The article by Abaci et al in this issue of Circulation draws our attention to a very important and novel observation that patients with diabetes mellitus (DM) have a lesser ability to develop collateral blood vessels in the presence of coronary artery disease. This is somewhat surprising, because DM is known to stimulate angiogenesis, at least in the retina of the eye, and is, because of capillary leakiness, a major cause of blindness. This article by Abaci et al is a good example for drawing attention to the recently appreciated fact that not all vascular growth should be called angiogenesis. The functionally more important collateral vessels of the heart are not the product of angiogenesis but rather of “arteriogenesis.”

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Angiogenesis and Arteriogenesis: Two Distinct Types of Vessel Growth

Angiogenesis is the sprouting of capillaries. It results in a capillary network. However, it is important to recognize that these capillary tubes lack vascular smooth muscle cells. Any new developing network of endothelial tubes that is not surrounded by mural cells is fragile and prone to rupture, remains susceptible to hypoxic regulation, fails to become remodeled, and is unable to sustain proper circulation; it cannot adapt to changes in physiological demands of blood supply. Angiographically, angiogenesis results in a higher capillary density, which is often estimated with increased contrast media density.

Arteriogenesis is defined as structural enlargement by growth of preexisting arteriolar connections into true collateral arteries. These vessels, bypassing the site of occlusion, have the ability to markedly increase their lumen by growth to provide enhanced perfusion to the jeopardized ischemic regions after acute and chronic arterial occlusions. It is important to recognize that the proliferation of collateral arteries is not a process of passive dilatation but of active proliferation and remodeling. Under normal flow conditions and depending on the pressure gradient between the interconnecting arterial networks, there is only minimal net forward flow, but small amounts of flow may oscillate within the network. In a sudden arterial occlusion or a slowly progressing stenosis, a steep pressure gradient along the shortest path within the interconnecting network develops that increases blood flow velocity and hence fluid shear stress in these vessels that now assume the new function as “collaterals.”

The effect of this sustained increase in shear is the upregulation of distinct processes in the collateral arteries: upregulation of adhesion molecules (eg, vascular cell and intercellular adhesion molecules), increased endothelial production of several cytokines (monocyte chemoattractant protein-1, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-α), attraction of circulating monocytes along the chemotactic gradient to the activated endothelium, production of nitric oxide, adhesion and invasion of monocytes, and maturation to macrophages. These in turn create an inflammatory environment and produce fairly large amounts of growth factors, particularly fibroblast growth factor-2 (FGF-2).

The invasion of monocytes is soon followed by the first wave of mitosis of the endothelial and smooth muscle cells (proliferating phase). Besides mitosis, the perivascular inflammation creates the space for the greatly expanding collateral vessel that can increase its diameter up to 20 times. The old structure is, in large part, dismantled and replaced primarily by new intimal and medial smooth muscle cells (remodeling phase). Finally, arteriogenesis results in a functional “new” artery originating from a preexisting arteriole.

What Is the Physiological Basis of an Efficient Perfusion of Internal Organs or Hind-limbs?

After sudden or slowly progressing stenosis of a major artery, the survival of ischemic limbs or internal organs like heart and brain can be guaranteed only if relatively large blood volumes per unit of time are made available to perfuse the ischemic territories. Taking the law of Ohm into account, blood pressure, resistance, and blood flow are closely linked to each other. The bigger the diameter of a vessel, the lower the resistance and hence the higher the blood flow. Preexisting collateral anastomoses, for instance, have the ability to conduct, after adaptive growth, relatively large blood volumes per unit of time. In many cases, collateral arteries can minimize or even prevent the fatal consequences of sudden arterial obstruction. This protective role of collateral arteries depends largely on their ability to increase their vessel diameter in a very short period of time by active proliferation. In the rabbit hindlimb, for example, collateral arteries increase their lumen 20-fold after experimentally induced femoral artery ligation. This restoration of blood flow cannot be achieved by an increased number of capillaries, the result of stimulated angiogenesis. Depending on the diameter of a single collateral artery (rabbit hindlimb after 7 days of femoral occlusion; collateral artery, 200 to 300 μm), many hundred thousands of these capillaries (diameter, 4 to 6 μm) would be needed to replace 1
collateral artery (despite significant energy losses inherent to blood flow in small vessels).

What Are the Promoters of Angiogenesis or Arteriogenesis?

There is increasing evidence that angiogenesis relies on hypoxia, whereas arteriogenesis does not. Hypoxia is known to transcriptionally upregulate the expression of vascular endothelial growth factor (VEGF), but posttranscriptional mRNA stabilization may be even more important. VEGF is able to circumvent the hypoxia-induced translation inhibition, and in a rabbit model of hindlimb ischemia, VEGF expression and capillary growth are indeed restricted to ischemic regions. However, collateral artery growth (arteriogenesis) occurs in nonhypoxic tissue.7 Resting blood flow in the thigh muscles where collaterals develop after femoral artery occlusion is not decreased, its ATP and phosphocreatine content is normal, and hypoxia-induced gene transcription (LDH-A, VEGF) is not activated. The distance between ischemic regions and the predilection sites for collateral growth can be absurdly large: up to 70 cm between a patient’s gangrenous big toe and collaterals spanning a femoral or popliteal occlusion. Despite that, collateral artery growth is controlled not only by the availability of mitogenic peptides but also by the presence of its receptors: endothelial cells in vivo and under normal physiological conditions apparently do not present their receptors. Only certain experimental or pathological situations (explantation, in vivo culture, embryonic development, and cytokine application) induce the expression and presentation of receptors, the mechanism of which is largely unknown. Only the simultaneous presence of the growth factor and its receptor can orchestrate the initiation of arterial vessel growth.

However, if hypoxia is not primarily responsible for arteriogenesis, which factor induces the rapid proliferation of preexisting collateral anastomoses? The earliest concept that explained the growth of collateral arteries compensating for the consequences of an atherosclerotic occlusion was that of Thoma,18 who stated in 1893 that the velocity of blood flow is the key factor that compensates for atherosclerotic occlusion. Despite that, collateral artery growth (arteriogenesis) occurs in nonhypoxic tissue.7 Resting blood flow in the thigh muscles where collaterals develop after femoral artery occlusion is not decreased, its ATP and phosphocreatine content is normal, and hypoxia-induced gene transcription (LDH-A, VEGF) is not activated. The distance between ischemic regions and the predilection sites for collateral growth can be absurdly large: up to 70 cm between a patient’s gangrenous big toe and collaterals spanning a femoral or popliteal occlusion. Despite that, collateral artery growth is controlled not only by the availability of mitogenic peptides but also by the presence of its receptors: endothelial cells in vivo and under normal physiological conditions apparently do not present their receptors. Only certain experimental or pathological situations (explantation, in vivo culture, embryonic development, and cytokine application) induce the expression and presentation of receptors, the mechanism of which is largely unknown. Only the simultaneous presence of the growth factor and its receptor can orchestrate the initiation of arterial vessel growth.

What Do We Learn From the Study by Abaci et al?

Abaci et al have elucidated in a larger cohort of coronary artery disease patients the effect of diabetes on coronary collateral vessel development. The 306 patients were analyzed according to the Rentrop classification for collateral artery formation. It was seen that in subjects with DM, the coronary collateral vessel development is severely impaired compared with non-diabetic patients. Despite the descriptive, retrospective, and non-randomized character of this study, a very important finding has to be pointed out. It is known that DM and hence increased levels of blood glucose lead to many alterations in nearly every type of tissue. However, the most deleterious effects occur in arterial tissue, increasing the incidence of diabetic retinopathy and peripheral and coronary artery disease. These pathological changes in the arterial tree can be easily identified angiographically: Coronary arteries look like a burned tree, and more importantly, capillary sprouting is increased in the heart and more prominently in the retina of diabetic patients (antiangiogenesis as a therapeutic strategy). Taken together, these 2 concomitant phenomena give further evidence that angiogenesis and arteriogenesis are 2 very distinct mechanisms of vessel growth.

The clinical study by Abaci et al should stimulate basic scientists to unravel the basic mechanisms that increase angiogenesis but decrease arteriogenesis in DM. The authors should be lauded for drawing our attention to an experiment of nature.

The search for truth is in one way hard and in another easy, for no one can master it fully nor miss it fully, but each adds a little to our knowledge of nature, and from all things assembled there arises a certain grandeur.—Aristotle

References

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