Vessel, Plaque, and Lumen Morphology after Transluminal Balloon Angioplasty
Quantitative Study in Distended Human Arteries
Ross T. Lyon, Christopher K. Zarins, Chien-Tai Lu, Chien-Fang Yang, and Seymour Glagov

We performed transluminal balloon angioplasty in 24 cadaver and nine amputated limb superficial femoral arteries under controlled experimental conditions. The cadaver arteries were excised, restored to in situ length, redistended, and maintained at 100 mm Hg intraluminal pressure at 37°C throughout the angiographic and dilation procedure and during fixation. The amputated limb arteries were dilated and pressure perfusion-fixed after dilation. Quantitative analysis of cadaver vessels revealed that arteries with prominent atherosclerotic lesions had the same internal elastic lamina (IEL) circumference (15.6 ± 1.0 mm) as those with little or no stenosis (16.8 ± 0.5 mm) but lumen area (8.8 ± 1.7 mm²) was markedly reduced compared to nonstenotic sites (20.0 ± 1.9 mm², p < 0.01). Lesions occupied 49 ± 6% of the area circumscribed by the IEL in cadaver arteries with prominent plaques. After dilatation, lumen areas at stenotic sites were enlarged 43% on histologic sections (12.6 ± 1.8 mm² vs 8.8 ± 1.7 mm², p < 0.01) and 31% as determined by angiography when compared to immediately adjacent nondilated regions. The increased lumen area was associated with splitting of the intima near the edges of the plaque, separation of the edges of the plaque from the media, and stretching of the media and adventitia, often with accompanying rupture of the media. There was no evidence of plaque compression, fragmentation, deformation, or herniation into the media. The detached wedge-shaped edges of the lesions formed flaps projecting into the lumen, resulting in a marked increase in lumen irregularity on cross-section. Dilatation of clinically significant stenoses and completely occluded arteries was accomplished by the same mechanism with fracture of the plaque, separation of the plaque from the underlying artery wall and stretching of the artery wall to create or enlarge the artery lumen.

Although percutaneous transluminal angioplasty by means of balloon dilatation is now widely used clinically to reduce atherosclerotic stenosis or to recanalize totally occluded arteries, the morphologic changes that account for the immediate increase in lumen size are incompletely defined. Some reports assert that plaque splitting is the primary mechanism of dilatation. Other mechanisms that have been proposed to explain the way balloon dilatation relieves arterial stenoses include plaque compression, modeling, or redistribution of plaque components, and dissection of arterial wall layers. These proposed mechanisms are based upon clinical speculation, study of postmortem specimens, and experiments utilizing animal models of atherosclerosis. However, in those experiments using postmortem specimens, it is unclear whether dilatations were performed at physiologic temperatures or during distention at physiologic pressures. These variables are likely to be significant determinants of the rigidity and configuration of atherosclerotic plaques and may therefore profoundly affect the consequences of balloon dilatation. Animal models permit in vivo controlled dilatation and allow the study of lesions at various intervals after angioplasty. However, most experimental lesions are composed largely of lipid-laden macrophages (foam cells) and are therefore significantly different in both composition and consistency from the advanced human atherosclerotic lesions treated by balloon dilatation. In addition, previous investigations on human arteries and in laboratory animals have been based largely on the examination of arteries fixed in the collapsed state. Both qualitative and quantitative estimates of the effects of balloon dilatation angioplasty on such vessels are likely to be deceptive, for marked discrepancies between clinical and morphologic findings have been shown to occur when excised arteries are not studied while distended.

In an effort to gain further insight into the immediate effects of balloon dilatation, we attempted to simulate the conditions prevailing during clinical angioplasty in excised cadaver superficial femoral arteries by restoring the vessel temperature and distention during balloon dilation and
vessel fixation. The quantitative and qualitative findings in cadaver arteries with moderate lesions were compared to qualitative findings after balloon dilation of clinically significant stenoses and occlusions in amputated limbs.

**Methods**

**Cadaver arteries**

Superficial femoral artery segments (n = 24) 15 to 20 cm in length were excised from cadavers (aged 44 to 70 years) within 12 hours of death. Before excision, the adventitia of each artery was marked at reference points placed 10 cm apart. Arteries were then excised, cannulated at each end, suspended in a physiologic buffer solution maintained at 37°C and pH 7.4, restored to in situ length and orientation, and redistended with a physiologic buffer solution at an intraluminal pressure of 100 mm Hg. The inlet cannula was connected to a manifold which enabled passage of a balloon catheter, continuous pressure monitoring, and which permitted switching from the buffer solution to a radiopaque contrast medium (Renografin-60, Squibb and Sons, Incorporated, Princeton, New Jersey) or to a fixative without loss of distending pressure. The distal outlet cannula was fitted with a clamp which provided peripheral resistance and, when opened slightly, allowed intravascular flow. The vessel effluent was collected and visually inspected by transillumination for the presence of tissue fragments, which in a clinical setting could result in distal embolization. After infusion of the radiopaque contrast medium, radiographs were taken in multiple projections in order to identify and record the precise location and luminal configuration of the atherosclerotic lesions.

Intraluminal balloon dilatation was then performed at selected sites by passing an angioplasty balloon catheter over a guide wire to the approximate site of greatest narrowing, and inflating the balloon to 4 to 6 atm. pressure for one minute. Selection of balloon size for dilating stenoses or occluded vessels was made by one of the authors (C-FY), an experienced radiologist, to correspond to sizes used clinically. In these instances, balloon diameters were selected so that the maximal balloon diameter was equal to the maximum apparent vessel diameter away from the stenoses. In vessels without stenotic lesions, balloons with diameters 2 to 3 mm larger than vessel lumens as judged by angiography were chosen. Radiographs were again taken during balloon dilatation to record the precise location of the balloon with respect to the atherosclerotic lesion.

After dilatation, the balloon catheter was removed and multiple projection angiograms were repeated (Figure 1). The vessels were then fixed by replacing the contrast medium and the surrounding fluid with 3% buffered glutaraldehyde for 45 minutes while intraluminal pressure was maintained at 100 mm Hg. Based upon the angiographic documentation of the location of the balloon catheter within each vessel, transverse histologic sections of each vessel were taken proximal, through, and distal to the dilatation sites and these were processed by the usual paraffin embedding technique. Sections 7 μm in thickness were stained with hematoxylin and eosin, Weigert-Van Gieson, and Gomori trichrome-aldehyde fuchsin stains.

Sections were projected onto a digitizing plate coupled to a microcomputer. Contour tracings were made of the lumen, internal elastic lamina, and external limit of the media. Computations were performed to provide values for cross-sectional areas of the lumen, intima or plaque; the area encompassed by the internal elastic lamina (IEL); the circumference and thickness of the media; and the circumference of the IEL. The predilatation lumen cross-sectional area was estimated at dilatation sites by tracing the length of the discontinuous intimal segments excluding the additional length contributed by the angioplastica-

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**Figure 1.** Angiograms of an excised postmortem human superficial femoral artery. A. Before balloon angioplasty; B. During balloon dilatation. C. After completion of dilatation. The vessels have been restored to in situ length, distended at 100 mm Hg pressure and maintained at 37°C. A centimeter scale is at the far left. Markers delineate the segment of the vessel that was dilated. After dilatation the vessel lumen diameter was increased and an intimal flap is seen (arrow).
ration. These combined lengths were used to calculate the predilatation lumen area based on lumen circumference, assuming a circular lumen configuration and minimal stretching of the intimal surface. The dilated areas were also compared to adjacent nondilated vessel segments immediately proximal and distal to the dilatation site to give quantitative values for vessel circumference and medial thickness. The angiograms taken before and after dilatation were inspected for the presence of luminal irregularities consisting of intimal flaps, and the films were assessed quantitatively for changes in lumen size by use of calipers and a metric scale.

A total of 26 dilatations were performed on the 24 cadaver superficial femoral arteries. Of these, 12 were performed in vessels without luminal narrowing on angiograms, 11, in vessels with definite local narrowings, and three, in arteries at sites of complete luminal occlusion.

**Amputation Specimens**

Superficial femoral and proximal popliteal arteries were harvested from nine above-knee amputation specimens immediately after amputation. All vessels were severely diseased and were known by preoperative angiography to be totally occluded in a segment of or in all of the excised length. If no lumen was present at either end of the excised segment, a 2 to 3 cm endarterectomy was performed to allow insertion of the inlet cannula. Radiopaque contrast material was infused and x-rays were taken in an effort to identify a lumen. A guide wire was passed through the occluded segment and a balloon angioplasty catheter was passed over the guide wire and inflated to 4 atm. for 2 minutes. After deflation and removal of the catheter, postdilatation angiography was performed at an intraluminal pressure of 100 mm Hg and the artery was fixed by controlled pressure perfusion as previously described. Multiple histologic cross-sections were taken through the dilatation site to give quantitative values for vessel circumference and medial thickness. The angiograms taken before and after dilatation were inspected for the presence of luminal irregularities. The quantitative results based on computer-assisted contour, and no evidence of medial or adventitial dissection. The quantitative results based on computer-assisted measurements of histologic sections showed that in vessels without atherosclerotic stenosis, balloon dilatation did not result in a significant change in lumen size, vessel circumference, medial thickness, or lumen irregularity. There was no difference in the intimal cross-sectional area between dilated and nondilated areas (see Table 1). Postdilatation angiograms showed no significant changes when compared to predilatation films.

**Arteries without Stenoses**

In cadaver arteries without stenoses, inflation of a balloon 2 to 3 mm larger than the lumen diameter resulted in disruption of the artery wall in 4 of the 12 trials, but no obvious changes in vessel morphology in the absence of mural disruption. When medial rupture occurred, a single disruption of both the intima and media occurred at the same location, and the adventitia was not affected (Figure 2). Disruptions at multiple points about the circumference were not observed. In addition, there was little or no separation of the intima from the media, little change in lumen contour, and no evidence of medial or adventitial dissection. Statistical analysis of quantitative values for vessel circumference and medial thickness showed that in vessels without atherosclerotic stenosis, balloon dilatation did not result in a significant change in lumen size, vessel circumference, medial thickness, or lumen irregularity. There was no difference in the intimal cross-sectional area between dilated and nondilated areas (see Table 1). Postdilatation angiograms showed no significant changes when compared to predilatation films.

**Arteries with Stenoses**

In the 11 arteries with stenoses, balloon dilatation resulted in partial separation of the plaque from the underlying media and stretching and disruption of the artery wall (Figure 3). This effect was observed in 10 of the 11 specimens. The separation of the intima from the media occurred as a cleavage of the lesion from the media at the IEL, starting at one or both lateral edges of the plaque and extending circumferentially toward the thick central portion (Figure 4). The separations on either side of the attached portion of the plaque totaled more than 30° of arc in 8 of the 11 dilated segments, with a maximum separation of 270° in one vessel. The plaque separation extended axially along the length of the dilated portion of the plaque. Plaques were

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<th>Table 1. Quantitative Morphologic Changes in Arteries after Balloon Dilatation</th>
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<td><strong>No lesions (n = 12)</strong></td>
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<tr>
<td>Predilatation</td>
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<td>Lumen area (mm²)</td>
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<td>Area of intimal plaque (mm²)</td>
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<td>Arterial circumference at IEL (mm)</td>
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*Predilatation values are based on measurement of proximal and distal sections.
†Predilatation values are based on measurement of dilated sections.
§Significance was determined using paired Student's t test (‡p<0.01; §p<0.05).
never completely detached from the media and remained adherent at or near the thickest portion of the lesion as well as proximal and distal to the dilated area. Although separated from the media, the plaques appeared to maintain their original crescent-like shapes on cross-section, and were remarkably similar to the lesions seen on sections taken just proximal and just distal to the site of angioplasty. Gross fragmentation of the lesions was not observed on histologic sections or on inspection of fluid flowing from the outlet cannula, nor was there evidence of plaque compression, herniation, or modeling. Rupture of the media occurred in 3 of the 11 dilatations.
of stenotic lesions. No rupture occurred at the central thickness zone where lesions remained attached to the media. The adventitia maintained vessel integrity in all but one instance where adventitial perforation occurred.

The quantitative results in dilated arteries with atherosclerotic narrowing revealed that the predilation estimated lumen cross-sectional area (based on composite intimal circumference) was 8.8 ± 1.7 mm² and increased to 12.6 ± 1.8 mm² after dilatation (p < 0.01). This represents an average increase in lumen cross-sectional area of 43%. In comparing immediately adjacent nondilated locations to dilated segments, arterial circumference (measured at the IEL) was noted to increase from 15.6 ± 1.0 mm to 16.9 ± 0.9 mm (p < 0.05) whereas medial thickness decreased from 0.33 ± 0.03 mm to 0.27 ± 0.2 mm (p < 0.05). The cross-sectional area of intimal plaque was increased in dilated, when compared to nondilated, sections (8.6 ± 1.0 vs 6.1 ± 1.1 mm²). Angiographic observations were consistent with changes observed on histologic cross-sections. Dilatation of stenotic lesions resulted in a 31% increase in lumen size (p < 0.05). Intimal flaps were seen on 36% of these angiograms after dilatation (Figure 1). Angiographic intimal flaps corresponded to pronounced intimal plaque separations seen on histologic sections.

**Amputation Specimens**

All excised superficial femoral arteries were severely diseased throughout their length and were totally occluded at some point. The guide wire could be advanced in all specimens and created a path or channel for introduction of the balloon catheter. Calcified plaques could be seen easily on predilation angiograms but were often obscured by the contrast medium on postdilation angiograms (Figure 5). The guide wire and balloon catheter passed in one

![Figure 5](http://atvb.ahajournals.org/)

**Figure 5.** Pre- and postdilation x-rays of totally occluded superficial femoral artery obtained at amputation. A. Balloon catheter has been passed over a guide wire through the totally occluded segment. Note the calcified plaque and patent distal lumen. Arrows mark the ends of dilating balloon. B. After balloon dilation and removal of catheter. Note enlarged lumen, now filled with contrast. Arrows denote limits of dilatation. Note the continued patency of distal lumen.
of two planes. In arteries with severely stenotic plaque or with plaques occluded by soft thrombus, the guide wire passed through the stenosis or occluding thrombus into the distal lumen. Dilation resulted in rupture of the plaque, separation of plaque from the artery wall, and stretching of the adventitia to enlarge the lumen as noted and described in the controlled study of stenotic arteries (Figure 6). This often resulted in a marked lumen irregularity and subintimal dissection planes and intraluminal filling defects were seen on postdilatation angiograms. The calcified plaques occasionally fragmented but they remained attached to the artery wall.

In arteries that were totally occluded by plaque or by long-standing organized thrombus, the guide wire and balloon did not pass through the plaque but entered a plane between the plaque and the artery wall. This is the same plane surgeons use in operative endarterectomy. Under these conditions, the occlusive plaque did not rupture, but remained intact and undisturbed. The media was usually atrophic or ruptured and the artery wall, composed mainly of adventitia, was stretched to create a lumen (Figure 7). When plaque rupture did not occur, intraluminal filling defects and dissection planes were usually absent, and postdilation angiograms had a smooth contour. The depth of dissection and fracture planes was not always constant when traversing a totally occluded segment (Figure 8). The path of the guide wire was not controllable or predictable in most totally occluded segments. However, the true lumen was usually reentered distal to the occlusion regardless of the level of dissection plane.

Discussion

Excised cadaver superficial femoral arteries are well suited for a controlled, quantitative study of balloon angioplasty because they are prone to severe atherosclerosis and are uniform in size and configuration. Except for the study by Faxon et al., previous morphologic studies on the effects of balloon dilatation have not utilized controlled pressure fixation of specimens. When vessels are fixed in a collapsed state, lumen and vessel contours, tissue relationships, and thicknesses can only be surmised. Controlled pressure fixation, on the other hand, restores vessels to a distended state providing a closer approximation to in vivo dimensions and configurations, and this permits quantitative estimates of these features.

Since it is not possible to examine the same vessel segment histologically both before and after balloon dilatation, lumen size before dilatation was approximated from measurements on the sections of the dilated vessel segments. To accomplish this, we added the length of the discontinuous intimal segments on histologic sections. Assuming that intimal stretching was negligible, we used this value as the predilation lumen circumference. The approximate area of the predilatation lumen was then calculated assuming a circular predilatation contour. These assumptions are justified by other studies which indicate that lumen configuration associated with uncomplicated plaques remains approximately circular under conditions of normal pressure distention; in addition, intimal stretching in atherosclerotic vessels is likely to be small because of the low compliance of fibrous intimal plaques.

Figure 6. Cross-section of a severely stenosed superficial femoral artery obtained at amputation after balloon dilation. The plaque is fractured and disrupted and separated from the underlying artery wall. The media is stretched (arrows) to enlarge the lumen.

Figure 7. Cross-section of a long-standing occluded superficial femoral artery after balloon dilatation. The guide wire and balloon catheter passed in a plane between the plaque and media resulting in an extensive cleavage plane as the artery wall was stretched away from the plaque. There was rupture of the media (*) and stretching of the adventitia (arrows) to enlarge the lumen. There was no plaque disruption.
Morphologic features and quantitative values for vessel IEL circumference, plaque size, medial thickness, and lumen irregularity before balloon dilatation were based upon measurements of immediately adjacent nondilated regions. Thus, dilated vessel segments were compared to immediately adjacent nondilated areas. With these methods we believe that we have arrived at reasonable quantitative and qualitative conclusions concerning the morphologic consequences of balloon angioplasty.

Except for detachment of the plaque edges from the underlying arterial wall, the morphologic features of plaques at the site of dilatation were remarkably similar to those of plaques immediately proximal and distal to the experimental sites. We found no evidence of plaque compression or loss of plaque volume. In fact, the intimal cross-sectional area was greater in dilated sections than in adjacent nondilated areas, reflecting the selection of the most stenotic portions of the artery for dilatation. The plaques maintained their integrity as well as their shapes, and they appeared to be remarkably rigid and cohesive regardless of size. Temperature control is likely to be an important factor in this respect because lipid-laden plaques probably become less compliant and increasingly fragile below normal body temperature.

Increased lumen area after dilatation resulted principally from stretching of the media and adventitia after their separation from the relatively rigid intimal plaque. Intimal rupture at the periphery of the plaque or at its thinnest portion, plaque separation from the underlying media, and medial thinning occurred in all instances where lumen area was increased. Lumen area did not increase in the one instance where separation of the plaque from the media did not occur. Thus, the rigidity and cohesiveness of the fibrocalcific plaque seem to preclude not only lesion redistribution, change in plaque volume, or loss of plaque components, but also an increase in lumen area unless separation of the plaque from the underlying media occurs. We must, therefore, attribute the increase in lumen area mainly to the stretching of the media and adventitia allowed by the release of the media from the noncompliant atherosclerotic plaque. Castaneda-Zuniga et al.1 and Block et al.2 have come to similar conclusions from observations on nonperfusion-fixed human postmortem specimens. Had these specimens been perfusion-fixed, it is likely that the dramatic changes in lumen contour resulting from angioplasty would have been apparent. Separation of the intima at the periphery of the intimal plaque and stretching of the underlying media and adventitia allow separation of the plaque from an underlying media, changing the lumen from a roughly circular to an irregularly shaped contour. Faxon et al.3 have found many of these same features after dilating foam cell lesions in rabbits caused by arterial trauma and hyperlipidemic diets. This suggests that more immature lesions may respond similarly to balloon angioplasty. Separation of the edges of the atherosclerotic lesion from the underlying arterial wall extends axially along the length of the plaque. While this results in lumen cross-sectional irregularity and in extensive dissection planes which can be seen on angiography, it usually does not result in vessel occlusion.

Angioplasty-induced plaque separation is probably attributable to the difference in compliance between the lesion and media. The media and adventitia are stretched by the enlarging balloon while the rigid, incompressible plaque resists deformation and maintains its shape. As a result, shearing forces between the plaque and media are greatly increased as the media is displaced relative to the plaque, and a plane of cleavage develops and undermines...
the edges of the plaque. Since the total arterial wall thickness is greatest at the central portion of the plaque, tangential stress and shear are least in this region. This probably accounts for the persistence of plaque attachment at the thickest areas and separation at its periphery. Greater plaque adhesiveness in more central regions of the plaque could also account for the persistence of attachment at this location. As the media beneath the periphery of the plaque is freed from the lesion, the effective radius of the vessel wall increases and the luminal circumference becomes increasingly defined by the underlying media. The increase in radius results in a corresponding increase in medial and adventitial tangential tension according to the law of La Place (i.e., \( T = Pr \), where \( T \) = the tangential tension, \( P \) = the distending pressure and \( r \) = the radius).

After dilatation, the vessel establishes a new equilibrium with a higher tangential tension that tends to keep the vessel open. Overstretching of the media and medial rupture may be advantageous clinically, resulting in a larger postdilatation lumen size and a reduced tendency to develop spasm on restenosis. This may result in greater long-term patency.

In dilated segments, the newly created luminal surface of the vessel consists of uninvolved intima, the luminal surface of the plaque, and the newly exposed undersurface of the plaque and underlying media. Subsequent endothelial sloughing and the formation of a platelet carpet over the denuded intimal surface have been observed in experimental models.18 Endothelial trauma, exposure of collagen and other thrombogenic plaque and medial wall components, and the instabilities of flow engendered by the partially detached plaque would seem to predispose clinically dilated segments to acute thrombosis. To minimize this complication, heparin and antiplatelet agents are frequently administered to patients after the dilatation procedure. Extensive separation and plaque dissection may allow intermittent or persistent valve-like obstruction of the dilated arterial segment by the freely floating edges of the partially detached plaque. These events may explain a portion of angioplasty failures, and may account for postdilatation variability in ankle pressures often observed during the first few days after successful femoral artery dilatation.20

Dilatation of occlusive lesions which were clinically significant (as evidenced by ischemia to the point of requiring amputation) occurred by a mechanism similar to that demonstrated in the cadaver study. Despite marked calcification of many lesions, histologic sections demonstrated the same features of disruption and stretching. The catheter traversed the occlusion either through a soft occluding thrombus or in a plane between plaque and media or adventitia. The media was stretched and usually ruptured so that vessel integrity had to be maintained by the adventitia. The intimal plane of dissection may also occur between the outer media and adventitia, especially when the media is atrophic. Dissection in this plane may permit dilatation without resulting in significant luminal irregularity. A favorable clinical result depends principally upon reentry of the catheter into the native arterial lumen distal to the occlusive plaque. Dotter2 and Jester and Sinapius8 have demonstrated similar paths of catheter dissection in cadaver arteries by this mechanism and have reported relatively long-term vessel patency in living patients. Faxon et al.3 have likewise shown catheter-induced dissection of experimentally produced obstructing lesions in rabbits. These features may account for the lower clinical success when lesions are completely occluded.

Although the data reported here provide information about the morphologic consequences of balloon angioplasty and insight into the basis for both successful and unsuccessful dilatation of superficial femoral artery atherosclerotic plaques, they do not necessarily correspond to changes encountered with lesions in other vessels such as the coronary arteries. Similar controlled studies should be undertaken utilizing other arteries amenable to treatment by balloon dilatation, since different features and consequences of balloon dilatation may become apparent.

Acknowledgments

The authors thank Agris Siesers and Tom Pooley for their excellent technical assistance and Teresa Kirkpatrick for preparation of this manuscript.

References


Index Terms: atherosclerosis • balloon angioplasty • perfusion fixation • artery morphology
Vessel, plaque, and lumen morphology after transluminal balloon angioplasty. Quantitative study in distended human arteries.
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doi: 10.1161/01.ATV.7.3.306

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