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# *What anaesthesiologist should know about the leucocytes and their effect on microcirculation*

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## Abstract

Alterations in microvascular circulation are observed in different pathological conditions, but acute changes in morphotic elements of blood are not well recognised. In conditions like septic shock, severe cardiac failure and others extreme pathophysiologic states, these alteration may influence patient's outcome. Therefore the knowledge of leukocytes behaviour at microcirculatory level in pathophysiologic conditions could be helpful in understanding how different choice of anaesthetic affects microcirculation. *Anestezjologia i Ratownictwo 2019; 13: 122-126.*

*Keywords: microcirculation, volatile anaesthetic agents, leucocytes, endothelium, reactive oxygen species, cytokines*

Morphotic blood elements affect the blood flow dynamics in microcirculation. As white blood cells are larger in size and undergo less deformation than the red blood cells, they may play an important role in microcirculation blood flow regulation [1,2]. Observation of the white cell survival in microcirculation allows appreciation of their spherical shape; they may undergo passive deformation under conditions of hemodynamic stress and flow in the capillary network [3]. In normal conditions these cells do not undergo any active change in their shape during transit through the circulatory system. Spontaneous deformation affects non-differentiated forms of the leucocytes and occurs in vivo during the cells' migration through the endothelium along the chemotactic gradient and during phagocytosis [4,5].

The overall outline of white cells is spherical; however, the corrugated cellular membrane creates an excess surface, allowing for deformation of a cell without increasing its surface area [5-7].

In 1946 Nicoll and Webb recorded a transient blockage in the blood flow at the capillary level caused by the presence of white blood cells [8]. This research was confirmed in 1970 by Chen and Skalak and again in 1980 by Schmid-Schonenbein, who investigated the blood flow in small vessels in vivo [4,9]. White blood cells affect the blood flow in the microvessels by the following mechanisms: adhesion to the vascular wall, closure of the vascular lumen during the slowed flow, including complete closure of the vessel patency, by mutual interaction of microvessels in which the resistance was increased, as well as by their presence in the extracellular space [10-12].

In small capillaries the white blood cells have to undergo deformation, sometimes even down to half of their original dimension and their further flow is possible only because of encapsulating the white cell structure by a plasma "sleeve." White cells also affect the blood flow at sites where new vessels branch off causing their occlusion at the very origin of division. If a white cell enters the lumen of a vessel, which has a diameter smaller than its own, a definite time is required for blood cell deformation to occur to allow the cell to get through the vessel. During this deformation the vessel is completely occluded, which makes any blood flow through its lumen impossible. This blood flow occlusion may have a significant effect on the distribution of blood in

the capillaries, depending on how long the deformation process lasts [13-15]. It is unclear what is more important in terms of effect on the microcirculation of the blood flow: deformation time or occlusion time . Mathematical formulas developed by Needham and Hochmuth in 1989 and Fenton in 1985 provided no definite answer to this question. They suggest that the higher the pressure force of the inflowing blood up stream, the shorter the deformation time [16,17]. Adhesion of white cells to the vascular wall is more frequent when the blood flow in the vessel is slowed down [18]. This promotes margination of white cells, which thus become more susceptible to chemotactic substances [19].

It is known that the higher volume and viscosity of white blood cells compared to red blood cells (one white cell is equivalent to 700 red cells) leads to much faster mechanical arrest of blood flow in vessels 5 micrometres in diameter [20,21]. Other in vivo studies proved that the increase of resistance in the capillary network and the incidence of lumen occlusion by leukocytes are dependent on the capillary network structure. Variation of pressure values in the capillary network, depending on the number of occlusions, also depends on intervascular canals within the network. A higher number of canals within the capillary network leads to lower variation of pressure values, in consequence increasing the time of vessel occlusion by leukocytes. Reversely, in borderline conditions where no canals between the capillaries are present within the network, the pressure increase will correspond to the pressure value at the capillary network entrance, and the leukocyte occlusion will be very quickly reversed [11,12,21].

Another important feature of the capillary network geometry is the number of branching within the network, as they affect the leukocyte behaviour [22,23]. Experimental models of microcirculation in skeletal muscle showed that significant number of vessels must become occluded before delayed vascular resistance increase is observed in the network [9,15,24]. For instance, a network model comprised of 60 parallel vessels shows no signs of resistance increase until at least five main paths of this network are totally occluded. Above this number, a slight increase in the vascular resistance, not exceeding 9% of the baseline value, was recorded. In the tree-branched vascular network, occlusion of a small number of capillaries causes a high increase in flow resistance since in this structure a much larger number of capillaries remains devoid of blood flow [13,15,25]. There are differences in capillary network structure, which may significantly affect flow disturbances and change the so-called capillary reserve, depending on the organ being affected or subjected to surgery [12,26].

The effect of white blood cells on the increase in flow resistance is also dependent on changes in blood viscosity. Medications and substances, as well as pathological lesions formed in the system and affecting white cell deformation and viscosity affect the capillary network resistance [13,27].

In addition, occlusion of capillaries by white cells affect further white cell distribution in the capillary network and is directly responsible for the phenomenon of highest flow pathway selection [28]. When one of the vessels is occluded, white blood cells flow is transferred to another capillary network. The more vessels are occluded, the more white cells are dispersed within the entire network [4,5,29].

Postcapillary venules are primary receptacles for blood passing through the capillary network; concurrently it is the last anatomical and functional structure of microcirculation [30]. They play a key role in venous insufficiency of a free skin flap, free muscle flap, composed of multiple tissues or transplanted organs [31,32]. Blockage of flow through some of postcapillary venules results in congestion of an isolated or transferred muscle flap or other tissue, with slowed blood flow through its arteries and is often combined with irreversible changes due to severe abnormalities of metabolism in cells located in the affected area [33,34].

Reduced accumulation of white blood cells in the postcapilalry venule directly results in improvement of capillary perfusion, significantly delays development of endothelial edema that eventually results in complete blockage of blood flow. This observation is a basis for the speculation that changes in Ca++ pump system activity is associated with changes in Ca++ in white blood cell cytosol; reduced activity of white blood cells as observed during halothane anaesthesia [35-38]. Therefore, white blood cell activity would depend on the level of active Ca++. Dirnagl et al. and Warnke et al. believe that increased white blood cell activity is associated with hypoperfusion [39,40]. Multiple substances are responsible for increased white blood cell activity in the hypoxic tissue. Leukotrienes and peroxides disrupt glycoprotein complex that adheres to the white blood cell surface. Peroxides also change the behaviour of white blood cells in the microcirculation, by stimulating endothelial release of GMP-140

(Granule Membrane Protein 140) (integral membrane glycoprotein) that causes enhanced adhesion of white blood cells to the vessel wall. TNF and interleukin-1 are responsible for production of a factor that causes increased activation of blood platelets along with stimulation of monocytes/macrophages binding to a specific endothelial receptor. All these events result in enhanced white blood cell adhesion to the vascular endothelium, promoting its destruction, microcirculatory, release of toxic agents (oxygen free radicals), proaggregatory factors produced by white blood cells (PAF), resulting in slowing of blood flow in the microcirculation and migration of white blood cells to extravascular tissue [39,41,42].

Blais and Akata believe that in a certain situation, inhaled anaesthetics, including halothane and sevoflurane, may be responsible for vascular spasm and increased permeability through release of oxygen free radicals [2,43,44]. Both anaesthetics could result in such phenomenon through their effect on endothelial guanylate cyclase [45-48]. Akata et al. used 1 MAC for halothane and sevoflurane in their studies but did not find any interference with endothelial guanylate cyclase [43]. Mechanism of this phenomenon is not entirely clear, however vascular contraction in the postcapillary venule seems to be triggered by oxygen free radicals in the presence of inhaled anaesthetics. It is also triggered by xanthine oxidase, flavonoid enzymes and electron transport, resulting in formation of specific, vasoconstrictive prostanoids [5,49-51]. Moreover, protective effects of halogenated anaesthetics were more pronounced in arterial than in venous microcirculation: first, vein walls are almost three-fold less sensitive to inhaled anaesthetics that arterial walls [8], second, protective effect of any anesthetic on metabolic abnormalities in the venous circulation must be less pronounced since hypoxemia is a physiological phenomenon there. Park et al. clearly confirmed that isoflurane had similar mechanism of action to that of sevoflurane and halothane and was responsible for concentration-dependent release of oxygen free radicals [52]. On the contrary, Shayevitz et al. claim that although oxygen free radicals are responsible for injury of the vascular endothelium in the presence of halothane and isoflurane, these anaesthetics are not responsible for the release of reactive oxygen species or their enhanced production, but simply they cause endothelial hyperresponsiveness to these compounds [53-55].

Drinagl et al. studied brain ischemia related to hypoperfusion and subsequent reperfusion. The authors observed that during hypoperfusion, in particular at its onset, white blood cells form plugs that block the blood flow in microcirulation. However, they were not directly responsible for postichemic hypoperfusion of cerebral cortex, but other, local agent (unidentified by the authors) played dominant role [39]. Structure of brain microcirculation is significantly different from anatomical and physiological characteristics of the peripheral microcirculation [56]. In vitro studies proved that undisturbed white blood cells migrated through an artificial blood brain barrier and did not damage it, while permeability to plasma proteins was unchanged. These studies suggest that this phenomenon may be associated with white blood cell deformation during CNS ischemia that facilitates their migration from the vascular lumen, while in peripheral circulation they migrate outside the vascular lumen only after the endothelium has been damaged [57,58]. On one hand, this phenomenon may be beneficial, since it facilitates reperfusion. However, on the other hand demage processes related to increased white blood cell activity, take place directly in tissues. However, it seems that reduced white blood cell activity in the lumen of the postcapillary venule (white blood cells rolling and adhering to its endothelium) under halothane and sevoflurane anaesthesia favors better capillary perfusion and does not disturb important metabolic processes. If most of toxic mediators related to white blood cell aggregation in the tissues would cause its destruction, these processes must be triggered by intracellular Ca++, while halothane and sevoflurane are inhibitors of the latter [38]. These considerations may have practical implications for the selection of anaesthetics for complex and prolonged surgical procedures involving reconstruction of a complex transplants composed of several tissues, including face transplantation.

Conflict of interest
Brak/None

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