Editorial

Review Focus Series

Hypoxia in lung vascular biology and disease

Norbert Weissmann, Friedrich Grimminger, Werner Seeger

* University of Giessen Lung Center (UGLC), Medical Clinic II and V, Justus-Liebig-University Giessen, Klinikstrasse 36, 35392 Giessen, Germany

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With the evolution of photosynthesis, organisms had to cope with a dramatic environmental change: the presence of oxygen. Despite the initial toxicity of this gas, the presence of molecular oxygen offered a more effective energy metabolism. As a result, animals and humans require oxygen to survive, and a shortage of oxygen, hypoxia, can evoke life-threatening conditions. To maintain an optimal energy supply for the body, the lung is the first-line organ functioning as an interface between the body and the environment. This organ is the focus of an overview of the various aspects of “Hypoxia in the Pulmonary Circulation” in this Review Focus Series.

The lung structure is designed to achieve a very rapid and effective gas exchange. This is accomplished by two components, a large gas exchange surface and an extremely thin diffusion barrier between the alveolar gas and the blood [1]. The large capillary surface and the fragile diffusion barrier require a low blood pressure in the lung compared to the systemic circulation. In fact, pulmonary arterial blood pressure ranges <20 mmHg in healthy humans to prevent the risk of lung oedema and bleeding. In addition to the structural components, lung physiology is important to assure an efficient gas exchange. Even in healthy subjects, alveolar ventilation has been proven to be heterogeneous. This heterogeneity is compensated by an adaptation of the local blood flow to the regional ventilation that is achieved by a local vasoconstriction in the precapillary vessels of underventilated and thus hypoxic areas of the lung. This hypoxic pulmonary vasoconstrictor response, also known as the von Euler–Liljestrand mechanism, shifts blood from poorly to well ventilated regions of the lung [2]. However, under conditions of general alveolar hypoxia, permanent vasoconstriction throughout the lung induces pulmonary hypertension. If general alveolar hypoxia becomes chronic, pulmonary hypertension is then morphologically fixed by a vascular remodelling process, including proliferation and reduced apoptosis of various lung vascular cells.

In contrast to this slowly developing process of vascular remodelling, rapid ascent to high altitude and thus to a hypoxic environment can induce life-threatening pulmonary oedema by an abrogation of the integrity of the alveolo-capillary barrier. Despite the importance of both the acute and the chronic effects of hypoxia in lung physiology and pathophysiology, the underlying oxygen sensing and signal transduction processes are not yet fully resolved. Elucidation of such mechanisms will allow development of new therapeutic strategies targeting hypoxia-associated diseases of the pulmonary vasculature.

Against this background, this Review Focus presents several overviews covering the diverse aspects of hypoxia for lung physiology, pathophysiology, and disease.

Focussing on acute oxygen sensing mechanisms, we summarize the current knowledge about oxygen sensing in hypoxic pulmonary vasoconstriction [3] (HPV). As outlined above, HPV is essential to maintain pulmonary gas exchange, especially under conditions of disturbed local alveolar
ventilation. Perturbations to HPV, such as those occurring in pneumonia, the adult respiratory distress syndrome, and liver failure, may result in hypoxemia. Deciphering the signalling pathways underlying this basic physiological mechanism could suggest novel approaches to address both failure in HPV resulting in hypoxemia and permanent activation of HPV resulting in pulmonary hypertension. In this article, the current oxygen sensing concepts involving mitochondria, NADPH oxidases, and cytochrome P450 enzymes as well as the role of reactive oxygen species are addressed. In a complementary review, Weir and Olschewski then summarize the role of ion channels in the acute and chronic responses of the pulmonary vasculature to alveolar hypoxia [4]. Although ion channels are not suggested to act as oxygen sensors themselves, potassium channels and calcium channels play a key role in HPV. There is no doubt that hypoxia inhibits several potassium channels, leading to membrane depolarization and contraction of pulmonary arterial smooth muscle cells. This contraction process involves a rise in the intracellular \( \text{Ca}^{2+} \) concentration. \( \text{Ca}^{2+} \) sensitization has been suggested to be involved in this process. Weir and Olschewski not only summarize the current knowledge about the role of these channels in the acute vascular effects of hypoxia, but they also address the role of these channels in chronic hypoxia and thus the vascular remodelling process that morphologically stabilizes pulmonary hypertension [5].

In addition to the role of ion channels, a variety of mediators, such as endothelin-1, NO, erythropoietin, serotonin, VEGF, and PDGF, have been suggested to be involved in the vascular remodelling process of hypoxia-induced pulmonary hypertension. Interestingly, a variety of the mediators suggested to be involved in this process are under control of the hypoxia-inducible transcription factor HIF. In fact, about 2–5% of the whole human genome is suggested to be controlled by HIF. Fandrey, Gorr, and Gassmann highlight the current knowledge on the oxygen sensing process regulating this important transcription factor in their contribution [6]. Notwithstanding the importance of this transcription factor for survival, physiology, and pathophysiology under hypoxia, the oxygen sensing process regulating HIF was only poorly understood until recently. The remarkable progress made in this area is thoroughly addressed in the overview by Fandrey and colleagues.

Picking up these threads in next month’s issue, Ghofrani et al. summarize the current state-of-the-art in the therapy of hypoxia and non-hypoxia-induced pulmonary hypertension [7]. After introducing the different categories of pulmonary hypertension, this review then highlights the currently established therapies with \( \text{Ca}^{2+} \) channel blockers, prostanoids, PDE 5 inhibitors, and endothelin receptor antagonists. It becomes clear from this review that for therapy of pulmonary hypertension, pulmonary as well as an intrapulmonary selectivity of the respective drugs is desirable: systemic side-effects (i.e. a decrease in systemic arterial blood pressure) as well as a deterioration of gas exchange by an antagonism of HPV in poorly ventilated lung areas have to be avoided. In addition to the vasodilatory therapy, the promising new approach of anti-proliferative treatment of pulmonary hypertension is highlighted.

Finally, Marco Maggiorini gives a thorough overview about the third (besides vasoconstriction and remodelling) effect of hypoxia on the pulmonary vasculature: high altitude-induced pulmonary oedema [8] (HAPE). HAPE strikes almost every second mountaineer and trekker during rapid ascent to altitudes above 4000 m. The hallmark of HAPE is an excessive pulmonary arterial pressure with consecutive pulmonary oedema. In this review, the pathophysiological background, the factors contributing to HAPE, and its prevention and therapy are outlined.

We are convinced that this comprehensive overview about the diverse aspects of hypoxia in the pulmonary circulation — vasoconstriction, vascular remodelling, and pulmonary hypertension as well as mismatch of perfusion and ventilation and HAPE — will be attractive to both basic scientists and clinicians and enhance their understanding of the fundamental role of hypoxia in lung biology and disease.

References