LABORATORY INVESTIGATION

ANGIOPLASTY

The mechanism of transluminal angioplasty: evidence for formation of aneurysms in experimental atherosclerosis

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ABSTRACT Quantitative histologic examination (morphometric analysis) of pressure-perfused rabbit atherosclerotic arteries was used to determine whether compression of atheromatous material occurs with transluminal angioplasty. Experimental atherosclerosis was developed in both iliac arteries, with transluminal angioplasty performed on the left iliac while the right iliac served as a nondilated control. Angiography showed equal degrees of luminal narrowing before angioplasty (p = NS). Angioplasty reduced the left iliac narrowing in all animals studied. Morphometric analysis of histologic sections of the left and right iliac arteries disclosed significant differences in luminal and total vessel areas (p < .05), whereas arterial wall (intima and media) areas were similar (p = NS). Dilated areas often demonstrated marked intimal splitting with dissection into the media. At higher magnification, loss of nuclear staining and dense layers of extracellular matrix consistent with stretching were frequently seen. It is concluded that the major mechanism of successful transluminal angioplasty is stretching of the vessel, resulting in localized aneurysm formation. Intimal splitting implies inelasticity of the neointima. No evidence of compression and remodeling of atheromatous material was disclosed in this study. Circulation 68, No. 5, 1136–1140, 1983.

THE MECHANISM by which transluminal angioplasty dilates obstructive atherosclerotic lesions is not completely understood. Originally, it was proposed that the procedure remodeled the atheromatous material in the arterial wall by compressing it into a smaller volume,1–3 with release of its fluid constituents.4 More recently, human postmortem5–7 and in vivo animal studies8–10 investigating the histopathologic effects of transluminal angioplasty suggest an alternative mechanism of intimal splitting, dissection, and stretching rather than compression. In the present study, quantitative analysis of morphologic sections of pressure-perfused dilated and control segments of rabbit iliac atherosclerotic lesions are compared to determine whether compression of the lesion or formation of aneurysm represents the mechanism of successful angioplasty.

Methods

Experimental preparation and design. Atherosclerosis was induced in the aorta and iliac arteries (left and right) of seven 3 kg male New Zealand white rabbits. After thiopental anesthesia, a No. 3F Fogarty catheter was passed retrograde through the left and right femoral artery to 20 cm, inflated to occlude the vessel, and slowly removed as described by Baumgartner.11 Denudation of the aortic and iliac endothelia was ensured by passing the Fogarty balloon twice to 20 cm. All animals were subsequently placed on a 2% cholesterol diet mixed with 10% peanut oil for 6 weeks. Previous studies have shown the development of significant diffuse iliac atherosclerosis in animals placed on this atherogenic diet for this period.9,10 Both iliac arteries were denuded in a similar manner to ensure that angiographic and morphometric comparisons could be made between the dilated (left) and nondilated (right) iliac arteries. After 6 weeks of the atherogenic diet, the animals were anesthetized with thiopental and a No. 5F Swan-Ganz catheter was inserted through the right carotid artery and advanced to the aortic bifurcation. Cineangiography was performed with 3 ml of meglumine diatrizoate (Renografin) as previously described to visualize the left and right iliac arterial lesions.9,10 From a femoral arteriotomy, a Gruentzig intraoperative transluminal angioplasty catheter 2.5 mm in diameter was advanced retrograde up the left femoral artery to the site of greatest iliac stenosis, inflated three times to five atmospheres for 30 sec, and removed.9,10 This balloon size was carefully chosen to closely approximate the size of the least diseased portion of the proximal iliac vessel to avoid overdilation. Repeat angiography was performed immediately after angioplasty, and care was...
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taken to maintain similar position of the image intensifier for both angiograms. A 1 cm grid was positioned at the spine to permit calculation of the actual luminal diameter and to provide correction for magnification differences between films. The following day the animals were killed and the aorta and iliac vessels were surgically removed after perfusion with formalin at 80 mm Hg as previously described.12

Angiographic, histologic, and morphometric analyses. Cineangiograms taken before and after dilation were compared on two side-by-side Vanguard projectors by measuring luminal diameter with calipers. A change in luminal diameter of 0.4 mm (corrected for magnification) could easily be resolved by this technique and was considered significant. Each angiogram was read independently by two angiographers, and discrepancies were resolved by a subsequent simultaneous reading.

With use of the cineangiogram to identify the anatomic location of the dilated and control stenoses, the iliac vessels were examined histologically. Three serial sections 0.5 cm apart were made through the dilated segment of the left iliac artery, while three serial sections taken from the nondilated stenosis of the right iliac artery served as controls. Sections were stained with hematoxylin-eosin or Verhoff-van Gieson-elastin stain and were reviewed by at least two investigators; a consensus reading was made as to the histologic findings. Intimal splitting was defined as a radial tear through the intima, dissection was defined as a circumferential tear along the internal elastic membrane, and stretching was defined as a thinning of the wall with loss of nuclear staining.

Morphometric analysis was performed by the following method: Stained histologic sections were projected onto a Zeiss MOP II digital image analyzer (Carl Zeiss, New York) to allow calculation of the cross-sectional areas of the left and right iliac arterial lumina and walls (neointima plus media as demarcated by the external elastic lamina). Total vessel cross-sectional area was calculated by addition of the arterial wall and lumen areas. Analysis of variance and unpaired t test were used to determine statistical significance, and a p value <.05 was accepted as significant.

Results

Experimental atherosclerosis. After 6 weeks on the atherogenic diet, all seven rabbits had angiographic and histologic evidence of marked atherosclerotic disease as previously reported.9,10 Their lesions were characterized by marked intimal thickening associated with large accumulations of foam cells. A section from a nondilated right iliac artery used as a control is shown in figure 1.

Angiography. A summary of the individual angiographic results before and after transluminal angioplasty is shown for each animal in table 1. A representative angiogram is displayed in figure 2. The mean luminal diameters of the left and right iliac arteries before angioplasty were similar (1.1 and 1.0 mm, respectively), indicating equal degrees of atherosclerosis. In all seven dilated left iliac arteries a significant increase in luminal diameter was noted after angioplasty. The resultant mean luminal diameter was 2.3 mm, which closely approximated the mean diameter of the more proximal segments with less marked disease (2.5 ± 0.2 mm). All seven dilated left iliac artery narrowings showed a significant increase in luminal diameter after angioplasty. Dissection, defined as an angiographic linear density, was seen in one animal. Angiographic evidence for aneurysm formation was seen in two animals. No evidence of extravasation of dye, catheter perforation, or total occlusion of a vessel after angioplasty was noted. Similar angiographic results of transluminal angioplasty in this experimental preparation have been reported elsewhere.9,10

Pathology. As described previously,9,10 three types of histologic results were seen in the dilated segments. Figure 3 is a representative example photographed at the same magnification as the sample in figure 1. Gross splitting of the thickened intima, dissection along the internal elastic lamina, and thinning and bulging of the media are noted. The incidence and a qualitative assessment of the degree of neointimal splitting, dissection along the internal elastic lamina,

FIGURE 1. Nondilated right iliac control artery. Foam cells predominate in the thickened neointima and media. The slit along the internal elastic lamina is an artifact of histologic preparation. (Original magnification ×50.)
TABLE 1
Angiographic and histologic results

<table>
<thead>
<tr>
<th>Rabbit (control segment)</th>
<th>Right iliac Stenosis before TA</th>
<th>Left iliac Stenosis after TA</th>
<th>Nonstenotic</th>
<th>Histology</th>
<th>Intimal splitting</th>
<th>Dissection</th>
<th>Stretching</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>0.7</td>
<td>2.3</td>
<td>2.5</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>1.8</td>
<td>2.3</td>
<td>2.8</td>
<td>+</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
<td>1.8</td>
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<td>0</td>
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<tr>
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<td>++</td>
<td>++</td>
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</tr>
<tr>
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<td>0.9</td>
<td>0.9</td>
<td>2.3</td>
<td>2.3</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>1.4</td>
<td>1.8</td>
<td>2.3</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>0.9</td>
<td>0.9</td>
<td>2.3</td>
<td>2.5</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Mean</td>
<td>1.0</td>
<td>1.1</td>
<td>2.2</td>
<td>2.5</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>SD</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TA = transluminal angioplasty; + = local splitting, dissection, stretching; ++ = marked changes; 0 = no change.

and stretching are shown in table 1. None of these changes was noted in control segments (figure 1). Morphometric analysis of lumen, arterial wall (intima and media), and total vessel cross-sectional areas are shown in table 2. Analysis of variance of the three sections of each dilated and control segment revealed no significant interanimal or intra-animal variance. There were significant differences in the lumen and total vessel cross-sectional areas between the dilated and nondilated vessels (p < .05), while the arterial wall (intima and media) cross-sectional area was similar in both groups (p = NS).

Discussion

As originally proposed by Dotter and Judkins,1 the mechanism of transluminal dilation was attributed to compression and local redistribution of atheromatous material so that the atheroma functioned as a malleable substance. The compression of the core into a smaller volume occurs presumably by release of its fluid constituents.4 On the basis of histologic studies of transluminal angioplasty in postmortem human coronary, renal, superior mesenteric, and iliac arteries, it was later suggested that intimal splitting rather than compression of the atherosclerotic plaque may be the mechanism of transluminal angioplasty.5-7 Indeed, in vivo studies of atherosclerotic rabbit iliac arteries have demonstrated splitting of the intimal plaque and stretching of the noninvolved portion of eccentric lesions.7-10 In addition, histologic findings in three patients who died within 3 days of transluminal angioplasty provided additional evidence for splitting of atherosclerotic vessels.5 Furthermore, in our recent study on experimental atherosclerosis,10 release of ei-

FIGURE 2. Angiographic example demonstrating symmetrical disease of the left and right iliac vessels before (A), during (B), and after (C) successful angioplasty.

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TABLE 2
Morphometric analysis of iliac vessels

<table>
<thead>
<tr>
<th>Animal artery</th>
<th>Cross-sectional areas (mm²)</th>
<th>Arterial wall</th>
<th>Lumen</th>
<th>Total area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondilated right iliac</td>
<td>1.13 ± 0.56</td>
<td>0.62 ± 0.34</td>
<td>1.76 ± 0.39</td>
<td></td>
</tr>
<tr>
<td>Dilated left iliac</td>
<td>1.35 ± 0.68</td>
<td>1.23 ± 0.46</td>
<td>2.59 ± 0.95</td>
<td></td>
</tr>
<tr>
<td>p = NS</td>
<td>p &lt; .05</td>
<td>p &lt; .05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^Results are presented as mean ± SD.

Neither the lipid or solid contents of atheroma and embolization distally was not found to represent a major mechanism of angioplasty.

In the present study, morphometric analysis of pressure-perfused rabbit iliac atherosclerotic vessels was performed to more precisely determine quantitatively whether compression of the atheroma or stretching of the vessel occurred after angioplasty. The significant difference in the luminal area between dilated and control segments was expected, since angioplasty increased luminal diameter angiographically in all seven animals. Since similar degrees of atherosclerosis were present before dilation, the lack of a difference in arterial wall (intima and media) cross-sectional area indicates that compression of atherosclerotic material did not occur in the animals of the present study. Rather, expansion of the vessel wall to accommodate the increased luminal area with localized aneurysm formation could be demonstrated both qualitatively and quantitatively. We believe that aneurysm is an appropriate description of this vessel expansion after angioplasty because the vessel is abnormal histologically, with the intimal splitting and a circumscribed dilation of the artery. These observations are not the result of sampling error between individual segments, since no significant intra-animal or interanimal variance was found. In addition, since care was taken to use a balloon size that approximated the diameter of the least diseased portion of the proximal vessel, overdistension caused by inappropriate balloon size was avoided. The diagram in figure 4 is a schematic representation of the proposed mechanism of angioplasty, indicating the intimal splitting and expansion of the vessel wall without compression of the atheroma.

The determinants of the extent of splitting and aneurysm formation remain to be established. In a preliminary report in human postmortem coronary arteries, the duration of balloon inflation was found to be an important factor in vessel diameter enlargement. Other factors, such as the pressure or volume of balloon inflation as well as the elasticity of the vessel wall, obviously play a role. If the vessel wall is compliant, lumen enlargement with stretching of the vessel wall and aneurysm formation result. However, if a vessel is inelastic, intimal splitting and/or dissection may result.

That the immediate and long-term effects of intimal

FIGURE 3. Dilated left iliac artery taken at the same magnification as the sample in figure 1. The thickened neointima is fractured and separated from the stretched media, resulting in a larger lumen. (Original magnification × 50.)
splitting may be undesirable is implicated in a case report of a patient dying 2 days after angioplasty. At autopsy, a fractured plaque was found with a dissecting hematoma almost occluding the coronary lumen. Intimal splitting with acute thrombus formation on the disrupted arterial wall may also be the cause of acute coronary occlusion immediately after transluminal angioplasty, as evident in a report of three cases of recanalization of total occlusion after angioplasty with streptokinase. The frequency of deleterious effects secondary to intimal splitting remains to be determined.

In summary, in an experimental preparation of atherosclerosis, morphometric analysis disclosed that dilated iliac arterial segments had significantly larger lumen and total vessel areas without a difference in the arterial wall area (intima and media) when compared with the nondilated iliac vessels. Thus aneurysm formation rather than compression and release of debris appears to be the mechanism of transluminal angioplasty. Further studies are necessary to examine what factors provide the best possible results. Factors such as duration of balloon inflation, pressure, and volume as well as intrinsic vessel wall elasticity need further investigation to gain a better understanding of their contributions to successful angioplasty.

References
2. Leu HJ, Gruentzig A: Histopathologic aspects of transluminal recanalization. In Zeitler E, Gruentzig A, Schoop A, editors: Percu-

FIGURE 4. Longitudinal and cross-sectional reviews of the proposed mechanism of angioplasty.
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