Regional Remodeling of Atherosclerotic Arteries: A Major Determinant of Clinical Manifestations of Disease

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In this review we present the current data on remodeling, based on in vivo ultrasound imaging or postmortem histologic analysis of native peripheral and coronary arteries from animal models and studies in patients (coronary artery saphenous vein bypass grafts, lesions of restenosis after balloon angioplasty and other catheter-based interventions). Histologic and ultrasound imaging studies of arteries with atherosclerosis and after vascular injury reveal that arterial remodeling is common and that the cross-sectional area of the vessel is not constant. Compensatory enlargement, inadequate compensatory enlargement and shrinkage at the site of atherosclerotic lesions occurs in coronary and peripheral arteries. Current studies demonstrate that arterial remodeling is a major determinant of vessel lumen size.

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The severity of lumen narrowing of atherosclerotic arteries has long been believed to depend on the extent of accumulation of plaque along the arterial wall. The changes in overall dimensions of the arterial wall were not appreciated. Therefore, it was thought that there was a direct relation between the severity of lumen stenosis and plaque area size. Only recently has it been appreciated that concomitant changes in the total cross-sectional area of the arteries (vascular remodeling) occur that are of the utmost importance in determining the final size of the lumen and hence the degree of blood flow impairment and severity of ischemia. Data gathered by histologic examination and ultrasound imaging of native arteries with atherosclerosis and after vascular injury, both in experimental models and in patients, have shown that the cross-sectional area of the vessel is not constant. Compensatory enlargement, inadequate compensatory enlargement and shrinkage at the site of atherosclerotic lesions have all been described in coronary and noncoronary arteries.

In this report we review the published data on remodeling on the basis of in vivo ultrasound imaging or postmortem histologic studies from 1) animal experiments in native iliofemoral and coronary arteries; 2) native human iliofemoral, carotid and coronary arteries; 3) coronary artery saphenous vein bypass grafts; 4) lesions of restenosis after balloon angioplasty in animal models (both coronary and noncoronary arteries); and 5) lesions of restenosis in human coronary arteries after catheter-based interventions. The methods used to assess remodeling in the studies that we reviewed were either histologic examination or ultrasound imaging of the arteries by epicardial high resolution echocardiography (coronary arteries), duplex ultrasound (carotid arteries) or intravascular ultrasound (IVUS) (for peripheral and coronary arteries), combined in some of the studies with angiographic measurements of lumen diameter. Both histologic and ultrasound imaging studies (Fig. 1) enable measurement of the lumen cross-sectional area of the artery (the area circumscribed by the external elastic lamina [EEL area]), the internal elastic lamina (IEL) area, the intimal area (IEL area minus lumen area) and the medial area (EEL area minus IEL area). However, in advanced and calcified lesions, acoustic shadowing prevents detection of the IEL and EEL by ultrasound. The studies described in this review have used either histomorphometric methods or ultrasound imaging for measuring the various components of the artery at the site of interest and comparing them with either an adjacent reference site with the least atheroma, a control group without atheroma or the same site at different time points. Another method used in some studies compares the difference in lumen size between the lesion site and a reference point, or over time at the same site (by angiography), with the difference in wall thickness (measured by histologic analysis or ultrasound). If the decrease in lumen size is less than the increase in vessel wall thickness, compensatory remodeling is considered to be present; but if the reduction in lumen size is greater than the increase in vessel wall area, then inadequate vascular remodeling or shrinkage is considered to have occurred (Fig. 2).
Atherosclerotic Disease: Native Lesions

Animal Models

Peripheral arteries (Table 1). Armstrong et al. (1) studied the iliofemoral arteries of monkeys fed either an atherogenic or a regular diet. After 1.5 years, the control animals had no gross atherosclerotic lesions in the limb arteries, whereas those fed the atherogenic diet developed atherosclerosis. After 6 years of the atherogenic diet, there was progression of the lesions, with marked intimal thickening and deposition of extracellular lipids. The media of the atherosclerotic arteries showed focal thinning and atrophy; however, the total medial mass was not changed. Despite marked intimal thickening, the arterial lumen size tended to be larger in monkeys fed an atherogenic diet than in the control monkeys, because of a compensatory enlargement of the total circumference of the artery (1) (Table 1). This study therefore suggested that compensatory enlargement of the peripheral arteries occurs during the early development of intimal thickening and prevents narrowing of the arterial lumen.

Coronary arteries. Similarly, monkeys fed an atherogenic diet developed diffuse coronary atherosclerosis, but coronary artery lumen narrowing did not occur (2,3). Moreover, monkeys on an atherogenic diet that also exercised had greater enlargement of the diameter of their coronary arteries and less lumen narrowing than similar monkeys that did not exercise (4). A paradoxic increase in lumen size, associated with an increase in plaque size, was described in the left anterior descending coronary artery (LAD) of monkeys fed an atherogenic diet (Table 1) (3). This could be partially explained by the loss of arterial wall mass due to thinning of the media in these lesions (5), compensating for the increase in plaque area or resulting in weakening of the arterial wall and remodeling, which results in arterial dilation.

These experimental studies demonstrate that compensatory enlargement is a prominent feature in early atherosclerosis in the peripheral and coronary arteries of monkeys fed an atherogenic diet.

Human Studies

Peripheral vascular studies (Table 2). Using IVUS, Losordo et al. (6) assessed paired, adjacent normal and atherosclerotic superficial femoral artery segments of patients undergoing peripheral vascular interventions (Table 2). As expected, the lumen area was smaller in the atherosclerotic segments than in the reference sites with the least atherosclerotic plaque area. However, at the same sites, the total arterial cross-sectional area (EEL area) was larger in the atherosclerotic sites than in the reference sites. Regression analysis revealed a positive correlation between plaque area and EEL area ($R = 0.70$). These results confirmed that in human femoral arteries, there is a compensatory expansion of the...
outer wall of the arteries at discrete sites of atherosclerotic narrowing of the lumen. Moreover, arterial enlargement occurred as a local response of the arterial wall to the narrowing of the arterial lumen by the accumulation of atherosclerotic plaque rather than a generalized response to the development of atherosclerosis (6). However, Pasterkamp et al. (7) reported that in more advanced femoral lesions, shrinkage of the arterial wall may predominate (Table 2). Patients with claudication were studied by IVUS before routine balloon angioplasty of the superficial femoral artery. Ultrasound images were selected every 0.5 cm from a total of 23 arterial segments ~10 cm in length. In addition, histologic analysis of postmortem human femoral artery segments was performed (Table 2). Both analyses showed that the IEL area of the segments with <25% lumen cross-sectional stenosis tended to be larger than the reference site. However, for lesions with >25% area stenosis, the cross-sectional area of the vessel was smaller than the IEL area at the reference site (i.e., shrinkage had occurred) (7). The cross sections that showed arterial wall constriction contained more plaque than the reference sites. Therefore, in lesions with mild lumen stenosis, compensatory enlargement dominates (6,7); however, in more advanced femoral artery lesions, contraction of the vessel may contribute to the encroachment of the lumen by the expanding plaque. In another study, using IVUS and histologic examination, Pasterkamp et al. (8) found a large variation in the correlation of the regression between plaque area and IEL area \( (r = -0.40\) to 0.89 for IVUS; \( r = -0.13\) to 0.91 for histologic analysis) and slope \( (-0.28\) to 1.29 for IVUS; \(-0.18\) to 1.32 for histologic analysis). In the majority of the segments there was no significant correlation between plaque area and IEL area. Thus, there was considerable local variation in arterial remodeling (9). Pasterkamp et al. (9) hypothesized that compensatory enlargement of the small arteries starts earlier because the segments that tend to have compensatory enlargement are usually smaller than segments without remodeling. It might be that the same amount of plaque accumulation results in more profound hemodynamic changes in small arteries than in larger arteries (8). It has been suggested by Glagov et al. (10) as well as by Fujii et al. (11) that the degree of compensatory enlargement is greater in eccentric lesions with a partially disease-free wall.

In patients with nonstenotic carotid plaques, three-dimensional plaque reconstruction of high resolution duplex

<table>
<thead>
<tr>
<th>Study (ref no.)</th>
<th>Artery Studied</th>
<th>Diet</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al. (1)</td>
<td>Iliofemoral</td>
<td>Atherogenic vs. regular</td>
<td>1.5 or 6 yr</td>
<td>Atherogenic-fed monkeys developed atherosclerosis; IA ↑; no overall change in MA; focal atrophy; LCSA ↑ after 6 yr</td>
</tr>
<tr>
<td>Kramsch et al. (4)</td>
<td>CAs</td>
<td>Atherogenic (with or without exercise) vs. regular</td>
<td>2 yr</td>
<td>Among atherogenic-fed monkeys, CA diameter of exercising monkeys was larger than that of nonexercising group; exercising group had less atherosclerosis than atherogenic diet nonexercising group</td>
</tr>
<tr>
<td>Clarkson et al. (3)</td>
<td>LAD</td>
<td>Atherogenic</td>
<td>6 yr</td>
<td>IA ↑; LCSA ↑ after 6 yr</td>
</tr>
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CA = coronary artery; IA = intimal area; LAD = left anterior descending coronary artery; LCSA = lumen cross-sectional area; MA = medial area; ref = reference; ↑ = increased.

### Table 1. Simian Models (histologic studies)

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### Table 2. Human Studies: Peripheral Arteries

<table>
<thead>
<tr>
<th>Study (ref no.)</th>
<th>No. of Pts</th>
<th>Artery Studied</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS</td>
<td>Losordo et al. (6)</td>
<td>20 (62 segs)</td>
<td>Femoral</td>
</tr>
<tr>
<td>Pasterkamp et al. (7)</td>
<td>19 (23 segs)</td>
<td>Femoral</td>
<td>IEL of segs with &lt;25% LCSA stenosis was larger than that at ref site; IEL of segs with &gt;25% LCSA stenosis was smaller than that at ref site</td>
</tr>
<tr>
<td>Histologic</td>
<td>Pasterkamp et al. (7)</td>
<td>32</td>
<td>Femoral</td>
</tr>
<tr>
<td>HRDS</td>
<td>Steinke et al. (12)</td>
<td>32</td>
<td>Carotid</td>
</tr>
</tbody>
</table>

CSA = cross sectional area; EEL = external elastic lamina area; HRDS = high resolution duplex scanning; IEL = internal elastic lamina area; IVUS = intravascular ultrasound; OD = outer diameter; PA = plaque area; Pts = patients; segs = segments; ↓ = decreased; ↑ = increase, increased; other abbreviations as in Table 1.
scans at baseline and at two follow-up examinations after 6- to 12-month intervals revealed plaque progression in 41%, regression in 3% and no change in 56% of cases (Table 2) (12). Most lesions with plaque progression were associated with enlargement of the outer diameter of the artery, whereas among lesions with unchanged plaque, less than one third had an increase in arterial diameter. None of the duplex follow-up analyses demonstrated a reduction in carotid artery diameter (12). The degree of plaque progression was correlated (r = 0.7, p < 0.01) with the degree of arterial enlargement at the lesion site. Hence, in the human carotid arteries, similar to femoral arteries, progression of small atheromatous plaques is associated with arterial enlargement that delays the development of lumen narrowing.

These studies clearly show that remodeling of human femoral and carotid arteries is a dynamic process. Plaque progression is usually associated with compensatory enlargement of the arterial wall, at least in the early stages of atherosclerosis, whereas more advanced lesions may be associated with incomplete enlargement or even constriction of the arterial wall.

Coronary arteries. Histologic studies (Table 3). In a pioneering study of histologic sections of postmortem human left main coronary arteries, Glagov et al. (10) detected a correlation between the IEL area and the area of the lesion. Their work demonstrates that coronary arteries enlarge as the plaque area increases. When the lumen area was plotted against the percent stenosis of the lumen area (Lesion area/IEL area × 100), a biphasic relation was present. For lesions with <40% stenosis, there is no relation between lumen area and percent stenosis, whereas when there is >40% stenosis, the lumen area decreases markedly as the stenosis increases. In vessels with ≤20% lumen stenosis, the IEL area correlates with lesion area, indicating that for small lesions, vessel enlargement may even overcompensate for the increase in plaque area. Therefore, as in femoral and carotid arteries, compensatory enlargement of the human left main coronary artery may delay the progression of lumen stenosis induced by the enlarging atheromatous plaque. However, when there is narrowing of >30% to 40% of the “potential” lumen area (the IEL cross-sectional area that is occupied by the plaque), a sharp decline in lumen occurs (10). Figure 3 is a schematic presentation of the possible sequence of changes in atherosclerotic arteries.

Zarins et al. (13) investigated LAD samples taken at four standard sites in 125 pressure–perfusion-fixed postmortem human hearts. The IEL area correlated with the plaque area at each LAD level (p < 0.0001). Stepwise regression analysis revealed that plaque area was the major determinant of IEL area at each LAD level. In the proximal LAD, the most severely diseased arteries (highest quartile) had a larger plaque area and a smaller lumen area than arteries in the lowest quartile. However, as shown in Figure 4, the arteries in the highest quartile had also 62% greater IEL area than the arteries with the least plaque. Despite a 6.7-fold (670%) larger plaque area, the lumen area decreased by only 25% due to compensatory enlargement of the IEL area. In the midportion of the LAD, the plaque area was 10 times larger in the highest quartile; however, the lumen area was not different because of an 80% increase in IEL size. As shown in Figure 4, in the distal LAD segments, despite a 14-fold increase in plaque area, the lumen area almost doubled because of a more than 2-fold increase in IEL size. It was calculated that if no compensatory enlargement of the arteries had occurred, the most severely diseased proximal segments would have developed a 92% lumen stenosis rather than the observed 25% stenosis, and distally, a 65% lumen stenosis rather than the observed 85% increase in lumen size, would have occurred. The distal LAD segments demonstrated a greater propensity to enlarge in response to expanding plaque than the proximal segments. These findings are in accordance with those in human femoral arteries (8), showing that arteries with smaller diameters tend to have more compensatory enlargement than larger arteries. Intrinsic local differences in wall composition, geometric configuration and wall tension and differences in the rate of plaque deposition may account for the varying tendency of different arterial segments to develop stenosis or dilation. For example, smaller arteries may have more smooth muscle and fewer elastic and collagen fibers than larger ones.

In a postmortem coronary angiographic and histologic study of human hearts with and without coronary artery disease, Stiel et al. (14) found a significant correlation between the IEL area and the plaque area. Because of this compensatory enlargement of the vessels at the lesion site, the degree of stenosis, assessed by in vitro angiography, is underestimated compared with that assessed by histologic analysis.

Another postmortem histologic study (3) of coronary arteries from patients (28 with and 72 without coronary artery disease) also demonstrated compensatory dilation of the LAD coronary artery in segments with atheromata. However, there was a great deal of variability in lumen size. Paradoxically, instead of a decrease in lumen size, the arteries have a small increase in mean lumen size with increasing intimal area. The plaque size could explain only 7.5% of the variability in lumen area. Hence, lumen size and therefore severity of blood flow impairment are determined mainly by factors other than the size of the atheromatous plaque.

These histologic postmortem studies of coronary arteries demonstrate that compensatory enlargement occurs in the initial stages of atherosclerosis. Vascular remodeling may be more pronounced in the distal parts of the coronary arteries and may be an important mechanism in preventing encroachment of the lumen by the expanding atheromatous plaque.

High frequency epicardial echocardiography (Table 3). Before the development of IVUS, McPherson et al. (15,16) demonstrated that atherosclerotic plaques may be much larger, and coronary artery disease more diffuse, than suspected by angiographic evaluation. High frequency epicardial echocardiography in patients with and without coronary artery disease performed at the time of cardiac surgery showed that the severity of lumen narrowing is not dependent on plaque size. Atheromatous plaque can expand outward and not into the
Table 3. Human Studies: Coronary Arteries

<table>
<thead>
<tr>
<th>Study (ref no.)</th>
<th>No. of Pts</th>
<th>Artery Studied</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glagov et al. (10)</td>
<td>136</td>
<td>LMCA</td>
<td>Correlation between IEL and PA ($r = 0.44, p &lt; 0.001$), suggesting that CAs enlarge as PA↑. Compensatory enlargement of LMCA may delay progression of LCSA stenosis induced by PA expansion; however, when &gt;30–40% of IEL is occupied by PA, a sharp decline in LCSA occurs. In 42 vessels with ≥20% lumen stenosis, IEL correlates with LCSA ($r = 0.76, p &lt; 0.001$). In these lesions, the LCSA↑2.3 mm² for every 1-mm² PA↑.</td>
</tr>
<tr>
<td>Zarins et al. (13)</td>
<td>125 (481 segs)</td>
<td>LAD</td>
<td>CSA↑ in response to PA↑, which can prevent lumen narrowing. In proximal LAD, the most severely diseased CSAs (highest quartile) had a larger PA than CAs in lowest quartile (8.5 vs. 1.1 mm²) and a smaller LCSA (6.4 vs. 8.5 mm², $p = 0.02$). CAs in highest quartile also had 62% greater IEL than CAs with least plaque (14.9 vs. 9.2 mm², $p = 0.0001$). In midportion of LAD, PA was 10 times larger in highest quartile (5.4 vs. 0.5 mm²); however, LCSA was not different due to 80% IEL↑ (11.4 vs. 6.6 mm², $p = 0.0001$). In distal LAD segs, despite a 14-fold PA↑ (1.4 vs. 0.1 mm² in highest vs. lowest quartile), LCSA↑ (3.7 vs. 2.0 mm², respectively, $p = 0.0004$) because of IEL↑ (5.1 vs. 2.1 mm², respectively, $p = 0.0001$). Compensatory enlargement was more profound in distal than proximal LAD.</td>
</tr>
<tr>
<td>Stiel et al. (14)</td>
<td>40</td>
<td>CAs</td>
<td>Significant correlation ($r = 0.85, p ≤ 0.0001$) between IEL and PA, suggesting that CAs enlarge as PA expands.</td>
</tr>
<tr>
<td>Clarkson et al. (3)</td>
<td>100</td>
<td>LAD</td>
<td>Small LCSA↑ with IA↑. IA could explain only 7.5% of variability in LCSA. LCSA, and therefore severity of blood flow impairment, is determined mainly by other factors and not by PA.</td>
</tr>
<tr>
<td>HREUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McPherson et al. (15)</td>
<td>32</td>
<td>CAs</td>
<td>Severity of LCSA narrowing is dependent not only on PA. There are cases in which the PA expands without IA↑.</td>
</tr>
<tr>
<td>McPherson et al. (16)</td>
<td>33</td>
<td>LAD/RCA</td>
<td>CSA was larger, whereas LCSA was smaller, at stenotic lesions than at proximal CA.</td>
</tr>
<tr>
<td>IVUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermiller et al. (17)</td>
<td>44 (80 segs)</td>
<td>CAs</td>
<td>IEL correlated with PA. For lesions with &lt;30% stenosis, IEL correlated well with PA ($r = 0.79, p = 0.0001$). For each 1-mm² PA↑, IEL↑ 2.7 mm²; however, %LCSA stenosis did not correlate with absolute LCSA due to progressive IEL↑; however, for &gt;30% stenosis, LCSA↑ as PA↑. Compensatory enlargement occurred in early (&lt;30% stenosis) lesions.</td>
</tr>
<tr>
<td>Gerber et al. (18)</td>
<td>60</td>
<td>LMCA</td>
<td>CSA of CA was larger in pts with than without plaque in LMCA ($p &lt; 0.001$). CSA correlated with PA. LCSA was comparable between CAs with &lt;40% LCSA stenosis and CAs without plaque (24.0 vs. 24.2 mm², respectively). However, LCSA↓ sharply (to 14.9 mm², $p &lt; 0.0001$) in CAs with ≥40% LCSA stenosis.</td>
</tr>
<tr>
<td>Nishioka et al. (19)</td>
<td>30 (35 segs)</td>
<td>CAs</td>
<td>CSA↓ could explain 39% and 7% of LCSA↓ in lesions with inadequate (n = 9) and intermediate remodeling (n = 7), respectively. PA↑ could explain 6% and 93%, respectively. In lesions with adequate remodeling (n = 19), 82%↑ in CSA partially compensated for 182%↑ in PA.</td>
</tr>
<tr>
<td>Mintz et al. (20)</td>
<td>550 (603 lesions)</td>
<td></td>
<td>Inadequate remodeling (lesion EEL/ref site EEL ≤ 0.78) found in 15% of lesions. Only predictor of inadequate remodeling was arc of superficial lesion calcium.</td>
</tr>
<tr>
<td>Nakamura et al. (21)</td>
<td>12 (60 segs)</td>
<td>CAs</td>
<td>In angiographically normal segs, LCSA↑ ($r = 0.68, p = 0.0001$), CSA↑ ($r = 0.87, p = 0.0001$), and IEL↑ ($r = 0.87, p = 0.0001$) as PA↑. Compensatory enlargement at lesion site delayed development of angiographically detectable lumen narrowing.</td>
</tr>
<tr>
<td>Fujjii et al. (11)</td>
<td>36</td>
<td>CAs</td>
<td>Vascular remodeling kept LCSA open until area stenosis was &gt;50%. Vascular remodeling greater in eccentric than concentric lesions.</td>
</tr>
<tr>
<td>Blank and Yeung (22)</td>
<td>55 (58 segs)</td>
<td>CAs</td>
<td>Concentric lesions showed more remodeling than eccentric lesions. Concentric lesions exhibited highest remodeling when %PA was &lt;55% and showed lower indexes when %PA &gt;55%. Eccentric lesions showed compensatory remodeling only for %PA &gt;55%.</td>
</tr>
<tr>
<td>Kornowski et al. (23)</td>
<td>60 with IDDM, 139 with NIDDM, 614 non-diabetic</td>
<td></td>
<td>For every mm² increase in lesion site PA, pts with IDDM had significantly smaller CA CSA↑ and, hence, more lumen compromise than either non-diabetic pts ($p = 0.0001$) or pts with NIDDM ($p = 0.0019$).</td>
</tr>
</tbody>
</table>

HREUS = high resolution epicardial ultrasound; IDDM = insulin-dependent diabetes mellitus; LMCA = left main coronary artery; NIDDM = non-insulin-dependent diabetes mellitus; RCA = right coronary artery; ↓ = decrease; decreased; ↑ = increase, increases, increased; other abbreviations as in Tables 1 and 2.
IVUS (Table 3). Hermiller et al. (17) studied human coronary artery segments by IVUS and found, as in previous studies, that the IEL area increases as the plaque area (IEL area minus lumen area) increases. In vessels with <30% lumen area stenosis (plaque area divided by IEL area times 100), the IEL area correlated well with plaque area. In lesions with <30% stenosis, there was no correlation between percent area stenosis and lumen area. However, in more advanced lesions, lumen area significantly decreased. This finding suggests that arterial “compensatory” enlargement mechanisms are very effective for early atherosclerotic lesions; but as lesions become more progressive, these mechanisms can no longer compensate, and lumen narrowing occurs. IVUS studies by Gerber et al. (18) found plaque in 45% of left main coronary arteries (27 of 60). In left main coronary arteries with plaque, the vessel area was significantly larger than in those without atherosclerotic plaque, and the degree of enlargement correlated with plaque area (r = 0.46). In accordance with the findings of Glagov et al. (10), in patients with left main coronary arteries with <40% stenosis, the lumen area was not significantly different from that in patients without left main coronary artery plaque. However, the lumen area decreased sharply in arteries with ≥40% stenosis (18). Thus, compensatory remodeling preserves lumen size in early lesions (<40% stenosis); but when the plaque expands to occupy >40% of the cross-sectional area of the vessel, this protective mechanism fails to compensate for further increases in plaque mass, and the lumen area decreases (10,17,18).

Nishioka et al. (19) used IVUS to evaluate to what extent native coronary artery stenosis is accompanied by vessel wall thickening or inadequate compensatory remodeling (relative vessel constriction). Compensatory enlargement was considered present when the vessel area at the lesion site was larger than that at the proximal reference site. Inadequate compensatory enlargement was considered present when the vessel area at the lesion site was smaller than that at the distal reference site, and intermediate remodeling was considered present when the vessel cross-sectional area at the lesion site was intermediate between the proximal and distal reference sites. Figure 5 shows an artery with compensatory enlargement of the vessel at a site of lumen narrowing (upper panel) and an artery with inadequate enlargement of the vessel cross-sectional area. In this example, the vessel cross-sectional area at the lesion site was smaller than both the proximal and distal reference sites. As shown in Figure 6, compensatory enlargement was observed in 54% (n = 19), intermediate remodeling in 20% (n = 7) and inadequate remodeling in 26% (n = 9) of 35 lesions. In lesions with inadequate remodeling, 39% and 61% of the decrease in arterial lumen area could be attributed to the reduction in total cross-sectional area of the vessel and
the increase in wall thickness (plaque expansion), respectively. In the intermediate remodeling group, inadequate enlargement of the total cross-sectional area contributed 7%, and an increase in wall thickness 93%, to the reduction of lumen area. In contrast, in the compensatory enlargement group, there was a marked increase in wall area (182%) that was partially (82%) compensated by the increase in vessel cross-sectional area (19). The report by Mintz et al. (20) corroborates the findings of Nishioka et al. (19). Studying 603 lesions in 550 patients, Mintz et al. found inadequate remodeling (Lesion EEL area/Reference site EEL area <0.78) in 15% of lesions. There was only poor correlation between angiographic or IVUS indexes of lesion severity and remodeling (20). The only predictor of inadequate remodeling was the arc of superficial lesion calcium (20). In angiographically normal coronary segments, Nakamura et al. (21) found that the mean percent area stenosis of these segments by IVUS was 36 ± 5%. Both total arterial cross-sectional area and IEL area increased as the plaque expanded. The lumen area also increased as the plaque area expanded. The medial area (EEL area minus IEL area) did not correlate with the plaque area. Thus, this study also confirms that compensatory enlargement at the sites of mild arterial atherosclerosis appears to delay the development of angiographically detectable lumen narrowing. In the early stages of atherosclerosis, arterial enlargement may result in a paradoxic increase in lumen size despite expansion of the plaque area. Because there was no reduction in medial area, this does not seem to be the mechanism of compensatory enlargement.

It has been suggested (10,11) that the degree of compensatory enlargement would be greater in eccentric lesions with a partly disease-free wall that can respond to vasodilatory stimulation. Fujii et al. (11) found that the degree of vascular remodeling was greater in eccentric than in concentric lesions. In contrast, Blank and Yeung (22) report that remodeling is more pronounced in concentric lesions. In their study, concentric lesions showed remodeling relatively early, when the plaque area occupied <55% of the vessel area, but the degree of remodeling was less for more advanced lesions (plaque area >55% of the vessel area). Conversely, eccentric lesions showed
compensatory remodeling only in advanced lesions (plaque area >55% of the vessel area) (22). This finding could be possibly explained by concentric lesions having a vasodilatory response that is impaired earlier (due to more diffuse disease) than in eccentric lesions, hence the stimulus for remodeling might start earlier.

In patients with insulin-dependent diabetes mellitus, the adaptive remodeling in primary coronary lesions is blunted (23). Kornowski et al. (23) compared patients with insulin-dependent diabetes mellitus with patients with non–insulin-dependent diabetes mellitus and patients without diabetes and reported that for every mm² increase in lesion site plaque area, patients with insulin-dependent diabetes had a significantly smaller increase in cross-sectional area of the artery and, as a consequence, more lumen compromise than either nondiabetic patients or patients with non–insulin-dependent diabetes mellitus. It has also been reported (24) that in smokers, in contrast to nonsmokers, focal constriction at sites of stenosis is more common than compensatory enlargement.

Remodeling in Coronary Artery Saphenous Vein Bypass Grafts

Nishioka et al. (25) investigated whether compensatory enlargement occurs in human coronary saphenous vein bypass grafts. Forty-three saphenous vein grafts from patients who had not undergone previous catheter intervention were assessed by IVUS. In addition, seven fresh saphenous veins, harvested from patients undergoing coronary artery bypass surgery were investigated by IVUS. Lumen area was smaller at the lesion site than at the reference site (5.5 vs. 15.8 mm²) or in the fresh saphenous veins (16.5 mm²). Whereas vessel wall area was larger at the lesion site (19.0 mm²) than at the reference site (8.4 mm²) and fresh saphenous veins (7.4 mm²), there was no difference in vessel cross-sectional area (24.5, 24.0 and 23.9 mm² at the lesion site, reference site and fresh saphenous veins, respectively) (Fig. 7). No focal enlargement or constriction of the vessel was found at the lesion site. Thus, the absence of focal compensatory enlargement appears to be a potentially important contributing factor in the progression of lumen stenosis in coronary saphenous vein bypass grafts. In contrast, Mendelsohn et al. (26) and Ge et al. (27) found that the cross-sectional area of vein grafts does increase at the lesion site. Mendelsohn et al. (26) assessed 24 lesions in 21 saphenous vein grafts. The mean vessel area at the lesion site was 25.4 ± 8.2 versus 20.2 ± 8.5 mm² at the reference site (p < 0.001). Vessel area was associated with plaque area (r = 0.83). Ge et al. (27) studied 43 saphenous vein bypass grafts and also found that the cross-sectional area of the vessel at the lesion site was 19.0 mm² compared with 12.8 and 12.9 mm² at the proximal and distal reference sites. The difference between the studies may be the presence of venous valves in the bypass grafts in the latter studies. In the patients included in the study by Nishioka et al. (25) and Siegel et al. (28), venous valves were eliminated by the surgeons from the segments chosen for saphenous vein bypass conduits. Venous graft atherosclerosis is enhanced at the site of venous valves and, as shown in Figure 8, the cross-sectional area at these sites is larger than the reference site. Hence, the increase in vessel area at the lesion sites in the studies by Mendelsohn et al. (26) and Ge et al. (27) may not be due to remodeling but rather to the presence of atherosclerotic lesions at venous valves.

Restenosis After Percutaneous Catheter Interventions

Restenosis is the most frequent complication of percutaneous revascularization and remains its most serious limitation (29,30). Initially, neointimal hyperplasia was thought to be the predominant mechanism of restenosis after balloon angioplasty on the basis of animal experimental models (31,32), human autopsy studies (33,34) and histologic specimens obtained by directional coronary atherectomy (DCA) (35,36). However, numerous experimental and clinical interventions have failed to reduce the incidence of restenosis (37,38). Most of these studies were based on the assumption that smooth muscle cell proliferation and migration and matrix synthesis constitute the principal pathogenetic basis for restenosis (39–42). These data suggest that in addition to intimal hyperplasia, there are other mechanisms responsible for restenosis in humans (38,43).
Animal Models

Rabbit models. Table 4 cites six recent studies of restenosis in rabbit arteries (five in the iliofemoral and one in the carotid artery). Most of these studies show that intimal hyperplasia only partially explains the late loss in lumen area (44,45). Kakuta et al. (46) reported compensatory enlargement of the IEL area at the site of balloon angioplasty 4 weeks after the procedure versus immediately after PTCA. However, their conclusions might be limited because the investigators ligated the distal femoral arteries after balloon angioplasty of the iliac arteries. No control group in which ligation of the femoral arteries was performed without angioplasty is presented. It might be that the enlargement of the vessel was due to the increased resistance after ligation of the femoral arteries. Nevertheless, the restenotic lesions had a significantly smaller total cross-sectional (IEL) area than the nonrestenotic lesions. In the restenotic lesions, the slope of the correlation between IEL area and intimal area was comparable to that of adjacent normal arteries (five in the iliofemoral and one in the carotid artery). Most of these studies show that intimal hyperplasia may be more marked in animals fed an atherogenic diet. Andersen et al. (49) reported similar findings in the LAD of pigs fed a normal diet after induction of a deep arterial wall injury by inflating and withdrawing an oversized chain-encircled angioplasty balloon. Serial coronary angiography revealed that the lumen diameter changed from 3.4 ± 0.4 to 4.2 ± 0.6 mm after dilation and to 1.6 ± 0.4 mm after 2 to 4 weeks. Postmortem histologic studies 3 weeks after dilation revealed that the injury was deep (had reached the adventitia) in all arteries and was circumferential in all but two arteries, with adventitial thickening and neointimal proliferation. There was no correlation between lumen size and extent of neointimal proliferation. Lumen size correlated with vessel size (r = 0.74, p = 0.000005), and the extent of late loss in lumen diameter observed angiographically substantially exceeded that caused by neointimal proliferation seen by histologic analysis. In this model of deep vessel wall injury, as in many of the other animal models of restenosis, arterial remodeling was more important than neointimal proliferation in causing late lumen loss (49).

It might be that the mechanism of restenosis is different after different types of vascular injury (50). Injury that is associated with intense inflammation (as induced by copper stent implantation) may lead to more vascular remodeling than injury that results in less inflammation and more fibrosis, such as thermal injury. Therefore, injury that causes inflammation may weaken the arterial wall and thus enable dilation. It is also possible that the inflammatory process enhances release of mediators and growth factors that facilitate remodeling. However, as is discussed later, stent implantation prevents constriction of the arterial wall and promotes intimal proliferation. As a consequence, it is not clear whether the difference seen is due to inflammation or to the fact that a stent was implanted, thereby preventing shrinkage of the vessel total cross-sectional area.

Human Studies

There are several studies that have found intimal hyperplasia at the site of restenosis and have therefore suggested that intimal hyperplasia is a major mechanism for restenosis in humans after PTCA (41,51) (Table 5). However, more recent data suggest that remodeling may be more important in determining the final lumen size and, hence, the recurrence of myocardial ischemia.

Restenosis after PTCA. Mintz et al. (52) investigated the differences in appearance of primary and restenotic coronary artery lesions on IVUS. The EEL area at the target lesion and reference sites and the plaque plus medial area were similar for vessels with primary and restenotic lesions. However, plaque burden, defined as (Plaque plus media area) * 100/EEL area, was smaller in the restenotic lesions (p = 0.01). Restenotic lesions also had smaller plaque plus medial area normalized for the reference segment. The primary and restenotic lesions had the same distribution of soft, fibrotic and calcific plaque elements. In contrast, the arc of target lesion calcium and the rabbit models, intimal hyperplasia may be more marked in animals fed an atherogenic diet. Andersen et al. (49) reported similar findings in the LAD of pigs fed a normal diet after induction of a deep arterial wall injury by inflating and withdrawing an oversized chain-encircled angioplasty balloon. Serial coronary angiography revealed that the lumen diameter changed from 3.4 ± 0.4 to 4.2 ± 0.6 mm after dilation and to 1.6 ± 0.4 mm after 2 to 4 weeks. Postmortem histologic studies 3 weeks after dilation revealed that the injury was deep (had reached the adventitia) in all arteries and was circumferential in all but two arteries, with adventitial thickening and neointimal proliferation. There was no correlation between lumen size and extent of neointimal proliferation. Lumen size correlated with vessel size (r = 0.74, p = 0.000005), and the extent of late loss in lumen diameter observed angiographically substantially exceeded that caused by neointimal proliferation seen by histologic analysis. In this model of deep vessel wall injury, as in many of the other animal models of restenosis, arterial remodeling was more important than neointimal proliferation in causing late lumen loss (49).
arc of superficial calcium were greater in the restenotic lesions (52). If restenosis were the result of smooth muscle proliferation, then plaque mass should be greater in the restenotic lesions. The composition of restenotic and primary lesions was similar, except for less plaque burden in the restenotic lesions. Luo et al. (53) studied patients with clinical and angiographic evidence of restenosis at an average of 7 ± 6 months after balloon angioplasty and compared them with control patients after balloon angioplasty without evidence of restenosis. Figure 9 shows two IVUS studies of a lesion with and one without restenosis. In the restenotic lesion, lumen area as well as vessel cross-sectional area are smaller at the lesion site than at the proximal and distal reference sites. In the lesion without restenosis, both lumen area and vessel cross-sectional area are of superficial calcium were greater in the restenotic lesions (52). 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angioplasty. In patients undergoing PTCA, a chronic reduction in the EEL area was the principal mechanism for restenosis (67%) and was prevalent in lesions with a mixed or calcific composition. Restenosis after PTCA could occur despite minimal or moderate intimal hyperplasia (54). In a serial IVUS study, Kimura et al. (55) evaluated coronary artery lesions at

Table 5. Restenosis After Percutaneous Catheter Interventions: Human Studies (intravascular ultrasound)

<table>
<thead>
<tr>
<th>Study (ref no.)</th>
<th>No. of Lesions or Pts</th>
<th>Procedure</th>
<th>Time After Procedure (mo)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mintz et al. (52)</td>
<td>857 (323 restenotic, 534 primary lesions)</td>
<td>Primary vs. restenotic lesions</td>
<td>EEL at lesion and ref sites and PA plus MA were similar between primary and restenotic lesions. Plaque burden [(PA + MA) × 100/EEL] was smaller in restenotic than primary lesions. Restenotic lesions had smaller PA plus MA normalized for ref segs. Hence, restenotic lesions are not due to neointimal proliferation.</td>
<td></td>
</tr>
<tr>
<td>Luo et al. (53)</td>
<td>17 with, 14 without restenosis (control)</td>
<td>PTCA</td>
<td>7 ± 6</td>
<td>In pts with restenosis, EEL at restenotic lesion sites was smaller than that of both proximal and distal ref sites (10.1 vs. 14.8 and 13.8 mm², respectively, p &lt; 0.001), whereas in patients without restenosis it was similar. Vessel wall area was slightly increased at angioplasty site (8.0 vs. 7.6 and 6.7 mm², respectively, p = NS). 83% of late LCSA ↓ could be explained by EEL ↓. Only 17% of the LCSA ↓ could be explained by intimal hyperplasia. There was no difference in vessel wall area between restenotic and control groups.</td>
</tr>
<tr>
<td>Di Mario et al. (54)</td>
<td>34 (18 PTCA, 16 DCA)</td>
<td>PTCA vs. DCA</td>
<td>6</td>
<td>PA↑ accounted for 92% and 32% of restenosis after DCA and PTCA, respectively. After PTCA, EEL ↓ accounted for 67% of restenosis.</td>
</tr>
<tr>
<td>Mintz et al. (57,58)</td>
<td>212 primary lesions</td>
<td>Transcatheter interventions (excluding stent)</td>
<td>73% of LCSA ↓ (from 6.6 ± 2.5 to 4.0 ± 3.7 mm², p &lt; 0.0001) was due to EEL ↓, and 27% (from 13.5 ± 5.5 to 14.2 ± 5.4 mm², p &lt; 0.0001) was due to increase in PA plus MA. Change in LCSA correlated more with change in EEL (r = 0.75, p &lt; 0.0001) than change in MA plus PA (r = 0.28, p &lt; 0.0001); 22% of lesions had EEL ↓. LCSA in these lesions did not change (decrease of 0.1 ± 3.3 mm²), and they had less restenosis. In lesion with EEL ↓ at lesion site, LCSA ↓ significantly (3.6 ± 2.3 mm², p &lt; 0.0001). Despite a greater MA plus PA↑ in lesion with adequate remodeling, these lesions showed a smaller restenosis rate (26% vs. 62%, respectively, p &lt; 0.0001) and had a larger incidence of late LCSA gain (49% vs. 1%, p &lt; 0.0001) than lesions with no EEL ↓.</td>
<td></td>
</tr>
<tr>
<td>de Vrey et al. (60)</td>
<td>18</td>
<td>DCA</td>
<td>6</td>
<td>Plaque volume did not change much at any time point (227 ± 93 mm³ before, 198 ± 87 mm³ immediately after and 193 ± 76 mm³ 6 mo after procedure). Progressive lumen loss after the procedure correlated with gradual ↓ in arterial volume (r = 0.90, p &lt; 0.0001) but not with ↑ in plaque volume (r = 0.25, p = 0.07).</td>
</tr>
<tr>
<td>Kojima et al. (61)</td>
<td>78</td>
<td>DCA</td>
<td>6 ± 6</td>
<td>Good correlation was found between change in PA and change in CSA (r = 0.78). Compensatory enlargement of vessel at restenotic sites was common.</td>
</tr>
<tr>
<td>Sumitsuji et al. (62)</td>
<td>94 pts</td>
<td>DCA</td>
<td>Mean 190 d</td>
<td>In restenotic lesions (n = 13), 88% of LCSA ↓ was due to PA↑; only 12% was due to CSA ↓. In nonrestenotic lesions (n = 81), PA at follow-up was smaller than that in stenotic lesions, whereas CSA was comparable.</td>
</tr>
<tr>
<td>Kimura et al. (55)</td>
<td>61</td>
<td>PTCA</td>
<td>6</td>
<td>1 mo after PTCA, there was progressive increase in LCSA and EEL. During the next 5 mo, EEL ↓ and LCSA ↓. Late LCSA ↓ (&gt;1 mo) was due to EEL ↓.</td>
</tr>
<tr>
<td>Kornowski et al. (56)</td>
<td>60 diabetic pts, 162 nondiabetic pts</td>
<td>PTCA, stent</td>
<td>5.6</td>
<td>Late LCSA ↓ was more profound in diabetic than nondiabetic pts (5.2 vs. 2.0 mm² for stented lesions, 3.2 vs. 2.3 mm² for nonstented lesions). Intimal hyperplasia was greater in diabetic pts (5.0 vs. 1.8 mm² for restented lesions, 1.3 vs. 0.6 mm² for nonstented lesions). CSA↑ occurred in 16% of diabetic and 28% of nondiabetic pts.</td>
</tr>
</tbody>
</table>

d = days; DCA = directional coronary atherectomy; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Tables 1 to 3.
baseline, immediately after the procedure and at 24 h and 1 and 6 months after the procedure. Serial changes in lumen area closely paralleled changes in the EEL area. Early vessel enlargement (up to 1 month) resulted in a progressive increase in lumen size, followed by late reduction of the EEL area and therefore marked reduction in lumen size at 6 months (relative to 1 month after the procedure). Late constriction of the total cross-sectional area of the artery was the major mechanism of restenosis (55).

Patients with diabetes mellitus have an increased rate of restenosis after transcatheter interventions. In diabetic patients, intimal hyperplasia may be more profound than in nondiabetic patients (56). Comparing patients with and without diabetes mellitus, Kornowski et al. (56) found that 5.6 months after procedure, there was greater late lumen loss in the diabetic patients. The change in cross-sectional area was comparable between the two groups (1.9 vs. 1.8 mm²). Late increase in the vessel cross-sectional area occurred in 28% of the nondiabetic patients but in only 16% of the diabetic patients (p = 0.08).

In conclusion, late constriction of the vessel cross-sectional area and not intimal proliferation appears to be the major mechanism of restenosis after balloon angioplasty of the coronary arteries. However, in patients with diabetes mellitus, intimal proliferation may be more important.

Restenosis after other percutaneous transcatheter-based interventions. Di Mario et al. (54) compared the mechanisms of restenosis after PTCA and DCA. Patients treated with either PTCA or DCA were studied by IVUS before, immediately after and 6 months after coronary intervention. Plaque increase was the predominant mechanism of restenosis after DCA but not after PTCA, accounting for 92% and 32% of the late lumen loss after DCA and PTCA, respectively. In contrast to post-PTCA restenosis, DCA caused a more hyperplastic response due to deeper vessel wall injury (54). Mintz et al. (57,58) investigated native coronary target lesions in patients that underwent transluminal catheter interventions. Only patients that underwent IVUS imaging immediately after the procedure and at follow-up (due to recurrence of symptoms or as part of clinical protocols) were analyzed. Patients with stent implantation at the lesion site, ostial coronary artery lesion and extensive calcification and those in whom follow-up IVUS imaging could not be performed were not included in this study. At follow-up, 73% of the decrease in lumen was due to a decrease in the EEL area, and only 27% was due to an increase in plaque plus media area (EEL area minus lumen area). The change in lumen area correlated more strongly with the change in the EEL area than with the change in the plaque plus media area. Forty-seven lesions (22%) had adequate remodeling (an increase in EEL area). In the lesions with an increase in EEL area, lumen cross-sectional area was not changed significantly. In contrast, in the lesion in which the EEL area at the lesion site decreased, there was a significant decrease in lumen area. Despite a greater increase in plaque plus media cross-sectional area in the lesion with adequate remodeling, these lesions showed a smaller restenosis rate and had a larger incidence of late lumen area gain than lesions with no increase in EEL area (57). Mintz et al. (57) found that type of procedure (balloon angioplasty, DCA, rotational atherectomy or excimer laser angioplasty) did not predict the direction

Figure 9. A, Comparison of lumen area, vessel wall area and total cross-sectional area (EEL area, arrows), at the proximal reference, restenotic and distal reference sites of coronary arteries with restenosis after balloon angioplasty. The measurements were made by IVUS. Although there is no difference in vessel wall area, the vessel cross-sectional area is smaller at the restenotic sites than at the proximal and distal reference sites. B, Comparison of lumen area, vessel wall area and total cross-sectional area (EEL area, arrows), at the proximal reference, postangioplasty and distal reference sites of coronary arteries without restenosis after balloon angioplasty. Lumen area and vessel wall area at the postangioplasty site are similar to the proximal and distal reference sites, and the vessel cross-sectional area is comparable among the three groups. Hence, lumen narrowing in restenotic sites is caused by constriction of the vessel wall and not by hyperplasia of the vessel wall or expansion of the plaque area. C = catheter. Reproduced with permission from Luo et al. (53).
Atherectomy Study (ABACAS), 88% of late lumen loss was due to the increase in plaque area, whereas only 12% was due to decrease in the cross-sectional area of the vessel. Thus, the data concerning the mechanism of restenosis after DCA atherectomy are controversial. Moreover, although some of the studies reported compensatory enlargement of the vessels at the lesion site, others found shrinkage. Although it has been demonstrated (63) that during the first month after balloon angioplasty or DCA there was an increase in vessel cross-sectional area, and shrinkage occurred only during the subsequent 5 months, the duration of the follow-up period was comparable among the studies. Thus, differences in duration of follow-up cannot explain the variance. Perhaps differences in the depth and extent of tissue removal and, therefore, the severity and depth of tissue injury and the magnitude of adjuvant artery balloon dilation are the underlying mechanisms of the differences among the studies.

**Restenosis after stent implantation.** In stented lesions, neointimal hyperplasia appears to be the major mechanism for restenosis (56,58,64). Changes in the cross-sectional area of the artery within the stent are minimized by the stent (58). However, restenosis at the proximal or distal margins of the stent may be due to remodeling (65). In 64 patients studied 6 months after stent implantation, the increase in plaque area was responsible for 52% of late lumen loss at the proximal margin of the stent, 96% inside the stent, 12% at the articulation of the stent and 24% at the distal margin of the stent.

Most clinical data indicate that restenosis after transcatheter interventions, except for stent implantation, is primarily determined by the magnitude of vessel wall remodeling. The IVUS studies of Luo et al. (53), Mintz et al. (52) and Kimura et al. (55) have found that 73% to 83% of lumen loss is due to remodeling rather than coronary intimal proliferation. An increase in vessel cross-sectional area (the area circumscribed by the EEL) is adaptive, whereas a decrease contributes to lumen narrowing. It may be that after procedures that are associated with more severe and deep vessel wall injury, such as DCA, and after stent implantation that prevents remodeling, intimal hyperplasia is more important (54,58).

**Mechanism of Vascular Remodeling**

Active remodeling of the vessel wall is common both in native atherosclerotic lesions and after transcatheter interventions. In the early stages of atherosclerotic plaque development, compensatory enlargement of the cross-sectional area of the artery occurs. As the plaque expands and occupies >30% to 40% of the vessel wall, this adaptive mechanism can no longer compensate and lumen narrowing occurs. At later stages, fibrosis and contraction of the plaque may cause constriction of the arterial wall and augmentation of lumen narrowing. It is still unclear whether inadequate remodeling is an early (failure of the adaptive compensatory dilation) or late event (active arterial shrinkage) (20). However, inadequate remodeling is more prevalent in lesions with a large arc of superficial calcium (20). Fibrocalcific elements may limit the...
adaptive remodeling to plaque accumulation (14,20). Alternatively, the maturing atherosclerotic plaque, with its increase in fibrous and calcific deposits and diminished lipid content as well as apoptosis, may result in retraction. Consequently, there may be a decrease in the plaque plus media area and, hence, in the vessel cross-sectional area as well. Superficial calcium, which has been associated with inadequate remodeling, may also be a marker of more advanced atherosclerosis (20).

The arterial wall is composed of intimal, medial and adventitial layers with endothelial, smooth muscle and fibroblast cells (66). These components are coupled to one another in a complex autocrine–paracrine interaction. The cells in the vascular wall sense changes within their milieu and integrate these signals by intercellular communication. Local production of mediators influences the structure and function of the arterial wall (66). The intracellular and intercellular mechanisms that lead to compensatory enlargement of the arteries in early atherosclerosis are not known, but several theories exist:

1. It has been suggested (5,67) that atrophy and thinning of the media induced by atherosclerosis may lead to weakening of the arterial wall and, hence, to enlargement. Armstrong et al. (1) found that the media in atherosclerotic arteries of atherogenic diet-fed monkeys exhibited focal atrophy and thinning. Isner et al. (67) demonstrated similar findings of medial atrophy in the presence of coronary atherosclerosis. Because the pressure inside the artery is higher than that outside, focal thinning of the media may lead to progressive passive dilation of the artery.

2. The vessel wall is affected by changes in shear stress. An increase in wall shear stress and a decrease in lumen size by the expanding atheroma may lead to compensatory dilation of the vessel until normalization of the shear stress (45). However, in all the studies of early atherosclerosis mentioned before, lumen area increased during early plaque growth. No study has documented a bidirectional relation, initial decrease in lumen and then progression. This suggests that local release of vasodilator mediators because of a decrease in lumen is probably not the mechanism. In more advanced lesions, when vascular narrowing is severe, the reduction in wall tension due to a Venturi effect could contribute to paradox constrictive constriction of the vessel wall.

After arterial wall injury by transcatheter devices (e.g., balloon angioplasty, DCA), there might be an initial increase in vessel cross-sectional area, followed by a further increase or pathologic shrinkage of the arterial wall, leading to restenosis. Most likely, the severity and depth of the arterial wall injury; the extent of the inflammatory reaction; and the pressure, wall stress and flow through the lesion determine the direction of vascular remodeling. Adventitial fibrosis may lead to contraction of the vessel wall in many cases of vascular damage during percutaneous interventions, especially where there is deep vessel injury (38,49). During balloon angioplasty in humans, the rigid atherosclerotic plaque is separated from the more compliant vessel wall components (plaque-free intima, media and adventitia). Tears usually extend deeply into the vessel wall (41,68). The adventitial damage caused by stretch and tears may trigger inflammation, a proliferative reaction with subsequent contraction of the adventitial scar that may cause late lumen narrowing.

IVUS appears currently to be the only reliable technique for measuring plaque burden and the evolution of atherosclerotic vascular disease. Ideally this method should have been used in studies investigating the effects of drug interventions, such as angiotensin-converting enzyme inhibitors, antioxidants and lipid-lowering agents on the progression and regression of vascular atherosclerotic lesions (69). However, to date no such information is available. The invasive aspect of IVUS, the cost of this procedure, the difficulty in correctly matching sites of measurement on follow-up studies with the site assessed on the initial ultrasound study may limit its use in clinical studies using pharmacotherapy for lesion remodeling (69). However, Lim et al. (70) recently reported that in transplanted hearts, serial IVUS studies have shown that early coronary atherosclerosis is associated with an increase in vessel cross-sectional area that overcompensates for the increase in intimal area in 49% of lesions, whereas no compensation or shrinkage was detected in only 22% of lesions.

**Limitations of Studies Reviewed**

The studies described in this review used either histomorphometric methods or IVUS to measure the various components of the artery at the site of interest and to compare them with either an adjacent reference site with the least atheroma, a control group without atheroma or the same site at different time points.

1. Only the minority of the studies used repeated measurements of the same lesions over time. Comparison of the lesion site with a reference site may be inaccurate because atherosclerosis is a diffuse process, and remodeling of the artery may occur at the early stages of plaque development. Therefore, the reference site may have already undergone remodeling from its original size and may not reflect the true reference site.

2. Histomorphometric measurements rely on careful histologic techniques that aim to minimize the contraction of the artery during processing. Hence, in some of the studies, lumen diameter was measured by in vivo angiography, and changes in lumen area, measured by histologic analysis, were verified by angiographic measurements.

**Conclusions**

The human arterial system is not composed of rigid pipes. Rather, the arterial wall is a biologically active integrated organ, composed of endothelial cells, smooth muscle cells, fibroblasts, collagen, elastin and other extracellular proteins and a vascularized adventitial outer layer. Arterial wall remodeling is common both in primary atherosclerotic lesions and after transcatheter interventions and is a major determinant of lumen size. Early in the course of atherosclerosis, compensatory enlargement predominates and delays the development of lumen narrowing. However, in more advanced stages of ath-
Remodeling when the plaque occupies >30% to 40% of the vessel area, and especially after deep vascular wall injury (as seen after percutaneous interventions), this protective mechanism fails, and inflammatory changes and fibrosis may lead to constriction of the arterial wall. This pathologic remodeling seems to be the principal mechanism of restenosis after percutaneous intracoronary interventions.

References


