The Influence of Oxygen Supply, Hemorheology and Microcirculation in the Heart and Vascular Systems

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Abstract The microcirculation is an important system, containing resistance arterioles, capillaries and venules, whose main function is to transport oxygen and nutrients to the tissues. Endothelial cells are the main cell types of the microcirculation; their homeostasis is modulated by constant shear stress. Altered hemorheology induces a change in the production of vasodilator and vasoconstrictor agents. The most important pattern inducing endothelium dysfunction is an increase in oxidative stress, which decreases the amount of nitric oxide and favors microvascular phlogosis. In this review we will consider the main scientific reports about the cardiovascular risk factors such as smoking, hypercholesterolemia, hyperviscosity, hypertension, diabetes, stress and increased homocysteine levels, all having as common etiopathogenetic factor alterations in microcirculation and in tissue oxygenation. We also focus on their influence on endothelial cells, inducing endothelial changes and dysfunction related to altered oxygen supply and linked to increased oxidative stress. Also important are endothelial stem cells, that are able to repair vascular endothelial damage, especially in cardiovascular patients, with or without endothelial dysfunction. Under these circumstances the numbers of these stem cells are altered, which means there is a decrease in regeneration capability (post ischaemia modified albumin, etc.). This could be an important negative prognostic factor. Microcirculation and tissue oxygenation are very important factors strongly linked to hemorheology, especially in cardiovascular patients, and their alterations could cause impairment, or initiate cardiovascular pathologies.

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E. Takahashi, D.F. Bruley (eds.), *Oxygen Transport to Tissue XXXI*, Advances in Experimental Medicine and Biology 662,
DOI 10.1007/978-1-4419-1241-1_4, © Springer Science+Business Media, LLC 2010

1 Microcirculation Anatomy

Organs are not isolated islands in our body. They are all connected by a "big sea" and together compose the continent that we call the body. That "sea" is blood and the channels in which it flows is the circulation. To take what they need for their "life", organs need a microcirculation, which could be considered as an organ itself, being composed of the smallest blood vessels all over the body including resistance arterioles, capillaries and venules. Its most important function is the transport of oxygen to peripheral parts of the body and the removal of the CO_2 produced.

All mechanisms that regulate blood flow into the microcirculation are designed to ensure this transport function. In the intima the endothelial cell layer regulates coagulation, fibrinolysis and vasomotion. In the endothelial tunica there are muscular cells that modulate vascular contractility; in the adventitia tunica the connective tissue, nerves and capillaries provide mechanical shielding, innervation and nutrition to vessel walls respectively [1].

2 Endothelial Physiology

The main cell types of microcirculation are the endothelial cells, which form the inner lining of all blood vessels. A constant shear stress modulates vascular endothelium homeostasis, increased shear stress leading to a change in the secretion of vasodilator and vasoconstrictor agents. Increased oxidative stress is a major pathogenetic mechanism of endothelial dysfunction, causing decreased nitric oxide (NO) bioavailability and microvascular inflammation [2].

The endothelium contributes to the local balance between pro- and anti-inflammatory mediators, hemostatic balance, as well as vascular permeability and cell proliferation. Normal endothelium cells show vasodilator, anticoagulant and anti-adhesive properties, and release vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (endothelin 1, thromboxane A2). NO is synthesized from the amino acid L-arginine in a reaction catalyzed by a family of enzymes called NO synthases (NOSs) requiring tetrahydrobiopterin (BH4) as co-factor; this leads to relaxation of smooth muscle cells by increasing intracellular cyclic guanosine-monophosphate levels [3, 4] (Fig. 1).

The endothelium modulates fibrinolysis, coagulation, vascular tone, leukocyte adhesion, platelet aggregation, vascular permeability, cell proliferation, and myocardial contractility. All these mediators are important for the living micro-circulatory homeostasis. Also produced are phlogosis mediators (interleukins), procoagulants (thromboxane A_2), anticoagulants (antithrombin – AT-III, heparin, plasminogen activator – PAF), vasodilators (NO), and vasoconstrictors (TXA_2, Endothelin ET-1) [5].

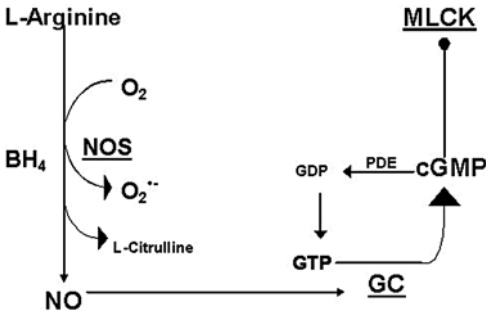

Fig. 1 NOS produces NO starting from L-Arginine and oxygen. NO stimulates the guanylyl cyclise (GC) function that increases cGMP production, which inhibits the Myosin Light Chain Kinase (MLCK) with the final result of relaxation of smooth muscle cells. Enzymes are *underlined*

3 Hemorheology and the Microcirculation

Interesting is the capability of the red cell (RBC) to pass through narrow capillaries. The diameter of arterioles is about 3.5 μm while the diameter of RBC is about 7 μm; RBC transit and oxygen transport to the cells is only possible due to RBCs being able to deform themselves.

The first experiments in hemorheology were performed in 1675 by Antoni von Leewenhoek (The Netherlands), who was the first to study the shape of RBCs with his newly developed microscope [6]. From these early experiments hemorheology has continued to develop and finally led to development of the Laser Assisted Optical Rotational Red Cell Analyzer (LORCA). This is a computerized instrument, served by a dedicated software, and able to detect RBC deformability (Elongation Index, EI) evaluated at different shear stresses from 0.3 to 30 Pascals (Pa), as well as RBC aggregability [7–9].

Shear stress influences the release of mediators by the endothelium, but also influences the possibility of RBCs to gain entrance into the smallest capillaries. Studying how RBCs deform themselves, using LORCA, enables us to understand potential problems with peripheral perfusion. Changes in RBC rheological properties are due to many factors, such as genetic defects, alterations in RBC metabolism, oxidative damage, micro-enviromental influences on RBC etc.; LORCA is able to investigate these.

Many types of changes can influence blood composition, such as alterations in hematocrit, increased number of leukocytes, and damage to plasma composition [10]. These changes can lead to altered aggregation, which can also result from changes in plasma composition, alterations in RBC deformability, and alterations in the surface properties of the RBCs.

4 Vessels and Oxidative Stress

Reactive Oxygen Species (ROS) and their derived Reactive Nitrogen Species (RNS) are synthesized in all vascular cells. It has been shown that an increase in ROS and RNS production induces damage such as hyper- cholesterolemia, diabetes, and hypertension [11, 12]. The most important species for the cardiovascular system is the superoxide anion (O_2^-). When this anion links itself with nitric oxide it produces the peroxinitrite ($ONOO^-$), which is the most toxic to cells.

Oxidative stress is physiologically present in our cells, but the scavenger system balances their production, to protect cells. In the presence of exogenous stimuli like smoking, diabetes, hypertension, hypercholesterolemia or stress, in combination with the physiological increase in oxidative stress due to age, scavengers are not able to protect cells, resulting in a net production of ROS and RNS. These anions react with lipoproteins, which starts an endothelial phlogosis, that damages endothelium, leading to atherosclerosis. One of the main effects of atherosclerosis is vascular remodelling, that increases the risk of a possible major event, such as infarction, aneurism or stroke. This is the reason why cardiologists consider smoking, hypercholesterolemia, hypertension and diabetes as major risk factors in infarct pathogenesis, and try to prevent infarction by reducing these risk factors [11–16].

Very important is the rarefaction and the desertification detected with capillaroscopy in some areas in vascular patients, especially hypertensives and cardiac patients. Karch et al. analyzing patients suffering from cardiac disease, showed that there were differences between the groups of hearts analyzed: the infarcted heart had the worst scenario compared with both controls and dilated hearts, with an increase in heart capillaries distance, an increase in cell diameter and a decrease in capillary density [17].

5 Microcirculation and the Heart

Capillary density (evaluated using computerized videocapillaroscopy) and spatial arrangement of capillaries are determinants in maintaining the balance between myocardial oxygen demand and supply. These indices may be seriously altered in patients with heart failure caused by idiopathic dilated cardiomyopathy, ischemic cardiomyopathy, or inflammatory cardiomyopathy. Cardiac remodelling includes changes in both the myocytes and the extracellular matrix. Dilated cardiomyopathy and ischemic cardiomyopathy are associated with apoptosis, myocyte hypertrophy, and increased interstitial fibrosis, ultimately leading to decreased capillary density, and thus to increased diffusion distances and impaired oxygen delivery to capillaries from myocytes.

Endothelial activation is the main cause of the vessel wall light phlogosis that ends in endothelial dysfunction. This dysfunction is not only related to

cardiovascular risk; tissue ischemia and a reduction of shear stress increase the oxidative stress. This, combined with the increase in cytosolic calcium (due to the ATP-K^+ channel block with the consequent depolarization and Ca^{2+} channel opening) this increases NO and $ONOO^-$ production with an alteration in the secretion of vasoconstrictors, an increase of the membrane oxidation, cell proliferation and leukocyte adhesion.

All the above mechanisms result in an increase of the risk of coagulation and of the possibility that platelets could clot on plaque. When this happens, the event that could increase damage to cells is ischemia. An obstructive thrombus is like a major accident on a motorway at rush hour. Due to the decreased arterial flow, blood can not arrive at the peripheral cells; these try to survive for some time before dying with tissue hypoxia, which occurs just before necrosis. The attempt to survive needs a metabolic switch from aerobic to anaerobic metabolism, causing a consequent increase in glycolisis producing enough energy to give ATP to the cell that dies after six hours. If revascularization can be achieved in time, functional failure of the stunned myocardium is reversible. However, if cells suffer more than they could repair the damage, they die with necrosis in contractile bands with the mitochondrial calcium phosphate (if the reperfusion is done within 40 min) or without. Thus, the heart could dilate its chambers with the consequent ventricular aneurism. In the case of non- reflow coagulative necrosis results.

Cells try to compensate for ischemic damage by producing pro-angiogenetic molecules like VEGF and FGF. These molecules stimulate the neoangiogenesis; but this mechanism is not useful in the heart. Revascularization is scarce in the heart and it happens only at the peripheral infarcted area close to the still functioning capillaries.

Garmy-Susini et al. showed that endothelial stem cells from bone marrow were able to repair vascular endothelial damage in systemic circulation [18]. Especially in cardiovascular patients with or without endothelial dysfunction, the number of these stem cells is decreased and this means that there is a decreased regeneration capability (post-infarction, decreased neoangiogenesis). This could also be an important negative prognostic factor. Thus, the use of endothelial stem cells injected directly into the infarcted area is the new clinical perspective.

6 Microcirculation and Pathology

When considering the role of microcirculation and its most important variables (vessels, haematocrit, blood viscosity), a current definition of the ischemic syndrome, could be that the resistance microvessels are not able to compensate for the effects of a decrease in perfusion pressure following stenosis and/or change in systemic blood pressure, with resulting impairment of the supply of nutrients and oxygen and the removal of catabolites. Besides

this physiopathologic role, the microcirculation, where exchange between vessels and tissues occurs has a very important role in inducing complications (i.e. renal damage, cardiac or cerebral damage) during hyper-tension, diabetes, vasculitis, immunological inflammatory syndromes; hyperviscosity syndromes, and cardiovascular risk factors such as hypercholesterolemia, age, smoking, etc [19].

Finally the microcirculation has an important etiopathogenetic role in venous ulcers, in vascular vertigo, in sepsis, in a good acceptance of organ transplantation, in cancer neoangiogenesis and in other pathologies. The study of the microcirculation and its hemorheology is a very large area of investigation with many clinical implications and fields of research. Due to its ability to alter oxygen supply and delivery in various tissues, the microcirculation is strongly linked to blood perfusion and tissue exchange.

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