New Insights on Pulmonary Arterial Hypertension

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The 3rd World Symposium on Pulmonary Arterial Hypertension has been a forum for the presentation and discussion of overviews on several aspects of this devastating disease, including pathology and pathobiology, genetics, epidemiology, nomenclature and classification, diagnosis and assessment, medical treatments, interventional and surgical treatments and future directions.

This editorial will provide a brief overview of the new findings emerging in this field including new pathologic and pathobiologic concepts, changes in the clinical classification and in the diagnostic definitions. In addition, new treatment strategies and future perspectives will be discussed.

Key words: *Pulmonary hypertension. Endothelial dysfunction. Medical treatment.*

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Nuevas aportaciones en hipertensión arterial pulmonar

El Tercer Simposio Mundial sobre Hipertensión Arterial Pulmonar ha sido un foro para la presentación y discusión de diversos aspectos genéricos de esta grave enfermedad, como su anatomía patológica y su patobiología, sus características genéticas, su epidemiología, su nomenclatura y clasificación, su diagnóstico y evaluación, sus tratamientos médicos, sus tratamientos quirúrgicos y de intervención, así como las líneas futuras de investigación.

Este editorial recoge de manera breve los nuevos avances que están teniendo lugar en este campo, como son los nuevos conceptos anatomopatológicos y patobiológicos, las modificaciones en la clasificación clínica y los cambios en las definiciones diagnósticas. Además, se exponen las nuevas estrategias terapéuticas y las perspectivas futuras.

Palabras clave: *Hipertensión pulmonar. Disfunción endotelial. Tratamiento médico.*

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death.[1] The median life expectancy from the time of diagnosis in patients with idiopathic PAH (IPAH) without targeted treatments is 2.8 years.[2]

In recent years we have witnessed major advances in our understanding of the mechanism of disease development, in the diagnostic process and in the treatment of PAH.

The 3rd World Symposium on PAH held in Venice, Italy on June 24-26, 2003 has given the opportunity to evaluate multiple new findings into the pathogenesis and the management of this devastating disease. The scientific discussions were arranged in 7 Task Forces according to specific topics:

– Pathology and pathobiology.
– Genetics.
– Epidemiology, nomenclature, and classification.
– Diagnosis and assessment.
– Medical treatments.
– Interventional and surgical treatments.
– Future directions.

PATHOLOGY AND PATHOBIOLOGY

PAH includes IPAH[3] and pulmonary hypertension associated with various conditions such as collagen vascular diseases, congenital systemic-to-pulmonary shunts, portal hypertension and HIV infection.[4] All these conditions share virtually identical obstructive pathologic changes of the pulmonary vasculature.[5] Three main pathological pictures have been identified:[5] *a)* pulmonary arteriopathy; *b)* pulmonary occlusive venopathy, and *c)* pulmonary

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microvasculopathy. Pulmonary arteriopathy is characterized by medial hypertrophy, intimal thickening, and complex lesions such as plexiform lesions, colander lesions and arteritis with infiltration of inflammatory cells. Pulmonary occlusive venopathy accounts for a relatively small proportion of cases of PAH and is characterized by extensive and diffuse occlusion of pulmonary venules and veins of various sizes. Pulmonary arterioles can show remodeling with medial hypertrophy and intimal fibrosis. Pulmonary microvasculopathy is a rare condition characterized by localized capillary proliferation within the lung.

A variety of cellular abnormalities have been described in the pulmonary vasculature of PAH patients that may play important roles in the development and progression of the disease.[6] These include pulmonary endothelial dysfunction[7] characterised by altered synthesis of nitric oxide, thromboxane A_2, prostacyclin, and endothelin, impaired potassium channel and altered expression of the serotonin transporter in the smooth muscle cells and enhanced matrix production in the adventitia.[6] All these abnormalities both elevate vascular tone and promote vascular obstructive remodeling. The process of pulmonary vascular remodeling involves all vessel wall layers and is characterised by proliferation and obstructive changes that involve several cell types including endothelial, smooth muscle and fibroblast.[5] Even though many pathobiological mechanisms have been identified in the cells and in the tissues of PAH patients, the exact interactions between them in the initiation and progression of the pathologic processes are still not well understood.

Genetics

The identification of mutations in the bone morphogenetic protein receptor 2 (BMPR2) in the majority of cases (50%-60%) of familial pulmonary artery hypertension has been a major advance in the elucidation of the pathogenic sequence in PAH.[8] However the pathobiological linkages between this genetic abnormality and the development of pulmonary vascular hypertensive disease have not been clarified. The high frequency of sporadic IPAH cases and reduced penetrance of familial PAH (only 20% of *BMPR2* gene mutation carriers manifest the disease), suggest that additional triggers are required for the development of the condition. There may be further genes, possibly related to the BMP/TGF-β pathway, to be identified. In fact, mutations in the TGF-β receptors, activin-receptor-like kinase 1 (ALK-1) have been identified in PAH patients with a personal or family history of hereditary hemorrhagic telangiectasia.[9] Genetic assessment of PAH patients is currently a research tool available in few specialized laboratories.

EPIDEMIOLOGY, NOMENCLATURE, AND CLASSIFICATION

The Third World Symposium on PAH has provided the opportunity to assess the impact and the usefulness of the Evian classification[10] and to propose some modifications.

It was decided to maintain the general architecture and philosophy, however some relevant changes were proposed: to abandon the term "primary pulmonary hypertension—(PPH)" and to replace it with "idiopathic pulmonary arterial hypertension—(IPAH)," to reclassify pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH), to update risk factors and associated conditions for PAH, and to propose some guidelines in order to improve the classification of congenital systemic-to-pulmonary shunts.[1]

The term "primary" was removed in order to avoid the widespread and confusing use of the term "secondary" that has been utilized to describe almost all conditions with PH.

New possible risk factors for PAH were described such as splenectomy, sickle cell disease, β-thalassemia, chronic myeloproliferative disorders, type Ia glycogene storage disease, Gaucher's disease, and hereditary hemorrhagic telangiectasia.

Congenital systemic-to-pulmonary shunts were classified according to the type, the size, the associated extracardiac abnormalities and the correction status.

DIAGNOSIS AND ASSESSMENT

The diagnostic approach has been more clearly defined according to the new clinical classification and with consensus reached on algorithms of various investigative tests and procedures that exclude other causes and ensure an accurate diagnosis of PAH.[11]

Besides clinical history and physical examination, the investigations include ECG, chest radiograph, transthoracic Doppler-echocardiography, pulmonary function tests, arterial blood gases, ventilation and perfusion lung scan, high resolution CT of the lung, contrast enhanced spiral CT of the lung and pulmonary angiography, blood tests and immunology, abdominal ultrasound scan, exercise capacity assessment and hemodynamic evaluation.

A new definition for acute vasoreactivity as assessed by nitric oxide (NO) administration during right heart catheterization was proposed.[11] The definition requires both a reduction of mean pulmonary pressure of at least 10 mm Hg to reach an absolute value of less than 40 mm Hg. In addition, no change or an increase of cardiac output is also required. Vasoreactive patients, though a minority (about 10%), are more likely to respond favorably to the long-term administration of high doses of calcium channel blockers.

In addition, noninvasive markers of disease severity, either biomarkers or physiological tests that can be widely applied, have been proposed to reliably monitor the clinical course.[11,12] Predictors of outcome include clinical parameters (NYHA functional class), exercise capacity assessment (6 minutes walking distance and baseline peak VO$_2$), echocardiographic parameters (pericardial effusion size, etc), hemodynamics, blood tests (BNP, troponin, uric acid, etc).

MEDICAL TREATMENTS

The numerous controlled clinical trials performed recently in PAH can allow us to abandon a clinical based treatment strategy and adopt an evidence-based therapy that includes new classes of drugs such as prostanoids,[13] endothelin receptor antagonists,[14] and phosphodiesterase-5 inhibitors.[15]

The analysis of placebo-treated groups in the various trials has allowed a better understanding of the natural history of PAH on conventional treatment. In fact, signs of functional and hemodynamic deterioration are detectable as early as after 3 months also in previously stable patients. The new trials have similar designs, duration and end points but relevant differences including the baseline NYHA functional class and the etiology profiles need to be taken into account in the comparative evaluation of these studies. Each new compound presents side effects that are unpredictable in the individual patients and require appropriate attention to treatment initiation and maintenance. The lack of effect on mortality can be explained by the study protocols that were not designed for assessing this end point and by the overall low mortality of the study populations as compared to the historical controls. Extension, open label studies will help to understand if the favorable effects and safety profiles observed in the randomized phases are maintained in the long-term. Unfortunately, in these cases, the effects on mortality can be assessed only by comparison with historical controls.

The discussion in the Task Force on medical treatments has been focused on the attempt to derive an evidence-based treatment strategy that includes all available treatments already approved or tested. The treatment strategy is targeted to patients in NYHA functional class III and IV which is the patient population predominantly enrolled in clinical trials. For NYHA functional class I and II patients the most appropriate strategy has still to be determined.

The traditional approach to treat patients with oral anticoagulant drugs and diuretics if needed has been confirmed even if controlled studies are lacking. The vasoreactivity test is also mandatory to identify the minority of patients with a favorable acute response. In this group, a chronic treatment with high doses of calcium-channel blockers is justified but clinical,

functional and hemodynamic improvements need to be confirmed after 3 to 6 months with formal non-invasive and invasive investigations. In patients that are non responders to acute vasoreactivity tests or those responders with no favorable effect of chronic calcium-channel blockers treatment who are in NYHA functional class III, a treatment with an endothelin receptor antagonist (ERA) or with a prostanoid is indicated. Up to now, the only commercially available and approved ERA is the oral active dual antagonist bosentan that has been successfully tested in 2 controlled clinical trials. The endothelin receptor type A (ET$_A$) selective ERA sitaxetan has been tested in an uncontrolled and a controlled trial and a second study is ongoing while the ET$_A$ selective ERA ambrisentan has been tested in an uncontrolled trial and controlled studies are ongoing. Among prostanoids, treprostinil, administered subcutaneously has been approved in the USA; it was tested in two controlled clinical trials and the primary end-point was fulfilled only in one. Iloprost, administered by aerosol, has been approved in Europe and Australia and it has been tested successfully in one controlled trial. Beraprost is administered orally and is approved in Japan and Korea; it was tested in 2 controlled clinical trials and the primary end-point was fulfilled only in one. The first class of drug and the specific compound to be initiated are related to different factors including the approval state, the preferred way of administration, the side effects profile and the specific experience of the centers. The orally active phosphodyesterase V inhibitor sildenafil has not yet been approved for the treatment of PAH patients even though multiple uncontrolled favorable experiences and one randomised controlled study with favourable results have been published. Sildenafil should currently be considered in subjects who have failed or are not candidates for other approved therapy. The role of this drug will be better understood after the evaluation of the pivotal controlled clinical study that is currently ongoing. In patients with NYHA functional class III the continuous intravenous administration of epoprostenol should also be considered as first choice (2 controlled clinical trials with favorable results) because the best effects on survival are observed in this functional class.

Continuous intravenous administration of epoprostenol is the treatment of choice in patients in NYHA functional class IV and it is approved in USA and in Europe. In these cases bosentan and treprostinil have an official approval by the Food and Drug Administration but, given the small number of patients included in the clinical trials, the experts consider these treatments as a second choice. Iloprost administered intravenously is approved in New Zealand, even though no controlled trials are available.

Continuous intravenous administration of epoprostenol

may be indicated also in NYHA class III patients who have no favorable effects with ERAs or with other prostanoids.

Combination therapy (e.g. ERA + prostanoids) has to be considered in any case of no improvement or deterioration with the first treatment even if data on this specific strategy are few and uncontrolled. Appropriate protocols for timing and dosing to limit possible side effects of the combination have yet to be implemented.

In case of failure and/or unavailability of medical treatments balloon atrial septostomy and/or lung transplantation are indicated. These procedures should be performed in experienced centers.

INTERVENTIONAL AND SURGICAL TREATMENTS

Interventional procedures in patients with PAH include balloon atrial septostomy and lung transplantation.

Balloon atrial septostomy is a procedure that is intended to produce a graded inter-atrial septal defect according to several experimental and clinical observations suggesting that such a condition might be of benefit in the setting of severe PH. In fact, the presence of an atrial septal defect would allow right-to-left shunting to increase systemic output (in spite of the fall in systemic arterial oxygen saturation) and decompression of the right atrium and right ventricle.

The role of balloon atrial septostomy in the treatment of PAH patients is uncertain because its efficacy has been reported only in small series and case reports.[16,17] In most circumstances, this intervention has been performed in severely ill patients as a palliative bridge to lung transplantation, which may explain a procedure mortality rate ranging from 5% to 15%. At present, balloon atrial septostomy is indicated for advanced NYHA class III and class IV patients with recurrent syncope and/or right heart failure despite all available medical treatments.

Heart-lung, single and bilateral lung transplantation have been performed for IPAH and these operations have been combined with repair of cardiac defects for the Eisenmenger syndrome.

The 3 and 5 year survival after lung and heart-lung transplantation is approximately 55% and 45%, respectively.[18] Recipient survival rates have been similar after single and bilateral transplantation for PAH while in Eisenmenger Syndrome patients, a survival advantage of heart-lung transplantation has been shown due to ventricular septal defects.

Lung and heart-lung transplantation are indicated in PAH patients with advanced NYHA class III and class IV symptoms that are refractory to available medical treatments.

FUTURE DIRECTIONS

Future research on the pathobiology of PAH is focusing on the definition of the relative importance of the various molecular and cellular processes and on the interactions between the different pathways. Additionally, the intermediate steps involved in the transduction of signals related to BMPR2 are going to be explored in order to better understand how impaired BMPR2 signaling leads to hypertensive pulmonary vascular disease.

The role of biological markers such as BNP and troponin in the definition of prognosis and assessment of treatments will be analysed.

The available treatments in combination constitute an attractive option to add favorable effects and should be tested in formal studies. New targeted treatments aimed to correct additional molecular and cellular changes will be explored including angiotensin activity, vasoactive intestinal peptide synthesis, and activity, and the serotonin pathway.

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