Impact of Plaque Morphology and Composition on the Mechanisms of Lumen Enlargement Using Intracoronary Ultrasound and Quantitative Angiography After Balloon Angioplasty

Jose Baptista, MD, PhD, Carlo di Mario, MD, PhD, Yukio Ozaki, MD, Javier Escaned, MD, PhD, Robert Gil, MD, Pim de Feyter, MD, PhD, Jos R. T. C. Roelandt, MD, PhD, and Patrick W. Serruys, MD, PhD

Limited information is provided by angiography on plaque morphology and composition before balloon angioplasty. Identification of plaque associated with reduced lumen gain or a high complication rate may provide the rationale for using alternative revascularization devices. We studied 60 patients with quantitative angiography and intracoronary ultrasound (ICUS) before and after balloon dilation. Angiography was used to measure transient wall stretch and elastic recoil. ICUS was used to investigate the mechanisms of lumen enlargement among different plaque compositions and in the presence of a disease-free wall (minimal thickness <0.6 mm). Compared with ultrasound, angiography underestimated the presence of vessel calcification (13% vs 78%), lumen eccentricity (35% vs 62%), and wall dissection (32% vs 57%). ICUS measurements showed that balloon angioplasty increased lumen area from 1.82 ± 0.51 to 4.81 ± 1.43 mm². Lumen enlargement was the result of the combined effect of an increase in the total cross-sectional area of the vessel (wall stretching, 43%) and of a reduction in the area occupied by the plaque (plaque compression or redistribution, 57%). Vessels with a disease-free wall had smaller lumen gain than other types of vessels (2.13 ± 1.26 vs 3.59 ± 1.51 mm², respectively, p <0.01). Wall stretching was the most important mechanism of lumen enlargement in vessels with a disease-free wall (79% vs 37% in the other vessels). Angiography revealed a direct correlation between temporary stretch and elastic recoil that was responsible for 26% of the loss of the potential lumen gain. Thus, lumen enlargement after balloon angioplasty is the combined result of wall stretch and plaque compression or redistribution. ICUS indicates that vessels with a remnant arc of disease-free wall are dilated mainly by wall stretching compared with other types of vessels and are associated with a smaller lumen gain. (Am J Cardiol 1996;77:115-121)

Contrast angiography, the gold standard for the evaluation of coronary artery disease, provides limited information regarding plaque dimensions and composition. Therefore, the impact of plaque morphology and composition, in vivo, on the outcome of balloon angioplasty remains to be fully elucidated. Likewise, restenosis occurring after balloon dilation cannot be accurately predicted by angiography.

Balloon angioplasty is a nondirectional technique; during balloon inflation, factors, such as differences in plaque thickness and composition, may cause an unequal transmission of the balloon circumferential stress to the vessel wall, resulting in different responses of the vessel wall to balloon dilation. Identification of particular plaque types associated with a suboptimal result may provide the rationale for use of alternative devices for a particular lesion. Intracoronal ultrasound (ICUS) provides a unique opportunity not only to identify different plaque compositions but also to identify different mechanisms of lumen enlargement during balloon angioplasty. This study evaluates the influence of plaque morphology and composition on the mechanisms of lumen enlargement after balloon angioplasty using quantitative angiography and ICUS.

METHODS

Patient group: Sixty consecutive patients undergoing balloon angioplasty were studied with ICUS before and after intervention. Thirty-four patients presented with unstable angina (class IIIb and IIIb, and IIC and IIB under the Braunwald classification), and 26 presented with stable angina pectoris. The investigations were approved by the institutional board of the cardiology department of the Dijkzigt Ziekenhuis, and all patients were studied only after giving informed consent.

Quantitative coronary angiography: All 35 mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, Maastricht, The Netherlands). The automated edge detection of this system has been validated and described in detail elsewhere.

Lesion symmetry (Figure 1) was defined as the coefficient of the left-hand and right-hand distances between the reconstructed interpolated reference diameter and actual vessel contours at the site of obstruction. In this

From the Intracoronary Imaging and Catheterization Laboratories, Thoraxcenter, Erasmus University, Rotterdam, The Netherlands. Dr. Baptista is the recipient of a grant from the Portuguese Society of Cardiology, Lisbon, Portugal. Manuscript received May 12, 1995; revision received and accepted September 26, 1995.

Address for reprints: Patrick W. Serruys, MD, PhD, Intracoronary Imaging and Catheterization Laboratories, Thoraxcenter, Erasmus University Rotterdam, Postbus 1738 3000 DR Rotterdam, The Netherlands.
Figure 1.
The largest distance between the actual and reconstructed contours becomes the denominator, so that a perfectly symmetric lesion has a value of 1 and a severely eccentric lesion has a value of 0.7. A lesion was classified as eccentric when the eccentricity index was ≤0.5.

**Dissections, wall stretch, and elastic recoil with angiography:** Dissections were evaluated according to the modified classification of the Heart, Lung, and Blood Institutes. A dissection was classified as type A in the presence of a small radiolucent area within the lumen of the vessel and as type B or C when there was an extravasation of nonpersisting or persisting contrast medium, respectively. A dissection was classified as type D in the presence of a spiral-shaped filling defect with delayed distal flow, and as type E if a persistent lumen defect with delayed anterograde flow was seen on the final angiogram. A filling defect accompanied by a total coronary occlusion was classified as type F dissection.

Temporary wall stretch was defined as the difference between the mean balloon diameter (of the largest and last balloon used) and minimal lumen diameter after balloon dilation, normalized for vessel size (Figure 2). Elastic recoil was defined as the difference between minimal balloon diameter and the minimal lumen diameter after coronary angioplasty normalized for vessel size. This was measured 5 minutes after the last balloon inflation.

**Ultrasound study:** Before and after coronary interventions, a 4.3Fr mechanical 30 MHz intravascular ultrasound catheter (INSIGHT “3” ultrasound system, CVIS, Sunnyvale, California) was introduced along a 0.014-inch high-torque floppy guidewire. The catheter was advanced distal to the stenosis and a slow manual pullback or (last 22 patients) motorized mechanical pullback at 1 mm/s was performed from the distal area to the proximal area of the lesion. The segment comprising the stenotic lesion was examined along the entire length using side branches as landmarks, and the images were recorded on S-VHS videotape. The measurement system was digitally calibrated, and after review of each videotape, 1 image at the site of the minimal luminal cross-sectional area before and after intervention was selected for quantitative analysis. Landmarks such as side branches or a particular location of calcium were used to assure the same site of analysis after intervention.

The integrated information acquired during the pullback maneuver along the stenotic segment was used to classify plaque composition according to their ultrasonic appearance as follows:

- **Plaques with low echogenicity (“soft plaques”)** = >75% of the plaque area is composed of tissue with an echo density less than the reference adventitia.
- **Plaques with high echogenicity (“hard plaques”)** = >75% of the plaque area is composed of bright echoes, as bright or brighter than the reference adventitia, but without acoustic shadowing.
- **Diffuse calcific plaques** = bright echoes within a plaque with acoustic shadowing and occupying >180° of vessel wall circumference.
- **Plaques with a mixed echogenicity** = when a combination of different types of plaque composition occurs.

Additionally, vessel dimensions were measured as follows: Lumen area was defined as the integrated area central to the leading edge of the intimal echo. The external elastic membrane area was defined as the integrated area central to media-adventitia interface. The plaque plus media area was defined as the difference between external elastic membrane area and luminal area. From

![FIGURE 1. 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 the 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. CSA = cross-sectional area.](image1)

![FIGURE 2. Changes in lumen dimensions during balloon (Bal) dilation. During balloon inflation there was a change in lumen dimensions from 1.08 mm before (Pre) dilation to 2.93 mm during maximal balloon pressure (i.e., representative of the transient wall stretch [S]). After balloon deflation, there was a decrease in the lumen dimension, from the theoretically maximal lumen dimension toward the final lumen size (Post). This loss in lumen size is the result of elastic recoil (R). The difference between transient wall stretch and elastic recoil is the actual lumen gain (LU Gain). Reference diameter (Ref d) is also shown for comparison.](image2)
comparison of these measurements at the site of the minimal luminal cross-sectional area before and after angioplasty, several indexes were calculated including: (1) wall stretch or acute vessel, which is the dilation difference in external elastic membrane area before and after intervention. This differs from transient wall stretch measured with angiography, because this is the “permanent” plastic wall deformation occurring after the deflation of the angioplasty balloon; and (2) plaque reduction, which is the difference in plaque plus media area before and after intervention. In the presence of calcific plaques, the contour of the external elastic membrane was drawn assuming a circular vessel shape in the shadowed segment or drawing the contour of the continuous vessel segment without calcium. ICUS eccentricity index was obtained dividing the minimal by the maximal plaque thickness. A plaque was considered eccentric when the eccentricity index calculated as the minor diameter divided by the major diameter was ≤0.5. A vessel was classified as having a disease-free wall when the plaque minimal thickness was ≤0.6 mm, irrespective of its eccentricity (Figure 3).

Variability of the intravascular ultrasound-determined lumen dimensions: Values of the variability of ICUS dimensions have been previously published by our group.\textsuperscript{10,11}

Tears and Dissections: Tears or fractures were defined as a demarcated, focal, superficial break in the linear continuity of the plaque that extended only in a radial direction.\textsuperscript{12} Dissections were defined as demarcated ruptures of the plaque with circumferential or longitudinal involvement of the internal elastic membrane.\textsuperscript{12}

Procedure technique: During the procedures all patients received aspirin (250 mg) and intracoronary isosorbide dinitrate (1 to 3 mg) before and after the procedure, and underwent total anticoagulation with heparin, so that the activated clotting time was >300 seconds. Selective coronary arteriography was performed in multiple matched views before and after the coronary interventions. After the passage of a 0.014-inch guidewire across the target lesion, ICUS was performed with the guidance of a fluoroscopic window and multiple contrast injections. This assured proper comparison between ultrasound and angiographic images. Coronary angioplasty was performed according to standard practice.

**Statistical analysis:** All continuous variables are expressed as mean ± SD. The Student’s t test was used for analysis of continuous data. The chi-square test and Fisher’s exact test were used to compare differences between proportions. Agreement between the 2 techniques was determined using the Cohen Kappa coefficient. A p value <0.05 was considered statistically significant.

**RESULTS**

Patient and target lesion characteristics prior to balloon dilation are shown in Table I. Fluoroscopy underestimated the presence of calcium at the target lesion compared with ultrasound (8 patients [13%] vs 47 patients [78%], respectively, p <0.0001). An eccentric plaque was more often judged to be eccentric with ultrasound (37 patients, 62%) than with angiography (21 patients, 35%, p = NS) (Table II). Patients presenting with unstable coronary syndromes had a plaque composition similar to patients with stable angina.
TABLE I  Patient and Target Lesion Characteristics Before Balloon Dilation (n = 60)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>50 ± 9 years</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>50 (83)</td>
</tr>
<tr>
<td>Women</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Angina type</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>26 (43)</td>
</tr>
<tr>
<td>Unstable</td>
<td>34 (57)</td>
</tr>
<tr>
<td>Coronary artery</td>
<td></td>
</tr>
<tr>
<td>Left anterior ascending</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>14 (23)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>19 (32)</td>
</tr>
<tr>
<td>ICUS characteristics</td>
<td></td>
</tr>
<tr>
<td>Soft plaques</td>
<td>26 (43)</td>
</tr>
<tr>
<td>Hard plaques</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diffuse calcific</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Mixed plaques</td>
<td>29 (48)</td>
</tr>
<tr>
<td>No calcium</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Calcium</td>
<td>47 (78)</td>
</tr>
</tbody>
</table>

ICUS = intracoronary ultrasound.

Angiographic measurements: The minimal lumen diameter increased significantly after balloon angioplasty, from 1.08 ± 0.43 to 2.04 ± 0.48 mm (p < 0.0001) (Table III). Balloon artery ratio using the measured mean balloon diameter balloon was 1.12 ± 0.25. Temporary wall stretch during balloon inflation was 0.65 ± 0.25 of the reference vessel size. After balloon dilation, 0.26 ± 0.17 of the target reference size was lost due to elastic recoil.

Temporary wall stretch and elastic recoil were not significantly influenced by the determined angiographic eccentricity. Temporary wall stretch was directly correlated with relative elastic recoil (Y = 0.275x + 0.071, r² = 0.168, p < 0.005).

Ultrasound measurements: After balloon dilation there was a significant increase in lumen area, from 1.82 ± 0.51 to 4.81 ± 1.43 mm² (p < 0.0001) (Table IV). This was achieved by a combination of plaque reduction (1.72 ± 1.86 mm², 57% of lumen gain) and wall stretch (1.27 ± 1.84 mm², 43% of lumen gain) (Figure 4). Plaque composition did not seem to influence the magnitude of lumen gain after balloon dilation (2.62 ± 1.43 mm² for soft plaques vs 3.29 ± 1.66 mm² for other types of plaques, p = NS). The presence of an area of disease-free wall was associated with lower lumen gain after intervention (2.13 ± 1.26 mm² for disease-free wall vs 3.59 ± 1.51 mm² for no disease-free wall, p < 0.001). Also, lumen enlargement after balloon angioplasty was obtained by different mechanisms according to the pres-

![Figure 5](image-url)  
**FIGURE 5.** Left panel, comparison of the lumen gain by ultrasound after balloon angioplasty in patients with a lesion with a remnant arc of disease-free wall (DFW) and in patients without a disease-free wall (No-DFW). Right panel, relative change in plaque reduction (Δ P+M-A) and wall stretch (Δ EEM-A) for the final lumen gain in these 2 groups of patients.

![Figure 6](image-url)  
**FIGURE 6.** Left panel, comparison of the lumen gain by ultrasound after balloon angioplasty in patients with an eccentric plaque (ECC) and in patients with concentric plaques (CONC). Right panel, relative change in plaque reduction (Δ P+M-A) and wall stretch (Δ EEM-A) for the final lumen gain in these 2 groups of patients.
ence or absence of a disease-free wall (Figure 5). In patients with a disease-free wall, lumen enlargement was achieved mainly by wall stretch (1.68 ± 1.45 mm², 79% of lumen gain) and, additionally, by plaque compression or redistribution (0.45 ± 1.35 mm², 21% of lumen gain). This contrasted with the mechanisms of lumen enlargement when there was no preserved arc of normal wall (wall stretch 1.33 ± 1.85, 37% of lumen gain, plaque compression, or redistribution, and 2.26 ± 2.02, 63% of lumen gain). These differences in the mechanisms and magnitude of balloon dilation were due to the presence of an area of disease-free segment and not the result of plaque eccentricity (Figure 6), since eccentric plaques with or without a disease-free wall had a similar lumen gain after balloon angioplasty when compared with concentric plaques (3.00 ± 1.70 mm² for eccentric plaques vs 2.95 ± 1.34 mm² for concentric plaques, p = NS) and comparable mechanisms of lumen enlargement (wall stretch 1.59 ± 1.75 mm², 53% of the lumen gain for eccentric plaques vs wall stretch 1.36 ± 1.72 mm², 46% of lumen gain for concentric plaques).

**Lumen morphology after balloon dilation:** ICUS detected dissections more frequently than angiography (34 patients [57%] vs 19 patients [32%], respectively, p = 0.01). Additionally, an irregular lumen contour was identified in 21 more patients (35%) with ICUS. The degree of agreement between the 2 techniques for the detection of dissections was low (kappa 0.27) (Table V). Figure 7 is an example of dissection starting at the transition of the normal wall with the atheroma. The dissection rate after balloon dilation was not associated with plaque composition (12 of 26 [46%] for soft plaques vs 22 of 34 [65%] for other types of plaques, p = NS) or with the presence of calcium in the target lesion (28 of 47 [60%] for calcific plaques vs 7 of 13 [54%] for no calcium, p = NS). Likewise, ICUS-determined plaque eccentricity was not associated with a higher likelihood of developing dissection after balloon dilation (24 of 37 [65%] for eccentric plaques vs 10 of 23 [45%] for concentric plaques, p = NS). A nonsignificant larger lumen gain was associated with the presence of wall dissections detected with ICUS after balloon dilation (3.23 ± 1.70 mm² for dissection vs 2.71 ± 1.40 mm² for no dissection, p = NS).

**DISCUSSION**

Until recently, the mechanisms of lumen enlargement after balloon angioplasty were mainly derived from necropsy, animal models, or in vitro studies.13-15 Extrapolation of these data to a clinical setting may be misleading because several biases may occur. For instance, patients dying after balloon angioplasty may have a higher rate of extensive dissections than survivors. Animal
studies of induced atherosclerosis have a preponderance of soft young plaques, different from the more heterogeneous plaque composition found in vivo patients; therefore, different mechanisms of lumen enlargement may operate.\textsuperscript{16}

Despite the high success rate of balloon angioplasty, the same treatment (balloon inflation) is applied to most plaques, irrespective of their histologic composition and morphology. It is appealing to think that new devices may have a higher impact if used on plaque types associated with a lower success rate or high complication rate after balloon dilation.

We found that there are important discrepancies between ICUS and angiography for the correct identification of plaque calcification, plaque eccentricity, and residual plaque burden. All these parameters were underestimated by angiography, and our results are in agreement with others.\textsuperscript{17} Undetected vessel calcification and eccentricity may have an impact on the outcome of some revascularization techniques, such as laser and atherectomy.\textsuperscript{17,18} Therefore, ICUS guidance may be of considerable help in the selection of the most appropriate revascularization device. Importantly, the angiographic unsuspected residual plaque burden\textsuperscript{19} may bear important impact on the renarrowing process.\textsuperscript{20} A recent interim analysis of the Guidance by Ultrasound Imaging for Decision Endpoints trial\textsuperscript{20} identified residual plaque burden by ultrasound as one of the most important predictive factors for restenosis among several angiographic and ultrasound parameters.

**Comparison with previous studies:** Although the first described mechanism of lumen enlargement was plaque compression,\textsuperscript{16} necropsy studies identified plaque dissection as the most significant mechanism.\textsuperscript{16,21} Only recently, ICUS was used to elucidate the mechanisms of lumen enlargement after balloon dilation in vivo.\textsuperscript{22-25} In peripheral arteries, dissections were reported in a high percentage of patients and were selected as the most important mechanism of vessel enlargement secondary to neolumen formation.\textsuperscript{22} However, the relative contribution of this mechanism is more difficult to assess in coronary arteries, because the relatively bulky ultrasound catheters can “tack-up” dissections against the vessel wall, rendering the detection of dissections more elusive. In our study, ultrasound clearly identified wall dissection in 57% of patients, and an irregular lumen contour compatible with small intimal tears in >35% of patients. Therefore, the true incidence of plaque fractures is underestimated even with ICUS, as shown by angioscopy that identifies flaps and dissections in 94% of patients after balloon dilation.\textsuperscript{25} It is possible that plaque fracture is a prerequisite to achieve acute wall dilation, as it has been suggested by necropsy\textsuperscript{16} and ultrasound studies.\textsuperscript{26} In addition, Honye et al\textsuperscript{26} observed a higher restenosis rate in concentric plaques without dissection, suggesting that limited wall dissection can be beneficial for a long-term lumen patency. In our study, wall stretch and plaque compression or redistribution contributed in similar proportions to the final lumen dimensions after angioplasty (43% vs 57%, respectively). Our results are a compromise between those reported by Braden et al,\textsuperscript{24} who identified wall stretch as the major factor responsible (81% of the lumen gain) for lumen gain, or those of Sunjea et al,\textsuperscript{25} who reported plaque reduction as major mechanism of angioplasty (94% of the lumen gain). These discrepancies in the mechanisms of balloon dilation may be in part the result of different plaque morphologies. Although wall stretch is an important mechanism of lumen enlargement, angiography identified that 26% of the potential lumen gain was immediately lost after balloon deflation as a result of the elastic recoil. The only variable related to the magnitude of the elastic recoil was temporary stretch, as already described by others.\textsuperscript{27} The poor correlation between angiographic and ultrasound lumen dimensions after angioplasty\textsuperscript{2} may explain the lack of correlation between plaque composition or morphology and the magnitude of the elastic recoil.

**Influence of plaque composition and thickness on the results of balloon dilation:** Necropsy studies have indicated that eccentric plaques with a disease-free wall are mainly dilated by localized wall stretching.\textsuperscript{16} Our study confirms in vivo that the presence of an area of relatively disease-free wall has considerable impact on the mechanisms of lumen enlargement after balloon angioplasty. Stenotic lesions with a disease-free wall were associated with lower lumen gains after balloon dilation (2.13 ± 1.26 mm\textsuperscript{2} for disease-free wall vs 3.59 ± 1.51 mm\textsuperscript{2} for diseased wall, p <0.001), and this lumen enlargement was mainly obtained by wall stretch (79% of lumen gain) as opposed to plaques without a disease-free wall (37% of lumen gain). Moreover, this phenomenon was specifically related to the presence of a disease-free wall, because eccentric plaques as opposed to concentric plaques did not respond in a different manner after balloon angioplasty. These findings are supported by other studies that demonstrate that lesions with a disease-free wall may be more prone to vasospastic phenomena and higher elastic recoil because they have a preserved segment of media.\textsuperscript{16} However, recoil is most likely the explanation for the lower lumen gain obtained by these plaques, since intracoronary isosorbide dinitrate was given routinely before each ultrasound examination to relieve any abnormal vasomotor tone. These data are in disagreement with necropsy data showing larger lumen gains observed in eccentric plaques after angioplasty.\textsuperscript{21} In postmortem analysis, balloon dilation has taken place before morphometric analysis, so that plaque remodeling and redistribution induced by the barotrauma may have interfered and thereby invalidated the conclusions of these necropsy studies. In our study, plaque thickness and the eccentricity index were measured before balloon dilation.

Dissections after angioplasty generally occur at areas of local high shear stress,\textsuperscript{28} at transitions between normal wall and atheroma\textsuperscript{29} or near deposits of calcium.\textsuperscript{30} Our data did not clearly identify a particular plaque type with a higher likelihood of developing dissection. However, in most of the patients, calcium was present in <25% of the vessel circumference, and the true incidence of plaque fractures is underestimated by ICUS in the coronary arteries.\textsuperscript{25}