Canadian Journal of Cardiology 31 (2015) 391–406

Review

Right Ventricular Adaptation and Failure in Pulmonary Arterial Hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is an obstructive pulmonary vasculopathy, characterized by excess proliferation, apoptosis resistance, inflammation, fibrosis, and vasoconstriction. Although PAH therapies target some of these vascular abnormalities (primarily vasoconstriction), most do not directly benefit the right ventricle (RV). This is suboptimal because a patient's functional state and prognosis are largely determined by the success of the adaptation of the RV to the increased afterload. The RV initially hypertrophies but might ultimately decompensate, becoming dilated, hypokinetic, and fibrotic. A number of pathophysiologic abnormalities have been identified in the PAH RV, including: ischemia and hibernation (partially reflecting RV capillary rarefaction), autonomic activation (due to G protein receptor kinase 2-mediated downregulation and desensitization of β-adrenergic receptors), mitochondrial-metabolic abnormalities (notably increased uncoupled glycolysis and glutaminolysis), and fibrosis. Many RV

RÉSUMÉ

L'hypertension artérielle pulmonaire (HAP) est une vasculopathie pulmonaire obstructive caractérisée par la prolifération excessive, la résistance à l'apoptose, l'inflammation, la fibrose et la vasoconstriction. Bien que les traitements contre l'HAP ciblent certaines de ces anomalies vasculaires (principalement la vasoconstriction), le ventricule droit (VD) n'en tire directement pour la plupart aucun avantage. Ces traitements sont donc sous-optimaux puisque l'état et le pronostic fonctionnels d'un patient sont en général déterminés par la réussite de l'adaptation du VD à l'augmentation de la postcharge. Le VD s'hypertrophie dans un premier temps, mais pourrait finalement décompenser, puis entraîner une dilatation, une hypokinésie et une fibrose. Plusieurs anomalies physiopathologiques ont été observées dans le VD HAP, dont l'ischémie et l'hibernation (reflétant partiellement la raréfaction capillaire du VD), l'activation du système nerveux autonome (due à la régulation à la baisse médiée par les kinases 2

Pulmonary arterial hypertension (PAH) is a pulmonary vasculopathy defined by a resting mean pulmonary artery pressure (mPAP) $>$ 25 mm Hg and pulmonary capillary wedge pressure (PCWP) $<$ 15 mm Hg.[1] Right ventricular (RV) function is a major determinant of prognosis and functional capacity in PAH.[2-4] RV failure in PAH reflects maladaptive responses to the increased afterload that defines PAH (pulmonary vascular resistance [PVR], $>$ 3 Wood units). RV failure requiring admission to an intensive care unit and inotropic support has an inpatient mortality rate of $>$ 40%.[5] Approaches to the support of the failing RV varies considerably among providers and centres,[5,6] and limited interventional options are currently available for RV failure.[7] There are currently no official guidelines for the treatment of RV failure in PAH, because of the lack of effective, evidence-based therapies.[8] A National Heart, Lung, and Blood Institute-sponsored working group has highlighted the need to develop a basic understanding of the unique properties of the RV, to advance the understanding and therapy of RV failure in PAH.[9] Among the important features that might lead to RV failure in pulmonary hypertension (PH) are: (1) the RV's limited contractile reserve which, despite hypertrophy, limits capacity for adaptation to an increase of the transpulmonary gradient[10]; (2) ischemia due to reduced perfusion pressure of the right coronary artery (RCA), because increasing pulmonary artery pressure decreases the aorta-RV pressure gradient thereby reducing epicardial systolic flow[11] and/or RV

Received for publication November 7, 2014. Accepted January 19, 2015.

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See page 402 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.01.023

abnormalities are detectable using molecular imaging and might serve as biomarkers. Some molecular pathways, such as those regulating angiogenesis, metabolism, and mitochondrial dynamics, are similarly deranged in the RV and pulmonary vasculature, offering the possibility of therapies that treat the RV and pulmonary circulation. An important paradigm in PAH is that the RV and pulmonary circulation constitute a unified cardiopulmonary unit. Clinical trials of PAH pharmacotherapies should assess both components of the cardiopulmonary unit.

des récepteurs couplés aux protéines G et la désensibilisation des récepteurs β-adrénergiques), les anomalies du métabolisme mitochondrial (particulièrement l'augmentation du découplage entre la glycolyse et la glutaminolyse) et la fibrose. Plusieurs anomalies du VD sont détectables au moyen de l'imagerie moléculaire et pourraient servir de biomarqueurs. Certaines voies moléculaires telles que celles qui régulent l'angiogenèse, le métabolisme et la dynamique mitochondriale sont perturbées de façon similaire dans le VD et la vasculature pulmonaire, ce qui offre la possibilité de traiter le VD et la circulation pulmonaire. Un important paradigme de l'HAP est que le VD et la circulation pulmonaire constituent un ensemble cardiopulmonaire unifié. Les essais cliniques sur les pharmacothérapies de l'HAP devraient évaluer les deux composantes de l'ensemble cardiopulmonaire.

microvascular rarefaction[11,12]; (3) a metabolic shift from oxidative mitochondrial metabolism to the energetically inefficient cytosolic process of aerobic glycolysis[12,13]; and (4) β-adrenoreceptor downregulation and desensitization.[14]

Approved PAH therapies do not directly target the right ventricle and their effects on RV contractility are largely unknown, because they have been approved based primarily on their ability to improve 6-minute walk test distance. Even in PAH patients who experience a decrease in PVR in response to pulmonary vasodilators, RV function can deteriorate.[15] In this review, we will discuss the clinical, pathophysiological and therapeutic features of RV failure and discuss future directions for RV research, indicating potential therapeutic strategies (Fig. 1).

Clinical Features of RV Failure

RV failure reflects the inability of the right ventricle to perfuse the lung circulation adequately to ensure left ventricle (LV) filling while maintaining normal diastolic pressures. RV failure is characterized by a decreased cardiac index (< 2.5 L/min/m^2) and increased right-sided cardiac filling pressures, including right atrial (RA) pressure (RAP) ≥ 8 mm Hg.[16]

RV failure in PAH causes pedal edema, neck vein distension, abdominal fullness, and exertional dyspnea (which portends poor survival[17]) (Table 1). Palpitations due to supraventricular tachycardia occur in 12% of PAH patients and reflect the progressive anatomical distortion and enlargement of the RV and right atrium.[18,19] Presyncope and syncope occur in approximately 4% of PAH patients and indicate a poor prognosis.[20] Exertional syncope is particularly common in PAH and reflects the inability of the right ventricle to overcome the fixed pulmonary vascular obstruction and increase cardiac output in the face of systemic vasodilatation.

On physical examination, the signs of RV failure include an increase in jugular venous pressure (JVP), often associated with a prominent V-wave, due to severe tricuspid regurgitation (Video 1; view video online), dependent edema, and hepatic congestion.[2] Carvallo sign (increase in volume of tricuspid regurgitation murmurs during inspiration) distinguishes this systolic murmur from mitral regurgitation.[21] Precordial palpation might reveal an RV lift or heave, indicating RV enlargement. Auscultation in the tricuspid area sometimes reveals a right-sided third heart sound (S_3), reflective of a failing and noncompliant right ventricle. A high-pitched early diastolic murmur reflecting pulmonary regurgitation (the Graham Steell murmur) might occur in RV failure.[22] Manoeuvres that increase venous return might expose the signs of RV failure in patients who are euvolemic or hypovolemic. These manoeuvres include hepatojugular reflux, characterized by a sustained increase in JVP of 4 cm with 15-30 seconds of pressure over the liver,[23] and Kussmaul sign, in which the JVP increases with inspiration, rather than the normal decline.

The lateral chest radiograph (CXR) often reveals RV enlargement, evident as a loss of the retrosternal space and the posterior-anterior CXR shows evidence of RV and RA enlargement. In addition, by time that there is RV failure the CXR might also show pruning of the vasculature (Fig. 1A). The electrocardiogram patterns in patients with PAH include sinus rhythm or sinus tachycardia with RA enlargement (P-pulmonale), right axis deviation ($> 90°$), an early R-wave transition (R/S ratio > 1 in lead V_1), a right bundle branch block and/or an RV strain pattern, evident as the $S_1Q_3T_3$ pattern (Fig. 2). In patients with RV failure there is often T-wave inversion in leads $V_{1\text{-}3}$, consistent with RV strain.

Although the physical examination is helpful, advanced cardiac imaging and invasive hemodynamic measurements are required to solidify the diagnosis of PAH and assess RV failure. Invasive hemodynamics should always precede initiation of PAH-specific therapy.

RV Imaging in PAH

Chronic RV pressure overload in PAH can induce RV hypertrophy (RVH), which might initially be adaptive; however, over time concentric RVH with preserved RV function can evolve to RV dilatation and systolic dysfunction (Fig. 1B).

Echocardiography

Traditionally, echocardiographic evaluation of the right ventricle is difficult, because of the crescent shape, which confounds modelling of simple geometric estimation of volume using 2-dimensional methods[24]; however, the recent application of real-time 3-dimensional echocardiography has improved the ability to use ultrasound to serially monitor RV function.[25] Many echocardiographic RV parameters predict prognosis in PAH (Table 2), including RVH, defined as an end-diastolic free-wall thickness > 5 mm,[30] reflecting an