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Editorial:

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The microcirculation in hypoxia: The center of the battlefield for oxygen

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Abstract. In the past years the microcirculation has gained increasing attention not only by basic scientists, but also by clinicians and translational researchers. In the clinical scenario, it has been convincingly described that the microcirculation is a key predictor of outcome and of central pathophysiological relevance. A vast body of evidence demonstrates the central role of the smallest vessels in inflammation, hyperviscosity, cell-cell-interaction, endothelial function, tissue edema, hemodynamic and blood flow regulation and its important role in the interaction with soluble factors. A central feature of different diseases and a strong regulator of different changes is hypoxia, the lack of oxygen. Also, the microcirculation is on one hand a central component responding with dynamic changes to hypoxia but also the central place where hypoxia mediates its unfavorable effects. These changes and associated interactions are the topic of this special thematic issue “Hypoxia” in *Clinical Hemorheology and Microcirculation* and it seems logical that important and relevant findings are presented.

Keywords: hypoxia, microcirculation, perfusion, oxygen, vessels

In the past years the microcirculation has gained increasing attention not only by basic scientists, but also by clinicians and translational researchers [13, 17]. In the clinical scenario, it has been convincingly described that an impaired microcirculation predicts outcome of critically ill patients [12] and that the microcirculation shifts more and more towards a therapeutic target in these patients [11,14]. In addition, modern diagnostic tools became available including non-invasive methods to quantify microvascular perfusion allowing individualized treatment strategies in order to optimize organ perfusion and oxygenation. A vast body of evidence demonstrates the central role of the smallest vessels in – among others–inflammation, hyperviscosity, cell-cell-interaction, endothelial function, tissue edema, hemodynamic and blood flow regulation and its important role in the interaction with soluble factors [5]. Most strikingly, one central function of the microperfusion of tissues and organs is the exchange of gases, nutrients and cell waste. One of the most important changes in a broad variety of disorders occurs when tissue or cells lack oxygen, namely hypoxia [9]. The clinician is interested to restore oxygenation to avoid irreparable tissue damage, the basic scientist is eager to describe the pathophysiological changes occurring under hypoxia searching for master switches in physiology or therapeutic windows. The microcirculation is on one hand a central component responding with dynamic changes triggered by hypoxia but also the central place where hypoxia mediates its unfavorable effects. In consequence, it seems logical that this special thematic issue “Hypoxia” of *Clinical Hemorheology and Microcirculation* presents important findings. It has been well established that erythrocytes, red blood cells (RBC), also contribute to the regulation of microvascular flow either by changing their deformability or by interfering with the vasodilatory nitric oxide (NO) pathway [6]. In the present issue, Brinkmann and coworkers present a study on the effect of endurance training on RBC in non-insulin-dependent type 2 diabetic patients showing that this increases RBC deformability in young erythrocytes [4]. While NO synthase activation was unchanged in young RBC, NO synthase activation was decreased in old RBC, possibly involved in the clearance of RBC from the circulation. Another study published in this issue investigates the changes occurring in RBC following remote ischemic preconditioning which has been shown to be protective

for remote organs and consists of repetitive ischemic circles. This leads in consequence to the activation of adaptive possible mechanisms which have not been understood completely so far [3]. Grau et al. present a study exploring the influence of four cycles of no-flow ischemia on the subsequent reactive hyperemia within the forearm in twenty male participants. Of note, RBC deformability improved in the treated arm inline with increased RBC NO synthase activity. In addition and underlining the possible relevance of RBC in remote conditioning, RBC deformability and RBC NO synthase activity were also increased following cycles three and four in the control arm [7]. The same group present a comprehensive paper on RBC deformability and NO metabolism under mild as well as severe hypoxia *in-vitro* and *in-vivo*, applying hypoxic chamber experiments. The authors were able to show that after an initial decrease in RBC deformability, there was an increase in deformability under severe hypoxia, both *in-vitro* and *in-vivo*. The findings were complemented with mechanistic observations demonstrating non-enzymatic NO production under severe hypoxia [8]. Hypoxia also affects all other parts of the blood, including white blood cells and thrombocytes as well as the non-cellular components. Janes' o and coworkers investigated in an animal model of infrarenal aortic occlusion the consequences of controlled reperfusion with crystalloid reperfusion solution. In this setting, controlled reperfusion reduced postischemic oxidative stress and inflammatory responses in the early reperfusion period as well as less muscle degradation in the lower limb. Although this needs to be confirmed in more settings and the clinical scenario, controlled reperfusion might be a potential therapeutic strategy in vascular surgery [10]. Another study also applied the model of infrarenal aortic clamping to study controlled reperfusion: Kenyeres and coworkers showed that controlled reperfusion using reperfusion solution improves hemorheological properties such as blood viscosity [16]. A detailed study on differences on hemorheology between chronic intermittent hypoxia versus continuous hypoxia was done by Kang et al. Since the field of intermittent hypoxia is of clinical relevance for patients with obstructive sleep apnoea, rats were divided in three groups with normoxia, hypoxia and intermittent hypoxia. Of note, both hypoxia models increased plasma viscosity, erythrocyte and thrombocyte aggregation rate as well as fibrinogen levels with a stronger effect of chronic exposure compared to intermittent exposure [15]. Investigations on inflammatory cells under hypoxic conditions were performed by Rohm et al. Circulating dendritic cells were quantified following an alpine passive escalation to 3000 above sea level revealing a hypoxia induced decrease of circulating with reconstitution after return to sea level [20]. Although the exact mechanism remains elusive, in the light of other studies in this field [21] a recruitment of inflammatory cells seems to take place in hypoxic organs being involved in local inflammatory responses. Besides local inflammatory reactions, hypoxia is also of relevance in systemic consequences of inflammation, which is the topic of an article by An and coworkers. In their study, in an animal model of septic shock microcirculatory parameters were investigated using intravital microscopy [19] and correlated with oxygen metabolism [1, 13]. Of central pathophysiological importance is the finding that an increase in oxygen extraction rate cannot be weakened by microcirculatory failure which also needs to be confirmed in the clinical scenario. An excellent view on human *in-vivo* microcirculation is possible in the eye, allowing a direct visualization and quantification due to the direct access. Two studies presented the changes occurring in high altitude. The study by Baertschi et al. one more time emphasises the fact that the microcirculation is strongly dependent on systemic pressure and venous pressure, but also tissue (intraocular) pressure. In hypoxic conditions, ocular perfusion pressure decreased, retinal venous pressure increased and intraocular pressure remained unchanged [2]. Further elaborated analyses were performed by Neumann and coworkers: Retinal vessel reaction to flickering light, representing an endothelial function test, was studied in normobaric hypoxia as well as in hypobaric hypoxia. Under both circumstances, retinal and venous vessels react to hypoxia with a diameter increase and an impaired response to flicker light [18]. The various studies highlight the central role of the various components determining the microcirculation in hypoxia. Unless our organs are dependent on oxygen we should continue our efforts to understand physiology and pathophysiology, as well as diagnostic and therapeutic options. After we have overcome this dependence on oxygen we can stop this focusing on conquering other planets without atmosphere!

Competing interests

None.

Authors contributions

CJ, FJ and MK drafted the manuscript. All authors read and approved the final manuscript.

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