In 1946, Ulf von Euler and Goran Liljestrand published revolutionary findings on the impact of hypoxia as a stimulant for vasoconstriction in the pulmonary circulation. More than 50 years later, exploring the mechanistic basis for this relationship is still a vital area of research. Among the many factors involved in the development of pulmonary hypertension in disease states, hypoxic pulmonary vasoconstriction and vascular remodeling are the most influential dynamic factors. The January through March 2005 issues of the Journal will address very fundamental factors contributing to the development of pulmonary hypertension and associated physiological conditions with a series of original research and mini-review articles that focus on “Pulmonary Circulation and Hypoxia.”

In a Historical Perspectives article entitled “Insight by Peruvian scientists into the pathogenesis of human chronic hypoxic pulmonary hypertension,” Drs. J. Reeves (deceased 15 September 2004) and R. Grover reviewed the groundbreaking investigations of a team of Peruvian scientists led by Dante Penaloza in the 1950s and 1960s. Dr. Penaloza and his team were the first to demonstrate chronic hypoxic pulmonary hypertension in humans, showing that arteriolar medial hypertrophy leads to hypertension. These investigators also examined the development and regression of hypertension over time and its relation to age and disease. Their findings have been verified by numerous subsequent studies, and yet the details surrounding this remarkable body of scientific work are neither widely known nor appreciated. Drs. Reeves and Grover highlight this still timely work that, despite its important impact to research in the area of hypoxic pulmonary hypertension, has gone largely uncelebrated for decades.

In a mini-review entitled “Hypoxic pulmonary vasoconstriction,” Dr. R. Moudgil and colleagues present a critical appraisal of theories of the mechanisms of hypoxic pulmonary vasoconstriction, namely, the roles of a redox-based oxygen sensor and voltage-gated ion channels. As an adaptive vaso-motor response to alveolar hypoxia, hypoxic pulmonary vasoconstriction redistributes blood to optimally ventilated lung segments by an active process of vasoconstriction, particularly involving the small, muscular resistance pulmonary arteries. Although hypoxic pulmonary vasoconstriction is modulated upstream by the endothelium and downstream by Ca\(^{2+}\) sensitization of the contractile apparatus (Rho kinase), the primary mechanism of hypoxic pulmonary vasoconstriction is a redox-based oxygen sensor that generates a diffusible redox mediator. This mediator is withdrawn under hypoxic conditions, leading to hypoxic inhibition of voltage-gated K\(^{+}\) channels in the pulmonary artery smooth muscle cells. Inhibition of such oxygen-sensitive K\(^{+}\) channels allows influx of Ca\(^{2+}\) via voltage-gated Ca\(^{2+}\) channels, thereby regulating vascular tone.

In a mini-review entitled “Hypoxic pulmonary vasoconstriction: redox events in oxygen sensing,” Drs. G. Waypa and P. Schumacker elaborate on the role of mitochondria in hypoxic pulmonary vasoconstriction. Although mitochondria are thought to play a key role as the site of oxygen sensing underlying hypoxic pulmonary vasoconstriction, two seemingly contradictory theories of how mitochondria react to decreased partial oxygen pressure (P\(\text{O}_2\)) have been proposed. One theory proposes that decreased rate of generation of mitochondrial reactive oxygen species (ROS) coincides with a drop in P\(\text{O}_2\) and results in a decrease in oxidant stress and accumulation of reducing equivalents that inhibit voltage-gated K\(^{+}\) channels, depolarize the membrane, and allow influx of Ca\(^{2+}\). The second theory suggests that hypoxic conditions stimulate increased mitochondrial ROS, triggering the release of intracellular Ca\(^{2+}\) stores, recruiting Ca\(^{2+}\) channels, and causing contraction.

In a mini-review entitled “Hypoxic pulmonary vasoconstriction: role of ion channels,” Dr. J. Mauban and colleagues offer a review of the basic cell biology of hypoxic pulmonary vasoconstriction, including the roles of ion channels and intracellular Ca\(^{2+}\). Whereas acute hypoxia stimulates vasoconstriction of the pulmonary arteries, chronic hypoxia induces structural remodeling of those arteries. Intracellular Ca\(^{2+}\) is thought to play a central role in both pulmonary vasoconstriction brought on by acute hypoxia and chronic hypoxia-induced remodeling of the vasculature. These authors discuss how K\(^{+}\) and Ca\(^{2+}\) channels are involved in modulating Ca\(^{2+}\) homeostasis (i.e., sarcolemmal influx and intracellular release) and membrane potential during the vasoconstrictive and proliferative responses to hypoxia.

In the February issue, in a mini-review entitled “Hypoxia, leukocytes, and the pulmonary circulation,” Dr. K. Stenmark and colleagues review evidence for the increased expression of lung inflammatory cytokines, chemokines, and adhesion molecules and accumulation of leukocytes within both the lungs and lung blood vessels under moderate hypoxic conditions. For most mammals, including humans, extended exposure to either persistent or intermittent low oxygen concentrations induces chronic pulmonary hypertension and pulmonary vascular remodeling. Most studies investigating the development of chronic pulmonary hypertension and vascular remodeling have focused on resident smooth muscle cells or adventitial fibroblasts. However, an accumulating body of evidence indicates that nonresident circulating cells, for example, monocytes or fibroblast progenitor cells, may contribute to remodeling. Recent studies of other pathophysiological conditions of the lung, such as fibrosis in asthma, have shown that nonresident cells may contribute significantly to increases in cell mass and accumulation of extracellular matrix protein, both of which are characteristic of the pulmonary arteries in chronic hypoxic pulmonary hypertension.

In a March mini-review entitled “Remodeling of the pulmonary vasculature in chronic hypoxia,” Dr. M. Rabinovitch explores the role of elastolytic enzyme in the pathobiology of pulmonary vascular remodeling and also addresses the relevance of new data concerning aberrant gene regulation by redox alterations. Chronic hypoxia stimulates remodeling of the pulmonary circulation and leads to development of pulmonary hypertension. When hypoxic conditions are remedied, hypertension tends to regress. In lung disease, blood flow inequalities and tissue loss exacerbate remodeling of the vasculature, and the condition becomes far less likely to be reversible. Neuromuscularization of peripheral arteries, medial and adventitial thickening of proximal arteries, and loss of distal vessels contribute to vascular remodeling. Thickening of the adventitia may occur when stem cells emigrate from the
angiogenic vasculature. In addition to vasoactive mediators such as endothelin, possible mediators of vascular remodeling may include hypoxia inducible factor, hemoxygenase, elastase inhibitor elafin, vascular endothelial growth factor, nitric oxide synthase, and K⁺ channel activity.

In the March issue, in a mini-review entitled “Physiological aspects of high altitude pulmonary edema,” Dr. P. Bärtsch and colleagues discuss factors involved in the development of high altitude pulmonary edema. Rapid, abnormally excessive rise in pulmonary artery pressure caused by hypoxic pulmonary vasoconstriction is the crucial factor in the pathophysiology of high altitude pulmonary edema. The physiological relevance of the von Euler-Liljestrand reflex or pulmonary arteriolar vasoconstriction in healthy humans who ascend to high altitude has not yet been fully understood. Moderately elevated pulmonary arterial pressure may serve to optimize oxygen delivery by recruiting ventilated, but not blood-perfused, lung areas. However, an excessive rise in pulmonary pressure may be harmful and may lead to high-altitude pulmonary edema, which can occur after rapid ascent without proper acclimatization. Such high pulmonary pressure may also result in subacute mountain sickness, also known as congestive right heart failure of high altitude. In Tibetans, the human population best adapted to life at high altitude, hypoxic pulmonary vasoconstriction has virtually vanished, suggesting that it may be a physiological disadvantage at high altitudes and that it can be abolished without deleterious consequences.

In a mini-review entitled “Comparative physiology of hypoxic pulmonary hypertension: historical clues from Brisket disease,” Dr. Jann Rhodes offers a review of inter- and intraspecies variability in pulmonary vascular remodeling in response to chronic hypoxia. The variable nature of the pulmonary circulatory response to hypoxia both within and among species is one of the more puzzling aspects of the pulmonary circulation. The bovine species was the first animal model used to study hypoxic pulmonary hypertension and became the springboard for studying the disorder in other species. Factors that contribute to variability in chronic hypoxia-induced pulmonary vascular remodeling include thickness of the medial layer of small pulmonary arteries, presence or absence of collateral ventilation, age, gender, and evolutionary history. However, despite all that is known, the specific mechanisms that differentiate hypo- from hyperresponders have yet to be elucidated. Recent studies indicate that a new hypoxia-inducible factor-1 splice variant, mast cell density, expression of transforming growth factor-β1, circulating vascular progenitor cells, and vascular smooth muscle cell heterogeneity may be potential mechanisms. Understanding these mechanisms that determine why some people and animals exhibit a marked susceptibility to hypoxia is an important endeavor and one with far-reaching implications.

The Associate Editors and I hope that this Highlighted Topics series will serve to promote work aimed at understanding the mechanisms of the underlying effects of hypoxia on pulmonary circulation. As always, we welcome the publication of future work in this still vital area of research in the *Journal of Applied Physiology*.

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