Arteriolar vessels that interconnect adjacent vascular territories in the form of networks or arcades exist normally in the skeletal\(^1\) and cardiac muscle\(^2\) of most mammals including man. They usually function as a means of efficient flow distribution, acting as capacitors for blood displacement in non-synchronously contracting muscles, or are just remnants of the embryonic vascular network that has not reached its full potential. These vessels can expand by growing when pressure gradients develop, the most likely cause of which is the unilateral fall in pressure by a stenosis or occlusion of one of the arteries that feed into the network\(^2\). Although total blood flow into the network is now reduced (or unaltered due to compensating vasodilatation) the velocity of blood flow in the vessels, representing the shortest connection to the distal distribution of the occluded vessel, is markedly increased. This creates an increase in fluid shear stress\(^3\) in the shortest pathway within the network which activates the endothelium.

Activated endothelium has a typical synthetic and proliferative phenotype (increased endoplasmic reticulum, free ribosomes, loss of volume control, swelling) and is characterized by upregulation of adhesion molecules\(^2\) and of monocyte chemoattractant protein (MCP-1)\(^4\). As a result of activation, monocytes adhere to the endothelium, become activated and produce TNF-alpha and several other growth factors, cytokines and chemokines\(^5,6\). This starts vascular growth, which begins with endothelial proliferation and is soon followed by that of smooth muscle. Parallel with proliferation, or maybe preceding it, proteolytic activity starts to create the space for the expanding vessel and to remodel the given structures of the vessel itself\(^7\). This begins with digestion of the internal elastic lamina, and lysis of the extracellular matrix which enables the smooth muscle layers to slide under the influence of the intravascular pressure, thereby enlarging the vessel passively at first, giving it a vein-like appearance. This is followed by new smooth muscle which arranges itself in two directions: circular and longitudinal, the latter forming the neointima\(^6\). In a typical dog heart, where one or two of the epicardial arteries had been slowly occluded, the collagen vessels increase their diameter by a factor of 20 times their internal diameter and the tissue mass increases by 50-fold. This is only possible by mitosis of the vascular cells. The mitotic index of the endothelial and smooth muscle cell populations increase up to over 100-fold at the maximum of growth activity\(^2\).

Most of the growth factors that are needed for mitosis are already present in the tissue (the FGFs are stored in the extracellular matrix) or are produced by invading cells like monocytes; T-cells and basophiles transform into mastcells and are also producers of growth factors. Several growth factors are produced constitutively at low levels (VEGF, FGF-1 and -2) and their rate of transcription can be increased within a very short time or the stability of their respective mRNAs can be drastically increased within minutes\(^8,9,10\).

The abundance of growth factors under physiological conditions and the inefficiency of growth factor application under non-pathological conditions suggest that growth factor receptors are down-regulated normally. An acute occlusion of the femoral artery in the rabbit upregulates FGF-receptors for a limited time window of 12 h (mRNA) and makes the tissue receptive for growth factor action. This means that the regulation of arteriogenesis is achieved via the availability of the receptors and not the ligands\(^9\).

The invading monocytes become activated themselves in the process of adherence to the activated endothelium; stimulated by MCP-1, secreted by activated endothelium or infused intra-arterially for experimental arteriogenic therapy, they express tissue factor, MIP-1 alpha and MIP-1 beta, as well as IL-8. These cyto- and chemokines exert a procoagulative effect\(^11,12\).

In addition to the pro-inflammatory effects of arteriogenesis (invasion of mononuclear cells, perivascular
inflammation during the early stages\(^{[13,14]}\), the pro-coagulative effect adds to the pro-atherogenic effect and will become a very important issue in the development of an arteriogenic medicine to balance the ‘good’ against the ‘bad’ effects.

MCP-1, the most potent of the arteriogenic stimulants, is also one of the most potent atherogenic peptides because of its chemotactic effects on monocytes that invade plaques and convert into foam cells. But this contrasting spectrum of effects is not exclusive to MCP-1, it is also shared by VEGF that is overexpressed in human arterial biopsy material, leads to the formation of vasa vasorum which may rupture and bleed or vascularization of plaques that may rupture themselves under the pressure of ruptured and bleeding new vessels. In addition, VGEF induces, like MCP-1, the expression of tissue factor in monocytes and is thus prothrombotic.

Although the ‘good’ effects of arteriogenesis dominate under experimental conditions in otherwise healthy animals undergoing acute or chronic occlusions, the end result, even under ideal experimental conditions, is far from a constitutio ad integrum: only abut one third of the maximal conductance of the artery before occlusion is obtained by the arteriogenic process. It is unknown why the process stops prematurely, but probably because the shear stress that had been driving it fell under a critical value due to enlargement of the collateral vessels.

A characteristic feature of collateral vessels is their tortuosity: they grow in length as well in width\(^{[2]}\). To accommodate the unneeded extra length the vessel arranges itself in loops and turns. This may reflect the genetically determined embryonic development, where vessels always grow in length and width. Arteriogenesis in the adult organ is more probably a recapitulation of embryonic angiogenesis and arteriogenesis.

The tortuosity of collateral vessels is the cause of energy loss and is one of the causes of non-ideal adaptation: the extra length as well as the curvature and the non-physiological angle of entering the recipient distribution system cause frictional energy losses that are reflected in marked reductions of distal pressure with only moderately increasing flows. Some of these pressure losses can be prevented by additionally induced growth via external application of growth factors, but it will perhaps not be entirely avoidable. Prevention of longitudinal growth is the answer, but at present how to achieve this remains unknown.

The role of tissue ischaemia

Conventional wisdom states that vascular growth in the adult organism is usually associated with tissue hypoxia/ischaemia, with the exception of angiogenesis in the female reproductive tract, and arteriogenesis of the uterine artery during pregnancy. There is no doubt that angiogenesis, the sprouting of new capillaries from pre-existing ones\(^{[14]}\), is mainly caused by hypoxia: VGEF\(^{[15]}\) is upregulated by activation of a variant of the ‘hypoxia-inducible factor’ hif-1, a nuclear protein which binds to responsive sequence in the VGEF promoter, thereby increasing transcription. Furthermore, an RNA binding protein is activated in the cytoplasm that binds to various regions of the VGEF mRNA and prevents its degradation. While this mechanism remains undisputed in angiogenesis, it is probably not applicable to arteriogenesis because arteriogenesis proceeds in an environment that is not ischaemic, or much less ischaemic than tissue where angiogenesis occurs. In an animal model of femoral artery occlusion, only the lower leg becomes transientsly ischaemic and angiogenic, but not the upper leg where arteriogenesis occurs\(^{[13]}\). This is also reflected in the human situation where gangrene of the big toe develops but bridging collaterals occur in the upper thigh. The occurrence of small foci of ischaemia cannot be excluded in the vicinity of growing arteries, especially not since these develop preferentially within aerobic red skeletal muscles. However, ischaemia is an unlikely stimulus for arteriogenesis because VGEF, the only growth factor with a clear connection to hypoxia, is not a mitogen for smooth muscle cells and is not induced near or in growing collaterals.

Summary

Arteriogenesis, the process of collateral artery growth, as an adaptation to major arterial occlusion, can be life- and tissue-saving and may alter the natural course of the consequences and organ manifestations of arterial disease. This is achieved by an active growth process that is coupled to complete arterial remodelling with activation of proteases and destruction of organ tissue in the immediate vicinity of the growing vessel, to create the space for a new artery which expands to about 20 times its original diameter. Much of the growth and remodelling is achieved by attraction, adhesion, activation and invasion of circulating cells, mostly monocytes, but also T-cells and basophiles. Growth factors that are already present, as well as those that are produced by invading cells, create an environment of inflammation and facilitate coagulation and are therefore pro-atherogenic. It will be a challenge for future therapies with growth factors, chemokines and cytokines to neutralize their atherogenic and to maximize their arteriogenic properties.

References


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