Review Article

Pulmonary arterial hypertension and heart failure with preserved ejection fraction: are they so discordant?

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Abstract: Heart failure with preserved ejection fraction (HFpEF) and pulmonary arterial hypertension (PAH) are two emerging diseases focusing the attention of numerous researchers. In the last PAH guideline, there is a crossroad between the two diseases and pulmonary hypertension (PH) due to heart failure (HF) is categorized as subtype 2. In order to assess the correct diagnosis and management, it should be better understood the points of convergence and divergence of two diseases. Although, risk factors, demographic characteristics and haemodynamics are different, we report several similarities regarding vascular alterations, some aspects of cardiac remodelling, and clinical presentation. This model suggests HFpEF and PAH as two comparable conditions, with different cardiac adaptation and trajectories, linked to the intrinsic properties of either right and left ventricles. In both diseases the early pathophysiological mechanisms appear to begin from peripheral vasculature and to be backward transmitted to the larger arterial vascular district, and eventually to the myocardial structure. In this paper we would propose a simple approach to recognize the concordances and, all at once, distinguish the peculiarities of the two diseases.

Keywords: Pulmonary arterial hypertension (PAH); heart failure with preserved ejection fraction (HFpEF); right heart (RH); pathophysiology

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Introduction

One of the most important diagnostic challenges in clinical practice is the distinction between pulmonary hypertension (PH) due to primitive pulmonary arterial hypertension (PAH) and PH due to left heart diseases (LHD). Both diseases deliver some common characteristics and pathophysiological pathways, making the two processes similar for several aspects.

If the presence of LHD is clear in many cases such as heart failure with reduced ejection fraction (HFrEF), in case of heart failure with preserved ejection fraction (HFpEF), given the patient's history and the clinical and echocardiographic findings, the LHD should be not evident.

HFpEF is a heterogeneous clinical syndrome, accounts about 50% of heart failure (HF) patients (1), and is characterized by the contemporary presence of several comorbidities, which often contribute to decompensate these patients (2). HFpEF patients, during an acute HF episode, experience an increase of left ventricle (LV) and left atrium (LA) filling pressures, with a passive backward transmission, often enhanced by a dynamic increase in mitral regurgitation and loss of LA compliance, leading to

PH. PH due to HFpEF (HFpEF-PH) usually is an isolated post-capillary (Ipc) PH, although in several cases it could be combined, pre- and post-capillary PH (3). According to the previous findings, HFpEF patients may show increased systolic pulmonary artery pressure (PAPs) in compensated phases, and in the most recent PH classification these patients are included in the second group including both patients with HFrEF and HFpEF (4). PAH represents a multifactorial disease, comprising genetic and molecular mechanisms, which involve primary pulmonary arteries structure and function, with subsequent implication of pulmonary circulation vascular beds (5,6). This syndrome results in remodelling of pulmonary arteries and right heart (RH), that is the main responsible of clinical presentation and outcome (7).

This review will aim to point out the points of convergence and divergence existing between PAH and HFpEF regarding prevalence, pathophysiology, clinical characteristics and outcome.

Definitions

According to the European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guidelines, PH is defined by right heart catheterization (RHC) estimation as an increase in mean pulmonary artery pressure (PAPm) ≥25 mmHg at rest (4). In this definition either PAH (Group 1) and PH due to LHD (Group 2) are included. Both diseases are characterized by increased pulmonary artery pressures, thus involving the right ventricle (RV), and causing RH failure. Currently, RHC is the only one method able to distinguish PH subgroups through direct hemodynamic measurements. In PAH, together with PAPm ≥25 mmHg at rest, there are two mandatory criteria for diagnosis: pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Woods unit (WU), in absence of chronic lung diseases, or chronic thromboembolic PH, or other rare diseases. This disorder involves pulmonary arteries with normal LA pressures. Otherwise, group 2 encompasses PH due to LHD (4). This group does not distinguish between two main HF phenotypes: PH in HFrEF and in HFpEF. Data from recent registries demonstrate that HFpEF is epidemiologically relevant, representing up to one half of HF population. Patients with HFpEF could develop PH as a result of increased LA pressure, and subsequent pulmonary venous congestion (8). This mechanism lacks of significant pulmonary vasoconstriction or remodelling and leads to development of Ipc PH-HFpEF. RHC shows PAPm ≥25 mmHg, PAWP >15 mmHg and PVR <3 WU, with clinical signs and symptoms of HF. In some case of HFpEF, a combined pre-capillary and post-capillary (Cpc) PH may be present because of chronic increased left-sided filling pressure and subsequent pulmonary arterial vasoconstriction and remodelling. In this subgroup, RHC shows PAPm ≥25 mmHg, PAWP >15 mmHg, and PVR >3 WU (3). Recently, the definitions have been changed including Ipc-PH and Cpc-PH (9).

Prevalence and outcome

Because of lack of randomization, confounding factors and selection bias, the registries evaluating the real incidence, prevalence and outcome of PAH in general population are extremely different. By literature only two registries in this setting have similar definitions and inclusion criteria: in the first French registry, prevalence and incidence of PAH in France were 15.0 cases/million of adult and 2.4 cases/million of adult for year. The same registry showed 1-year survival of these patients of 88% and 3-year survival about 60% (10,11). More recently, data from REVEAL registry showed that prevalence of PAH and idiopathic PAH were respectively 2.0–10.6 cases/million of adult and 0.9 cases/million of adult. Five-year survival rate of these patients ranged from 80% to 30% according to functional class I/II/III/IV and timing of diagnosis (newly versus previously diagnosis) (11-13).

The prevalence of PH-HFpEF, is still unclear. Most of the data are based on echocardiography examination and in particular on increased PAPs values. Data from TOPCAT trial demonstrated that percentage of patients with tricuspid regurgitant velocity >2.9 m/s (equivalent to estimated PAPs >35 mmHg) was 36% (14). In other studies, this percentage was higher ranging from 52% to 83% (15,16). This variability could be due to different PAPs cut-off values and non-invasive methodology employed to define PH. Similarly, the real prevalence of Cpc PH-HFpEF is under debate because lacking of reproducible hemodynamic findings. Several studies assessed the prevalence of Cpc PH-HFpEF from 7% to 12% (3,17). Although several studies demonstrated the strong relationship between increased PAPs and poor outcome, it appears plausible that Ipc PH-HFpEF has a better survival than Cpc PH-HFpEF (18,19). Therefore, the increased PAPs seems to be linearly related to outcome: the Danish multicentre study highlighted that a cut-off of 39 mmHg is able to discern subjects with worse

prognosis (20). According to this data Lam *et al.* showed that for every 10% of PAPs rise correspond a risk elevation of 28% during 3-year follow-up (15).

Histology

Parenchymal and vascular alterations in PAH and HFpEF have specific characteristics: in PAH the dysfunction occurs at pre-capillary site and it is mainly due to endothelial dysfunction causing capillaries and arteriole vasoconstriction, vascular obliteration and pulmonary blood fluid redistribution from basal site to apical district. Pulmonary vessels dysfunction is due to an increase of parietal fibrosis, extracellular matrix deposition, and myocyte hypertrophy related to the reduced vasodilatation properties of the endothelium. The initial alteration begins at peripheral pulmonary vascular level but it is quickly transmitted to the medium and larger arterial lumen up to the involvement of the two main branches of pulmonary artery. In the larger pulmonary vessel and increase of media and adventitia layers is appreciable, nevertheless due to the inconspicuous muscular component, the progressive lumen enlargement became evident after short period of PAH occurrence (5). In HFpEF the main pulmonary vascular alteration occurs initially at venous level and they are due to an increased venous lumen with a partial attempt of parietal thickness and collagen deposition. Enlarged veins and chronic congestion, lead to an increased vessel permeability related to the left atrial pressure increase. The reduced vein capacitance and relative pressure elevation are backward transmitted to the capillary district in which oxygen exchange became impaired. Due to the augmented extracellular capillary composition, gas exchange is reduced and it causes a further vasoconstriction. Such modifications could involve also the pulmonary arteriole developing a mixed PH with double pre and post capillary etiology (21).

Pathophysiology

Points of convergence

PH occurrence is the final stage of PAH and HFpEF, and RH adaptation is the common consequence of both diseases. The pathophysiological common pathway is probably the nitric oxide (NO)—soluble guanylate cyclase (sGC)—cyclic guanosine monophosphate (cGMP) inhibition. The reduction in NO delivery and production is well demonstrated by the clinical efficacy of therapies aimed to restore this pathway in PAH, although in HFpEF current drugs have been poorly tested and not significative benefit is reported. NO activates sGC by binding its prosthetic heme group, thereby catalyzing cyclic cGMP synthesis. cGMP causes vasodilation and may inhibit smooth muscle cell proliferation and platelet aggregation. Intracellular cGMP is rapidly inactivated to GMP by the activity of phosphodiesterases-5 (PDE-5). Inhibition of the cGMP-specific PDE-5 leads to an accumulation of cGMP, enhancing the action of NO (22). In PAH PDE-5 is the most abundantly expressed isoform and appears to be up-regulated. Similarly, in HFpEF cGMP phosphorylation leads to NO release inhibition, that impairs endothelial and cardiac elastance, and it increases the activation of protein kinase G responsible for an upregulation of titin isoform. This process appears mediated by increased inflammatory status, oxidative stress and increased pro thrombotic mechanisms.

These common bio-molecular adaptations could explain the occurrence of increased PVR, pulmonary vascular lumen narrowing due to thickening of the vessel media, changes in functional parameters of the lung vasculature, and RV hypertrophy in both diseases (23). The processes inducing RH adaptation are probably analogous in both diseases. The first portion of RH which bears increased pulmonary pressure is the outflow tract, that begins to distend; this process is associated to a myocardial fibres remodelling, stretching and thickening in all RV districts, but particularly in the right region of interventricular septum. When the thickening is the prevalent mechanism, it will afford an adaptive remodelling. Oppositely, when distention and stretching are the leading processes, a maladaptive remodelling will occur. Adaptive remodelling is characterized by more concentric remodelling (higher mass-volume ratio), with preserved RV systolic and diastolic function. Maladaptive remodelling appears to be a consequence of continuous RV pressure overload, leading to RV wall stress and dilatation, secondary tricuspid regurgitation and subsequent systo-diastolic dysfunction and failure (7,8,18). These mechanisms also lead to RV dyssynchrony, which depends on RV myocytes that prolong their contraction time delaying systolic leftward septal movement. Some other items, such as neuro-hormonal activation, coronary perfusion and myocardial metabolism could influence the severity of PH and RV remodelling. Another causal factor of maladaptive remodelling is ventriculo-arterial uncoupling, which represents the lack of relationship between RV contractility and afterload

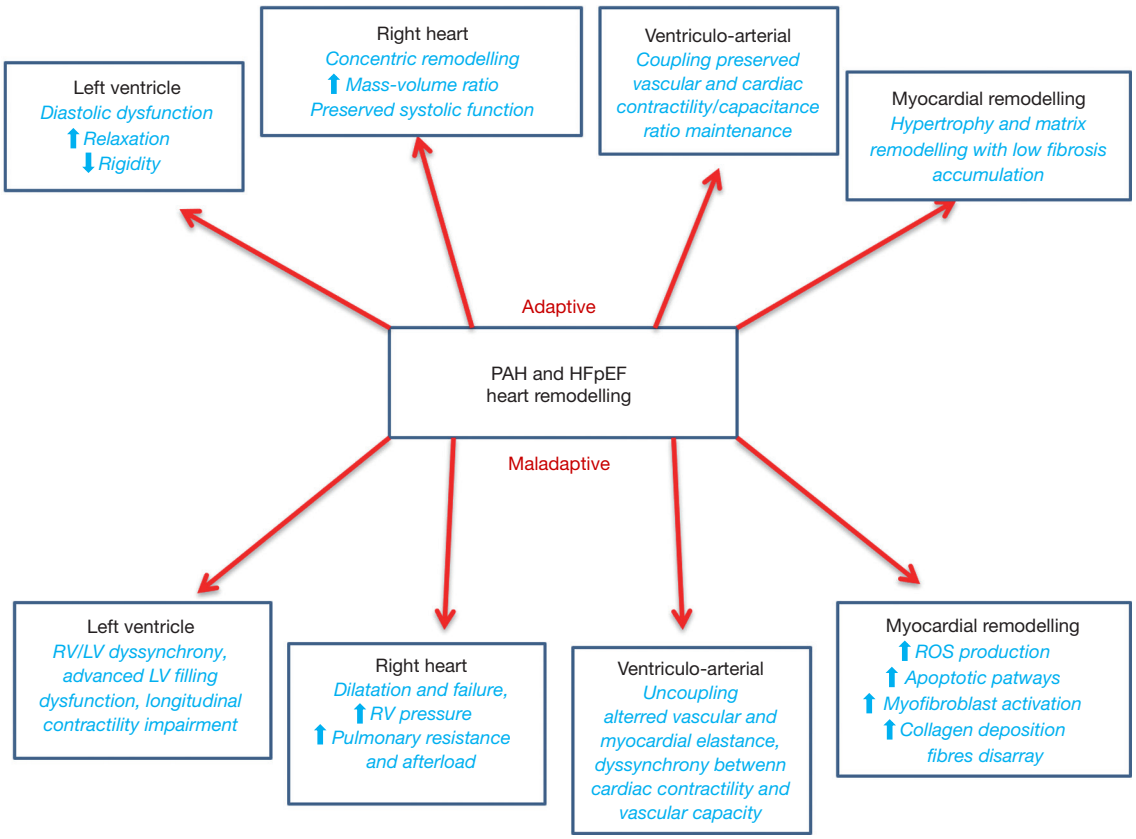

Figure 1 Heart remodelling in PAH and HFpEF. PAH, pulmonary arterial hypertension; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; RV, right ventricle; ROS, reactive oxygen species.

(3,24,25). This mechanism depends on lacking of ventricular and arterial elastance, and discordance between cardiac contractility and vascular compliance in the decompensated phases of both diseases.

In HFpEF, vascular and endothelial dysfunction increasing systemic vascular stiffness could be transmitted to the pulmonary circulation leading to, increase in cardiac afterload and RV chamber stiffness and hypertrophy. Thus, in more advanced stages LV and RV morphological adaptations became haemodynamically relevant, inducing altered filling pressure, myocardial relaxation and reduced compliance. Current haemodynamic and structural changes result in increased end diastolic pressure, reduced atrio-ventricular diastolic blood flow, and consequent fluid accumulation in pulmonary vein district (*Figure 1*).

Points of divergence

RH adaptive mechanisms are similar for both PAH and HFpEF, even if the reasons of increased pulmonary pressures are different. In PAH patients, PH is due to sustained vasoconstriction, pulmonary vascular remodelling, endothelial cell proliferation, and thus thrombosis *in situ*, which causes increased pulmonary arterial resistance. Inflammation and autoimmune mediators are involved in these mechanisms, as well as genetic factors (5). In particular, activation of the endothelin (ET) system is an exclusive determinant of PAH and the increased plasma and lung tissue levels appear one of the most important causative mechanisms. Indeed, ET blockade has become an important target for PAH treatment. The ET-1 exerts vasoconstrictor and mitogenic effects by binding two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, ETA and ETB receptors. ETB receptors are also present in the endothelial cells and their activation leads, in physiological conditions, to the release of vasodilators and antiproliferative substances, such as NO and prostacyclin, that may counterbalance the deleterious effects of ET-1. In

pathological condition, ETB receptors overexpression leads to vascular remodelling and narrowing (26,27). In HFpEF the ventriculo-arterial uncoupling has been recently described as substantial contributor identifying the lack of relationship between RV contractility and afterload. The main drivers of PH are impaired LV filling pressure due to diastolic dysfunction and impaired cardiac relaxation related to increased myocardial stiffness. Diastolic dysfunction occurs from increased type 1 collagen deposition in interstitial space and myocardial fibrosis. Increased stiffness is also related to cardiomyocyte hypertrophy structural disarray, cytoskeletal dysfunction, and titin alterations. All these alterations reduce cardiac elastance and increase myocardial rigidity, leading to a LV filling pressure increase (1,28). Thus, LV overload increases LA pressure, LA volume and remodelling, reducing fibres contractility and elastance. Permanent elevated LA pressure is transmitted backward to pulmonary veins and it promotes chronic pulmonary venous congestion, which in turns is responsible of pathologic changes in both arterial and venous districts. The elevated capillary pressure induces intimal fibrosis and medial hypertrophy, as well as luminal narrowing, with subsequent increased arterial resistance. The final product of all these factors is precapillary PH, defined as Cpc-PH in HFpEF. In this form, plexiform lesions pathognomonic of PAH are not found (3,8,9). Probably, the real causal factors of these microvascular and structural alterations are comorbidities, such as hypertension, diabetes and dyslipidemia. Ipc-PH and Cpc-PH represent two phases of the same process. During the early Ipc-PH phase, RV substantially maintains the systo-diastolic function, but undergoes adaptive remodelling (9).

RH characteristics

The initial RV dysfunction and subsequent maladaptive remodelling, are probably due to septal dysfunction. Indeed, a substantial component of RV contractility is due to LV, through shared short axis fibers and trans-septal contribution. In HFpEF patients, despite normal ejection fraction (EF), LV evidences some degrees of impaired contractility (due to reduced longitudinal systolic function or diastolic dysfunction) and consequently impaired RV/LV interactions (29). In this setting RV loses its ability to compensate the pressure overload, causing a ventricular-vascular uncoupling. This phenomenon is characterized by increased pulmonary arterial stiffness and increased afterload, leading to subsequent RV volumetric overload and irreversible failure (24,25) (*Figure 2*).

In a recent position paper about RV evaluation in HFpEF a staging based on clinical signs and RV dysfunction has been introduced. Although this classification is not yet supported by cross sectional data, it reflects the pulmonary and systemic congestion together with clinical assessment (7). Conversely to the LV, the RV is more compliant to volume loading even if the function of one ventricle is strictly dependent of the other and impacts to the opposite side by the pressure gradient across interventricular septum. Since RV dysfunction is more strictly related to afterload with respect to LV, identification of RV dysfunction may be better described in relation to ventriculo-systolic coupling. On the basis of different patterns and adaptations we can distinguish between appropriate and disproportional RV remodeling and these adaptations could vary in acute and chronic conditions as well as in PAH and in HFpEF. Although traditional approach in PH due to left-side HF encompasses post-capillary PH, some studies have recently demonstrated the concomitant presence of pre capillary PH even in HF due to left side dysfunction in a certain percentage of patients. In this subset hemodynamic is characterized by significant increase of both PVR and wedge pressure in combination with diastolic pressure gradient. The recognition of these patients appears of clinical relevance because of worse outcome and much more deterioration of RV contractility associated with RV and RA larger dimension and further pulmonary pressure increase. This is confirmed by recent study comparing echo with haemodynamic data in which patients with combined pre and post capillary hypertension had impaired outcome compared with isolated post capillary hypertension (9).

In primitive PAH, RV maladaptation occurs over a short timing course because of poor adaptation of RV to the sudden pulmonary pressure increase and pre capillary overload. RV dilatation with specific enlargement of the outflow tract reflecting increased PVR is typical. Therefore, in a consistent percentage of PAH patients a dilatation of main pulmonary tract is appreciable. The systolic function in terms of RV EF and longitudinal function are both reduced and both pulmonary and tricuspid regurgitation became significative after early period. Due to the persistent post load increase, the tricuspid annulus tends to became enlarged with further increase of valve regurgitation and RA dilatation. Increased RA pressure leads to reduced systemic vein return and central vein pressure elevation.

The above described characteristics, are replaced by invasive haemodynamic analysis: the main difference

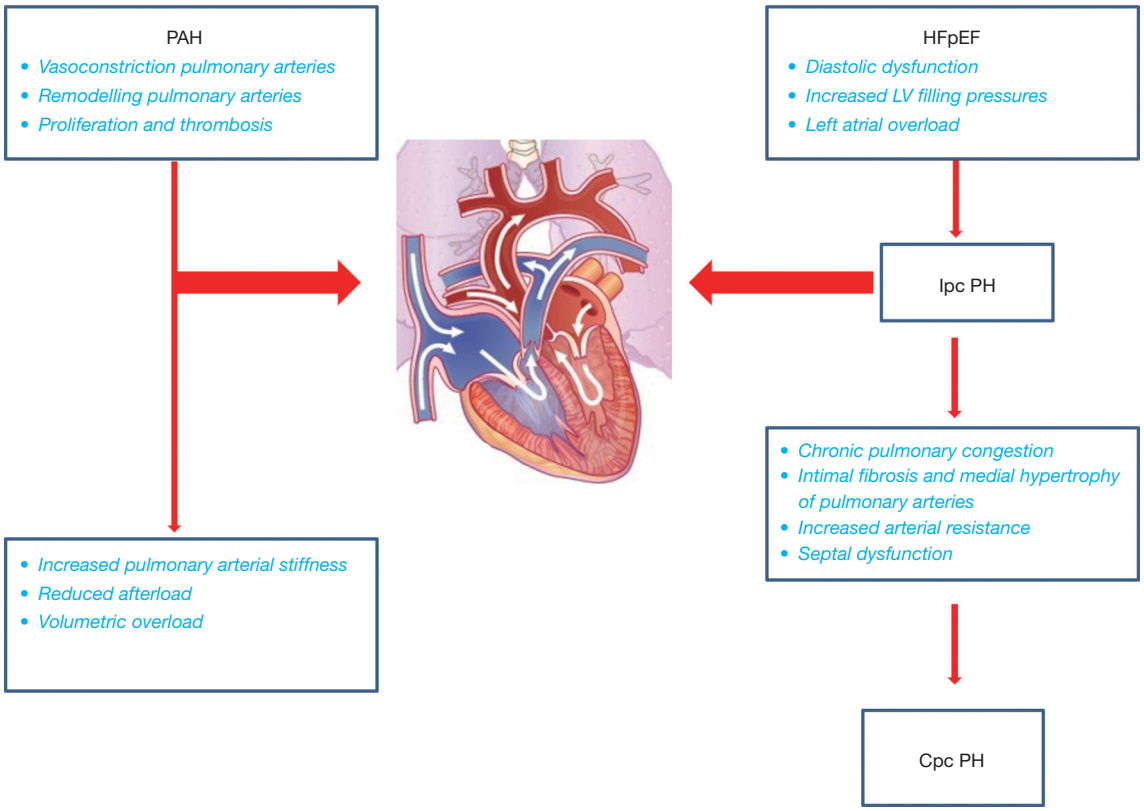

Figure 2 Pulmonary hypertension pathophysiology in HFpEF and PAH. PAH, pulmonary arterial hypertension; HFpEF, heart failure with preserved ejection fraction; Cpc, capillary and post-capillary; Ipc, isolated post-capillary; PH, pulmonary hypertension.

between PAH and HFpEF patients is PAWP. This measurement is a mirror of increased LA pressures and should be recorded as the mean of three measurements. Some patients have PAWP =15 mmHg and are initially classified in PAH group (4,8,30,31). To elucidate this situation, it could be helpful a bolus administration of 500 mL of saline solution, which causes increase in LV filling pressures, LA pressure overload, and subsequent increased PAWP (>15 mmHg) (32). Another invasive parameter able to discriminate PAH from HFpEF patients is PVR. This value is >3 WU in patients with pre-capillary PH, but lower in HFpEF (33). The measurements capable to differentiate HFpEF patients in Ipc-PH or Cpc-PH are trans-pulmonary gradient (TPG = PAPm – PAWP) and diastolic pulmonary gradient (DPG = diastolic PAP – PAWP). In patients with Ipc PH-HFpEF, TPG is <12 mmHg, DPG <7 mmHg, PAWP >15 mmHg and PVR <3 WU. Patients with Cpc PH-HFpEF due to vascular remodelling and subsequent precapillary PH, display PAWP >15 mmHg, DPG ≥7 mmHg and PVR >3 WU (9,16,32,34-36). Finally, in PAH patients who underwent RHC, a vasoreactivity test is usually also done. This test consists of administration of intravenous (IV) adenosine, IV prostacyclin, in order to assess pulmonary artery pressures reduction. If PAPm reduction is >10 mmHg, with an absolute value of PAPm <40 mmHg, patients have a positive response, which permits the treatment with high dose of calcium channel blockers (4). By now, RHC remains the universal method able to discern patients with precapillary PH (*Table 1*).

Clinical characteristics

Points of convergence

The first common point between PAH and HFpEF is gender. In both PAH and HFpEF females are more often affected, with a particularly high percentage in PAH, ranging from 60% to 80% (10,12,13,30). Similarly, many studies confirmed in HFpEF the female gender prevalence, ranging from 50% to 70% (30,31,37-43).

Table 1 Echocardiographic and hemodynamic difference between PAH and HFpEF

Variables	PAH	HFpEF
Echocardiographic variables		
LV ejection fraction (%)	≥50	≥50
Left atrial enlargement	Rare	Present
Right atrial enlargement	Present	Rare
RV hypertrophy	Common	Rare
LV mass index	Normal	Increased
LV hypertrophy	Absent	Present
Lateral mitral E/E'	<8	≥12
Diastolic dysfunction degree	Grade I	Grade II and III
RVOT mid-systolic notching	More frequent	Less frequent
Mitral flow DT (ms)	>200	<200
Hemodynamic variables		
LA pressures (mmHg)	Normal	Increased
PAPs (mmHg)	≥40	≥40
PAPm (mmHg)	≥25	≥25
PAWP (mmHg)	≤15	>15
PVR (WU)	>3	≤3

PAH, pulmonary arterial hypertension; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; RV, right ventricle; E/E', ratio of peak early Doppler mitral valve flow velocity and early diastolic mitral valve flow velocity; RVOT, right ventricular outflow tract; DT, deceleration time; LA, left atrium; PAPs, systolic pulmonary artery pressure; PAPm, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance.

Clinical presentation of both diseases is comparable. The most common symptoms are shortness of breath, fatigue, weakness, angina and syncope. These symptoms are not specific and mainly related to increased RV pressures (3,4). During the early stage, both HFpEF and PAH patients complain of shortness of breath during exercise. In PAH this symptom is sometimes associated with nausea and dyspepsia (4). In more advanced stages, a sustained increase of pulmonary pressure could lead to RV failure and central venous pressure increase. During end-stages of both diseases, independently from etiology, patients show symptoms and signs of congestion: dyspnea at rest, jugular venous dilation, hepato-splenomegaly, ascites, peripheral oedema and cool extremities (4,44). The untreatable systemic congestion is the final clinical picture of both diseases, although in subjects with HFpEF an arrhythmic adverse event could occur earlier.

Points of divergences

PAH and HFpEF are quite distinct respect to epidemiological and demographic findings. Firstly, patients with diagnosis of HFpEF are older (about 60–70 years) than patients affected by PAH (35–50 years), even if most recent registries of idiopathic PAH show a trend towards an increased mean age (up to 70 years) (10-13,37-43). HFpEF patients demonstrate a higher rate of traditional risk factors and comorbidities in comparison with PAH patients. HFpEF subjects have, respect to PAH patients, higher prevalence of atrial fibrillation (AF), hypertension, LV hypertrophy, and diabetes. Several studies confirmed the high comorbidities burden of HFpEF. The MAGGIC registry showed an elevated prevalence of hypertension, AF, diabetes and coronary artery disease (40). The I-PRESERVE trial evidenced in hospitalized patients an even higher prevalence of hypertension (86%), AF (34%) and diabetes (31%) (41).

Table 2 Demographic and clinical characteristics in PAH and HFpEF patients

Variables	PAH	HFpEF
Demographic characteristics		
Age (years)	40–65	60–70
Female gender (%)	60–80	50–70
WHO functional class	III/IV	III/IV
BMI (kg/m^2)	~26	~30
Comorbidities		
Hypertension (%)	20–30	50–85
Diabetes mellitus (%)	5–10	30–50
Obesity (%)	10–15	30–40
Coronary artery disease (%)	4–7	20–35
Renal dysfunction	Absent	Common
Atrial fibrillation	Rare	Common

PAH, pulmonary arterial hypertension; HFpEF, heart failure with preserved ejection fraction; BMI, body mass index.

Furthermore, the OPTIMIZE-HF registry, comparing HFpEF to HFrEF, showed that patients with preserved EF were more likely to be older, female, and to have non-ischemic etiology (42). Bhatia *et al.*, in a population-based study reported an increased rate of hypertension (51% *vs.* 49%), AF (32% *vs.* 23%) and diabetes (32% *vs.* 38%) in HFpEF respect to HFrEF (43). The only cross-sectional study comparing PAH and HFpEF showed that HFpEF patients presented higher mean age (69 *vs.* 47 years), body mass index (30 *vs.* 26 kg/m^2), and rate of diabetes (57% *vs.* 19%) (37). Thenappan *et al.* studied the comorbidities burden in HFpEF patients, and found that indeed these patients appear more frequently affected than PAH patients by obesity (46% *vs.* 15%), coronary artery disease (27% *vs.* 4%), hypertension (79% *vs.* 29%), diabetes (37% *vs.* 8%), and renal dysfunction (30) (*Table 2*).

Non-invasive diagnostic tools

Points of convergence

Echocardiography is the most usual imaging tool to assess LV and RV morphology and function. In either PAH and HFpEF, the common point in between is the normal range of LV systolic function. Both diseases show preserved LV EF, defined as EF ≥50%. Moreover, all these patients experience an increased PAPs value ≥35 mmHg in the first phases. In more advanced stages with severe RV dysfunction, echocardiographic findings remain similar: both diseases are characterized by reduced tricuspid annular plane systolic excursion (TAPSE) <16 mm, RV outflow tract enlargement and RV dysfunction (45-47). An emerging technique for RV study is cardiac magnetic resonance (CMR). Cine CMR, can precisely measure RV EF, stroke volume, and segmental and global parietal kinesis, as well as eventual dyssynchrony between the RV and LV chambers. The RV outflow tract and pulmonary valve morphology, difficult to visualize by traditional ultrasound, can also be detected by this technique. CMR also provides information on pulmonary arteries dimensions, distensibility, and lung blood flow distribution, that can be reduced in the apical segments (48,49). Oppositely, other diagnostic methods, such as electrocardiogram (ECG), chest X-ray and natriuretic peptide measurement are discordant in PAH and HFpEF.

Points of divergence

Different ECG patterns characterize PAH and HFpEF. Most patients with PAH are in sinus rhythm with QRS right axis deviation and RV hypertrophy. Oppositely, in HFpEF, there is often AF, with LV hypertrophy and left axis deviation. Chest X-ray pattern is often different: it is possible to observe enlarged RH profile with dilated pulmonary artery in PAH; lung-heart arc, pulmonary

congestion and Kerley B-lines appear more pronounced in HFpEF (4,8,29,44). On echocardiography patients with HFpEF present LV hypertrophy and LA dilatation, absent in PAH. The LA enlargement is the real echocardiographic sign to discriminate both diseases. In PAH LA is into normal range and in advanced phases, it is possible to observe RA enlargement with pressure overload (4,8,50). Echocardiography could also assess various diastolic dysfunction degrees. Isovolumic LV relaxation time (IVRT), ratio of peak early (E) and peak atrial (A) Doppler mitral valve flow velocity (E/A), deceleration time (DT), and ratio of E and early diastolic mitral valve flow velocity (E') (E/E') are all measures of diastolic function. In HFpEF patients there are low E/A, prolonged DT and increased E/E', providing diagnostic evidence of diastolic dysfunction. In particular, an elevated E/E' ratio >15 is an unmistakable sign of raised LV filling pressure. In this sense, HFpEF shows a typical pattern defined by increased E/E' (≥12), increased E/A (>0.8) and reduced DT (<200 ms), with pseudonormal or restrictive filling trans-mitral patterns. In PAH patients it is possible to observe mild diastolic dysfunction with abnormal relaxation pattern (grade I), with E/E' <8 and DT >200 ms (8,30,33,51). RV outflow tract mid-systolic notching pattern, evaluable on pulse-wave Doppler echocardiography, could assist in characterization of PVRs and hemodynamic proprieties of PH (8,31). Finally, laboratory parameters used in HF diagnosis, as B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NTproBNP), are elevated in both diseases; however, HFpEF patients show higher serum levels of natriuretic peptides respect to PAH patients (4,44,52) (*Table 1*).

Conclusions

Although HFpEF and PAH are two distinct diseases, with peculiar pathophysiological and causal factors, for some aspects they appear similar. Both illnesses seem to arise at peripheral level, at systemic and pulmonary vascular districts respectively, with comparable alterations into arterial and pulmonary capillary structures (53). At vascular systemic level, endothelial dysfunction and vessel rigidity are induced by reduced NO availability, increased oxidative stress and rigidity, probably mediated from several external factors, such as elevated comorbidity burden and metabolic diseases. Similarly, at pulmonary level the increased pressure results first in vasoconstriction and reduced compliance, mediated by cGMP reduction and abnormal ET levels. In both diseases vascular modifications are characterized by collagen deposition, vascular narrowing, smooth muscle cells migration and over expression. The different central cardiac adaptations depend on intrinsic characteristics of the LV and RV. Thus, the two processes tend to distinguish each other because of different adaptation mechanisms and different capacity to respond to increased afterload. From functional and morphological points of view, they have further similarities, due to preserved LV EF and dilated RH, with common increase in pulmonary pressure values. The only typical divergences are the precapillary pressure and PVR values, which in turns are due to different vascular and cardiac compensation mechanisms in either pulmonary and systemic districts. Similarly, tailored therapy really effective on outcome in both diseases is still lacking. Most clinical studies found some improvement in exercise capacity, quality of life, and pulmonary pressure, but they failed to demonstrate a significant benefit in terms of mortality. Because of the above cited biomolecular convergences, current and novel treatments proposed in PAH should be tempted also in HFpEF, and vice versa. A new agenda, clarifying the precise vascular dysfunction mechanisms in PAH and HFpEF, appears mandatory to optimize management and ameliorate the life expectancy in both conditions.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure forms (available at: http://dx.doi.org/10.21037/cdt-19-405). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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