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REVIEW

Vascular adaptation to extreme conditions: The role of hypoxia

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Abstract The study of vascular adaptation to extreme conditions, and in particular to hypoxia, represents a unique opportunity in cardiovascular physiology, with relevant translational implications. First, it has crucial clinical consequences for about 140 million people worldwide living at high altitude and chronically exposed to hypobaric hypoxia. Second, an increasing number of lowlanders are exposed to high altitude for recreational or working purposes, including aged, diseased individuals: in these cases, hypoxia could be a trigger for acute cardiovascular events. Finally, hypoxia plays a major role in the pathogenesis of many diseases and chronic conditions, as respiratory (i.e. chronic obstructive pulmonary disease and obstructive sleep apnea syndrome) and cardiovascular disorders (i.e. heart failure, ischemic heart disease and cerebrovascular disease). Thus, results from field studies at high altitude might be important for a deeper understanding of their pathophysiology. This review is aimed at summarizing the main findings in the field of chronic and acute vascular adaptation to hypoxia, focusing on the role of nitric oxide (NO) and endothelial function, as well as large artery behavior.

Contents

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Introduction

During human evolution, several homeostatic mechanisms, involving the cardiovascular, respiratory and neuroendocrine system, have been developed in order to maintain stable tissue O_2 levels. NO is a key molecule in systemic and pulmonary vascular physiology, for its vasodilating, antithrombotic and antimitotic properties.[1] Reduced NO availability in the systemic circulation, which is the main feature of endothelial dysfunction, has been recognized as the first step towards development of atherosclerosis.[1] During exposure to hypoxia, NO is crucial to ensure O_2 and nutrients delivery to tissues and it is considered the main responsible for early hypoxic vasodilation. For example, NO metabolites such as nitrite are supposed to be converted again to NO under hypoxic conditions and may induce vasodilation both by endothelium-dependent and -independent pathways.[2] An increased expression of several NO synthase (NOS) isoforms has also been demonstrated.[3] The balance between reactive oxygen species (ROS) and NO pathway seems also to be crucial for successful vascular adaptation to hypoxia, since increased ROS production is the main cause of NO destruction. Indeed, low O_2 concentrations may be a cause of overproduction of ROS together with decreased levels of antioxidant capacity, leading to oxidative damage to lipids, proteins, and DNA, and finally to cellular death.[4] Under a more prolonged exposure to hypoxia, other regulatory mechanisms take place. After few hours-days, hypoxia-induced peripheral vasoconstriction, sympathetically mediated as a consequence of chemoreflex activation, prevails on direct vasodilation,[5] leading to increased blood pressure.[6] Sympathetic activation is also able to induce endothelial dysfunction,[7] while oxidative stress per se is also able to induce sympathetic activation,[8] thus inducing a vicious circle. A late effect of high altitude acclimatization is an increased proliferation of red blood cells, aimed at achieving a greater oxygen-carrying capacity to overcome the low ambient oxygen tension. Subsequent hyperviscosity might also influence negatively cardiovascular homeostasis and vascular function. The key for successful adaptation to hypoxia probably resides in the complex balance between these contrasting forces. In this framework, the study of individuals and populations naturally predisposed to successful acclimation to high altitude, a powerful challenge to the cardiovascular system triggering mechanisms underlying most chronic non-communicable diseases,[9] might suggest novel strategies and therapeutic targets for cardiovascular disease.

Acute adaptation to hypoxia

A number of vascular abnormalities were reported after acute exposure to normobaric hypoxia[10,11] and high altitude, including impairment of endothelial function and arterial stiffening[6,12–15] As explained above, among mechanisms hypothesized, hypoxia-induced ROS production, sympathetic and endothelin system activation are supposed to play a relevant role.[13,16] On the other hand, exposure to 2–4-h simulated hypobaric hypoxia did not modify flow-mediated dilation[17] or reactive hyperemia index[18] in young healthy individuals. In a recent study by our group, endothelial dysfunction after 4-h hypobaric hypoxia was present only in individuals prone to develop acute mountain sickness, but not in the asymptomatic ones.[19] An overview of the main characteristics and findings of the studies dealing with this topic is in Table 1. A high degree of inhomogeneity emerges between different studies both in the techniques used and districts studied for the exploration of vascular function and structure, in the ascent protocol and in the study timeline, making it difficult to draw firm conclusions. However, beyond methodological issues, some physio-pathological aspects are worth special consideration.

A major variable to be taken into account is concomitant physical exercise. Comparing studies conducted with same technique and standardized methodology for the assessment of endothelial function,[13,15,17,19] an impaired endothelial function is evident only in studies in which high altitude was reached by exerting a prolonged physical effort, which might be associated per se with increased levels of circulating biomarkers of inflammation and endothelial activation.[20] However, there is also the intriguing possibility that the great inter-individual differences that have been reported in acute vascular response to hypoxia might represent a key factor in determining successful adaptation. In the Resamont-2 study we tested the hypothesis that vascular response to hypoxia is early impaired in individuals who will develop acute mountain sickness (AMS) after 24 h-hypobaric hypoxia. For this purpose, we recruited 34 apparently healthy individuals, born and living at sea level. Endothelial function, aortic and arterial stiffness were evaluated in Aosta, Italy 583 m.s.l. and 4 h after passive ascent by cable car to 3842 m.s.l. in Aiguille du Midi, France. The volunteers were re-evaluated for AMS occurrence after 24 h at 3842 m.s.l. Individuals who developed AMS had a greater SO_2 worsening and FMD reduction after 4-h hypobaric hypoxia, well before symptoms onset.[19] Conversely, FMD was unchanged in asymptomatic individuals, and accompanied by a significant increase in shear rate area under the curve. Based on these results, we hypothesized that in lowlanders with successful adaptation to hypoxia, maintenance of preserved flow-mediated dilation is conceivably obtained through an increased post-ischemic response in the microcirculation, probably attributable to a favorable balance between hypoxia-induced vasoconstrictor and vasodilator pathways, as described in the