**TABLE 265e-1 ENDOTHELIAL FUNCTIONS IN HEALTH AND DISEASE**

| Homeostatic Properties | Dysfunctional Properties |
|---|---|
| Optimize balance between vasodilation and vasoconstriction | Impaired dilation, vasoconstriction |
| Antithrombotic, profibrinolytic | Prothrombotic, antifibrinolytic |
| Anti-inflammatory | Proinflammatory |
| Antiproliferative | Proproliferative |
| Antioxidant | Prooxidant |
| Permselectivity | Impaired barrier function |

impairs this endothelium-dependent vasodilator function and may contribute to excessive vasoconstriction in various pathologic situations. Measurement of flow-mediated dilatation can assess endothelial vasodilator function in humans (Fig. 265e-2). By contrast, endothelial cells also produce potent vasoconstrictor substances such as endothelin in a regulated fashion. Excessive production of reactive oxygen species, such as superoxide anion ($O_2^-$), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II), can promote local oxidative stress and inactivate NO.

The endothelial monolayer contributes critically to inflammatory processes involved in normal host defenses and pathologic states. The normal endothelium resists prolonged contact with blood leukocytes; however, when activated by bacterial products such as endotoxin or by proinflammatory cytokines released during infection or injury, endothelial cells express an array of leukocyte adhesion molecules that bind various classes of leukocytes. The endothelial cells appear to recruit selectively different classes of leukocytes in different pathologic conditions. The gamut of adhesion molecules and chemokines generated during acute bacterial infection tends to recruit granulocytes. In chronic inflammatory diseases such as tuberculosis and atherosclerosis, endothelial cells express adhesion molecules that favor the recruitment of mononuclear leukocytes that characteristically accumulate in these conditions.

The endothelium also dynamically regulates thrombosis and hemostasis. NO, in addition to its vasodilatory properties, can limit platelet activation and aggregation. Like NO, prostacyclin produced by endothelial cells under normal conditions not only provides a vasodilatory stimulus but also antagonizes platelet activation and aggregation. Thrombomodulin expressed on the surface of endothelial cells binds thrombin at low concentrations and inhibits coagulation through activation of the protein C pathway, inactivating clotting factors Va and VIIIa and thus combating thrombus formation. The surface of endothelial cells contains heparan sulfate glycosaminoglycans that furnish an endogenous antithrombotic coating to the vasculature. Endothelial cells also participate actively in fibrinolysis and its regulation. They express receptors for plasminogen and plasminogen activators and produce tissue-type plasminogen activator. Through local generation of plasmin, the normal endothelial monolayer can promote the lysis of nascent thrombi.

When activated by inflammatory cytokines, bacterial endotoxin, or angiotensin II, for example, endothelial cells can produce substantial quantities of the major inhibitor of fibrinolysis, plasminogen activator inhibitor 1 (PAI-1). Thus, in pathologic circumstances, the endothelial cell may promote local thrombus accumulation rather than combat it. Inflammatory stimuli also induce the expression of the potent procoagulant tissue factor, a contributor to disseminated intravascular coagulation in sepsis.

Endothelial cells also participate in the pathophysiology of a number of immune-mediated diseases. Lysis of endothelial cells mediated by complement provides an example of immunologically mediated tissue injury. The presentation of foreign histocompatibility complex antigens by endothelial cells in solid-organ allografts can promote allograft arteriopathy. In addition, immune-mediated endothelial injury may contribute in some patients with thrombotic thrombocytopenic purpura and patients with hemolytic-uremic syndrome. Thus, in addition to the involvement of innate immune responses, endothelial cells participate actively in both humoral and cellular limbs of the immune response.

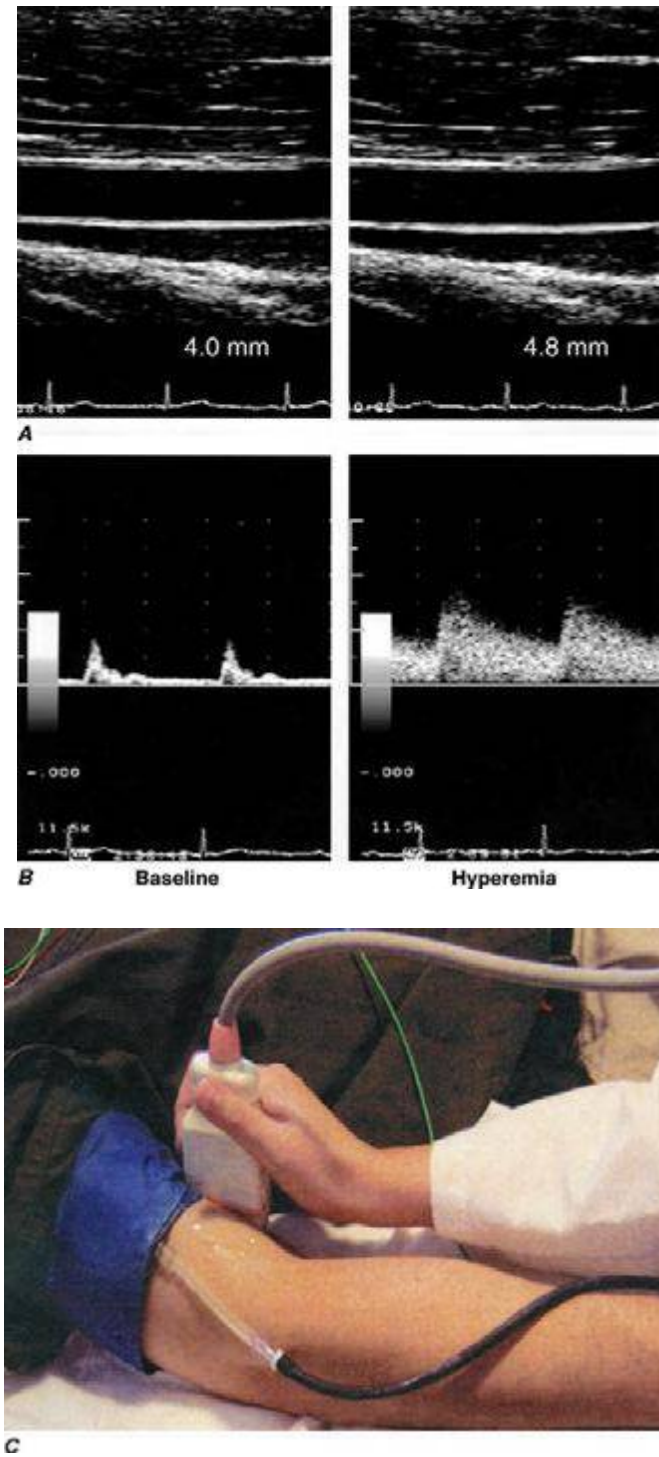


**FIGURE 265e-2 Assessment of endothelial function in vivo using blood pressure cuff occlusion and release.** Upon deflation of the cuff, an ultrasound probe monitors changes in diameter (***A***) and blood flow (***B***) of the brachial artery (***C***). *(Reproduced with permission of J. Vita, MD.)*

Endothelial cells regulate growth of subjacent smooth-muscle cells. Heparan sulfate glycosaminoglycans elaborated by endothelial cells can inhibit smooth-muscle proliferation. In contrast, when exposed to various injurious stimuli, endothelial cells can elaborate growth factors and chemoattractants, such as platelet-derived growth factor, that can promote the migration and proliferation of vascular smooth-muscle cells. Dysregulated elaboration of these growth-stimulatory molecules may promote smooth-muscle accumulation in atherosclerotic lesions.