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Review Article

Endothelial Function and Cardiovascular Health

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Abstract

Systemic vascular disease is a major public health issue all over the world. Vascular disease causes significant morbidity and excessive mortality. Risk factors for vascular disease like hypertension, diabetes, hyperlipidemia, and tobacco consumption inflict vascular disease by causing endothelial dysfunction. Endothelium, the innermost layer of the blood vessels governs vascular tone and vasomotion. Abnormal endothelial function promotes vasoconstriction and atherothrombosis. Thus, endothelial dysfunction predisposes to vascular disease affecting target organs --- brain, heart, and the kidneys, etc. Endothelial dysfunction, thus, is a precursor in the onset and progression of systemic vascular disease and atherosclerosis. Future interventions to prevent vascular disease should include modalities to preserve endothelial function and to reverse endothelial dysfunction. Endothelial function is critical to maintain holistic public health.

Key words: Cardiovascular Disease (CVD), Endothelium, homeostasis

Cardiovascular disease (CVD) is the leading global cause of premature mortality and excessive morbidity. A number of predisposing factors contribute to the pathogenesis of CVD. Etiological factors such as hypertension, diabetes, obesity, sedentary life style, tobacco consumption, and genetics participate in the onset and progression of CVD. Age and gender may also play an important role in the causation of CVD. An important critical fundamental basis for CVD is endothelial dysfunction. Circulatory homeostasis is regulated by the cells that line the vascular system – the endothelium.^[1,2] Originally, endothelium was merely considered as an inactive physical barrier between the blood and vascular smooth muscle but it is now recognized as playing a central role in the development of vascular disease/atherosclerosis. While it is not absolutely clear whether it is the cause or consequence of CVD, endothelium is intimately linked to vascular pathology.^[3,4] Given its (physical) location between the blood stream and vascular smooth muscle, endothelium is the locus for biological and mechanical actions of cardiovascular risk factors.

The endothelium is the largest organ in the body serving paracrine, endocrine, and numerous other regulatory functions in determining the cardiovascular health and CVD [Figure 1]. In response mechanical, biological, and endocrine stimuli, endothelium produces vasoactive substances which govern the vascular structure and function. The consequences of this phenomenon are vasoconstriction or vasodilation or thrombus formation.^[5,6] Endothelium thus controls vascular remodeling, hemostasis, and inflammation. A principal function of the endothelium is to regulate vasomotor tone (contraction or dilation) [Table 1]. A prominent function of endothelium is nitric oxide (NO) metabolism and other vasodilatory substances such as prostacyclins.^[7-9] The endothelium [Figures 2 and 3] also modulates vasoconstrictor components such as thromboxane A₂, endothelin, and angiotensin II [Figure 4]. The vascular growth factors are also modulated by the endothelium. In other words, the endothelium is the maestro conducting the cardiovascular orchestra [Figures 5 and 6].

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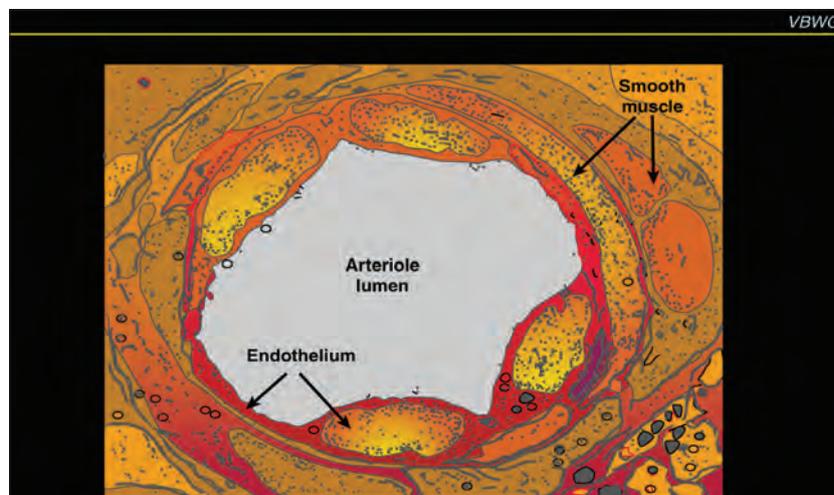
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Table 1: Endothelial function/vascular health

Healthy endothelium maintains a balance between opposing states:	
•	Dilation vs constriction
•	Growth inhibition vs growth promotion
•	Antithrombosis vs prothrombosis (antifibrinolysis vs profibrinolysis)
•	Anti-inflammation vs proinflammation
•	Antioxidation vs pro-oxidation

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**Figure 1:** The endothelium: A living organ**Vasodilating Factors/Endothelium****NO**

The seminal discovery by Furchgott of endothelium derived relaxing factor (EDRF) confirmed that normal endothelium is essential to induce vasodilation.^[10] Subsequent research has led to uncovering that EDRF is NO. Endothelium produces NO by stimulating guanosine monophosphate (GMP). NO regulates vasomotor tone, myocardial contractility, cell permeability, vascular proliferation, and exerts anti-thrombotic effects. NO synthase produces NO from L-arginine. NO synthase in the endothelium is acNOS, an inducible enzyme. In the normally functioning endothelium, acNOS continually produces NO to maintain physiological vasodilation constantly.^[11,12]

In addition, bradykinin and acetylcholine also stimulate acNOS. Hypoxemia and vascular shear stress are important

stimuli for the release of NO. It is of interest to note that NO production is highest in the small arteries (resistance vessels) but NO activity is highest in the large diameter arteries. NO is involved in auto-regulation of blood flow in the arteries of all sizes, thus assuring required distribution of blood among various vascular networks. NO also modulates growth factors and vasoconstrictors. During atherogenesis, platelet-derived growth factor (PDGF) β inhibits the activity of NO. Thus, positive and negative control mechanisms are present in the endothelium.

Prostacyclin and Bradykinin

Prostacyclin is elaborated in response to shear stress and other factors influencing NO. But when compared to NO, the contribution of prostacyclin to vasodilation is negligible. Endothelial cells produce and release bradykinin in response to

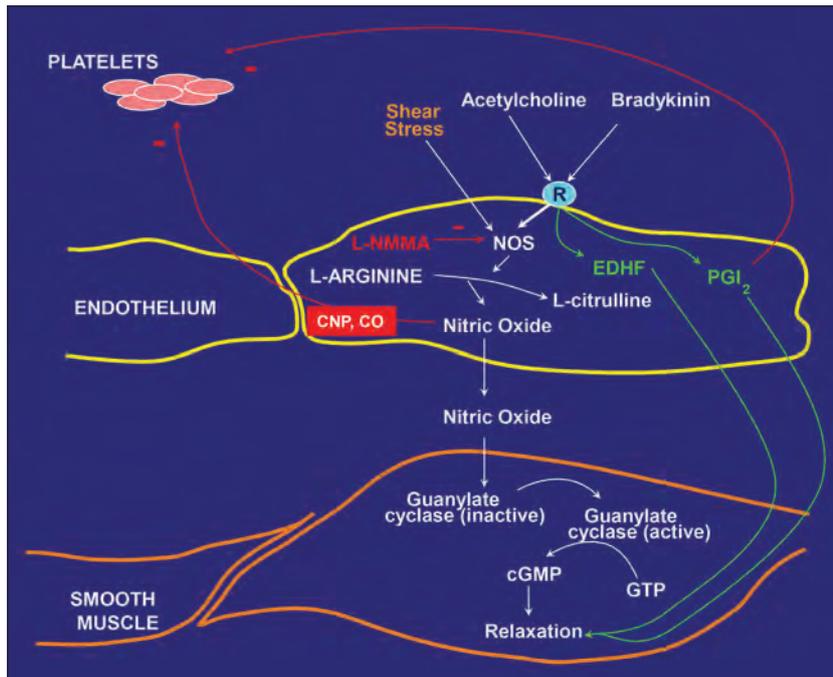


Figure 2: Cellular pathways of nitric oxide actions at the blood vessel

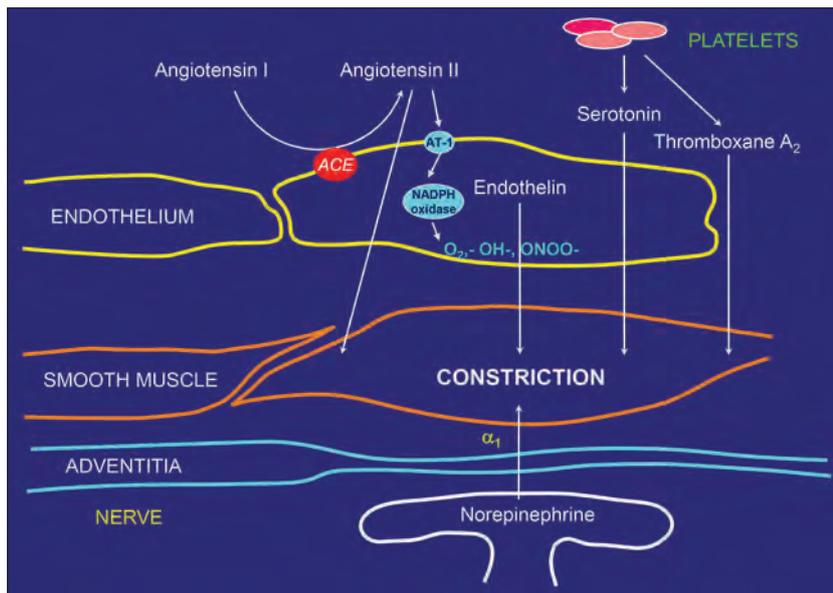


Figure 3: Cellular pathways of nitric oxide actions at the blood vessel

blood flow. Bradykinin in turn binds to β_2 receptor to activate L-arginine – NO pathway. Bradykinin has dual vasodilating properties – direct and indirect through stimulation of NO. Bradykinin causes nitrite release from coronary arteries. Bradykinin (like NO) also inhibits platelet aggregation and thrombosis. By stimulating tissue plasminogen activator (t-PA), bradykinin promotes an anti-thrombotic effect.

Vasocontracting factors/endothelium

Endothelium may prevent vasodilation or cause vasoconstriction through thrombin, acetylcholine, arachidonic acid, prostaglandin, H₂, and high potassium levels as well as by hypoxia and vascular stretch. Examples of endothelium derived contracting factors include endoperoxides and thromboxane A₂.

Endothelin

Endothelin, a 21 – amino acid peptide is a potent vasoconstrictor. It is produced by the endothelin in response to thrombin, angiotensin II, arginine vasopressin, interleukin – I, and calcium ionophores, etc. In healthy individuals, circulating levels of endothelin are very low. Endothelin production is influenced by cGMP-dependent inhibition, cAMP-dependent inhibition, and an inhibitory factor produced by vascular smooth muscle cells. Formation of NO by normal endothelium offsets the negative actions of endothelin.

Angiotensin II

Angiotensin II is a powerful vasoconstrictor produced by angiotensin converting enzyme present in the endothelial cells. In addition to causing direct vasoconstriction, angiotensin II stimulates endothelin and hence with resultant vasoconstriction.

Endothelium dependent – vasomotion

The pivotal role of endothelium --- dependent vasodilation in maintaining normal vasomotion is a well-established concept. It is well known that acetylcholine, an endothelium --- dependent factor causes coronary vasorelaxation in the normal vessels but causes paradoxical vasoconstriction in atherosclerosis arteries. The paradoxical vasoconstriction is explained by the loss of normal endothelial function in the diseased arteries. This pathological observation is seen well before the angiographic dissection of atherosclerotic lesions. Substances that inactivate NO such as methylene blue and free hemoglobin blocks acetylcholine mediated vasodilation. In addition to NO, other endothelium derived vasodilators such as histamine and substance P cause coronary vessel dilation.^[13] In summary, vascular endothelium plays a major role in maintaining vascular tone and tissue blood flow in health and in disease.

Vasculoprotective Properties of the Endothelium

Vascular growth

The endothelium produces a number of growth factors such as --- fibroblast growth factor, PDGF, angiotensin II, and endothelin. At the same time, the endothelial cells also produce growth inhibitors such as TGF - β , heparan sulfates, and heparin. Importantly, NO has significant anti-proliferative effects. NO inhibits vascular smooth muscle proliferation and fibroblast mitogenesis. Overexpression of NOs and precursors of NO inhibit and prevent endothelial injury. The superoxide generation by angiotensin II can be blocked by NO.

Anti-coagulant effects

The normal endothelium maintain a critical balance between the factors that regulate fibrinolysis and thrombosis.^[14,15] The endothelium protects against thrombus formation by synthesizing glycosaminoglycans that bind to antithrombin. The endothelial

cells synthesize thrombomodulin which transforms thrombin and converts it to an activator of protein C; these activated proteins have anticoagulant properties. In addition, protein C – causes fibrinolysis (through interaction with plasminogen activator inhibitor [PAI]). A vital fibrinolytic property of the endothelium is its ability to produce t-PA that converts plasminogen to plasmin. Endothelial cells synthesize PAI- 1 which determines the rate of fibrinolysis. The balance between t-PA and PAI-1 is tilted toward thrombosis by angiotensin II.

The endothelial cells can inhibit platelet aggregation and adhesion, prostacyclin produced by the endothelium also blocks platelet activation. Platelets also contain NO synthase which is turned on by platelet aggregation. NO blocks ADP-induced platelet adhesion and aggregation. In totality then, NO inhibits platelet adhesion to the vascular endothelial cells. The antithrombotic actions of endothelium are due to synergistic effects of NO and prostacyclin. The vasospasm and thrombus formation are prevented by joint actions of NO and prostacyclin.

Anti-inflammatory effects

Leukocyte adhesion is attenuated by NO produced by the endothelium.^[16] NO also inactivates superoxide anion. Deficiency of NO causes vascular permeability and protein leakage hallmarks of vascular inflammation. An imbalance between NO and superoxide anion induces vascular inflammation by promoting leukocyte migration and mast cells. The endothelial cells normally prevent leukocyte adhesion, damaged endothelium expresses leukocyte adhesion molecules which is a pro-inflammatory state. Oxidized LDL cholesterol also causes an inflammatory reaction in the endothelium. The metabolic stress induced by hypertension and hyperlipidemia, for example, causes superoxide anion generation and vascular smooth muscle hypertrophy.

NO and anti-atherosclerotic effects

Besides blocking the leukocyte-endothelial interaction, NO also prevents other mechanisms involved in atherosclerosis. NO inhibits vascular smooth muscle hypertrophy and migration and eliminates oxidative modification of LDL. NO deficiency results in vascular dysfunction and thrombus formation. Low levels of NO may stimulate angiotensin and block bradykinin production. NO blocks adhesion molecules and chemotactic proteins. For all these reasons, NO is considered as a natural anti-atherogenic molecule.^[17,18]

Exposure to vascular shear stress augments NO activity, thereby inhibiting monocyte adhesion to the blood vessel wall and promoting vasodilation. On the other hand, low shear stress is accompanied by reduced NO activity, exaggerated vasoconstriction, and platelet aggregation. Regions of low shear stress are vulnerable to atherosclerosis (typically seen in the arterial branches or bifurcations). Non-aligned cells are found in low shear stress areas whereas aligned cells are found in high shear stress areas. These observations emphasize that endothelial functions are sensitive to hemodynamic changes in the circulatory state.^[19,20]

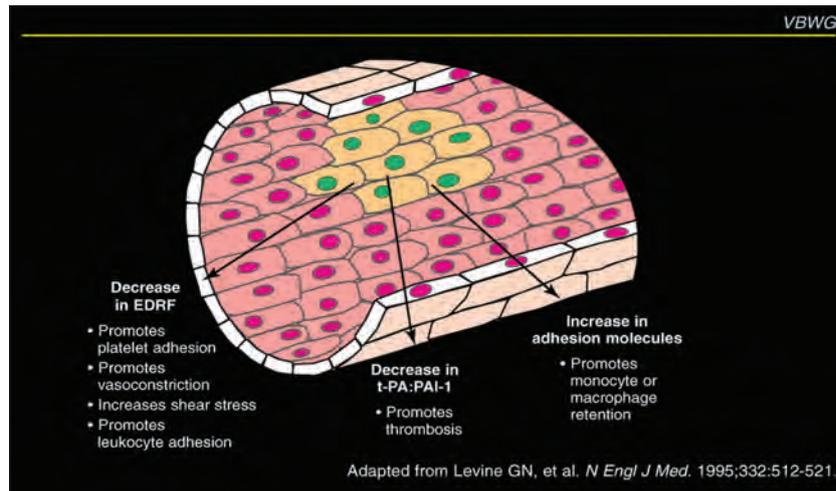


Figure 7: Dysfunctional endothelial cells in dyslipidemia and atherosclerosis

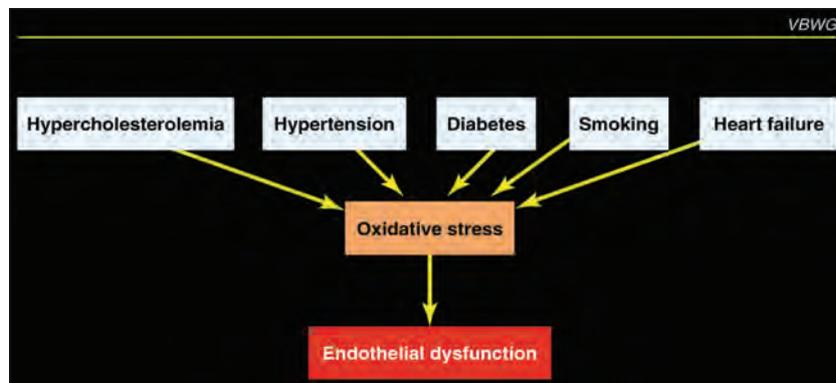


Figure 8: Risk factors and endothelial dysfunction mediator role of oxidative stress

Summary

The endothelium is an important organ which governs and maintains cardiovascular homeostasis. Located strategically between the blood stream and vascular smooth muscle, it plays a critical role in maintaining cardiovascular health. Normal endothelial function is responsible for physiological blood flow, oxygenation, and prevention of thrombus formation. Endothelial dysfunction predisposes to vasoconstriction, hypoxemia, and thrombus formation leading to ischemia and infarction of the tissue. Endothelial damage has widespread pathophysiological consequences and implications. Abnormal endothelial function promotes vascular inflammation and vascular hypertrophy. The end result of endothelial dysfunction is vascular insufficiency and target organ damage. Risk factors which predispose to endothelial damage include – hypertension, diabetes, hyperlipidemia, tobacco consumption, obesity, sedentary life style, and genetic factors [Figures 7 and 8]. To prevent vascular disease and to protect endothelial function, risk factors should be identified early and treated aggressively. In addition to the control of risk factors, vascular health can be

maintained by therapies which promote NO release. Thus, a broad spectrum therapeutic approach is required to maintain endothelial integrity and cardiovascular health. Understanding of endothelial physiology and pathophysiology is necessary to preserve and to protect global public health.

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