Endothelial Control of Vascular and Myocardial Function in Heart Failure

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Summary. The effect of vascular endothelium, endocardium, and coronary endothelium on vascular tone and myocardial contraction-relaxation sequence in heart failure is discussed. Vascular endothelium affects underlying vascular smooth muscle through paracrine secretion of relaxing and constricting factors. In heart failure, systemic vasoconstriction results not only from neuroendocrine activation, but also from disturbed local endothelial control of vascular tone because of impaired endothelial-dependent vasodilation and because of increased plasma concentration of endothelin. Experimental evidence obtained in isolated cardiac muscle strips established the influence of endocardial endothelium on the duration of myocardial contraction and on the onset of myocardial relaxation. By analogy to vascular endothelium, both diffusible agents that abbreviate (endothelial-derived relaxation factor-like substance) and those that prolong (endoocardin) myocardial contraction have been shown to be released from the endocardium. Similar agents are released from the coronary endothelium and, because of the close proximity of capillaries and myocytes, could exert a major effect on myocardial performance. Endothelial dysfunction and concomitant lack of release of myocardial relaxant factors could explain left ventricular relaxation abnormalities observed in the cardiac allograft or in arterial hypertension. Since endothelial-derived relaxation factor or nitric oxide mediates the coronary reactive hyperemic response, a negative inotropic action of nitric oxide could contribute to left ventricular failure when left ventricular wall stress is elevated, as occurs after myocardial infarction in the noninfarcted zone and during left ventricular volume or pressure overload in the absence of adequate hypertrophy.

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The importance of the endothelial lining of blood vessels as a control mechanism of cardiovascular function was first appreciated by Furchgott and Zawadski [1], who demonstrated that the presence of vascular endothelium was required to elicit acetylcholine-induced relaxation of isolated arteries. Since this initial report, the role of the endothelium has been further expanded beyond paracrine secretion of relaxation and constricting factors. Apart from release of these vasoactive agents, the endothelium plays a central role in prevention of coagulation by formation of the antiaggregant prostacyclin, in the immune barrier by secre-
cent medial layers, to a mechanoreceptor function that senses flow or pressure and modulates vascular tone accordingly [6], and to a barrier function, which prevents vasodilatory stimuli from exerting direct vasoconstrictor effects on vascular smooth muscle [7].

The paracrine action of vascular endothelium appears to be based on the secretion of vasodilator (endothelium-derived relaxation factors) and vasoconstrictor (endothelium-derived constriction factors) substances (Figure 1). The precise nature and metabolic pathways of production and breakdown of endothelium-derived relaxation factor have been an area of intense investigation. Endothelium-derived relaxing factor is a labile, potent relaxing factor with a short biological half-life, which limits its action to adjacent vascular smooth muscle [8]. Addition of free radical scavengers, such as superoxide dismutase, extends its biological half-life [9,10] and suggests inactivation by the superoxide radical. Based on this evidence, endothelium-derived relaxation factor was thought to be nitric oxide or a closely related nitric-oxide-releasing substance [11]. Nitric oxide is produced in the endothelial cell from L-arginine by a calcium-, calmodulin-, and NADPH-dependent constitutive synthase enzyme. Apart from the constitutive nitric-oxide synthase enzyme, recent evidence has demonstrated the existence of an inducible nitric oxide synthase enzyme in myocardial cells. This inducible nitric oxide synthase enzyme is expressed in the presence of endotoxin or cytokines, and plays a role in the depressed cardiac function observed in endotoxic shock or in acute myocarditis or allograft rejection. Its expression is inhibited by dexamethasone, which does not affect the endothelial constitutive nitric-oxide synthase enzyme. Following production and release, endothelial-derived relaxation factor diffuses to the vascular smooth muscle and raises its cyclic GMP content by activating guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine 3',5' monophosphate. Cyclic GMP, in turn, activates protein kinase enzyme, which dephosphorylates light myosin chain, thereby inducing smooth muscle relaxation. Production and release of endothelium-derived relaxing factor is triggered by binding to endothelial receptors of a variety of substances, such as acetylcholine, 5-hydroxytryptamine, bradykinin, substance P, thrombin, and vasopressin. Apart from endothelium-derived relaxing factor or nitric oxide, vascular endothelium secretes other substances with relaxant effects on vascular smooth muscle, such as endothelium-derived hyperpolarizing factor [12], which affects Na, K-ATPase or prostacyclin (PGI2), which inhibits platelet aggregation and acts through cyclic AMP.

**Fig. 1.** Endothelial control of vascular smooth muscle cell tone through paracrine secretion of vasodilator (EDRF, PGI2) and of vasoconstrictor (endothelin) substances. Release of endothelium-derived relaxation factor is triggered by binding to endothelial receptors of a variety of substances, such as acetylcholine to the muscarinic (M) receptor, 5-hydroxytryptamine to the 5-HT (S) receptor, thrombin to the thrombin (T) receptor, and vasopressin to the vasopressin (V) receptor.