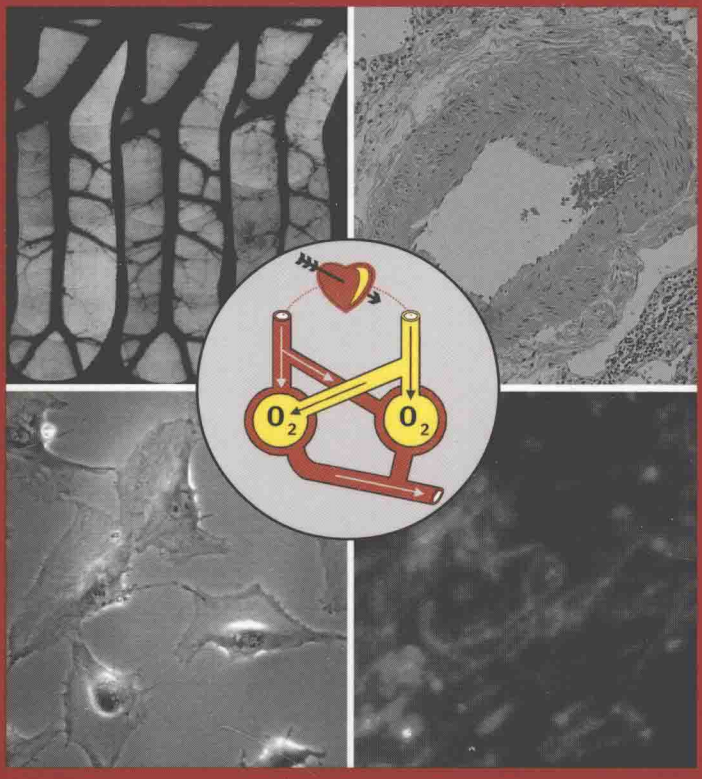
Hypoxic Pulmonary Vasoconstriction

Cellular and Molecular Mechanisms



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Preface

Hypoxic pulmonary vasoconstriction (HPV) serves a regulatory function by matching perfusion to ventilation and shunting blood flow away from the poorly oxygenated regions of the lung. HPV is a critical physiological mechanism of the lung to ensure maximal oxygenation of the venous blood in the pulmonary artery. Persistent alveolar hypoxia, however, causes pulmonary hypertension which is characterized by sustained pulmonary vasoconstriction and pulmonary vascular remodeling. The hypoxia-mediated pulmonary hypertension causes right heart failure in patients with a variety of cardio-pulmonary diseases, including chronic obstructive pulmonary disease, congenital heart disease, and mountain sickness. Over the last decade, considerable progress has been made in understanding the cellular and molecular mechanisms involved in HPV and hypoxia-induced pulmonary vascular remodeling. These significant findings provide an essential basis to specify the precise sequences of events of HPV, to identify the etiology of hypoxia-mediated pulmonary hypertension, and to develop new therapeutic approaches for patients with pulmonary hypertension.

The major objective of this book is to provide a timely and long lasting guide for investigators in the fields of cardiovascular physiology and pathophysiology, pulmonary vascular disease, and high-altitude physiology and medicine. This will establish a solid scientific foundation for subsequent applications in clinical practice. The book is divided into eight sections: I. Physiology and pathophysiology of HPV; II. Role of intracellular Ca^{2+} and Ca^{2+} sensitivity in HPV; III. Role of ion channels in HPV; IV. Role of the endothelium in HPV; V. Mechanisms of oxygen sensing in the pulmonary vasculature; VI. Oxygen-sensing mechanisms in other organs and tissues; VII. Pathology and mechanisms of hypoxia-induced pulmonary hypertension; and VIII. Experimental models for the study of HPV.

Subsections in each of the main sections address critical aspects related to hypoxia-induced pulmonary vasoconstriction and pulmonary hypertension. Section I highlights the physiological function (Chapter 1) and heterogeneity (Chapter 2) of HPV, as well as the physical principles of pulmonary circulation, gas exchange, and HPV and their correlation with gene actions (Chapter 3). Intracellular Ca^{2+} is not only a major trigger for smooth muscle contraction, but also an important signal transduction element that mediates gene expression, protein synthesis, cell migration, and cell proliferation. Section II discusses how intracellular Ca^{2+} signals are regulated by hypoxia to induce HPV and pulmonary vascular smooth muscle cell proliferation. Four chapters are devoted to aspects of recent findings on the roles of Ca^{2+} sparks (Chapter 4), agonist-mediated Ca^{2+} transients (Chapter 5), Ca^{2+} mobilization from the sarcoplasmic reticulum (Chapter 6), and Ca^{2+} sensitization (Chapter 7) in the development of HPV. How acute hypoxia regulates cytoplasmic, nuclear, and intracellularly-stored Ca^{2+}

concentration in pulmonary artery smooth muscle cells is also discussed in this section. Section III is designed to explore the role of ion channels in HPV. Chapter 8 discusses the functionally expressed ion channels along with their regulation in the pulmonary vasculature. Two chapters focus on the regulation of K^+ channel activity by a mitochondrial redox sensor (Chapter 9) and by acute exposure to hypoxia (Chapter 10). The functional role of K^+ channels (especially voltage-gated K^+ channels) in regulating membrane potential and cytoplasmic Ca^{2+} concentration (via altering activity of voltage-gated Ca^{2+} channels) in pulmonary artery smooth muscle cells, the transcriptional regulation of K^+ channel genes by chronic hypoxia, and the role of dysfunctional K^+ channels in the development of hypoxia-induced pulmonary hypertension are also discussed extensively in Chapters 9 and 10. Furthermore, the contribution of transient receptor potential channels and capacitative Ca^{2+} entry to the development of HPV is reviewed in Chapter 11. Section IV includes an elegant discussion on the role of endothelium in HPV.

Section V is designed to describe the putative and potential mechanisms of oxygen sensing in the pulmonary vasculature. It is focused on oxygen radicals (Chapters 13 and 14), mitochondrial oxidative phosphorylation chain (Chapters 15 and 17), cellular redox status (Chapter 16), and cADPR accumulation (Chapter 18). In addition to the pulmonary vasculature, there are many tissues and cells whose function is regulated by oxygen. Section VI is focused on the cellular mechanisms involved in oxygen-sensitive gene expression (Chapter 19), as well as the oxygen sensing mechanisms and oxygen-sensitive ion channels in arterial chemoreceptor (Chapter 20), chromaffin cells (Chapter 21), and pheochromocytoma cells (Chapter 22). Section VII discusses current knowledge on the etiology and pathological characterization of hypoxia-induced pulmonary hypertension and right heart failure. It is focused on the hypoxia-sensitive agonists, mitogens, and transcription factors found in animal and human lung tissues (Chapters 25, 28, and 29); the role of the heterogeneity in hypoxia-induced pulmonary vascular smooth muscle cells proliferation (Chapter 26); the potential mechanisms involved in pulmonary vascular remodeling and hypoxic pulmonary hypertension (Chapters 23, 24, and 28); the pathophysiology and treatment of persistent pulmonary hypertension in the newborn (Chapter 27); and the strain difference of hypoxia-induced pulmonary hypertension (Chapter 30). Section VIII includes three chapters on how to use animal and *in vivo* models (Chapter 31) and transgenic animal models (Chapter 32) for studying HPV and hypoxia-mediated pulmonary hypertension. A chapter on patch clamp and fluorescence microscopy techniques (Chapter 33) for measuring ion channel currents and intracellular Ca^{2+} is included.

In summary, this book not only covers the current state-of-the-art findings relevant to cellular and molecular processes of hypoxic pulmonary vasoconstriction but also provides the underlying conceptual basis and knowledge regarding etiological mechanisms and experimental therapeutics for

hypoxia-mediated pulmonary hypertension. I hope this book will be something of use not only to those who are experienced basic science investigators in the research fields of hypoxic cardiopulmonary physiology and pathophysiology and pulmonary vascular diseases, but also to a large community of clinicians or physician scientists whose primary subspecialty is in pulmonary and critical care medicine, cardiology, cardiothoracic surgery, environmental medicine, and sports medicine.

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Jason X.-J. Yuan
San Diego, California
October, 2003

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