RESEARCH COLLECTION ON

PULMONARY HYPERTENSION

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Chapters from books edited by: **Jean Elwing** and **Roxana Sulica**

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Preface

This book draws together high-quality research from experts worldwide to give the reader an informed and up-to-date understanding of pulmonary hypertension, a relatively rare but serious condition that can cause heart failure and death. The book includes introductory-level discussions as well as more advanced presentations of emerging approaches and challenges to provide a comprehensive resource for this condition. The first part of the book considers clinical presentation, pathophysiology, diagnosis and management. This section includes an overview of pulmonary arterial hypertension, as well as discussions of the pathogenesis of pulmonary hypertension, the participation of nitric oxide in pathophysiology and treatment, and perioperative considerations for patients with the condition. The second part of the book presents new research and clinical challenges. Topics include dyspnoea in pulmonary hypertension, clinical syndromes associated with pulmonary hypertension in new-born babies and considerations of pulmonary hypertension in pregnancy. The book will be useful for students, researchers and practitioners with specialist interests in cardiopulmonary science and medicine.

PULMONARY HYPERTENSION

Edited by **Jean M. Elwing** and **Ralph J. Panos**

Pulmonary Arterial Hypertension: An Overview

Saleem Sharieff

Additional information is available at the end of the chapter

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1. Introduction

Pulmonary hypertension (PH) is a hemodynamic state defined by a resting mean pulmonary artery pressure (PAP) at or above 25 mm Hg.[1] with normal left ventricular filling pressure (mean pulmonary wedge pressure) 15 mmHg or less.

Pre-capillary PH is defined as mean PAP ≥25 mm Hg in association with PAOP ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units. This include group 1, 3, 4 and 5 (Table 1). [2] Post-capillary PH (group 2 as shown in Table 1) is characterized by a mean PAP ≥25 mm Hg in association with PAOP >15 mm Hg and PVR ≤3 Wood units.[3] This differentiation in pre- and post-capillary PH is important as it narrows the differential diagnosis and also has treatment implications.

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia

1.5 Persistent pulmonary hypertension of the newborn

1=. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease

2.1. Systolic dysfunction

2.2. Diastolic dysfunction

2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4. Sleep-disordered breathing

3.5. Alveolar hypoventilation disorders

3.6. Chronic exposure to high altitude

3.7. Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

5.1. Hematologic disorders: myeloproliferative disorders, splenectomy

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis.

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

Adapted from Simonneau et al. Updated clinical Classification of pulmonary hypertension. J Am Coll Cardiol 2009; Vol. 54 (1): S43–54

Adapted with permission from ELSEVIER.(ref 11)

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

2. Epidemiology

Pulmonary arterial hypertension (PAH) is a rare disease, with an estimated prevalence of 15-50 cases per million.[4] Idiopathic PAH (IPAH) has an annual incidence of 1-2 cases per million people in the US and Europe and is 2-4 times as common in women as in men.[5], [6] The REVEAL Registry demonstrates a 4.1:1 female-to-male ratio among patients with IPAH, and a 3.8:1 ratio among those with associated pulmonary arterial hypertension (APAH). [4] The mean age at diagnosis is around 45 years.[7] IPAH accounts for at least 40% of cases of PAH, with APAH accounting for the majority of the remaining cases. [8]

The REVEAL Registry population tends to be overweight, with a BMI of 29 kg/m[2]; hence, obesity may be a risk factor for the development of PAH. A variety of comorbid conditions

were identified, including systemic hypertension, obstructive lung disease, sleep apnea, and prior venous thrombo-embolism, which were not believed to represent the principal cause for the patients' pulmonary hypertension. [6]

The median interval from symptom onset to diagnosis remains unacceptably high at 1.1 years in current registry data, [6] unchanged from the experience from the 1980's.[9] Overall survival has improved somewhat, with 3-year survival of 48% in the NIH registry [10], compared to 67% in both US [11] and French [12] contemporary registries.

3. Etiology

Pulmonary arterial hypertension (PAH) is comprised of idiopathic, heritable and associated forms. IPAH was previously referred to as primary pulmonary hypertension. During the 4th World Symposium on pulmonary hypertension in 2008 at Dana Point, California, USA, the group updated the Evian –Venice classification of 2003 of pulmonary hypertension based upon mechanism. [2] (Table 1)

4. Pathophysiology

PAH is a proliferative vasculopathy which is histologically characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, fibrosis and in-situ thrombi of the small pulmonary arteries and arterioles.[13], [14]

Genetic mutations — Predisposition to pulmonary vascular disease may be related to genetic mutations in the bone morphogenetic protein receptor type II (BMPR2), activin-like kinase type 1, and/or 5-hydroxytryptamine (serotonin) transporter (5HTT) genes. Abnormal BMPR2 may play an important role in the pathogenesis of IPAH, with up to 25 percent of patients with IPAH having abnormal BMPR2 structure or function. [15], [16], [17]

5. Pathobiologic basis of therapy

The pathophysiology of IPAH is not fully elucidated An elevated pulmonary vascular resistance seems to result from an imbalance between locally produced vasodilators and vasoconstrictors, in addition to vascular wall remodeling.

Three major pathobiologic pathways (nitric oxide, endothelin, and prostacyclin) play important roles in the development and progression of PAH.

5.1. Nitric Oxide (N.O)

The endothelium-derived relaxing factor nitric oxide (NO), a potent pulmonary vasodilator, is produced in high levels in the upper and lower airways by nitric oxide synthase II (NOSII)