In-vivo assessment of the natural history of coronary atherosclerosis: vascular remodeling and endothelial shear stress determine the complexity of atherosclerotic disease progression

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Purpose of review

Atherosclerotic disease progression is determined by localized plaque growth, which is induced by systemic and local hemodynamic factors, and the nature of the wall remodeling response. The purpose of this review is to summarize the processes underlying the heterogeneity of coronary atherosclerosis progression in relation to the local hemodynamic and arterial remodeling environment.

Recent findings

Multiple competing biological processes in the extracellular matrix define the extent of vascular remodeling and disease progression. The remodeling phenomenon is not consistent but is characterized by great phenotypical heterogeneity which reflects the complex effect of systemic, genetic and hemodynamic factors on the arterial wall response to plaque formation and progression. The exaggeration of expansive remodeling (i.e., excessive expansive remodeling) likely contributes to the transformation of an initially favorable action into an excessive course of vessel expansion, continued disease progression and plaque instability. Extremely low endothelial shear stress and excessive expansive remodeling establish a vicious cycle which leads to the formation of severe plaques with high-risk characteristics.

Summary

The dynamic interplay between the local hemodynamic environment and the wall remodeling behavior determines the complexity of the natural history of atherosclerosis and explains the development of localized plaque vulnerability.

Keywords

atherosclerosis, extracellular matrix, imaging modalities, remodeling, shear stress

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Introduction

The burden of atherosclerotic cardiovascular disease is growing globally, and coronary artery disease (CAD) is projected to be the leading cause of morbidity and mortality worldwide in the following decades [1]. Acute clinical manifestations are responsible for the increased mortality and often constitute the end-result of a long and slow subclinical course of disease which has not caused any symptoms during the previous years [2••]. Treatment strategies are often made after an acute event in many patients who were fortunate to survive. Current diagnostic and management strategies are limited in identifying high-risk lesions because there is a high occurrence of adverse cardiac events in patients with known CAD, even when treated with aggressive systemic management, and an increased incidence of acute coronary syndromes in nonculprit lesions following successful percutaneous coronary intervention [3,4]. In-vivo assessment of the natural history of atherosclerosis would be of paramount importance for providing insight into the distinct nature of high-risk and stenotic plaques compared with quiescent ones before an event, thereby potentially enabling their identification and the application of pre-emptive strategies to avert an adverse clinical event.

Although atherosclerosis is a systemic disease, its distribution is multifocal and heterogeneous such that multiple atherosclerotic lesions with various morphologies and at different stages of progression typically co-exist in the coronary arteries of affected individuals [5]. Local hemodynamic factors determined by flow properties exhibit remarkable heterogeneity over short distances and are causally related to the heterogeneity in the spatial distribution of atherosclerotic plaques [6]. Endothelial shear stress (ESS), in particular, exerts pathobiological effects on

the arterial endothelium and wall that are associated with increased atherosclerosis susceptibility, initiation and development [7].

Localized accumulation of plaque in the vessel wall was previously considered to be the principal determinant of lumen narrowing. However, vascular remodeling, initially reported in humans by Glagov *et al.* [8] as the ability of the vessel wall to adapt and accommodate a growing plaque by an increase of the internal elastic lamina area, is a fundamental component of atherosclerosis. Recent understanding of this phenomenon as a response of the vessel wall to hemodynamic, mechanical, and biochemical stimuli has been of major importance in revealing the nature of the disease process. Furthermore, the remodeling response to plaque accumulation is not consistent because the degree of compensation varies significantly between arterial segments [9], different remodeling patterns (i.e., constrictive and expansive) co-exist in the same artery, and temporal changes in remodeling patterns can also occur in response to drug treatment [10]. This high variability in the remodeling response is an additional feature increasing considerably the complexity of the atherosclerotic disease progression.

The purpose of this review is to summarize the molecular mechanisms and histopathological characteristics associated with atherosclerotic disease progression and the dynamic nature of vascular remodeling in relation to the hemodynamic environment, and thus provide insight into the complexity of the natural history of atherosclerosis.

Localized plaque growth and biology of the endothelial shear stress effect

Atherosclerosis predominantly forms in specific regions of the vasculature determined by local vascular geometry, and blood flow-induced ESS is causally related to the focal and heterogeneous spatial distribution of atherosclerotic plaques. Local low ESS, in particular, determines proatherogenic endothelial cell morphologic and functional characteristics that induce localized development of lesions [7]. Spatial gradients of ESS in geometrically irregular regions, as well as temporal ESS gradients due to flow pulsation, have also been implicated in atherogenesis [11]. Arterial regions of naturally occurring disturbed flow and low or oscillatory ESS, such as inner surfaces of curvatures, branch points and bifurcations, are the regions primarily involved in atherosclerosis initiation and development [12].

Cardiovascular risk factors (e.g., diabetes, hyperlipidemia, hypertension, cigarette smoking) lead to endothelial dysfunction associated with lipid and, consequently, macrophage influx to the intima. Disease progression is essentially determined by the magnitude of lipid influx, lipid oxidation, the resultant degree of inflammation, and the wall response. In the setting of systemic risk factors, low ESS leads to the formation of atherosclerotic lesions through a multifactorial influence on the arterial wall, which involves the conversion of biomechanical stimuli to biochemical responses by endothelial cells [13•]. In-vitro and animal experiments have shown that low ESS-induced activation of the nuclear factor kappa B (NF-κB) signaling inflammatory pathway and muting of the Kruppel-like factor-2 (KLF-2) atheroprotective transcriptional pathway leads to increased expression of adhesion molecules (e.g., inter-cellular adhesion molecule-1, vascular cell adhesion molecule-1, selectins) and chemokines (e.g., monocyte chemoattractant protein-1, interleukin-8, fraktalkine) [14], which mediate the recruitment of inflammatory cells in the intima, and decrease of atheroprotective molecules, such as nitric oxide and prostacyclin [15••]. Low ESS has also been recently implicated in the dedifferentiation of smooth muscle cells (SMCs), which acquire a more synthetic phenotype and contribute to plaque growth [16•]. At more advanced stages of atherosclerosis, low ESS exacerbates additional growth in regions that already contain significant plaque, underscoring the critical role of proatherogenic flow conditions in both atherogenesis and disease progression [17•].

Flow-mediated physiological adaptation of the normal arterial wall

The arterial wall is capable of undergoing major reshaping, as evident by arterial adaptations during physiological processes (e.g., vessel formation during embryogenesis). An abnormal change in the drag forces on the wall activates feedback mechanisms which return these forces to 'normal' values. In adult mammals, arteries establish a diameter which, in conjunction with their normal flow rate delivery, results in a mean and uniform ESS value throughout the vasculature. If ESS is altered from its physiologic state for a long period, the arterial diameter responds by changing in such a way as to recover the physiologic range of ESS. In normal arteries high ESS elicits an expansive remodeling response, and low ESS a constrictive one. Recent work has shown that there are large variations in the remodeling response among different inbred animal strains, underscoring the marked genetic influences on the remodeling phenomenon [18]. Flow-mediated physiological adaptation is genetically determined by certain genes causing fundamental alterations in sensing or transducing the hemodynamic signals and thus influencing the vascular wall's ability to normalize ESS to physiological values [19,20••].

Cellular and molecular mechanisms underlying the remodeling phenomenon

Extracellular matrix, which consists of elastins, collagens and proteoglycans, provides support to tissue and

maintains the integrity of the arterial wall. Remodeling of the extracellular matrix allows the arterial wall to adapt to disturbances in flow and restore physiological ESS, yet also contributes to disease processes, such as the development of atheroma within the arterial wall. A controlled process regulated by the balance between matrix protein synthesis and enzymatic breakdown is involved in the remodeling phenomenon. Synthesis is mediated by matrix-producing cells, primarily vascular SMCs and fibroblasts. Matrix-degrading proteases are key mediators of matrix breakdown and include mainly matrix metalloproteinases (MMP-1, MMP-2, MMP-9) [21•,22], cathepsin cysteine proteases (cat L, K, S) [23,24] and serine proteases of the plasminogen activator system [urokinase plasminogen activator (uPA)] [25•], produced by SMCs, endothelial cells and macrophages. Dynamic equilibria also regulate the function of SMCs and the activity of proteolytic enzymes. SMC proliferation and apoptosis [26], and thus matrix production, are physiologically under the control of growth-promoting factors (e.g., platelet-derived growth factor, vascular endothelial growth factor, basic fibroblast growth factor, angiotensin II) and inhibitors (e.g., tissue growth factor (TGF)β, nitric oxide, interferon-γ, heparan sulfate). Similarly, the enzymatic activity of MMPs, cathepsins and uPA is the net result of their expression and post-transcriptional activity, and their inhibition by tissue inhibitors of matrix metalloproteinases (TIMPs), cystatins and plasminogen activator inhibitors (PAIs), respectively.

Interactions between SMCs, growth factors, matrix protein synthesis, and proteolytic enzymes and their inhibitors create a complex system of vascular homeostasis. The upregulation and downregulation of each of these components essentially favor either extracellular matrix degradation or collagen synthesis and fibrosis, which may consequently lead to vessel expansion or constriction, respectively.

Matrix turnover and degradation as well as inflammatory infiltration are important features in outward remodeling. A recently described molecule, the Toll-like receptor 4 (TLR4), is an important cellular receptor affecting collagen turnover by decreasing collagen density and promoting vessel expansion [27]. Furthermore, severe disruption of the internal elastic lamina, which facilitates SMC migration, occurs in atherosclerotic lesions with decreased levels of endogenous protease inhibitors [28,29]. Factors known to be involved in cardiovascular pathologies, such as biochemical stress, vessel injury, mechanical stretch [30], shear-mediated mechanisms [31], cytokines and oxidative stress [32], can affect the dynamic equilibria in the extracellular matrix and potentially stimulate protease expression, production and activation [33]. Macrophage-derived foam cells, which accumulate in growing lesions as a response to lipid intake, release reactive oxygen species via NAD(P)H oxidase and increase enzymatic matrix degradation, thereby facilitating expansive remodeling [34,35••]. Low ESS is also associated with intense inflammatory cell infiltration, severe fragmentation of the internal elastic lamina and cap thinning [36], and enhanced expression and activity of MMPs and cathepsins in relation to their inhibitors (Fig. 1) [37•]. In addition to intensive inflammation and matrix degradation, low ESS promotes SMC apoptosis and attenuates matrix synthesis [38].

The predominance of fibroproliferative processes leads to the development of inward, or constrictive, remodeling. Such regions are characterized by decreased infiltration of inflammatory cells, low protease activity and increased matrix production. An important role in SMC phenotypic modulation, migration and proliferation has been found for uPA and its receptor [39], which is upregulated in dedifferentiated SMCs and can alter the expression of pro-inflammatory and oxidation-related genes promoting neointima formation and vessel constriction [40••]. Furthermore, a healing response in sites of silent plaque (micro)ruptures favors an increased rate of SMC proliferation with a decrease in macrophage content and inflammatory and apoptosis markers over time [41••]. The initiation of the coagulation cascade in regions of healed plaque rupture or endothelial erosion leads to fibrin deposition, intra-intimal foci of thrombi and collagenous proteoglycan-rich neointima showing demarcation of the hemorrhage [42]. SMCs interact with the fibrin clot and, ultimately, such regions undergo scarring followed by retraction of the internal elastic lamina and likely constriction [43,44].

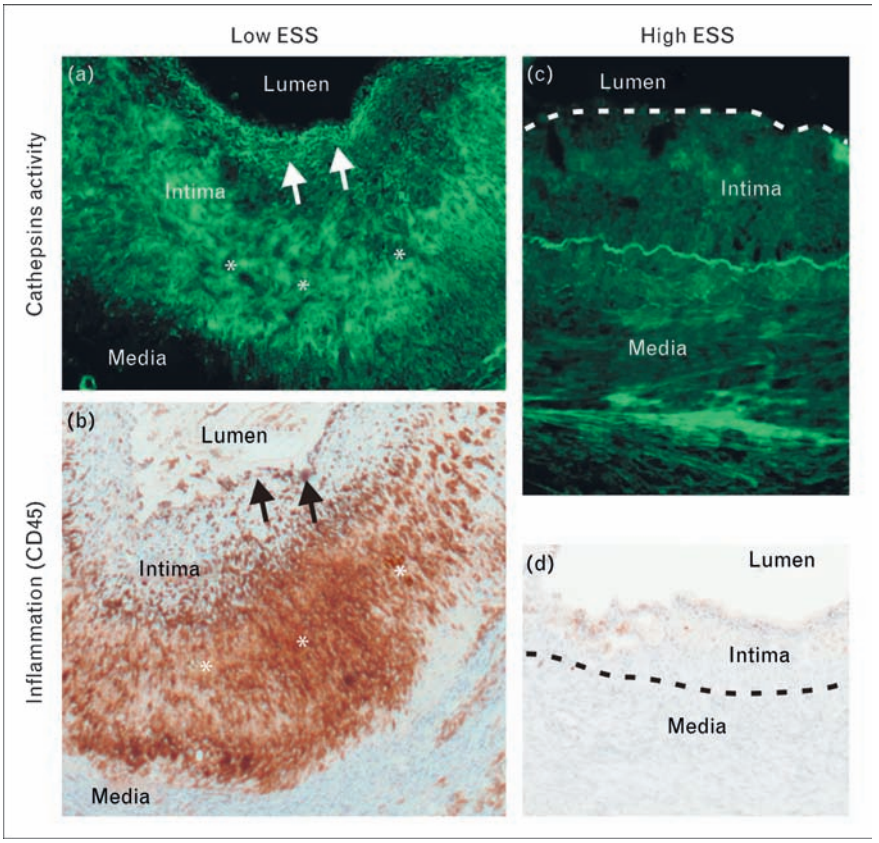
Genetic factors also exert a role in the remodeling phenomenon in atherosclerotic arteries since gene variants that enhance the susceptibility to vascular damage and affect vascular remodeling have been identified [45] and gene transfer (e.g., VEGF165, TGFβ3) interventions are reported to be capable of modifying the remodeling response [46,47]. Furthermore, gene–environment interactions are implicated in SMC proliferation and matrix protease activity and are regulated by epigenetic mechanisms such as histone acetylation and DNA methylation [48••].

The remodeling process is clearly the result of multiple interacting molecules regulating complex biological pathways in the vascular wall constituting a fine balance of matrix protein synthesis and breakdown as a response to exogenous factors.

Heterogeneity of the remodeling response in atherosclerotic arteries

Although most (>50%) arterial segments with minimal disease exhibit compensatory expansive remodeling,

Figure 1 Differential degree of elastolytic activity and inflammation in coronary regions with low vs. high endothelial shear stress



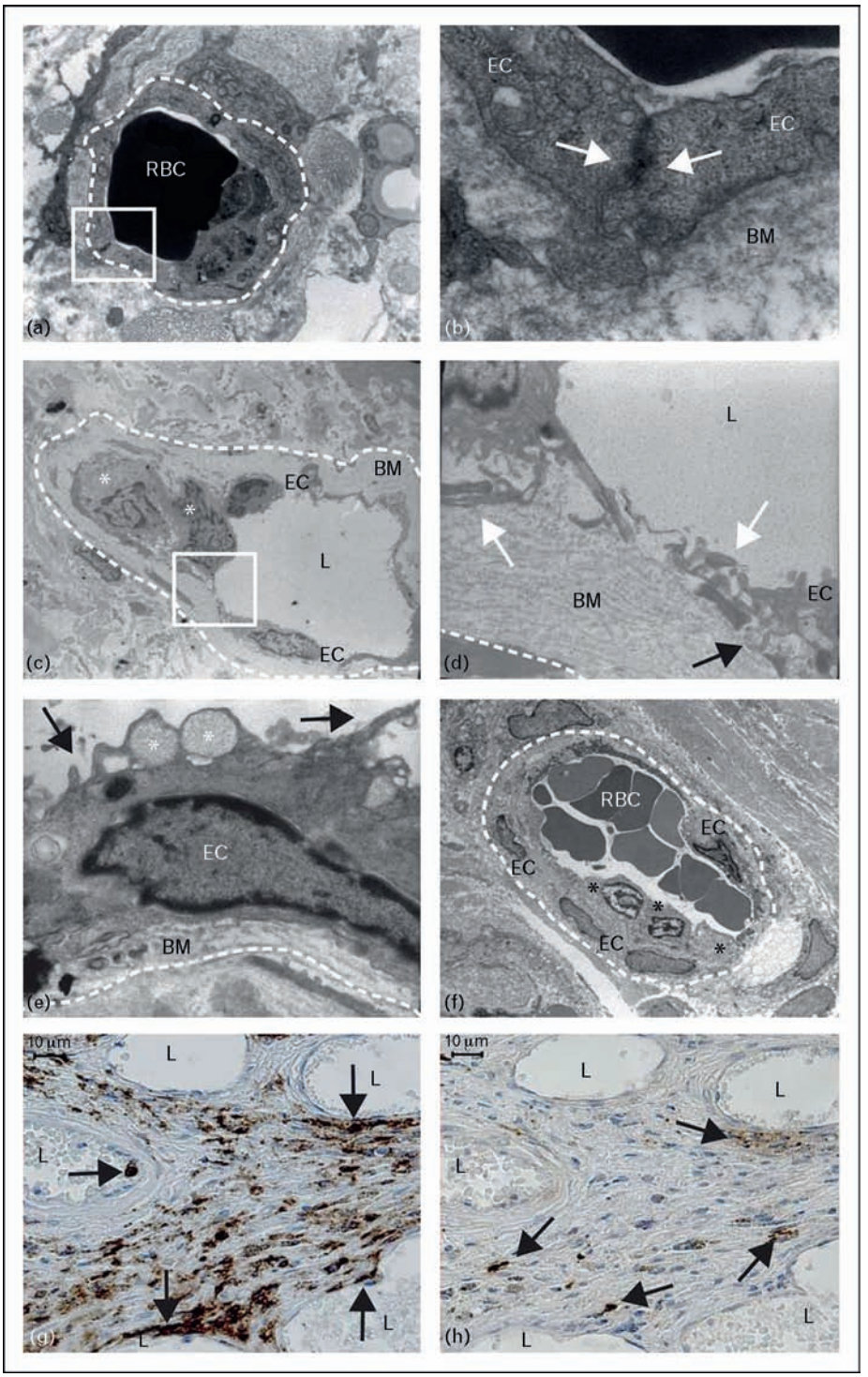
A porcine coronary artery section showing increased elastolytic activity (a, in-situ zymography for cathepsins activity), which colocalizes with profound inflammatory infiltration (b, immunostaining with CD45) in a region of low endothelial shear stress (ESS). Conversely, in a region with high ESS, there is absence of elastolytic activity (c) and inflammation (d). Arrows indicate the cap and asterisks the deep intimal area. ESS, endothelial shear stress. Reproduced with permission from [37•].

some segments excessively remodel (excessive expansion) showing an increase in both vessel and lumen compared with reference nondiseased areas, and some fail to remodel outward or even appear to constrict in response to plaque [49,50]. Insulin requirements and metabolic control have been found to influence the remodeling pattern [51••], and smoking is known to attenuate the adaptive remodeling response [52]. Furthermore, a marked heterogeneity in remodeling response exists across coronary arteries within the same patient [49], and variations in remodeling patterns between different vascular beds have also been described [53•].

Vascular remodeling patterns and atherosclerotic disease progression

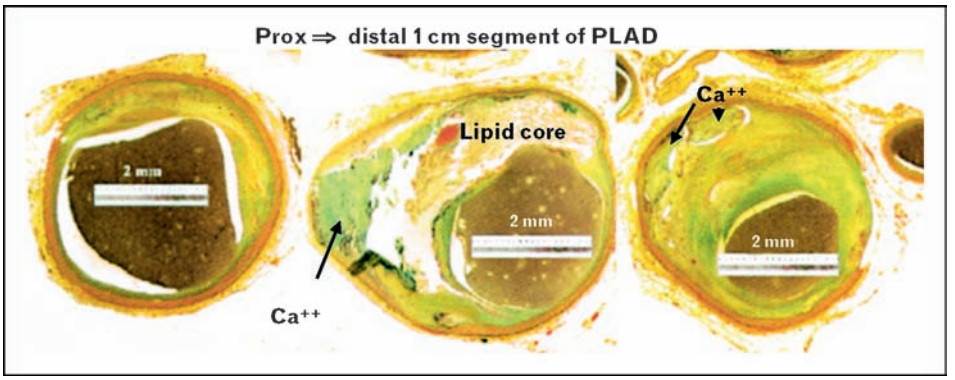
Compensatory expansive remodeling is an important component in atherosclerosis aimed at delaying the development of significant lumen compromise. However, in arterial segments with overcompensation, this initially favorable remodeling action may eventually increase the vulnerability of macrophage-rich atherosclerotic plaques [54], which do not typically cause a stenosis, but may lead to an unheralded acute event. When the imbalance in matrix synthesis and degradation shifts towards proteolysis, then increased fragmentation of the internal elastic lamina ensues and the vessel expands excessively. This process of intense inflammation and matrix breakdown characterizing excessive expansive remodeling may result in significant intraplaque oxidation, necrosis and ischemia, which are major stimuli for release of angiogenic factors leading to vasa vasorum neovascularization [55••]. Neovessels nourish the highly inflamed plaque with extra lipids, cytokines and inflammatory cells and are detrimental by causing further plaque growth and instability; intraplaque hemorrhage due to neovessel fragility also contributes significantly to necrotic core expansion, possibly by accumulation of the cholesterol-rich erythrocyte membranes (Fig. 2) [56••,57•,58•]. The extent of expansive (excessive vs. compensatory) remodeling appears to

Figure 2 Intraplaque microvessels show abnormal endothelial cell morphology, aberrant junctions, and leukocyte infiltration as shown by electron microscopy



(a) Ultrastructure of an adventitial microvessel (dashed line indicates circumference) in a nondiseased coronary artery with luminal RBCs (electron microscopy, ×8000). (b) Magnification of the boxed region in (a) of microvessel with intact BM and interendothelial junction indicated by close contact (white arrows) between ECs (×20 000). (c) Ultrastructure of intraplaque microvessel with leukocytes (white asterisks) (×650). (d) Magnification of the boxed region in C showing aberrant inter-EC junction (white arrows) and BM detachment (black arrow) (×4600). (e) Dysfunctional EC ultrastructure in an intraplaque microvessel (×6300): membrane blebs (black arrow) and intracytoplasmic vacuoles (white asterisk). (f) Leukocytes (asterisks) adhering to intraplaque microvessel endothelium (×460). (g) Immunohistochemistry shows $CD45^{+}$ cells in and near microvessels (arrows). (h) Immunohistochemistry showing mast cell tryptase-positive cells at larger distance from microvessels (arrows). BM, basement membrane; EC, endothelial cell; L, lumen; RBC, red blood cell. Reproduced with permission from [56••].

Figure 3 Vascular wall expansion with large lipid core vs. internal elastic lamina retraction with luminal narrowing following a healed plaque rupture



On left panel (proximal reference segment), the internal elastic lamina (IEL) area is 13.2 mm^2, the percentage of stenosis is 22%, and the lumen area is 9.0 mm^2. Immediately (4 mm) distal to this (middle panel), the IEL area is 16.6 mm^2, the percentage of stenosis is 66%, and lumen is 5.6 mm^2; in this segment, there is a large lipid core and calcification. In the healed rupture site (right panel) further distal (8 mm from reference segment), the IEL is 11.6 mm^2, the percentage of stenosis is 75%, and lumen is 2.9 mm^2; this segment is predominantly fibrous. PLAD, proximal left anterior descending artery. Reproduced with permission from [44].

influence the nature and degree of subsequent plaque progression [17•].

Failure of the remodeling phenomenon or, even worse, development of constrictive remodeling significantly accelerates the narrowing of the lumen. Constrictive remodeling has been shown to occur early in the formation of some plaques and to be a dominant contributor of lumen compromise in coronary arteries [59,60]. Such lesions are rich in fibrotic content, which characterizes a more stable plaque phenotype [44,54]. Furthermore, constrictive remodeling frequently represents a late-stage phenomenon in the setting of prior repetitive ruptures of an inflamed high-risk plaque, and wound contraction during plaque healing processes has been reported as an important mechanism of arterial narrowing beyond the magnitude of plaque burden alone (Fig. 3) [42,44].

The role of endothelial shear stress in determining the extent of expansive remodeling in atherosclerotic arteries

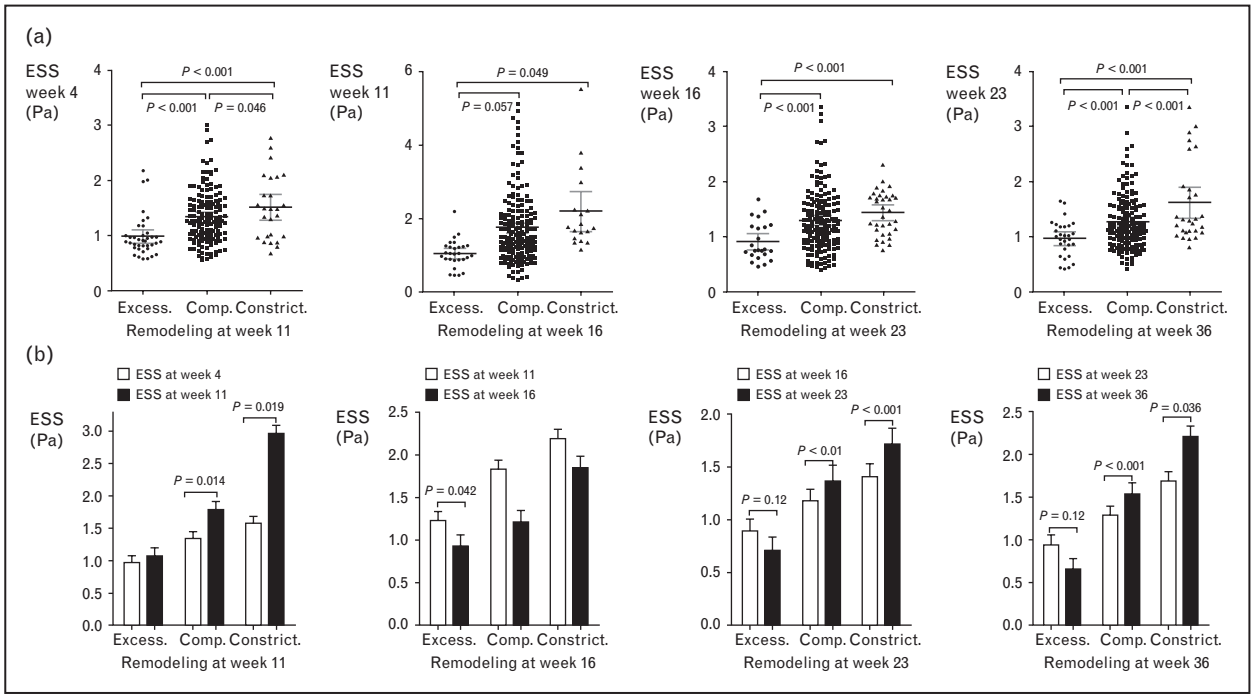
As described above, local ESS influences key mediators in the arterial wall which play a vital role in the balance of matrix protein synthesis and degradation, and thus it can potentially determine the critical point beyond which the favorable compensatory remodeling phenomenon transforms into an adverse excessive expansive response. The magnitude of low ESS is directly related to the intensity of local inflammation and matrix breakdown, and extremely low ESS leads to the development of highly inflamed thin cap fibroatheromas characterized by excessive expansive remodeling [61•]. A disproportionate vessel expansion to plaque growth due to extremely low ESS is accompanied by lumen increase, which further decreases ESS, and establishes a vicious cycle between persistently very low ESS and excessive expansive remodeling, promoting intense plaque inflammation and internal elastic lamina fragmentation. In contrast, arterial regions with low, but not extremely low, ESS are characterized by moderate plaque inflammation and a balanced matrix turnover, which result in a controlled expansion of the vessel wall compensating for the growing plaque. Lesions with compensatory expansive remodeling have higher ESS at preceding time points compared with those with excessive expansive remodeling and result in a serial increase of ESS, thereby ameliorating the initial adverse low ESS stimulus (Fig. 4) [17•].

The value of low ESS that is 'extremely low' and, consequently, elicits the aforementioned transformation of compensatory expansive remodeling to excessive expansive remodeling is not absolute but is relative and dependent on the nature and magnitude of concomitant systemic risk factors. Recent work has shown, for example, that the greater the serum cholesterol, the higher is the ESS threshold associated with the formation of advanced high-risk plaques [62•]. Although the local hemodynamic environment is important in explaining the nonuniform response of vascular remodeling to lesion progression and, consequently, the heterogenic nature of atherosclerosis, the pathobiologic effects triggered by the local hemodynamic environment are clearly modulated by systemic risk factors.

Temporal variability and dynamic nature of vascular remodeling

Recent intravascular ultrasound (IVUS) serial assessments of vascular remodeling at two time points in

Figure 4 Interrelationship between the hemodynamic and remodeling environment in a serial experimental study of coronary atherosclerosis

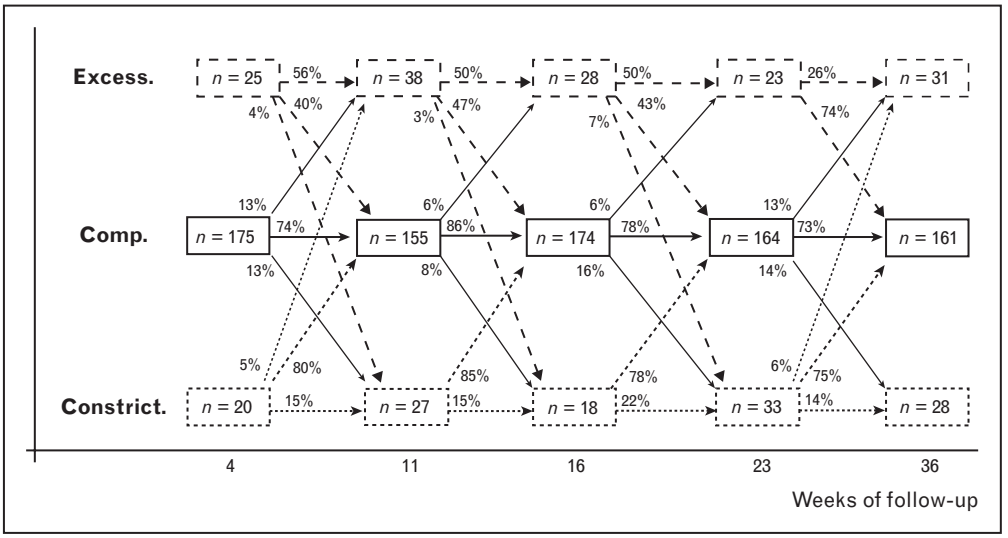


(a) Local ESS at weeks 4, 11, 16, and 23 in segments categorized by the remodeling pattern at the immediately following time point, that is, week 11, 16, 23, and 36, respectively. At all time points, segments with excessive expansive remodeling had significantly lower preceding ESS compared with segments with compensatory or constrictive remodeling. (b) Impact of each remodeling pattern on local ESS. For segments with each remodeling pattern at all time points, local ESS at any given time point of remodeling assessment is compared with the local ESS at the immediately preceding time point. ESS generally tended to decrease further in segments with excessive expansive remodeling, and increased in segments with compensatory or constrictive remodeling. ESS, endothelial shear stress. Reproduced with permission from [17•].

patients under lipid-lowering treatment have provided a greater understanding of the variable nature of the remodeling response compared with single-time measurements, and have demonstrated temporal changes in remodeling patterns following drug therapy [63]. Our group recently demonstrated that there was remarkable heterogeneity of the remodeling response over time in a novel study of experimental atherosclerosis with serial IVUS measurements at five time points. Although the majority of arterial segments initially displaying compensatory remodeling remained with that remodeling pattern over time, a substantial proportion of coronary arterial segments evolved through different remodeling patterns demonstrating highly variable remodeling trajectories (Fig. 5) [17•]. The relationship between plaque growth and vascular remodeling is not monotonic over time, but the arterial wall dynamically and continuously responds to its local environmental influences, including the progressing plaque. Each remodeling pattern (i.e., compensatory expansive, excessive expansive and constrictive) may change into a different one at a subsequent time point, and such changes may occur multiple times.

Although it is not clear why some plaques change remodeling pattern whereas other plaques remain with the same remodeling pattern, a number of hypotheses may be pertinent. Changes in the local hemodynamic environment over time could potentially explain the dynamic nature of the remodeling response. The longitudinal distribution of local ESS may indeed significantly change in response to the changes in local arterial geometry induced by a growing plaque, and distinct hemodynamic environments are gradually created upstream, downstream and at the throat of a stenosis (Fig. 6) [64•]. Upstream regions exposed to low ESS have been demonstrated to develop highly inflamed lesions, whereas downstream regions exposed to low oscillatory ESS develop stable fibrotic ones [65]. It would then be plausible to speculate that these local variations in the morphology of the neighboring upstream and downstream regions of growing plaques would subsequently elicit a differential vascular remodeling response: upstream regions would exhibit excessive or compensatory expansive remodeling at a subsequent time point depending on how low a value of ESS is created, whereas downstream regions may develop compensatory

Figure 5 Vascular remodeling behavior at five time points in a serial study utilizing a diabetic, hyperlipidemic model of coronary atherosclerosis

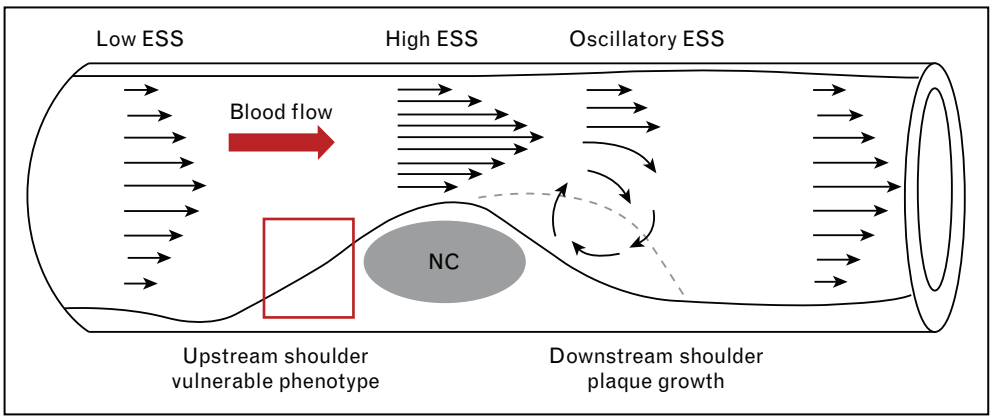


Individual segments, which developed significant plaque (max intima-media thickness $\geq$0.5 mm) by week 36 ($n = 220$), often evolved through different remodeling patterns throughout their natural history. The majority of segments with compensatory remodeling remained with that remodeling pattern over time. Only a small minority of segments with either excessive expansive or constrictive remodeling at week 4 continued to exhibit the same remodeling pattern throughout their evolution. Reproduced with permission from [17•].

expansive or even constrictive remodeling. In addition, an initial course of excessive vessel expansion, continued disease progression and plaque instability could eventually lead to a plaque (micro)rupture with subsequent healing and, consequently, a constrictive remodeling response at subsequent time points [42].

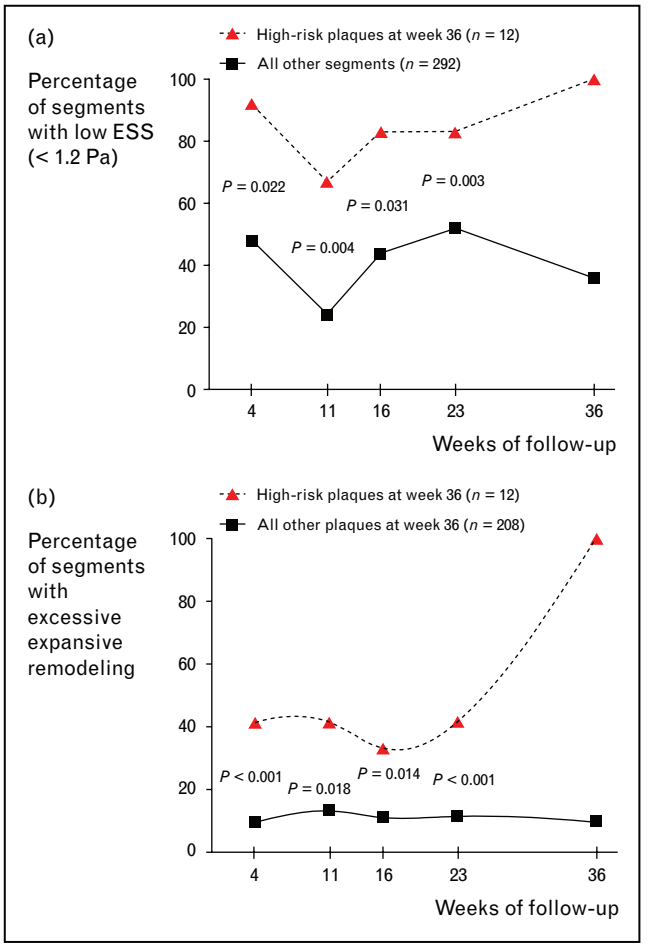
The observations of the dynamic changes of vascular remodeling patterns based on a pig experimental model and their relevance to humans need to be further investigated. The rapid development (9 months) of coronary atherosclerosis in pigs under severe hyperlipidemic and diabetic conditions compared with the slower (40–50 years) atherosclerotic progression in humans, who may also start a lipid-lowering therapy at some point in their lives, may limit the applicability of these findings to a clinical setting in humans. However, the dynamic and ongoing interplay of ESS with the local remodeling

Figure 6 Differential spatial distribution of endothelial shear stress along the course of a plaque partially obstructing the lumen



The upstream shoulder is exposed to low ESS. Local ESS is elevated in the throat, and low/oscillatory ESS occurs in the downstream shoulder of the developing plaque. These local ESS conditions promote the formation of a vulnerable, rupture-prone plaque phenotype, indicated by the red rectangle, upstream of the lesion, and additional growth, indicated by the dashed line, downstream of the plaque. Arrows represent velocity vectors. ESS, endothelial shear stress; NC, necrotic core. Reproduced with permission from [64•].

Figure 7 Association of persistently low endothelial shear stress and excessive expansive remodeling with high-risk plaques in an in-vivo serial study



(a) Percentage of segments with low ESS (<1.2 Pa) over time in segments that culminated in high-risk plaque at week 36, defined as the combination of maxIMT greater than 1.0 mm and excessive expansive remodeling at week 36, vs. all other coronary segments. (b) Percentage of segments with excessive expansive remodeling over time in segments that culminated in high-risk plaque at week 36 vs. all other segments with significant plaque (maxIMT ≥0.5 mm) at week 36. ESS, endothelial shear stress; maxIMT, maximum intima-media thickness. Reproduced with permission from [17•].

response to plaque formation and subsequent growth is likely critical in determining the vascular pathobiology of the lesion and the subsequent natural history of the developing plaque [36]. Regions with persistently low ESS and excessive expansive remodeling are expected to culminate in plaques with the most marked progression and high-risk characteristics (Fig. 7) [17•,65]. Both local ESS and the nature of vascular remodeling may be of value in predicting the localization of high-risk plaques. Integration of these variables into one predictive risk score may also be useful to provide a screening tool for risk-stratification of early individual lesions [17•,66].

Assessing *in vivo* the course of coronary atherosclerosis: clinical implications

Early in-vivo assessment of CAD by coronary angiography allowed visualization of the lumen only without providing any knowledge about the vascular wall. Postmortem pathology studies [8], as well as investigations with imaging modalities (IVUS in particular), led to the appreciation that the development, progression and stability of plaques within the arterial wall characterize the disease's natural history. Although baseline and follow-up (i.e., at two time points) measurements capture serial changes in plaque progression and regression, and the corresponding remodeling response, the complexity of the natural history of coronary atherosclerosis is likely to include continuous changes of the remodeling phenomenon over time. Optimal understanding of the long-term natural history of CAD likely necessitates in-vivo assessments at multiple (i.e., more than two) time points [17•].

Detailed combined knowledge of the local hemodynamic environment and remodeling behavior of coronary arterial regions is likely to be essential for risk-stratification and prognostication. Catheter-based approaches using angiography and IVUS have been exclusively applied until now for vascular profiling of coronary arteries in patient series and have provided accurate assessments of mid-term (6–12 months) serial changes in wall morphology (i.e., plaque growth and vascular remodeling pattern) and their association with the hemodynamic environment [67]. A natural history clinical study (the PREDICTION trial) is currently under way to explore the predictive value of ESS and vascular remodeling in identifying sites of plaque progression and rupture.

Incorporation of a combined assessment of ESS and vascular remodeling into clinical practice as a wide-scale screening tool would be facilitated by the development of noninvasive techniques, and recent work on the use of computed tomography angiography (CTA) for this purpose has provided promising results [68•,69•,70]. Furthermore, latest advances in molecular imaging are now enabling noninvasive in-vivo imaging of the pathophysiology of atherosclerosis [71•]. Stand-alone (e.g., MRI) or hybrid [e.g., positron emission tomography (PET) coupled with CTA] techniques using novel nanoparticles and agents can be used to trace regions of intense inflammation, macrophage trafficking, endothelial activation or protease activity [72] and possibly predict culprit lesions of subsequent acute events. First-in-human applications demonstrate the great potential of this emerging field in providing measures of plaque vulnerability in coronary arteries [73,74••] and indicate the need for intensifying the technological efforts to improve the resolution and quantitative accuracy of such

techniques, especially for imaging the coronary arterial tree.

The realization of the goal to predict the subsequent natural history of atherosclerotic regions and to characterize early high-risk plaques may ultimately enable the development of therapeutic strategies to reduce vascular risk before clinical events occur. Aggressive systemic treatments (e.g., statins and angiotensin II receptor blockers), proven to influence the remodeling behavior and slow down or reverse plaque progression and vulnerability [75••,76••], could be adopted even among low-risk profile patients according to current criteria. Highly selective, prophylactic local interventions, such as implantation of bio-absorbable stents [77••,78•] or novel stenting devices tailored to 'shield' vulnerable plaques [79•], could also be justified if they were proven to be safe and more effective in reducing future events than the best available systemic medical therapy.

Conclusion

Vascular remodeling is a critical component of the process of plaque formation and progression and has an important role in determining the complexity of the natural history of atherosclerosis. A fine balance between matrix protein degradation and synthesis influenced by inflammatory and healing processes underlies the remodeling phenomenon in atherosclerotic arteries. ESS is a principal determinant of the localization of atherosclerotic plaques and the heterogeneity of the remodeling phenomenon, largely by driving the extent of vascular inflammation and expansion. The dynamic interplay of ESS with the local remodeling response to plaque formation, and subsequent growth, is critical in determining the vascular pathobiology of the lesion and the subsequent natural history of the developing plaque. Regions with extremely low ESS and excessive expansive remodeling culminate in large high-risk plaques. Incorporation of noninvasive in-vivo serial ESS measurements complemented by molecular imaging into clinical practice could provide a more complete diagnostic approach to assess the likelihood of a particular atherosclerotic lesion to evolve into a thin cap fibroatheroma prone to rupture and precipitation of an acute coronary syndrome or to evolve to a more fibroproliferative phenotype causing lumen obstruction and stable angina. Once the risk-stratification of individual lesions becomes feasible, the value of local prophylactic interventions in preventing future cardiac events can be investigated in large randomized trials.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 652–653).

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