Chapter 23

PULMONARY HYPERTENSION IN HIGH-ALTITUDE DWELLERS: NOVEL MECHANISMS, UNSUSPECTED PREDISPOSING FACTORS

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Abstract: Studies of high-altitude populations, and in particular of maladapted subgroups, may provide important insight into underlying mechanisms involved in the pathogenesis of hypoxemia-related disease states in general. Over the past decade, studies involving short-term hypoxic exposure have greatly advanced our knowledge regarding underlying mechanisms and predisposing events of hypoxic pulmonary hypertension. Studies in high altitude pulmonary edema (HAPE)-prone subjects, a condition characterized by exaggerated hypoxic pulmonary hypertension, have provided evidence for the central role of pulmonary vascular endothelial and respiratory epithelial nitric oxide (NO) for pulmonary artery pressure homeostasis. More recently, it has been shown that pathological events during the perinatal period (possibly by impairing pulmonary NO synthesis), predispose to exaggerated hypoxic pulmonary hypertension later in life. In an attempt to translate some of this new knowledge to the understanding of underlying mechanisms and predisposing events of chronic hypoxic pulmonary hypertension, we have recently initiated a series of studies among high-risk subpopulations (experiments of nature) of high-altitude dwellers. These studies have allowed to identify novel risk factors and underlying mechanisms that may predispose to sustained hypoxic pulmonary hypertension. The aim of this article is to briefly review this new data, and demonstrate that insufficient NO synthesis/bioavailability, possibly related in part to augmented oxidative stress, may represent an important underlying mechanism predisposing to pulmonary hypertension in high-altitude dwellers.

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INTRODUCTION

High altitude constitutes an exciting natural laboratory for medical research. Over the past decade, the scope of high altitude research has broadened considerably, since it has become clear that besides of being of importance for the prevention and/or treatment of altitude related diseases in climbers, the results of this research also may have important implications for the treatment of patients at low altitude, and for the understanding of diseases in the millions of people living permanently at high altitude.

Our group, after having devoted a decade or so, to the study of short-term adaptation to high altitude in mountaineers, has recently started to translate some of this new knowledge gained during these studies, to the study of long-term adaptation in high-altitude dwellers. In this article, we will first briefly summarize some of the salient results gathered during the short-term high altitude studies (with particular focus on pulmonary artery pressure and mechanisms of pulmonary edema), and then demonstrate the potential importance of this new knowledge for the long-term adaptation of high-altitude dwellers.

SHORT-TERM ADAPTATION TO HYPOXIA

Mechanisms underlying exaggerated pulmonary vasoconstrictor responsiveness during short-term high altitude exposure

Over the past two decades, studies in subjects susceptible to high-altitude pulmonary edema (HAPE), a condition characterized by exaggerated hypoxia-induced pulmonary vasoconstriction, have provided important new insight into the regulation of pulmonary-artery pressure at high altitude.(41)

Nitric oxide

These studies have provided evidence for the importance of pulmonary vascular endothelial and alveolar epithelial nitric oxide (NO) synthesis in the regulation of pulmonary vascular responsiveness to high-altitude exposure. The evidence is as follows: NO plays an important role in the regulation of pulmonary vascular tone in humans, because inhibition of NO synthesis by L-NMMA infusion potentiates the pulmonary vasoconstrictor response evoked by short-term hypoxic breathing. (6) In certain populations, HAPE susceptibility has been found to be associated with eNOS polymorphisms and impaired vascular NO synthesis. (1, 15) NO, when administered by inhalation, lowers pulmonary-artery pressure to a much larger extent in HAPE-susceptible subjects than in control subjects who never experienced HAPE.(42) These observations suggest that defective pulmonary endothelial NO synthesis is one of the mechanisms contributing to exaggerated hypoxic pulmonary hypertension in humans. Parenthetically, it is interesting to note here that at physiological concentrations, NO attenuates oxidative stress, a mechanism that has been implicated in