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Review

Pathophysiology and Clinical Relevance of Pulmonary Remodelling in Pulmonary Hypertension due to Left Heart Diseases

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ABSTRACT

Pulmonary hypertension (PH) in left heart disease, classified as group II, is the most common form of PH that occurs in approximately 60% of cases of reduced and preserved left ventricular ejection fraction. Although relatively much is known about hemodynamic stages (passive or reactive) and their consequences on the right ventricle (RV) there is no consensus on the best hemodynamic definition of group II PH. In addition, the main pathways that lead to lung capillary injury and impaired biology of small artery remodelling processes are largely unknown. Typical lung manifestations of an increased pulmonary pressure and progressive RV-pulmonary circulation uncoupling are an abnormal alveolar capillary gas diffusion, impaired lung mechanics (restriction), and exercise ventilation inefficiency. Of several classes of pulmonary vasodilators currently clinically available, oral phosphodiesterase 5 inhibition, because of its strong selectivity for targeting the cyclic guanosine monophosphate pathway

RÉSUMÉ

L'hypertension pulmonaire (HP) en cas de cardiopathie gauche, classifiée dans le groupe 2, est la forme la plus commune d'HP qui apparaît chez approximativement 60 % des cas de diminution ou de préservation de la fraction d'éjection ventriculaire gauche. Bien que nous en connaissions déjà beaucoup sur les stades hémodynamiques (passif ou réactif) et leurs conséquences sur le ventricule droit (VD), il n'existe aucun consensus quant à la meilleure définition du profil hémodynamique de l'HP du groupe 2. De plus, nous en connaissons très peu sur les principales voies qui mènent aux lésions des capillaires pulmonaires et à la détérioration des petits processus biologiques du remodelage artériel. Les manifestations pulmonaires typiques d'une augmentation de la pression pulmonaire et d'un découplage progressif entre le ventricule droit et la circulation pulmonaire sont une diffusion alvéolocapillaire anormale, une détérioration de la mécanique ventilatoire (restriction) et une inefficacité de la ventilation durant l'effort. Parmi les nombreuses classes de

"Focusing on the pulmonary artery pressure in left heart disease could be like staring at the tree that hides the forest…"

Pulmonary hypertension (PH) associated with left heart disease (LHD), classified as group II PH,[1] represents the most prevalent form of PH. Group II differentiates from group I PH, which has been historically referred to as pulmonary arterial hypertension (PAH), because the pathological process resides at the level of the vasculature and chronic elevation of mean pulmonary arterial pressure (mPAP) $\geq$ 25 mm Hg occurs in combination with an increased pulmonary capillary wedge pressure (PAWP; $\geq$ 15 mm Hg).[2] The widespread use of transthoracic echocardiography, which allows estimation of the right ventricular systolic pressure from the velocity of tricuspid regurgitation by adding a given right atrial pressure, has led to increased appreciation of the burden of PH in patients with cardiovascular disease.[3,4] Estimated right ventricular systolic pressure is often used interchangeably with pulmonary artery systolic pressure (PASP), an assumption that relies on the absence of pulmonary valve stenosis. PH is considered mild if the echo-estimated PASP is 35-45 mm Hg, moderate if it is 46-60 mm Hg, and severe when $>$ 60 mm Hg. However, it is important to appreciate that correlations between echo and invasive data are modest ($r \approx 0.7$)[5] and substantial disagreement might be observed using the gold standard invasive measure. Previous studies have shown inaccurate PASP estimation ranging from 48% to 54%, and PASP might be over- or underestimated according to the tricuspid regurgitant velocity.[2]

Catheterization remains essential to make the diagnosis of PH and is particularly critical when clinical decisions and therapeutic interventions are to be made based on

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in the pulmonary circulation, is increasingly emerging as an attractive opportunity to reach hemodynamic benefits, reverse capillary injury, and RV remodelling, and improve functional capacity. Guanylate cyclase stimulators offer an additional intriguing opportunity but the lack of selectivity and systemic effects might preclude some of the anticipated benefits on the pulmonary circulation. Future trials will determine whether new routes of pharmacologic strategy aimed at targeting lung structural and vascular remodelling might affect morbidity and mortality in left heart disease populations. We believe that this therapeutic goal rather than a pure hemodynamic effect might ultimately emerge as an important challenge for the clinician.

vasodilatateurs pulmonaires cliniquement disponibles en ce moment, les inhibiteurs de la phosphodiestérase de type 5 par voie orale, en raison de leur forte sélectivité à cibler la voie de la guanosine-5'-monophosphate dans la circulation pulmonaire apparaît de plus en plus comme une opportunité intéressante pour obtenir les avantages hémodynamiques, inverser les lésions capillaires et le remodelage VD, et améliorer la capacité fonctionnelle. Les stimulateurs de la guanylate cyclase offrent une opportunité additionnelle remarquable, mais le manque de sélectivité et les effets systémiques pourraient empêcher d'obtenir certains des avantages anticipés sur la circulation pulmonaire. Des essais subséquents détermineront si les nouvelles stratégies pharmacologiques ciblant le remodelage structurel et vasculaire pulmonaire pourraient effectivement influer sur la morbidité et la mortalité des populations souffrant de cardiopathie gauche. Nous croyons que cet objectif thérapeutique plutôt que de cibler seulement un effect effet hémodynamique pourrait finalement apparaître comme un enjeu important pour le clinicien.

mPAP measurements. Moreover, right heart catheterization is mandatory for measuring cardiac output and calculating total pulmonary resistances (mPAP/cardiac output) and pulmonary vascular resistance (mPAP − PAWP/cardiac output) that excludes the pulsatile loading from the left atrium to the right ventricle (RV) afterload, measuring the exclusive precapillary component of PH.

Group II PH might be caused by systolic dysfunction, diastolic dysfunction, valvular heart diseases, or more rarely by congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies. Cardiovascular specialists and family physicians alike are therefore exposed to this condition frequently, if not daily. Despite major advancements in the pharmacological and surgical therapies targeting LHD, PH associated with LHD remains an important factor limiting the quality of life and adversely affecting prognosis.[6-8]

The first organ directly affected by LHD is the lung. In response to physical and biological stressors, remodelling of the pulmonary circulation and parenchyma are responsible for the development of a restrictive respiratory physiology negatively affecting gas exchange and contributing to the development of PH.[9] Initially, right ventricular adaptation with hypertrophy and increased contractility compensate for the increase in pulmonary vascular resistance. Ultimately, however, right ventricular uncoupling to the demands of the pulmonary circulation leads to RV failure, a major determinant of mortality.[10,11] Better understanding of the pathophysiology and awareness of the clinical effect of the pulmonary remodelling processes are key to the development of novel therapies targeting these pathways.

The Lungs as a Primary Target Organ Affected by LHD

Dyspnea, the cardinal symptom of LHD, first occurs when left filling pressures are increased, resulting in pulmonary capillary congestion. This initiating event, depending on its severity, frequency, and duration, can trigger a response to injury characterized by lung parenchymal remodelling and pulmonary vascular endothelial dysfunction and remodelling.[9]

It has long been recognized that the increase in lung capillary pressure can result in capillary stress failure and alveolar edema.[12] There is, however, less awareness on the chronic consequences of repeated cycles of lung capillary injury and repair leading to alveolar remodelling and a restrictive lung syndrome impairing lung function and gas exchange.[9,13-16] In animal models of chronic heart failure (HF) caused by coronary artery ligation in rats or aortic banding in guinea pigs and mice, there is important lung remodelling in which myofibroblasts play a central role.[17-20] This pathophysiologic process in which myofibroblast activation and proliferation predominates has also been well described in human lung histological specimens from subjects with LHD.[9,20]

Myofibroblasts will activate and proliferate in response to inflammatory lung injury after capillary stress failure and in response to the neurohumoural mediators activated in HF (Fig. 1).[9] It has been shown that lung myofibroblasts can differentiate from resident lung mesenchymal cells, transdifferentiate from other lineage, or originate from resident or marrow-derived stem cells.[21,22] Myofibroblasts produce collagen and interstitial matrix, reducing alveolar-capillary permeability. Although this mechanism is initially protective against the development of pulmonary edema and explains the greater tolerance of subjects with LHD to chronically increased filling pressures, the process becomes maladaptive as the lung-restrictive physiology contributes to impaired gas exchange and reduced exercise tolerance.[23] In preclinical models of LHD, lung myofibroblast proliferation and the resulting restrictive lung syndrome can be reduced by angiotensin receptor blockade[17] and statins,[24] but not by use of endothelin receptor blockade[24] or by aldactone.[25] Interestingly, caveolins-1 and -2 expression, the principal structural proteins of the vesicular invaginations of the endothelial plasma membrane, are markedly reduced in lungs from rats with HF due to myocardial infarction.[26] The fact that caveolin knockout mice develop lung structural remodelling similar to that found in LHD suggests that caveolins play a protective role in the process.

Unfortunately, no human studies have specifically evaluated the effect of therapies on lung remodelling associated