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REVIEW

Update on pulmonary arterial hypertension☆

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Abstract Pulmonary arterial hypertension is a rare and progressive disease that mainly affects the pulmonary arterioles (precapillary), regardless of the triggering etiology. The prevalence of pulmonary hypertension and pulmonary arterial hypertension in Spain is estimated at 19.2 and 16 cases per million inhabitants, respectively. The diagnosis of pulmonary arterial hypertension is based on hemodynamic criteria (mean pulmonary artery pressure ≥25 mmHg, pulmonary capillary wedge pressure ≤15 mmHg and pulmonary vascular resistance >3 Wood units) and therefore requires the implementation of right cardiac catheterisation. Sequential therapy with a single drug has been used in clinical practice. However, recent European guidelines recommend combined initial therapy in some situations. This review conducts a critical update of our knowledge of this disease according to the latest guidelines and recommendations.

PALABRAS CLAVE
Hipertensión pulmonar;
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Inhibidores de la fosfodiesterasa

Actualización en hipertensión arterial pulmonar

Resumen La hipertensión arterial pulmonar es una enfermedad rara y progresiva que afecta principalmente a las arteriolas pulmonares (precapilar), independientemente de la etiología desencadenante. En España se estima que la prevalencia de hipertensión pulmonar y de hipertensión arterial pulmonar es de 19,2 y 16 casos por millón de habitantes, respectivamente. El diagnóstico de hipertensión arterial pulmonar se basa en criterios hemodinámicos (presión media de la arteria pulmonar ≥25 mmHg, presión de enclavamiento capilar pulmonar ≤15 mmHg, y resistencia vascular pulmonar >3 unidades Wood) y por tanto requiere la realización de un cateterismo cardiaco derecho. En la práctica clínica se ha utilizado la terapia secuencial con un solo fármaco. Sin embargo, las recientes guías europeas recomiendan la

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tipo 5;
Análagos de prostaciclina

terapia combinada de inicio en algunas situaciones. En esta revisión se realiza una actualización crítica de los conocimientos sobre esta enfermedad de acuerdo a las últimas guías y recomendaciones.

Background

Pulmonary hypertension (HP) is classified into 5 groups according to the histopathological findings and hemodynamic profiles, which involve a common therapeutic strategy.

Pulmonary arterial hypertension (PAH), which corresponds to group 1 of the classification, is a rare (5 cases per million individuals) and progressive disease of the pulmonary vasculature that mainly affects the pulmonary arterioles (precapillary), regardless of the triggering etiology. Without treatment, PAH has an ominous prognosis, with a mean survival similar to that of patients with metastatic breast cancer (i.e., stage III).[2]

In recent years, there have been significant therapeutic developments in HP, which have been collected in very recently published European guidelines.[3,4] This article is a clinical update mainly on PAH, and its objective is to provide an update on the knowledge and developments of the pathogenesis, diagnosis and treatment of this disease, from a practical perspective for clinicians.

Definitions

The diagnosis of PAH is based on hemodynamic criteria and therefore requires the implementation of right cardiac catheterization. The hemodynamic parameters that need to be present for the diagnosis are as follows:

1. Mean pulmonary artery pressure (mPAP) $\geq$25 mmHg.
2. Pulmonary capillary wedge pressure (PCWP) $\leq$15 mmHg.
3. Pulmonary vascular resistance >3 Wood units.[5]

These measurements are performed at rest. The exercise-induced increase in mPAP increases with age and lacks a universal cutoff that can be used for defining PAH according to the mPAP measured after physical effort.

The latest European guidelines also recommend the measurement of the diastolic pressure gradient (DPG [i.e., the difference between the diastolic pressure of the pulmonary artery and the pulmonary capillary wedge pressure]). This parameter helps reclassify those patients with PH and pulmonary capillary wedge pressure >15 mmHg into 2 groups: isolated postcapillary PH, if the DPG is <7 mmHg, and combined PH (precapillary and postcapillary), if the DPG is $\geq$7 mmHg.[3] The latter group has greater vascular remodeling and mortality and replaces the previously named ''disproportionate PH''.[6]

Another important aspect incorporated into the guidelines is the identification of a risk group, characterized by patients who have ab mPAP between 21 and 24 mmHg (normal value $\leq$20 mmHg) and predisposing factors for developing PAH (connective tissue diseases, especially scleroderma, and first-degree relatives with hereditary or familial PAH). These cases should be closely monitored so that the onset of HAP can be detected early on.[7,8]

Lastly, the guidelines recommend a vascular reactivity test to select patients who can benefit from treatment with calcium antagonists but only in patients with idiopathic PAH. In the other patients, this test should not be performed routinely, because patients who ''respond'' are extremely rare, and the results can be unreliable.[9]

New classification: what has changed?

The classification into 5 groups (Table 1) remains with few changes in terms of groups 2 and 3. A new term has been suggested for group 4: chronic thromboembolic PH and other pulmonary artery obstructions. For group 5 (unclear multifactorial mechanisms), the most relevant issue is the inclusion of an unusual hemodynamic condition, segmental PH, which occurs in patients with congenital heart disease (e.g., tricuspid or pulmonary atresia), in which only a specific area of the lung irrigated by aortopulmonary collateral vessels is affected. This group also includes PH secondary to chronic hemolytic anemia (previously belonging to group 1),[1] especially represented by sickle cell anemia, because the histological changes typical of vasculopathy (plexiform lesions) and the hemodynamic characteristics that define PAH have not been detected.[10–12]

Group 1 can be associated with numerous diseases (such as human immunodeficiency virus infection, portal hypertension secondary to liver disease, connective tissue diseases, schistosomiasis and congenital heart disease) and hereditary/familial or idiopathic forms. Although there have not been significant advances in this group's classification, a number of developments have been incorporated:

(A) New mutations associated with the development of hereditary PAH have been found, specifically... (1) the mutation of caveolin-1 (CAV1), a membrane protein abundantly present in endothelial lung cells; (2) the mutation of KCNK3, a protein member-3 of the superfamily of potassium channels; and (3) the mutation of Smad 9 (mothers against decapentaplegic 9), a protein which belongs to the superfamily of transforming