Collateral Artery Growth
Making the Most of What You Have

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The primary role of the vascular system is to carry blood and oxygen to tissue. This task is complicated by the vastly differing needs of tissues for oxygen according to their metabolism. Moreover, the metabolic activity in a given organ, and thereby its need of blood flow and oxygen, may dramatically change in time scales varying from seconds (during the onset of muscular exercise for example) to months or years (growth of organs, ischemic processes). Therefore, to ensure good organ function, the vasculature must adapt to these heterogeneous needs. Because blood vessels are highly distributed in space, one marvels at how a vascular bed manages to adapt structurally to the local environment, and how individual segments within the vascular network succeed in supplying the right amount of blood and oxygen to tissues in the most economical way. The mechanisms leading to the development of large collateral vessels capable of conducting blood efficiently differ from those usually involved in angiogenesis. Consequently, the term “arteriogenesis” was established to encompass both angiogenesis and collateral growth, recognizing the pivotal differences between these processes.

The association of blood flow with arterial remodeling has been researched using different experimental techniques and conditions. In this regard, one of the most comprehensive models to investigate small artery response was developed by Jo de Mey. Persistent changes in blood flow were induced in juvenile rats by ligating every other first-order side branch of the superior mesenteric artery distally, near the bifurcation of second-order branches. Thus, open arteries were exposed to high flow (roughly twice that normally observed), while occluded mesenteric arteries had practically no blood flow. This chronic low flow resulted in decreased passive lumen diameter, hyper trophy of the artery wall, and both loss and atrophy of smooth muscle cells. On the contrary, high flow led to increased lumen diameter and artery wall hypertrophy. Completion of the vascular remodeling process required 16 days in both low-flow and high-flow arteries, and both conditions were associated with apoptotic cell death. A major role for the RhoA/Rho kinase system in flow-related small artery remodeling was also established using his experimental model. Moreover, the same surgical model was adapted to mice to study the extracellular matrix and cell-structural proteins involved in the mechanotransduction of shear stress. It was shown that resistance arteries of mice lacking the gene encoding for dystrophin do not adapt properly to a chronic increase in flow, inasmuch as the increases in diameter, endothelial NO synthase expression, and flow-mediated dilation do not occur.

The molecular mechanisms by which shear stress acts on the vessel wall, stimulating the endothelium, has been extensively studied in vitro. The main receptors and signaling cascades induced by shear stress in endothelial cells are summarized in Figure 2. Many of these pathways are involved in acute and chronic responses to changes in blood flow, among which NO plays a predominant role. Stress stimulus is not only the most important physiologic activator of endothelial NO production, but it has been shown to increase endothelial NO synthase (eNOS) expression. In addition, studies from different laboratories reported between 40 and 567
125 genes to be modulated by shear stress in cultured endothelial cells. High shear stress levels result in activation of the genes encoding for tissue factor, cyclooxygenase type-1, C-natriuretic protein, basic fibroblast growth factor, and transforming growth factor-β1, among others, many of which may contribute to expansive vascular remodeling.

In the present issue of *Circulation Research*, Eitenmüller and colleagues used an original surgical model to increase the shear stress in the collateral vessels. The authors associated occlusion of 1 femoral artery with an arteriovenous fistula, performed immediately below the arterial ligature, to drain the collateral flow from the distal end of the occluded femoral artery directly into the femoral vein. Thus, the collateral vessels beside the occluded segment of the femoral artery were submitted to sustained high values of fluid shear stress. The major finding of this work is the demonstration that the whole limb hemodynamic conductance was markedly improved by a drastic and sustained increase of shear stress in the femoral collateral arteries. At least 2 molecular mechanisms were involved in the collateral development, Rho kinase and NO. The Ras-ERK pathway was identified as a downstream signaling cascade induced by NO, whereas the Akt-pathway remained unaffected by surgery.

The physiological basis for the development or remodeling of femoral collateral arteries relies on a simple principle of fluid mechanics: the blood flow rate between 2 points in a vessel is proportional to the driving pressure (ie, the pressure gradient) between these 2 points. Under control conditions (with a normally permeable femoral artery), the pressure gradient is quite similar at both ends of the femoral collateral arteries, such that flow and fluid shear stress are very low in these vessels. After femoral occlusion, a pressure gradient between the upstream and the downstream part of the femoral artery results in increased blood flow in the collateral network. However, because this blood pressure gradient is limited by the resistance vessels lying downstream of the occlusion, and is further diminished as collateral flow increases, the remodeling of the collateral vessels is restrained. This would explain why only 35% to 40% of the maximal physiological conductance is restored after arterial occlusion. The experimental model developed by Eitenmüller and colleagues associated both femoral occlusion and femoral arteriovenous fistula, bypassing that downstream resistance arteries. The pressure gradient between the upstream and downstream segments of the occluded femoral was therefore quite significant, representing 60 to 70 mm Hg, driving a pronounced increase in collateral artery blood flow. The authors used this clever surgical model to demonstrate that higher blood flow in collaterals results in more extensive

**Figure 1.** Acute and chronic vascular adaptations to changes in local metabolic demands.

**Figure 2.** Schematic representation of receptors and signaling cascades induced by shear stress in endothelial cells.
remodeling such that maximal limb conductance reaches normal values or is even surpassed. This experimental process could be compared with events occurring during muscular exercise: there are several lines of evidences suggesting that the molecular mechanism of exercise-induced upregulation of vascular eNOS expression are closely related to the changes in fluid shear stress in the vasculature. Exercise increases heart rate, which in turn increases blood flow and vascular shear stress, leading to enhanced NO production.15

Beyond their effects on vascular remodeling, low shear stress is associated with a proatherosclerotic phenotype and high shear stress with an atheroprotective phenotype.16 Atherosclerosis in turn leads to dramatic reductions in blood flow, bringing about organ dysfunction, morbidity, and death. Although some patients may have developed the ability to escape or to minimize this disorder by bridging the arterial occlusion or stenosis segment with “naturally growing by-passes”,17 most patients have to undergo surgical or intravascular catheter interventions to reestablish sufficient blood flow and oxygen supply. Thus, understanding the molecular mechanisms of collateral artery growth may help to identify new treatments of ischemic vascular diseases.

This experimental work opens the door to new questions: (1) how is it possible to maintain collateral femoral arteries opened under control conditions, ie, at normal blood flow and shear stress, in the absence of a significant pressure gradient; (2) is it possible to promote collateral growth in clinical practice? Can local intensive pharmacological vasodilator treatment mimic the increased blood flow produced by the femoral arteriovenous fistula; (3) what happens when collateral conductance returns to “normal” low values after fluid shear stress goes down to physiological values in collateral vessels ie, after closure of the arteriovenous fistula; and (4) shear stress-induced vessel remodeling is altered in pathological conditions such as diabetes, hypertension and atherosclerosis. Is it possible to induce collateral growth in patients or experimental models of cardiovascular diseases associated with endothelial dysfunction?

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References

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