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Relation of Arterial Geometry to Luminal Narrowing and Histologic Markers for Plaque Vulnerability: The Remodeling Paradox

GERARD PASTERKAMP, MD, PHD,*†‖ ARJAN H. SCHONEVELD, MSC,*‖
ALLARD C. VAN DER WAL, MD, PHD,‡ CHRISTIAN C. HAUDENSCHILD, MD, PHD,§
RUUD J.G. CLARIJS, MD,* ANTON E. BECKER, MD, PHD,‡ BEREND HILLEN, MD, PHD,†
CORNELIUS BORST, MD, PHD, FACC*

Utrecht and Amsterdam, the Netherlands and Rockville, Maryland

Objective. **To relate local arterial geometry with markers that are thought to be related to plaque rupture.**

Background. **Plaque rupture often occurs at sites with minor luminal stenosis and has retrospectively been characterized by colocalization of inflammatory cells. Recent studies have demonstrated that luminal narrowing is related with the mode of atherosclerotic arterial remodeling.**

Methods. **We obtained 1,521 cross section slices at regular intervals from 50 atherosclerotic femoral arteries. Per artery, the slices with the largest and smallest lumen area, vessel area and plaque area were selected for staining on the presence of macrophages (CD68), T-lymphocytes (CD45RO), smooth muscle cells (alpha-actin) and collagen.**

Results. **Inflammation of the cap or shoulder of the plaque was observed in 33% of all cross sections. Significantly more CD68 and CD45RO positive cells, more atheroma, less collagen and less alpha-actin positive staining was observed in cross sections with the largest plaque area and largest vessel area vs. cross sections with the smallest plaque area and smallest vessel area, respectively. No difference in the number of inflammatory cells was observed between cross sections with the largest and smallest lumen area.**

Conclusion. **Intraindividually, pathohistologic markers previously reported to be related to plaque vulnerability were associated with a larger plaque area and vessel area. In addition, inflammation of the cap and shoulder of the plaque was a common finding in the atherosclerotic femoral artery.**

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Rupture of atherosclerotic plaque exposes thrombogenic atheroma to flowing blood and initiates thrombus formation that may lead to coronary occlusion and subsequent myocardial infarction (1–3). Histopathologic research revealed that plaque rupture is often colocalized with the presence of macrophages and T-lymphocytes, suggesting that local inflammation is a provoking factor for plaque rupture (4–6). In addition, a thin cap overlying the atherosclerotic plaque with relatively small amounts of collagen and smooth muscle cells and a large percentage of atheroma within the plaque may predispose to plaque rupture (7). Most of these postmortem studies, however, have been performed in patients who died of myocardial infarction (1,4,5,7). The prevalence in the general population of histopathologic markers associated with plaque rupture has rarely been studied (8). We analyzed 50 atherosclerotic femoral arteries obtained from patients who did not specifically die of cardiovascular disease and related the presence of histopathologic markers for plaque vulnerability to both luminal narrowing (9–11) and local arterial remodeling, that is, compensatory enlargement (12–16) or paradoxical shrinkage (16–23). We hypothesized that histopathologic markers for plaque vulnerability are more frequent in compensatory enlarged segments; this might explain the higher incidence of plaque ruptures at minor angiographic stenoses (9–11).

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Methods

Human femoral arteries. Femoral arteries of 28 donated corpses (17 men and 11 women, age 79.2 ± 6.8 years, history of cardiovascular disease unknown) were pressure fixed with 4% formalin in situ (pressure: age + 100 mm Hg). The femoral arteries were decalcified in 10% EDTA solution (pH 7.4) and divided in 1.0 cm segments. Each 1.0 cm segment was cut in two 0.5 cm segments. The matching cutting faces were used for morphometric analysis and immunologic stains, respectively.

From the Departments of *Cardiology and †Functional Anatomy, Utrecht University Hospital, Utrecht; ‡Department of Cardiovascular Pathology, Academic Medical Center, Amersterdam; §Department of Pathology, Red Cross Holland Laboratory, Rockville, Maryland; the ‖Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands. This study was supported by the Dutch Heart Foundation (94-115). G. Pasterkamp is a Fellow of the Catharijne Foundation, Utrecht University Hospital, Utrecht, the Netherlands.

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Address for correspondence: Dr. G. Pasterkamp, Experimental Cardiology Laboratory, Utrecht University Hospital, Room G02-523, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. E-mail: g.pasterkamp@hli.azu.nl.

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For morphometric analysis, one 0.5 cm segment was stained with Lawson's elastic tissue stain and studied under magnification. Staining of the entire 0.5 cm segment avoided cutting artefacts due to histologic sectioning prior to analysis. Macroscopic images of the cross sections were recorded on VHS videotape with a 3CCD video camera for analysis of geometry. A ruler was used for distance calibration.

Image analysis. Cross sections (n = 1,521) recorded on videotape were analyzed with a digital video analyzer as described previously (24). In each cross section, the lumen area and the vessel area, that is, the area encompassed by the internal elastic lamina, were measured. The plaque area was calculated by subtracting the lumen area from the vessel area.

Selection and staining. In each artery, the 0.5 cm segments that fulfilled one or more of the following criteria were selected for additional staining and analysis: 1) largest lumen area; 2) smallest lumen area; 3) largest plaque area; 4) smallest plaque area; 5) largest vessel area; 6) smallest vessel area. This selection of cross sections with the extreme geometric differences in lumen area, plaque area and vessel area allowed a paired intraarterial, intraindividual analysis of the relation of histopathologic markers for plaque rupture and these six geometric categories.

Two totally occluded femoral arteries as well as four arteries with negligible plaque were excluded from further analysis. Eight selected cross sections in the group with cross sections that contained the least amount of plaque with no plaque or minimal adaptive intimal thickening were also excluded from further analysis together with the corresponding cross sections with the largest plaque load from the same artery. Thirty cross sections selected according to the six categories appeared to be identical for two categories. Thus, a total of 254 cross sections obtained from 50 femoral arteries were selected after quantitative analysis and subsequently stained and analyzed.

Paraffin-embedded segments were serially sectioned at 5 μm thickness and mounted on different microscopic slides.

For histomorphology and morphometry, the sections were stained with picro Sirius red and elastica van Gieson. Adjacent serial sections were used for immunohistochemistry. To visualize the presence of macrophages, smooth muscle cells and T-lymphocytes, a mouse-antihuman CD68 monoclonal antibody (Dakopatts, Denmark), mouse-antihuman alpha-actin monoclonal antibody (Sigma, St. Louis, MO) and anti-CD45RO antibody were used, respectively. To make the CD68-epitope accessible for the anti-CD68 monoclonal antibody, the transverse cross sections were boiled in sodium citrate buffer (10 mM, pH 6.0) for 15 min. Immunohistochemical detection of the preferred epitopes was performed according to the indirect horseradish peroxidase or alkaline phosphatase technique.

Analysis. All stained cross sections were analyzed by three observers (G.P., A.H.S. and R.J.G.C.). Thrombus formation is most likely to occur due to erosion of the cap and rupture of the cap near the shoulder of the plaque (1–6). Therefore, analyses were specifically performed in these regions within the plaque (Fig. 1). The cap was defined as the plaque overlying the atheromatous core or the luminal part of the plaque if no confluent atheromatous core was present. In the event that plaque accumulated along the entire circumference of the arterial wall, the location with the strongest increase of plaque thickness over the circumference was considered representative for the shoulder.

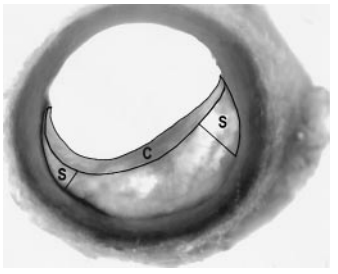


Figure 1. Schematic presentation of regions within the plaque that were analyzed in the present study: cap (**C**) and shoulder (**S**). Shoulder was defined as the area at the periphery of the plaque adjacent to the normal intima beneath the cap of the plaque.

For the stains listed below, cross sections were semiquantitatively arranged in three groups:

- picro Sirius red staining combined with polarized light microscopy: 1) no staining along part of the luminal border; 2) minor or moderately deep staining along the entire luminal border; 3) at least moderate deep staining along the entire luminal border (Fig. 2).
- CD68 positive cells: 1) absent or minor staining with negative or few scattered cells; 2) moderate staining, clusters of cells with >10 cells present; 3) heavy staining, clusters of cells >20 cells strongly dominating over alpha-actin positive cells (Fig. 2).
- Alpha-actin positive cells: 1) minor staining over the entire circumference with absent staining at parts of the circumference of the arterial wall; 2) positive cells along the circumference of the luminal border, with locally minor staining with few scattering cells; 3) large number of positive cells along the entire circumference of the arterial wall strongly dominating over CD68 positive cells (Fig. 3).
- CD45RO positive cells: 1) no cells present; 2) few scattered cells present; 3) scattered cells and clusters >10 cells.

The classification of the cross sections was performed relative to the extent of the plaque area. The cross section was arranged in a category if at least two observers agreed upon classification. In 13% of all cross sections, one observer disagreed with the two other observers upon classification. Never did all three observers disagree upon classification.

The content of the core was analyzed in the cross sections stained with picro Sirius red: if collagen was found to be absent, then that part of the plaque was considered to be atheromatous. The percentage atheroma of the total area of the plaque was visually estimated using the picro Sirius red and polarized light. Two groups were considered based on the percentage of atheroma in the plaque being >40% and <40%

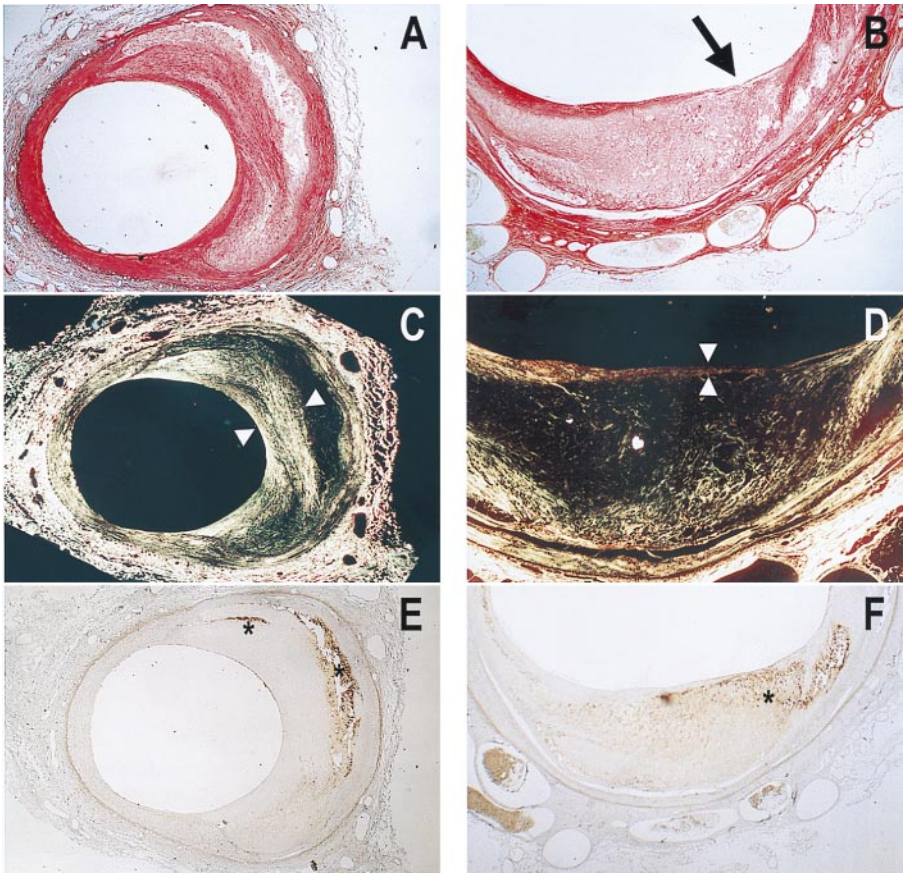


Figure 2. Arterial segment with atheromatous core with heavy staining of picro Sirius red within the cap confirmed with polarized light microscopy (**A** and **C**), and absent staining for CD68 in the cap and moderate CD68 staining in the shoulder and heavy CD68 staining at the base of the plaque (**E**) (**asterick**). Arterial segment with atheromatous core and thin/local absent picro Sirius red staining of the cap confirmed by polarized light microscopy (**B** and **D**). CD68 staining was heavily positive for cap and shoulder (**F**).

(7). In each cross section the presence of a plaque rupture was considered present if a tear was observed with thrombus formation at the surface or beneath the tear. The presence of old thrombus was also looked for by staining for the presence of hemosiderin (Perls' test).

Statistics. Differences in classification for the different stains among groups were calculated using a Wilcoxon matched pairs signed rank test. Each artery was treated as an experimental unit, thus, it was assumed that each artery was independent of the other arteries. The following groups were compared: cross sections with smallest lumen area vs. largest lumen area; smallest plaque area vs. largest plaque area; smallest vessel area vs. largest vessel area. The percentage atheroma within the plaque was compared among groups using a paired *t* test. All values are presented as mean ± standard deviation. A $p < 0.05$ was considered significant.

Results

The mean lumen area, vessel area and plaque area of the cross sections arranged in the six categories are shown in Table 1. On average, differences in lumen area between the cross sections with the smallest lumen area and the cross sections with the largest lumen area (17.4 mm^2, Table 1) could not be fully explained by an increase in plaque area (5.9 mm^2). The difference in vessel area (11.5 mm^2) accounted for the major part (66%) of this difference in lumen area among these two groups.

The cap and/or shoulder of the plaque revealed moderate or heavy staining of CD68 and CD45RO in 33% and 21% of all cross sections, respectively. In the cap of the plaque, positive staining for CD68 and CD45RO positive cells was observed in at least one cross section in 23 (46%) and 14 (28%) of the femoral arteries, respectively. The shoulder of the plaque revealed CD68 and CD45RO positive cells in at least one cross section in 16 (32%) and 14 (28%) of the femoral arteries, respectively. In two cross sections, a rupture of the initial surface was observed. Heavy CD68 positive and CD45RO staining was observed near the rupture site in both cases.

Figures 4–7 show the prevalence of selected cross sections that revealed minor (0), moderate (1) and heavy staining (2) of the shoulder or cap of the plaque for CD68, CD45RO, alpha-actin and picro Sirius red, respectively. Overall, markers that have previously been related to plaque rupture (high number of macrophages, T-lymphocytes and low number of smooth muscle cells, minor collagen staining and large percentage atheroma in the plaque) were observed more often in the cross sections with the largest plaque area and largest vessel area compared with the cross sections with the least amount of plaque and smallest vessel area, respectively. This trend was less evident if the cross sections with the largest lumen area and the smallest lumen area were compared: no

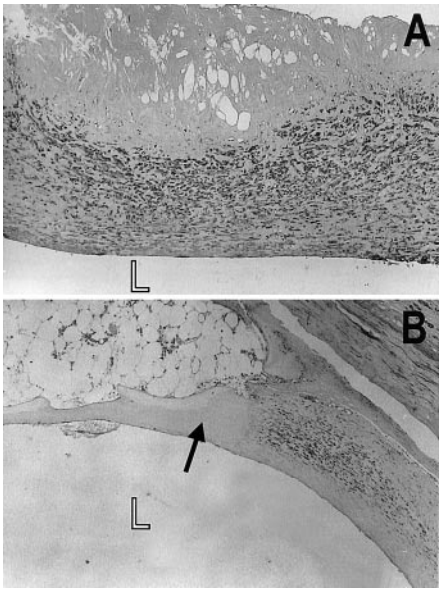


Figure 3. Alpha-actin staining of lipid-rich lesions revealing strongly positive staining of the cap **(A)** and absent staining of that part of the cap overlying the atheromatous core **(arrow) (B)**. **L** = lumen.

increase of parameters for inflammation (CD68 and CD45RO) were observed between cross sections with the smallest lumen area vs. the cross sections with the largest lumen area. The number of cross sections in which the plaque consisted of >40% of atheroma did not differ significantly between the cross sections with the largest lumen areas and the cross sections with the smallest lumen areas (Fig. 8). However, the percentage of plaque area that consisted of atheroma differed strongly between the cross sections with the largest and smallest plaque area and vessel area, respectively (40.0 ± 24.7% vs. 10.5 ± 15.3% and 23.8 ± 24.8% vs. 12.6 ± 15.4%, respectively, both $p < 0.05$).

Discussion

The results of the present study indicate that immunohistologic markers that are often related to plaque rupture, that is, presence of inflammatory cells, lack of smooth muscle cells and collagen and large percentage of atheroma in the plaque,

Table 1. Lumen Area, Vessel Area and Plaque Area of Cross Sections Arranged in the Six Sections

	N	Lumen Area (mm^2)	Vessel Area (mm^2)	Plaque Area (mm^2)
LA ↑	50	31.0 ± 13.7	38.9 ± 16.4	7.9 ± 5.6
LA ↓	50	13.6 ± 8.2	27.4 ± 9.6	13.8 ± 6.8
PA ↑	42	17.7 ± 11.6	41.2 ± 23.3	23.5 ± 14.6
PA ↓	50	27.7 ± 13.0	44.2 ± 23.5	16.5 ± 14.3
VA ↓	50	15.8 ± 8.9	23.8 ± 9.9	7.9 ± 5.2

The largest lumen area LA ↑, the smallest plaque area = PA ↓, the largest vessel area = VA ↑ and the smallest area = VA ↓

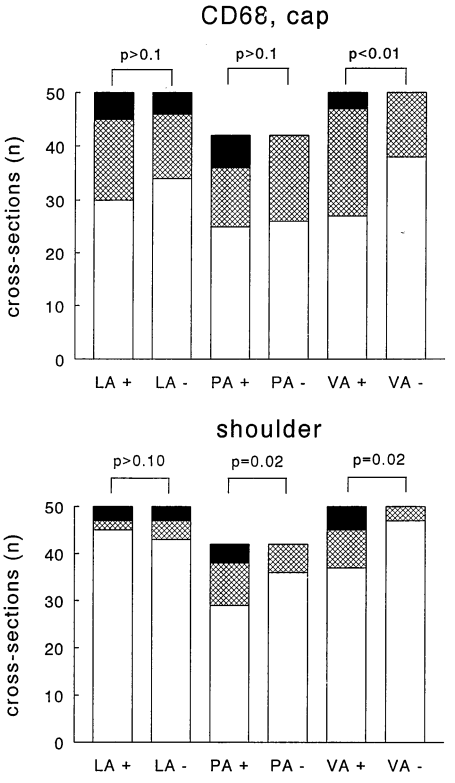


Figure 4. Number of cross sections with absent/minor (0), moderate (1) and heavy (2) staining for CD68 positive cells in the cap **(top panel)** and shoulder **(bottom panel)** of the plaque at the locations with the largest lumen area (LA +), smallest lumen area (LA −), largest plaque area (PA +), smallest plaque area (PA −), largest vessel area (VA +) and smallest vessel area (VA −). **Open bar** = 0; **hatched bar** = 1; **solid bar** = 2.

are associated with a large plaque area and a large vessel area. Within the same arterial segments, differences in lumen area were not consistently associated with changes in plaque architecture. In addition, a larger lumen area was observed in the cross sections with the largest vessel area compared with the cross sections with the smallest vessel area.

The finding that a larger lumen area is often accompanied with a large vessel area confirms previous observations on the impact of the type and degree of remodeling on luminal narrowing: compensatory enlargement of the vessel area may retard luminal narrowing, whereas inadequate enlargement or shrinkage may accelerate luminal narrowing (17–21). On the other hand, plaque vulnerability may be enhanced in enlarged arterial segments compared to nonenlarged segments. Thus, compensatory enlargement may have opposite consequences with respect to the prognosis of atherosclerotic disease: on the one hand, chronic luminal narrowing by plaque formation is retarded while on the other hand the risk of plaque rupture and acute luminal narrowing or occlusion is augmented.

Arterial geometry and markers for plaque vulnerability. Angiographic luminal diameter narrowing is not a predictive value for the onset of plaque rupture with subsequently superimposed thrombus formation (9–11). In a pathologic

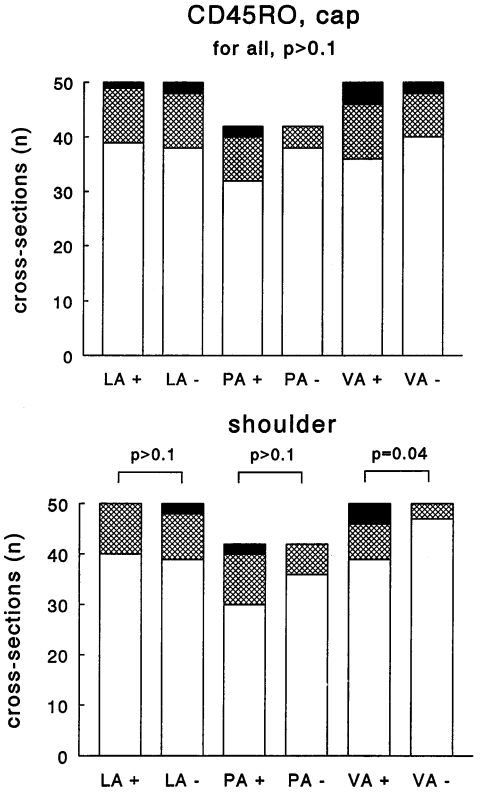


Figure 5. Number of cross sections with absent/minor (0), moderate (1) and heavy (2) staining for CD45RO positive cells. For further explanation see the legend to Figure 4. **Open bar** = 0; **hatched bar** = 1; **solid bar** = 2.

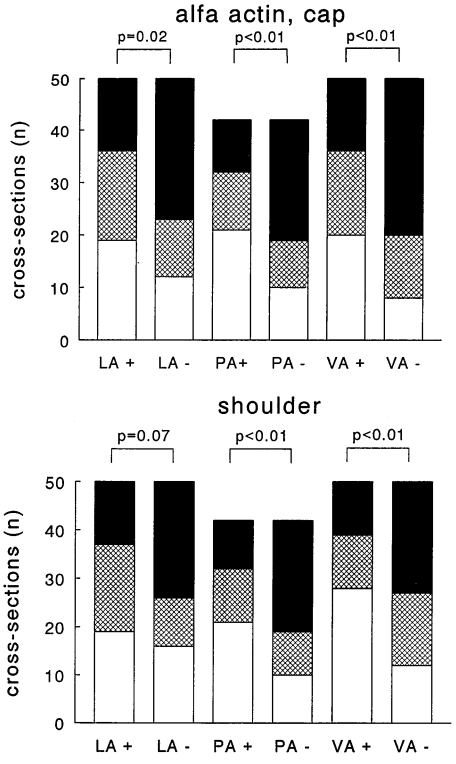


Figure 6. Number of cross sections with absent/minor (0), moderate (1) and heavy (2) staining for alpha-actin positive cells. For further explanation see the legend to Figure 4. **Open bar** = 0; **hatched bar** = 1; **solid bar** = 2.

study, Mann and Davies (25) showed that the size of the lipid core and cap thickness, considered determinants of plaque vulnerability, were not related with the degree of luminal stenosis or absolute plaque size. We also did not find convincing evidence that the lumen area is related with these histologic markers for plaque vulnerability. However, we did find more markers for plaque vulnerability in cross sections that contained the largest amount of plaque. These conflicting observations may be explained by differences in methodology. First, in the present study cross sections with minimal and maximal plaque load obtained from the same arteries were compared, whereas Mann and Davies (25) used a linear regression analysis of pooled cross sections to determine the relation between plaque size and relative core size. Second, Mann and Davies examined advanced coronary plaques of type IV and V, whereas type III lesions might have been included in the present study. Our results suggest that not small but rather large plaques, which may not produce significant luminal stenosis, are the vulnerable lesions that may undergo rupture with subsequent thrombosis. These findings are supported by the hypothesis postulated recently by Fishbein and Siegel (26).

The absent relationship between plaque vulnerability and luminal stenosis is often explained as a statistical phenomenon: the lesions with potentially vulnerable plaques with minor luminal narrowing outnumber the lesions that are hemodynamically significantly narrowed (6,11). The latter, however, cannot explain the absent relation between lumen area and plaque vulnerability observed in this study in which within the same arterial segments a paired analysis was performed between the cross sections with the largest and those with the smallest lumen areas.

The reason that markers for plaque vulnerability are particularly dominant in lesions with a larger vessel area remains unclear. One could argue that as a response to injury, scar contraction may have occurred within the artery leading to the formation of a collagen-rich fibrous plaque with subsequent reduction of arterial diameter. On the other hand, enlarged arterial segments may contain large amounts of necrotic atheromatous core with little fibrous response, but rather enhanced proteolytic degeneration of the media at the base of the plaque. It may be hypothesized, therefore, that enlargement of the vessel area and fibrous cap rupture are initiated by the same mechanisms. Inflammatory responses may lead to the release of matrix degrading enzymes, metalloproteinases (27). These enzymes may degrade matrix components beneath the fibrous cap as well as beneath the medial layer at the base of the plaque, leading to weakening of the fibrous cap and weakening of the arterial collagenous "skeleton," respectively. Subsequently, the former may initiate plaque rupture (27) and the latter may lead to compensatory enlargement or even aneurysm formation (28).

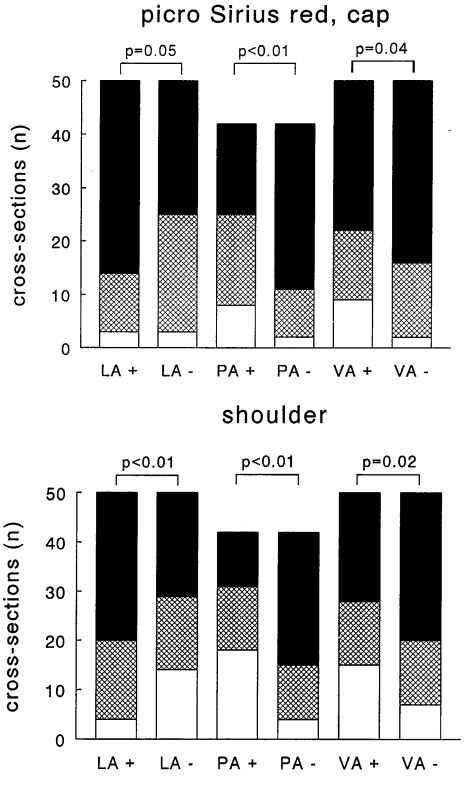


Figure 7. Percentage of cross sections with absent/minor (0), moderate (1) and heavy (2) staining for picro Sirius red. For further explanation see the legend to Figure 4. **Open box** = 0; **hatched bar** = 1; **solid bar** = 2.

Prevalence of inflammation in the atherosclerotic arterial wall. Inflammation has a role in both the initiation of atherosclerosis and the sudden progression of luminal narrowing by plaque rupture (2,4–7). In the present study, femoral artery specimens were investigated from elderly individuals (mean 79.2 years) who were expected to suffer from long-lasting atherosclerotic disease, thereby allowing the study of the prevalence of inflammatory cells within advanced lesions. We assumed that an inflammatory response in these individuals was more likely to be related to progression of advanced atherosclerosis rather than initiation. This is relevant since previous studies have emphasized that the presence of inflammatory cells is related to rapid progression of luminal narrowing and plaque rupture (4–7,29). The present study revealed that in 33% of all cross sections moderate or heavy inflammation was observed within the cap and/or shoulder of the plaque. This number exceeded 50% if the center of the plaque is taken into account also (data not shown). The present results suggest that, although plaque rupture is always accompanied by the presence of inflammatory cells, local inflammation of the cap is a frequently observed feature in atherosclerotic plaques and may therefore not necessarily reflect immediate danger for plaque rupture. Our data support the findings of van der Wal et al. (29) who observed substantial numbers of macrophages and T-lymphocytes, with an increased human leukocyte antigen-DR expression, in atherectomy specimens of patients suffering from notably unstable but also stable angina pectors. The present study, however, clearly shows that apart from the presence of inflammatory cells, other morphologic plaque characteristics considered typical for plaque vulnerability, such as lack of smooth muscle cells and collagen and a large percentage atheroma, were observed more often in cross sections with a large vessel area and large plaque area.

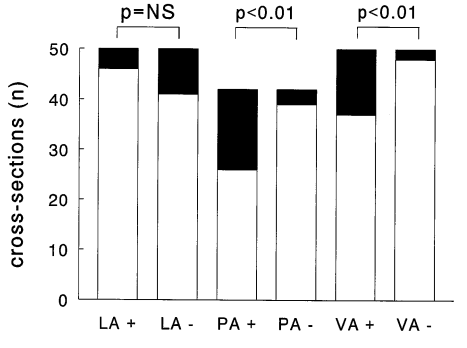
Recent studies have reported that markers for systemic inflammation are raised in patients who have an increased risk for myocardial infarction or stroke (30). We report that local differences in inflammation of the plaque may be observed intraindividually. At least one cross section with moderate or heavy inflammation was observed in 46% of all arteries. Inflammation of the cap or shoulder of the plaque in every cross section under study was observed in five arteries (10%). In the remaining 36% of the arteries, the number of cross sections that showed inflammatory response varied strongly, suggesting that arterial inflammation appears locally rather than generalized.

Potential limitations of this study. In the present study it was assumed that previous observations in coronary arteries on the relation between plaque rupture and the presence of inflammatory cells can be extrapolated to the femoral artery. However, our data obtained from femoral artery segments may not be representative for other arteries affected by atherosclerosis, like the coronary arteries. To study variations in geometry in arterial segments, one should correct for arterial tapering. The femoral artery is ideal to study local geometric alterations because the artery does hardly taper (17) and no major side branches originate. In the coronary artery, in which atherosclerotic remodeling is studied in short arterial segments to rule out the influence of tapering, the results are consistent with the findings in the femoral artery (19–21).

Selection of cross section was based on morphometric criteria. Cross sections with absent or minimal plaque mass, suggestive of adaptive intimal thickening, were excluded from further analysis. However, the group of cross sections that contained the least amount of plaque may still contain slices with only age-related adaptive intimal thickening.

Femoral arteries were studied from elderly individuals who

Figure 8. Number of cross sections in which more or less than 40% of the plaque consists of atheroma. **Open bar** = 0–40%; **solid bar** = >40%.



were expected to suffer from advanced atherosclerotic lesions. The prevalence of inflammatory cells was not studied in younger individuals. Although arterial geometry has been related to markers for plaque vulnerability intraindividually, interindividual variations may have been obscured. Previously, however, we demonstrated that the prevalence of the different modes of atherosclerotic remodeling in this highly aged patient group was comparable with a lower aged population suffering from claudication.

The type of analysis of the stains (semiquantitative) merits careful consideration. Although disagreement was low (13%) among the three observers, consistent overestimation or underestimation of, for instance, the percentage atheroma may have occurred.

In the present study only histoimmunologic parameters have been studied as possible markers for plaque vulnerability in relation to the degree of remodeling. Mechanical factors like local wall stress may also play an important role in plaque rupturing. In the present study, however, these mechanical factors have not been considered.

Intravascular ultrasound. Both plaque area and vessel area, and thereby the degree of local arterial remodeling, can easily be determined using intravascular ultrasound (17–23,31,32). Recently, Nishioka et al. (33) reported that unstable angina is more frequently observed in compensatorily enlarged coronary artery lesions as visualized with intravascular ultrasound. Postmortem, unstable angina is also found to be associated with the presence of inflammation in the vascular wall (5,29). Our data may support the observations of Nishioka et al. (33). Thus, intravascular ultrasound might be a diagnostic modality with predictive value for the risk of acute myocardial infarction.

Conclusions. In the atherosclerotic femoral artery, inflammation was a common finding. Both plaque and vessel area were geometrical determinants of the presence of markers related to plaque vulnerability. The type of arterial remodeling may have a dual impact on luminal narrowing. Compensatory enlargement will retard chronic luminal narrowing, but it might enhance the risk of plaque rupture and, hence, acute luminal narrowing or occlusion. Conversely, paradoxical shrinkage will accelerate chronic luminal narrowing, but it might reduce the risk of plaque rupture and, hence, acute luminal narrowing or occlusion. Future studies using intravascular ultrasound are needed to verify the inferred predictive value for unstable angina and acute myocardial infarction of compensatorily enlarged lesions.

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