



Pulsatile flow: A critical modulator of the natural history of atherosclerosis

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Received 28 January 2006; accepted 2 February 2006

Summary Atherosclerosis is a systemic process with multi-focal distribution which progresses or regresses in an entirely independent manner within each patient. The low and oscillatory shear stress along with the geometrical particularities of the coronaries modulate an atherogenic microenvironment in susceptible to atherosclerosis regions and determine the disease's rate of progression. However, the atherogenic effect of flow pulsation remains ambiguous. Since the pulsatile nature of the blood constitutes the major generator of the oscillatory shear stress, one could hypothesize that this physiological process might exert a synergistic effect to low SS by facilitating the lesion progression. The heart rate determines directly the frequency of flow pulsation; therefore, its reduction could potentially decelerate the progression of atherosclerosis by alleviating the local atherogenic hemodynamic environment. This perspective might constitute an insight into the beneficial role of heart rate lowering agents with most significant representative the β -blockers, which have been proved quite efficient anti-atherosclerotic drugs.

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It is well established that although atherosclerosis is a systemic chronic inflammatory disease, however, its distribution is multi-focal progressing or regressing in an entirely independent manner within each patient [1]. It is most likely that the local hemodynamic forces, and the shear stress (SS) in particular, along with the geometrical particularities of the coronaries modulate an atherogenic microenvironment in atherosclerosis-prone regions and under the influence of both local and systemic risk factors the atherosclerotic lesions grow [2,3].

Shear stress (SS), the frictional force exerted by the flowing blood on the endothelial surface, plays a complex and multi-faceted role in the localization, generation and growth of atherosclerotic lesions [1,2]. Physiologically, in unbranched arterial portions, where usually laminar flow occurs, the SS forces vary within a normal range (15–70 dyn/cm²) forcing the endothelial cells to generate molecules that promote a vasodilatory, anti-coagulant, anti-inflammatory and growth-inhibitory surface [1,2,4]. Conversely, at branches, bifurcations and inner curvatures disturbed flow occurs modulating a low and oscillatory shear stress environment [1,2,4]. Abnormally low shear stress (<4 dyn/cm²) stimulates specific mechanosensors

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located on endothelial cells. In particular, membrane integrins, ion channels, platelet-derived growth factor receptors and G proteins have been recognized as mechanoreceptors converting the SS stimuli into biochemical signals [5]. These signals in turn trigger downstream intracellular signaling pathways, which eventually increase the activity of specific transcription factors. Binding of these factors to endothelial DNA activates numerous atherogenic genes that promote vascular inflammation, smooth muscle cell proliferation, apoptosis and secretion of pro-thrombotic molecules [5]. Moreover, these gene alterations affect the cytoskeletal fibers causing structural changes of the endothelial cells [2]. As a result the endothelium becomes more permeable to the circulating lipoproteins and other biologically active substances [2]. This phenomenon is further augmented by the blood stagnation that occurs in low blood flow regions [2,4]. Consequently, in these regions the residence time of blood atherogenic particles is increased, thus their subendothelial migration through the damaged endothelium is facilitated.

Furthermore, recent studies have revealed an added effect of SS on endothelial cells which involves the stimulation of them to produce reactive oxygen species [6]. These substances in turn lead to the degradation of nitric oxide in endothelial and vascular smooth muscle cells and the increase of intracellular oxidative stress. The consequences of the generated oxidative stress include loss of endothelium-dependent vasodilatation, atherogenic gene expression and inflammatory responses. Ultimately, these processes confer a predisposition to atherosclerosis.

The complex three-dimensional coronary geometry, the blood molecular viscosity and the flow pulsation constitute the major determinants of the intravascular blood flow patterns and shear stress [1,3,4]. The coronary blood flow is pulsatile by its nature. The epicardial coronaries which mostly affected by atherosclerosis are mainly perfused during diastole, while in systole their flow exhibits marked deceleration. Since SS is defined as the product of molecular viscosity and the gradient of blood velocity near the wall, the blood flow patterns affect directly the SS variations. Hence, in regions prone to atherosclerosis the pulsatile flow generates an oscillatory SS, whereas in regions where laminar flow occurs a pulsatile SS is produced. The critical difference between oscillatory and pulsatile SS is that the former requires a mean flow of zero, while the latter has a non-zero mean.

As long as the oscillatory SS is a clear atherogenic factor one could hypothesize that the pulsatile flow

could modulate an atherogenic environment in the entire coronary bed contributing to the diffuse development of atherosclerosis [1,2]. However, this hypothesis looks rather oversimplified since, as mentioned, the atherosclerotic lesions exhibit focal development. It seems that the major determinant of the localization and progression of atherosclerosis is the low SS developed in susceptible regions along the coronaries [7]. It is in these regions that the pulsatile flow might acts deleteriously by generating significant SS oscillations. These oscillations could be regarded as a "flagellum", which intensifies the atherogenic effect of low SS. Over the time

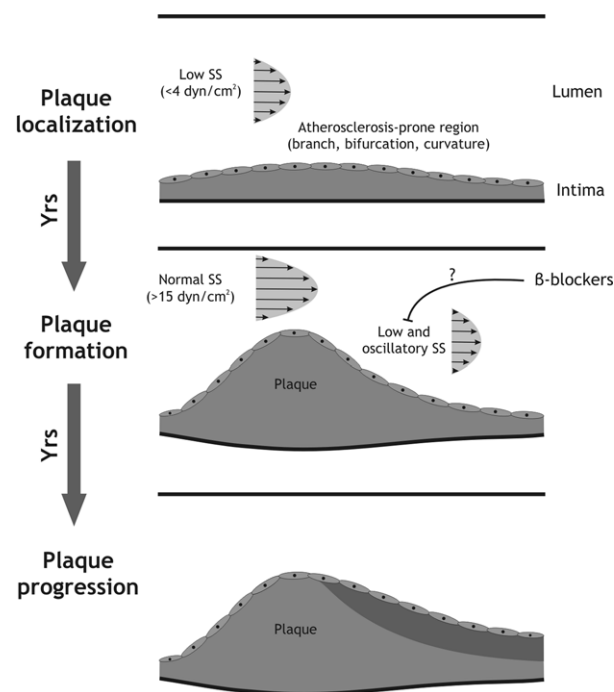


Figure 1 Hypothetical model of the effect of pulsatile flow on the natural history of atherosclerosis. Initially, in susceptible to atherosclerosis regions (branches, bifurcations, curvatures) where low shear stress (SS) occurs a lesion starts to develop (top). Over the long term and under the influence of the systemic risk factors, complex remodelling processes are involved leading gradually to the formation of the plaque (middle). Although, the growing plaque restores the local SS to an "average" value observed under normal flow conditions, however, at the post-stenotic regions low and disturbed flow occur (middle). It is most likely that in these regions the flow pulsation which generates the oscillatory SS further augments the atherogenic environment facilitating the progression of the lesion (bottom). Since the heart rate determines directly the frequency of flow pulsation, its reduction by heart lowering agents and in particular β -blockers could hypothetically reduce the number of SS oscillations per minute thus decelerating the progression of atherosclerosis.

this amplification is gradually accumulated exerting a chronic "fatigue effect" [8]. Therefore, it seems that the pulsatile flow does not promote the atherogenesis by itself, however, it might offer a synergic or complementary action by facilitating the lesion formation and progression and determining the conversion of a quiescent plaque to a vulnerable plaque that may lead to an acute coronary syndrome (Fig. 1).

As mentioned the pulsatile SS is a physiological process compatible with the pulsatile nature of the blood flow. However, the elimination of flow pulsation might exert potentially an atheroprotection in that it could eliminate the chronic "fatigue effect" caused by the oscillatory SS in atherogenic regions. Since the heart rate determines directly the frequency of flow pulsation, its reduction could potentially reduce the number of SS oscillations per minute. Therefore, the reduction of heart rate could potentially decelerate the progression of atherosclerosis by alleviating the local atherogenic hemodynamic environment. The atheroprotective effect of the reduced heart rate is indirectly supported by the fact that the high heart rate has been found to be associated with atherosclerosis in a manner rather independent of sympathetic overactivity [9–11]. This phenomenon might constitute an insight into the beneficial role of heart rate lowering agents with most significant representative the β -blockers, which have been proved quite efficient anti-atherogenic drugs [12]. According to clinical observations lowering the heart rate by 10 beats per minute, from 70 to 60, would increase human life expectancy from 80 to 93.3 years [13]. Whether low heart rate could prolong life in humans and whether this effect might be linked with the alleviation of flow pulsation constitutes a quite fascinating, and at the same time oversimplified, hypothesis. Nonetheless, this hypothesis offers the basis for many exciting research opportunities in the future.

Conclusively, the pulsatile flow, although a physiological phenomenon exerts an adverse effect in regions prone to atherosclerosis by generating severe SS oscillations. In these regions it seems most likely that intensifies the atherogenic action of low SS and along with the systemic risk factors (hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus and family history) pro-

motes the plaque development and determines the natural history of atherosclerosis.

Acknowledgement

Granted by the Greek State Scholarships Foundation.

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