The right heart and pulmonary circulation (v)

Current Diagnostic and Prognostic Assessment of Pulmonary Hypertension

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Recently, our view of pulmonary hypertension has been changed by the significant progress made in understanding the pathobiology, epidemiology and prognosis of the disease. The increasing number of different conditions now associated with pulmonary hypertension and the appearance of new diagnostic techniques have led to a need for a systematic diagnostic approach and a new disease classification. This review article presents an update on developments in the epidemiology and pathobiology of pulmonary hypertension, on changes in the clinical classification of the disease, and on alterations in the diagnostic algorithm. In addition, it contains detailed descriptions of the treatment recommended for patients in whom an elevated systolic pulmonary pressure is discovered on echocardiography, of the differential diagnosis of pulmonary arterial hypertension and pulmonary hypertension associated with left heart disease, and of multifactorial approaches to determining prognosis, which are three of the most actively debated topics today. Finally, a care program for patients with pulmonary arterial hypertension is proposed.

Key words: *Pulmonary arterial hypertension. Epidemiology. Prognosis. Referral centre.*

Evaluación diagnóstica y pronóstica actual de la hipertensión pulmonar

Recientemente se han producido importantes avances en el conocimiento de la biopatología, la epidemiología y el pronóstico de la hipertensión pulmonar que han cambiado la perspectiva de la enfermedad. El número creciente de enfermedades asociadas a la hipertensión pulmonar y la aparición de nuevas técnicas diagnósticas obligan a sistematizar el procedimiento diagnóstico y definir una clasificación.

En esta revisión se actualizan las principales novedades en epidemiología y patobiología, las modificaciones en la clasificación clínica y los cambios en el algoritmo diagnóstico. Se desarrolla con detalle el manejo recomendado del hallazgo de presión sistólica pulmonar elevada en el ecocardiograma, el diagnóstico diferencial entre hipertensión arterial pulmonar e hipertensión pulmonar asociada a cardiopatía izquierda y la valoración multifactorial del pronóstico, que forman parte de los aspectos más controvertidos actualmente. Finalmente, se propone una organización asistencial para los pacientes con hipertensión arterial pulmonar.

Palabras clave: *Hipertensión arterial pulmonar. Epidemiología. Pronóstico. Unidad de referencia.*

INTRODUCTION

Pulmonary hypertension (PH) is defined[1] as an increase in mean pulmonary arterial pressure (PAP) >25 mmHg at rest as determined by right heart catheterization (RHC). Currently, the normal behavior of pulmonary pressure on exercise remains unknown, and it presents wide variability according to age and the degree of physical fitness in the healthy individual. Thus, a definition of PH on exercise cannot be established.

CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension can be found in different clinical conditions[3,4] and are classified into 5 groups: group 1, pulmonary arterial hypertension (PAH); group 2, pulmonary hypertension associated with left heart disease (PHLHD); group 3, pulmonary hypertension associated with lung disease or hypoxemia; group 4, chronic thromboembolic

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ABBREVIATIONS

CTEPH: chronic thromboembolic pulmonary hypertension
HIV: human immunodeficiency virus
IPAH: idiopathic pulmonary arterial hypertension
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
PWP: pulmonary wedge pressure
RHC: right heart catheterization

pulmonary hypertension (CTEPH); and group 5, pulmonary hypertension with unclear or multifactorial mechanisms.

This classification[1] (Table 1) is based on clinical data, and groups together the different processes and diseases that share pathophysiological mechanisms, clinical presentation and therapeutic approaches. In relation to previous classifications, substantial modifications have been made to group 1. The term familial PAH has been replaced by heritable PAH, since specific gene mutations have been identified in sporadic cases with no family history of the disease. Among the heritable forms of PAH are sporadic idiopathic PAH (IPAH) with germline mutations and clinical cases with a family background with or without identified mutations. This new category of heritable PAH does not require genetic testing, as this would not change its clinical management.

The classification of congenital heart disease underlying PAH has been updated to include a clinical version (Eisenmenger's syndrome, PH associated with systemic-to-pulmonary shunt, PH associated with small defects and PH after shunt repair) and an anatomical-pathophysiological version (Table 2) to better define each patient.

It remains difficult to classify pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis in group 1, because they share some characteristics with IPAH, but also present some differences. Finally, it was decided to include them in a different, but not entirely separate, category to that of PAH, and thus have been denominated as clinical group 1'.

TABLE 1. **Updated Classification of Pulmonary Hypertension[1]**

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK-1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3. Unknown
   1.3. Induced by drugs and toxins
   1.4. Associated with PAH
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis
      1.4.6. Chronic hemolytic anemia
   1.5. Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive patterns
   3.4. Sleep-related breathing disorder
   3.5. Alveolar hypoventilation disorders
   3.6. Chronic exposure to high altitudes
   3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear or 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 kidney failure on dialysis

ALK-1 indicates activin receptor-like kinase 1 gene; BMPR2, bone morphogenetic protein receptor, type 2; PAH, pulmonary artery hypertension; HIV, human immunodeficiency virus.

PATHOBIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension is clinically defined as a group of diseases characterized by a gradual increase in pulmonary vascular resistance leading to right ventricular failure and early death.[5] Prognosis is related to complex pathophysiological interactions between the progression (or regression) rate of the obstructive changes in pulmonary microcirculation and the response of the overloaded right ventricle (RV). The known main prognostic factors in this disease are derived from right ventricular function (hemodynamic, clinical and biochemical). The increase in afterload remains the main determinant of heart failure in patients with PAH and CTEPH, because its elimination as an outcome of lung transplantation or pulmonary