Intimomedial Interface Damage and Adventitial Inflammation Is Increased Beneath Disrupted Atherosclerosis in the Aorta
Implications for Plaque Vulnerability

Pedro R. Moreno, MD; K. Raman Purushothaman, MD; Valentin Fuster, MD, PhD; William N. O’Connor, MD

Background—Atherosclerotic plaque progression is frequently accompanied by compensatory enlargement to preserve the lumen. These enlarging plaques develop features of vulnerability, however, leading to disruption and lumen obstruction. This complex transition from compensatory expansion to plaque disruption may not derive solely from progressive intimal disease. Concurrent changes at the intimomedial interface and within the tunica media and adventitia may play a role in plaque instability. We tested this hypothesis by investigating whether interface changes, including internal elastic lamina (IEL) rupture, and medial and adventitial changes, including inflammation, fibrosis, and atrophy, more frequently accompany disrupted than nondisrupted atherosclerotic plaques.

Methods and Results—Computerized planimetry and ocular micrometry were used for systematic quantification of intimal, medial, and adventitial histopathological features in 598 human aortic plaques according to the AHA classification. Disrupted plaques exhibited larger plaque and lipid pool areas (P=0.0001) and a higher incidence of rupture of the IEL (P=0.0001). Medial and adventitial inflammation (P=0.01), medial fibrosis (P=0.0001), and medial atrophy (P=0.0001) were also higher in disrupted plaques. Furthermore, medial thickness was reduced in disrupted plaques (P=0.0001). Logistic regression analysis identified rupture of the IEL as an independent predictor for fibrous cap disruption (P=0.0001).

Conclusions—Compared with nondisrupted plaques, disrupted plaques have an increased incidence of IEL rupture, medial and adventitial inflammation, medial fibrosis, and medial atrophy. These intimomedial interface and adventitial changes may play a role in the natural history of complex atherosclerotic lesions. The interaction between medial and adventitial pathology and the intimomedial atherosclerotic process deserves further investigation. (Circulation. 2002;105:2504-2511.)

Key Words: atherosclerosis ■ plaque ■ inflammation ■ aorta ■ remodeling

In coronary arteries affected by atherosclerosis, plaque disruption occurs more frequently in mildly stenotic than in severely stenotic segments.1-3 Disrupted plaques have larger areas, however, a paradox reflecting compensatory enlargement of the vessel segment to preserve the lumen.4-7 The complex transition from compensatory enlargement to plaque disruption may not derive solely from progressive intimal disease. Rupture of the internal elastic lamina (IEL), allowing expansion of the atherosclerotic process into the tunica media, is a recognized feature of complex atherosclerotic plaques.8-9 Furthermore, adventitial inflammation may also contribute to intimal disease.10,11 Although these features could be seen as a passive secondary change, such evolving pathology at the intimomedial interface, including rupture of the IEL, medial and adventitial inflammation, fibrosis, and atrophy, may actively contribute to the complex phase that characterizes advanced disrupted atherosclerotic plaques.

This study was designed to test the hypothesis that IEL rupture and medial and adventitial changes, including inflammation, fibrosis, and atrophy, are more frequently found in disrupted than in nondisrupted atherosclerotic plaques.

Methods
Histological sections from 598 lesions were taken sequentially at autopsy from 22 human abdominal aortas. Sections were stained with hematoxylin and eosin and with elastic trichrome. Lesions were characterized according to the American Heart Association (AHA) classification,12 as shown in Figure 1. Early (flat) lesions were classified as nonspecific intimal thickening (class I), fatty streak (class II), and preatheroma (class III). Advanced (raised) lesions were classified as atheroma (class IV), fibroatheroma (class Va), calcific (Vb), fibrotic (Vc), and complex (class VI) lesions.12 Advanced lesions were further categorized as nondisrupted (AHA class IV to Vc) and disrupted (AHA class VI). Sections with intimal, medial, or adventitial cutting artifacts were excluded from analysis.

Morphometry
Plaque area and lipid area were microscopically quantified in square millimeters by computerized planimetry by use of the Zedec Quantim software. After processing, lipid appeared as
predominantly solvent-treated empty spaces in stained sections. We defined lipid pool as morphologically distinct spaces composed of clear, needle-shaped cholesterol clefts (representing ghost outlines of dissolved crystals) and/or clear, bubbly, granular, mostly anucleate necrotic debris of foam cells. Taken together, these are light-microscopic characteristics of lipid gruel. Early lesions (flat, no lipid pool) did not undergo plaque or lipid area quantification.

Fibrous cap thickness was quantified in micrometers by manual ocular micrometry. Rupture of the IEL and medial and adventitial changes were identified by ocular microscopy. Although minor discontinuity of the IEL is associated with aging in the human aorta, we defined rupture of the IEL as extensive fracture of the IEL associated with ongoing medial changes, including inflammation, fibrosis, and/or smooth muscle cell atrophy (Figure 2). Inflammation was defined as the presence of ≥25 mononuclear round cells per field in hematoxylin-eosin–stained sections seen with the 40× magnification objective (Figure 3, A and B). The normal human tunica media in the abdominal aorta is composed of 28±1.5 lamellar units, as shown in Figure 3C. Because minor loss of lamellar units (1 to 4) and a decrease in medial collagen also occurs with aging, we defined atrophy as loss of >4 U and/or lamellar collapse (Figure 3D). Fibrosis was defined as increased collagenization within the tunica media (Figure 3E). Medial thickness was also quantified in micrometers by computerized ocular micrometry both at the center and at the peripheral site of the plaque, which is the junction between the plaque and normal intima, also known as the “shoulders” of the plaque (Figure 3F). Central thickness was measured in all lesions. Peripheral thickness was measured only in advanced (raised) lesions.

**Statistical Analysis**

Data are presented as mean±SD. Probability values of *P* <0.05 are considered significant. Multiple group comparisons (planimetry data by AHA classification) were performed by 1-way analysis of variance with the Bonferroni correction. Discrete samples were compared by the Pearson *χ*² test. Gaussian samples were compared by the 2-tailed Student’s *t* test. Logistic regression analysis identified independent predictors of plaque disruption and IEL rupture. The Statistical Package for the Social Sciences (SPSS) 10.0.5 software was used for analysis.
Results

Histological Characteristics of Plaques by the AHA Classification

Histological characteristics of early (class I–III) and advanced (class IV–VI) plaques tabulated according to the AHA classification are shown in Table 1.

IEL changes: Rupture of the IEL was rarely seen in early lesions (0% to 8%) and more frequently seen in advanced lesions (18% to 85%). Rupture of the IEL was highest in class VI, disrupted plaques ($P=0.0001$).

Plaque morphometry: Plaque area was lower in class IV lesions and larger in class VI, disrupted plaques ($P=0.0001$). Lipid area and percent lipid area were lower in class Vc, fibrotic plaques, and larger in class VI, disrupted plaques ($P=0.0001$). Fibrous cap thickness was lower in class VI, disrupted plaques, and larger in class Vc, fibrotic plaques ($P=0.0001$).

Medial characteristics of early and advanced plaques tabulated according to the AHA classification are shown in Table 2.

Medial inflammation was absent in early lesions and frequently seen in advanced lesions. Medial inflammation was lower in class Vc, fibrotic plaques, and larger in class VI, disrupted plaques ($P=0.008$).

Medial fibrosis was absent in class I and II lesions. Medial fibrosis was seen, however, in class III (preatheroma) lesions (20%). Medial fibrosis was larger in class VI, disrupted plaques ($P=0.0001$).

Medial atrophy was absent in early lesions and frequently seen in advanced lesions. Medial atrophy was lower in class Vc, fibrotic plaques, and larger in class VI, disrupted plaques ($P=0.0001$).

Medial thickness (central and peripheral) is shown in Figure 4. Central medial thickness was preserved in type I
and II lesions. Central medial thickness, however, was reduced in type III (preatheroma) lesions. Central medial thickness was lower in advanced plaques (P=0.0001), as shown in Figure 4A. Peripheral medial thickness was similar in advanced lesions (Figure 4B).

Adventitial characteristics of early and advanced plaques tabulated according to the AHA classification are shown in Table 3. Plaque area, lipid area, and percent lipid area were larger in disrupted than in nondisrupted plaques (P=0.01 to 0.0001). Peripheral medial thickness was similar in advanced lesions (Figure 4B).

Adventitial inflammation was rarely seen in early lesions (0% to 3%) and more frequently seen in advanced lesions (22% to 79%). Adventitial inflammation was larger in class VI, disrupted plaques (P=0.003), as shown in Figures 5B and 6.

Adventitial fibrosis and atrophy were absent in both early and advanced lesions.

**Histological Evaluation of Advanced Plaques**

**Disrupted Versus Nondisrupted Plaques**

Histological characteristics of advanced plaques related to the integrity of the fibrous cap are shown in Table 3. Plaque area, lipid area, and percent lipid area were larger in disrupted than in nondisrupted plaques (P=0.0001). Fibrous cap thickness was lower in disrupted than in nondisrupted plaques (P=0.0001). Rupture of the IEL: medial changes, including inflammation, fibrosis, atrophy, and medial thickness were more frequently present in disrupted than in nondisrupted plaques (P=0.01 to 0.0001).

**Plaques With Ruptured IEL Versus Plaques With Intact IEL**

Histological characteristics of advanced plaques related to the integrity of the IEL are shown in Table 4. Plaque area, lipid area, and percent lipid area were larger in plaques with IEL rupture than in plaques with intact IEL (P=0.0001 for all comparisons). Fibrous cap thickness was lower in plaques with IEL rupture than in plaques with intact IEL (P=0.0001). All 3 medial changes, including inflammation, fibrosis, and atrophy, were found more frequently in plaques with IEL rupture than in plaques with intact IEL (P=0.0001 for all comparisons). Central medial thickness was lower (P=0.0001) and peripheral medial thickness was similar in plaques with IEL rupture compared with plaques with intact IEL (P=0.48). Adventitial inflammation was found more frequently in plaques with IEL rupture than in plaques with intact IEL (P=0.01).

**Plaques With Medial Changes Versus Plaques Without Medial Changes**

Histological characteristics of advanced plaques related to medial changes are shown in Table 5.

Medial inflammation: Plaque area and lipid area were larger in plaques with medial inflammation than in plaques without medial inflammation (P=0.0001 and 0.014, respectively). Percent lipid area and fibrous cap thickness were similar, however, in plaques with and without medial inflammation. Rupture of the IEL was found more frequently in plaques with medial inflammation than in plaques without medial inflammation (P=0.0001).

Medial fibrosis: Plaque area, lipid area, and percent lipid area were larger in plaques with medial fibrosis than in plaques without medial fibrosis (P=0.0001). Fibrous cap thickness was significantly reduced in plaques with medial fibrosis compared with plaques without medial fibrosis (P=0.0001). Rupture of the IEL was found more frequently in plaques with medial fibrosis than in plaques without medial fibrosis (P=0.0001).

Medial atrophy: Plaque area, lipid area, and percent lipid area were larger in plaques with medial atrophy than in

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**TABLE 1. Characteristics of Plaques According to the AHA Classification**

<table>
<thead>
<tr>
<th>AHA Classification</th>
<th>No. (%)</th>
<th>RIEL, %</th>
<th>Plaque Area, mm²</th>
<th>Lipid Area, mm²</th>
<th>Lipid Percent, %</th>
<th>FCT, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intimal thickening (I)</td>
<td>55 (9)</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Fatty streak (II)</td>
<td>26 (4)</td>
<td>4</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Preatheroma (III)</td>
<td>92 (15)</td>
<td>8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Advanced lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atheroma (IV)</td>
<td>68 (12)</td>
<td>18</td>
<td>6.7±3.5</td>
<td>2.6±1.9</td>
<td>38±15</td>
<td>198±15</td>
</tr>
<tr>
<td>Fibroatheroma (Va)</td>
<td>164 (27)</td>
<td>26</td>
<td>10.1±5.6</td>
<td>4.2±3.2</td>
<td>40±15</td>
<td>237±210</td>
</tr>
<tr>
<td>Calcific plaque (Vb)</td>
<td>59 (10)</td>
<td>20</td>
<td>11.3±6.5</td>
<td>3.6±3.2</td>
<td>31±26</td>
<td>183±183</td>
</tr>
<tr>
<td>Fibrotic plaque (Vc)</td>
<td>15 (3)</td>
<td>27</td>
<td>11.7±4.7</td>
<td>1.6±1.4</td>
<td>15±14</td>
<td>452±384</td>
</tr>
<tr>
<td>Disrupted plaque (VI)</td>
<td>119 (20)</td>
<td>85</td>
<td>14.1±6.6</td>
<td>7.4±3.8</td>
<td>53±15</td>
<td>34±16</td>
</tr>
<tr>
<td>Total and P value</td>
<td>598 (100)</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

RIEL indicates rupture of the IEL; FCT, fibrous cap thickness.

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**TABLE 2. Medial Changes by the AHA Classification**

<table>
<thead>
<tr>
<th>AHA Classification</th>
<th>Inflammation, n (%)</th>
<th>Fibrosis, n (%)</th>
<th>Atrophy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal thickening (I)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatty streak (II)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Preatheroma (III)</td>
<td>0 (0)</td>
<td>18 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Atheroma (IV)</td>
<td>17 (25)</td>
<td>11 (16)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Fibroatheroma (Va)</td>
<td>30 (18)</td>
<td>37 (23)</td>
<td>36 (22)</td>
</tr>
<tr>
<td>Calcific plaque (Vb)</td>
<td>10 (17)</td>
<td>18 (30)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Fibrotic plaque (Vc)</td>
<td>2 (13)</td>
<td>3 (20)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Disrupted plaque (VI)</td>
<td>42 (35)</td>
<td>65 (55)</td>
<td>81 (68)</td>
</tr>
<tr>
<td>P</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values of central and peripheral medial thickness in micrometers.
plaque thickness was significantly reduced in plaques with medial atrophy compared with plaques without medial atrophy \((P=0.0001)\). Rupture of the IEL was found more frequently in plaques with medial atrophy than in plaques without medial atrophy \((P=0.0001)\). Ad: vential inflammation: There was a trend toward larger plaque area in plaques with adventitial inflammation than in plaques without adventitial inflammation \((11.2\pm6.2 \text{ mm}^2, P=0.07)\). Lipid area was larger in plaques with adventitial inflammation than in plaques without adventitial inflammation \((5.3\pm4 \text{ versus } 3.6\pm3 \text{ mm}^2, P=0.0001)\). Percent lipid area was larger in plaques with adventitial inflammation \((46\pm18\% \text{ versus } 37\pm17\%, P=0.0001)\). Fibrous cap thickness was similar in plaques with adventitial inflammation \((134\pm160 \text{ } \mu\text{m})\) compared with plaques without adventitial inflammation \((160\pm178 \text{ } \mu\text{m})\) \((P=0.2)\).

**TABLE 3. Intimal and Medial Changes in Disrupted and Nondisrupted Plaques**

<table>
<thead>
<tr>
<th>Morphometry</th>
<th>Disrupted (n=119)</th>
<th>Nondisrupted (n=306)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tunica intima</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque area, \text{mm}^2</td>
<td>14\pm6.6</td>
<td>9.7\pm5.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lipid area, \text{mm}^2</td>
<td>7.4\pm3.8</td>
<td>3.6\pm3.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Percent lipid area, %</td>
<td>53\pm15</td>
<td>37\pm18</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fibrous cap thickness, \text{ } \mu\text{m}</td>
<td>34\pm16</td>
<td>226\pm209</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n (%)</th>
<th>n (%)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tunica media</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial inflammation, %</td>
<td>42 (35)</td>
<td>59 (19)</td>
</tr>
<tr>
<td>Medial fibrosis, %</td>
<td>65 (55)</td>
<td>69 (23)</td>
</tr>
<tr>
<td>Medial atrophy, %</td>
<td>81 (68)</td>
<td>59 (19)</td>
</tr>
<tr>
<td>Central thickness, \text{ } \mu\text{m}</td>
<td>281\pm86</td>
<td>306\pm91</td>
</tr>
<tr>
<td>Peripheral thickness, \text{ } \mu\text{m}</td>
<td>393\pm97</td>
<td>408\pm100</td>
</tr>
</tbody>
</table>

Logistic regression analysis identified rupture of the IEL \((P=0.0001)\), lipid area \((P=0.0001)\), medial atrophy \((P=0.015)\), and cap thickness (negative predictor; \(P=0.0001)\) as independent predictors for plaque disruption. Finally, logistic regression analysis also identified plaque disruption \((P=0.0001)\), medial fibrosis \((P=0.0001)\), medial atrophy \((P=0.0001)\), and lipid area \((P=0.032)\) as independent predictors for rupture of the IEL.

**Discussion**

This study was designed to identify pathological changes in the IEL, the tunica media, and the adventitia in early and advanced atherosclerotic plaques according to the AHA classification. Early lesions, such as nonspecific intimal thickening (class I) and fatty streaks (class II), showed preserved IEL, normal tunica media with preserved thickness, and a very low incidence of adventitial inflammation. The preatheroma (class III) had a mild incidence of IEL rupture (8%) with increased medial fibrosis (20%) and decreased medial thickness. Adventitial inflammation was still very low in class III lesions. In contrast, IEL rupture, medial changes, and adventitial inflammation were present in advanced plaques (class IV to Vc) and highest in disrupted (class VI) plaques. Extensive areas of IEL rupture were present in 18% to 27% in advanced plaques and increased to 85% in disrupted plaques. In addition, rupture of the IEL predicted fibrous cap disruption and was associated with an increased incidence of medial inflammation, fibrosis, and atrophy.

Previous studies have shown that structural changes of the intimomedial interface with enlargement of the IEL area and medial atrophy are associated with compensatory enlargement in vulnerable atherosclerotic plaques.\(^5\)\(^-\)\(^7\)\(^,\)\(^14\) In this study, positive remodeling may be inferred from the larger plaque and lipid areas of atherosclerotic lesions. This assumption is justified on the basis of the results of several cross-sectional postmortem and intravascular ultrasound studies.\(^4\)\(^-\)\(^7\)\(^,\)\(^14\) The remodeling response of individual lesions, however, is most frequently defined by a comparison of the lesion site with an adjacent reference site. Recently, Burke et al\(^14\) performed morphometric analysis of coronary lesions with positive
remodeling defined by comparison with a reference site. Ruptured plaques with hemorrhage showed significantly more remodeling than fibrous plaques, erosions, or total occlusions. Furthermore, lipid area and medial atrophy were identified as primary determinants of positive remodeling, suggesting an important association between intimal and medial structures in the process of remodeling.

Medial atrophy was absent in our evaluation of early plaques but present in 13% to 25% of advanced plaques and increased to 35% in disrupted plaques. Inflammatory cells have been studied extensively in late stages of atherosclerotic plaques. Their role in the tunica media, however, is still unclear. Recently, Pasterkamp et al identified increased macrophage infiltration in the intimomedial interface and increased content of macrophage-derived matrix metalloproteinases 2 and 9 in plaques with positive remodeling. Plaques with compensatory enlargement also show markers of vulnerability for disruption, suggesting an association between medial inflammation and plaque disruption. Furthermore, an increased expression of matrix metalloproteinases associated with medial atrophy has been documented in abdominal aortic aneurysms.

Medial atrophy was absent in our evaluation of early plaques but present in 7% to 29% in advanced plaques and increased to 68% in disrupted plaques. Medial thickness was also reduced in disrupted plaques. Medial atrophy is a primary determinant of positive remodeling in advanced coronary lesions, suggesting a possible role for medial atrophy in plaque disruption. The tunica media is composed of a structural element also known as a lamellar unit, described by Wolinsky and Glagov in 1967. The medial lamellar unit is the single structure responsible for wall tension in the mammalian aortic wall. This unit consists of a group of commonly oriented smooth muscle cells invested by a fine meshwork of collagen fibers surrounded by elastic fibers. Medial lamellar units provide significant mechanical strength to the vessel wall, with average tangential tension of 2000 dynes/cm, regardless of species. Therefore, medial thickness is a major determinant of vessel wall circumferential stress. Alterations of biomechanical forces may play a significant role in plaque instability. Plaque disruption occurs when forces acting on the vessel wall exceed its tensile strength. Thus, the loss of smooth muscle cells with

Figure 5. Adventitial inflammation in early and advanced atherosclerotic plaques. A, Bar graph showing incidence of adventitial inflammation in early plaques and advanced plaques. Early plaques are shown in blue, advanced nondisrupted plaques in green, and advanced disrupted in red. B, Bar graph showing adventitial inflammation in advanced, nondisrupted (green), and disrupted plaques (red).

Figure 6. Histological examples of tunica adventitia from advanced lesions showing no adventitial inflammation in A and severe adventitial inflammation in B. Hematoxylin-eosin stain.
reduced thickness observed in medial atrophy may lead to increased circumferential wall stress, favoring plaque disruption.

In contrast to medial inflammation and medial atrophy, medial fibrosis was actually present in 20% of class III early plaques, ranged from 16% up to 30% of advanced plaques, and increased to 65% in disrupted plaques. In addition, medial thickness was normal in class I and II lesions and significantly reduced in class III lesions. Therefore, class III lesions (so-called preatheroma), which are characterized by the absence of a lipid core, may already have chronic medial changes, such as fibrosis and thinning. This finding suggests that the transition between early and advanced plaques may involve medial changes. The contribution of medial fibrosis and thinning to subsequent advances in plaque evolution remains to be elucidated.

Medial fibrosis, characterized by increased collagenization, was also associated with rupture of the IEL at the intimalmedial interface. Studies show that collagen and elastin account for ≈60% of the dry weight of the media. The collagen fibers are dispersed in the interstices between lamellar units and aligned circumferentially. The close association between elastin, collagen, and smooth muscle in the aortic media results in the viscoelastic properties responsible for normal arterial compliance. Thus, medial fibrosis and atrophy may reduce arterial compliance, increasing vessel wall circumferential stress. Previous experimental studies have shown a close relationship between increased circumferential stress and reduced fibrous cap thickness. Indeed, finite-element model studies have identified multiple concentration sites with increased circumferential stress in disrupted coronary plaques after fatal myocardial infarction.

Adventitial inflammation was absent in our evaluation of early plaques but was present in 22% to 69% in advanced plaques and increased to 79% in disrupted plaques. Inflammatory infiltrates consisting mainly of lymphocytes, plasma cells, and mast cells were previously observed in the coronary adventitia of patients with unstable angina or acute myocardial infarction. In addition, adventitial cells are involved in the remodeling process after arterial injury. Furthermore, there is direct evidence of neointimal migration of adventitial fibroblasts after balloon injury in vivo. Finally, adventitial inflammation may play a role in proliferation of vasa vaso- sum into the intima, a finding that may increase plaque vulnerability for disruption.

Study Limitations

Degenerative changes of the IEL and tunica media have been described with hypertension and aging. Only extensive areas of IEL discontinuity and extensive loss of lamellar units far beyond the ones induced by hypertension or aging were included. Furthermore, disrupted plaques were selected randomly from all autopsy specimens, so no correction for hypertension was made. No specific immunostaining was used to identify inflammatory cells. An experienced pathologist blinded to the hypothesis performed the analysis, however, using established criteria for cell morphology.

The intimalmedial interface changes and adventitial inflammation observed in this study may occur before or after
plaque disruption. Sequential, prospective studies evaluating the intimal, medial, and adventitial layers may be necessary to completely elucidate this process. Finally, this observational study provides evidence for the coexistence of medial changes and adventitial inflammation with plaque disruption. Further prospective, sequential studies are needed to establish causality between these changes and plaque disruption.

Conclusions
Disrupted plaques have an increased incidence of IEL rupture, medial inflammation, fibrosis, and atrophy compared with nondisrupted plaques. These medial changes may play a role in the natural history of complex atherosclerotic lesions. The interaction between medial pathology and the intimal atherosclerotic process deserves further investigation.

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References

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