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Maladaptation of Right Ventricle to High Pulmonary Hypertension in an Adult Patient with Patent Ductus Arteriosus

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ABSTRACT

Pulmonary arterial hypertension is an obstructive pulmonary vasculopathy and the RV is considered a major determinant of survival in patients with precapillary pulmonary hypertension. The transition from adaptive to maladaptive phenotype remains poorly understood and clinically unpredictable. Several mechanisms having been suggested in right heart disease but the causes of maladaptive cardiac remodeling remain unknown and require further research. We report the case of PAH in the context of an overlooked patent ductus arteriosus in adulthood with RV consequences.

KEYWORDS: Pulmonary Arterial Hypertension - Patent Ductus Arteriosus - Right Ventricule Maladaptation.

INTRODUCTION

Pulmonary arterial hypertension is an obstructive pulmonary vasculopathy and the right ventricle is considered a major determinant of survival in patients with precapillary pulmonary hypertension.

The right ventricle initially hypertrophies but may ultimately decompensate, becoming dilated, hypokinetic and fibrotic.

We report the case of PAH in the context of an overlooked patent ductus arteriosus in adulthood with right ventricle consequences.

CASE REPORT

A 50-year-old women was admitted for evaluation and stabilization of a severe right heart failure in the context of idiopathic pulmonary arterial hypertension. The patient was hospitalized in the ICU, she was in stage 4 of NYHA. On physical examination there were a diffuse swollen painful liver, severe ascites and oedema involving not only the ankles and lower extremities but also the thighs, abdomen, and chest. The heart exam showed a low blood pressure at 90/50/42 mmHg in the upper limb, the pulse was 90bpm with an increased intensity of the second cardiac sound in the second area and a grade 3/6 pansystolic murmur accentuated by deep inspiration. The EKG showed a sinus rhythm, incomplete right bundle branch block and T wave inversion in several leads, and there was a phenomenal cardiomegaly on the chest-Xray.

The TTE evaluated the right ventricle which was dilated and hypokinetic with a pulmonary systolic pressure of 87mmHg measured on the flow of a severe tricuspid regurgitation and a mild pericardial effusion. The right atrium surface was high, and the pulmonary artery tree was enlarged. This TTE of admission suspected the presence of an arterial patent ductus on the presence of some calcifications at the level of the isthmic zone but the dopplers were negative without any color or continuous flow. Since the patient has been admitted to an Intensive Care Unit and treated with inotropic support, the systemic parameters had improved and then the control TTE showed a color flow of a PDA that has become visible.

In the cath-lab the hemodynamic evaluation concluded to pre and postcapillary pulmonary hypertension, the total pulmonary vascular resistance was up to 10uW with a low cardiac index and a negative reactivity test. The presence of an arterial patent ductus was confirmed with an inversed shunt.

As injectable drugs are not available, the combination of a dual oral therapy associated to the adjuvant treatment was inefficient and the patient passed away one month later.

DISCUSSION

Pulmonary hypertension (PH) is a group of heterogenous pathologies characterized by right ventricular (RV) hypertrophy and pulmonary vascular remodeling. Death is mainly caused by right ventricle dysfunction [1]. In adult PAH patients, RV failure requiring inotropic support and admission to an intensive care unit has an inpatient mortality rate over 40%, far higher than the 13–14% mortality for patients admitted to hospital with left ventricular failure requiring inotropes. [2]

Right heart failure (RVF) in patients with PH is the result of insufficient blood delivery to the heart and/or increased systemic venous pressure secondary to elevated right ventricle afterload represented by pulmonary arterial pressure or pulmonary vascular load [3]. The right ventricle adapts to the increased afterload by increasing its wall thickness and contractility. [4]. The RV with the pressure overload, develop an adaptative RV hypertrophy (RVH) characterized by concentric hypertrophy with minimal right ventricle dilatation or fibrosis, preservation of exercise capacity, preserved right ventricle ejection fraction and cardiac output. The adaptive right ventricle accumulates molecular and metabolic abnormalities until a point where it cannot overcome the persistent pressure overload and therefore becomes maladaptive, characterized by reduced exercise capacity, significant reduction in right ventricle ejection fraction, and decreased cardiac output [5], in our case caused by an overlooked PDA.

Tricuspid regurgitation, which is often secondary to annular dilation, may also lead to adverse ventricular remodeling and decreased flow reserve. Right-to-left shunting through a patent foramen oval is also observed more frequently in patients with maladaptive remodeling and more severe right heart failure [4].

There is heterogeneity in RVH in terms of its effects on cardiac output and the likelihood of progression to RVF that is not explained by differences in RV mass or RV pressure overload. Some patients have maladaptive forms of RVH and rapidly decompensate whilst others remain stable for decades, despite similar elevations in RV pressure and RVH. [3]

There is a consensus that dilatation of RV is caused by PH and pulmonary vascular remodeling and is supported by the fact that lung transplantation reverses ventricle hypertrophy. But it is not always the case. In a small study of 12 patients with PAH who underwent lung transplantation, there was modest decrease in RV volume after 3 months. However, these changes observed in RVH and RVF after lung transplant for PAH are pale in comparison to that seen in, chronic thromboembolic pulmonary hypertension (CTEPH), where RV function typically returns to normal within weeks after pulmonary endarterectomy (PEA) [6]. Which highlight the complex mechanism of right heart maladaptation to PH and the different outcomes depending on the underlying etiology.

RV adaptation and ventricular remodeling in PAH is a complex process that depends not only on the severity of pulmonary vascular disease but also on the interplay between neuro- hormonal activation, coronary perfusion, and myocardial metabolism. Other factors that may influence RV adaptation include the rate and time of onset of pulmonary hypertension, its underlying etiology, and, although not yet well defined, genetic and epigenetic factors. [4]

There are multiple mechanisms that are linked to maladaptive right ventricle that do not only involve the overload pressure. First, right ventricular ischemia caused by impaired blood supply to the RV in PH, due to hypoxia that cause capillary rarefaction seen in rats [3]. Ultimately, coronary perfusion may fail to meet the increased demands for oxygen in right ventricle hypertrophy, leading to right ventricle ischemia, and then failure. Ischemia cannot be explained solely by diminished RCA perfusion pressure [3] but it is still unclear if it is because of reduced global perfusion due to a lower driving pressure and/or to capillary rarefaction. [8]

The decreased mitochondrial activity is resulting in a switch from aerobic to anaerobic metabolism that might also be involved in the transition from compensated RV hypertrophy to maladaptive remodeling [4], causing a decrease in glucose intake, resulting in acidosis which impairs the right ventricle function.[3]

The maladaptive phenotype is also associated with chronic activation of the sympathetic system with a downregulation of the parasympathetic system. At the early stages of RHF, the activation of the sympathetic system is considered beneficial as it offers inotropic support, peripheral vasoconstriction, hydric retention to maintain cardiac output. However, chronic sympathetic activation leads to desensibilization of b-adrenergic receptors, causing pathological RV remodeling, impairs inotropic reserve of the RV, shifts energy metabolism, enhances cardiomyocytes apoptosis, delays HR recovery and increases mortality. [8]

Normally, fibrosis is a process of host defense and wound healing but results sometimes in uncontrolled disease. In cardiac tissue, fibrosis is triggered by early inflammation in response to pressure overload. It is still unclear at what point during right ventricle hypertrophy fibrosis transits from reparative process into excessive extracellular matrix deposition and pathological remodeling of myocardium [1] and is associated with worsened prognosis [3].

The transition from adaptive to maladaptive phenotype remains poorly understood and clinically unpredictable. Progression of right ventricle dysfunction is not always lung-dependent. Increased afterload caused by pulmonary vascular remodeling initiates the right ventricle hypertrophy. Ischemia in a hypertrophic right ventricle may directly contribute to right heart failure. Cardiac muscle reacts to an increased afterload by over-activation of sympathetic system and downregulation of b-adrenergic receptors. Fibrosis, an evolutionary conserved process in host defense and wound healing, is dysregulated in maladaptive cardiac tissue contributing directly to right ventricle failure. [1]

These right ventricle abnormalities offer new potential therapeutic targets for the management of pulmonary arterial hypertension. [5]

Despite promising advances in understanding RV remodeling in PAH, there remains a continued need for further studies on the biomechanical effects of these remodeling events, to

facilitate the design and personalization of potential therapeutics aiming to induce reverse remodeling. [9]

In this case, the clinical presentation was dominated by signs of right heart failure with critical RV dilatation, hypokinesis and severe systolic dysfunction in the context of underdiagnosed aortopulmonary shunt.

CONCLUSION

The transition from adaptive to maladaptive phenotype remains poorly understood and clinically unpredictable. Several mechanisms having been suggested in right heart disease, but the causes of maladaptive cardiac remodeling remain unknown and require further research for a better medical management.

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