Relationship Between Coronary Artery Remodeling and Plaque Vulnerability

Amanda M. Varnava, MD, MRCP; Peter G. Mills, MD, FRCP; Michael J. Davies, MD, FRCP, FRCPATH

Background—In vivo studies with intravascular ultrasound have shown that complex plaque anatomy and plaque rupture are more frequent in the presence of marked outward remodeling. A large lipid core and a high macrophage count are recognized histological markers for plaque vulnerability. The link between plaque vulnerability in terms of these markers and remodeling in coronary arteries has not been explored.

Methods and Results—In 88 male subjects who died suddenly with coronary artery disease, 108 plaques were studied. The percent remodeling was calculated. Lesions with remodeling ≥0% were considered to have positive remodeling, and those in which remodeling was <0% were considered to have negative remodeling. Percent lipid core and macrophage count at the plaque were assessed. Of 108 plaque sites, 64 (59.2%) had undergone no remodeling or positive remodeling, and 44 (40.7%) had negative remodeling (vessel shrinkage). Lesions with positive remodeling, compared with lesions with vessel shrinkage, had a larger lipid core (percent mean lipid core was 39.0±21.0% versus 22.3±23.1%, respectively; P<0.0001) and a higher macrophage count (mean macrophage count was 15.6±12.3 versus 8.9±11.6, respectively; P=0.005).

Conclusions—We have shown that coronary artery plaques with positive remodeling have a higher lipid content and macrophage count, both markers of plaque vulnerability. These results may explain why plaque rupture is often apparent at sites with only modest luminal stenoses (but marked positive remodeling). (Circulation. 2002;105:939-943.)

Key Words: coronary disease ■ remodeling ■ plaque

It is now clear that coronary arteries may respond to plaque growth by either outward expansion of the vessel wall (positive remodeling)\(^1\)\(^2\) or vessel shrinkage (negative remodeling).\(^3\)\(^-\)\(^5\) There is evidence to suggest that positive remodeling may be advantageous (providing benefit in terms of avoiding luminal stenosis) but also harmful in that marked compensatory remodeling may make the plaque more vulnerable to rupture.\(^6\)\(^-\)\(^8\) In contrast, lesions with negative remodeling may be associated with higher grade stenoses\(^5\)\(^,\)\(^9\) but may appear more stable.

A large lipid core and a high macrophage count are recognized histological markers for plaque vulnerability.\(^10\)\(^,\)\(^11\) The link between plaque vulnerability in terms of these markers and remodeling in human coronary arteries has not yet been explored. Therefore, we set out to determine the relationship between plaque composition (examining lipid core size and macrophage count as indicators of the risk of a plaque undergoing rupture) and coronary artery remodeling.

In addition, we set out to test the hypothesis that negative remodeling is associated with an increase in constrictive adventitial fibrosis and thickening. Therefore, we investigated the vessel wall characteristics both in the plaque-free segment of the vessel wall and in the vessel wall behind the plaque to better characterize the histological differences between coronary artery lesions with positive versus negative remodeling.

Histopathology

Hearts were obtained at postmortem examination from 88 male patients who died suddenly and in whom no cause of death other than coronary artery disease was detectable by detailed autopsy, including toxicology. All hearts were perfusion-fixed at physiological pressure with 10% buffered formalin. After dissecting out the 3 major epicardial vessels, the tissue was decalcified in formic acid on tissue blocks taken in the transverse plane every 3 mm through the artery. Tissue was prepared for histology in a standard manner and stained with Sirius red. Immunohistochemistry was performed to enable visualization of macrophages by the expression of CD68 (Dako). Because of the problems of measuring plaque size at sites of acute thrombosis, all sites of plaque rupture were excluded, and examination was confined to discrete fibrolipid plaques in which an adjacent, plaque-free, histologically normal segment was available as a reference site.

All measurements were made by computerized planimetry, and each plaque was examined at the point of maximum plaque size. For each target segment, the following measurements were made: the
area circumscribed by the external elastic lamina (the total vessel cross sectional area [CSA]), the area bordered by the intima (luminal area), and the area occupied by plaque. In addition, each plaque was stained with Sirius red and examined under polarized light (in which collagenous tissue is seen as black) by using the Optomax automated system (AMS Cambridge). The lipid core (noncollagenous and, therefore, seen as white) was quantified as a percentage of the total plaque size.

Reference CSA and luminal areas were measured at the nearest proximal and distal segments judged to be free of plaque, and a mean value was calculated. For each plaque, the arc of the vessel circumference that was free of disease was measured in millimeters.

The percent luminal stenosis was calculated as follows: 
\[
\text{Percent luminal stenosis} = \frac{\text{Reference Luminal Area} - \text{Luminal Area at Plaque}}{\text{Reference Luminal Area}} \times 100
\]

Thus, positive values reflect luminal narrowing, and negative values reflect luminal dilatation (eg, in coronary ectasia or aneurysm formation). Percent vessel remodeling was calculated as follows: 
\[
\text{Percent vessel remodeling} = \frac{\text{Reference CSA} - \text{CSA at Plaque}}{\text{Reference CSA}} \times 100
\]

Because plaque size varies with vessel size and thus larger vessels tend to have larger plaques, we corrected for vessel size and expressed this as plaque burden, for which percent plaque burden was calculated as follows: 
\[
\text{Percent plaque burden} = \frac{\text{Plaque Area}}{\text{CSA at Plaque}} \times 100
\]

To assess the relative contribution of the lipid core to plaque area, a percentage was derived; thus, percent lipid core = (lipid core area in millimeters squared/plaque area in millimeters squared) \times 100.

Vessel calcification was measured at the arc of the vessel with the least plaque and at the vessel wall opposite the plaque, 3 values were measured for each, and a mean value was taken. In the case of concentric plaques, measurements were made at the arc with the most plaque bulk and at the arc of the vessel with the least plaque. To assess the change in medial or adventitial wall thickness with plaque development, medial and adventitial wall thicknesses at the plaque site were adjusted for reference site measurements; thus, change in medial or adventitial wall thickness at the plaque site equals medial-adventitial wall thickness at the plaque site minus reference medial-adventitial wall thickness (in millimeters).

A quantitative assessment was made of the total macrophage number within the plaque. Within the adventitia, a semiquantitative count was made of the small cell infiltrate (lymphocytes and neutrophils) behind the plaque and of the vessel wall opposite the plaque; thus, 0 indicates no staining; 1, minor staining; 2, moderate staining; and 3, deep staining.

**Statistical Analysis**

All data are presented as mean±SD values. Data were analyzed by an independent t test and by correlation and regression analysis with the use of the SPSS statistical program, version 6.0. A value of \( P<0.05 \) was considered significant.

**Results**

Histologically normal reference sites were found for 108 lesions. The mean percent luminal stenosis was 48.9±20.6%.

### Positive Versus Negative Remodeling

Of 108 plaque sites, 64 (59.2%) had undergone no remodeling or positive remodeling, and 44 (40.7%) had undergone negative remodeling (vessel shrinkage). A comparison of the plaque features for those sites with positive versus negative remodeling is shown in Table 1.

Lesions with positive remodeling, compared with lesions with vessel shrinkage, had a larger lipid core (mean lipid core was 39.0±21.0% versus 22.3±23.1%, respectively; \( P<0.0001 \)) and a higher macrophage count (mean macrophage count was 15.6±12.3 versus 8.9±11.6, respectively; \( P=0.005 \)) (see Table 1 and Figures 1 and 2).

Lesions with negative remodeling had significantly greater luminal stenoses and a significantly more circumferential...

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**Table 1. Pathological Characteristics of Lesions With Negative Versus Positive Remodeling**

<table>
<thead>
<tr>
<th>Pathological Characteristic</th>
<th>Negative Remodeling (n=64)</th>
<th>Positive Remodeling (n=64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid core, %</td>
<td>22.3 (23.1)</td>
<td>39.0 (21.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Macrophage count</td>
<td>8.9 (11.6)</td>
<td>15.6 (12.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Eccentricity, degrees</td>
<td>24.7 (41.8)</td>
<td>66.9 (62.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in target site medial wall thickness behind plaque</td>
<td>-64.1 (42.7)</td>
<td>-71.7 (44.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Change in target site medial wall thickness opposite plaque</td>
<td>-86.0 (63.9)</td>
<td>-37.2 (54.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in target site adventitial wall thickness behind plaque</td>
<td>174.4 (93.0)</td>
<td>143.9 (107.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Change in target site adventitial wall thickness opposite plaque</td>
<td>-57.4 (92.4)</td>
<td>1.3 (88.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vessel calcification</td>
<td>1.63 (1.1)</td>
<td>1.56 (1.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>Inflammatory cell count behind the plaque</td>
<td>0.22 (0.6)</td>
<td>0.48 (1.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Inflammatory cell count at the plaque free segment</td>
<td>0.63 (0.9)</td>
<td>1.0 (1.2)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are mean (SD).

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**Figure 1.** Bar chart showing percent lipid core in lesions with negative vs positive remodeling. Error bars show 95.0% CI of mean; bars show means.
distribution of plaque (lower eccentricity index) than did lesions in which there had been positive remodeling (see Table 1).

Lesions with negative remodeling had significantly greater thinning of the medial and adventitial wall opposite the plaque (mean change in medial wall thickness $-86 \pm 63.9$ mm versus $-37.2 \pm 54.1$ mm, $P<0.0001$; mean adventitial wall change $-57.4 \pm 92.4$ mm versus $1.3 \pm 88.1$ mm, $P=0.001$) and a trend toward greater adventitial thickening behind the plaque (mean change in adventitial wall thickness $174.4 \pm 93.0$ versus $143.9 \pm 107.2$ mm, $P=0.1$). There were no significant differences between lesions with negative or positive remodeling regarding medial wall changes behind the plaque (see Table 1).

There was greater inflammatory activity at the adventitial aspect of lesions with positive remodeling than of lesions with vessel shrinkage (see Table 2); however, significance was not achieved.

**Eccentric Versus Concentric Plaques**

Plaque distribution was eccentric in 56 lesions and concentric in 52 lesions. Concentric plaques, compared with eccentric lesions, had significantly greater luminal stenoses (mean luminal stenosis $58.6 \pm 21.3\%$ versus $39.9 \pm 15.1\%$, respectively; $P<0.0001$), lower lipid content (mean lipid core $27.2 \pm 25.0\%$ versus $36.8 \pm 20.7\%$, respectively; $P=0.03$), and fewer macrophages (mean macrophage count $10.2 \pm 12.0$ versus $15.4 \pm 12.3$, respectively; $P=0.03$). Concentric lesions were associated with significantly greater medial and adventitial wall thickening at the segment of the vessel with the least plaque (mean change in medial wall thickness $-106.8 \pm 50.1$ mm versus $-11.03 \pm 29.2$ mm, $P<0.0001$; mean change in adventitial wall thickness $-86.9 \pm 75.1$ mm versus $37.1 \pm 66.5$ mm, $P<0.0001$) and greater adventitial wall thickening behind the bulk of the plaque (mean increase in adventitial wall thickness $137.3 \pm 94.1$ mm and $176.7 \pm 107.7$ mm, $P=0.04$).

**All Plaques**

The correlation coefficients for vessel remodeling as continuous variables against the pathological features for both the reference and plaque sites are shown in Table 2. Vessel remodeling also correlated weakly, but significantly, with percent lipid core ($r=0.4$, $P<0.0001$) and with macrophage number ($r=0.3$, $P=0.007$).

There was a weak, but significant, relationship between the eccentricity index (arc of normal wall segment at the target site) and the degree of remodeling; thus, the more eccentric the distribution of plaque, the greater is the remodeling. Conversely, the more circumferential the distribution of plaque, the greater is the degree of vessel shrinkage.

Remodeling was correlated directly with thickening of both the medial and adventitial walls opposite the plaque ($r=0.4$, $P<0.0001$; $r=0.3$, $P=0.001$) and inversely with thickening of the adventitial wall behind the plaque ($r=-0.3$, $P=0.02$) (see Figure 3).

**Relationship Between Plaque Vulnerability, Plaque Size, and Luminal Stenosis**

A direct relationship was seen between lipid core size and macrophage count ($r=0.6$, $P<0.0001$). No significant relation was seen between these histological markers of plaque vulnerability and either luminal stenosis or plaque burden.

**Table 2. Comparison of Remodeling as a Continuous Variable Versus the Other Pathological Characteristics Assessed**

<table>
<thead>
<tr>
<th>Pathological Characteristic</th>
<th>Mean (SD)</th>
<th>Correlation Coefficient Against Remodeling</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid core, %</td>
<td>32.2 (23.3)</td>
<td>0.4*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Macrophage count</td>
<td>12.9 (12.4)</td>
<td>0.3*</td>
<td>0.007</td>
</tr>
<tr>
<td>Eccentricity, degrees</td>
<td>49.7 (58.3)</td>
<td>0.2†</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in target site medial wall thickness behind plaque</td>
<td>52.3 (38.4)</td>
<td>$-0.05$</td>
<td>0.6</td>
</tr>
<tr>
<td>Change in target site medial wall thickness at plaque free segment</td>
<td>63.8 (58.7)</td>
<td>0.4*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in target site adventitial wall thickness behind plaque</td>
<td>264.7 (95.2)</td>
<td>$-0.3†$</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in target site adventitial wall thickness at plaque free segment</td>
<td>85.7 (84.9)</td>
<td>0.3*</td>
<td>0.001</td>
</tr>
<tr>
<td>Vessel calcification</td>
<td>1.6 (1.1)</td>
<td>$-0.02$</td>
<td>0.8</td>
</tr>
<tr>
<td>Inflammatory cell count behind the plaque</td>
<td>0.4 (0.8)</td>
<td>0.01</td>
<td>0.9</td>
</tr>
<tr>
<td>Inflammatory cell count at the plaque free segment</td>
<td>0.8 (1.1)</td>
<td>0.2†</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Correlation significant at the 0.01 level (2-tailed).
†Correlation significant at the 0.05 level (2-tailed).
Discussion

In vivo studies using intravascular ultrasound have shown that complex plaque anatomy and plaque rupture are more frequent in the presence of marked outward remodeling.6,7 It is also well established that plaques with a high lipid content are more vulnerable to rupture. This pathological study has now shown that coronary artery plaques that undergo positive remodeling have a significantly larger lipid core and a higher macrophage count than do those that undergo vessel shrinkage. Therefore, these findings explain the basis of plaque vulnerability at sites of excessive vessel remodeling and suggest a possible explanation for the apparent paradox of positive remodeling, which may be both beneficial (avoiding luminal stenosis) and harmful (promoting plaque vulnerability). The common link between compensatory remodeling and plaque rupture may center on macrophage-derived foam cell expression of the metalloproteinases (MMPs),12 a group of proteins involved in cell matrix breakdown. Thus, plaques with a high lipid content and macrophage count might stimulate MMP production and allow outward remodeling at sites made vulnerable by the soft lipid core. In contrast, lesions with vessel shrinkage had a low index of vulnerability to plaque rupture in terms of a low lipid content and scanty macrophage count.

In line with previous in vivo studies using intravascular ultrasound,13 the present results have confirmed that vessel shrinkage is associated with a more circumferential distribution of plaque. This suggests that vessels that undergo shrinkage may do so because of circumferential stimulation to inward remodeling by the plaque. In contrast, lesions with positive remodeling and an eccentric distribution of plaque may undergo a more regionalized restructuring of the vessel wall, allowing outward expansion.

It has been postulated that shrinkage is the result of constricting adventitial fibrosis and thickening. Our results support this suggestion, inasmuch as an inverse relationship between adventitial wall thickening behind the plaque and vessel remodeling was seen. Thus, adventitial wall thickening increased with increasing vessel shrinkage.

We also found that lesions exhibiting vessel shrinkage had significantly greater medial and adventitial thinning of the vessel wall opposite the plaque that was consistent with the well-documented medial wall changes found in the atherosclerotic process.14 In contrast, lesions with positive remodeling exhibited less medial thinning of the vessel wall opposite the plaque and little change in the adventitial wall thickness. These results probably reflect the circumferential involvement of the medial and adventitial layers in lesions with negative remodeling (the vast majority of which have a circumferential distribution of plaque). In contrast, lesions with positive remodeling that have a mostly eccentric plaque distribution would retain an arc of the vessel wall that would remain uninvolved in the atherosclerotic process.

These findings have potential implications for the mechanisms that underlie arterial remodeling. It has been thought that positive remodeling largely occurs as a result of outward stretch of the vessel wall behind the plaque, as a direct response to the plaque release of MMPs. Certainly, some plaques are virtually extruded, giving an elliptical cross section (as seen in Figure 4). However, our results suggest an alternative model whereby an eccentric plaque might, in addition, stimulate outward vessel remodeling and stretch at the plaque-free arc of the vessel wall. In contrast, lesions with circumferential plaques would have no plaque-free vessel arc to allow for outward remodeling. Instead, the vessel wall would be completely involved in the atherosclerotic process.

Thus, in this model, vessel shrinkage would represent the vessel wall response to plaque growth behind the plaque, whereas outward remodeling would be possible only in a disease-free arc.

Interestingly, there was a weak, but significant, relationship between remodeling and chronic inflammatory cell
infiltrate at the adventitial wall opposite the plaque. Furthermore, a trend was seen for greater inflammatory activity at the adventitial layer in lesions with positive remodeling than in lesions with vessel shrinkage. These results are rather surprising because vessel shrinkage has been considered the most likely response to adventitial inflammation. However, these results support a model in which outward vessel remodeling is a process active at the plaque-free arc of the target site, perhaps stimulated by the presence of a small cell infiltrate.

By examining only those plaques in which there is a histologically normal reference site available, we limited the number of plaques examined per patient. This may have led to a selection bias toward those lesions in which the atherosclerotic process is highly localized, in contrast to the clinical situation in which a diffuse atherosclerotic process is commonly seen along the whole vessel length. In addition, although we used the term histologically normal, it is possible that the very early changes of atherosclerosis that may lead to prestenotic/poststenotic dilatation may have been missed. If this is the case, then the number of lesions with vessel shrinkage may have been overestimated.

In contrast to in vivo studies, our present study revealed a significant difference between the reference CSA and luminal area between lesions with positive versus negative remodeling. We believe that these differences are due to the effect of prestenotic and/or poststenotic dilatation of the vessel adjacent to an area of plaque growth. This effect will be particularly marked in lesions with higher-grade stenoses (and, hence, more marked in lesions with vessel shrinkage, in which greater luminal stenosis is seen). Thus, the reference site CSA will be larger in lesions with negative rather than positive remodeling.

In summary, we have shown that coronary artery plaques with positive remodeling have a higher lipid content and macrophage count, which are both markers of plaque vulnerability. These results may explain why plaque rupture is often apparent at sites with only modest luminal stenoses.

Furthermore, we have shown that negative remodeling is associated with a circumferential plaque distribution and adventitial thickening behind this, whereas lesions with outward remodeling have eccentric plaques with less thinning of the media and adventitia in the plaque-free segment and a greater small cell infiltrate in the adventitia. These results suggest that positive remodeling may be due to the plaque-free segment of the vessel wall dilating around the fixed point of the plaque. In contrast, vessel shrinkage may be due to changes in the vessel wall behind the plaque.

Because postinterventional restenosis is characterized by vessel shrinkage, these results have significant clinical implications and might explain the apparent disparity between the relatively low mortality rate seen after intervention despite the high rate of recurrent morbidity in terms of chest pain. Thus, although angioplasty may render the patient more symptomatic because of the development of vessel shrinkage and restenosis, these patients will be relatively protected from plaque rupture because of the more stable nature of these restenotic lesions. More important, if we can detect those plaques that are at high risk of rupture, they may be considered targets for intervention. The addition of stenting to this regimen would further optimize the outcome by negating the legacy of vessel shrinkage and recurrent symptoms. Currently, there are no routinely available methods to identify such plaques, but recent work (eg, with thermodetection catheters) suggests that the development of these methods may not be far off.

References
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