Contribution of Localized Calcium Deposits to Dissection After Angioplasty
An Observational Study Using Intravascular Ultrasound

Peter J. Fitzgerald, MD, PhD; Thomas A. Ports, MD, FACC; and Paul G. Yock, MD, FACC

Background. Atherosclerotic plaque fracture and dissection of the arterial wall are frequent concomitants of the balloon angioplasty process. The composition and morphology of plaque within the vessel may be critical in determining the extent of plaque fracture and dissection during balloon angioplasty. To examine this potential association in the clinical setting, we studied patients with intravascular ultrasound imaging after balloon angioplasty.

Methods and Results. Forty-one patients were studied with intravascular ultrasound after angioplasty in both peripheral and coronary arteries. Ultrasound images representing the target lesion cross section were digitized, stored on computer, and analyzed off-line. The presence of intralesional calcium and the relative size of dissection for each lesion was computed. Thirty-one patients (76%) had ultrasound evidence of significant dissection or plaque fracture immediately after balloon dilation. In 23 of 31 (74%) of the lesions, the ultrasound scans showed significant localized calcium deposits within the plaque substance. In 87% of these cases, the dissections were adjacent to the calcific portion of the vessel wall. In addition, the relative size of dissections referenced to the neolumen area were significantly larger (p<0.002) in the calcified vessels (27.5±12.3%) compared with the size of the dissections in lesions without calcium (11.2±5.8%).

Conclusions. The presence of calcium within the vessel wall appeared to be significantly associated with both the location and size of the dissected tissue arm from the vessel wall. These data suggest that localized calcium deposits have a direct role in promoting dissection, presumably by increasing shear stresses within the plaque. (Circulation 1992;86:64-70)

KEY WORDS • intravascular ultrasound • dissection • angioplasty • vessel calcium

Plaque fracture and dissection of the arterial wall are frequent concomitants of the balloon angioplasty process.1-3 Postmortem studies using excised vessels have demonstrated that expansion of the balloon causes shear forces that crack plaque and often separate the plaque from the underlying wall.4-6 Although this sequence may be necessary in many cases for satisfactory enlargement of the arterial lumen, the degree of damage to the arterial wall by the balloon is difficult to control. In some cases, extensive dissection occurs, resulting in acute closure of the vessel.7 In addition, there is increasing evidence that medial injury may accelerate the restenosis process.8-11

The likelihood of dissection has been related to a number of angiographic features, including plaque eccentricity,12 vessel tortuosity or branching,13 length of lesion,14 and the balloon–artery size ratio.15 The presence of calcification in the vessel, as judged fluoroscopically, has been anecdotally linked to dissection.16,17 Recent animal studies have shown that significantly higher balloon pressures are required to dilate arterial segments containing calcium.18 Biomechanical modeling studies of plaque suggest that the presence of calcium is in part responsible for high shear forces during balloon inflation, substantially increasing the likelihood of dissection.19

Although fluoroscopy allows a general impression of the presence of calcification within the vessel wall, it does not provide an accurate description of the amount or location of calcium within the plaque substance. Intravascular ultrasound, on the other hand, generates a very precise image of calcium deposits that are recognized as areas of bright reflections of ultrasound with shadowing beyond.20 We have recently had the opportunity to perform high-resolution, 20- and 30-MHz catheter ultrasound scans in a series of patients undergoing balloon angioplasty. Analysis of this experience reveals a striking association between the occurrence of dissections and the presence of calcium within the plaque. The purpose of the current report is to describe and quantify, for the first time in an in vivo study, the highly significant association between localized calcium deposits and arterial dissection during angioplasty.

Methods

Image Acquisition

Fifty-one patients were studied with intravascular ultrasound after angioplasty at several centers partici-
pating in validating prototype ultrasound imaging catheters (see “Appendix” for list of centers). Intravascular ultrasound imaging was performed using a commercially available ultrasound system (CVIS, Sunnyvale, Calif.). Coronary imaging was performed using a 5F, over-the-wire catheter with a center frequency of 30 MHz. Peripheral images were obtained using either an 8F, 20-MHz catheter or, in the small peripheral vessels, a 5F, 30-MHz catheter. After each intervention, the ultrasound catheter was positioned beyond the dilated segment, and the catheter was slowly withdrawn through the entire length of the lesion. In each case, the time-gain control (TGC) settings were adjusted to provide an optimal dynamic range. In the near field, the TGCs were adjusted to deemphasize the blood speckle. In the far field, the TGCs were set to gradually increase across the region representing the plaque and vessel wall, compensating for signal attenuation throughout the endovascular tissue structures. The complete ultrasound case was recorded on high-quality (sVHS) half-inch videotape for off-line analysis. There were no complications in any of the cases resulting from the placement of the intravascular imaging device.

Image Analysis

For each patient, an image within the dilated lesion was chosen, digitized in eight bits (RasterOps, Santa Clara, Calif.), and stored on computer disk. Because the morphological appearance of dissection can be variable,21 the frame used for analysis was standardized in each case as the cross section in which the dissected tissue arm was clearly observed to originate from the vessel wall. Calcium was identified as an abnormally bright ultrasound region with a corresponding shadow in the far field.

The frames selected in this fashion were recalled from memory and analyzed by a cursor-controlled planimeter. To facilitate tracing of luminal borders, the overall contrast and brightness were optimized with respect to the 600×400-line display monitor. No selective regions were enhanced, nor was image processing performed on the images before analysis. Calibration of each image was accomplished by the cross hair markers on the video image.

Calcium Measurement

Ultrasound evidence of calcium was deemed relevant when its presence was a significant part of the cross-sectional vessel wall. For example, small flecks of calcium <0.25 mm were judged as not being significant to contribute to the overall elasticity of the vessel wall. The arc that calcium contributed to the overall vessel cross section was computed in each case by two observers (P.F., P.Y.). Within the chosen cross section, each end of the calcified segment was identified, and the angle from the geometric center of the catheter was calculated. The result was expressed in degrees.

Dissection Measurement

To compare the extent of dissection between patients, an index was computed that reflected the relative amount of dissected tissue compared with the vessel cross section. For each cross section, the area of the dissected arm was planimetrized and compared with the neolumen cross-sectional area (excluding the plaque arm) and expressed as a ratio (dissection area index, DAI). For each case, DAI was computed from the planimetrized regions by two individuals, and the intraobserver variation for all measurements was determined. Figure 1 shows an arterial dissection after balloon angioplasty and illustrates computation of the DAI. The corresponding schematic overlay demonstrates the relative amounts of dissected plaque arm \(\left(A_p\right)\) occupying the vessel cross-sectional area \(\left(A_L\right)\).

Statistics and Intraobserver Variation

Data are expressed as mean±1 SD for measurements of dissection size and calcium arc for each vessel group. Analysis of the two-sample groups were tested (unmatched \(t\) statistic) for the null hypothesis, which asserts that there is no difference between the population means. A level of significance of \(p<0.01\) was established. Twenty-two ultrasound cross sections from 21 patients were randomly selected from the patients in this study and measured by two individuals. Two mea-
measurements were computed: DAI and calcium arc. Interobserver variability is reported in terms of mean±SD of the difference between each group.

Results

Dissection by Ultrasound

A total of 51 patients were studied with ultrasound after balloon angioplasty. Ten of these cases were judged to be uninterpretable because of poor image acquisition. Reasons for inadequate imaging included 1) inability to scan the entire length of the target lesion (three cases), 2) dilated segment diameter <1.7 mm (four cases), and 3) poor ultrasound signal-to-noise ratio from the prototype catheters (three cases). The remaining 41 ultrasound studies (22 peripheral, 19 coronary) were analyzed for evidence of dissection within the entire dilated segment. Cases with ultrasound evidence of dissection were accepted for this series only when a distinct arm of plaque could be identified to have torn free from the vessel wall with evidence of flow occurring within the dissection area. A total of 31 of 41 scans (76%) met this criterion. Dissections after angioplasty were more apparent (19 of 22 cases) in the peripheral studies compared with the coronary studies (12 of 19 cases). Twenty-four percent (10 of 41) of the cases showed no evidence of dissection by this criterion.

Dissection and Calcium

A total of 31 cross-sectional ultrasound scans showing clear evidence of arterial dissection after angioplasty were analyzed. In 23 of 31 (74%) of these cases, deposits of calcium were located deep within the plaque substance. In one case, a portion of the calcium was contained within the plaque arm itself; in all other cases, the calcium remained with the portion of plaque deep to the tear. There were eight of 31 cases (26%) of clear dissection in our series that occurred within non-calcified plaque. The size of the calcium, measured as the length of the arc represented by the calcium deposit around the vessel wall, was computed for each dissected vessel. The average arc of calcium for all dissected vessels was 86.2±26.8°, or nearly one quarter of the vessel wall cross section. Interobserver variability for this calcium arc measurement showed close agreement. The mean and standard deviation of the difference between the two observers was −1.87±11.39.

In the 41 patients analyzed, 10 patients exhibited no evidence of dissection by ultrasound within the lesion after angioplasty. In this group, three patients did, however, have evidence of calcium within their lesions. In these patients, the arc of calcium within the vessel was significantly smaller than in the dissected vessels (15.2°, 20.1°, and 38.5°, respectively). Figure 2 shows several representative cross-sectional ultrasound images illustrating dissection and/or intimal fractures occurring in lesions without calcium (panels A and B) or in association with localized calcium deposits (panels C–F).

The presence of calcium within the vessel wall appeared to be significantly associated with both the location and size of the dissected tissue arm from the vessel wall. After angioplasty, 87% (20 of 23) of the ultrasound studies with dissection showed calcium positioned on the same side of the vessel wall as the origin.
of the dissected tissue arm. In only three of 20 cases was the calcium located within a portion of wall that was distant from the base of the dissected tissue arm. Figure 3 demonstrates cross-sectional ultrasound images from two cases in which dissection was observed after coronary angioplasty; panels A and B are images of the circumflex and left anterior descending coronary arteries in different patients after angioplasty. The plaque arm extending into the dilated segment is observed to originate from the vessel wall adjacent to a large rim of calcium. In panel A, the relative amount of dissected plaque is 21% compared with the area of the neolumen. Panel B shows 36% of dissected tissue extending into the lumen compared with the neoluminal area.

For the series as a whole, the size of the dissected tissue arm was larger in the calcified vessels compared with the noncalcified vessels. The DAI was significantly greater ($p \leq 0.002$) for vessels with localized calcium deposits ($27.5 \pm 12.3 \%$) compared with vessels without calcium ($11.2 \pm 5.8 \%$). Intraobserver variability testing for this measurement was performed by two blinded individuals. The mean and standard deviation of the difference between observations was $1.39 \pm 3.22$. Figure 4 shows ultrasound images from peripheral and coronary studies after balloon therapy; panel A demonstrates dissection after angioplasty in which the dissected tissue arm occupies 11% of the lumen. In this example, no calcific disease is observed in the vessel wall. Panel B shows a vessel with calcific disease in which the dissected tissue arm occupies a larger percentage (29%) of the lumen after angioplasty. Note in this case that the dissection appears to have fractured near the edges of the calcific rim.

**Discussion**

Plaque fractures, intimal tears, and medial dissections are thought to be important components of the balloon angioplasty process. The type and extent of disruption caused by balloon inflation is a function of the biomechanical properties of the plaque itself. Several in vitro studies have demonstrated that dissections typically originate at regions where a transition occurs between plaque deposition and more normal portions of vessel wall, i.e., at the edge of a plaque accumulation. Richardson et al.\(^9\) used computer modeling to predict the interaction of plaque composition and stress distribution in the formation of intimal tears. Their analysis suggests that high tensile stress within a diseased vessel segment occurs at junctions between tissue types with differing elastic properties, e.g., regions of transition between plaque and normal wall or between areas of soft and calcific plaque.

Intravascular ultrasound is unique among currently available imaging technologies in its ability to provide relatively high-resolution images of the internal components of plaque. This offers the potential for characterizing the types of plaque architecture that may generate high tensile stress and result in severe fracture or dissection. In a preliminary in vitro study using excised plaque from the aorta, Lee et al.\(^23\) demonstrated that intravascular ultrasound can correctly identify plaque types that have significantly different elastic properties.
as quantified by static strain measurements. Leon and coworkers\textsuperscript{17} have addressed the same issue from a clinical standpoint in a preliminary study characterizing the results of balloon angioplasty by intravascular ultrasound imaging. These investigators demonstrated an increased incidence of dissection in lesions characterized as being “hard” on ultrasound scanning.

Our study is the first to specifically associate the location and extent of plaque fractures and dissections to focal calcium deposits within plaque. A high proportion (74\%) of the cases of clearly defined dissections in our series had localized deposits of calcium detected by intravascular ultrasound imaging. In the large majority of these cases (87\%), the dissected tissue arm was in direct apposition to the localized calcification. Although dissection morphology with ultrasound can be quite variable,\textsuperscript{21} a pattern that was common in our series showed the dissected tissue arm tracking along the rim of the calcified portion of vessel wall (Figures 2, 3, and 4).

The current study provides clear evidence that the composition of plaque affects the angioplasty process in the clinical setting. Demer\textsuperscript{18} recently studied the effects of calcification on mechanical response of arteries to balloon dilation. This in vivo study demonstrated significantly larger values of balloon resistance in angiographically apparent calcific segments compared with noncalcified segments, indicating the need for higher balloon pressures within calcific arteries to achieve the same volume expansion. When a balloon is inflated within a lesion, the areas within plaque and vessel wall with the highest gradient of tensile stress are most susceptible to tearing. When the dilating force is applied to plaque with relatively homogeneous elastic properties, the distribution of stress is fairly uniform. Our study suggests that the resultant neolumen contains comparatively smaller cracks and tears within the plaque substance. However, if inelastic components such as calcium are present within plaque, balloon expansion will result in nonuniform energy distribution and lead to the formation of deeper cracks and tears associated with the calcium deposits. This process is shown schematically in Figure 5; the dark arrows indicate the development of high shear forces at the calcium/soft plaque interface during balloon inflation.

The ability to analyze the dynamics of plaque fracture and dissection in the context of angioplasty may be of considerable clinical use. Dissection is the major factor in abrupt closure and the primary acute failure mode of percutaneous transluminal coronary angioplasty.\textsuperscript{7} In addition, there is mounting evidence to suggest that deep subintimal tears may initiate a particularly aggressive restenosis response. In a recent clinicopathological study, Nobuyoshi et al\textsuperscript{9} reported that the degree of intimal proliferation was nearly doubled in patients with dissections extending into media compared with those with tears limited to the intima alone. These data on dissection create a potential dilemma for the angioplasty operator in light of other studies suggesting that
restenosis rates for various catheter devices are reduced when the neolumen created is as large as possible.14

This initial evidence from ultrasound studies on an association between calcium and dissection leaves some important questions unanswered about the clinical significance of localized calcium deposits. It is possible that deep calcium deposits at the intimal/medial border may actually protect against severe medial injury during balloon inflation despite generating large plaque fractures. Dissection planes are established along a path of least resistance, and a barrier such as calcium may retard or deflect a fracture from encroaching deep into the medial layer, thereby decreasing the myointimal response and decreasing restenosis. Theoretically, if the risk of severe dissection or increased restenosis for a given lesion could be predicted on the basis of known mechanical properties of plaque, more judicious selection of balloon sizes and inflation parameters might be made in order to maximize the lumen area without creating deep medial dissections.

Although intravascular ultrasound is potentially suited to provide this type of information in the clinical setting, several important limitations must be considered. In our study, of the 51 intravascular ultrasound cases attempted, 10 of 51 (20%) did not yield sufficient image quality for clinical interpretation. Image quality from the various catheter systems continues to improve at a rapid rate, but the dynamic range of the miniature transducers may not be sufficiently clear to give an accurate assessment of plaque components in all cases. Fortunately, calcium deposits, the most rigid component of atherosclerotic plaque, are the easiest to identify even in poor-quality ultrasound scans. Of greater significance is the fact that current ultrasound catheters are imaged in a plane perpendicular to the catheter tip, so that the catheter must actually be inserted within the lesion in order to be imaged. Catheters presently in clinical trials are in the 3.5–4.8F range, which is significantly larger than standard balloon catheters. The size limitation prevents crossing many tight lesions and potentially subjects those lesions that can be crossed to "dottering" forces. In addition, fewer dissections were observed in the coronary vessels compared with the peripheral vessels. Because of the relatively larger size of the imaging catheter compared with standard angioplasty catheters, it may "prop up" a dissection and potentially hide the presence and/or severity of coronary dissection.24 In larger vessels, the dissection may be sufficiently displaced away from the wall so that a higher number of dissections may be apparent in the peripheral arteries. A third complicating issue is the fact that plaque fracture is a three-dimensional process. The analysis presented here identifies the association between localized calcium and plaque fracture in a set of optimal two-dimensional image planes. Determination of the elasticity and shear forces within the heterogeneous, three-dimensional plaque structure is a significantly more complex problem.

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Appendix

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P J Fitzgerald, T A Ports and P G Yock

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