified owing to an ostial location of the lesion.

Following the inclusion and exclusion criteria described above, 70 coronary lesions in 70 coronary arteries (41 left anterior descending, 7 left circumflex, and 22 right coronary arteries) of 70 patients (52 men, 18 women; mean age: 66 ± 12 years) with known or suspected stable angina pectoris were included in this study.

Risk factors of the studied patients such as hypertension (undertreatment or blood pressure >140/90 mm Hg), hypercholesterolemia (undertreatment or serum total cholesterol >220 mg/dl), diabetes mellitus (undertreatment, fasting blood glucose >140 mg/dl or diabetic pattern by glucose tolerance test), smoking (regular smoker during the previous 12 months) and history of myocardial infarction were identified by reviewing patients' medical records. History of myocardial infarction was defined by the presence of a myocardial perfusion defect at rest by SPECT at the perfusion territories of the imaged coronary arteries by IVUS.

IVUS system and imaging procedure. In this study, two IVUS systems were used; one is a combination of a 3.5F, 30-MHz short monorail imaging catheter (Sonicaid, Boston Scientific, Boston, Massachusetts) and a HP Intravascular System imaging console (M2400A, Hewlett-Packard, Andover, Massachusetts) and the other is a combination of 2.9F, 30-MHz-long monorail imaging catheter (MicroView, Boston Scientific, Boston, Massachusetts) and a CVIS imaging console (ClearView, Boston Scientific, Boston, Massachusetts).

Informed consent was obtained from each patient before the IVUS procedure. After the completion of angiography, the imaging catheter was introduced into the target artery through an 8F or 9F coronary guiding catheter over a 0.014-in. (0.036 cm) or 0.018-in. (0.046 cm) guide wire. To prevent possible vasospasm reported in up to 3% of IVUS studies (22,23) and to obtain maximum vasodilatation, 100 to 200 μg of nitroglycerin was administered directly into the coronary artery immediately before the IVUS imaging. After advancing the imaging catheter across the lesion to the distal portion of the vessel under fluoroscopic guidance, IVUS imaging was performed during the slow pullback (1 mm/s) of the imaging catheter. The X-ray fluoroscopy was used to confirm the coaxiality of the imaging catheter at a region of interest in the coronary artery. The IVUS images were recorded on a 0.5-in. (1.27 cm) Super-VHS videotape for subsequent review and quantitative analysis.

Image analysis. All IVUS images were analyzed off-line with a HP Intravascular System. In each coronary artery a 1–2-cm vessel segment of interest was identified in which the most severe stenosis was included and no apparent side branches were observed by angiography and IVUS imaging. Using digital angiographic images as a road map, three sites were selected for quantitative IVUS analysis in this vessel segment. The three sites included the lesion site that had the smallest lumen area by IVUS, and the proximal and distal reference sites that had the largest lumen area by IVUS in the proximal and distal portion of the vessel segment adjacent to the lesion site.

For these three sites in each coronary artery, the vessel lumen areas (proximal reference lumen area, lesion lumen area and distal reference lumen area, mm²) were measured by tracing the lumen-intimal borders using a planimeter.
Contrast medium was injected to enhance the ultrasound definition of the lumen in cases in which the lumen-intimal border was ambiguous. The EEL of the vessel was defined as the outer border of the sonolucent zone, which has been reported to represent media (24,25) and the areas within the EEL were measured as the EEL areas (proximal reference EEL area, lesion EEL area, and distal reference EEL area, \( \text{mm}^2 \)) by planimetry. Three different stenosis indices using three different reference sites, as well as other IVUS indices, were defined and calculated as follows (see Fig. 1):

1. Mean reference lumen area = \( \frac{(\text{proximal reference lumen area} + \text{distal reference lumen area})}{2} \)
2. Mean reference EEL area = \( \frac{(\text{proximal reference EEL area} + \text{distal reference EEL area})}{2} \)
3. Luminal percent area stenosis = \( \frac{(\text{mean reference lumen area} - \text{lesion lumen area})}{\text{mean reference lumen area}} \times 100 \)
4. Lesion percent area stenosis = \( \frac{(\text{lesion EEL area} - \text{lesion lumen area} / \text{lesion EEL area})}{\times 100} \)
5. Corrected percent area stenosis = \( \frac{(\text{mean reference EEL area} - \text{lesion lumen area} / \text{mean reference EEL area})}{\times 100} \)
6. Mean reference percent area stenosis = \( \frac{(\text{proximal reference EEL area} - \text{proximal reference lumen area})}{\text{proximal reference EEL area} + (\text{distal reference EEL area} - \text{distal reference lumen area})/\text{distal reference EEL area}} \times \frac{1}{2} \)
7. EEL area ratio = \( \frac{(\text{lesion EEL area} / \text{mean reference EEL area})}{100} \)

Assuming that the coronary lumen and the EEL are completely circular, theoretical percent diameter stenosis of the lesion was also calculated as

\[ 1 - \sqrt{1 - \text{luminal percent area stenosis}/100} \times 100. \]

**Angiographic studies.** Angiograms were performed by conventional femoral approach (Judkins' technique) using biplane (Advantex, DXC, GE Medical System, Wakeshaw, Wisconsin) or single-plane (COROSKOP HICOR, Siemens, Erlangen, Germany) digital acquisition at 30 frames/s. Multiple manual injections of contrast medium were performed, and images were acquired using a 7-in. (17.78 cm) image intensifier field size on a 512\(^2 \times 8\) format. Images were displayed on 17-in. (43.18 cm) or 19-in. (48.26 cm) monitors with extended dynamic range and spatial edge...
enforcement filtration. Angiograms were interpreted by the consensus of three experienced interventional cardiologists using a semiquantitative grading system (0, 25, 50, 75, 90, 99 or 100% diameter stenosis) recommended by the American Heart Association (26).

Rest/stress myocardial perfusion SPECT protocol. In 38 patients, SPECT was performed using the previously described rest thallium-201/stress technetium-99m sestamibi dual isotope protocol (27,28). Briefly, thallium-201 (2.5 to 3.5 mCi) was injected at rest, and SPECT imaging was performed 10 min later. Either symptom-limited treadmill exercise or pharmacologic stress with adenosine infusion (140 mcg/kg/min for 6 min) was then performed. Technetium-99m sestamibi was injected at peak effect (near peak exercise and at the end of the third minute of adenosine infusion). Sestamibi SPECT was begun 15 min after injection of the isotope in the exercise protocol and after 60 min in the adenosine protocol. A large-field-of-view gamma camera and a high-resolution collimator were used to obtain 64 projections at 20 s/projection over a semicircular 180° arc extending from the 45° right anterior oblique to the 45° left posterior oblique position.

In 32 patients, ordinary exercise and redistribution thallium-201 SPECT imaging was performed. The patients underwent symptom-limited treadmill exercise testing. A dose of 3.0 mCi of thallium-201 was injected intravenously at near-peak exercise, and the exercise was continued for another minute. The patients were scanned with a dual-detector SPECT system (Starcom 4000XC/T, GE Medical System, Wakeshaw, Wisconsin) equipped with a low-energy, parallel-hole, all-purpose collimator. The thallium-201 stress images were obtained within 10 min after the thallium injection using a 180° semicircular orbit, from the 45° right anterior oblique to the 45° left posterior oblique, in 32 projections at 30 s/projection. Redistribution imaging was performed 4 h later using the same acquisition measurements.

A semi-quantitative visual interpretation was performed utilizing short-axis and vertical long-axis myocardial tomograms and a 20 segment model as previously described (27,28). These segments were assigned on six evenly spaced regions in the apical, mid-ventricular and basal slices of the short-axis views and two apical segments on the mid-ventricular vertical long-axis slice. Each segment was scored by the consensus of two expert observers using a 5-point scoring system (0 = normal; 1 = equivocal; 2 = moderate; 3 = severe reduction of isotope; and 4 = absence of detectable tracer uptake in a segment). A SPECT study was judged abnormal if there were two segments with a stress score of 2, or one segment with a stress score of 3. A reversible perfusion defect was defined as a stress defect (score 2 to 4) associated with a rest score of 1 or a stress defect with a score of 4 and an associated rest score of 2. The method of assignment of tomographic myocardial segments to vascular territories was performed as previously described (27). An abnormal coronary territory was defined as having at least one segment with a stress perfusion defect score of 2.

Statistical analysis. All data are expressed as mean ± 1 SD. Measured and calculated data between two groups were compared using the unpaired Student t test. Data of three different sites within the same artery were compared using repeated-measures analysis of variance (ANOVA), and the comparison of data among three different groups was performed using ordinary one-way ANOVA with the Bonferroni test as the post hoc test in both comparisons. The Fisher exact test was used to compare frequencies between two groups. A p < 0.05 was considered statistically significant.

RESULTS

The IVUS studies of human in vivo coronary arteries were completed without any complications.

In total, 49/70 patients had positive SPECT with a reversible perfusion defect (SPECT (+) group) and 21/70 patients had negative tests without reversible defect (SPECT (−) group). As shown in Table 1, among 70 patients studied, hypertension, hypercholesterolemia, diabetes mellitus or smoking was noted in 29 (41%), 28 (40%), 8 (11%) or 21 (30%) patients, respectively, and 11 (16%) patients had myocardial perfusion defects at rest in the perfusion territories of the imaged arteries by IVUS. Between the SPECT (+) group and the SPECT (−) group, there was no difference found in the prevalence of these factors except for smoking (18% vs. 57%, p <0.01).

The IVUS measurements of SPECT (+) and SPECT (−) groups are summarized in Table 2. Between the two groups, the proximal and distal reference lumen area and EEL area, and the lesion EEL area, were almost identical and no statistical difference was observed. As expected, the SPECT (+) group showed significantly smaller lesion lumen areas (3.3 ± 2.3 vs. 6.7 ± 2.7 mm², p < 0.01) and more severe lesion percent area stenosis (78.0 ± 12.2 vs. 59.7 ± 15.7%, p < 0.01), luminal percent area stenosis (69.4 ± 14.4 vs. 43.8 ± 17.4%, p < 0.01) and corrected percent area stenosis (78.5 ± 11.6 vs. 60.1 ±
When the significant coronary stenosis is defined as lesion lumen areas than the SPECT (both the SPECT (sponding to the vessel size (mean reference EEL area) in lumen areas (minimum luminal area) of all vessels corre-

Figure 2 shows the lesion

As expected, the average of this percent diameter stenosis between 30% and 70%, with the average value of 40 (51/70) of the lesions showed intermediate stenoses be-

73% and 50% diameter stenosis by semiquantitative angiographic assessment are not accurate for differentiating significant (p < 0.001) smaller than the lesion percent area stenoses and the corrected percent area stenoses.

Among 70 coronary arteries studied, only 3 (4%) arteries showed 90%, 22 (31%) arteries showed 75%, 32 (46%) arteries showed 50%, and 13 (19%) arteries showed 25% diameter stenosis by the semiquantitative grading system used in this study. The SPECT results showed positive tests in 23/25 (92%) of cases with more than 75% diameter stenosis by angiography and negative tests in 11/13 (85%) with 25% angiographic diameter stenosis. Out of 32 cases with 50% angiographic diameter stenosis, 24 showed positive SPECT results and 8 showed negative SPECT results. Accordingly, when more than 75% diameter stenosis is considered significant, the sensitivity and specificity of this variable were as 49% (24/49) and 90% (21/21), respectively. When the definition of a significant stenosis is changed to more than 50% diameter stenosis, the sensitivity and specificity were as 96% (47/49) and 52% (11/21). Therefore, the cutoff points of 75% and 50% diameter stenosis by semiquantitative angiographic assessment are not accurate for differentiating significant from nonsignificant coronary stenoses.

Using the theoretically estimated percent diameter stenosis derived from IVUS measures, 60% (42/70) of the lesions had intermediate stenoses between 40% and 70%, and 73% (51/70) of the lesions showed intermediate stenoses between 30% and 70%, with the average value of 40 ± 15%. As expected, the average of this percent diameter stenosis was significantly greater in the SPECT (+) group than in the SPECT (−) group (p < 0.01, 46.0 ± 12.1 vs. 26.0 ± 12.7%).

Lumen area at the lesion site. Figure 2 shows the lesion lumen areas (minimum luminal area) of all vessels corresponding to the vessel size (mean reference EEL area) in both the SPECT (+) and the SPECT (−) groups. As already described above, the SPECT (+) group had significantly smaller lumen areas than the SPECT (−) group. When the significant coronary stenosis is defined as lesion lumen area equal to or less than 4.0 mm² (under the dotted line in Fig. 2), the sensitivity and specificity of this definition were 88% and 90%, respectively, using the SPECT result as the “gold standard.” When the solid cutoff line on Figure 2 (Y = 0.1X + 2.6) was used for discrimination of the SPECT (+) and the SPECT (−) groups, the sensitivity of this definition improved from 88% to 92%, whereas the same specificity of 90% was unchanged compared to those when the cutoff value of 4.0 mm² was used.

Three IVUS-derived stenosis indexes. As shown in Table 2, all three IVUS-derived stenosis indices were significantly (p < 0.01) more severe in the SPECT (+) group than in the SPECT (−) group. The luminal percent area stenosis showed a significantly (p < 0.01) smaller value compared with lesion percent area stenosis and corrected percent area stenosis.

Figure 3 illustrates all data of the lesion percent area stenosis (Y-axis) corresponding to each EEL area ratio (X-axis), which represents the degree of coronary remodeling. Using a cutoff value of 73% shown as the dotted line on Figure 3, the sensitivity and specificity of the lesion percent area stenosis were 84% and 81%, respectively. The EEL area ratio of more than 100% or less than 100% indicates an enlarged or constricted lesion site, respectively, compared to the mean vessel sizes at proximal and distal reference sites. When the solid cutoff line on Figure 3 (Y = 0.23X + 47.0) was used for discrimination of SPECT (+) and SPECT (−) groups, as shown in Table 3, the sensitivity improved from 84% to 92%, but the specificity decreased from 81% to 76% compared to those when the cutoff value of 73% was used, although both differences were not statistically significant.

Figure 4 shows all data of the luminal percent area stenosis (Y-axis) corresponding to mean reference percent area stenosis (X-axis). Using the cutoff value of 59% shown as a dotted line on Figure 4, the sensitivity and the specificity of the luminal percent area stenosis were 86% and 81%, respectively. When the cutoff line on Figure 4 (Y = −0.21X + 68.0) was used as shown in Table 3, the sensitivity and specificity of the luminal percent area stenosis above this line improved from 86% to 88% and from 81% to 90%, respectively, compared to those when the cutoff
value of 59% was used, although both differences were not statistically significant.

Figure 5 demonstrates the effect of mean reference percent area stenosis (X-axis) on corrected percent area stenosis (Y-axis). Using cutoff value of 75% shown as the dotted line on Figure 5, the sensitivity and specificity of the corrected percent area stenosis were 86% and 81%, respectively. When the solid cutoff line on Figure 5 (Y = 0.24X + 66.0) was used as shown in Table 3, the sensitivity and specificity of the corrected percent area stenosis above this line improved from 86% to 90% and from 81% to 90%, respectively, compared to when the cutoff value of 75% was used, although both differences were not statistically significant.

DISCUSSION

This is the first study to validate IVUS criteria to quantitatively discriminate significant from nonsignificant coronary artery stenoses. Angiographic assessment of coronary stenoses can be problematic (4–21). IVUS is frequently used to define coronary stenosis severity in this setting. In this in vivo IVUS study in human coronary arteries, we used stress myocardial perfusion SPECT to identify the lesion lumen area and three IVUS-derived stenosis indices that have sensitivities and specificities ranging between 80% and 90% for identifying a significant coronary stenosis.

Effects of vessel size, coronary remodeling and diffuse coronary atherosclerosis. To distinguish the SPECT (+) group from the SPECT (−) group, a simple cutoff value of 4.0 mm² showed excellent diagnostic values of 88% sensitivity and 90% specificity. Theoretically, it could be hypothesized that a relatively large lumen area could result in a significant stenosis in a large vessel, and that a small lumen area does not necessarily cause ischemia in a small vessel. Actually, considering the size of imaged vessel using a cutoff line on Figure 2, the sensitivity of the lesion lumen area slightly improved from 88% to 92% without decrease in specificity. However, the improvement was not statistically significant, and the impact of the imaged vessel size was not striking.

Compensatory enlargement (29–37) at the lesion site is considered to result in a larger vessel EEL area and a more severe percent area stenosis than in other vessels without compensatory enlargement (36,37). Using a cutoff line in Figure 3 considering the degree of coronary remodeling, the sensitivity of lesion percent area stenosis improved from 84% to 92% compared to a simple cutoff value of 73%; however, it was not statistically significant, and there was a decrease in the specificity from 81% to 76%. Consideration of coronary remodeling did not significantly improve the sensitivity and specificity of the lesion percent area stenosis in this study population.

Similar to coronary angiography (4), diffuse coronary atherosclerosis involving the reference site could affect the interpretation of the luminal percent area stenosis. Diffuse coronary atherosclerosis also could influence the interpretation of corrected percent area stenosis through the vessel remodeling developed at the reference sites. It is assumed
that the vessels with more severe reference site stenoses tend to have more compensatory enlargement at the reference site, which results in more severe corrected percent area stenosis compared to the vessels with milder reference site atherosclerosis. As shown in Table 3, considering reference site atherosclerosis using the cutoff lines on Figures 4 and 5, the sensitivity and specificity of luminal percent area stenosis improved from 86% and 81% to 88% and 90%, and those of corrected percent area stenosis improved from 86% and 81% to 90% and 90%, respectively, compared to those when simple cutoff values were used. However, these improvements were statistically nonsignificant, and the effect of reference-site atherosclerosis was not apparent in this study, although it is reported to significantly affect the interpretation of angiographic stenosis severity (4).

Comparison with other intracoronary diagnostic methods. Recently, new intracoronary modalities for evaluating coronary stenosis severity have become available, such as intracoronary Doppler flow and intracoronary pressure measurements. Intracoronary Doppler flow measurements with reduced coronary flow reserve have been shown to predict the functional significance of coronary stenoses, which cause stress-inducible myocardial perfusion abnormalities (14–17). However, the best cutoff point of coronary flow reserve varies among studies (14–18), and this technique is affected by several factors, which include epicardial coronary stenoses and microvascular abnormalities, as well as the loading conditions such as systemic blood pressure and heart rate. A recent study by Abizaid et al. (18) showed a good correlation between the lesion lumen area by IVUS and the coronary flow reserve by Doppler technique. It demonstrated a high

### Table 3. Functionally Significant Coronary Artery Stenosis Determined by Intravascular Ultrasound Imaging

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition of Significant Stenosis</th>
<th>All Cases (n = 70)</th>
<th>3 Cases Excluded* (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Lesion lumen area</td>
<td>≤4 mm²</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>≤cutoff line</td>
<td>92%</td>
<td>90%</td>
</tr>
<tr>
<td>Lesion percent area stenosis</td>
<td>≥73%</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>≤cutoff line</td>
<td>92%</td>
<td>76%</td>
</tr>
<tr>
<td>Luminal percent area stenosis</td>
<td>≥59%</td>
<td>86%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>≤cutoff line</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>Corrected percent area stenosis</td>
<td>≥75%</td>
<td>86%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>≤cutoff line</td>
<td>90%</td>
<td>90%</td>
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</tbody>
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Each cutoff value or cutoff line was determined as the value or line that can best discriminate SPECT (+) group from SPECT (−) group. See also Figures 2 through 5. *Consists of 67 cases, excluding three cases in which microcirculatory alteration was considered to have markedly affected the SPECT results. SPECT = single-photon emission computed tomography.
diagnostic accuracy of an IVUS lumen area of 4.0 mm² at the lesion site in predicting an abnormal coronary flow reserve of 2.0. Our results are also concordant with their findings. Other investigators (19–21) have reported that fractional flow reserve derived from intracoronary trans-stenotic pressure measurements closely correlate to relative flow reserve derived from positron emission tomography, and could successfully differentiate functionally significant coronary stenoses from nonsignificant stenoses. This technique has advantages because the measurements are constant under variable hemodynamics and can even evaluate collateral flow; however, it underestimates coronary stenosis severity in patients with microvascular disease or diffuse coronary atherosclerosis, because coronary flow increase is restricted after adenosine administration in these vessel territories.

The IVUS measurements are unique because the technique assesses the severity of the imaged lesion and is not affected by microvascular abnormalities, which may or may not be useful in comparison to intracoronary Doppler flow and trans-stenotic pressure measurements.

**Effect of microcirculation.** In this study we compared IVUS measurements with SPECT imaging results that evaluate both epicardial coronary stenosis and alterations of the microvasculature. Some of the discordance between IVUS imaging and SPECT imaging might be caused by the concomitant presence of microvascular disease. Conversely, some of the cases with positive IVUS and negative SPECT results might be due to the inability of IVUS measurements to detect collateral flow that prevents stress-inducible myocardial ischemia. Actually, two SPECT-positive cases with angiographically mild (25%) stenosis showed minimal disease by IVUS (15% and 21% area stenoses) and could be explained by microvascular disease, and a SPECT-negative case with a 90% coronary artery stenosis by angiography showed severe luminal narrowing by IVUS (1.5 mm² lumen area). This patient had abundant collateral circulation, which might have been enough to prevent myocardial ischemia. By excluding these three cases in which microcircularity alterations were considered to have markedly affected the SPECT results. The sensitivity of the IVUS indexes improved by 3% and the specificity improved by 5% (Table 3).

To assess the influence of the microcirculation on the SPECT results, the frequency of hypertension, hypercholesterolemia, diabetes mellitus, smoking or history of myocardial infarction was compared between the SPECT (+) group and the SPECT (−) group, as shown in Table 1. The only difference was the frequency of smoking, which was higher in the SPECT (−) group. Therefore, in this study population the microcirculation is not considered to have played a dominant role for provocation of ischemia compared with epicardial coronary stenoses in most patients.

**Study limitations.** Our findings are based on the observation of de novo native coronary arterial lesions that exclude ostial lesions as well as coronary arteries with severe calcification. Therefore, our findings might not be applicable to cases with heavily calcified, restenotic, ostial or bypass graft lesions. This study included only patients with known or suspected stable angina pectoris. Functionally significant IVUS measurements in patients after coronary interventions, thrombolytic therapy or those suffering acute myocardial infarction might be different from our results.

We used an intracoronary injection of 100 to 200 μg of nitroglycerin (NTG) to prevent vasospasm, and actually no angiographic change was observed before and after the intravascular ultrasound imaging procedure. However, the administration of NTG does not guarantee that local vasospastic activity is eliminated.

**Clinical implications.** When preinterventional angiography shows an intermediate coronary stenosis, assessment of the functional significance of this lesion is essential for clinical decision making. For this purpose, stress nuclear perfusion imaging, stress echocardiography, intracoronary Doppler flow measurement and trans-stenotic pressure measurement are available. However, all these techniques are influenced by the effect of the microcirculation and could possibly overestimate or underestimate the epicardial coronary stenosis severity in some cases. Conversely, IVUS measurements are not affected by the microcirculation and could be a precise diagnostic imaging modality for independently assessing the epicardial coronary stenosis severity from the microcirculation.

The IVUS-determined measures, including the lesion lumen area, the lesion percent area stenosis, the luminal percent area stenosis and the corrected percent area stenosis, showed similar and high sensitivities and specificities, and could be clinically used as tools to discriminate significant from nonsignificant coronary stenosis. The lesion lumen area is the simplest among the indexes presented; it is highly accurate and useful. The other three indexes may be utilized to aid the interventional cardiologist in assessing lesion severity when the lesion lumen area shows a borderline value or when the native artery being evaluated is extraordinarily small or large. When, owing to the ostial location of the lesion or calcification, the reference lumen area and the reference or lesion EEL cannot be measured, at least one of these three potentially interchangeable measurements could be used to confirm the lesion stenosis severity.

**Conclusions.** Comparing IVUS measurements and stress myocardial perfusion SPECT, the lesion lumen area and three IVUS-derived stenosis indices showed sensitivities and specificities ranging between 80% and 90%. The lesion lumen area ≤4 mm² is a simple and highly accurate criterion for significant coronary narrowing. Therefore, quantitative IVUS measurements that are independent from microcirculatory alterations can be reliably used for identi-
fying significant epicardial coronary artery stenoses in the coronary interventional laboratory.

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