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REVIEW

Pulmonary arterial hypertension: Basic knowledge for clinicians

Hypertension artérielle pulmonaire : connaissances de base pour les cliniciens

Diana Santos-Ribeiro [a], Pedro Mendes-Ferreira [a], Carolina Maia-Rocha [a], Rui Adão [a], Adelino F. Leite-Moreira [a], Carmen Brás-Silva [a,b,*]

[a] *Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, Cardiovascular Research and Development Centre, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal*

[b] *Faculty of Nutrition and Food Sciences, University of Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal*

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Summary Pulmonary arterial hypertension is a progressive syndrome based on diverse aetiologies, which is characterized by a persistent increase in pulmonary vascular resistance and overload of the right ventricle, leading to heart failure and death. Currently, none of the available treatments is able to cure pulmonary arterial hypertension; additional research is therefore needed to unravel the associated pathophysiological mechanisms. This review summarizes current knowledge related to this disorder, and the several experimental animal models that can mimic pulmonary arterial hypertension and are available for translational research.

Abbreviations: BMPR2, bone morphogenetic protein receptor type 2; cGMP, cyclic guanosine monophosphate; ET, endothelin; Kv channel, voltage-gated potassium channel; mPAP, mean pulmonary artery pressure; NO, nitric oxide; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cell; PDE-5, phosphodiesterase type 5; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle/ventricular.

* Corresponding author. Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, Cardiovascular Research and Development Centre, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal.
E-mail address: carmensb@med.up.pt (C. Brás-Silva).

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Mécanismes physiopathologiques et modèles expérimentaux de l'HTAP

Résumé L'hypertension artérielle pulmonaire (HTAP) est un syndrome progressif caractérisé par une augmentation persistante de la résistance vasculaire pulmonaire et par une surcharge du ventricule droit, ce qui conduit à une insuffisance cardiaque et la mort. À l'heure actuelle, l'HTAP est incurable et, par conséquent, davantage de recherche est nécessaire pour comprendre les mécanismes physiopathologiques associés. Cette revue résume les connaissances actuelles liées à ce trouble et les différents modèles animaux de l'HTAP disponibles pour la recherche translationnelle.

Background

Pulmonary arterial hypertension (PAH) is a syndrome based on diverse aetiologies and pathogenesis, potentially leading to right heart failure and death. PAH is characterized by excessive pulmonary vascular remodelling, pulmonary arterial obstruction and elevated pulmonary vascular resistance (PVR), which result in a marked increase in right ventricle (RV) afterload. Eventually, the RV is unable to cope with the increase in load and heart failure develops [1].

PAH is defined by a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest, and is haemodynamically characterized by the presence of precapillary pulmonary hypertension (PH), which implies a normal pulmonary capillary wedge pressure or left ventricular end-diastolic pressure $\leq$ 15 mmHg, with a PVR > 3 Wood Units [1,2]. So far, there is insufficient evidence to add an exercise criterion to this definition [3].

Pathophysiology

Histopathology

PAH is considered a vasculopathy and, in general, all PAH subgroups (i.e. idiopathic, heritable, drug or toxin-induced, or associated with connective tissue disease, human immunodeficiency virus [HIV] infection, portal hypertension, congenital heart disease or schistosomiasis) and other forms of PH (i.e. PH resulting from lung disease and/or hypoxia) exhibit several arterial abnormalities that are mainly present in the small pulmonary arteries and arterioles [1]. The most common pathological features in PH are medial hypertrophy, local dilation and intimal atheromas, and because they are present in all forms of PH, they are of poor diagnostic value. However, PAH is characterized by constrictive lesions, which include medial hypertrophy and intimal and adventitial thickening, and by complex lesions that include plexiform and dilation lesions, as well as arteritis [4].

Medial hypertrophy is defined by an increase in the diameter of the medial layer, measured between the internal and external elastic lamina, exceeding 10% of the cross-sectional diameter of the arteries. This abnormality appears in all PAH subgroups, and occurs as a result of pulmonary arterial smooth muscle cell (PASMC) proliferation and/or recruitment to the tunica media. This lesion is considered an early event in PAH pathogenesis, but it is usually regarded as reversible [4]. Intimal and adventitial thickening occurs as a result of the proliferation and recruitment of connective tissue cells and, consequently, by the interstitial deposition of collagen, leading to fibrosis. This thickening can be uniform (concentric) or focal (eccentric); the former is often associated with thrombotic events [5]. The presence of plexiform lesions in the vascular compartments is very characteristic of PAH [6], and is a consequence of local and excessive pulmonary arterial endothelial cell proliferation, which leads to the formation of capillary-like channels within the arterial lumen [7]. These lesions are responsible for the expansion and destruction of the arterial wall, as they tend to enlarge into the perivascular space. Fibrin, thrombi and platelets are frequently encountered in these lesions, as well as dilation lesions, which are thin-walled vein-like vessels that are a potential cause of haemorrhages and subsequent fibrosis. The artery wall may also accumulate necrotic and fibrotic tissue and/or be infiltrated with inflammatory cells, leading to arteritis [4].

Cellular factors

The main mechanisms responsible for pulmonary vascular dysfunction are the abnormal proliferation of PASMCs and pulmonary arterial endothelial cells, infiltration of inflammatory cells and fibrosis [5]. However, PAH is not only associated with cell proliferation, but also with apoptotic processes, as the imbalance between these two events is the major cause of the narrowing of the pulmonary arteries in PAH [8].

All forms of PAH have in common the migration and proliferation of PASMCs, which in general is accompanied by the migration of fibroblasts and the formation of an extracellular matrix layer. The uncontrolled proliferation of PASMCs ultimately leads to medial hypertrophy, also contributing to the thickening of the intima and adventitia layers of the pulmonary vessels [9]. The formation of an extracellular matrix and myofibroblasts between the endothelium and internal elastic lamina is termed neointima. Another feature characteristic of PAH is the increase in vasa vasorum neovascularization, which mainly affects the adventitia, and can expand to the media [10].

Beyond the intrinsic dysfunction present in both pulmonary arterial endothelial cells and PASMCs in PAH,

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