Advantages and Limitations of Intracoronary Ultrasound for the Assessment of Vascular Dimensions

CARLO DI MARIO, M.D., Ph.D., JAVIER ESCANED-BARBOSA, M.D., JOSE BAPTISTA, M.D., JÜRGEN HAASE, M.D., YUKIO OZAKI, M.D., Ph.D., JOS R.T.C. ROELANDT, M.D., Ph.D., and PATRICK W. SERRUYS, M.D., Ph.D.

From the Intracoronary Imaging Laboratory and Cardiac Catheterization Laboratory, Thoraxcenter, Rotterdam, The Netherlands

Introduction

Quantitative angiography has been used to validate the accuracy of the measurement obtained with the early intravascular ultrasound catheters. In more recent reports it was suggested that intravascular ultrasound can be superior to quantitative angiography in the assessment of complex lesions (eccentric stenoses, asymmetric lesions, vascular dissections). In this article, advantages and limitations of the two techniques in the assessment of vascular dimensions are discussed based on the results reported in the literature and of our experience in 94 patients with coronary artery disease.

Previous Studies Comparing Intravascular Ultrasound and Angiography for the Assessment of Vascular Dimensions

The results of 11 clinical studies in which quantitative angiography and intravascular ultrasound were compared are summarized in Table 1. Differences in equipment and methods of analysis limit the comparison and interpretation of data.

Linear regression analysis is most commonly used as a statistical test in these studies. However, a regression coefficient close to 1 is not sufficient to conclude that the two techniques provide similar quantitative measurements. The mean difference of the paired measurements and indexes of dispersion along the line of identity are more meaningful parameters, but are not always reported. With the exception of the study by Tobis et al., the results indicate that there is a good correlation between intravascular ultrasound and angiographic measurements in normal or moderatley diseased segments. In general, larger cross-sectional areas were measured with intravascular ultrasound than with angiography. A major limitation for a precise comparison is that the measurement of the same arterial cross-section is difficult, particularly when a major change of vascular cross-sectional area occurs in a very short segment. An angiogram of sufficient quality to be quantitatively analyzed cannot be obtained during the echographic measurements since the catheter positioned in the stenosis causes a severe arterial occlusion, limiting the distal opacification. In eccentric lesions or lesions treated with balloon angioplasty a poor correlation and a large scatter of the paired measurements was found immediately after balloon dilatation. After angioplasty, Tobis et al. observed that the cross-sectional areas measured with intracoronary ultrasound were up to 50% larger than the corresponding angiographic cross-
Table 1. Quantitative Angiography vs Intravascular Ultrasound: Clinical Comparative Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Examined Arteries</th>
<th>‘r’</th>
<th>SEE</th>
<th>Mean Difference</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson et al.</td>
<td>21 patients undergoing cardiac catheter</td>
<td>femoroliliac arteries</td>
<td>0.97</td>
<td>1.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheikh et al.</td>
<td>15 patients undergoing cardiac catheter</td>
<td>femoral arteries</td>
<td>0.95</td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The et al.</td>
<td>8 patients undergoing cardiac catheter</td>
<td>femoroliliac arteries</td>
<td>0.96</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartorelli et al.</td>
<td>8 patients undergoing cardiac catheter</td>
<td>normal common femoral arteries</td>
<td>0.96</td>
<td>—</td>
<td>0.3 mm</td>
<td>4%</td>
</tr>
<tr>
<td>Tobis et al.</td>
<td>27 CAD patients undergoing PTCA</td>
<td>normal sites</td>
<td>0.26</td>
<td>—</td>
<td>2.1 mm²</td>
<td>30%</td>
</tr>
<tr>
<td>Nissen et al.</td>
<td>8 normal subjects</td>
<td>normal coronaries</td>
<td>0.18</td>
<td>—</td>
<td>1.7 mm²</td>
<td>51%</td>
</tr>
<tr>
<td>Werner et al.</td>
<td>14 CAD patients</td>
<td>normal sites</td>
<td>0.92</td>
<td>0.21</td>
<td>−0.05 mm</td>
<td>1%</td>
</tr>
<tr>
<td>St. Goar et al.</td>
<td>20 cardiac transplant recipients</td>
<td>normal coronaryles</td>
<td>0.86</td>
<td>0.43</td>
<td>0.05 mm</td>
<td>2%</td>
</tr>
<tr>
<td>Jain et al.</td>
<td>6 CAD patients</td>
<td>normal coronaries (angiographically)</td>
<td>0.77</td>
<td>0.77</td>
<td>0.06 mm</td>
<td>2%</td>
</tr>
<tr>
<td>Hodgson et al.</td>
<td>34 CAD patients undergoing PTCA</td>
<td>saphenous vein bypass grafts</td>
<td>0.34</td>
<td>0.05</td>
<td>−0.02 mm</td>
<td>12%</td>
</tr>
<tr>
<td>Hause et al.</td>
<td>20 CAD patients</td>
<td>reference segment</td>
<td>0.53</td>
<td>—</td>
<td>2.3 mm²</td>
<td>—</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty.

Sectional areas calculated assuming a circular mode.

Percent Diameter and Cross-Sectional Area Stenosis: Which Technique Provides the Correct Measurements?

The use of different reference measurements for the calculation of relative vascular dimensions with quantitative angiography and intravascular ultrasound may explain the large discordance between the results obtained with the two techniques (Fig. 1). Reference diameter and cross-sectional area are measured in an angiographically normal segment of the vessel with quantitative angiography. In muscular arteries intravascular ultrasound allows a direct measurement of the area inside the internal elastic lamina, the so-called original lumen area which is equal to the sum of lumen and plaque area. This area is used as a reference in intravascular ultrasound. Intimal thickening is often present in angiographically normal reference segments (Fig. 2). Furthermore, a compensatory enlargement of the vessel is almost invariably present at the stenotic site, as confirmed also in recent studies with intracoronary ultrasound. These reasons explain why the angiographic reference lumen cross-sectional area is smaller than the ultrasonic reference area so that less severe percent diameter and cross-sectional area stenosis will be calculated with quantitative angiography than with intravascular ultrasound (Fig. 3). In Figure 1, in the presence of a ½-mm thick intimal lesion in the reference segment, a major difference is observed in percent diameter and cross-sectional area stenosis between quantitative angiography and intravascular ultrasound.

Percent diameter and cross-sectional area stenosis are physiologically important parameters and are major determinants of the pressure drop.
Figure 1. Calculation of percent diameter and cross-sectional area stenosis based on intravascular ultrasound and quantitative angiographic measurements. The reference lumen diameter is measured with quantitative angiography in the normal segments of the vessel while intravascular ultrasound directly measures the thickness of the atherosclerotic plaque at the stenosis site. In the presence of compensatory enlargement of the stenotic site or, as in this example, of a diffuse eccentric intimal thickening involving also the angiographic reference segment, the intravascular ultrasound reference diameter, traced within the black band representing the muscular media, is larger than the angiographic reference diameter. As a result the angiographically moderate percent stenosis is considered more severe, “significant” according to the normally used criteria (≥ 50% diameter stenosis and ≥ 75% cross-sectional area stenosis) with intravascular ultrasound.

Advantages of Intravascular Ultrasound

Advantages and disadvantages of intravascular ultrasound versus angiography are summarized in Table 2.

No Calibration is Required. For angiography the measurement of a radiopaque structure of known dimension is required for calibration. When the tip of the catheter is used as a scaling device, possible sources of error are off-plane position of the catheter and the examined vessel, tapering of the catheter at the distal end, and discordance between true catheter diameter and diameter reported by the manufacturer. Furthermore, calibration must be repeated for every angiographic view. A potentially more precise, but even more cumbersome approach is the geometric correction for beam divergence, based on the measurement of the distances between x-ray source, imaged object, and image amplifier (isocenter technique).

The measurement of a distance with ultrasound is based on the wavelength of the ultrasound beam and the velocity of sound in the medium. When the instrument is calibrated for the ultrasound speed in blood (1,560 m/sec) a negligible overestimation occurs when saline is injected to replace the more echogenic blood and delineate the intimal contour.

Instantaneous Measurements are Available. Recently introduced digital angiographic equipment
allows the performance of on-line measurements of vascular dimensions. As a consequence, quantitative angiography can be used for guidance and immediate evaluation of interventional procedures. The time required for the analysis, however, is still considerable when compared to the really instantaneous measurement available with ultrasound.

**No Contrast Medium Required: A Continuous Monitoring is Possible.** Angiography requires the injection of contrast material to delineate the vascular lumen. As a consequence, angiography cannot be used for a continuous monitoring of vascular dimension. Other disadvantages of the use of contrast medium are the modification of the intraluminal pressure during the forceful contrast injection and the vasoactive properties of these agents.

Intravascular ultrasound allows a continuous real-time measurement of vascular dimensions, a great potential advantage for monitoring interventions and assessment of the effects of vasoactive agents on vascular dimensions and dynamics.²³

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**Figure 2.** Digital angiogram of a right coronary artery with the reference diameter positioned at the site examined with intracoronary ultrasound. Note that in this angiographically normal reference segment intracoronary ultrasound shows the presence of a concentric plaque inducing a 445 diameter stenosis. Calibration: 0.5 mm.

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**Figure 3.** (A) Cineangiogram after automatic contour detection showing a severe proximal stenosis of the left anterior descending coronary artery (left panel) and a regular lumen (ca 10% residual diameter stenosis) after implantation of a Gianturco Roubin stent (right panel). (B) Ultrasonic cross-sectional area in the most severe stenotic segment before angioplasty (left panel), after a predilatation with a 3.0-mm angioplasty balloon (mid-panel), and after implantation of a 3.0-mm Gianturco Roubin stent (right panel). The lower panels show the same ultrasonic cross-sections after on-line manual tracing of the lumen and plaque contours. Note that a similar plaque area is present before dilatation and after balloon dilatation and stent implantation (12.2 mm² and 11.1-11.9 mm², respectively) despite the large increase in lumen area (from 2.1 mm² before treatment to 4.6 mm² and 6.6 mm² after balloon dilatation and stent implantation, respectively). The increase in lumen area after balloon angioplasty is the consequence of multiple irregular fractures of the plaques while a regular circular luminal cross-sectional area is present after stent implantation. Calibration: 0.5 mm.
VASCULAR DIMENSIONS BY INTRACORONARY ULTRASOUND

Figure 3

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Morphometric Analysis of the Vessel Wall. Angiography provides only a shadowgram of the vascular lumen, so that the presence of vascular lesions is derived indirectly from irregularities of the luminal contour. The only information on the composition of atherosclerotic plaques concerns the presence of fluoroscopically visible vessel wall calcification. Pathology studies and, more recently, the application of intraoperative and intravascular high frequency ultrasound have shown that coronary arteries undergo a progressive enlargement in relation with increases in plaque area, so that a reduction of lumen area is delayed until the atherosclerotic lesion occupies more than 40% of the area circumscribed by the internal elastic lamina.* (Fig. 4). These findings explain why angiographically normal arterial segments may show an extensive atherosclerotic involvement at autopsy and upon direct surgical inspection. Several reports have confirmed that intravascular ultrasound can detect atherosclerotic changes in angiographically normal segments** (Fig. 2). Furthermore, intravascular ultrasound displays the components of the atherosclerotic plaque with a different intensity proportional to their backscatter power,26-28 allowing their qualitative differentiation. In vitro studies have shown that intravascular ultrasound has a high sensitivity and specificity in the detection of intimal lesions and in the differentiation between fibrous, calcific, and lipid containing plaques.29 Plaque thickness can be measured, especially if the presence of an echographically hypoechoic medial layer facilitates the delineation of plaque contours and if no shadowing or attenuation from plaque components is present.29

The possibility to provide information on plaque morphology and dimension at the same time makes intravascular ultrasound an ideal technique for the assessment of the mechanism of the different coronary interventions and the modalities of progression/regression of the atherosclerotic plaque. Wall stretching and wall dissection have been reported as the main operative mechanism of balloon angioplasty in both coronary30 and peripheral arteries.31 A significant plaque compression (absolute reduction of plaque area) has been more recently reported.32 In 18 coronary stenoses treated with balloon angioplasty and examined with three-dimensional intracoronary ultrasound, Mintz et al.33 observed that an axial redistribution of the plaque away from the narrowest cross-sectional area, without significant changes in the total plaque volume. An example of the usefulness of three-dimensional reconstruction of intracoronary ultrasound in the assessment of the results of coronary interventions is shown in Figure 5.

Standard methods used in quantitative angiography for the assessment of regression of atherosclerosis are the measurement of mean luminal area and severity of edge irregularities (roughness profile). A long-term follow-up of large cohorts of patients is necessary to show a statistically significant trend toward regression or delayed progression of plaques in peripheral35 and coronary36,37 atherosclerotic disease.

Intravascular ultrasound has the potential of detecting atherosclerotic wall disease in the prestenotic phase and allows the measurement of both lumen and plaque area.38 Dietary and pharmacological interventions may cause a more rapid and complete regression of the vascular changes in the early "prestenotic" phase of atherosclerosis rather than in the more advanced phases.39 Animal studies have shown that intravascular ultrasound can detect plaque progression earlier and more accurately than quantitative angiography.40-42 The possibility to differentiate

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** Table 2. Advantages and Limitations of Intravascular Ultrasound for Quantitative Assessment of Vascular Dimensions **

<table>
<thead>
<tr>
<th>Advantages of Intravascular Ultrasound</th>
<th>Limitations of Intravascular Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) No calibration required</td>
<td>1) Introduction of the catheter is necessary</td>
</tr>
<tr>
<td>2) Instantaneous and continuous</td>
<td>2) Potential errors due to catheter malalignment</td>
</tr>
<tr>
<td>measurements available</td>
<td></td>
</tr>
<tr>
<td>3) No contrast medium required</td>
<td>3) Artifacts from non-uniform rotation; near-field artifacts; low sampling rate; detection difficult</td>
</tr>
<tr>
<td>4) Independent of lumen eccentricity or complex lumen geometry (dissection)</td>
<td>4) Automatic edge detection</td>
</tr>
<tr>
<td>5) Simultaneous morphometric analysis of wall components</td>
<td>5) Reproducibility of the measurements not yet tested</td>
</tr>
</tbody>
</table>

* single element mechanically rotating systems; ** multielement synthetic aperture array systems.
Figure 4. (A) Angiographic and intracoronary ultrasonic examination 4 months after stenting (Gianturco Roubin) of the mid-segment of the right coronary artery. The ultrasonic cross-sections on the right (B) show the segment where the stent was implanted (note the highly echogenic wire, close to the arterial lumen, in the lower left corner). A de novo lesion was present in the proximal segment (A), with the presence of a large concentric plaque with a low echoreflectivity and without calcification. Note that the plaque area in A (10.1 mm²) is similar to the plaque area in B (9.9 mm²), despite the large difference in luminal cross-sectional area and percent cross-sectional area stenosis (76% in position A vs 57%, position B). (B) In the same artery after balloon dilation of the proximal segment, a large echo-free area behind the stent wires and communicating with the arterial lumen (right panel) indicates a malapposition of the stent to the arterial wall in a segment of aneurysmatic dilatation (arrow in the cineangiogram in the right panel). Calibration: 0.5 mm.
Plaque Eccentricity. In most cases, with the use of multiple projections, an angiogram perpendicular to the maximal thickness of the plaque can be obtained. In < 50% of the cases, however, appropriate orthogonal projections, amenable to quantitative analysis, can be obtained to measure lumen area from its long and short axis when an elliptical area is present. Furthermore, angiography determines the eccentricity of a stenosis comparing the proximal and distal segments of the vessel, assumed as "normal" reference segments so that a misinterpretation is possible if the eccentric plaque involves also the reference segments (Fig. 6).

Intravascular ultrasound detects the eccentricity of the lesion from a direct measurement of the maximal and minimal thickness of the plaque. The eccentricity index calculated with intravascular ultrasound is independent from the characteristics of the contiguous segments. The advantage of the direct visualization of eccentric plaques is obvious in the guidance of percutaneous recanalization techniques that allow selective removal of atheromatous plaque, avoiding a potentially dangerous treatment in areas of thin, normal wall.

Complex Lumen Geometry (Wall Dissection). Pathology studies have shown that splitting of the vessel wall is extremely frequent after balloon angioplasty and is one of the major mechanisms of effective lumen enlargement. Only large dissections are angiographically evident after balloon angioplasty. Several reports have confirmed that intravascular ultrasound is more sensitive than angiography in the detection of plaque rupture. The absence of echographically evident plaque rupture has been recently reported to increase the risk of restenosis. The quantitative measurement of residual stenosis early after balloon angioplasty is a poor indicator of the functional result of the procedure as assessed by coronary flow reserve and persistence of scintigraphic and electrocardiographic signs of reversible myocardial ischemia. Several reasons may explain these findings. In some cases, the comparison between echographic and
Figure 6. Eccentricity index calculated with quantitative angiography and intravascular ultrasound. Intravascular ultrasound allows the direct assessment of the wall thickness so that the eccentricity index is based on the ratio between plaque thickness and thickness of the opposite wall. Quantitative angiography estimates the eccentricity of a plaque from the distance between the center of the lumen and the luminal contours at the site of the stenosis. In this example, however, the presence of a different thickness of the wall also in the angiographically normal segment induces an underestimation of the plaque eccentricity.

quantitative angiographic measurements suggests that an overestimation of the lumen available for blood passage may occur when a geometric technique (edge detection) is used (Fig. 7). Densitometric measurements have been suggested in order to overcome the limitations of edge detection in lesions of complex geometry (including stenosis postangioplasty and eccentric lesions). Densitometry, however, requires a homogeneous filling of the lumen with contrast and a perfect orthogonality of the x-ray beam to the vessel lumen, is highly dependent on the radiographic setting and modalities of film processing and cannot directly provide absolute measurements.

Limitations of Intravascular Ultrasound (Table 2)

Necessity of Catheter Insertion. Intravascular ultrasound requires the examination with the echo-catheter of the entire vascular segments to be studied. Instrumentation of a coronary vessel is the current practice for all the interventional techniques. However, especially in the examination of the coronary arteries, the insertion of the echo-catheter increases the complexity and duration of the procedure and carries out a potential risk of complications. Recent improvements in catheter flexibility and miniaturization allow the examination of the proximal and middle coronary arteries in most patients. A possible limitation, however, concerns the examination of severe coronary stenosis before interventions, one of the most interesting potential applications of intravascular ultrasound. A quantitative angiographic study of large cohorts of candidates to balloon angioplasty has shown that the measured minimal luminal diameter before balloon dilatation (1.02 ± 0.37 mm) is similar to the diameter of the recently introduced second generation of catheters (from 3.5Fr to 4.3Fr, equal to 1.15–1.4 mm).

The intravascular ultrasound examination is facilitated after successful therapeutic interventions by the increased lumen diameter. However, recrossing large, unstable dissection flaps carries a potential risk of acute occlusion. Furthermore, a correct assessment of the real morphology of a complex spiral dissection and the consequent impairment to blood passage is difficult because it would require a three-dimensional reconstruction of the ultrasonic cross-sections and because the communication between true and false lumen is modified by the physical presence of the catheter. Proximal injection of saline or agitated contrast can help in delineating vessel lumen and in detecting the presence of stagnant blood flow. However, an effective injection through the proximal guiding catheter is not always possible while the relatively large ultrasound catheters are still in place.

Dropouts may occur in segments of dissected wall which are explored with an unfavorable angle of incidence of the ultrasound beam. In our experience, such complex artifacts are more frequent in peripheral than in coronary arteries, because in these latter small vessels the physical presence of the ultrasound catheter modifies the orientation of the dissected flap.

The combination of intravascular ultrasound imaging and balloon angioplasty or alternative de-
Figure 7. The upper right panel shows a subocclusive stenosis of the mid-segment of the left anterior descending coronary artery with a minimal anterograde flow. The lumen enlargement and the normalization of flow after dilatation with a 3.0-mm balloon is evident in the lower right panel, where an arrow indicates a Type B dissection involving also the poststenotic segment. Note, in the panels on the left, the complex luminal cross-section after balloon dilatation. Note that the eccentric plaque has been dissected at the site of its insertion on the normal wall. The complex lumen after angioplasty cannot be correctly measured with angiography, even using multiple angiographic projections. Calibration: 0.5 mm.

bulking techniques in the same catheter can facilitate the use of intravascular ultrasound before and after interventions and can allow continuous monitoring and guidance during the procedure. At present, however, only prototypes of catheters for directional atherectomy mounting ultrasound crystals are in the phase of preliminary clinical evaluation and in the already available echo-balloon catheters the transducer is mounted proximal to the balloon.\textsuperscript{63,64} This configuration maintains a low profile of the balloon and avoids the artifacts induced by the balloon membrane, but precludes the possibility of continuous assessment before, during, and immediately after balloon dilatation.

Catheter Malalignment. A central position of the catheter in the vessel lumen is not frequent in intravascular ultrasound. With a simple eccentricity of the catheter position, the echographic cross-section is still perpendicular to the long axis of the vessel so that no change in the measured area is expected. When the catheter is not only eccentric, but also nonparallel to the long axis of the vessel the vascular lumen is distorted, with an
angle dependent overestimation of the vascular lumen. In a tortuous artery the ultrasound catheter can assume an orientation nonparallel to the long axis of the vessel. Fortunately, the small size of the coronary arteries in comparison to the catheter diameter limits the practical relevance of this problem.9

**Nonuniform Rotation, Near Field Artifact, Inadequate Sampling Rate.** With mechanically rotating catheters, a 1:1 rotation of the ultrasound element (or mirror) can be impossible if the catheter is inserted in very tortuous vessels, resulting in a variable distortion of the ultrasound image. In the multielement systems these artifacts are not present. A limitation of these systems, however, is that the near field artifact is partially obscuring the structures close to the catheter. Artifacts can also result from the phasic changes of the position of the catheter inside the vessel throughout the cardiac cycle. A too low sampling rate can result in inability to accurately measure the systo-diastolic changes of vascular dimensions.

**Application of Automatic Measurements.** Sophisticated techniques of edge detection or videodensitometry have been developed for quantitative angiography.65 The difference in brightness between the radiographic contrast filling the vascular lumen and the background facilitates the application of the proposed algorithms for computer-assisted automatic contour detection. In intravascular ultrasound, on the contrary, the relatively similar echoreflectivity of blood and of the underlying vessel wall is a potential obstacle to fully automatic measurements of lumen area. Manual redrawing of part of the lumen contours is frequently necessary, resulting in an increase variability of the results of the analysis.66 A fully automatic technique, based on the measurement of the vessel wall displacement from a semiautomatic defined template image, has been developed at our institution and is currently used to measure the systo-diastolic changes of vascular dimensions.67

**Reproducibility of the Measurements.** Changes in vascular tone, variability of repeated measurements, modifications of radiographic projections and setting, cardiac and respiratory movements influence short- and long-term reproducibility of angiographic measurements, limiting the reliability of angiography in assessing the development of changes in vascular dimensions. Although intravascular ultrasound is less limited by these factors, accurate serial measurements are possible only when the echo-catheter is positioned exactly at the same site in the vessel, a trivial requirement which is practically very difficult to satisfy.

**No Assessment of Blood Flow.** Various angiographic techniques have been described which use the contrast medium as a marker of flow and calculate relative changes of blood flow based on contrast appearance time and/or on changes in the density of the myocardium.68–70 This principle is not applicable with the current intravascular ultrasound imaging catheters. An alternative ultrasound based technique is the measurement of the Doppler shift induced by the motion of the red blood cells to directly calculate blood flow velocity. Prototypes of combined imaging-Doppler catheters have been described71,72 and Doppler guidewires which can integrate the ultrasound imaging catheters are in current clinical use73–75 (Fig. 8).

**Conclusions**

Intravascular ultrasound can accurately assess luminal dimensions and has potential advantages on quantitative arteriography in the presence of eccentric lesions and lumens of complex geometry. The application of this technique, however, increases duration, risk, complexity and cost of a conventional diagnostic or interventional procedure based on a purely angiographic quantitative assessment. In clinical practice, therefore, it seems unlikely that quantitative arteriography can be replaced by intravascular ultrasound as a routine technique of measurement of luminal dimensions.

Intravascular ultrasound has a potential role as a research tool for the assessment of vessel dynamics and effects of pharmacological interventions. The information concerning characteristics and composition of the atherosclerotic plaque is not available with angiography and makes intravascular ultrasound potentially more suitable than angiography for the follow-up of interventions aimed at the regression of atherosclerotic lesions. Improvements in catheter technology...
can make quantitative intravascular ultrasound a valuable tool for the correct planning and guidance of interventional procedures.

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