Coronary hemodynamics and atherosclerotic wall stiffness: A vicious cycle ☆

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Summary Local hemodynamic environment, including low shear stress and increased tensile stress, determines the localization, growth and progression of coronary atherosclerosis. As atherosclerotic lesions evolve, the diseased coronary arteries undergo local quantitative and qualitative changes in their wall, and progressively become stiff. Arterial stiffening amplifies the atherogenic local hemodynamic environment, initiating a self-perpetuating vicious cycle, which drives the progression of atherosclerosis and the formation of atherosclerotic plaque. In vivo evidence indicates that endothelial dysfunction is associated with arterial stiffness, an association that creates a challenging perspective of utilizing stiffness as an early marker of endothelial dysfunction and future atherosclerosis. Coronary stiffening is also associated with vascular remodeling, which is a major determinant of the natural history of atherosclerotic plaques. Thus, arterial stiffness may constitute a useful marker for the identification of the remodeling pattern, in particular expansive remodeling, which is closely associated with high-risk plaques. The early identification of endothelial dysfunction, or a high-risk plaque may enable the early adoption of preventive measures to improve endothelial function, or justify pre-emptive local interventions in high-risk regions to prevent future acute coronary syndromes. Further experimental and perspective clinical studies are needed for the investigation of these perspectives, whereas the development of new modalities for non-invasive and reliable assessment of coronary stiffness is anticipated to serve these studies.

Introduction

Arterial stiffness has been proposed to be an important determinant of cardiovascular risk [1].

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Although several studies have focused on the pathophysiology of stiffening of large elastic-type arteries (e.g. aorta, carotid arteries, brachial arteries) [2—4], the pathophysiology of coronary arterial stiffening remains unclear. In this work we provide the theoretical foundation of normal coronary arterial structure and function, and discuss the pathophysiologic basis of the continuous and dynamic interplay between the local coronary hemodynamic environment and wall stiffness, an interplay that eventually drives the development and progression

of atherosclerosis, as well as arterial remodeling. Better understanding of the pathogenetic mechanisms of atherosclerotic wall stiffening is anticipated to advance our knowledge about the pathobiology of coronary atherosclerosis.

Structural, functional and flow characteristics of normal coronary arteries

The coronary arteries originate from the aorta, continue along the surface of the heart surrounded by the pericardium (i.e. epicardial segments), and penetrate into the myocardium (i.e. intramyocardial segments), where they deliver blood [5]. There are several structural and functional differences between the epicardial and intramyocardial coronary segments [5]. The former are elastic-type conduit arteries, and their wall extracellular matrix (ECM) contains a complex mixture of collagen and elastin fibers within a ground substance of proteoglycans and glycosaminoglycans. Collagen fibres primarily provide integrity and tensile strength to the arterial wall, whereas elastin fibres regulate the elastic properties of the wall. Both these ECM proteins, as well as their cellular sources (i.e. vascular smooth muscle cells, VSMCs) are the major structural determinants of the ability of an artery to distend, the so-called compliance [6]. The content of collagen and elastin within the arterial wall remains relatively stable through a dynamic process of synthesis and breakdown, thereby maintaining normal wall compliance. Functionally, the epicardial arteries are responsible for the conduction of blood to intramural segments, as well as for the buffering effect, storing blood during systole and discharging it in diastole. Contrary to extramural arteries, intramural arteries are primarily muscle-type arteries responsible for the coronary peripheral resistances.

In normal, non-atherosclerotic coronary arteries, blood flow varies over the cardiac cycle [5] (Fig. 1). The major determinants of coronary flow are the compressive resistance of the ventricular myocardium and the driving pressure (i.e. the difference between aortic and intraventricular pressure); these forces create forward and backward compression waves (''pushing'' effect) and expansion waves (''pulling'' effect), which interplay with each other and determine eventually the direction of flow at each time-point of the cardiac cycle [7,8]. In systole, the intramural arteries, especially in the left coronary system, experience a retrograde flow due to the myocardial compression. Unlike subendocardial arteries, the subepicardial and epicardial segments are mainly characterized by a slow systolic anterograde flow accompanied by an increase in their diameter [7−10]. Although it would be anticipated that during systole the backward flow derived by the collapsed subendocardial vessels would induce a retrograde flow in the subepicardial and epicardial arteries, in fact, this retrograde flow is concealed by the high capacitance of the extramural epicardial arteries, which are dilated due to their elastic properties. Also, forward compression waves derived by the increased aortic pressure contribute to the systolic forward epicardial flow [7,8]. However, a small component of backward flow may occur, especially at the onset of ventricular contraction, accounting for the complexity of the systolic flow [8]. In diastole, as the ventricular myocardium relaxes, the compressive impediment to intramyocardial arteries resolves, and the dilated extramural segments discharge the stored blood through the microcirculation, resulting in a forward and accelerated flow in the entire coronary arterial bed in order to maintain myocardial perfusion [7,8].

Local hemodynamic environment promotes atherosclerosis

The local hemodynamic environment within the coronary arteries constitutes a major determinant of focal atherogenesis and atherosclerotic plaque development [11] (Fig. 2). The main components of this environment include shear stress (SS) and tensile stress (TS) [6]. SS is the tangential force derived by the friction of the flowing blood on the endothelial cells (ECs). SS is defined as the product of the blood viscosity (μ) and the flow velocity gradient at the wall (SS = $\mu*$dv/ds). TS is the blood pressure-derived force imposed circumferentially on the arterial wall. TS is primarily sensed by VSMCs, and can be approximated by an equation related to the law of Laplace, $T = P*r/t$, where P is the blood pressure, r is the lumen radius, and t is the wall thickness. According to this equation, higher blood pressures, larger lumen diameters, and thinner arterial walls lead to increased TS.

Although the entire coronary tree is exposed to the atherogenic effect of the systemic risk factors, atherosclerotic lesions form at specific regions of the arterial tree, such as in the vicinity of branch points, the outer wall of bifurcations, and the inner wall of curvatures [11]. In these regions disturbed laminar flow occurs, yielding a low and oscillatory SS, which is characterized by low time-averaged values (<10−12 dyn/cm^2), as well as significant variations in direction and magnitude over short distances [11−13] (Fig. 2). Low and oscillatory SS
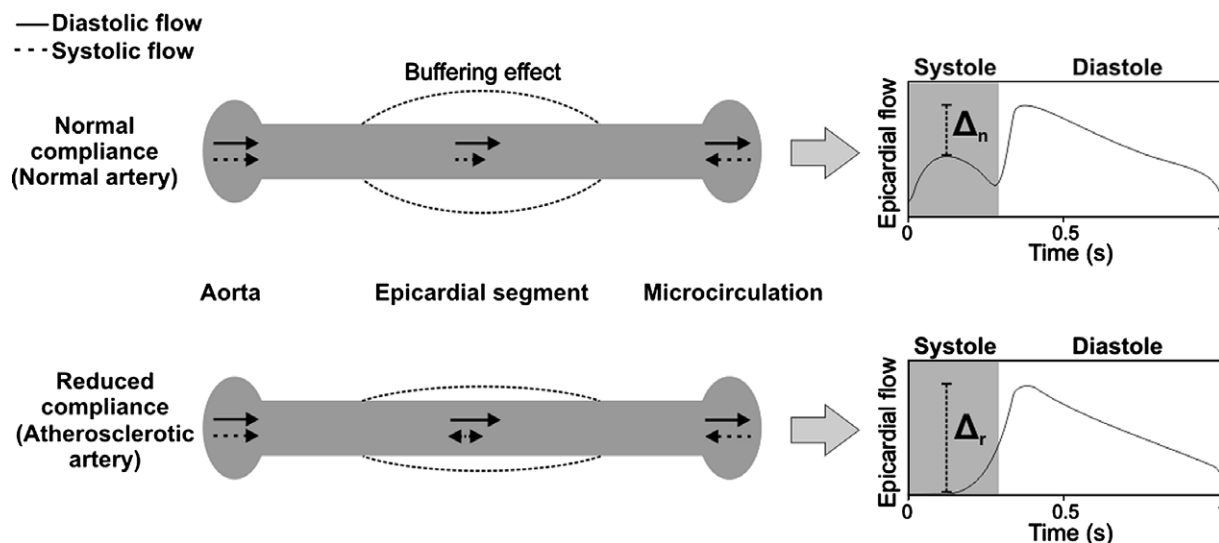
Figure 1 Conceptual model presenting the implication of reduced coronary wall compliance in the modulation of a local atherogenic hemodynamic environment. Physiologically, the systolic buffering effect in non-diseased elastic epicardial segments (upper left) results in a normal biphasic flow pattern during the cardiac cycle with a difference Δ_n between peak systolic and peak diastolic flow (upper right) [5,6,10]. On the contrary, in atherosclerotic coronaries, reduced compliance attenuates the systolic buffering effect (lower left), thereby augmenting the biphasic flow pattern ($\Delta_r > \Delta_n$), and leading to lower and more oscillatory shear stress, especially in regions susceptible to atherosclerosis (lower right). Dashed lines represent the change of the coronary lumen during systole.
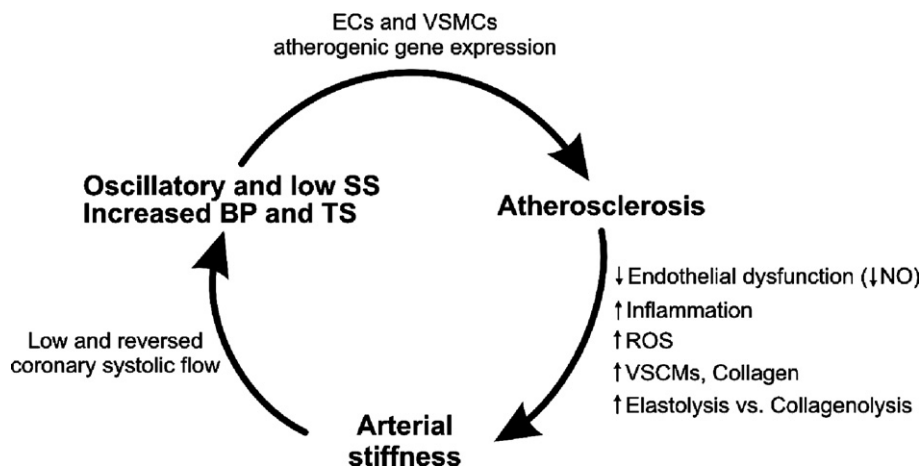

Figure 2 Local hemodynamic environment, atherosclerosis, and arterial stiffness are involved in a self-perpetuating vicious cycle, ultimately regulating coronary wall function, plaque formation and progression, and vascular remodeling.

modulate endothelial gene expression through a complex network of intracellular signal transduction cascades (mechanotransduction), ultimately impairing nitric oxide (NO) bioavailability, and subsequently vascular tone regulation, increasing endothelial LDL uptake and permeability, promoting the expression of monocyte adhesion molecules (e.g. VCAM-1, ICAM-1) and chemoattractants (e.g. MCP-1), enhancing the generation of reactive oxygen species (ROS), and accentuating ECs and VSMCs apoptosis and proliferation [11,14].

Through mechanotransduction pathways similar to those initiated by low and oscillatory SS, elevated TS modulates endothelial and VSMC gene expression, so that VSMCs acquire an atherogenic phenotype [15] (Fig. 2). More specifically, elevated TS promotes VSMCs proliferation, and subsequent ECM production, stimulates EC and VSMC plasma membrane NADPH oxidase, therefore promoting ROS generation, and upregulates endothelial expression of several pro-inflammatory (e.g. VCAM-1, ICAM-1, MCP-1) and vasoconstrictive

molecules (e.g. endothelin-1). Also, elevated TS appears to induce direct endothelial injury, thereby impairing the integrity of endothelial surface, and increasing the endothelial permeability to circulating lipoproteins and monocytes [16].

Atherosclerosis promotes arterial wall stiffening

As the atherosclerotic lesions develop, the diseased coronary segments progressively become stiff [17,18] (Fig. 2). Pathophysiologically, arterial stiffening is based on dysregulation of the balance between collagen and elastin towards excessive elastin breakdown and overproduction of abnormal collagen [2]. The major mediators of this imbalance between collagen and elastin are the population of the matrix producing VSMCs, as well as the activity of the matrix degrading proteases. As mentioned, both low SS and high TS constitute potent stimuli for VSMCs to migrate from the media to intima, differentiate to a more ''synthetic'' phenotype secreting collagen, and proliferate [19]. Also, the atherosclerotic process by itself promotes the fibro-proliferative processes within the intima through overproduction of ROS and pro-inflammatory cytokines (e.g. interleukin-1, tumor necrosis factor-α) by the ECs, macrophages, and VSMCs [19].

Matrix proteases (e.g. matrix metalloproteinases [MMPs], notably MMP-2 and MMP-9, and cathepsins) constitute a broad category of proteolytic enzymes, primarily responsible for the degradation of the intramolecular bonds of collagen and elastin fibers. Increased levels of MMP-2 and MMP-9 were found to be independent predictors of arterial stiffness [20]. One could speculate that in some cases, and for yet unknown reasons, the elastolysis prevails against collagenolysis, thereby diminishing the elastin content of the wall, and gradually promoting arterial stiffening [2].

Finally, not only the quantitative changes of VSMCs and matrix degrading enzymes, but also a qualitative reorganization of the existing wall material, including the connections between ECM proteins and VSMCs, may contribute to arterial stiffness [21].

Arterial stiffness amplifies the local atherosclerotic hemodynamic environment and drives the progression of atherosclerosis

The structural changes that coronary arteries undergo with their stiffening may augment the otherwise atherogenic local hemodynamic environment, thereby sustaining the progression of atherosclerotic lesions [2]. More specifically, the stiff epicardial segments have diminished capacitance to store the systolic backward flow derived by the collapsed intramyocardial microcirculation. One could speculate that a very low forward, or even reversed, systolic flow is then developed, accompanied by a regular anterograde diastolic flow [4] (Fig. 1). This low or reversed systolic flow may amplify the otherwise disturbed local flow in atherosclerosis-prone regions, resulting eventually in a more oscillatory and lower local SS [2,4] (Fig. 2). In addition, within a stiff coronary wall, blood pressure, and therefore circumferential TS, increase due to increased local arterial resistances [2,4] (Fig. 2). Such a hemodynamic environment characterized by an amplified low and oscillatory SS, and increased TS precipitates the progression of atherosclerosis, which in turn deteriorates vascular stiffening. Ultimately, a self-perpetuating vicious cycle is established among local hemodynamics, atherosclerosis, and arterial stiffening.

Coronary wall stiffness as a potential early marker of endothelial dysfunction and future atherosclerosis

Several in vivo and experimental studies indicated that impaired flow-mediated vasodilation decreases vascular elasticity [3,22,23]. Physiologically, the ability of an artery to distend is dependent not only on VSMCs population and ECM proteins content (structural determinants), but also on the endothelial NO production (functional determinant), which regulates VSMCs tone. Endothelial dysfunction reduces NO production, and this, in turn, diminishes arterial distensibility (Fig. 2). Reduced endothelial NO production is also one of the major pathogenetic mechanisms through which low SS and increased TS promote arterial stiffening. Although evidence supports the role of endothelial dysfunction in arterial stiffness, recent studies have suggested that the opposite may occur as well, i.e. the structural stiffening deteriorates endothelial function, and thereby worsens stiffening. The association of endothelial dysfunction and arterial stiffening, notably in the early stages of atherogenesis, suggests that vessel distensibility could be used as an early marker of endothelial dysfunction, and potentially as a predictor of future atherosclerosis [1,4] (Fig. 3).
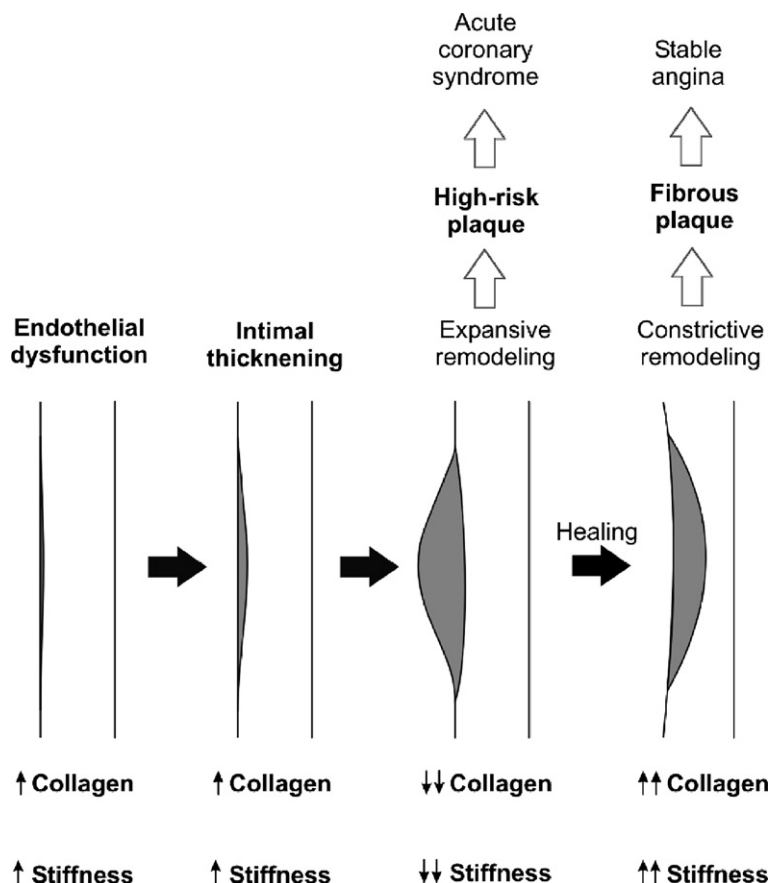
Figure 3 Coronary stiffness is closely associated with the natural history of atherosclerosis. During atherogenesis, endothelial dysfunction reduces the arterial compliance by reducing the production of NO. At the early stages of atherosclerosis (intimal thickening) the content of collagen in the wall increases due to the fibroproliferative processes, gradually resulting in arterial stiffening. As atherosclerotic plaque grows the increased local inflammatory response weakens the arterial wall, decreases local distensibility, and promotes expansive remodeling. This pattern of remodeling is associated with high-risk plaques which lead to acute coronary syndromes. Over time, some of the high-risk plaques may evolve to fibrous plaques through a process of repetitive microruptures, VSMCs proliferation and collagen deposition. As a response, arterial wall undergoes constriction and becomes stiff. Such plaques become gradually occlusive and manifest with stable angina. Whether arterial stiffness is the cause or effect of the remodeling response to local plaque growth, or another underlying pathology exists, remains elusive.

Atherosclerotic wall stiffness is associated with coronary arterial remodeling: a potential marker for the identification of high-risk plaques?

Coronary stiffening is not only associated with endothelial dysfunction and development of atherosclerosis, but also with vascular wall remodeling, a major determinant of the natural history of atherosclerosis (Fig. 3). Vascular remodeling is a dynamic and complex process that involves a permanent adaptation of arterial size in response to plaque growth [24]. Expansive remodeling is associated with high-risk plaques leading to acute coronary syndromes, whereas constrictive remodeling is associated with more fibrous plaques manifested

with stable angina [24,25]. IVUS studies in coronary patients demonstrated that eccentric, unstable plaques associated with expansive remodeling had higher distensibility compared to stable ones associated with constrictive remodeling [18,23,26]. The amount of collagen and consequently the arterial stiffening appear to play a critical role in determining the direction of vascular remodeling, and thus the natural history of atherosclerosis, and subsequent clinical events [27]. Given that coronary wall elasticity, and consequently the remodeling response to plaque growth, are both determined by the equilibrium between the degree of inflammation (matrix degrading effect) and fibroproliferation (matrix producing effect) [24], it could be postulated that in highly inflamed high-risk lesions the remodeling capacity of the vascular wall

increases due to the extensive matrix breakdown, and the wall eventually expands. On the contrary, in fibrous lesions excessive production of collagen increases the local arterial stiffness, and over time the arterial wall undergoes constriction. However, whether arterial compliance is the cause or effect of local remodeling response, or another underlying pathology exists, remains elusive.

Notably, the arterial compliance is not fixed throughout the natural history of an individual atherosclerotic plaque, but may undergo dynamic changes, which are dependent on the balance between inflammation and fibroproliferation (i.e. primarily collagen content) in the wall (Fig. 3). At early stages of atherosclerosis, the fibroproliferative processes prevail and the wall becomes stiff. As the early lesions evolve to high-risk plaques, then the wall loses its strength and becomes highly distensible, permitting expansive remodeling. Finally, as the high-risk plaques evolve to fibrous plaques through repetitive microruptures and subsequent healing [28], the wall becomes stiff and constricts. Therefore it appears that the changing nature of arterial compliance is consistent with the changing nature of local remodeling response and the subsequent natural history of atherosclerosis. In this setting, arterial stiffness could be used as a reliable marker of the natural history of an individual atherosclerotic plaque, having the potential to reveal high-risk plaques.

Current and future diagnostic armamentarium for the assessment of coronary wall stiffness

In order for a clinical marker to be applicable it should be easily measurable. Currently, there are several non-invasive techniques for the assessments of aortic, carotid, or brachial arterial stiffness [29]. However, the complex anatomic configuration of the coronaries does not permit direct application of these non-invasive approaches in the coronaries. Instead, the existing diagnostic modalities for the assessment of coronary stiffness are mainly invasive. These include the intravascular ultrasound (IVUS), and the pressure wire [30]; their combination enables the indirect assessment of local arterial compliance, as IVUS provides accurate measurements of the changing lumen and wall size over the cardiac cycle, whereas pressure wire measures the intracoronary pressure changing over time. This is another modality used for the assessment of vascular stiffness. This is an IVUS-based modality, which assesses the local elastic properties of the coronary wall using its deformation caused by a cyclic variation of intraluminal pressure in order to characterize the wall composition [31].

The development and in vivo application of a specific catheter capable of providing simultaneous IVUS and pressure data of exactly the same coronary region could potentially be an extremely useful clinical tool for the direct and on-site estimation of coronary stiffness. Also, the development of new CT- or MRI-based imaging modalities for the assessment of vascular wall stiffness in a non-invasive manner constitutes another challenging area for future research with important clinical implications.

Conclusion and clinical perspectives

The local hemodynamic microenvironment, atherosclerosis and arterial stiffness are involved in a self-perpetuating vicious cycle, ultimately regulating the coronary wall function, atherosclerotic plaque development and progression, and arterial remodeling. The association of arterial stiffness with endothelial dysfunction, as well as with vascular remodeling and the subsequent natural history of atherosclerosis, suggests that arterial stiffness may constitute a useful marker for the early identification of endothelial dysfunction or a high-risk plaque, respectively. This perspective would justify the early adoption of preventive measures to improve endothelial function, or the application of pre-emptive local interventions in high-risk arterial regions to prevent future acute coronary syndromes. Further experimental and follow-up studies in general healthy population are needed for the investigation of these perspectives. The development of new modalities for non-invasive and reliable assessment of coronary stiffness is anticipated to serve these studies.

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