The Endothelium and Endothelin: Beyond Vascular Reactivity

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The vascular endothelium is the largest organ in the body. The vessel wall is 5 times the size of the heart in mass and 6 times the size of a tennis court in area. The vessel wall is an active, integrated organ composed of three separate layers: intima, media and adventitia. Histologically, the endothelial cells are very specialized, metabolically active, polyhedral cells that form a continuous layer that lines the internal surface of blood vessels. In small vessels, endothelial cells possess a well-defined basal membrane with fine elastic fibrils (the subendothelium) in contact with the smooth muscle cells of the media. Since the discovery that the endothelium is the main regulator of vascular tone, capable of releasing numerous vaso-active substances, a large number of studies have been carried out in the endeavor to explain its pathophysiology.

The functions of the endothelium

The main functions of the endothelium are the following: regulation of vasodilation and vasoconstriction, regulation of vascular permeability, regulation of leukocyte-and platelet-vessel wall interaction, and vascular proliferation and remodeling. As far as the autocrine function is concerned, the main activity of the endothelium is the release of vasoactive substances (endothelium derived relaxing factors EDRF and endothelium derived constricting factors EDCF), which regulate vascular tone.

Endothelial dysfunction is important in the pathophysiology of hypertension. This causes endothelial cells to decrease production of some compounds and increase production of others. Production of nitric oxide (NO), a potent vasodilator, is decreased, while production of vasoconstrictors, notably endothelin (ET) and angiotensin II (AII) is increased.

It was Sir Henry Dale who, in 1914, observed that the intravenous injection of acetylcholine (ACh) increased blood flow, but it was not until 1985 that Furchgott realized that ACh-induced relaxation was endothelium-dependent; for this reason he named this substance EDRF. Two years later, Moncada proved that EDRF was identical to nitric oxide (NO). Nitric oxide (NO) mediates vasodilation via activation of soluble guanylyl cyclase in vascular smooth muscles, where the subsequent generation of cyclic GMP (cGMP) results in smooth muscle relaxation. Indeed, this is mechanism by which NO donors such as nitroglycerin induce vasodilation within the vasculature. However, there is growing evidence that NO exerts effects on the cardiovascular system that are independent of cGMP. Thus, the functional roles of NO in the cardiovascular system surpass those of an exogenous form of the drug such as nitroglycerin.

NO is synthesized in many cell types from the conversion of the amino acid L-arginine to L-citrulline. At least three distinct NO synthetases (NOSs) have been identified and are found to produce various amounts of NO under different conditions. For example, both the neuronal (nNOS or NOS1) and endothelial (eNOS or NOS3) isoforms are usually expressed stably or constitutively with little change in NOS protein levels over time in those tissues where they are expressed. These isoforms are activated by a rise in intracellular calcium. In contrast, sustained high levels of NO can be produced in endothelial and smooth muscle cells by the inflammatory cytokine-inducible form of NO synthetases termed "inducible" NOS (iNOS or NOS2).

Normal vascular endothelial cells support cardiovascular function by promoting vasodilation and by inhibiting platelet aggregation, white blood cell adhesion, and smooth muscle cell proliferation. In contrast, dysfunctional endothelium is characterized by an impaired endothelium-dependent vasodilatation response; it favors platelet aggregation, white blood cell adhesion, and promotes smooth muscle cell proliferation. Endothelial dysfunction is characterized by a decreased production and/or local bioavailability of NO. It plays a pivotal role in the development, progression, and clinical manifestations of atherosclerosis, as well as in the development of ischemia and thrombosis in late stages of the disease by promoting coronary vasoconstriction and thrombosis.

Impaired endothelium-dependent dilation in the coronary circulation is associated with coronary atherosclerosis and coronary risk factors,[1-2] and improves with risk reduction therapy.[3] Consequently, endothelial function has been defined as an "excellent barometer" of vascular health[4] and can be used to gauge cardiovascular risk. Previous studies demonstrated a pathogenic link between coronary endothelial dysfunction and cardiovascular events.[5,6] Coronary and peripheral endothelial dysfunction may be induced by several risk factors, as in familial hypercholesterolaemia, smoking, diabetes mellitus and hyperhomocysteinemia.

Endothelial dysfunction and hypertension

High blood pressure is an established independent risk factor for cardiovascular disease. Hypertension leads to cerebrovascular injury, atherosclerosis, and renal failure. Although previous studies have focused on sodium retention and excess production of endogenous vasoconstrictors such as angiotensin II and endothelin as causes of elevated blood pressure in this disease syndrome, there is growing evidence that some forms of hypertension result from a reduced amount of endothelium-derived NO (i.e., a decreased in eNOS expression or activity).

ENOS in endothelial cells can be activated by several mechanisms, including parasympathetic (muscarinic cholinergic) nerve release of ACh that results in local vasodilation. Individuals with clinical hypertension demonstrate impaired endothelium-dependent relaxation of their forearm vessels in response to pharmacologically administered ACh.[7]

Mutant mice lacking a functional eNOS gene (i.e., eNOS "knockout" mice) are hypertensive in both the systemic and pulmonary circulations.[8,9] Blocking eNOS activity with chemicals-such as the nonmetabolized arginine analogue N-nitro-L-arginine methylester (L-NAME) that mimic the enzyme's natural substrate, L-arginine, also increases systemic blood pressure.[10] Feeding L-arginine, the precursor of NO, to hypertensive rats increases eNOS activity and lowers systemic blood pressure.[11] Moreover, in vivo gene transfer of eNOS (i.e., the transfer of genetic information encoding the eNOS protein into blood vessels) effectively decreases the systemic blood pressure of spontaneously hypertensive rats.[12] The evidence indicates that, at least in animal models, a decline in eNOS-derived NO results in systemic hypertension.

In addition to a decline in eNOS activity, the inactivation of NO once generated by eNOS has also been implicated in the development of hypertension. For example, recent studies suggest that angiotensin II not only causes vasoconstriction but also increases production of superoxide anion, a highly reactive form of oxygen, from vascular wall cells.[13] Superoxide anion rapidly reacts with NO and, therefore, might indirectly cause high blood pressure by scavenging and inactivating locally generated NO within blood vessels. Conversely, antioxidants such as vitamin C might possibly enhance endothelium-derived NO activity by neutralizing oxidants such as superoxide anion in individuals with essential hypertension.[14]

Endothelin (ET)-1 is a potent vasoconstrictor and smooth -muscle mitogen that may in part mediate the pathogenesis of systemic and pulmonary hypertension.[15-17] Circulating plasma levels of ET-1 are increased in both systemic and pulmonary hypertension, and the balance of circulating ET-1 production and clearance is shifted from normal net clearance toward net excess production.[16,18,19] This may partly be due to the increased ET-1 gene expression and synthesis, particularly at the site of the microvascular

remodeling, which principally causes elevated systemic and pulmonary vascular resistance.

In this issue of the Annals of Saudi Medicine (see page 364), the study from United Arab Emirates by Obineche and colleagues provides some important insights on the significant value and role of ET-1 in development and severity of essential hypertension in a genetically homogenous Gulf Arab Bedouin population. They compared the circulating levels of ET-1 in a homogenous well-characterized group of 60 indigenous untreated Emirati Gulf Arabs with essential hypertensive with ET-1 levels in 60 age- and sex-matched normotensive volunteer controls. Both groups were considered to be a cross-section representative of the Emirati Gulf Arab population and comprised 35 men and 25 women. The over four times greater plasma ET-1 levels in hypertensive males and females than in the normotensive group was statistically significant. Raised ET-1 levels were significantly more correlated with systolic blood pressure. Despite the small number of subjects in the study group, Obineche and colleagues must be congratulated for this investigation, which provides us with important information to use in future large-scale prospective multi-centers trials in our region using ET-1 and other endothelial surrogate markers to detect hypertension and other cardiovascular diseases in the early stage or even in the pre-clinical phase in high-risk populations. Finally, the aim of therapeutic interventions against these disease entities should be to improve endothelial function. Therapeutic approaches can include use of ET-1 blockers, aII receptor blockers, angiotensin-converting enzyme inhibitors as well as other means of improving endothelial function such as the use of lipid-lowering drugs, increasing shear stress by physical exercise, appropriate body weight reduction, and the use of antioxidants and L-arginine.

References

1. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. N Engl J Med 1990; 32 (1): 27-36.
2. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990; 8(2): 491-497.
3. Vita JA, Keaney JF, Jr. Exercise-toning up the endothelium? N Engl J Med 2000; 342(7): 503-505.
4. Vita JA, Keaney JF, Jr. Endothelial function: a barometer for cardiovascular risk? Circulation 2002; 106(6): 640-642.
5. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000; 101(9): 948-954.
6. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000; 101(16): 1899-1906.
7. Panza JA, Quyyumi AA, Brush JE, et al. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990; 323: 22-27.
8. Moroi M, Gold HK, Yasuda T, et al. Mice mutant in endothelial nitric oxide synthase. Vessel growth and response to injury (abstract). Circulation 1996; 94: 1154.
9. Steudel W, Ichinose F, Huang PL, et al. Pulmonary vasoconstriction and hypertension in mice with targeted disruption of the endothelial nitric oxide synthase (NOS 3) gene. Circ Res 1997; 81: 34-41.
10. Dananberg J, Sider RS, Grekin RJ. Sustained hypertension induced by orally administered nitro-L-arginine. Hypertension 1993; 21:359-363.
11. Chen PY, St John PL, Kirk KA, et al. Hypertensive nephrosclerosis in the Dahl/Rapp rat. Initial sites of injury and effect of dietary L-arginine supplementation. Lab Invest 1993; 68: 174-184.
12. Lin KF, Chao L, Chao J. Prolonged reduction of high blood pressure with human nitric oxide synthase gene delivery. Hypertension 1997; 30: 307-313.
13. Munzel T, Sayegh H, Freeman BA, et al. Evidence for enhanced vascular superoxide anion production in nitrate tolerance. A novel mechanism underlying tolerance and cross-tolerance. J Clin Invest 1995; 95: 187-194.
14. Taddei S, Virdis A, Ghiadoni I, et al. Vitamin C improves endothelial dependent vasodilatation by restoring nitric oxide activity in essential hypertension. Circulation 1998; 97: 2222-29.
15. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988; 332: 411-415.
16. Stewart DJ, Levy RD, Cernacek P, et al. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991; 114: 464-469.
17. Wort SJ, Woods M, Warner TD, et al. Endogenously released endothelin-1 from human pulmonary artery smooth muscle promotes cellular proliferation. Am J Respir Cell Mol Biol 2001; 25: 104-110.
18. De Nucci G, Thomas R, D'Orleans-Juste P, et al. Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci U S A 1988; 85: 9797-9800.
19. Dupuis J, Cernacek P, Tardif JC, et al. Reduced pulmonary clearance of endothelin-1 in pulmonary hypertension. Ann Heart J 1998; 135: 614-620.