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Endothelial control of vasomotion and nitric oxide production

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In the past two decades, it has become clear that the endothelium has many roles in the modulation of vascular homeostasis. These roles include modulation of vasomotor tone, modulation of thrombosis, and regulation of inflammation. In addition, factors released by the endothelium that regulate vasomotion also influence the progression of atherosclerosis, the development of vascular hypertrophy, and the presence of vessel inflammation. Thus, vasomotor phenomena serve as markers of vascular health and disease. This article discusses factors that modulate endothelial control, how these are altered by disease, and the concept of endothelium-dependent vasomotion as a marker of vascular disease.

Normal role of the endothelium as a modulator of vascular tone

The endothelium releases various substances that modulate vascular tone (Fig. 1). These substances include nitric oxide ($NO^{\bullet}$), prostaglandins, hyperpolarizing factors, endothelin, and reactive oxygen species (ROS). Although these substances work in concert to regulate the contractile state of all size vessels, $NO^{\bullet}$ plays a predominant role in larger vessels, whereas the hyperpolarizing factor contributes to a greater extent in resistance vessels [1,2]. Many receptors for paracrine and endocrine agonists exist on the surface of endothelial cells and, when activated by their respective ligands, stimulate release of endothelial-derived vasodilators. In addition, many of these same receptors are present on the vascular smooth muscle cells in the vessel wall, and activation of these receptors leads to vasoconstriction. Thus, the ultimate effect of an agonist on vasomotor tone reflects the net effect of a vasodilator endothelial action and a vasoconstrictor vascular smooth muscle action. In the setting of a healthy endothelium, endothelium-dependent vasodilatation most often predominates; however, when the endothelium is absent or diseased, vasoconstriction predominates. In some cases, the endothelium may also release substances such as vasoconstrictor prostaglandins and endothelin, which also increase vascular tone. The ultimate consequence of these interactions is that the endothelium either directly or indirectly modulates the effect of almost all neurohormonal and paracrine substances. Adding to this complexity, the vessel is being bathed by a multitude of such agents at any one time, each of which may have different effects on the vascular smooth muscle and the endothelium.

In addition to neurohormonal stimuli, mechanical forces such as laminar shear stress and stretch potently mediate release of vasoactive agents from the endothelium. Laminar shear stress is an extremely potent stimulus for $NO^{\bullet}$ production [3]. Stretch, which is increased in the setting of hypertension, is a potent stimulus for production of ROS by the endothelium and vascular smooth muscle [4,5]. These considerations are important, because flow profiles seem

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