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REVIEW

Pulmonary hypertension due to left heart disease

L'hypertension pulmonaire liée aux maladies du cœur gauche

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Summary Pulmonary hypertension due to left heart disease, also known as group 2 pulmonary hypertension according to the European Society of Cardiology/European Respiratory Society classification, is the most common cause of pulmonary hypertension. In patients with left heart disease, the development of pulmonary hypertension favours right heart dysfunction, which has a major impact on disease severity and outcome. Over the past few years, this condition has been considered more frequently. However, epidemiological studies of group 2 pulmonary

Abbreviations: CMR, cardiac magnetic resonance; CO, cardiac output; ERS, European Respiratory Society; ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRCT, high-resolution computed tomography; LA, left atrial; LHD, left heart disease; LV, left ventricular; mPAP, mean pulmonary artery pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PFT, pulmonary functional test; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; WU, Wood units.

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hypertension are less exhaustive than studies of other causes of pulmonary hypertension. In group 2 patients, pulmonary hypertension may be caused by an isolated increase in left-sided filling pressures or by a combination of this condition with increased pulmonary vascular resistance, with an abnormally high pressure gradient between arteries and pulmonary veins. A better understanding of the conditions underlying pulmonary hypertension is of key importance to establish a comprehensive diagnosis, leading to an adapted treatment to reduce heart failure morbidity and mortality. In this review, epidemiology, mechanisms and diagnostic approaches are reviewed; then, treatment options and future approaches are considered.

MOTS CLÉS
Hypertension pulmonaire ;
Cardiopathie gauche ;
Physiopathologie ;
Prise en charge

Résumé L'hypertension pulmonaire liée aux maladies du cœur gauche, aussi classée comme hypertension pulmonaire du groupe 2 de la classification de l'ESC/ERS 2015, est la cause la plus fréquente d'hypertension pulmonaire. Chez les patients avec une maladie cardiaque gauche avancée, le développement d'une hypertension pulmonaire favorise la dysfonction cardiaque droite qui marque un tournant péjoratif dans l'évolution de la maladie. Cette hypertension pulmonaire est principalement causée par une augmentation des pressions de remplissage gauches, liée à une augmentation de la volémie ou à d'autres mécanismes. Dans certains cas évolués, il existe en plus une augmentation des résistances vasculaires pulmonaires, le gradient de pression entre les artères et les veines pulmonaires devenant anormalement élevé. En cardiologie, la découverte d'une hypertension pulmonaire doit conduire à un bilan étiologique bien codifié. Une meilleure compréhension des conditions sous-jacentes est d'une importance capitale pour établir un diagnostic complet, conduisant à un traitement adapté pour réduire l'évolution vers l'insuffisance cardiaque et la mortalité. Dans cette revue, l'épidémiologie, les mécanismes et approches diagnostiques sont exposés ; ensuite, les options thérapeutiques et les perspectives sont discutées.

Definitions and classification

The recent European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines have defined pulmonary hypertension (PH) as the elevation of mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest, as assessed by right heart catheterization (RHC) [1]. Normal pulmonary artery wedge pressure (PAWP) is $\leq$15 mmHg. Postcapillary PH is thus defined by mPAP $\geq$ 25 mmHg at rest and PAWP > 15 mmHg. On the other hand, precapillary PH is defined by mPAP $\geq$ 25 mmHg, PAWP $\leq$ 15 mmHg [1,2]. In some conditions, chronic elevation of the left-sided filling pressure may cause excess vasoconstriction, with or without vascular remodelling, thus leading to elevated pulmonary vascular resistance (PVR) > 3 WU. This condition has been described as ''reactive'', ''out-of-proportion'' or ''mixed'' PH, leading to a ''disproportionate'' increase in pulmonary artery pressure (PAP) [3,4]. For a long time, a ''transpulmonary pressure gradient'' > 12 mmHg (i.e. the difference between mPAP and PAWP) has been used to describe this feature, but this gradient may be influenced by volume load and cardiac function, and does not prognosticate outcome in PH [5]. The recent ESC/ERS guidelines favour measuring the diastolic pressure gradient (i.e. the difference between diastolic PAP and PAWP), which may be less dependent upon stroke volume and loading conditions [1,6]. In healthy subjects, this gradient is <5 mmHg [7]. Postcapillary PH is thus further classified as isolated postcapillary PH if the diastolic pulmonary gradient is <7 mmHg and/or the PVR is $\leq$3 WU, or as combined post- and precapillary PH, if the diastolic pulmonary gradient is $\geq$7 mmHg and/or the PVR is >3 WU [1,4] (Table 1).

The updated classification [8] categorizes four types of PH associated with left heart disease (LHD), according to their origin: PH due to heart failure with reduced ejection fraction (HFrEF); PH due to heart failure with preserved ejection fraction (HFpEF); PH due to left-sided valvular heart disease; and PH due to congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies (Fig. 1).

In the setting of mPAP $\geq$ 25 mmHg at rest, measuring the precise value of PAWP is of major importance to discriminate precapillary PH from group 2 PH. Differentiating group 1 from group 2 patients may be difficult, and an exercise or a saline loading test may be used to unmask venous PH. A recent study has shown that exercise testing is more sensitive than saline loading to detect haemodynamic changes indicative of HFpEF [9]. Combining mPAP > 30 mmHg and PVR > 3 mmHg*min per L is superior to mPAP > 30 mmHg alone for defining a pathological haemodynamic response of the pulmonary circulation during exercise [10]. However, in exercising patients, there are no reliable data that define which level of exercise-induced changes in mPAP has

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