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Hemodynamics Influence on Endothelial Function

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Abstract

The growth of the blood vessels, smooth muscle tone in the blood vessels, activity of platelets, inflammation, fibrinolysis and coagulation pathway are regulated by factors released from endothelium.^{1,2} Various factors can affect the endothelial function and promote atherosclerosis.^{3,4} In humans endothelial function is influenced by haemodynamics. Vascular endothelial cells act as a signal transduction interface between haemodynamic forces and the vascular smooth muscle cells. Steady hemodynamic forces stimulate cellular responses that are essential for endothelial cell function and are atheroprotective. Mechanical forces influence the development and progression of cardiovascular disease. Alterations in arterial structure are common in vascular diseases and are thought to occur primarily by vascular remodelling, in response to hemodynamic and vascular biomechanical stimuli.⁵⁻⁷ Endothelial dysfunction correlates with disease progression.⁸ Failure of the endothelium to respond to therapies is associated with higher risk.⁹ The hemodynamic forces directly dictates the function, of the endothelial layer. In the past several years, experimental and clinical studies have provided new information about the mechanisms and clinical relevance of haemodynamics influence on endothelial function. This review is to summarize recent

articles that have advanced in understanding the molecular basis of the hemodynamic influence on the endothelial function.

Key words: shear stress, endothelium, vascular biomechanical stimuli, mechanotransduction

Introduction

The endothelium of the circulatory system's health is essential to normal vascular physiology and its dysfunction can be a critical factor in the pathogenesis of vascular disease. The involvement of vascular endothelium in disease processes such as atherosclerosis has been recognized since the decades. We now appreciate that forces, generated by the pulsatile flow of blood can also influence the structure and function of endothelial cells. As the endothelium is in direct contact with blood, the endothelium bears the frictional forces imparted by the flow. As blood flows through a vessel, it exerts a physical force which generates a stress parallel to the vessel wall (shear stress) and a perpendicular stress (tensile stress). The shear stress exerts frictional force on the endothelial surface. The endothelium responds rapidly and sensitively to the mechanical conditions created by blood flow.¹⁰ Arterial blood flow in human is pulsatile hence, the absolute shear stress varies throughout the cardiac cycle. In straight parts of the arterial tree wall shear stress is high and directed and in branches and curvatures there is irregular distribution and shear stress is low. Experimental and clinical studies have provided new information about how the disturbed haemodynamics in branch points and curvatures can be the cause for the preferential localization of atherosclerotic lesions and in-stent restenosis. Arterial endothelial cells and venous endothelial cells differ both functionally and molecularly. On the molecular level, arterial endothelial cells express ephrinB2, whereas venous endothelial cells express EphB4. They are thought to be key molecules in the process of arteriovenous differentiation by endothelial cells^{11,12} and probably could be the cause for vein bypass graft failure. Studies have identified hemodynamic shear stress as an important determinant of the endothelial cell response to possibly by mechanotransducers intermediate signaling molecules, mitogen activated protein kinases and nitric oxide. Shear stress has not only been shown to be a critical determinant of vessel caliber,¹³⁻¹⁵ but has also been implicated in vascular remodeling^{16,17} and development of various vascular diseases, such as hypertension, thrombosis, and arteriosclerosis.^{18,19} This review summarizes the current knowledge on the molecular basis of the endothelium's ability

to sense the shear stress.

Molecular basis of endothelium's ability to sense shear stress

The molecular basis of endothelium's ability to sense the shear stress is still remains unclear. A number of mechanosensitive biological molecules have been identified, including mechanically gated channels (1), receptors (2), G proteins (3), enzymes (4), and cytoskeleton. It has been demonstrated that the apical surface of endothelial cells is decorated with various membrane-bound macromolecules that constitute the glycocalyx which senses the shear stress.²⁰ Ion channels are proposed as possible flow sensors by some of the studies which explains the sequence of events as, shear stress cause the K⁺ flux, initiating transmembrane hyperpolarisation which results in Ca²⁺ entry into the cell.^{21, 22} The amount of calcium entry into the cell which causes release of caveolae-bound endothelial nitric oxide synthase,²³ is in turn determined by the magnitude of shear stress.^{24, 25} Various theories are there on how these channels are activated. In a review by Boris Martinac, the author explores the theory of cytoskeleton participation in activation of these channels and provides the current best evidences supporting the same.²⁶ Mechanotransduction of shear stress is been linked with G-protein coupled receptors, human B2 bradykinin G protein-coupled receptor found to undergo conformation changes on being stimulated by fluid shear stress.²⁷ The endothelial cell responds to shear stress by secreting and releasing various mediators like endothelium derived hyperpolarising factor which brings relaxation of the smooth muscles in the blood vessel, as evidenced by various findings.^{27,28} Some of the recent studies have reported that hydrogen peroxide generated from CYP epoxygenases and xanthine oxidase can act as endothelium derived hyperpolarising factor.^{30, 31} Reactive oxygen species generated from nicotinamide adenine dinucleotide phosphate (reduced) oxidase, xanthine oxidase, uncoupled endothelium derived Nitric oxide synthase in response to shear stress is said to be involved in flow induced vasodilation.³²⁻³⁴

Altered haemodynamics results in endothelial dysfunction

Coarctation of the aorta is associated with substantial morbidity despite treatment. Coarctation of the aorta leads to altered wall shear stress which is said to cause alterations in the smooth muscle phenotype expression contributing to structural and functional changes.

These changes are not reversed upon blood pressure correction and may serve as markers of disease severity, which explains the persistent morbidity observed in coarctation of the aorta patients.³⁵ In type II diabetes mellitus the insulin resistance and free fatty acids act directly on endothelium derived nitric oxide synthase activity and mitochondrial function. This leads to oxidative stress and increase generation of superoxide radicals which affects the vascular tone leading to altered haemodynamics predisposing to development of atherosclerosis.^{36,37} In a review by Hua Cai and David G. Harrison, the authors explore the role of the oxidant stress involved in the pathogenesis of many cardiovascular diseases, including hypertension, hypercholesterolemia, atherosclerosis, diabetes, and heart failure and provides the current best evidences supporting the theory of reactive oxygen species generated in these diseases that could potentially inactivate nitric oxide.³⁸ In compensated heart failure the altered haemodynamics in the pulmonary artery affects the endothelium derived nitric oxide synthase messenger ribonucleic acid expression. This leads to pulmonary endothelial function leading to development of pulmonary hypertension.³⁹ Atherosclerosis is lipid accumulation in the artery wall resulting from the transendothelial entry of low density lipoprotein, followed by its oxidation and uptake by macrophages.⁴⁰ Local hemodynamic forces play a significant role in the focal nature of the lesions,⁴¹ by upregulating the expression of sterol regulatory element-binding proteins.⁴² Autologous vein grafts are the most common procedure for the reconstruction of arterial occlusive disease in the heart and peripheral circulation, the patency of these vein bypass grafts is still hampered due to the development of intimal hyperplasia. Vascular endothelial function of the graft is affected due the altered haemodynamics during the transition from venous to arterial flow dynamics.^{43,44} Evidences suggests that in addition to stimulating angiogenesis, modulating various aspects of endothelial cell function may reduces intimal hyperplasia and help in preserving and maintaining the graft.⁴⁵⁻⁴⁷ Endothelial function is impaired by coronary artery stenting, in-stent restenosis may be due to local factor as supported by recent observations of elevated inflammatory marker C-reactive protein, after stent implantation.⁴⁸ The use of drug-eluting stents for coronary artery disease has resulted in a reduction of acute vessel closure, but studies have reported that a high rate of in-stent restenosis persists,⁴⁹ which may be prevented by using Stent-based delivery of AdeNOS which enhances endothelial regeneration and reduction in neointimal formation.^{50,51}

Conclusion

The vascular endothelium plays a critical role in the regulation of arterial function through the synthesis and release of a number of antiatherogenic factors. Endothelial dysfunction results in impairment of normal homeostatic properties of the vasculature which leads to vasospastic, prothrombotic, and proinflammatory changes.⁵² The immense knowledge that we have obtained on the endothelial function and the influence of haemodynamics on its function, supports the notion that assessment of endothelial function should be integrated into our clinical practice. The clinical measurement of endothelial function is challenging, due to the complexity of the mechanotransduction of shear stress and heterogeneous functions of endothelium. In an editorial by Noyan Gokce, the author has elaborated on many tools available for clinical assessment of endothelial function.⁵³ Therapeutic intervention to prevent and reversal of endothelial dysfunction has been possible as evidenced by a growing list of modulators.⁵⁴⁻⁵⁷ Further studies should be directed at determining which non-invasive test or combination of tests of endothelial function may be useful in clinical arena, to guide treatment and change outcomes based on different populations.

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