Expert Review of Respiratory Medicine

ISSN: 1747-6348 (Print) 1747-6356 (Online) Journal homepage: informahealthcare.com/journals/ierx20

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To cite this article: Lewis J Rubin & Nicholas W Morrell (2011) New frontiers in pulmonary hypertension, Expert Review of Respiratory Medicine, 5:2, 139-140, DOI: 10.1586/ers.11.22

To link to this article: https://doi.org/10.1586/ers.11.22

Published online: 09 Jan 2014.

www.expert-reviews.com/toc/ers/5/2

New frontiers in pulmonary hypertension

Expert Rev. Resp. Med. 5(2), 139–140 (2011)

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"This special focus issue provides the reader with a broad but in-depth overview of important areas of pulmonary vascular disease that are rapidly evolving and are, therefore, of special interest and worthy of attention."

There are few areas in respiratory medicine in which a greater interest and understanding has led to more novel therapies over the past two decades than pulmonary hypertension. In addition, breakthroughs in our understanding of the pathobiology of the condition have opened the door for the development of experimental therapies specifically targeting the cell and molecular abnormalities leading to disease. As a result, physicians and scientists representing a variety of disciplines, ranging from epidemiology, cardiopulmonary medicine and physiology, immunology, genetics, and cellular and molecular biology have become interested in disorders of the pulmonary circulation, leading to a burgeoning amount of new information regarding the localized and systemic disorders that affect the lung circulation and lead to the hypertensive phenotype. Our objective for this special focus issue is to provide the reader with state-of-the-art reviews and special reports of key developments in these areas, written by those who have contributed substantively to our current understanding and approaches. It is their work, among others, that has brought us to our current level of recognition and management of pulmonary hypertension, and will pave the way for future developments for this life-threatening condition.

In the first article of this series, Montani *et al.* detail the unique features of pulmonary veno-occlusive disease, an uncommon but severe form of pulmonary hypertension that has challenged clinicians both with respect to its diagnosis and management [1]. Their experience at a large referral center has led to increased recognition of the clinical features of this condition and has provided us with an aggressive, tailored management strategy [1].

Pulmonary hypertension can occur in the background of all forms of connective tissue disease but occurs most frequently in systemic sclerosis. Additionally, pulmonary hypertension complicating systemic sclerosis has become a leading cause of death from this condition. Mathai and Hassoun review the underlying pathobiology and novel emerging concepts regarding its pathogenesis and management of this progressive disease [2].

Pulmonary vascular disease in children may result from inherited, congenital or acquired disorders, all of which pose unique challenges to physicians. In their articles, Tibboel *et al.* and Rosenzweig and Zuckerman review key aspects of two conditions, vascular abnormalities of the newborn [3] and sickle cell disease [4], respectively. As these patients are now living longer owing to improved medical and surgical therapies, these articles are of importance to physicians caring for children and adults alike.

Viral infections, particularly HIV, have been recognized with increasing frequency to be associated with pulmonary hypertension. In addition to posing new challenges for the management of these patients, this observation has led to exciting work on the immunologic mechanisms that may underlie both viral- and nonviral-mediated pulmonary hypertension. Cicalini *et al.* review the clinical features of HIV-associated pulmonary hypertension [5], while Cool *et al.* provide a perspective on the role of altered T-cell immunity in HIV and other viral conditions associated with pulmonary vascular disease [6].

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 10.1586/ERS.11.22 ISSN 1747-6348

Cardiopulmonary exercise testing has evolved from a physiologic research tool to study normal and abnormal cardiopulmonary function to a clinical modality used to diagnose and follow patients with a variety of heart and lung diseases. Patients with established pulmonary hypertension manifest characteristic patterns of abnormal responses to exercise and, more recently, abnormalities in cardiopulmonary exercise testing parameters have been reported in subjects with early pulmonary vascular disease, when symptoms are frequently mild and nonspecific and diagnostic studies performed at rest may be unrevealing. Arena *et al.* review the physiologic principles of exercise testing as they apply to disorders of the pulmonary circulation in particular [7], while Frantz reviews the role of exercise hemodynamic evaluation in both early and advanced pulmonary hypertension. Frantz also presents a novel perspective on the potential role of continuous invasive hemodynamic monitoring as a guide to management [8].

There are presently eight approved medical therapies for pulmonary arterial hypertension that target one of three endothelial-based abnormalities: deficiencies in nitric oxide (NO) and prostacyclin, and excessive production of endothelin. Mukherjee and Howard provide a perspective on the emerging approach of combination therapy in order to target multiple pathways, much like the strategies applied in heart failure, HIV infection and cancer [9]. Since most large clinical trials to date have been placebo-controlled monotherapy studies, future trials will hopefully address unresolved questions regarding optimal selection and timing of combination therapy.

As mentioned earlier, the NO pathway is dysfunctional in pulmonary hypertension and poses an appealing target for novel therapeutic approaches since inhaled NO in its current iteration is cumbersome, expensive and impractical. Hagan and Pepke-Zaba review our current understanding of the effects and role of inhaled NO and provides a glimpse of novel approaches to targeting this pathway with NO-generating or prodrug compounds [10]. Kadowitz *et al.* present the rationale for targeting soluble guanylate cyclase as a means of enhancing the activity of cyclic GMP, the mediator through which NO exerts its potent biologic functions [11]. Ewert *et al.* detail their experience using iloprost, a prostacyclin analogue that is administered by inhalation, as part of a combination strategy for PAH [12].

While pulmonary hypertension can complicate a variety of respiratory diseases, patients with interstitial lung disease tend to experience more severe pulmonary hypertension than those with obstructive lung disease. The dual insult to both gas exchange and oxygen transport that is characteristic of interstitial lung disease-mediated PH causes severe limitations in physical activity as well as premature death. Shlobin and Nathan review the clinical and physiologic features of this condition and provide insight in current and future management [13].

In summary, we believe that this special focus issue provides the reader with a broad but in-depth overview of important areas of pulmonary vascular disease that are rapidly evolving and are, therefore, of special interest and worthy of attention. We are deeply appreciative to our colleagues who took time from the demands of their laboratories and clinics to prepare these outstanding articles for this issue. We hope that you find them as informative and stimulating as we have.

Financial & competing interests disclosure

Nicholas W Morrell has received a research grant from Novartis and has provided consultancy for Actelion and Novartis. Lewis J Rubin is a member of the Scientific Board of United Therapeutics and is a consultant for Actelion, Bayer-Schering, Pfizer, GeNo, Aires, Gilead and GlaxoSmithKline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Huertas A, Girerd B, Dorfmuller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: advances in clinical management and treatments. *Expert Rev. Resp. Med.* 5(2), 217–231 (2011).

2 Mathai SC, Hassoun PM. Pulmonary arterial hypertension associated with systemic sclerosis. *Expert Rev. Resp. Med.* 5(2), 267–279 (2011).

3 Sluiter I, Reiss I, Kraemer U, de Krijger R, Tibboel D, Rottier RJ. Vascular abnormalities in human newborns with pulmonary hypertension. *Expert Rev. Resp. Med.* 5(2), 245–256 (2011).

4 Zuckerman WA, Rosenzweig EB. Pulmonary hypertension in children with sickle cell disease. *Expert Rev. Resp. Med.* 5(2), 233–243 (2011).

5 Cicalini S, Chinello P, Petrosillo N. HIV infection and pulmonary arterial hypertension. *Expert Rev. Resp. Med.* 5(2), 257–266 (2011).

6 Cool CD, Voelkel NF, Bull T. Viral infection and pulmonary hypertension: is there an association? *Expert Rev. Resp. Med.* 5(2), 207–216 (2011).

7 Arena R, Guazzi M, Myers J, Grinnen D, Forman DE, Lavie CJ. Cardiopulmonary exercise testing in the assessment of pulmonary hypertension. *Expert Rev. Resp. Med.* 5(2), 281–293 (2011).

8 Frantz RP. Hemodynamic monitoring in pulmonary arterial hypertension. *Expert Rev. Resp. Med.* 5(2), 173–178 (2011).

9 Mukherjee B, Howard L. Combination therapy in pulmonary arterial hypertension: do we have the right strategy? *Expert Rev. Resp. Med.* 5(2), 191–205 (2011).

10 Hagan G, Pepke-Zaba J. Pulmonary hypertension, nitric oxide and nitric oxide-releasing compounds. *Expert Rev. Resp. Med.* 5(2), 163–171 (2011).

11 Lasker GF, Maley JH, Pankey EA, Kadowitz PJ. Targeting soluble guanylate cyclase for the treatment of pulmonary hypertension. *Expert Rev. Resp. Med.* 5(2), 153–161 (2011).

12 Ewert R, Gläser S, Bollmann T, Schäper C. Inhaled iloprost for therapy in pulmonary arterial hypertension. *Expert Rev. Resp. Med.* 5(2), 145–152 (2011).

13 Shlobin OA, Nathan SD. Pulmonary hypertension secondary to interstitial lung disease. *Expert Rev. Resp. Med.* 5(2), 179–190 (2011).