

# Contents

**Preface: Challenges in Pulmonary Hypertension** **xv**

Alberto M. Marra, Alexander E. Sherman, Pietro Ameri, and Eduardo Bossone

**Mildly Elevated Pulmonary Hypertension: Gray Zone or Already a Disease?** **1**

Alberto M. Marra, Umberto Attanasio, Alessandra Cuomo, Carmen Rainone, Anna D'Agostino, Antonio Carannante, Andrea Salzano, Eduardo Bossone, Antonio Cittadini, Carlo Gabriele Tocchetti, and Valentina Mercurio

During the sixth World Symposium on Pulmonary Hypertension, the threshold of mean pulmonary arterial pressure (mPAP) for the definition of pulmonary hypertension (PH) has been lowered to a value of greater than 20 mmHg, measured by means of right heart catheterization at rest. In this review, we aim at describing the impact of the new definition of PH, analyzing the available data from the latest scientific literature concerning subjects with mPAP between 21 and 24 mmHg (defined as “mildly elevated PH”), discussing the impact of the new threshold for mPAP in the clinical practice, and highlighting the new perspectives in this field.

**Sex- and Gender-Related Aspects in Pulmonary Hypertension** **11**

Anna D'Agostino, Paola Guindani, Gerarda Scaglione, Alessandra Di Vincenzo, Sara Tamascelli, Riccardo Spaggiari, Andrea Salzano, Andrea D'Amuri, Alberto Maria Marra, Louise Pilote, and Valeria Raparelli

Biological sex and sociocultural gender are emerging as pivotal modifiers of health and diseases. Sex-based differences exist in the development, pathogenesis, and management of individuals with pulmonary arterial hypertension (PAH). The interplay between gender domains (ie, identity, roles, relations, and institutionalized gender) and PAH has been barely investigated. The aim of this narrative review is to describe up-to-date evidence on the integration of sex and gender in PAH research, highlighting areas for future investigation.

**Unusual Forms of Pulmonary Hypertension** **25**

Yuri de Deus Montalverne Parente, Natalia Fernandes da Silva, and Rogerio Souza

There are several forms of pulmonary hypertension that can be considered unusual not solely due to their prevalence but also due to their geographic distribution. The aim of this review is to highlight some of these forms, most of them classified within group 5 of the current pulmonary hypertension classification. This review also discusses on schistosomiasis-associated pulmonary hypertension, a prevalent form of pulmonary hypertension mostly limited to developing countries.

**Cardiopulmonary Exercise Testing in Pulmonary Arterial Hypertension** **35**

Alexander E. Sherman and Rajan Sagar

Cardiopulmonary exercise testing (CPET) is a comprehensive methodology well studied in pulmonary arterial hypertension (PAH) with roles in diagnosis, treatment response, and prognosis. Submaximal and maximal exercise data is a valuable tool in detecting abnormal hemodynamics associated with exercise-induced and resting pulmonary hypertension as well as right ventricular dysfunction. The increased granularity of CPET may help further risk stratify patients to inform prognosis and better individualize treatment decisions. This article reviews the most commonly implicated variables from CPET in PAH literature and summarizes the latest developments in CPET and exercise testing.

**Pulmonary Arterial Hypertension in Connective Tissue Diseases Beyond Systemic Sclerosis** 45

Christopher Lewis, Ryan Sanderson, Nektarios Vasilottos, Alexander Zheutlin, and Scott Visovatti

Pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD) (CTD-PAH) is a devastating condition that may progress rapidly to cause right ventricular dysfunction, resulting in significant morbidity and mortality. The pathobiology, epidemiology, natural history, early diagnosis, and treatment response of PAH associated with scleroderma (SSc-PAH) have been the subjects of intense research efforts over the previous decade. The success of these efforts has resulted in increased awareness and earlier detection of SSc-PAH. Practitioners are less aware of the risk of PAH associated with other CTDs; the aim of this article is to discuss the broader scope of CTD-PAH.

**Struggling Between Liver Transplantation and Portopulmonary Hypertension** 55

Arun Jose, Courtney R. Jones, and Jean M. Elwing

Portopulmonary hypertension (PoPH) is a progressive, ultimately fatal cardiopulmonary disease that occurs exclusively in patients with underlying portal hypertensive liver disease. PoPH outcomes are driven by both the severity of underlying liver disease and the degree of cardiac adaptation to elevated pulmonary pressures. The mainstay of treatment in PoPH is targeted pulmonary vascular therapy. Liver transplantation (LT) can be beneficial in some patients, but is associated with considerable risks in the PoPH population, and outcomes are variable. The optimal management strategy for PoPH, LT, or medical therapy alone, is unclear, and further research is needed to help guide clinical decision-making.

**Microscopic Examination of Clots from Percutaneous Mechanical Embolectomies in Pulmonary Embolism** 67

Vruksha Upadhyay, Shameek Gayen, Amandeep Aneja, Maruti Kumaran, Riyaz Bashir, Vladimir Lakhter, Joseph Panaro, Gary Cohen, Eduardo Bossone, Gerard Criner, and Parth Rali

Pulmonary embolism (PE) is a very common clinical entity with clinical symptoms that range from no symptom to complete hemodynamic collapse, sometimes with similar-appearing clot burden on computed tomographic pulmonary angiogram. Given highly variable clinical presentation, the authors wanted to investigate if there is clinical correlation based on the age of a clot with microscopic examination to clinical presentation. Thirteen thrombectomy aspirates from patients with an acute PE were microscopically analyzed. The goal was to age the thrombus based on histologic features and correlate it to clinical course.

**Pregnancy and Pulmonary Hypertension: From Preconception and Risk Stratification Through Pregnancy and Postpartum** 75

Jenny Y. Mei, Richard N. Channick, and Yalda Afshar

Pulmonary hypertension is one of the highest risk medical conditions in pregnancy and carries significant maternal morbidity and mortality as well as neonatal morbidity. Diagnosis is commonly delayed due to the nonspecific nature of early symptoms. Disease progression can lead to right ventricular failure, which carries mortality rates as high as 25% to 56%. Pregnancy-related complications arise from cardiac inability to accommodate increased plasma volume and cardiac output, decreased systemic vascular resistance, and hypercoagulability. Patients in this high-risk cohort necessitate preconception risk stratification and multidisciplinary care throughout their pregnancy and delivery planning.

**Genetics of High-Altitude Pulmonary Edema** 89

Christina A. Eichstaedt, Nicola Benjamin, Ding Cao, Eglė Palevičiūtė, and Ekkehard Grünig

High-altitude pulmonary edema (HAPE) is the main cause of nontraumatic death at high altitude. HAPE development is not only related to the mode and speed of ascent and the maximum altitude reached, but also individual susceptibility plays an important role. In susceptible individuals, hypoxic pulmonary vasoconstriction leads to exaggerated elevated pulmonary arterial pressures and capillary leakage in the lungs. Thus, this review provides an overview of studies investigating the genetic background in HAPE susceptibles by focusing on specific variants, entire genes, genome-wide signatures, or family studies.

**Use of Oral Anticoagulant Drugs in Patients with Pulmonary Hypertension** 97

Pablo Demelo-Rodriguez, Francisco Galeano-Valle, and Marco Proietti

Pulmonary hypertension (PH), in particular pulmonary arterial hypertension and chronic thromboembolic PH, burdens patients with relevant morbidity and mortality. The use of oral anticoagulants (OACs) seems able to mitigate the risk of adverse outcomes and death in these patients. Despite scarce evidence, the use of OAC is recommended to treat PH patients, mainly based on observational data. So far, data are still unclear about the impact of direct oral anticoagulant (DOACs), whereas vitamin K antagonists are the main drugs recommended. More data are needed to fully clarify the role of OAC and DOACs in PH patients.

**Management of COVID-19 in Patients with Pulmonary Arterial Hypertension** 107

Ioannis T. Farmakis and George Giannakoulas

In this review, we discuss the evidence regarding the course and management of COVID-19 in patients with pulmonary arterial hypertension (PAH), the challenges in PAH management during the pandemic and, lastly, the long-term complications of COVID-19 in relation to pulmonary vascular disease. The inherent PAH disease characteristics, as well as age, comorbidities, and the patient's functional status act synergistically to define the prognosis of COVID-19 in patients with PAH. Management of COVID-19 should follow the general guidelines, while PAH-targeted therapies should be continued. The pandemic has caused a shift toward telemedicine in the chronic care of patients with PAH. Whether COVID-19 could predispose to the development of chronic pulmonary hypertension is a subject of future investigation.

**Impact of Hormonal-Anabolic Deficiencies in Idiopathic Pulmonary Arterial Hypertension** 115

Alberto M. Marra, Anna D'Agostino, Andrea Salzano, Stefania Basili, Michele D'Alto, Eduardo Bossone, Antonio Cittadini, Carmine Dario Vizza, and Roberto Badagliacca

Anabolic deficiencies play a pivotal role in left-sided heart failure. Little is known about their impact on idiopathic pulmonary arterial hypertension (iPAH). Therefore, the aim of this study was to assess the impact of multiple hormone-metabolic deficiencies on clinical features and outcomes in idiopathic pulmonary arterial hypertension. We have demonstrated that the assessment of anabolic hormone levels in patients with iPAH allows the identification of a subpopulation with worse exercise capacity, pulmonary hemodynamics, right ventricular size, and function generating the hypothesis about the potential role of hormonal replacement therapy. These data should be confirmed by larger studies.

**How to Treat Right Heart Failure. Tips for Clinicians in Everyday Practice**

125

Giulia Crisci, Roberta D'Assante, Valeria Valente, Federica Giardino, Anna D'Agostino, Brigida Ranieri, Michele Arcopinto, Alberto M. Marra, Carmen Rainone, Michele Modestino, Salvatore Rega, Ludovica Fulgione, Chiara Sepe, Giuseppe Caruso, Eduardo Bossone, Andrea Salzano, and Antonio Cittadini

In recent years, several observations reported that intolerance of physical exertion and other cardinal symptoms in heart failure (HF) are closely related to the functionality of the right ventricular (RV), regardless of left heart. It has been demonstrated that the RV dysfunction complicates the course, aggravates the quality of life, and increases the mortality of HF patients. The present review is aimed to report tips physicians about the current therapeutic management of right HF during acute stage and chronic phase, shedding light on the RV and its failure and providing physicians with essential information for everyday clinical practice.

**Noncoding RNAs in Pulmonary Arterial Hypertension: Current Knowledge and Translational Perspectives**

137

Nadia Bernardi, Eva Bianconi, Andrea Vecchi, and Pietro Ameri

Several microRNAs and long noncoding RNAs contribute to pulmonary arterial hypertension (PAH) pathogenesis by impairing nitric oxide production, enhancing proliferation and migration and decreasing apoptosis of smooth muscle cells, and promoting endothelial-to-mesenchymal transition in pulmonary arteries. These noncoding RNAs (ncRNAs) could serve as both biomarkers and therapeutic targets for PAH. Nonetheless, the knowledge about their role in PAH is still incomplete. Furthermore, ncRNAs may vary across species and often act differently in different tissues and organs, and technical issues currently limit the implementation of ncRNA-based technologies. Additional studies are warranted to finally bring ncRNA into the clinical arena.