

## Pathophysiological Bases of Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction and Implications for Management

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Pulmonary hypertension (PH) associated with left heart disease is classified as group 2, and it encompasses both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).<sup>1</sup> In both diseases, the development of PH is associated with an unfavorable clinical course in the natural history of the disease, and knowledge about its pathophysiology is still uncertain, which may have practical implications from the diagnosis to the treatment of heart failure.<sup>2,3</sup>

### Prevalence, definition, and diagnosis

The prevalence of PH in patients with HFpEF is widely heterogeneous, with frequencies ranging from 36% to 81%,<sup>4</sup> and this is due to the diagnostic means used, to the time of progression of the underlying disease,<sup>3</sup> and to the different ejection fraction cut-off points used to define HFpEF. For example, in a subanalysis of the PARAGON study, the prevalence of PH in patients with HFpEF was 31%.<sup>5</sup> Moreover, the different phenotypes of HFpEF may present with a lower or higher degree of PH, depending on the increase in pulmonary vascular resistance, the increase in right atrial pressure, and associated concomitant chronic kidney disease.<sup>6</sup>

Group 2 PH is defined as mean pulmonary artery pressure > 20 mmHg and pulmonary capillary pressure > 15 mmHg. Right heart catheterization is considered the gold standard for accurate measurement of pulmonary pressures, and it is valuable in evaluation of the hemodynamic response to physical exertion, providing important information for differentiating between group 2 PH and other etiologies.<sup>1</sup>

However, in clinical practice, the most useful test for diagnosis of PH, regardless of ejection fraction, is Doppler echocardiogram. Although it is examiner-dependent and sensitive to variations in posture and blood volume, estimation of pulmonary artery systolic pressure on Doppler echocardiogram serves both as a diagnostic parameter of

HFpEF and as a prognostic parameter in estimating the degree of PH.

### Left ventricular dysfunction

The first pathophysiological change observed in HFpEF is impairment of left ventricular relaxation and filling with a consequent increase in left atrial pressure and backward transmission of this elevation to the pulmonary system, initially characterizing pulmonary venocapillary hypertension.<sup>7</sup>

Hypertrophy and diastolic dysfunction, which are common in hypertension and obesity, play a role in altering left ventricular relaxation. However, the multiple comorbidities that are common in patients with HFpEF also have negative effects on the myocardium, stimulating oxidative stress and hypertrophic pathways.<sup>8</sup>

Paulus and Tschope<sup>9</sup> have proposed a unifying hypothesis to centralize the role of pro-inflammatory pathways in increased proliferation of collagen in myocytes and in the impact on elasticity. In this hypothesis, the high rigidity of the myocardial wall would be sustained by increased titin protein phosphorylation, overexpression of growth factor- $\beta$  signaling, reduced expression of elastase, high mitochondrial oxidative stress, and epigenetic alterations that definitively impair cellular homeostasis.

### Left atrial remodeling and dysfunction

The change in left ventricular relaxation is followed by volume and pressure overload in the left atrium. The left atrium, in turn, is very sensitive to these elevations, and it initiates a process of remodeling and dysfunction, which play a determining role in the elevation of pulmonary pressures.<sup>7,10</sup>

The left atrium becomes more rigid early and dilates slowly, and this is a peculiar substrate in the induction of atrial fibrillation. Furthermore, the coexistence of other comorbidities and the inflammatory pathways described corroborate atrial remodeling and dysfunction and also contribute to the induction of atrial fibrillation. This phenotype is associated with mitral regurgitation and greater elevation of pulmonary vascular resistance in patients with HFpEF.<sup>10,11</sup>

Any increase in left atrial pressure directly influences pulmonary hemodynamics and exacerbates symptoms.<sup>7</sup> Although studies on pulmonary circulation in humans are scarce, some data have revealed that the chronic effects of increased left atrial pressure on the pulmonary vasculature may represent different phenotypes according to the level of left atrial pressure elevation.

### Keywords

Pulmonary Hypertension; Heart Failure; HFpEF

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## Pulmonary artery and venocapillary remodeling

The sustained increase in left atrial pressure is transmitted back to the pulmonary veins, which undergo a remodeling process consisting of luminal narrowing due to increased neointimal thickening and medial hypertrophy.<sup>11</sup> Some studies have shown a direct correlation between pulmonary artery systolic pressure and neointimal thickening, but the necessary trigger for this endothelial dysfunction is not yet known; or be it, we do not know what stage or degree of left atrial pressure elevation would be the necessary trigger for vascular alterations.<sup>12</sup>

The maintenance of high pressure on the pulmonary venocapillary system causes insufficiency of pulmonary capillaries and arterioles, with barotrauma that ruptures the endothelial layer and promotes swelling of fluids and proteins in the interstitium. This edema triggers a cascade of molecular and inflammatory markers that inhibit nitric oxide activity and increase endothelin expression, leading to luminal occlusion and alveolar septal thickening. The progression of this cascade leads to remodeling of the pulmonary arteriolar system and to reduced gas diffusion through the alveolar membrane, which, in the second stage, composes the arterial pattern of PH associated with HFpEF.<sup>7,12,13</sup>

The impairment of right ventricular function in HFpEF occurs in two ways: 1 – the sustained elevation of pulmonary pressures promotes hypertrophy, dilation, functional tricuspid insufficiency, and right ventricular dysfunction; 2 – right ventricular diastolic dysfunction and increased stiffness occur before systolic dysfunction, with slower progression to dilation and functional deterioration.

## Treatment

There is no specific treatment for group 2 PH, and the use of pulmonary vasodilators is contraindicated. Some experiments have tried, unsuccessfully, to test appropriate therapies for pulmonary arterial hypertension in patients with left ventricular diseases, but they may have run into phenotypic differences in patients with HFpEF.

It is believed that the variability of hemodynamic phenotypes in HFpEF (isolated pre-capillary hypertension or combined pre- and post-capillary hypertension) may interfere with the negative results with respect to the use of vasodilators for group 2 PH.

## Conclusion

PH in HFpEF has similar pathophysiological mechanisms, which are also different from PH in HFrEF. In both situations, the patients' prognosis and the natural course of the disease are compromised, and there is no specific treatment for this comorbidity, beyond the already widely known standard treatment for the underlying disease, heart failure.

## Author Contributions

Conception and design of the research e Acquisition of data: Freitas Jr. AF, Frota DCR, Rassi S; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Freitas Jr. AF.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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