The contribution of plaque and arterial remodeling to de novo atherosclerotic luminal narrowing in the femoral artery

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Background: **Atherosclerotic luminal narrowing is caused by plaque growth and arterial remodeling. In peripheral arteries, a role for constrictive remodeling in luminal narrowing has been recognized, but the impact on lumen decrease has not yet been assessed. We studied to what extent arterial remodeling and plaque formation contribute to luminal narrowing in the superficial femoral artery.**

Methods: **Elderly subjects (n = 79) were studied. Post mortem, pressure-fixed femoral arteries (n = 125) were dissected and divided into 0.5-cm segments (n = 3266). In each cross section, we measured lumen area, plaque area, and the area encompassed by the internal elastic lamina (IEL area). For each artery, the cross section with the least amount of plaque was considered the reference segment. In cross sections with a decrease in lumen area compared with the reference, we determined the contributions of both plaque increase and IEL area change.**

Results: **A decrease in lumen area was found in 2193 cross sections. In cross sections with >50% lumen stenosis, plaque increase (accompanied by IEL area increase) fully explained lumen decrease in 80 of 280 cross sections (29%). In the remaining 200 of 280 cross sections (71%), both plaque increase and IEL area decrease contributed to lumen stenosis. In 57 of 280 cross sections (20%), IEL area decrease was the major determinant of lumen decrease, dominating over plaque increase. In 143 of 280 cross sections (51%), plaque increase was the major determinant, dominating over IEL area decrease.**

Conclusion: **The results of this post mortem study suggest that in a substantial part (20%) of severely stenotic lesions in the femoral artery, constrictive remodeling, not plaque size, is the major determinant of lumen decrease. Further serial studies are needed to confirm these results. (J Vasc Surg 2002;36:1194-7.)**

In atherosclerotic disease, plaque formation is not the only determinant of luminal narrowing. Remodeling of the artery also influences the lumen.[1] Arterial remodeling is a structural change of the arterial size (or cross-sectional area of the artery).[1] Two types of arterial remodeling have been described in de novo atherosclerosis: expansive and constrictive remodeling.[2,3] In expansive remodeling, the vessel enlarges and compensates for lumen obstruction by plaque formation. In constrictive remodeling, paradoxic shrinkage of the artery accelerates luminal narrowing by plaque formation. Both autopsy studies and in vivo observations with intravascular ultrasound scan (IVUS) have revealed that both modes of arterial remodeling are frequently observed phenomenon in atherosclerotic arteries.[1] Arterial remodeling has been observed in various artery types and is now considered an important determinant of lumen stenosis in de novo atherosclerosis.

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In the superficial femoral artery, constrictive arterial remodeling has been observed,[3] but its relative contribution to lumen stenosis remains unknown. In this post mortem study, we determined to what extent plaque formation and arterial remodeling each contribute to de novo atherosclerotic luminal narrowing in the superficial femoral artery.

METHODS

Femoral arteries. Arteries in 79 donated corpses were pressure fixed systemically within 24 hours after death with 4% formaldehyde in situ (pressure, 100 mm Hg + age). Clinical data for these individuals were not available. However, no macroscopic or microscopic histologic signs of intervention were observed in these arteries. After systemic pressure fixation, the part of the femoral artery between 12 cm proximal to the adductor hiatus and 3 cm distal to this hiatus was dissected. The arteries were decalcified with 10% ethylenediamine tetraacetic acid in 5 days. Each artery was cut into 0.5-cm segments. The arteries were placed in a specially designed gauge to avoid oblique cuts through the artery. To visualize the internal elastic lamina (IEL), segments were stained with Lawson's elastic tissue stain and studied with magnification. The entire 0.5-cm segment was stained to exclude changes in morphology from cutting of histologic slices. Microscopic images of the cross sections were recorded on sVHS videotape with a Sony digital videocamera for further image analysis. Histologic sections

Lumen area, IEL area, plaque area, and number of cross sections with IEL area decrease and increase for different categories of lumen stenosis

	Lumen stenosis		
	0 to 25% (n = 1065)	*25% to 50% (n = 848)*	*>50% (n = 280)*
Lumen area (mm^2)	21.8 ± 8.4	15.6 ± 6.0	7.0 ± 4.8*
IEL area (mm^2)	32.1 ± 11.1	28.8 ± 11.1	23.5 ± 11.5*
Plaque area (mm^2)	10.3 ± 6.9	13.2 ± 8.0	16.5 ± 9.5*
IEL area decrease	322/1065 (30%)	489/848 (58%)	200/280 (71%)*
IEL area increase	743/1065 (70%)	359/848 (42%)	80/280 (29%)*

*$P < .001$ among groups with Kruskal-Wallis test for lumen area, plaque area, and IEL area and χ^2 test for prevalences in IEL area decrease and increase.

recorded on videotape were analyzed with a digital video analyzer as described previously.[4] For data acquisition, an IBM PC-based framegrabber (512 × 512 × 8 bits) was used. Data analysis was performed with TCL-image software (Multihouse, Amsterdam, The Netherlands).

Morphometric analysis. Of each cross section, the lumen area and the area encompassed by the IEL (IEL area) were measured. The plaque area was calculated by subtracting the lumen area from the IEL area. Of each artery, the cross section with the least amount of plaque was considered to be the reference, assuming that at this site the artery would have been least affected by atherosclerosis and de novo atherosclerotic arterial remodeling. The morphometric parameters (lumen area, plaque area, and IEL area) of the remaining cross sections were compared with the reference segment. Lumen stenosis of a cross section was defined as the percentage of decrease in lumen area as compared with the reference segment: (1 − [lumen/lumen reference]) × 100%. Compared with the reference segment, the axial changes in plaque area and the IEL area were calculated. In the cross sections with a decrease in lumen area compared with the reference segment, we studied which determinant (plaque area or IEL area decrease) was primarily responsible for lumen stenosis. In cross sections with a decrease in lumen area combined with an increase in IEL area (expansive remodeling), plaque area was considered the only determinant of luminal narrowing. In cross sections in which a decrease in IEL area (constrictive remodeling) and an increase in plaque area both contributed to a decrease in lumen area, we assessed which determinant contributed most to lumen stenosis. If plaque area increase was more than IEL area decrease, plaque increase was considered the main determinant of lumen stenosis. If IEL area decrease was more than plaque increase, IEL area decrease was considered the main determinant of lumen stenosis.

Statistical analysis. Proportions of categorized variables were compared with a χ^2 test. Between groups, continuous variables were compared with a Kruskal-Wallis test. Values are mean ± standard deviation. A *P* value of less than .05 was considered significant.

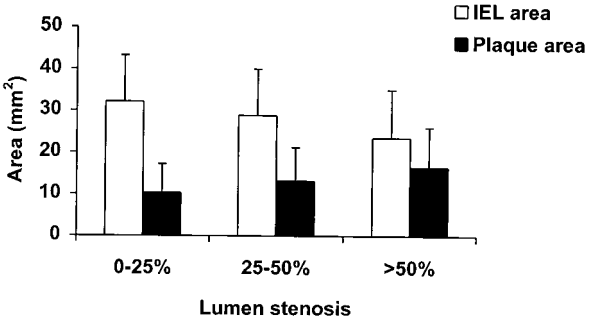

Fig 1. Average value of IEL and plaque area for different categories of lumen stenosis. With increasing lumen stenosis, average plaque area increases and average IEL area decreases.

RESULTS

One hundred twenty-five femoral arteries were dissected from 79 corpses (43 men, 36 women; mean age, 82.1 ± 8.5 years). From these arteries, 3266 0.5-cm segments were obtained (26.1 ± 6.1 per artery). The morphometric parameters of all arteries were: IEL area, 31.5 ± 12.3 mm^2; lumen area, 20.5 ± 9.9 mm^2; and plaque area, 11.0 ± 6.4 mm^2. The morphometric parameters of the reference segments were: IEL area, 27.8 ± 10.8 mm^2; lumen area, 23.5 ± 9.9 mm^2; and plaque area, 4.3 ± 4.2 mm^2.

Compared with the reference, a total of 2193 cross sections showed a decrease in lumen area. Mild lumen stenosis (<25% stenosis) was found in 1065 cross sections, intermediate lumen stenosis (25% to 50%) in 848, and severe lumen stenosis (>50%) in 280 (Table). In comparison of the different groups of lumen stenosis, the average plaque area increased and the average IEL area decreased from mild to severe lumen stenosis (Table; Fig 1).

Of the cross sections with lumen decrease, an increase of IEL area compared with the reference segment was observed in 1182 of 2193 cross sections (54%) and a decrease of IEL area was observed in 1011 of 2193 cross sections (46%). In comparison of the different groups of lumen stenosis, the percentage of cross sections with IEL

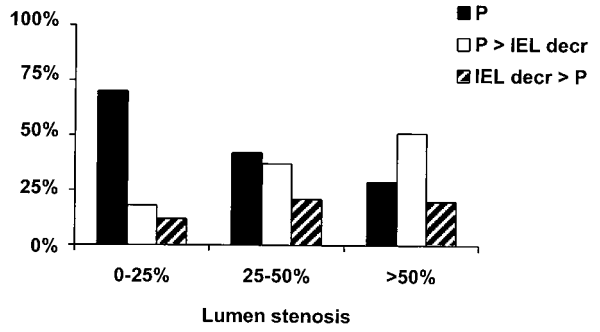

Fig 2. Percentage of cross sections in which plaque increase *(P)* or IEL area decrease was dominating determinant of lumen decrease for different categories of lumen stenosis. *P*, Plaque increase (accompanied by IEL area increase) is entirely responsible for lumen stenosis. *P > IEL decr*, Plaque increase more than IEL decrease and plaque increase and IEL area decrease are both responsible for lumen decrease, and influence of plaque dominates over influence of IEL area decrease. *IEL decr >P*, IEL decrease more than plaque increase and IEL area decrease and plaque increase are both responsible for lumen decrease, and influence of IEL area decrease dominates over influence of plaque increase.

area decrease increased from mild to severe lumen stenosis (Table).

In 743 of 1065 cross sections (70%) with <25% lumen stenosis, plaque increase (accompanied by IEL area increase) fully explained lumen decrease (Fig 2). In this group, IEL area decrease contributed to lumen decrease in 322 of 1065 cross sections (30%). In the group with 25% to 50% lumen stenosis, plaque increase (accompanied by IEL area increase) fully explained lumen decrease in 359 of 848 cross sections (42%). IEL area decrease contributed to lumen decrease in the remaining 489 cross sections (58%), of which it was the main determinant of lumen decrease in 175 cross sections (21%). In the group with severe lumen stenosis, plaque increase (accompanied by IEL area increase) fully explained lumen decrease in 80 of 280 cross sections (29%). In the remaining 71%, IEL area decrease contributed to lumen stenosis. In 57 of 280 cross sections (20%), IEL area decrease was the main determinant of lumen decrease. In 143 of 280 cross sections (51%), plaque increase was the major determinant, dominating over IEL area decrease.

In 109 arteries (87.2%), both IEL area increase and decrease were observed within the same artery. In 15 arteries (12.0%), only IEL area increase was observed, and in one artery (0.8%), only IEL area decrease was observed.

At least one cross section with severe lumen stenosis was observed in 62 arteries (50%). In this group of severe lumen stenosis, a decrease in IEL area compared with the reference segment in at least one cross section was observed in 52 arteries. In 28 arteries of this group, the decrease in IEL area was larger than the increase in plaque area compared with the reference segment in at least one cross section.

Luminal stenosis proximal of the reference segment was determined to assess whether the reference segments were poststenotic dilatations. In the cross sections proximal of the reference segment, no lumen stenosis was found in 36 cross sections (29%), mild lumen stenosis in 71 (57%), intermediate lumen stenosis in 12 (10%), and severe lumen stenosis in six (5%). These percentages were almost similar to the observed percentages for the total number of femoral artery segments.

DISCUSSION

There were three principal findings of this study in the femoral artery. First, in most lesions with severe (>50%) lumen stenosis, IEL area decrease contributed to luminal narrowing compared with the reference segment. Second, in 20% of lesions with severe lumen stenosis, IEL area decrease was the main determinant of luminal narrowing. And third, the prevalence of IEL area decrease increased from mild to severe lumen stenosis.

We observed that IEL area decrease or constrictive remodeling was present in 71% of severely stenotic lesions. In an IVUS study, constrictive remodeling has been reported in 71 of 121 symptomatic lesions (59%) of the femoral artery requiring balloon angioplasty.[5] The different percentage of shrunken lesions between this study and the mentioned IVUS study may be explained by different inclusion criteria. In the IVUS study, stenotic lesions causing clinical syndromes were included, whereas in this study, all severely stenotic lesions were studied. Another explanation could be the difference in definition of constrictive remodeling. In the IVUS study, a change in vessel area of more than 5% was considered arterial remodeling. In this study, we considered every decrease in IEL area to contribute to luminal stenosis. We made this choice because we aimed to study the relative contribution of remodeling to lumen decrease not only in severely stenotic but also in mildly stenotic lesions. In the latter lesions, even a small decrease in IEL area contributed significantly to lumen decrease. In another IVUS study, a decrease of vessel wall area was only found in two of 31 lesions (6%) of the femoral artery that required balloon angioplasty.[6] The explanation for this low prevalence could be that lumen stenosis was less than 50% in all except one lesion. In this study, we observed IEL area decrease compared with the reference segment in 30% of mildly stenotic lesions.

In severely stenotic lesions of the femoral artery, IEL area decrease was the main determinant of lumen stenosis in 20% of lesions. In a recent IVUS study in coronary arteries, constrictive remodeling was found to be the main determinant of lumen stenosis in 143 of 609 lesions (22%) requiring intervention.[7] In another IVUS study in coronary arteries, constrictive remodeling was observed in 26% of stenotic lesions, and in these lesions, reduction of vessel area contributed to 39% of lumen decrease.[8] In patients with stable angina, constrictive remodeling has been reported in 15% of lesions.[9] A decrease in vessel area was the only determinant of lumen stenosis in 21% of these shrunken lesions. Our finding suggests that the substantial

contribution of constrictive remodeling to severe lumen narrowing not only accounts for coronary arteries but also for femoral arteries.

The mechanisms underlying the different arterial remodeling modes are largely unknown. Recent studies revealed that expansive remodeling is frequently accompanied by a more instable plaque phenotype. In an autopsy study in femoral arteries, atherosclerotic lesions with the largest vessel area had a larger lipid-rich core, more inflammatory cells, and less collagen compared with lesions with the smallest vessel area obtained from the identical artery.[10] In a study in coronary arteries, macrophage burden, lipid core size, calcium, and medial atrophy were associated with expansive remodeling.[11] Plaques that were predominantly fibrous were associated with constrictive remodeling.[11] An inflammatory process with the release of matrix metalloproteinases likely plays a role in atherosclerotic remodeling.[1,12] A fibrotic response, comparable with scar contraction, has been suggested to play a role in constrictive remodeling.[1]

Limitations. In this study, all cross sections were compared with a reference segment within the same artery. The cross section with the least amount of plaque was considered as reference site, assuming that at this site the artery was least affected by atherosclerotic disease. However, because of the cross sectional design of this study, we cannot exclude that remodeling also influenced the geometry of the reference site. A reference segment may itself have undergone compensatory enlargement. If this would be the case, a decrease in IEL area compared with the reference segment may represent failure to enlarge. On the other hand, the reference segment might also have undergone arterial wall shrinkage. The latter would result in underestimation of the original IEL area and enhanced contribution of arterial wall shrinkage to luminal narrowing. Previously, we have shown that the femoral artery hardly tapers,[13] which makes it unlikely that these results have been affected by tapering. Post mortem pressure fixation may have induced changes in the tissue both histologically and at the cellular level, which may have influenced geometric parameters compared with the in vivo situation. However, previous studies of formalin fixated segments and in vivo measurements with IVUS revealed comparable remodeling patterns.[3,14] The least diseased segment might be an area of poststenotic dilatation. However, analysis of the segments proximal of the reference segments revealed similar stenosis percentages compared with all other femoral artery segments. This implies that the reference segment had no preference for a location distal of the stenosis sites.

In summary, in 71% of severely stenotic lesions in the femoral artery, a decrease in IEL area compared with the reference segment was observed. The results suggest that in a substantial part of severely stenotic lesions (20%), constrictive remodeling, not plaque size, is the major determinant of lumen stenosis. However, further serial in vivo imaging studies are needed to confirm these results.

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