VI

Chapter 101

Endotheliopathy

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PEARLS

- Because of their location, endothelial cells have the ability to interact with blood components, such as flow, soluble factors, and other cells. Endothelial cells integrate these signals into a cohesive regulation of vascular responses.
- The endothelium controls the vascular tone of the underlying smooth muscle cells through the production of vasodilator and vasoconstrictor mediators.
- Endothelial cell activation in response to inflammation changes endothelial cellular physiology and results in altered vascular function.

Until recently, scientists and clinicians considered the endothelium, the cell layer that lines the blood vessels, as an inert barrier separating the various components of blood and the surrounding tissues. The vascular endothelium is now recognized as a highly specialized and metabolically active organ performing a number of critical physiologic, immunologic, and synthetic functions. These functions include regulation of vascular permeability, fluid and solute exchange between the blood and interstitial space, vascular tone, cell adhesion, homostasis, and vasculogenesis.[1]

The normal vascular endothelium is only one cell layer thick, separating the blood and vascular smooth muscle. The endothelium responds to physical and biochemical stimuli by releasing regulatory substances affecting vascular tone and growth, thrombosis and thrombolysis, and platelet and leukocyte interactions with the endothelium. Normal endothelial functions include control over thrombosis and thrombolysis, platelet and leukocyte interactions with the vessel wall and regulation of vascular tone and growth. Of particular interest to intensivists is the fact that the endothelium secretes both powerful vasorelaxing (e.g., nitric oxide [NO]) and vasoconstricting substances (e.g., endothelin-1 [ET-1]). Since normal endothelial function plays a central role in vascular homeostasis, it is logical to conclude that endothelial dysfunction contributes to disease states characterized by vasomotor dysfunction, abnormal thrombosis, or abnormal vascular proliferation.

The endothelium lies between the lumen and the vascular smooth muscle, where it is uniquely positioned to "sense" changes in hemodynamic forces or blood-borne signals by membrane receptor mechanisms. The endothelial cells can respond to physical and chemical stimuli by synthesis or release of a variety of vasoactive and thromboregulatory molecules and growth factors. Substances released by the endothelium include prostacyclin, NO, endothelins, endothelial cell growth factors, interleukins, plasminogen inhibitors, and von Willebrand factor (vWF). The vascular endothelium possesses numerous enzymes, receptors, and transduction molecules, and it interacts with other vessel wall constituents and circulating blood cells. In addition to these universal functions, the endothelium may have organ-specific roles that are differentiated for various parts of the body, such as gas exchange in the lungs, control of myocardial function in the heart, or phagocytosis in the liver and spleen. From a structural perspective, endothelial cells from different sites of the vascular tree differ in size, shape, thickness, and nuclear orientation. For example, endothelial cells that line the pulmonary artery of the rat are larger and more rectangular than those lining the aorta, whereas endothelial cells in the aorta are thicker than their counterparts in capillaries or veins.[2]

Studies of endothelial structure and function have been accomplished by a variety of techniques, including ultrastructural studies, in vitro experiments for endothelial cell isolation and culture, physiologic studies in animals, and, most recently, clinical studies in humans. This knowledge has facilitated the development of treatment strategies based on administration of endothelial products, such as prostacyclin and NO, or their antagonists.

Normal Endothelial Function

Endothelial Cell Heterogeneity

Many vascular diseases appear to be restricted to specific vascular beds. For example, thrombotic events are often localized to single vessels. It is also common for certain vasculitides to specifically affect certain arteries, veins, or capillaries, or to affect certain organs. Tumor cells will often metastasize more commonly within particular vascular beds. The basis for this variability in vascular disease is poorly understood, but may be explained in the heterogeneity of endothelial cells. Recently, there has been a greater understanding of how endothelial cell heterogeneity may contribute both to the maintenance of organ-specific function and to the development of disorders restricted to specific vascular beds.[1-3]