Arterial Remodeling and Coronary Artery Disease: The Concept of “Dilated” Versus “Obstructive” Coronary Atherosclerosis

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Traditionally, the development of coronary artery disease (CAD) was described as a gradual growth of plaques within the intima of the vessel. The outer boundaries of the intima, the media and the external elastic membrane (EEM), were thought to be fixed in size. In this model plaque growth would always lead to luminal narrowing and the number and severity of angiographic stenoses would reflect the extent of coronary disease. However, histologic studies demonstrated that certain plaques do not reduce luminal size, presumably because of expansion of the media and EEM during atheroma development. This phenomenon of “arterial remodeling” was confirmed in necropsy specimens of human coronary arteries. More recently, the development of contemporary imaging technology, particularly intravascular ultrasound, has allowed the study of arterial remodeling in vivo. These new imaging modalities have confirmed that plaque progression and regression are not closely related to luminal size. In this review, we will analyze the role of remodeling in the progression and regression of native CAD, as well as its impact on restenosis after coronary intervention.

In vivo studies of human coronary arteries using intravascular ultrasound (IVUS) imaging found a similar correlation between atheroma and external elastic membrane (EEM) area (7). Using epicardial ultrasound, McPherson et al. (8) introduced the examination of arterial remodeling in individual lesions by comparing EEM area at the lesion and proximal reference site of the same vessel. Subsequently, in an IVUS study Ge et al. (9) reported that the EEM area of atherosclerotic segments was significantly larger than that of proximal segments. Further histologic and IVUS studies demonstrated that arterial remodeling could be bidirectional. “Positive remodeling” as observed by Glagov et al. (6) describes an expansion in EEM area and “negative remodeling” describes shrinkage of EEM area at the lesion site (Fig. 2) (10,11). Mintz et al. (12) used IVUS to examine 603 coronary atherosclerotic lesions in patients presenting with stable angina. Inadequate or negative remodeling was defined as a ratio of lesion EEM to proximal reference EEM area ≤0.78 and was found in 15% of lesions.

Diagnostic methods. Intravascular ultrasound and magnetic resonance imaging (MRI) are the primary clinical methods to investigate arterial remodeling in vivo. Intravascular ultrasound provides tomographic imaging of the vessel wall (Fig. 3) (13). During coronary angiography a transducer-tipped ultrasound catheter is advanced into the vessel beyond the target lesion site. The catheter is then withdrawn through the lesion, yielding a series of tomographic images. Each image is analyzed individually. Plaque morphology is classified as soft, fibrotic or calcific based on

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echodensity on a continuum from echolucent to echodense. However, the visual classification of plaque composition is limited because the categories available from qualitative evaluation of video images are coarse. Advanced analysis of the IVUS data with, for example, radiofrequency analysis may allow a more detailed description.

Intravascular ultrasound provides excellent boundary definition for tissue interfaces with an abrupt change in acoustic impedance. Although the media can not always be separated from the intima, the blood-intima border and the EEM are easily identified and allow the measurement of luminal area, intima-media area and EEM area (14). Therefore, with IVUS, the extent and direction of arterial remodeling can be derived from measurements of the EEM area at the target lesion site and a reference site. At each site, the EEM area is measured at the leading edge of the adventitia. The remodeling ratio is defined as the ratio of the EEM area at the lesion site to the EEM area at the proximal reference site (Fig. 2). Although the remodeling response is a continuous variable, its direction is often classified categorically. A frequently used definition differentiates positive remodeling, absence of remodeling and negative remodeling, defined as a remodeling ratio >1.05, 0.95 to 1.05 and <0.95 respectively (Figs. 2, 4 and 5) (15).

Magnetic resonance imaging is a noninvasive three-dimensional imaging technique that differentiates tissue structures on the basis of their proton magnetic properties. In recent human and serial animal studies MRI has been shown to accurately quantify the vessel wall area, allowing assessment of arterial remodeling (16,17). Significant technical improvements in resolution and gating are needed before this technique can be applied to the examination of coronary arteries in clinical settings (18).

**Definitions of remodeling.** Many methodologic problems remain regarding the optimal approach to define arterial remodeling. Theoretically, arterial remodeling describes dynamic changes of the EEM area over time. However, clinical studies of remodeling often examine this phenomenon at a single, static point in time. In most histologic investigations and some IVUS studies, the existence of remodeling is inferred from the comparison of plaque and EEM size in groups of lesions of differing severity (6,7). Positive remodeling is defined by a positive correlation between plaque and EEM area. In this type of analysis, the extent and direction of remodeling can be described for a large group of lesions, but not for specific sites.

To assess the extent and direction of remodeling in individual lesions, it is necessary to compare vessel size at the lesion site to an adjacent reference site that contains

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**Abbreviations and Acronyms**
- CAD = coronary artery disease
- EEM = external elastic membrane
- IVUS = intravascular ultrasound
- MRI = magnetic resonance imaging
- SVG = saphenous vein grafts
- TLR = target lesion revascularization rate

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**Figure 1.** Early plaque accumulation in human coronary arteries is associated with compensatory enlargement of vessel size (positive remodeling). Therefore, luminal size is initially not affected by plaque growth. These complex changes of lumen, plaque and external elastic membrane (EEM) may also affect plaque regression. Adapted from Glagov et al. (6). CAD = coronary artery disease.
minimal disease (Fig. 6) (8,19). Assuming that the original vessel size was similar at the lesion and reference site, this definition describes the extent of arterial expansion or shrinkage at the lesion site. Positive and negative remodeling is defined as larger or smaller EEM area at the lesion site than at an adjacent reference site (Fig. 2). However, the comparison of EEM size at the lesion and reference site has several limitations. Theoretically, the “normal” EEM area at any lesion should be smaller than the EEM area at a proximal reference site and larger than the EEM area at a distal reference site, because of vessel tapering. Therefore, the EEM area at the lesion site is influenced by its distance from the reference site. Furthermore, angiographically “normal” reference segments frequently contain mild to moderate atherosclerosis, and a truly normal segment from which to calculate the “normal” EEM area may not exist (20).

In contrast to describing the static extent of remodeling, serial observations of lesion sites can define the dynamic process of remodeling (Fig. 7). It is crucial to differentiate between dynamic and static observations, because both can coexist. For example, in a longitudinal designed pharmacologic intervention trial, a positive remodeled lesion (defined by the comparison of lesion and reference site before treatment) could subsequently undergo negative remodeling (defined by comparison of the lesion site before and after treatment) as a consequence of the drug effect.

**Pathophysiology and significance of remodeling in native coronary arteries.** The pathophysiology of vascular remodeling is not fully understood. However, available data suggest that remodeling is initiated by the detection of signals related to changes in hemodynamic conditions (flow, wall stretch, shear stress) and humoral factors (cytokines, vasoactive substances) (2,21,22). Hypothetically, these signals are relayed within the endothelium (23) and transmitted to adjacent cells, eventually causing the synthesis or activation of substances that influence cell growth, apopto-

**Figure 2.** Positive and negative arterial remodeling describes extremes of the remodeling response. Longitudinal sections through vessel segments with positively and negatively remodeled lesions are shown. EEM = external elastic membrane; remodeling ratio (RR) = EEM area lesion/EEM area proximal reference.

**Figure 3.** Intravascular ultrasound images show tomographic sections of the vessel, including lumen, vessel wall and adventitia. EEM = external elastic membrane.
sis, migration and the composition of the extracellular matrix (24). The extracellular matrix, which is the connective tissue scaffolding of the vessel wall, appears to have a central role in the remodeling process. A group of enzymes, the matrix-metalloproteinases, regulate the composition of the extracellular matrix by selective degradation of its components and may have an important role in the remodeling response (25–28). The respective role of changes in the media and adventitia in the process of remodeling is not completely understood. Several investigators have described a prominent contribution of the adventitia. Other groups demonstrate early changes in the media. Medial thinning appears to be an early and important finding in atherosclerotic lesions (3,29–32). The interaction between medial and adventitial pathology and the intimal atherosclerotic process deserves further investigation.

Positive remodeling was initially described as a compensatory mechanism in early coronary artery disease preventing luminal loss despite plaque accumulation. However, recent studies have revealed an association between the direction of remodeling and clinical presentation (33,34). Smits et al. (33) performed coronary angioscopy and IVUS in 34 patients before intervention. Lesions were classified by angiographic criteria as smooth or complex. Using IVUS the remodeling response was defined as the ratio of the EEM area at the lesion and reference site. Stable and unstable lesions were defined by the clinical presentation. Unstable lesions were more commonly characterized by positive than
negative remodeling (58% vs. 17%), whereas stable lesions more often showed negative than positive remodeling (50% vs. 12.5%). Also, angiographically complex lesions more often had positive than negative remodeling (57% vs. 14%).

The pathophysiologic mechanisms linking plaque vulnerability and remodeling have not been established with certainty. However, inflammation may represent a common link. Inflammatory markers such as macrophages and matrix-metalloproteinases have an established role in the pathophysiology of plaque rupture (35–37). Recent histologic studies suggest a similar relationship between inflammation and remodeling (28,38). Pasterkamp et al. (38) describes an association between histologic markers associated with plaque inflammation and positive arterial remodeling in femoral arteries.

It is an attractive hypothesis to describe the direction of remodeling in relation to the temporal development of plaques (Figs. 1 and 8). Positive remodeling may be a characteristic of early, “proliferative” lesions, allowing considerable plaque accumulation despite normal luminal size. These accumulating plaques, characterized by inflammatory and proliferative processes, may be particularly “vulnerable” to rupture leading to acute coronary syndromes (39). The fibrotic changes associated with negative remodeling of advanced plaques could lead to a reduced risk of plaque rupture and, therefore, plaque stabilization.

Plaque stabilization related to changes of lesion composition and architecture has been examined in animal experiments (40–44), but in only a few clinical studies. A relation between remodeling and lipid metabolism is suggested by epidemiologic studies demonstrating that high serum or plaque-tissue cholesterol levels are associated with positive remodeling (45). A small IVUS study examined the effect of three-year treatment with pravastatin on mildly diseased coronary arteries (46). During follow-up plaque area increased by 41% in the control group but decreased by 7% in the treatment group. External elastic membrane area increased by 9% in the control group but did not change in the treatment group. Luminal area decreased by 9% in the control group but increased by 10% in the treatment group. These preliminary results suggest that regression of atherosclerosis entails dynamic changes of plaque size, plaque composition and remodeling response of the vessel wall, but need to be confirmed in further prospective studies.

In summary, the observation of remodeling in native coronary arteries is important in the assessment of plaque vulnerability and stabilization. The concept that both arterial expansion and shrinkage can be manifestations of atherosclerosis is supported by basic research (47) and the clinical analogy between positive remodeling, abdominal aortic aneurysms (48–50) and coronary ectasia (51,52).

Remodeling and restenosis after coronary interventions. In animal models arterial remodeling has been shown to contribute to restenosis after coronary intervention (53,54). A direct correlation between chronic constriction of the EEM area (negative remodeling) and late residual stenosis was found. These results were confirmed in vivo with IVUS. Mintz et al. (55) studied 212 native coronary lesions immediately after percutaneous coronary intervention and at a follow-up catheterization 5.6 ± 3.4 months later. The ultrasound cross-section with the smallest luminal area at follow-up was compared with the matching site immediately after intervention. The EEM area increased from preintervention to postintervention (18.5 ± 6.3 mm² vs. 20.1 ± 6.4 mm²), but decreased subsequently between postintervention and follow-up to 18.2 ± 6.4 mm². Liminal area increased from preintervention to postintervention (1.7 ± 0.9 mm² vs. 6.6 ± 2.5 mm²) and then decreased to 4.0 ± 3.7 mm² at follow-up. Plaque area increased significantly between postintervention and follow-up (p < 0.0001). A total of 73% of luminal loss between postintervention and follow-up was attributable to a decrease in EEM area, compared with 23% caused by neointimal area growth. The change in luminal area correlated more strongly with the change in EEM area (r = 0.75, p <
In these studies, a significant decrease in EEM area between postintervention and follow-up was observed. Importantly, EEM area was either unchanged or only slightly different between preintervention and follow-up. In other words, vessel size at follow-up might have returned to its preprocedural baseline. It is important to differentiate between the passive process of elastic recoil and the active process of negative remodeling. Interventional procedures are associated with a mechanical expansion of the vessel wall. Wall stretch was shown in angiographic and IVUS to represent up to 43% of immediate luminal gain (57). Opposing forces defined by the elastic or viscoelastic properties of the vessel wall lead to elastic recoil. Immediate recoil is typically defined as the difference between the diameter of the interventional device and the immediate postinterventional diameter (58), and has been reported in several studies to cause a luminal loss between 23% and 46% shortly after balloon deflation (59,60).

The later changes that occur after this “immediate” period are often defined as negative remodeling, but controversy exists regarding the contribution of delayed elastic recoil. Delayed elastic recoil (the correct biomechanical term is “creep”) is related to the viscoelastic properties of the vessel wall (61). Although several studies found no significant decrease in minimal luminal diameter during the first 24 h after angioplasty (62–64), other studies describe delayed vessel shrinkage. Nobuyoshi et al. (65) studied 229 patients with angiography immediately and 24 h after percutaneous transluminal coronary angioplasty 12 months later. Stenosis diameter decreased from 1.91 ± 0.53 mm immediately after coronary angioplasty to 1.43 ± 0.67 mm at three months. Mean stenosis diameter did not change further after three months.

These studies suggest that arterial shrinkage occurring in native atherosclerosis may be different from that observed after intervention. After coronary angioplasty the postinterventional EEM diameter gradually returns to but does not fall below the preinterventional EEM diameter. On the other hand, negative remodeling in native vessels is characterized by a decrease of vessel size below baseline. Histologic studies indicate that negative remodeling of native coronary.
arteries is characterized by fibrosis (40,41), whereas restenosis is characterized by proliferation and inflammation (66–68). The significance of this difference is incompletely understood, but may indicate a different pathophysiology of vessel shrinkage in native arteries and after intervention.

Recent IVUS studies have examined the relation between preinterventional direction of remodeling and procedural outcome. Pasterkamp et al. (15) compared the immediate result and mechanism of balloon angioplasty in 121 human femoral artery lesions with positive and negative remodeling. The absolute luminal gain did not differ significantly between the remodeling groups, but there were differences in the mechanism. Stretch of the EEM area was significantly larger in the group with wall shrinkage than in the groups with compensatory enlargement. Subsequent luminal loss secondary to elastic recoil was not significantly different between the two groups.

Dangas et al. (69) examined whether the direction of preinterventional remodeling predicts target lesion revascularization rate (TLR) after nonstent intervention. Preinterventional IVUS images of 777 lesions were analyzed. The TLR rate was higher in the positive remodeling group than in the negative/intermediate remodeling group (31.2% vs. 20.2%, \( p = 0.007 \)). The remodeling index was strongly correlated with the probability of TLR (\( p = 0.0001 \)). An important limitation of this study is that lesions with positive remodeling were treated more often with directional atherectomy whereas balloon angioplasty alone was more frequent in the negative remodeling group. Another study found an association between preinterventional positive remodeling and creatine kinase elevation after intervention (70), suggesting a possible association between positive remodeling and distal embolization (71).

The role of remodeling after intravascular radiation therapy has recently been described. Waksman et al. (72) report results from an animal model showing that irradiated vessels were significantly larger than controls at follow-up. Using IVUS, Meerkin et al. (73) report absence of shrinkage in total coronary EEM area in humans during six-month follow-up after radiation. Recent reports describe the phenomenon of vessel expansion outside of stents after intracoronary irradiation.

Arterial remodeling after coronary artery bypass surgery and cardiac transplantation. Diffuse vascular remodeling of vein grafts early after coronary bypass surgery is related to hemodynamic changes affecting the graft (2). Graft luminal size and patency are critically dependent on flow, with suboptimal flow after surgery preventing the adaptive dilation of the graft (74,75). Superimposed on this early diffuse remodeling response is the later development of focal atherosclerotic plaques, leading to further changes in EEM and luminal size.

However, cross-sectional IVUS studies examining the remodeling response in bypass grafts show contradictory results. Nishioka et al. (76) examined 43 saphenous vein grafts (SVGs) with IVUS 8 to 23 years after bypass surgery. Cross-sectional area of the graft at the lesion and reference site was not significantly different, but lesion sites were characterized by significantly smaller lumen and larger plaque size. Contrary to these findings, other studies report compensatory enlargement in SVGs. Mendelsohn et al. (77) examined 24 SVG lesions with IVUS between 10 months and 16 years after surgery. The EEM area was larger at the lesion site in comparison with the reference site in 96% of the lesions. A significant correlation between plaque and EEM area was observed (\( r = 0.83, p < 0.001 \)).
The time interval between bypass surgery and IVUS examination likely explains some of the contradictory results in these studies, and data about serial examinations of vein grafts after surgery are preliminary.

The dynamic changes of transplant vasculopathy after cardiac transplant are reflected in complex time-dependent changes of remodeling (78–81). Superimposed is the progression of preexisting atherosclerotic lesions of the transplanted coronary vessels (donor disease) (82). Donor-related lesions may be a particularly interesting model of plaque progression/regression because of the significant differences in the risk factor profile of donor and recipient.

A comparison of the remodeling response in native atherosclerosis, vein graft disease and transplant vasculopathy shows several similarities, suggesting either a common pathophysiology (e.g., inflammation) or a common pathophysiologic response to different triggers.

Conclusions. In 1953, Crawford and Levene (3) wrote: “Atheromatous plaques do not project into the lumen but lie in a depression in the media which may bulge outwards. In this way the triad of atheroma, thrombosis and aneurysm become linked in one continuous pathological process.”

We have learned that expansion and shrinkage of coronary vessels is an important process in coronary artery disease (CAD). This process of “arterial remodeling” is fundamental to the pathophysiology of CAD in native coronary lesions and after interventional procedures such as angioplasty.

However, the clinical significance of these complex changes of vessel and plaque size is incompletely understood. The recent in vivo experience with IVUS has confirmed that both arterial expansion and shrinkage can be a manifestation of coronary atherosclerosis. Positive remodeling (arterial expansion) is frequently associated with unstable coronary syndromes whereas negative remodeling (arterial shrinkage) is associated with stable coronary syndromes. These changes of vessel size are clearly related to atherosclerotic disease progression and regression. Therefore, the observation of remodeling is important in the assessment of plaque vulnerability and stabilization.

In analogy to the terminology of cardiomyopathic processes, we propose to describe “dilated” and “obstructive” coronary atherosclerosis as extremes of a continuous pathologic process (Fig. 9). A better understanding of the remodeling response may have important implications in the diagnosis, prevention and treatment of CAD.

References


of blood flow rate on subendothelial proliferation in venous autografts used as arterial substitutes Circulation 1975;52 Suppl I: I163–72.


