Arterial disruption and remodeling following balloon dilatation


We studied immediate and long-term alterations in human atherosclerotic arteries subjected to balloon dilatation. Pathologic material included vessels obtained at amputation or autopsy that had been previously dilated in vivo and cadaver vessels dilated under physiologic pressure and temperature. All vessels were pressure-perfusion fixed, and morphologic observations were correlated with sequential angiograms obtained in 36 patients. Balloon dilatation resulted in disruption of both the plaque and the artery wall, with separation of the plaque from the tunica media, rupture of the tunica media, and stretching of the tunica adventitia to increase lumen cross-sectional area. The intimal plaque protruded into the lumen, accounting for the angiographic appearance of local flaps and dissection channels. Remodeling occurred by readherence of the intimal flaps with little change in plaque volume. Achievement of a sufficient radius of curvature may be necessary to achieve long-term potency. Restenosis may occur because of insufficient dilatation but may also result from extension of dissection channels into nondilated segments of the artery.

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Percutaneous transluminal angioplasty using a balloon catheter has been widely used in the treatment of peripheral arterial occlusive disease. Despite this large experience, the exact mechanism accounting for increase in lumen cross-sectional area remains unclear. Since histologic examination of arteries before and after dilatation in living patients is impossible, the immediate anatomic changes brought about by dilatation must be surmised from studies of postmortem arteries. Some investigators have suggested that atherosclerotic plaques are compressed, flattened, remodeled, fragmented, or redistributed, whereas other investigators have observed overt fractures, dissections, and separation of arterial wall layers. The eventual resolution of such acute changes in the plaque and artery wall is undoubtedly important in determining the long-term results of balloon dilatation.

To better define the morphologic alterations following balloon dilatation, we performed dilatations in excised human arteries under controlled conditions and correlated histologic observations with the in vivo angiographic appearance of lesions immediately after dilatation. The process of arterial remodeling was evaluated with repeat angiography in selected patients and histologic examination of previously dilated arteries obtained during subsequent operative revascularization or amputation.

METHOD

Mechanism of balloon dilatation. The mechanism by which balloon dilatation results in an increase in lumen cross-sectional area was studied in nine amputated limbs and 14 excised cadaver superficial femoral arteries. Amputated limbs were perfused with buffered saline solution through the transected artery until venous effluent was clear. Contrast arteriography was then performed, and selected lesions were dilated in situ by means of a balloon catheter inflated to a pressure of 4 to 6 atmospheres for 1 minute. After removal of the catheter, angiography was repeated. The dilated artery was fixed in situ by perfusion with formalin, and transverse sections were cut proximal, through, and distal to the dilated area. Sections were stained with hematoxylin and eosin and with Weigert,
van Gieson, and Gomori trichrome-aldehyde-fuchsin stains, and the morphologic features of the dilated and adjacent nondilated segments were examined. Eight popliteal and four tibial arteries were dilated.

To better control intraluminal pressure and to avoid morphologic distortion caused by vessel collapse, 14 atherosclerotic cadaver superficial femoral arteries were excised, cannulated, and mounted on a frame to restore original artery length. The artery was immersed in a physiologic buffer solution at 37° C and perfused so that intraluminal pressure was maintained at 100 mm Hg. After the vessel was filled with contrast material, multiple projection x-ray films were obtained to identify atherosclerotic plaques. Dilatation was performed by inflating a 4 mm balloon catheter to 4 to 6 atmospheres for 1 minute. Angiograms were obtained during balloon inflation and after removal of the catheter to precisely localize the site of dilatation. The vessel was fixed while distended with an intraluminal pressure of 100 mm Hg. Sections were cut proximal, through, and distal to the dilatation sites and stained as previously described. The lumen cross-sectional area was measured by means of computer-assisted planimetry.13

**Angiographic changes.** Angiograms of 130 patients undergoing percutaneous transluminal angioplasty at The University of Chicago since 1979 were reviewed. Thirty-six patients underwent repeat angiography that demonstrated the previously dilated lesion or lesions. Nineteen patients had one clearly defined lesion, 10 patients had 2 lesions, 6 patients had 3 lesions, and 1 patient had 4 lesions. These included 12 iliac artery lesions, 33 superficial femoral artery lesions, 10 popliteal artery lesions, and 6 lesions of the infrapopliteal arteries. There were 43 stenoses and 18 occlusions ranging in length from 0.5 cm to 20 cm. The time between balloon dilatation and repeat angiography ranged from 1 day to 39 months. Six lesions were restudied at 1 to 7 days, 21 lesions at 1 to 4 weeks, 4 lesions at 1 to 3 months, 15 lesions at 4 to 6 months, 7

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**Fig. 1.** A, Undilated, pressure-fixed superficial femoral artery with eccentric plaque. B, Immediately adjacent dilated segment with separation of plaque from the tunica media and protrusion of the plaque into the lumen. The media is thinner and has ruptured, and lumen integrity is maintained by the tunica adventitia.
Fig. 2. Dilated superficial femoral artery with rupture of the plaque and separation of the plaque from the tunica media over 270° of the circumference. The media has stretched and ruptured (arrow).

Fig. 3. Dilatation of a totally occluded superficial femoral artery by creation of a channel in the plane between the plaque and the media. The tunica media has ruptured and the tunica adventitia has stretched to encompass the new channel, sequestering the plaque to one side.

Fig. 4. Postdilatation angiogram demonstrating prominent intimal flaps and dissection channels in the iliac artery.

lesions at 7 to 18 months, and 8 lesions at 19 to 39 months.

Morphologic changes. The in vivo morphologic changes resulting from balloon dilatation were studied in 10 previously dilated arteries obtained at operation or amputation. Where possible, the artery was cannulated, perfused, and redistended to restore in vivo configuration prior to fixation. Predilatation and postdilatation angiograms were reviewed, and postmortem angiograms were obtained when possible. Multiple transverse sections were made through nondilated areas as well as through the previously dilated area. The location of each section was indicated on the postdilatation angiogram. The time interval between balloon dilatation and specimen fixation was 2 to 7 days in 4 patients, 3 to 6 weeks in 2 patients, and 3 to 20 months in 4 patients. A total of 15 dilated lesions
Fig. 5. A, Predilatation angiogram demonstrating a 12 cm occluded segment of superficial femoral artery. B, Postdilatation angiogram demonstrating a prominent dissection channel proximally with no dissection and a smaller lumen diameter distally. C, Repeat angiogram 7 months later, demonstrating continued patency proximally but restenosis distally.

Fig. 6. Dilatation of a short-segment occlusion of the superficial femoral artery (A) with restoration of normal lumen caliber and a smooth lumen contour (C). Diameter of the artery, as indicated by calcium in the wall (arrows), is increased. The calculated increase in lumen cross-sectional area was 21.2 mm² whereas artery wall cross-sectional area increased 19.1 mm².
were evaluated, including lesions in 2 iliac arteries, 8 superficial femoral arteries, 4 popliteal arteries, and 1 tibial artery.

RESULTS

Mechanism of balloon dilatation. Both in situ dilatations in amputation specimens and controlled dilatations in excised superficial femoral arteries demonstrated the same qualitative morphologic features. Balloon dilatation of eccentric atherosclerotic plaques resulted in enlargement of lumen cross-sectional area by separation of the plaque from the underlying tunica media and stretching and thinning of the media with frequent medial rupture. When this occurred, lumen integrity was maintained by the tunica adventitia. Protrusion of the plaque into the lumen produced an irregular lumen contour (Fig. 1).

Dilatation of circumferential plaques had a similar mechanism but involved rupture of the plaque at its thinnest portion and more extensive separation of the plaque, resulting in deep clefts between the plaque and the tunica media. These clefts could be seen as longitudinal filling defects on postdilatation angiograms. However, the plaque remained attached to the media at some point around the circumference and also remained attached proximal and distal to the dilated area (Fig. 2). Medial rupture usually occurred, and the enlarged lumen was contained by the stretched tunica adventitia. In instances where medial rupture did not occur, increase in lumen cross-sectional area was smaller or absent. There was no morphologic evidence of plaque compression, molding, fragmentation, or herniation.

Dilatation of occluded vessels was accomplished by dissection in a plane between the plaque and tunica media, rupture of the media, and stretching of the tunica adventitia to encompass the new channel (Fig. 3). Such a process did not result in clefts and protruding flaps into the lumen. In some instances, the guidewire dissected in a plane between the media and adventitia to create a new channel. In vessels occluded by a central thrombotic core, the guidewire frequently
passed through the original lumen. Under these circumstances, dilatation often resulted in intimal flaps that protruded into the lumen, paralleling the end result of dilatation of stenotic vessels.

**Angiographic changes.** Lumen contour irregularities with dissection channels and intimal flaps were visible on 66% of postdilatation angiograms (Fig. 4). The initial clinical success rate and subsequent restenosis rate did not appear to be related to the presence, absence, or size of the flaps. However, distal extension of the intimal flap to previously patent segments of artery was often associated with subsequent stenosis of the distal artery (Fig. 5).

Frequently, totally occluded segments could be dilated with restoration of normal lumen caliber but without flap formation. When calcification of the artery wall permitted measurement of wall diameter, the increase in lumen cross-sectional area, calculated from diameter changes, was similar to the increase in external artery cross-sectional area (Fig. 6). This supports the theory that the most important mechanism is artery dilatation, rather than plaque compression.

Remodeling of intimal irregularities was observed on follow-up angiograms as early as the third day, with shortening of dissection channels and smoothing of the lumen contour. By 1 month, intimal flaps were rarely seen. If dilatation achieved substantial initial increases in artery diameter, remodeling of extensive intimal flaps frequently resulted in a smooth contour and long-term patency (Fig. 7). In general, dilatations that did not result in major increases in lumen diameter were associated with a high restenosis rate.

**Morphologic changes.** The five specimens examined within 1 week of dilatation all demonstrated both fracture of plaques and dissection channels between the plaque and tunica media (Fig. 8). In three cases the media was thick and intact, and there was no evidence of rupture of the media or stretching of the artery wall. However, extensive separation of the plaque from the media was present.

Late evidence of intimal plaque disruption could be seen on sections as long as 20 months after dilatation. Organized thrombus and granulation tissue were seen at the site of medial disruption in a previously totally occluded artery that had remained patent for 4 months after dilatation and that thrombosed 1 month prior to amputation (Fig. 9). There was little evidence of general alteration in plaque configuration other than some curling of the thinnest portions of the separated plaque as it reattached to the artery wall and blunting of the sharp points of the plaque to smooth the contour (Fig. 10). It appeared that continued patency of the vessel depended on persistent overstretching of the layers of the artery wall, rather than plaque disappearance or remodeling.

**DISCUSSION**

Arterial disruption by the balloon catheter appears to be the most important factor in obtaining an increase in lumen cross-sectional area. Catheter dissection in the plane between the plaque and the tunica media has been previously noted, but unlike other investigators, we found no evidence for plaque compression, molding, plaque fragmentation, or loss of plaque substance. Our findings are similar to those of Block et al., who also noted separation of layers of the artery wall. However, in contrast to their findings, we observed no shearing off of plaque substance. The rigidity and inflexibility of fibrocalcific plaques make it unlikely that changes in plaque volume occur to any significant degree in the postangioplasty period.

Acute disruption of the tunica intima and the tunica media permits stretching of the lumen to increase the
Fig. 9. Superficial femoral artery 5 months after balloon dilatation. Note the ends of the previously ruptured plaque (P) with ingrowth of well-vascularized granulation tissue between them. The artery remained patent for 4 months and then thrombosed. The overstretched artery wall (arrow) is now redundant, since the vessel thrombosed and collapsed.

(T = Pr, where T = tangential tension, P = distending pressure, and r = effective radius of curvature). Such an increase in tension would tend to keep the vessel expanded and prevent collapse of the thin adventitial tube. If a sufficient increase in effective radius of curvature is not achieved, the increase in pressure alone may not be enough to prevent collapse of the dilated area.

The chronic alterations in morphology following balloon dilatation resemble the adaptive changes that have been observed in arteries with enlarging intimal plaques. The external diameter of an atherosclerotic artery tends to increase in proportion to increasing plaque volume.4 The eccentric nature of most plaques thus results in an oval rather than a round external wall contour, with sequestration of the plaque to one side (Fig. 1). This natural remodeling minimizes the effect of an enlarging plaque on lumen caliber. The end result of successful balloon dilatation may, to some extent, reflect this process.

Intimal flaps are a common finding on postdilatation angiograms and may explain the marked fluctuation in ankle-brachial pressure index during the first postdilatation week. Flaps may intermittently obstruct the lumen and predispose to early thrombosis. In recognition of this problem, we favor several days of intravenous heparin therapy after transluminal angioplasty. However, the presence of flaps and dissection channels
does not indicate a poor clinical result and, in fact, confirms that a substantial increase in lumen cross-sectional area has occurred. Unfortunately, plaques occasionally rupture and separate in an unfavorable manner, and dissection channels may propagate distally into nondilated areas. This results in plaque separation and lumen irregularity in areas where the effective radius of curvature has not been increased. Flow irregularities and subsequent stenoses often result. It is noteworthy that intimal dissections from transluminal angioplasty are generally longitudinal. This axial orientation differs from that of anastomotic intimal flaps and may account for the remarkably low (<5%) immediate thrombosis rate. In addition, the lack of fragmentation and the continued attachment of the plaque at some point explain the similarly low incidence of distal embolization.

In our clinical series, restenosis as determined by measurement of ankle-brachial pressure index occurs in approximately 50% of patients within 6 months.\textsuperscript{18} This restenosis rate may be lower in clinical series involving predominantly short-segment lesions,\textsuperscript{16} since localized increases in effective radius are more easily attained and the chance of distal propagation of dissection channels is less. Restenosis rates are undoubtedly influenced by systemic risk factors (smoking, diabetes, hyperlipidemia, and hypertension), as well as local factors (the number and length of lesions, overall extent of disease, and adequacy of outflow vessels).\textsuperscript{10,17}

Most investigations of the effects of balloon dilatation in human arteries have been based on arteries fixed in the collapsed state.\textsuperscript{3,5,6,11} Such fixation techniques result in major distortions of artery and plaque morphology, making precise judgments of in vivo morphology difficult if not impossible.\textsuperscript{19} Furthermore, without perfusion fixation, comparisons of in vivo angiography and pathology are subject to substantial error.\textsuperscript{11,12,19} In the current investigation, we attempted to limit these errors by restoring in vivo morphologic features by rewarming and redistending the arteries to normal intraluminal pressures.\textsuperscript{9}

Successful dilatation invariably depends on medial and intimal rupture. Increases in lumen size are reflected by bulging of the adventitia opposite the plaque and increases in external diameter. With time, the irregular lumen surface returns to a rounded and relatively smooth contour (Fig. 11).

Although these findings provide some insights into the reaction of human arteries and fibrocalcific lesions to balloon dilatation, they do not necessarily characterize the variations in response when lesions of different composition are dilated. Furthermore, our long-term
morphologic observations involve only arteries in which circulation failed and amputation or operation was required. Future autopsy series including previously dilated arteries that remain patent will further define the remodeling process following balloon dilatation.

REFERENCES

DISCUSSION
Dr. Henry D. Berkowitz (Philadelphia, Pa.). When Dotter first published his work on angioplasty, he believed that the procedure worked by plaque compression, and he likened it to compressing light, fluffy snow into a firm snowball. This never seemed to be an adequate explanation to vascular surgeons who saw these plaques at first hand and realized that most were firm, unyielding, often calcified masses—for the occasional totally occluded vessels, which often contained a central thrombotic core of soft, gelatinous material.

The authors present convincing evidence that the actual mechanism is just the opposite of what had been originally described—namely that cracking and overdilatation of the vessel wall occur with partial separation of the unyielding plaque and the formation of longitudinal cracks. Eventual remodeling of the vessel wall into a smooth lumen then takes place.

This mechanism certainly helps to explain why certain complications of angioplasty (such as distal embolization), which I think most of us would have expected to occur with a high frequency, do not happen more frequently. This is because the plaque is not sheared, molded, or extruded, as some have suggested, but rather remains unaltered and still fixed to the underlying tunica media over a significant part of its circumference.

This mechanism also explains why postdilatation angiograms can often look so terrible with evidence of dissection, and yet the vessels do not go on to occlude. Of course, as has been explained, this is due to the fact that these cracks are longitudinal rather than transverse. I think this theory is extremely good and certainly does fit in with observations that most of us have seen in practice.

I wish to ask two questions. It was not clear from the manuscript how much you actually dilated or overdilated your specimen. In other words, were the balloon catheters used of the type and of the size that would have been used in a clinical situation, or perhaps could you have overdilated your vessels, causing an artifact?

Second, you mentioned that in the totally occluded vessels the guidewire often passes through the wall of the vessel but can also go through the lumen. Since the central thrombotic core of the lumen is often soft, I wonder what you think happens under that circumstance. Perhaps this is a case where there still might be some compression of the underlying material.

Dr. W. Graham Knox (New York, N.Y.). I am aware of a symposium in Nuremberg, Germany, where some 8000 balloon angioplasty cases were collected. This radiology symposium included Dr. Gruntzig and other interested parties. They reported 2000 angioplasties performed on a superficial femoral artery with a two-year follow-up of approximately 65%. It is apparent, as I said previously before this group, that this procedure is here to stay. The only mark that we all are waiting for is the long-term follow-up.

Pursuant to the work of Drs. Katzen and Chang at St. Vincent's Hospital, which was presented before this group about 3 years ago, we certainly have been aware and most
fearful of the appearance of the dye studies after balloon angioplasty. However, in our follow-up it does seem that remodeling does occur, and it is usually complete sometime between the second and sixth weeks after the angioplasty.

The authors' restenosis rate of 50% within 6 months is a little discouraging but certainly not totally unexpected, and those of you who were exposed to the endarterectomy days of the superficial femoral artery—be it by gas or eversion endarterectomy or coring out the lumen of the vessel with internal strippers—are all aware of the prohibitive rate of occlusion that occurred in these cases unless venous patch grafting was performed, and the situation with these balloon techniques is not much different.

In our experience, we now have a 4-year follow-up in a decent number of cases. We are impressed with the patency rate in the iliac vasculature. We have an 85% patency rate, checked by angiograms and clinical appraisal in this area. In the femoral arteries, patency is about 65%, and I expect that is eventually going to fall significantly.

One thing I would like to stress is that our angiographers do not perform balloon angioplasty on totally stenotic or occluded iliac vessels, and we limit the angioplastic procedures on the femoral artery to lesions of 5 cm or less. That may be the reason we have a slightly improved follow-up rate.

Dr. Christopher K. Zarins (closing). Dr. Berkowitz, we tried to avoid artifacts in our ex vivo experimental study by performing the study in the clinical angiography suite using the same balloon catheters we use in patients. The catheters were inflated to a pressure of 4 to 6 atmospheres and selected for size based on the predilatation angiogram. However, the most important step we took to avoid artifacts was to pay careful attention to maintaining intraluminal pressure at 100 mm Hg throughout the angiographic, dilatation, and fixation phases of the experiment. Marked alteration in vascular morphology occurs when vessels collapse post mortem, and observations on such collapsed arteries may give erroneous impressions. The pertinent question is not whether we produced artifacts, because certainly one can produce artifacts in any experimental situation, but do our findings reflect the in vivo situation? I believe that they do, because the qualitative changes we observed in our experimental study were also present in arteries obtained from patients who had previously undergone dilatation. In addition, the same changes were visible on postdilatation angiograms in most patients, reassuring us that the experimental study was indeed a good reflection of the mechanism that occurs in vivo.

It appears that there are two general patterns seen after dilatation—one is characterized by plaque disruption and protrusion into the lumen with flaps seen on angiography, and the second is one in which the artery wall is pulled away from the plaque, leaving little in the way of flaps and a smooth lumen contour. As Dr. Berkowitz has indicated, a totally occluded vessel can have a relatively small plaque and have the central core filled with organized thrombus. In this situation the catheter can easily pass through the central thrombotic core, in which case the mechanism of plaque rupture and protrusion, as seen with stenotic lesions, may occur, and one may see flaps on the postdilatation angiogram. I do not know what happens to the thrombotic core, but there is no evidence that atherosclerotic plaque can be compressed by the balloon catheter.

With regard to Dr. Knox's comments about the restenosis rate, I would like to note that our 6-month restenosis rate as judged by ankle pressure index changes is high. This may be related to the fact that we are treating extensive lesions and have many end-stage patients treated for limb salvage. However, we have also seen frequent restenosis in patients with short-segment lesions. The most important factor in obtaining a good long-term result may be local disruption of the artery wall so that an adequate increase in lumen diameter is attained to restore normal flow. Flaps and dissection channels may be necessary to achieve such an increase in effective lumen diameter. Unfortunately, one cannot control the artery wall changes precisely, and dissection channels may extend distally to nondilated areas. If the tunica media has not been ruptured to enlarge the diameter, but the plaque has been detached, the conditions may be set up for stenosis at a more distal site. This might later be interpreted not as a failure of dilatation but as a progression of the patient's intrinsic disease. Such questions will need to be looked at more carefully in the future to fully evaluate the role and place of transluminal angioplasty.