Vasa vasorum hypoxia in arteriosclerosis obliterans, peripheral artery disease and restless leg syndrome

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Abstract
Introduction
With the ageing population circulation problems in the peripheral arteries decrease the quality of life. Arteriosclerosis obliterans, peripheral artery disease, intermittent claudication and restless legs syndrome are the main diseases associated with problems of the peripheral arteries. They cause unpleasant sensations all over the body. The vasa vasorum consist of the internal and external part and form a microvasculature of the arterial walls. The sympathetic nervous system releases noradrenaline (norepinephrine) directly into the blood and consequently from vasa vasorum into the outer layer of smooth muscle cells starting their contraction. The contraction is maintained by the stretching.

The Hypothesis
We propose two pathways for the pathophysiology of arteriosclerosis obliterans, peripheral artery disease and restless legs syndrome: (1) a new microvascular hypoxia hypothesis and (2) a sympathetic pathway via noradrenaline. However, both pathways lead to an increasing hypoxia of the main arterial wall and finally to the diseases. We propose that the most vulnerable part of vasculature is vasa vasorum. A minor arterial constriction leads to a significant decrease in blood flow in vasa vasorum and, thus, to a hypoxia and finally anoxia. Simultaneously, smooth muscle cells in hypoxia cannot relax due to a lack of adenosine triphosphate and the blood flow in the main artery is impaired. Therefore, these diseases can be classified as microvascular diseases.

Evaluation of Hypothesis
Based on the anatomy and physiology, it is obvious that oxygen supply via vasa vasorum is the evolutionary weak part of the circulation due to branching and low blood pressure against the high intramural pressure in the layer of the smooth muscle.

Conclusion
We propose a simple explanation for several vascular diseases. Their origin might be in the structural and functional weaknesses of the vasa vasorum, which lead to metabolic problems, hypoxia, in the smooth muscle layer of the main artery.

Introduction
In most arteries, the external vasa vasorum (v.v.) (‘vessels of vessels’) vascular bed is found¹ and their capillaries provide blood supply and nourishment of the arterial cell layers, especially for tunica adventitia as well as for tunica media and in hypoxia even to the tunica intima (Figure 1). Normally, tunica intima is oxygenated directly from the arterial lumen. Because the arterial wall is relatively thick and the diffusion to outer vascular layers is not possible, the external v.v. are necessary for the oxygen supply of outer layers. Because there is a pressure gradient across the main artery wall, the external v.v. from the low-pressure side cannot perfuse the high-pressure parts of media and intima. The v.v. internae originate directly from the main lumen of the artery and can partially supply oxygen to the internal layers, but their role in oxygen supply is small².

The tunica media of the medium size arteries contains many layers of smooth muscle cells (SBCs), which can alter the diameter of arterial lumen. The muscle cell contraction and relaxation need constant oxygen supply and adenosine triphosphate (ATP) synthesis. This oxygen supply comes essentially from v.v.³.

Some artery diseases such as arteriosclerosis obliterans (ASO) as well as peripheral arterial disease (PAD) are considered to be vascular diseases⁴. Restless leg syndrome (RLS) is regarded as a neurological disease with a high prevalence of 7.2%–11.5%⁵. The diseases are regarded as manifestations of atherosclerosis affecting an estimated 27 million PAD and over 50 million RLS in Europe and North America. With the population ageing this will become a major public health problem. The diseases are associated with pain, discomfort and muscle disability in the lower extremities and sometimes in arms as well. Particularly, RLS is characterised with sleeping problems and PAD with walking problems and intermittent claudication (IC)⁶.

There is no proper treatment for the diseases. In diabetic patients, amputation is a common final consequence of PAD. ASO and IC are considered to be an alternative form of coronary disease caused by cholesterol accumulation (cholesterol theory) and statins are used to prevent the diseases⁷. RLS has been proposed being a neurological disease⁸. Analgesic drugs are often used to relieve the pain associated with the diseases.

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Figure 1: A schematic presentation of two proposed pathways: (1) the first pathway is initiated by functional hypoxia of the v.v. and (2) the second pathway is initiated by an NA surge from the CNS. Both pathways lead to smooth muscle contraction and a decreased blood flow and progressive hypoxia (ischaemia), endothelial damage and inflammation in peripheral arteries. Finally RLS, ASO and PAD will develop. The hypoxia reduces ATP production.

However exercise and walking seem to reduce pain better than analgesic drugs. Microvascular origin of the diseases has not been proposed so far.

The direct mortality seems to be low in both diseases leading to under-diagnosis but the risk becomes dramatically higher in aged populations (>65 years) with other cardiovascular diseases. As shown by CT-3d analysis the higher the v.v. density the higher the vascular plaque probability. The coronary arteries are especially vulnerable to atherosclerosis. We proposed recently that the coronary disease might be more linked to the insufficiency of its v.v. than serum cholesterol levels. Risk factors of atherosclerosis such as cigarette smoking factors in the blood can damage endothelium, which in turn leads to extravasation of macromolecules such as high-density lipoprotein and low-density lipoprotein (HDL and LDL)-cholesterol. We find this as evidence suggesting a role of v.v. in ASO, PAD and RLS.

The Hypothesis
We hypothesise that many of the arterial diseases are originating from the hypoxic conditions in the v.v. in the media layer. The hypoxia is obvious because of three reasons: (1) low-pressure in v.v. versus high pressure of the arterial wall; (2) the branching anatomy of v.v. and (3) the v.v. are functional end arteries. The hypoxia in the contracting muscle cell layer will produce long-lasting acidic overload in the endothelium of v.v. and cause endothelial damages and gradually inflammation as well as stimulation of growth of the capillary bed. Macroparticles as found in atherosclerotic plaques such as cholesterol and its esters (LDL, HDL, very low-density lipoprotein), calcium and even microbes leak into the vessel wall through the damaged capillary endothelium.

The arteries of various thicknesses will contain SMCs from a few to tens of cell layers. Muscular function in larger arteries is to maintain the tension of the vascular wall during the heart pulse pressure to ensure the blood flow to peripheral capillaries. The sympathetic neurones of the central nervous system (CNS) release noradrenaline (NA) into the circulation. Via v.v. NA enters the outermost layer of SMCs leading to contraction spreading from cell to cell. Without NA the cells have minimally autonomous contractive action. Due to the decrease in diameter in v.v., it is likely that hypoxia will develop and synthesis of ATP is impaired. Smooth muscle action needs proper supply of oxygen and nutrition transport. ATP is needed for the muscle relaxation (Figure 1).

Both pathways will lead to decreased blood flow at various levels of extremities and thus ischaemic symptoms are variable. The hypoxia v.v. will lead to plaque formation in the tunica media and intima, which will affect the size of the vessel lumen and thus reduce the blood flow. The contraction of SMC by NA and stretch in stress situation also changes the blood flow in the skeletal as well as in vascular muscles (Figure 1).

Evaluation of Hypothesis
The authors have referenced some of their own studies in this hypothesis. These referenced studies have been
conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Pathophysiology of RLS, PAD and ASO: There is firstly a hypoxia and damage of v.v. leading to a prolonged contraction of the main artery. This is followed by a decreased blood supply to the periphery. As a symptom of this decreased blood supply there is an IC. PAD is the next step from RLS and the muscles lose their power depending on the severity of the hypoxia. In RLS, the initial step seems to be in CNS (NA release), but the next steps are identical: contraction-hypoxia-endothelial damage and others.

If these vascular syndromes have similar pathophysiology, it opens a new avenue for their treatment and prevention. v.v. seem to be more important for the blood circulation than considered earlier. Proper treatment of diabetes, cessation of smoking, regular physical exercise and decrease in stress appear to have great preventive value20. In the arterial surgery, v.v. should be considered21.

Discussion

There are several possibilities, how hypoxia may occur in v.v.: vasoconstriction by stress, high blood pressure, low oxygen saturation in blood and heart insufficiency. This in fact is more important because the recent evidence points out that plaque formation is correlated with the amount of v.v.21. It is important to note that before the actual ruptures (heart attack) the lumen of the coronary artery is narrowed and, thus, blood flow reduced (angina pectoris).

If the hypoxia is chronic, it may lead to artery diseases such as ASO, PAD as well as RLS. These syndromes usually are found in the arteries of legs and/or arms. The severity of the symptoms depends on where in the artery obstruction occurs and how long it has taken to develop. The v.v. are functionally end arteries, which makes them extremely vulnerable to changes in the blood flow. It is unlikely that the arterial wall would markedly be nourished by diffusion since oxygen is tightly bound to haemoglobin until pH decreases.

According to the Hagen–Poiseuille equation for the blood flow, viscosity and its resistance, the radius of the vessel is most important controlling the flow, that is, to the fourth power. The prolonged contraction of SMCs in the tunica media will reduce the diameter of the vessel lumen dramatically. Thus, if the radius is to be halved the resistance of the flow is increased 16 times and the blood flow is reduced to the same extent.

The peristalsis of the systemic arteries enhances the blood flow forward. If smooth muscle action is diminished by hypoxia, lack of ATP or inhibition of quinone 10 synthesis (statins) causes the risk for plaque formation to be higher because v.v. are likely to be damaged.

The present hypothesis also explains the different background of muscle cramps and RLS, where muscle cramps are directly associated with acto-myosin block of off-balance in electrolytes, which again may have neuronal sympathetic tone. The hypoxia in capillaries of pulmonary vessels and alveolar muscles21 can have similar consequences as disturbance in v.v. of leg arteries. The histopathological findings of diseased arteries support our hypothesis20,22. In all these syndromes the arteries to the legs are impaired.

Conclusion

We hypothesise that a hypoxia in v.v. leads to arterial diseases such as ASO, PAD as well as RLS. Therefore, these diseases can be classified as microvascular diseases.

Abbreviations list

ASO, Arteriosclerosis obliterans; ATP, adenosine triphosphate; CNS, central nervous system; HDL, high-density lipoprotein; IC, intermittent claudication; LDL, low-density lipoprotein; NA, noradrenaline; PAD, peripheral artery disease; RLS, restless legs syndrome; SMC, smooth muscle cell; v.v., vasa vasorum.

References


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