Right Heart-Pulmonary Circulation at High Altitude and the Development of Subclinical Pulmonary Interstitial Edema

Lorenza Pratali, MD, PhD

KEYWORDS

• Altitude • Hypoxia • Hypoxic pulmonary vasoconstriction • Interstitial pulmonary edema

KEY POINTS

- Hypoxic pulmonary vasoconstriction is an active process particularly involving the small muscular resistance pulmonary arteries and can be related to different mechanisms.
- The inhomogeneity of hypoxic pulmonary vasoconstriction may account for regional overperfusion of areas with weak vasoconstriction, where the capillary pressure increases for higher flow, and this mechanism may contribute to the development of interstitial lung edema.
- Subclinical pulmonary interstitial edema due to hypoxia exposure is a complex and multifactor phenomenon, still with unanswered questions, and might be one line of defense against the development of severe symptomatic lung edema.

Evangelista Torricelli was an Italian physicist and mathematician who in the seventeenth century realized that atmosphere above us creates a pressure; this discovery brought about the mercury barometer invention. Thank to this discovery, many years later the relationship between barometric pressure and altitude was described.[1] With increasing altitude a decrease in barometric pressure and inspired P_{O_2} is observed, and this condition is defined as hypobaric hypoxia. It is known that oxygen is the fundamental part of electron transport chain for energy production in cells, so complex circulatory, respiratory, and neuroendocrine systems have been developed in people to allow oxygen levels to be precisely maintained, since an excess or deficiency may result in death of cells, tissue or organism. A few years ago, it was discovered that all nucleated cells sense and respond to hypoxia through the hypoxia-inducible factor 1, a gene's expression's master regulator for oxygen homeostasis.[2] Normally, when the lungs are submitted to high altitude hypoxia exposure, several acute physiologic things happen (ie, cardiac and systemic pulmonary vascular responses).

In this article the attention has been focused on the response of the right heart pulmonary circulation unit in the case of hypobaric hypoxia exposure.

PULMONARY CIRCULATION INTRINSIC RESPONSE TO HYPOXIA

Pulmonary circulation is a low pressure, high flow circuit. These characteristics are crucial, because

Disclosure: The author has nothing to disclose.
Department of Institute of Clinical Physiology, National research Council, Via Moruzzi 1, Pisa 56214, Italy
E-mail address: lorenza@ifc.cnr.it

Heart Failure Clin 14 (2018) 333–337
https://doi.org/10.1016/j.hfc.2018.02.008

they prevent fluid from moving out from the pulmonary vessels into interstitial space, and allow the right ventricle to operate at minimal energy cost. Hypoxia exposure induces pulmonary vasoconstriction as observed by von Euler and Liljestrand in the cat.[3] This is an adaptive vasomotor response in case of lungs' localized hypoxia (ie, pneumonia or atelectasis) to redistribute blood to ventilated lung segments, but in altitude environment, the hypoxic pulmonary vasoconstriction causes a significant increase in pulmonary resistance and pulmonary artery pressure.

Mechanisms of Hypoxic Pulmonary Vasoconstriction

The hypoxic pulmonary vasoconstriction is an active process, particularly involving the small muscular resistance pulmonary arteries, and can be related to different mechanisms. The hypoxic contraction is intrinsic to pulmonary smooth cells mediated by endothelium-dependent and -independent mechanisms. One of the most important mechanisms is mediated by increased influx of Ca^{2+} within the cell through hypoxic inhibition of voltage-gated K+ channels (Kv).[4] Elevation of intracellular Ca^{2+} elicits contraction, principally via activation of Ca^{2+} -calmodulin-dependent myosin light chain kinase, can also regulate this response. Moreover endothelin-1,[5] angiotensin II,[6] arachidonic acid metabolites,[7] and sympathetic increases are other possible causes for hypoxic pulmonary vasoconstriction.[8]

To better define the hypoxic pulmonary vascular response, many integrative physiology studies were performed in healthy and diseased subjects. In patients with chronic pulmonary obstructive disease, it has been shown that pretreatment with nifedipine, an L-type, voltage-gated Ca^{2+} channels inhibitor, attenuated of 50% the hypoxia pulmonary vascular resistance without effect on systemic vascular resistance.[9] The results of this study underlined that the hypoxic pulmonary vasoconstriction is due largely to Ca2+ influx via L-type calcium channel that is an endothelium-independent mechanism. Interestingly the hypoxic pulmonary vasoconstriction elicited by hypoxia can be impaired by respiratory alkalosis caused by hyperventilation,[10] and this behavior could be useful when healthy people are exposed to a high-altitude environment.

Hypoxic pulmonary vasoconstriction has been shown to be effective in the case of lung disease (pneumonia or atelectasis) to shift the blood flow away from atelectatic lung,[11] but it is fundamental also in fetal pulmonary circulation.[12] Moreover, hypoxic pulmonary vasoconstriction is implicated in the pathophysiology of several diseases; one of the most studied is high-altitude pulmonary edema, a life-threatening pathology that can affect healthy people at an altitude higher than 2500 m.

Healthy and Asymptomatic Subjects Exposed to Hypobaric Hypoxia

In a human study, it was shown that isocapnic hypoxemic exposure elicited hypoxic pulmonary vasoconstriction with increasing in pulmonary artery pressure and pulmonary vascular resistance in minutes and reaching its maximum after 15 to 20 minutes; moreover after 40 minutes, there was reported a second gradual rising lasting constant between 2 and 8 hours and a return to normal values in normoxic conditions.[13] The hypoxic pulmonary vasoconstriction was not potentiated by repeated hypoxic challenges. Maggiorini and colleagues[14] some years ago performed a right heart catheterization with pulmonary hemodynamic measurements in 30 subjects ascended in less than 24 hours from 1130 m to 4559 m. The mean pulmonary artery pressure and pulmonary capillary pressure increased in controls and in high-altitude pulmonary edema-susceptible subjects, and in particular, the value of 19 mm Hg for pulmonary capillary pressure was a threshold for lung edema development. The increase in pressure was due to constriction, and in particular, hypoxic pulmonary venous constriction might offer an explanation for increased pulmonary capillary pressure. During high-altitude exposure, lungs are exposed to hypoxic conditions, but intrinsic hypoxic pulmonary vasoconstriction response is inhomogeneous as hypothesized by Hultgren 40 years ago,[15] and then confirmed with lung imaging perfusion techniques either in animal or human study.[16,17] Dehnert and colleagues[18] studied subjects with high-altitude pulmonary edema history compared with controls in normoxia and after 2 hours of normobaric hypoxia exposure (Fio_2 12%) using a dynamic contrast-enhanced MRI technique allowing the assessment of the perfusion of the regional and entire lung. During normoxia, both groups showed a comparable degree of lung tissue perfusion inhomogeneity that increased during hypoxia exposure, in particular in high-altitude pulmonary edema subjects, but present also in control subjects.

Possible mechanisms accounting for this nonhomogeneous hypoxic pulmonary vasoconstriction could be linked to the baseline inhomogeneity for ventilation-perfusion ratio in the lung with higher hypoxic vasoconstriction in segments where there is low ventilation compared with perfusion.[16] Other hypotheses are regional