Right ventricular diastolic dysfunction in pulmonary arterial hypertension

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Abstract

This thesis describes the diastolic function of the right ventricle in pulmonary arterial hypertension.

Chapter 2: Right ventricular diastolic impairment in patients with pulmonary arterial hypertension

We developed a load-independent method which estimates RV diastolic stiffness and is suitable for clinical practice. This is based on a modified end-diastolic elastance (Eed) estimation of the diastolic stiffness of the right ventricle. The classical Eed is only applicable for animal models since it requires preload reduction maneuvers. These can not be performed in PAH patients since they carry out risks associated with the hemodynamic instability of the patients. Nevertheless, the advantage of Eed over other estimates of RV diastolic function (right atrial pressure (RAP), E/A, E'/E, tau) is related to its load-independence and reflection of intrinsic RV properties. Therefore we developed a single-beat Ed method which circumvents the preload reduction maneuvers and measures load-independent intrinsic RV diastolic function in PAH patients. Furthermore, we observed that RV diastolic stiffness significantly associates with parameters of clinical worsening, such as RAP, stroke volume (SV), 6-minutes-walk-distance (6MWD) and NT-proBNP levels.
To understand the molecular mechanisms involved in the diastolic impairment of the right ventricle we assessed the passive properties of RV cardiomyocyte and the amount of myocardial fibrosis. RV cardiomyocytes were hypertrophied in PAH patients compared with controls and showed an increased sarcomeric stiffness and myofilament Ca^{2+}-sensitivity. We indicated that the giant protein titin may be responsible for the increase in sarcomeric stiffness in PAH cardiomyocytes. Furthermore, we found a significant but small increase in the fibrotic content of the RV, which could also contribute to myocardial stiffness.

Chapter 3: Protein changes contributing to right ventricular cardiomyocyte diastolic dysfunction

Important proteins regulating RV cellular diastolic function were found to contribute to the increased cardiomyocyte stiffness. A decreased Protein Kinase A (PKA) -dependent phosphorylation was observed in: 1) titin N2B domain leading to an increase in sarcomere stiffness, 2) troponin I leading to increased myofilament Ca^{2+}-sensitivity and 3) phospholamban (PLN), which via SERCA2a inhibition alters diastolic Ca^{2+}-clearance. We speculate that an abnormal adrenergic neurohormonal system is at the origin of the diastolic dysfunction of RV cardiomyocytes. The excessive neurohormonal activation present in heart failure ultimately leads to beta1-adrenergic receptor (β1-AR) downregulation on the RV cardiomyocyte membrane as a protective mechanism

against its apoptotic side-effects. However, reduced β1-AR signaling may also lead to a decrease in the adenylate-cyclase – PKA signaling pathway and an abnormal function of proteins modulated by PKA phosphorylation.

Chapter 4: Fibrosis- and cardiomyocyte-mediated stiffness in pulmonary arterial hypertension

Both the increase in cardiomyocyte diastolic stiffness and extracellular fibrosis contribute to the RV diastolic stiffness. However their relative contribution may be different in relation to the stage of the disease. Therefore we used two groups of rats with different PAH severity (mild RV dysfunction and severe RV dysfunction) to distinguish between the two components for diastolic stiffness. We found that RV myocardial stiffness is increased in rats with mild and severe RV dysfunction. In mild RV dysfunction, stiffness is mainly determined by increased cardiomyocyte stiffness. In severe RV dysfunction, both cardiomyocyte and fibrosis-mediated stiffness contribute to increased RV myocardial stiffness.

Chapter 5: Pressure-overload-induced right heart failure

In this review we discuss the integrative role of RV diastolic function in the progression of PAH to heart failure and give an overview of the mechanisms and molecular pathways incriminated in this process.

Chapter 6: Right ventricular-arterial coupling in patients with pulmonary arterial hypertension

A more pronounced diastolic impairment is associated with worse hemodynamic parameters and functional markers of disease severity (mean RAP, stroke volume, NT-proBNP levels and 6MWD). In this chapter we investigated whether RV diastolic dysfunction contributes to worsening of the disease or is merely an epiphenomenon of disease progression. We found that diastolic stiffness is compromised from an early disease stage and further increases as disease progresses. Unlike diastolic stiffness, systolic parameters are impaired only in a late disease stage. RV diastolic stiffness can be significantly decreased by current PAH treatment, an effect which is most likely due to a reduction of RV afterload.

Chapter 7: Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension

We further investigated whether diastolic stiffness in idiopathic PAH (iPAH) patients was associated with disease progression and survival. Treatment naïve patients had a better survival if they presented with lower RV diastolic stiffness, while in treated patients, those who maintained a high diastolic stiffness had a significantly lower survival. Interestingly, RV hypertrophy was not responsible for the high diastolic stiffness in the low-survival iPAH group. Rather than the hypertrophic response of the right ventricle, intrinsic molecular wall changes may influence RV diastolic properties.