Arterial Remodeling
Mechanisms and Clinical Implications

Michael R. Ward, MBBS, PhD; Gerard Pasterkamp, MD, PhD; Alan C. Yeung, MD; Cornelius Borst

The presentation of coronary atherosclerosis can be gradual, because of progressive flow-limiting stenosis and exertional angina, or dramatic, with plaque rupture and thrombosis causing unstable angina, myocardial infarction, or sudden death. The importance of arterial remodeling, or persistent change in vessel size, has recently become apparent in both situations. Arterial remodeling, not plaque size, has been identified as the primary determinant of lumen size in the presence of stable lesions. Similarly, luminal stenosis in transplant vasculopathy and with restenosis after angioplasty occur mainly because of inward remodeling rather than plaque growth. However, recent evidence also suggests that adequate outward remodeling may be associated with an increased risk of plaque rupture, the underlying cause of acute coronary syndromes and sudden cardiac death.

The term “arterial remodeling” has previously been used to describe any change in vessel wall structure. More recently, however, it has been used specifically to refer to a change in vessel size (or cross-sectional area within the external elastic lamina), and it is on this entity that this review is focused. Inward remodeling denotes a reduction in vessel size. Outward remodeling denotes an increase in vessel size. Various other terms are used in the literature (the Table). When outward remodeling is present but insufficient to prevent luminal stenosis, it is referred to as inadequate outward remodeling.

Remodeling as a Primary Determinant of Lumen Size

It has been known for more than a century that blood vessels enlarge to accommodate increasing flow to the organ downstream (eg, during natural growth or in left ventricular hypertrophy). Widespread interest in this phenomenon was stimulated by observations that radial enlargement of vessels (outward remodeling) can compensate for progressive growth of atherosclerotic plaques, thus postponing the development of flow-limiting stenosis.2,3 These pathological findings were subsequently supported by in vivo intravascular ultrasound (IVUS) studies that revealed just how ubiquitously outward remodeling occurs in the presence of atheroma and how such outward remodeling could hide sizeable plaques from angiographic detection.4,5

However, IVUS and postmortem studies have shown that the adequacy of outward remodeling in compensating for plaque growth varies widely between lesions only centimeters apart. Although most atherosclerotic segments exhibit some compensatory enlargement, it is often inadequate to completely preserve lumen size, and some vessels may paradoxically shrink at the lesion site (inward remodeling), exacerbating rather than compensating for lumen loss.6,7 The importance of this variable response is emphasized by the observation that luminal stenosis correlates more closely with the direction and magnitude of remodeling than with plaque size6,8 (Figure 1).

Methodological Issues in the Study of Remodeling

Investigation of atherosclerotic remodeling has been hampered by the absence of a good animal model. Although outward remodeling can also compensate for atherosclerotic plaque growth in animals, inward remodeling is not seen.2 Human studies of remodeling should ideally be longitudinal, measuring change in vessel area in response to plaque growth at the same site over time. However, slow growth of atherosclerotic plaques makes this impractical, expensive, and ethically difficult. To overcome this problem, many investigators use a minimally diseased reference site within the same vessel segment as the lesion for remodeling calculations, assuming that the reference vessel size resembles that at the lesion site at an earlier time. However, recent evidence suggests that remodeling may occur before the onset of plaque formation in atherosclerosis9 and in uninjured segments after angioplasty,10 creating further confusion over the validity of reference segments. The use of reference segments is also problematic in the presence of diffuse disease, such as in diabetes and transplant vasculopathy. There is also no consensus on correction for natural tapering of vessels between reference and lesion sites,7,11 prompting some authors to limit studies to arteries with minimal tapering, such as the common femoral.8 It is hoped that as noninvasive methods of coronary imaging including MRI develop, serial studies in humans may become more feasible.

From the Division of Cardiovascular Medicine, Stanford University Medical Center, Stanford, Calif (M.R.W., A.C.Y.); Department of Cardiology, Utrecht University Medical Center, Utrecht, the Netherlands (G.P., C.B.); and Interuniversity Cardiology Institute of the Netherlands, Utrecht.

Correspondence to Dr Michael R. Ward, Division of Cardiovascular Medicine, Stanford University Medical Center, 300 Pasteur Dr, Stanford CA 94305-5218. E-mail: mrward@stanford.edu

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Putative Mechanisms of Remodeling
The term “remodeling” is used in de novo atherosclerosis, restenosis, and transplant vasculopathy equally. However, it must be emphasized that the predominant mechanisms involved in remodeling in each pathology may be quite different.

Hemodynamic Stimuli and Remodeling
In normal arteries, remodeling is a homeostatic response to changes in the flow and circumferential stretch to restore normal shear stress and wall tension, respectively.12 Outward remodeling in response to increased flow is largely dependent on shear-responsive endothelial production of nitric oxide13 and the gelatinase matrix metalloproteinases (MMPs) MMP-2 and MMP-9.14 Nitric oxide appears to be central in this process because it can induce metalloproteinases,15 inhibit proliferation, and promote apoptosis of smooth muscle cells.16 In contrast, in low-flow states, accentuated production of mitogenic and fibrogenic growth factors, such as platelet-derived growth factor and transforming growth factor-β, probably mediates inward remodeling by increasing smooth muscle cell proliferation and collagen deposition/cross-linking, whereas metalloproteinase induction helps to reorganize vessel structure.17,18

The effect of stretch on remodeling is less clear. Most of the aforementioned mediators of shear-sensitive remodeling are also stretch responsive, and significant interaction between stretch and shear signals appears to exist.19 Elastin absorbs most of the energy of pulsatile pressure, and its production is highly stretch responsive. Vessel elasticity is the chief determinant of resting vessel size, and recent data suggest that altered production of elastin may be important in remodeling.20 It remains uncertain how these molecular and cellular events are spatially coordinated to bring about morphological change. However, the rapid turnover and exquisite shear and stretch sensitivity of connexins,21 transmembrane proteins that allow intercellular communication, suggest that they may play a role.

In theory, remodeling in response to hemodynamic stimuli may be prevented by endothelial dysfunction and increasing plaque depth through which effectors of remodeling must penetrate in atherosclerotic lesions and after angioplasty and transplantation. However, outward remodeling still occurs in response to increased flow in atherosclerotic monkeys.22 Localized remodeling in human atherosclerosis and after porcine angioplasty has been correlated with computer-modeled levels of shear stress.23 Furthermore, in focal lesions, acceleration of flow on the proximal side and deceleration of flow on the distal side of a protruding plaque are associated with comparatively less cellularity and collagen in the upstream side and plaque growth downstream,24 suggesting persistent shear sensitivity.

Figure 1. Top, Changes in cross-sectional area along nonbranching coronary artery segment obtained postmortem in which local lumen area is determined mainly by vessel size. Arterial segment is represented as if all lesions were completely concentric. Dotted line represents internal elastic lamina; solid line, luminal border. Diameter of schematic lumen (between solid lines) represents cross-sectional area of lumen. Bottom left, absence of significant relationship between lumen area and plaque area. Bottom right, significant relationship between lumen area and vessel area (remodeling).
Inflammation, Scarring, and Remodeling

Inflammatory cells likely play a major role in atherosclerotic remodeling because of their production of metalloproteinases. Recruitment of monocyte/macrophages by cell adhesion molecules, such as ICAM-1 and VCAM, is shear sensitive and partly explains the predominance of macrophages and T cells in the upstream side of focal lesions and in vessels in which outward remodeling is more prevalent. Hyperlipidemia also increases inflammatory cell infiltration into atherosclerotic lesions and promotes their expression of MMPs. Much of the metalloproteinase expression in plaques originates from macrophage foam cells, is readily reduced by lipid lowering or reduction in lipid oxidation, and may underlie the apparent stimulatory effect of hypercholesterolemia on outward remodeling response, which in extreme hypercholesterolemia may result in vessel ectasia. Ultrastructural changes in the internal elastic lamina induced by hypercholesterolemia are similar to those observed in high flow and suggest a common metalloproteinase-dependent mechanism of outward remodeling. Elevated local metalloproteinase activity induced by hypercholesterolemia may explain why some eccentric plaques appear to initiate remodeling in the vessel wall directly beneath the plaque and why medial thinning underlying a plaque is directly proportional to plaque burden.

Outward remodeling may be prevented by excessive collagen deposition within a lesion. When a sudden or focal fibrotic response is induced, such as after angioplasty or plaque rupture, scar contracture may even result in inward remodeling (Figure 2).

Clinical Observations Regarding the Mechanisms of Atherosclerotic Remodeling

Although many factors that promote plaque growth have been identified, much less is known about determinants of remodeling. Some of the variation in remodeling response depends on the vascular bed involved: The iliofemoral arteries are prone to inadequate outward or to inward remodeling, whereas it is uncommon in the renal arteries. The reasons underlying regional heterogeneity in remodeling responses are unclear but may reflect variability in endothelial responses to altered hemodynamics. In addition, some investigators have found that patient characteristics influence remodeling patterns: Inadequate outward remodeling and inward remodeling are more common in insulin-using than non–insulin-using diabetics, are more common in smokers compared with nonsmokers, and are less frequent with hypercholesterolemia.

Despite these systemic and regional factors, there is often marked variability in remodeling response along the same artery. Some lesion specificity in remodeling response can be attributed to the amount of calcium present and altered local hemodynamics. Low shear predisposes the inner curves of tortuous segments to develop atheroma and may impede outward remodeling in a similar manner. In theory, endothelium-dependent outward remodeling should be improved in eccentric lesions in which an arc of undiseased vessel is present. It is perhaps because eccentric atherogenesis frequently originates at sites of low or turbulent flow that also impairs outward remodeling that postmortem studies have found no relationship between remodeling and lesion eccentricity or extent of disease-free arc.

Remodeling in Accelerated Vasculopathies

Inward remodeling contributes significantly to luminal narrowing in more accelerated forms of vascular disease, such as transplant vasculopathy and restenosis after angioplasty. Their shorter time course facilitates sequential study in both humans and experimental animals.

Remodeling in Restenosis

Inward remodeling is a major factor in restenosis after angioplasty and atherectomy in humans as had been suggested in experimental animals. Longitudinal evaluation of restenosis after angioplasty and atherectomy with IVUS imaging at several time points has shown that inward remodeling occurs predominantly between 1 and 6 months after the procedure, thus distinguishing it from early elastic.
recoil. Stents eliminate inward remodeling but also result in excessive intimal growth. Porcine coronary angioplasty studies have suggested that adventitial cicatrization may be important in inward remodeling, the attenuation of which may partly underlie the benefits of radiation therapy. Regression of angiographic stenosis very late (6 months to 5 years) after angioplasty suggests that the ability to outwardly remodel may be restored and that the prominence of inward remodeling in the restenotic process may be due to the temporary absence or dysfunction of endothelium overlying the lesion. Endothelial dysfunction at the dilated segment may be due to inactivation of nitric oxide by the surge in oxidant stress after injury, because endothelial function can be restored by local delivery of the nitric oxide precursor L-arginine. The reduced restenosis rates with the antioxidant probucol, attributed by IVUS to a favorable effect on remodeling, may thus be due to a restoration of endothelial function and outward remodeling responses.

Data from animal and human studies also indicate that inward remodeling and restenosis may be accentuated by low flow. This may be due to stimulation of platelet-derived growth factor (PDGF) and transforming growth factor-β expression by low shear, because tyrosine kinase inhibition attenuates inward remodeling after pig coronary angioplasty. The reduction in restenosis after human angioplasty with trapidil, which inhibits PDGF, may thus be done through inhibiting inward remodeling.

Remodeling in Transplant Vasculopathy
Transplant vasculopathy, the most common cause of graft failure and death after heart transplantation, is characterized by diffuse angiographic luminal narrowing, which is frequently not amenable to revascularization. Recently, it has become apparent that in addition to progressive intimal thickening, inward or inadequate outward remodeling is common in transplanted hearts, and the importance of its contribution to lumen loss increases with time from transplantation. Despite diffuse endotheliopathy, some remodeling in response to hemodynamic stimuli appears to persist. Although sympathectomy prevents inward remodeling after angioplasty, the effect of denervation with transplantation on remodeling is unknown. Although such drugs as diltiazem and HMG CoA reductase inhibitors reduce angiographic progression of transplant vasculopathy, IVUS studies have attributed this to reduction in intimal growth rather than prevention of inward remodeling.

Remodeling and Plaque Rupture
Plaque rupture underlies most unstable angina, myocardial infarction, and sudden death from coronary artery disease. Many angiographic studies have demonstrated that most lesions responsible for myocardial infarction were minimally occlusive before rupture, consistent with the fact that many patients had no prior history of ischemia. Patients who died with plaque rupture without prior history of coronary disease showed large lesions, suggesting that considerable outward remodeling had prevented angiographic stenosis despite significant histological stenosis. Prevention of the development of a flow-limiting stenosis by outward remodeling unfortunately also removes the stimulus for the development of collaterals that could prevent myocardial infarction when plaque rupture with thrombotic occlusion occurs.
Several lines of evidence from recent observational studies have suggested that the process of outward remodeling may be associated with plaque rupture. Initially, it was noted that the remodeling response correlates with mechanical characteristics and clinical presentation of the plaque. In patients presenting for angioplasty, calcified plaques are associated with inadequate outward or with inward remodeling, whereas soft plaques exhibit better compensatory enlargement. Lesions responsible for unstable syndromes have larger, softer plaques with more outward remodeling than those in stable angina, which are more fibrous and calcified (Figure 3).62,63

It may be argued that IVUS studies of patients presenting with percutaneous revascularization are necessarily biased (If stable lesions had remodeled well, they would not need revascularization). However, a prospective IVUS study that related plaque morphology and risk of rupture found that plaques that subsequently ruptured were significantly larger than those that did not but had a larger vessel area that preserved lumen area. In addition, a postmortem study in which sections from the same artery were compared found that those sections with the largest plaque and vessel area (ie, the most outward remodeling) had the most macrophages and T lymphocytes and the least smooth muscle cells and collagen, all features of plaque vulnerability. These differences were most marked in the shoulder region of the plaque where rupture is most frequently seen.

Any relationship between remodeling and plaque rupture can be rationalized by the involvement of MMPs and apoptosis in both processes. It remains uncertain, however, whether this relationship is causal or is due to common mechanisms. If a causal relationship can be established, then longitudinal rates of remodeling may be able to predict acute events. Conversely, if MMP inhibitors are used to prevent plaque rupture, it may be at the expense of increasing luminal compromise and need for revascularization. In addition, if outward remodeling would result in plaque rupture, it would also be interesting to know whether subsequent fibrous healing culminates in inward remodeling (Figure 2).

The importance of the inflammatory response in the association between outward remodeling and plaque rupture would suggest that anti-inflammatory and lipid-lowering agents may reduce outward remodeling responses. This may help to explain why regression in angiographic lumen stenosis was minimal compared with the reduction in clinical events in lipid-lowering trials.60

Conclusions
The ubiquitous nature and the critical importance of arterial remodeling in forestalling or exacerbating flow-limiting stenoses in vascular disease have only recently been realized. In de novo atherosclerotic lesions, arterial remodeling determines the impact of plaque mass on luminal narrowing. Restenosis after angioplasty is determined primarily by inward arterial remodeling rather than by intimal hyperplasia. In transplant vasculopathy, luminal narrowing is also determined primarily by inward remodeling.

The effectiveness of outward remodeling in preventing ischemia in atherosclerosis would suggest that strategies to promote outward remodeling would be beneficial. Outward remodeling, however, appears to be a double-edged sword; it may be associated with plaque rupture and thus unstable angina, myocardial infarction, and sudden death. Further understanding of the relationship between arterial remodeling, inflammation, and plaque rupture may allow us to use the rapidly accumulating knowledge regarding the growth factors and proteases involved in remodeling to responsibly manipulate the process for the benefit of patient outcomes.

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References

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