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## Microvascular Plasticity and Experimental Heart Failure

Bernard I. Lévy

**A**ngiogenesis is an essential process in adulthood during wound healing and restoration of blood flow to injured tissues. Angiogenesis is regulated by a very sensitive interplay of growth factors and inhibitors; their imbalance can lead to very diverse diseases. Excessive angiogenesis is involved in malignant, diabetic retinopathy and inflammatory disorders (eg, rheumatoid arthritis, psoriasis, atherosclerosis). Conversely, insufficient angiogenesis may underlie conditions such as ischemic heart diseases, stroke, hypertension, and diabetes. Hence, during the evolution of these degenerative pathologies, inadequate blood vessel growth and insufficient microvascular density leads to poor circulation and tissue suffering or, ultimately, necrosis and death.<sup>1</sup>

In several physiological conditions, such as muscular exercise training and detraining, acclimatization to altitude, and aging, an adaptation of the microvascular network structure and function to new conditions has been reported.<sup>2,3</sup> Interestingly, there is a close link between cerebral angiogenesis and learning; during cognitive decline in relation to senescence or degenerative cerebral diseases, microvascular density is decreased in specific cerebral areas. Specifically, there is a striking relationship between the capillary density, the cerebral tissue blood flow, the local glucose use, and other measures of neuronal signaling, such as the  $\text{Na}^+/\text{K}^+$  ATPase (reviewed in Reference 4). Therefore, microvascular plasticity, defined as the ability of the arteriole and capillary network to adapt to the metabolic local conditions by proangiogenesis or antiangiogenesis processes, likely plays a key role in many tissue homeostatic processes.

### Microvasculature and Arterial Hypertension

In hypertension, the role of microcirculation (arteriolar and capillary) is of particular importance in increasing peripheral resistance by decreasing the number of vessels per unit of tissue volume; a phenomenon known as "microvascular rarefaction." Ruedemann,<sup>5</sup> in 1933, was the first to describe microvascular rarefaction in the conjunctiva of hypertensive patients. Rarefaction has also been observed by other investigators in humans and in different tissues in the majority of experimental models of hypertension,

particularly in the spontaneously hypertensive rat and the rat with Goldblatt hypertension. Experimental evidence suggests that microcirculatory rarefaction, which manifests as an increased intercapillary distance, is responsible for nonuniform tissue perfusion leading to hypoperfused and hypo-oxygenated areas in which oxygen partial pressure drops to extremely low values that can restrict metabolic activity.<sup>6</sup> Capillary rarefaction in hypertensive patients has even been suggested to be one of the reasons for the defective response to an insulin injection in increasing glucose uptake and vasodilation.<sup>7</sup>

Several mechanisms have been proposed to explain microvascular rarefaction. Prewitt et al<sup>8</sup> were the first to make a distinction between functional rarefaction and structural rarefaction. The former would be because of excessive (but reversible) vasoconstriction, causing occlusion of resistance arterioles and nonperfusion of distal capillaries. Structural rarefaction would be because of the anatomic absence of certain arterioles and capillaries. It is highly likely that the first precedes the second: abnormally high vasomotor tone would initially lead to nonperfusion of some vessels, which would then involute and disappear. Indeed, it is well known that endothelial shear stress leads to sustained endothelial nitric oxide release. The absence of flow and, therefore, of nitric oxide would lead to apoptosis and loss of nonperfused vessels. This theory ties in directly with the theory of protecting the capillary bed from hypertension by abnormal vasoconstriction. According to this hypothesis, microcirculatory rarefaction would be a result of hypertension.

### Capillary Density and Oxygen Supply During Ventricular Hypertrophy and Cardiac Failure

Although increased external load initially induces cardiac hypertrophy with preserved contractility, sustained overload eventually leads to heart failure through poorly understood mechanisms. Cardiac remodeling includes changes of both the myocytes and the extracellular matrix. Capillary density and spatial arrangement are important determinants in maintaining the balance between myocardial oxygen demand and supply. These indices may be seriously altered in patients with cardiac hypertrophy and heart failure.

The diffusion of oxygen from capillaries to cardiomyocytes depends, among other determinants, on the arterial oxygen pressure, the flow through the capillaries, and on the distance between any 2 adjoining capillaries. The capillary density and the intercapillary distance are both altered in cardiac hypertrophy related to ischemic disease or dilated cardiomyopathy. In a recent work, by using quantitative histological measurements, Karcha et al<sup>9</sup> evidenced that the mean diffusion distance increased from left

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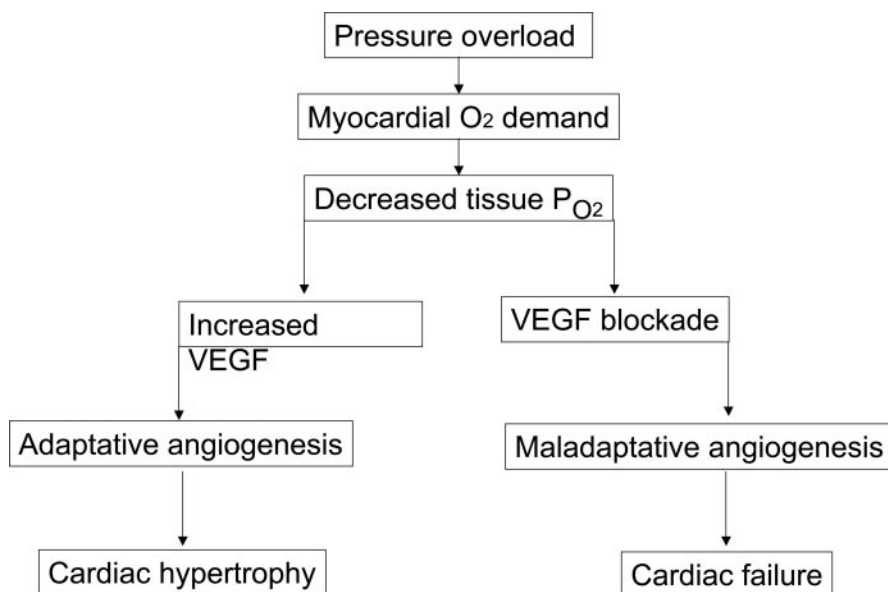
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Proposed mechanisms whereby VEGF may be an obligatory link among myocardial demand, microvascular coronary network, and cardiac hypertrophy or failure.

ventricular myocardium from control to dilated cardiomyopathy and ischemic and inflammatory cardiomyopathies. Therefore, insufficient supply of oxygen to myocardial tissue may lead to chronic hypoxia and myocytes dysfunction.

In the present issue of *Hypertension*, Izumiya et al<sup>10</sup> report a fascinating experimental study: they showed that administration of a vascular endothelial growth factor (VEGF) trap reagent, able to block signaling of all VEGF isoforms, to mice subjected to pressure overload by surgical aortic constriction resulted in diminished cardiac hypertrophy and promoted the progression to heart failure. The same group had described previously in conditional transgenic mice by the sequential development of adaptive cardiac hypertrophy with preserved contractility in the acute phase and dilated cardiomyopathy in the chronic phase after the induction of an activated Akt1 gene in the heart.<sup>11</sup> In this setting, coronary angiogenesis was enhanced during the acute phase of adaptive cardiac growth but reduced as hearts underwent pathological remodeling.

In the present study, the authors provided evidence that inactivation of endogenous VEGF impaired adaptive cardiac hypertrophy in response to pressure overload and contributed to the rapid progression from compensatory cardiac hypertrophy to heart failure. This underlines the importance of microvascular plasticity to allow adaptation of the vascular network and, thus, the oxygen supply, to increased metabolic demand related to the pressure overload. Adapted microvascular plasticity allows compensatory cardiac hypertrophy. In the absence of such vascular plasticity because of VEGF blockade, myocardium hypertrophy is unable to develop, thereby contributing to the switch toward cardiac failure, that is, to cardiomyocytes in vivo ultimately becoming maladaptive (Figure).

This important work raises at least 3 series of pathophysiological and clinical questions. First, is it possible and beneficial to stimulate expression of angiogenic growth factors in hypertensive cardiopathy to delay the

occurrence of heart failure? If yes, how can this be achieved? Are conventional pharmacological treatments able to increase VEGF expression in the myocardium? Second, is it possible, by restoring the production of VEGF, to stabilize heart failure and even to reverse it? Third, antiangiogenic agents, such as bevacizumab, have been rationally designed to target VEGF in patients with metastatic colorectal cancer to block tumor angiogenesis. The side effect profile of bevacizumab has been evaluated and makes it a suitable adjunct to standard chemotherapy; it is now approved for use in the United States, the European Union, and other markets worldwide. However, the most commonly observed adverse events is hypertension, which is generally mild to moderate and manageable.<sup>12</sup> Is hypertension related to capillary rarefaction in patients receiving anti-VEGF treatments? Could antiangiogenic therapy favor a mismatch between adaptive cardiac hypertrophy and coronary capillary density? Would it accelerate the switch from cardiac hypertrophy to heart failure in treated patients? Would these phenomena be reversible after cessation of the antiangiogenic treatment?

The present study by Izumiya et al<sup>10</sup> strongly suggests that defects and impairments in the main proangiogenic factors are likely involved in the occurrence of heart failure in a model of pressure overload-induced cardiac hypertrophy. If these findings are confirmed in a clinical setting, VEGF and its receptors could be a new molecular target for treating severe heart failure.

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