Expansive Arterial Remodeling: Location, Location, Location

Gerard Pasterkamp, Zorina S. Galis, Dominique P.V. de Kleijn

Abstract—The artery is a dynamic organ capable of changing its geometry in response to atherosclerotic plaque formation. Expansion of the vessel diameter retards luminal narrowing and is considered a compensatory response. However, the expansive remodeling response is a “wolf in sheep’s clothes,” because expansion is associated with the presence of inflammatory cells, proteolysis, and a thrombotic plaque phenotype. The prevalence and clinical presentation of expansively remodeled lesions may differ among vascular beds. However, it is evident that all types of atherosclerotic arterial expansive lesions share the presence of inflammatory cells and subsequent protease activities. The potential role of inflammation and protease activity in the development of the different remodeling modes is discussed. (Arterioscler Thromb Vasc Biol. 2004;24:650-657.)

Key Words: remodeling ■ atherosclerosis ■ toll-like receptor ■ inflammation ■ compensatory enlargement

Plaque formation has long been considered the only determinant of atherosclerotic luminal narrowing. The arterial wall, however, is not a rigid tube, but rather an organ capable of overall reshaping in response to hemodynamic, mechanical, and biochemical stimuli. For instance, the increase in the circumference of the artery can partially or totally compensate for the encroachment of the lumen caused by formation of atherosclerotic plaques or by intimal hyperplasia after arterial injury.1-3 However, the arterial wall may also respond with constrictive remodeling, thereby aggravating the luminal narrowing response4,5 (Figure 1).

Scientific interest in the role of arterial remodeling in occlusive arterial disease boomed with the upcoming use of the visualization technique of intravascular ultrasound (IVUS). With IVUS, it became apparent just how ubiquitously remodeling can prevent plaque from encroaching on the lumen and also how failure of an expansive remodeling response accelerates luminal stenosis in de novo atherosclerosis. The role of such geometrical remodeling response in relation to plaque formation is currently appreciated but has been traditionally strongly underestimated as a causal factor for arterial occlusive disease. It has recently become clear that the geometrical change in arterial size and plaque area may equally contribute to the luminal narrowing in atherosclerotic disease6 (Figure 2). For instance, it is possible to demonstrate that in 5% of patients eligible for coronary intervention, the plaque mass at the culprit lesion is actually smaller than that located at the angiographically normal reference site, indicating that in such lesions the degree of luminal narrowing is determined by the differences in vessel size rather than by the plaque mass.6

In this brief review, an overview of anatomical localization and local morphology of the different remodeling modes is given. We also discuss available results of mechanistic
research linking expansive remodeling and the presence of a local inflammatory response, which is the most general feature of expansively remodeled lesions.

**Expansive and Constrictive Arterial Remodeling: Location, Location, Location**

Most research on the role of geometric remodeling has focused on the coronary circulation. However, peripheral arteries also undergo circumferential changes in response to atherosclerotic lesion formation. In a postmortem study, we previously reported on the prevalence of the different remodeling modes in coronary and peripheral arteries prone to atherosclerotic lesions. This study revealed that constrictive remodeling was most prevalent in femoral arteries, whereas this was rarely observed in renal arteries (Table). Of note, the study was performed in arteries obtained from patients that did not die of cardiovascular disease. Constrictive remodeling is reported to occur in 15% to 63% of culprit lesions in coronary arteries and in 59% of femoral arteries of patients with claudication (Table). Zarins et al provided early indications that location strongly influences the remodeling mode after formation of the plaque. They showed that compared with proximal segments, distal arterial coronary segments are more prone to expand in response to plaque formation. This was confirmed by observations demonstrating that expansive remodeling is more evident in smaller arterial segments.

Some of the confusion regarding the reported prevalence of constrictive versus expansive remodeling can be explained by the lack of a unified definition for the assessment of atherosclerotic remodeling. In clinical studies, angiography reveals the size of the lumen while giving no indication regarding plaque burden and arterial remodeling. Subsequently, arteries mistakenly deemed as normal based on the size of its lumen may be used as a reference site. A strong inverse relation exists between luminal narrowing and the degree of expansive remodeling. Thus, if the section with the normal lumen and an expansively remodeled vessel wall is chosen as a reference, then the culprit lesion with maximal luminal narrowing is often found to be “constricted.” It merits careful consideration, however, that this cannot explain the differences in the prevalence of expansive and constrictive remodeling among vascular beds.

**Expansive Remodeling and Aneurysm Formation: Same Beast in a Different Location?**

A frequently raised question is whether expansive remodeling and aneurysm formation are the same processes. The common definition for aneurysm formation always refers to the geometry of the affected artery, but rarely to its morphology. Based on such general definition, aneurysms are a subset of expansively remodeled arteries. However, clinical presentation of expansively remodeled arterial segments differs...
widely based on their location within the cardiovascular system, ie, spontaneously outwardly ruptured aneurysms are mostly described for the abdominal aorta or cerebral arteries but are rare in carotid, coronary, or femoral arteries. In addition, the location of the compromised structure within the arterial wall differs as well, because aneurysmal dilatation is associated with the degradation of the outer layers and ruptures toward the outside, whereas the expansively remodeled coronary artery is usually disrupted intraluminally, either through plaque rupture or through plaque erosion. In this case, disruption does not lead to massive hemorrhage but rather to arterial occlusion caused by thrombosis followed by acute coronary syndromes. Although their trigger and clinical presentation may differ, these processes share many common cellular and molecular pathways. Specifically, inflammatory responses have been reported to be prevalent in expansively remodeled as well as aneurysmal arteries. In this review, we examine mainly the clues obtained so far from clinical and experimental investigations into the pathogenesis of expansive remodeling in atherosclerotic disease in coronary and femoral arteries. However, analogies with respect to abdominal aneurysm formation will be obvious. Expansive remodeling is considered a natural response to compensate for plaque formation. For reasons yet unknown, in aneurysms this natural response seems to be uncontrolled and exaggerated. To understand the pathogenesis of expansive remodeling and aneurysm formation, further knowledge is needed on the processes that promote and limit the extent of expansive remodeling.

Expansive Remodeling in Relation to Arterial Geometrical Parameters and Lysis of the Media

Three geometric parameters have been investigated in relation to the mode of arterial remodeling: lumen area, plaque area, and media area.

**Lumen**

The mode of remodeling, eg, constrictive versus expansive remodeling, is strongly related to lumen area\(^6\) (Figure 3). Unfortunately, most studies relating lumen stenosis and remodeling modes have been limited by their cross-sectional study design. In postmortem and intravascular ultrasound studies, segments revealing least atherosclerotic disease are often being used as reference, neglecting the fact that these segments are also susceptible to undergo changes in vessel size. However, serial studies using ultrasound have demonstrated the value of arterial remodeling as a determinant of luminal narrowing.\(^14\)

**Plaque**

Plaque mass is positively correlated with vessel area. Expansively remodeled arteries hide larger plaques than do constrictively remodeled arteries. As mentioned, plaque area may be identical or smaller at the culprit lesion site compared with sites that have a normal lumen angiographically.\(^6\)

**Media**

The degeneration of the medial layer under the lesions could provide the extra arterial wall space necessary to compensate the lumen size, despite the growth of massive atherosclerotic plaques. Although the degenerative changes of the medial layer in aneurysmal arteries of both patients and experimental

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**Prevalence of Remodeling Modes in Non-Culprit and Culprit Lesions**

<table>
<thead>
<tr>
<th>Non-culprit Lesions</th>
<th>Coronary (%)</th>
<th>Femoral (%)</th>
<th>Carotid (%)</th>
<th>Common Iliac (%)</th>
<th>External Iliac (%)</th>
<th>Renal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansive</td>
<td>803 (75)</td>
<td>891 (56%)</td>
<td>524 (50)</td>
<td>240 (53)</td>
<td>488 (50)</td>
<td>158 (51)</td>
</tr>
<tr>
<td>Neutral</td>
<td>118 (11)</td>
<td>301 (19%)</td>
<td>383 (37)</td>
<td>126 (28)</td>
<td>320 (32)</td>
<td>127 (41)</td>
</tr>
<tr>
<td>Constrictive</td>
<td>152 (14)</td>
<td>409 (25%)</td>
<td>135 (13)</td>
<td>86 (19)</td>
<td>178 (18)</td>
<td>26 (8)</td>
</tr>
</tbody>
</table>

**Culprit Lesions**

<table>
<thead>
<tr>
<th>Coronary Arteries</th>
<th>Smits et al</th>
<th>Birgelen et al</th>
<th>Schoenhagen et al</th>
<th>Femoral Arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansive</td>
<td>24 (35)</td>
<td>38 (48)</td>
<td>70 (53)</td>
<td>24 (20)</td>
</tr>
<tr>
<td>Neutral</td>
<td>16 (23)</td>
<td>22 (28)</td>
<td>26 (20)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Constrictive</td>
<td>29 (42)</td>
<td>19 (24)</td>
<td>35 (27)</td>
<td>71 (59)</td>
</tr>
</tbody>
</table>

Data have been obtained from reference 7 (non-culprit lesions) and references 15, 17, 19, and 69 (culprit lesions).

Non-culprit lesions have been obtained in postmortem studies. Culprit lesions were visualized using intravascular ultrasound.

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**Figure 3.** Quartiles of different degrees of remodeling against lumen, vessel, plaque, and media area. A total of 1595 sections were obtained from 112 femoral arteries at regular intervals of 0.5 cm. In each artery, the cross-section with the least amount of plaque was considered the reference. A percent increase in vessel area was calculated for other sections compared with this reference. Cross-sections were divided in the quartiles based on this relative remodeling percent. The lumen, vessel, plaque, and media of the reference sites were 21.6 ±9.1, 33.1±15.4, 13.1±9.4, and 7.0±3.4 mm\(^2\), respectively. \(^*P<0.05\).
Arterial Remodeling and Inflammatory Responses: A Double-Edged Sword

One would be easily inclined to think of arterial enlargement as a beneficial response and of constrictive remodeling as a harmful response to atherosclerotic plaque formation. After all, expansive remodeling prevents and constrictive remodeling accelerates the narrowing of the lumen. A paradoxical relation exists, however, between atherosclerotic luminal narrowing of the lumen and the mode of geometrical remodeling. Remodeling is a double-edged sword: although expansive remodeling compensates for plaque growth, such plaques that bulge toward the outside rather than inside are often the cause of unstable clinical cardiovascular syndromes. However, plaques in constrictively remodeled lesions appear to have a more stable phenotype associated with stable angina. 

Expansively growing plaques often hide inflammatory cells and an unstable phenotype. In postmortem studies in femoral and also in coronary arteries, we observed a strong association of histological markers for plaque vulnerability with local plaque size and local vessel area. Overall, the markers that have previously been related to plaque rupture, ie, high number of macrophages, T lymphocytes, and low number of smooth muscle cells, minor collagen staining, and large percentage of atheroma in the plaque, were observed more often in the cross-sections with the largest plaque area and the largest vessel area than in the cross-sections with the least amount of plaque and the smallest vessel area. In coronary arteries, these results were confirmed by studying the staining for macrophages MMP-2, MMP-9, and MMP-2 activity assessed by zymography in relation to the degree of remodeling. Of note, the aforementioned postmortem studies were performed in patients whose cause of death was not related to cardiovascular disease. More recent studies reported histoimmunological findings from coronary arteries segments obtained from patients that had severe coronary artery disease. Also in these studies, more macrophages, lipid core, and medial thinning were observed in lesions that revealed expansive remodeling. It seems, therefore, that specifically those lesions that underwent local enlargement of the vessel area hide plaques that reveal large numbers of inflammatory cells and have the phenotype prone to rupture. These postmortem observations were supported by clinical studies using IVUS, in which unstable coronary syndromes were associated with expansive remodeling at the culprit lesion site.

In the next paragraphs, 2 molecular targets that appeared to be involved in both the inflammatory response and the remodeling response are discussed in more detail.

Expansive Arterial Remodeling and Matrix Metalloproteinase

The role of MMPs has been studied in relation to nonatherosclerotic arterial geometrical remodeling in animal models. Inhibition of MMPs has resulted in impaired expansive remodeling after flow enhancement and in impaired constrictive remodeling after balloon angioplasty. Similarly, MMP-9 genetic deficiency inhibited injury-induced geometrical remodeling in mouse carotid arteries. The effect of MMP inhibition on human atherosclerotic expansive remodeling and plaque stability remains unknown. Nevertheless, the observed effects after MMP inhibition may provide insight into potentially common mechanisms driving expansive remodeling and plaque destabilization.

As mentioned, more seems to be known about the role of MMPs in aortic aneurysm formation. Aneurysmal arteries present with enhanced expression of gelatinase MMP-2 and gelatinase MMP-9 and degradation of the elastic structures. In animal models, formation of experimentally induced aneurysms was reduced by MMP inhibition in rats and by genetic MMP deficiency in mice. Interestingly, a decrease in desmosine, which is representative for elastin formation, was evident in the model by which aneurysm formation was blocked by a nonspecific hydroxamate-based MMP inhibitor, whereas the collagen content was not found to differ between control and MMP inhibitor-treated groups. Thus, the effect of this MMP inhibitor was mainly attributed to its effect on elastin content.

The specific role of the gelatinases MMP-2 and MMP-9, which also have elastolytic activity, in aneurysm formation has been investigated using knockout mouse models. Pyo et al reported that MMP-9 knockout mice did not have experimentally induced aneurysms, which was confirmed by Longo et al. The latter group also demonstrated that MMP-2–deficient mice also do not have aneurysms after aortic injury. Bone marrow transplantations of wild-type mice restored aneurysm formation in MMP-9–deficient mice, whereas it did not in the MMP-2–deficient mice, likely because of the fact that MMP-9 mainly originates from macrophages, available after the transfer of wild-type bone marrow, whereas MMP-2 is mainly produced by resident mesenchymal cells.
Experimental models suggest that increased hemodynamic pressure can lead to degradation of arterial elastin within the outer area of the medial layer, likely because of increased MMP activity. Co-localization of MMP activity and fragmentation of elastic laminae within the wall of porcine carotid arteries, which are elastic arteries like the aorta, were demonstrated after increasing the perfusion pressure ex vivo. This effect could contribute to elastin degradation in the outer layers of abdominal aorta, a site of increased hemostatic pressure and wall stress and a common location for atherosclerotic related aneurysmal dilatation. Such elastin degradation products have been shown in vitro and in vivo to be chemotactic and thus are suspected to attract infiltration of the outer aortic layers by inflammatory cells. Such cells could then exacerbate the tissue damage by producing additional elastolytic and proteolytic enzymes, including MMPs.

Local inflammation is thought to be causally related with the expansive remodeling of atherosclerotic lesions, but this is yet unseen in human atheroma. In mouse models, decreasing the percent of macrophages in the experimental lesions was associated with outward remodeling of carotid arteries, likely caused by the increased release of elastolytic MMPs. However, elastase activity has not been investigated specifically in relation to the expansive remodeling of human coronary or femoral arteries.

Chemical MMP inhibition was not found to affect the extent of aortic atherosclerosis in experimental animal models in which lesions are macrophage-driven. Interestingly, the authors reported, however, that aortic medial elastin destruction and ectasia grade were significantly reduced, which are changes they considered to represent "microaneurysms;" however, potential effects on geometrical remodeling were not specifically investigated.

Research on the potential role of elastin degradation in relation to atherosclerotic plaque destabilization is scarce, while the role of collagen fiber destruction has extensively been studied. Sukhova et al described the presence of elastases cathepsins K and S in atherosclerotic plaques at sites of matrix turnover. Smooth muscle cells and macrophages demonstrated the ability to use cathepsins to degrade elastin, suggesting a role for these enzymes in regulation of arterial matrix turnover. Expression of cystatin, an endogenous inhibitor of cathepsins S and K, was reportedly reduced in atherosclerotic and aneurysmal arterial lesions. In addition, cystatin levels were inversely related with the size of abdominal aneurysms. Thus, besides increased collagen degradation, elastin degradation may be a common phenomenon in expansive remodeling and might be related to enhanced destabilization of the atherosclerotic plaque.

In addition to MMPs, the fibrinolytic plasminogen/plasmin system is also capable of degrading extracellular matrix components. It has been demonstrated that the expression of urokinase plasminogen activator is associated with the presence and severity of atherosclerotic disease. Moreover, in an animal model, urokinase plasminogen activator overexpression resulted in enhanced intimal thickening and constriction remodeling. It has also been suggested that urokinase plasminogen activator is important in expansive aneurysm development. These results support the idea that the plasminogen activator system may play a role in the atherosclerotic remodeling response.

**Expansive Remodeling: A Role for Innate Immunity?**

In our laboratories, the role of the immune system in the expansive remodeling response is currently being investigated. The concept that immunological responses are important in arterial remodeling is not new, but it has been considered as a pathogenetical factor in the expansive geometrical remodeling response of collateral arteries within ischemic tissues, which is entitled arteriogenesis. The identification of mechanisms regulating collateral vessel growth offers significant potential for the treatment of ischemic heart and peripheral cardiovascular disease. Biomechanical effects of increased blood flow on the vascular wall are of primary importance for collateral vessel growth. It is still unclear how the vascular wall senses these biomechanical effects, but the endothelium plays an important role in its response. Flow changes can upregulate activation of MMPs, which are considered to be important for remodeling in general. Endothelial cells sense shear stress and various patterns of flow by regulating the expression of intracellular adhesion molecule 1, vascular adhesion molecule 1, monocyte chemoattractant molecule 1, MMP-9, and MMP-1. The role of monocytes in stimulating arteriogenesis is still unclear, but it has been suggested that their production of growth factors might play a role. Infusion of MCP-1 and of a bolus of lipopolysaccharide, which activates monocytes, stimulated arterial conductance after femoral artery occlusion in the rabbit. This not only supports the role of monocytes in arteriogenesis but also suggests a role for the Toll-like receptor 4 (Tlr4), which is the receptor for lipopolysaccharide, in arterial remodeling.

**Expansive Remodeling and Toll-Like Receptor 4**

Tlr4 is the receptor for exogenous lipopolysaccharide, endogenous heat shock protein 60, and the extra domain A of fibronectin present in alternatively spliced fibronectin, also known as cellular fibronectin. Tlr4 expression has recently been described in atherosclerotic arteries in endothelial cells, macrophages, and adventitial fibroblasts. Moreover, Tlr4 polymorphism is associated with carotid intima thickness in humans. Recently, Boekholdt et al found that Tlr4 polymorphism modifies the efficacy of statin therapy and the risk of cardiovascular events. This points again to a potential contribution of Tlr4 to cardiovascular disease, although the exact mechanistic role of Tlr4 remains obscure.

Using a mouse femoral cuff model, we recently demonstrated that Tlr4 is involved in neointima formation. Although the role of Tlr4 remains unknown, it has been shown that Tlr4 activation results in the in vitro production of cytokines and MMP-9, a protease associated with structural changes of the arterial wall involving cell migration and collagen (matrix) breakdown.

In the mouse femoral artery cuff model, Tlr4 activation by lipopolysaccharide stimulated plaque formation and subsequent expansive arterial remodeling in the atherosclerotic apoE3 (Leiden) transgenic mouse and in the wild-type mice.
Arterial remodeling is a major determinant of luminal narrowing. Prevalence and clinical presentation of expansively remodeled plaques may differ depending on location. The mechanisms that underlie the direction of the different remodeling modes remain unclear. In abdominal aorta aneurysms, a major role for inflammatory responses, and specifically for the matrix-degrading activity of MMPs, is suggested. However, mechanistic studies are still hampered because of lack of appropriate animal models harboring the opposing modes of arterial remodeling.

Summary

Arterial remodeling is a major determinant of luminal narrowing in all vascular beds. Prevalence and clinical presentation of expansively remodeled lesions may differ depending on location. The mechanisms that underlie the direction of the different remodeling modes remain unclear. As in abdominal aorta aneurysms, a major role for inflammatory responses, and specifically for the matrix-degrading activity of MMPs, is suggested. However, mechanistic studies are still hampered because of lack of appropriate animal models harboring the opposing modes of arterial remodeling seen in human cardiovascular disease.

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Expansive Atherosclerotic Remodeling: What Did We Learn From Animal Models?

Although the importance of geometrical remodeling as a determinant of luminal narrowing has been established, further investigation of de novo atherosclerotic remodeling is hampered by methodological problems. Ideally, atherosclerotic remodeling should be studied in humans in a longitudinal study at the same sites at multiple time points. However, the slow and unpredictable progression of atherosclerotic disease makes this impractical and ethically difficult, which emphasizes the importance of good animal models to study geometrical remodeling. Armstrong et al were the first to report that the arterial wall adapts to experimentally induced plaque formation in primates. Two years later, Glagov et al confirmed their results in human cadaver studies, promoting the notion of compensatory enlargement. Expansive remodeling has also been observed in genetically modified mice prone to atherosclerotic lesion development. In apoE−/− Leiden and apoE knockout mice, lesion development was found associated with expansive arterial enlargement, medial thinning, and increased elastolytical activity. These and other mouse model studies are rather descriptive, and the mechanistic link between atherosclerotic expansive remodeling and matrix degrading properties is therefore strongly suggested but yet unproven. Interventional studies using MMP inhibitors or atherosclerotic prone/protease double-knockout mice, similar to those performed in experimental models of aortic aneurysm, will be necessary.

More recently, very consistent and highly reproducible arterial expansion has been demonstrated at the aortic cusps in the apoE−/− mouse. This investigation of plaque formation in 3 adjacent coronary sinuses demonstrated that expansive remodeling was associated with the formation of plaque in the same, but not in the adjacent, sinuses. This report also raised the question whether this strong expansive remodeling response shared the definition of aneurysm formation.

The development of animal models with atherosclerotic remodeled lesions is important not only for the understanding of mechanisms but also for the development of interventional strategies. It remains unknown whether stimulation of vascular expansion to compensate for plaque growth will be desirable, because these plaques may hide a more rupture-prone phenotype. Representative animal models could facilitate the development of mechanical and pharmaceutical interventions that influence remodeling modes that compensate for plaque growth without destabilizing the atherosclerotic plaque.

Figure 4. Collagen density within the wall of contralateral (left) mouse carotid arteries before and after ligation of the right carotid artery. Top panels are digital gray value images of a picro Sirius red image with circularly polarized light. Left is wild-type left carotid artery 28 days after ligation. Right is Tlr4-deficient left carotid artery 28 days after ligation. Bottom graph shows quantification of collagen density in left carotid In gray bars, left carotid arteries before ligation in wild-type (cWT) and Tlr4-deficient mice (cTlr4 def) are shown. In black bars, left carotid arteries 28 days after right carotid ligation in wild-type (WT) and Tlr4-deficient mice (Tlr4 def) are shown. N=14 to 17 mice per group, *P<0.05.

However, in the Tlr4-deficient mice, no compensatory expansive arterial remodeling was observed in response to neointima formation. In another model, ligation of one of the common carotid arteries in wild-type mice resulted in expansive remodeling without neointima formation in the contralateral carotid artery. This effect was associated with an increase in Tlr4 expression and EDA and Hsp60 mRNA levels. In contrast, expansive remodeling was not observed after a similar carotid ligation procedure in the Tlr4-deficient mice. We determined that in the Tlr4-deficient mouse, collagen density increased significantly with expansive remodeling, whereas it did not change in the wild-type mouse (Figure 4). These results suggest that accumulation of collagen prevented the expansive remodeling, and that Tlr4 is an important cellular receptor affecting the collagen turnover. We suggest that regulation of Tlr4 and its endogenous ligands, EDA and Hsp60, are potential novel targets available for therapeutic control of expansive remodeling.

Wildtype Tlr4 defective

Collagen density in grey value/um

CWT WT CTR4 Def. Tlr4 Def.

0 5 10 15 20 25 30 35

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