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REVIEW

Novelties in Pulmonary Hypertension Secondary to Left Heart Disease

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ABSTRACT

Pulmonary hypertension due to left heart disease (PH-LHD) is the most common form of PH affecting approximately 1% of adults worldwide. Initially considered as just a passive consequence of increased pressure in the left chambers, new evidence shows the potential role of genetics, biological factors, or left atrial function. Along with the hemodynamic study, cardiac imaging techniques are essential to advance in the characterization of patients and select therapeutic strategies. Orphan of pharmacological treatments, new therapeutic targets are currently under investigation. The current review aims to review novelties in the fields of pathophysiology, diagnosis, and treatment in this entity.

Keywords: Left heart disease. Novelties. Pulmonary hypertension group 2.

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INTRODUCTION

Pulmonary hypertension (PH) involves multiple diseases characterized by increased pulmonary arterial pressure (PAP) and right ventricular (RV) dysfunction. They are currently classified into five groups by the World Health Organization based on common clinical characteristics, pathophysiological basis and hemodynamics[1,2] (Table 1). Group 2 or PH due to left heart disease (PH-LHD) represents the most prevalent form of PH worldwide. Up to two-thirds of the patients with heart failure (HF) with both reduced (HFrEF) and preserved (HFpEF) left ventricular ejection fraction[3-5] develop PH. Considering that HF affects 1-2% of the world population in developed countries, reaching up to 10% of patients older than 70 years, it is estimated that the prevalence of PH-LHD is around 1% of the adult population[6]. In addition, this prevalence is expected to increase in the following decades because of the aging population and the improvement in survival from cardiovascular processes.

Current clinical guidelines define PH as a mean PAP ≥ 25 mmHg measured by right heart catheterization (RHC)[2] however, a lower threshold of 20 mmHg in mean pulmonary artery pressure (mPAP) has been suggested in the last World Symposium on PH[1]. This proposal is based on an observed higher mortality in patients with mean PAP between 20 and 25mmHg compared to healthy individuals[7]. PH-LHD diagnosis also requires a pulmonary artery wedge pressure (PAWP) value > 15mmHg, a surrogate of left atrium (LA) pressure overload[2]. In this regard, an accurate determination of PAWP is critical to correctly classify patients with PH[8]. In addition, based on the presence of a precapillary component, PH-LHD can be further classified into isolated postcapillary PH (IpcPH) or combined pre- and post-capillary PH (CpcPH). CpcPH is characterized by higher pulmonary vascular resistance (PVR), more severe pulmonary arterial remodelling and poorer prognosis[9-11]. Table 1 shows the diagnostic criteria for both entities.

PH confers a higher risk to LHD patients. The incremental risk is associated with the hemodynamic severity[12] and more especially with the RV adaptation and failure[13]. Moreover, the excess in mortality in patients with borderline PAP values has also been confirmed in PH-LHD in a large cohort of patients[7]. Due to its high prevalence and associated bad prognosis, PH-LHD is currently considered a relevant medical need that deserves dedicated research. In the present paper, we will review novelties in the physiopathology knowledge, diagnosis, and management of the disease.

NOVELTIES IN THE KNOWLEDGE OF PH-LHD PHYSIOPATHOLOGY

Figure 1 illustrates the main physiopathological mechanisms of PH-LDH.

The continuum concept in PH

Despite PH groups 1 (pulmonary arterial hypertension [PAH]) and group 2 being traditionally considered completely distinctive entities, some researchers have pointed out a possible continuum of the disease from IpcPH to typical PAH, being CpcPH and atypical PAH halfway (Fig. 2). In this sense, several studies have shown a similar degree of pulmonary arterial remodelling in PAH and

Table 1. Hemodynamic and WHO classification of pulmonary hypertension

	Pulmonary hemodynamics	WHO classification
PH	mPAP ≥ 25 mmHg*	All
Precapillary PH	mPAP ≥ 25 mmHg*	Group 1 Pulmonary arterial hypertension
	PCWP ≤ 15 mmHg	Group 3 PH due to lung disease
	DPG ≥ 7 mmHg	Group 4 CTEPH
		Group 5 PH with multifactorial or unclear mechanism
Postcapillary PH	mPAP ≥ 25 mmHg	Group 2 PH LHD
	PCWP > 15 mmHg	
	DPG < 7 mmHg and/or PVR ≤ 3 mmHg	Isolated postcapillary PH
	DPG ≥ 7 mmHg and/or PVR > 3 mmHg	Combined pre- and postcapillary PH

*A threshold of 20 mmHg instead of 25 mmHg has been suggested in the last World Symposium on Pulmonary Hypertension[1].
CTEPH: chronic thromboembolic pulmonary hypertension; DPG: diastolic pulmonary gradient; mPAP: mean pulmonary artery pressure; LHD: left heart disease; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; WHO: World Health Organization.

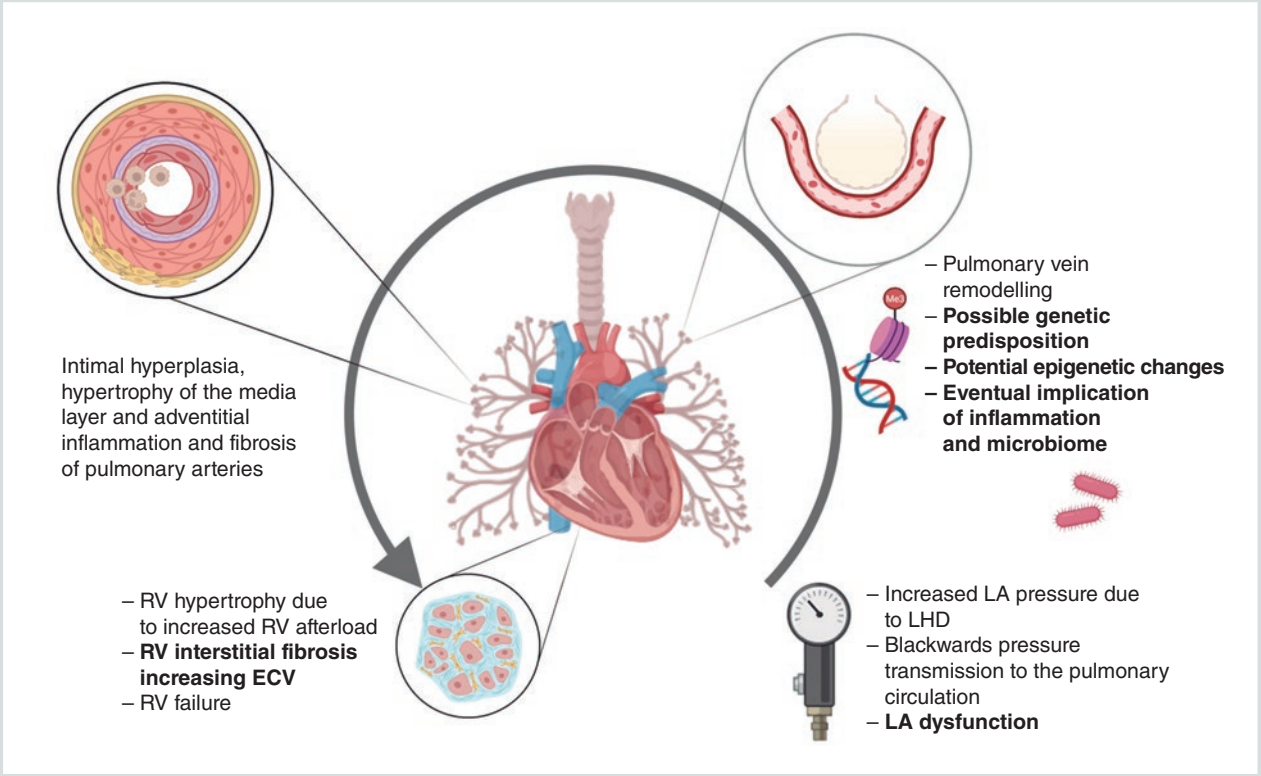

Figure 1. Main pathophysiological mechanisms involved in pulmonary hypertension due to left heart disease. In bold letters: novel mechanisms recently suggested to play a role in the physiopathology of the disease. Created with BioRender.
ECV: extracellular volume; LA: left atrial; LHD: left heart disease; RV: right ventricular.

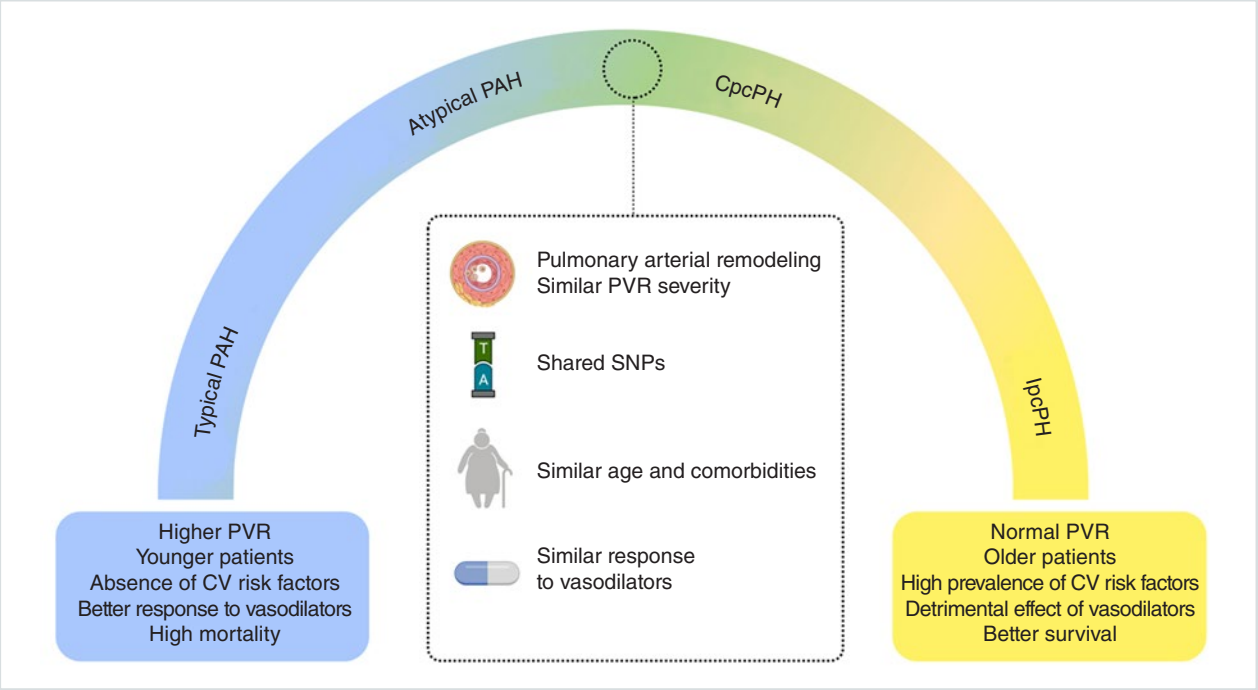

Figure 2. Spectrum of patients' characteristics from typical pulmonary hypertension to isolated postcapillary pulmonary hypertension and shared characteristics between atypical pulmonary arterial hypertension and combined pre- and postcapillary pulmonary hypertension. Created with BioRender.
CpcPH: combined pre- and postcapillary pulmonary hypertension; CV: cardiovascular; IpcPH: isolated postcapillary pulmonary hypertension; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistances; SNPs: single nucleotide polymorphisms.

CpcPH. Investigators from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) study found that patients with Cpc-PH closely resembled patients with PAH and associated cardiovascular risk factors (known as atypical PAH) in terms of clinical characteristics, hemodynamics, response to therapy and mortality[14]. Further evidence of this concept comes from the study of Assad et al.[15], who found a substantial number of single-nucleotide polymorphisms to be common between patients with CpcPH and PAH patients. Due to the challenging differential diagnosis in some patients, a pre-test evaluation to establish an LHD phenotype has been proposed during the 6th World Symposium on Pulmonary Hypertension[16] and extensive research is currently ongoing to better classify patients' phenotypes.

Fixed pulmonary hypertension

Fixed PH is considered irreversible if it persists after an acute vasodilator administration. Although related to the superimposed pre-capillary component in Cpc-PH patients, they are not synonymous terms. Fixed PH is of special interest in patients with advanced heart failure as it is one of the main concerns regarding eligibility for heart transplantation

(HT). The presence of fixed PH critically associates with the development of acute graft dysfunction after HT due to the damage of pressure overload in a non-adapted, stunned and ischemic RV. Values of PVR > 5 and gradient transpulmonary (GTP) > 16 after a vasodilator testing represent a contraindication for HT in most centers, while patients with PVR > 3 and GTP > 14 are considered high-risk recipients[17,18]. In the study by Ghio et al.[19] pulmonary hemodynamics improved significantly more in Cpc-PH than in Ipc-PH patients after vasodilator challenge, but the first maintained an unfavourable pulmonary arterial compliance (PAC)-PVR relationship and worse prognosis. These results suggest that the baseline hemodynamic profile (Cpc-PH versus Ipc-PH) cannot be used to predict the presence of irreversible PH (also known as fixed PH). Interestingly, PAC was the only hemodynamic parameter related to the irreversible component in Cpc-PH patients. The same authors subsequently showed that PAC < 1.2 mL/mm, and also diastolic blood pressure < 70 mmHg and PVR > 5 Wood units, were independently associated with a poor response to vasodilator testing and the presence of two of them was associated with a 90% of being a nonresponder[19].

Different treatment options have been tested in the scenario of fixed PH, including pharmacological approaches such as PAH vasodilators, or mechanical therapies as left ventricular support. The latest has shown better results regarding the hemodynamic profile with a greater reduction in PVR and improvement in cardiac output[20,21]. Moreover, long-term outcomes in patients treated with left ventricular assist device (LVAD) as a bridge to HT in the context of fixed PH seem not to differ from patients in which no fixed PH is present[22].

Differences in PH-HFrEF and PH-HFpEF

Postcapillary PH initiates by persisting backward transmission of elevated filling pressures in the left heart; however, differences regarding patient characteristics, putative molecular pathways associated with its development and persistence, and potential treatment vary between patients with HFrEF and HFpEF.

As brilliantly reviewed by Guazzi et al.[23], LA pressure elevation depends on LA adaptation to the type of LV remodeling, which in turn varies in HFpEF and HFrEF. In HFpEF, LV is characterized by concentric hypertrophy and increased diastolic stiffness, being hypertension, obesity and diabetes the main comorbid associated conditions. These conditions may directly affect the myocardium by stimulating oxidative stress, hypertrophy and inflammation, increasing collagen proliferation and consequently LV stiffness[5,24]. On contrast, LV involvement in HFrEF is mainly driven by excessive wall stress and ischemia causing chamber dilatation and eccentric hypertrophy. In this scenario, LA typically develops enlargement and eccentric remodeling due to severe mitral regurgitation (MR), whereas in HFpEF the LA becomes stiffer earlier, dilates more slowly and presents a higher incidence of atrial fibrillation[25]. Adir et al.[26] compared pulmonary hemodynamics in response to LA pressure elevation in PH-HFrEF and PH-HFpEF and found that for similar PAWP, PH-HFpEF presented higher diastolic pulmonary gradient (DPG) and PVR, similar PAC and less MR, suggesting more pronounced pulmonary vascular disease under similar pulsatile loading possibly associated with a more pronounced inflammatory environment. Patient phenotyping by

machine learning that includes hemodynamics, imaging and omics data may help to identify the future subsets of patients that could benefit from specific treatments (i.e., mitral reparation, LVAD, anti-inflammatory drugs, or others).

The role of the left atrium

The LA has acquired great value within the HF-PH continuum in recent years. The structural and functional changes in the LA are usually due to a chronic increase in intraatrial pressure which is transmitted to the pulmonary circulation, both at rest and especially under exercise.

LA remodeling is typically studied by echocardiography. Nowadays, the indexed volume of the LA has been consolidated as the best parameter for establishing structural changes and it is also well correlated with the risk and events due to HF[27]. According to the latest recommendations of the American and European guidelines[28], the dilation of the LA is defined as > 34 ml/m^2. LA is a dynamic structure that plays a role as a reservoir, passive conduit, and priming pump for the LV. The loss of atrial function contributes significantly to the onset of symptoms and progression of HF and can be determined using LA speckle-tracking/strain techniques. The most used techniques to study the LA function are the assessment of LA global strain (LA-GS) and its reservoir function determined by the peak of positive deformation of longitudinal LA strain (PALS). Numerous studies have shown that decreased LA strain is correlated with a worse prognosis, even independently of LA dilation and HF subtypes[29,30]. There is also a good correlation between the reduction in PALS and PAWP[29,30]. As already commented, LA remodeling is different in patients with HFrEF, who present greater eccentric atrial dilatation, and HFPEF, in which atrial stiffness predominates. Different structural phenotypes and atrial adaptation to exercise could explain the typically better pulmonary vasculature profile in patients with HFrEF[3,26]. Regardless of its phenotype, patients with impaired LA function, measured by strain, have higher PVR, lower PAC, and poorer RV function[32].

Genetics

Evidence regarding genetics in PH-LHD is scarce as compared with the available evidence in PAH. Rare mutations in genes typically involved in PAH disease, such as BMPR2, have been seldom described in patients with CpcPH[33]. In a cohort of patients with CpcPH, the presence of nitric oxide synthase (NOS3) rs1799983 polymorphism correlated with the transpulmonary gradient (TPG), suggesting a potential role of endothelial NOS in the pronounced pulmonary remodeling observed in CpcPH[34]. Assad et al.[15] found that CpcPH and PAH patients shared 75 single-nucleotide polymorphisms involving cell structure, extracellular matrix, and immune function, also suggesting a genetic predisposition for the development of exaggerated pulmonary vascular disease.

Interestingly, we know that genetics are not limited to the inherited genetic material but also to the result of its interaction with the environment through methylation, non-coding RNA and chromatin modification. Recent evidence points to the involvement of epigenetic changes in the pathogenesis of PH[35]. In this sense, miR-206, a muscle-specific RNA

associated with the regulation of cardiac myocytes and PA smooth muscle cell growth, has been found to be decreased in patients with PH-LHD[36].

The microbiome

Studies in HFrEF patients have shown changes in the composition of the microbiome [37-40] in both directions: a significantly higher intestinal permeability and larger quantities of pathogenic bacteria and candida species[37], and downregulation in key intestinal bacterial groups, such as Blautia, Collinsella, uncl. Erysipelothrichaceae and uncl. Ruminococcaceae[38]and Eubacterium rectae and Dorea longicatena, compared to healthy individuals[39]. Interestingly, Kummen et al.[40] reported an association between a low abundance of Lachnospiraceae NC2004 and T-cell activation marker soluble CD25, thus suggesting that altered gut microbiota might be associated with persistent T-cell activation. Trimethylamine-N-oxide (TMAO), a gut microbe-dependent metabolite of dietary choline and other trimethylamine-containing nutrients, is elevated in HF patients and has been related with cardiomyocyte mitochondrial dysfunction[41], myocardial hypertrophy and fibrosis in an experimental model of HF[42]. Regarding clinical implications, few trials have studied the effect of probiotics on heart disease with contradictory results. A pilot study by Costanza et al.[43] observed that a 3-month therapy with S. Boulardii resulted in a reduction of LA diameter and an improvement of LV ejection fraction. However, these results were not confirmed in a recent larger trial[44]. In this trial, neither S. boulardii nor rifaximin, an oral antibiotic with bactericidal activity against a broad array of enteric pathogens, had a significant effect on LV ejection fraction, microbiota diversity and function, circulating levels of TMAO or systemic inflammation. Although no specific studies are available addressing microbiome in PH-LHD, it is expected that if it is associated with the severity of HF, it will be also associated with an increased incidence of secondary PH. In addition, microbiome has shown predictive potential for PAH which opens the door for other forms of PH[45]. In this sense, projects like the Human Microbiome Project[46] will shed light to this branch of knowledge.

NOVELTIES IN THE DIAGNOSIS OF PH-LHD AND SUBTYPES

Figure 3 shows schematically the main tests performed for the diagnosis of PH-LHD.

Hemodynamic indices

The TPG, traditionally used for the definition of CpcPH, was removed from the latest clinical guidelines because it was considered to be easily influenced by volume load and LV filling pressure[47]. Instead, guidelines introduced a new approach using the DPG. This change was argued based on vascular physiology, as the pulmonary flow during diastole is low and thus less affected by loading conditions and stroke volume[47], and evidence of the correlation between DGP with histological pulmonary arterial remodelling[48]. However, DPG has not been definitively adopted by the cardiology scientific community for several reasons. On the one hand, DPG has not been demonstrated to increase the prognostic value of TGP or PVR in specific populations such as cardiomyopathies[49] or recipients of HT[50]. On

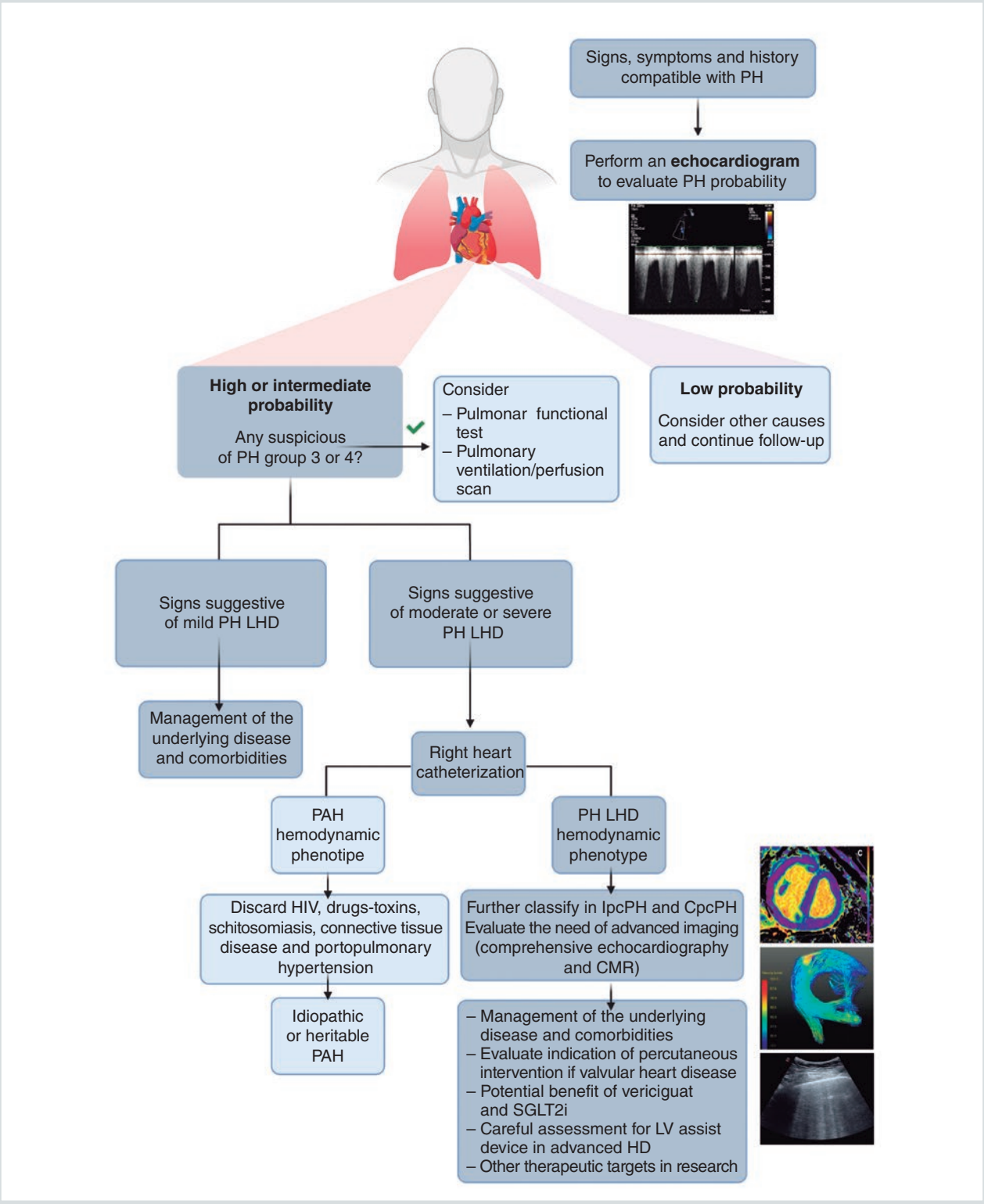

Figure 3. Diagnostic flow in patient with suspicion of PH. Created with BioRender.
CpcPH: Combined pre- and postcapillary pulmonary hypertension; ISGLT2: Sodium glucose co-transporter 2 inhibitors; LHD: left heart disease; LV: left ventricle; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension.

the other hand, DPG often presents a negative value related to errors in measuring the PAWP as observed in the metanalysis by Caravita et al.[51]. This metanalysis showed a 2% increase in the risk for events for every unitary increase in DPG, comparable with the prognostic impact of PVR[51]. For all this, PVR is currently considered the most robust parameter to define a pre-capillary component. New guidelines, expected to be published soon, will clarify the best approach to discriminate the specific subgroups of PH-LHD.

Two other hemodynamic parameters have gained attention in recent years: pulmonary artery pulsatility index (PAPi) and PAC.

PAPi, calculated as the ratio between PA pulse pressure and right atrial pressure, confers valuable information regarding the RV function. It has shown independent prognostic value for mortality or need for hospitalization in chronic HF[52] and, recently, in dilated cardiomyopathy[53]. Also, it has been demonstrated to predict RV failure, acute kidney injury and one-year mortality in patients undergoing HT[54] as well as the evolution of pulmonary hemodynamics after LVAD implantation[55].

PAC, calculated as SV/(sPAP-dPAP) (SV: stroke volume; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure), is a strong prognostic factor in postcapillary PH[56]. Lower indexed PAC has been associated with increased risk of right HF and mortality following LVAD implantation[57]. PAC tends to improve rapidly after LVAD implantation[58] which translates into an improvement in RV afterload[59]. However, in Cpc-PH patients PAC has been shown to remain lower at one year after HT[60].

Echocardiography

Current guidelines propose a new algorithm to assess the probability of PH depending on the tricuspid regurgitation peak velocity (TRPV) and indirect signs of PA-RV adaptation such as the PA diameter, the dilatation of the right atria or the interventricular septum flattening[2]. Although sPAP estimation by echocardiography is not an accurate diagnostic measurement, it retains an intrinsic value regarding risk stratification[61]. In addition, new non-invasive methods to differentiate between precapillary and postcapillary PH have been postulated. Thereby, Scalia et al.[62] found that the echocardiographic pulmonary to left atrial ratio, calculated as TRPV divided by the mitral E/e' ratio, significantly differed between patients with precapillary and postcapillary PH, and between IPcPH and CpcPH. Venkatesvaren et al.[63] used a slightly different approach by using the echocardiographic pulmonary to left atrial global strain ratio (TRPV/LA global strain) with similar results.

The accessibility of echocardiography as a non-expensive, non-invasive technique able to evaluate the right heart, great veins and proximal pulmonary artery confers a great value in all forms of PH. However, due to the retrosternal position and complex geometry of the RV, its evaluation by echocardiography continues to be challenging. In this regard, the use of 3D techniques and strain has gained relevance based on their increased reproducibility and prognostic value[64,65].

Lung ultrasound

Lung ultrasound (LUS) has emerged as a semi-quantitative, simple, and reliable method

to assess pulmonary congestion through the identification of "B-lines" (also known as "lung comets"). LUS had been routinely used for the differential diagnosis of acute dyspnoea but in recent years, its role has been extended to monitor congestion in patients with HF which associates with the probability of readmission[66]. The same group also reported the correlation between dynamic PAWP changes after volume administration with the increase of B-lines during LUS monitoring in patients with HFpEF and unexplained dyspnoea[67]. Similarly, Scali et al.[68] showed the exercise-induced B-lines in patients with HFrEF and their correlation with basal natriuretic peptides and maximum peak oxygen consumption. Moreover, the presence of more than 30 B-lines during exercise was significantly associated with cardiovascular events during a 12-month follow-up. These and other studies support the possibility of monitoring pulmonary congestion during exercise, and this aspect could help in the etiologic diagnosis of PH. The increase in the number of B-lines during exercise and, especially, their correlation with the systolic PAP estimated by echo, could guide the diagnosis of PH-LHD. However, this concept is a preliminary hypothesis and further studies are needed to confirm that.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) represents the gold standard technique for the evaluation of the RV. In addition to accurately assessing the overall structure and function of the RV, advances in the application of this technique in the area of PH by our group demonstrate that it is potentially useful to study the microstructure by detecting the expansion of myocardial extracellular volume (ECV)[69,70], evaluate segmental alterations in contractility[71], PA stiffness[72], RV-PA coupling[73,74] and to estimate and monitor PVR[75,76]. T1-mapping and flow imaging are probably leading the current research in this field.

T1 mapping allows tissue characterization based on a map of relaxation times (T1) and the estimation of ECV, which increases in myocardial disease[77]. Our group was the first demonstrating that native T1 and ECV values initially increased at the RV insertion points in an experimental model of postcapillary PH[69]. Their values correlated with RV-PA coupling, pulmonary hemodynamics and RV function. Moreover, ECV values significantly differed between animals with experimental PH but still normal RV ejection fraction and control individuals, thus suggesting its potential to early detect RV damage in PH. We could also demonstrate increased ECV at the RV insertion points in a model of PH generated by systemic to pulmonary shunt[70]. In this case, increased ECV at the LV was additionally observed because of LV volume overload. Later, further evidence in the same direction has been published in patients with PH-LHD[78] and other forms of PH[78,79].

CMR flow imaging technology allows visualization of intracavity and transvalvular flow[80]. We were also pioneers in the assessment of PA flow in PH patients and first used the PA mean velocity obtained by 2D flow for the estimation of PVR in patients with diagnosis or suspicion of PH[76]. Moreover, we could demonstrate that changes in PA mean velocity correlated with dynamic changes in PVR

in experimental models of postcapillary PH and repeated embolization with microspheres[69]. Subsequently, Kheyfets VO et al.[81] also developed a model to estimate PVR based on PA velocities as assessed by 4D flow. Several mechanisms may contribute to the tight relation between changes in PVR and changes in PA flow velocity. First, increased PVR in chronic PH is associated with vasoconstriction and remodelling of distal vessels, so blood transit through the pulmonary tree is hampered; and secondly, increased PVR subsequently causes PA dilatation and associated changes of flow pattern characterized by the presence of systolic retrograde flow and the formation of flow vortices. The presence and duration of vortex formations by 2D or 4D flow imaging have been found to be linearly related to mPAP[82,82]. This opens the possibility of PA hemodynamic estimation and monitoring in a non-invasive manner, particularly in patients with poor acoustic window, that could help to reduce the number of repeated RHC procedures during follow-up. Moreover, prognostic value CMR-estimated PVR has been reported in patients with chronic HF[84,85].

NOVELTIES IN THE TREATMENT OF PH-LHD

Pharmacological therapies

PAH SPECIFIC DRUGS

Although there are different pharmacological treatment options available in PAH, none of them have shown a beneficial effect on PH-LHD (Table 2). Randomized clinical trials evaluating the effect of prostanoids (epoprostenol)[86] and endothelin inhibitors (bosentan)[87,88] in patients with advanced HF and LV systolic dysfunction were stopped due to an increase in adverse events. While these initial clinical trials did not select the population based on the presence or absence of PH, the subsequent results of the Macitentan in Subjects With Combined Pre- and Post-capillary Pulmonary Hypertension (CpcPH) Due to Left Ventricular Dysfunction (MELODY) clinical trial[89], focused on patients with CpcPH, reinforced the message as no benefit was shown with macitentan compared to placebo. Phosphodiesterase 5 inhibitors have also failed to demonstrate robustly a benefit in PH-LHD patients. Within this group, in PH-LHD secondary to HFrEF, there is only one small single-centre study published by Lewis et al.[90] in which sildenafil improved exercise capacity and quality of life associated with a significant reduction in PVR, and some observational studies that have reported hemodynamic improvement prior to HT[91]. In HFpEF, the randomized study by Guazzi et al.[92] showed encouraging results; however, these were not replicated in the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial[93] or in the randomized trial by Hoendermis et al.[94], both neutral, and neither in the multicentre clinical trial Sildenafil for Secondary Pulmonary Hypertension Due to Valvular Disease (SIOVAC)[95]. In this latest trial, which included 200 patients with residual PH after valve surgery, the sildenafil-treated group demonstrated a higher rate of adverse events. In this regard, the consensus of the 6th World Symposium on Pulmonary Hypertension included a strong recommendation against the use of pulmonary vasodilators in PH-LHD[16].

Table 2. Main studies regarding the use of pulmonary vasodilators in pulmonary hypertension due to left heart disease

Author	Population characteristics	Drug	Outcomes	Result
Califf et al.[86]	n = 471 LVEF < 25% NYHA IIIb/IV PAWP > 15, CI < 2.2	Epoprostenol versus placebo	Primary: death, major event (need for mechanical ventilation, inotropic drugs, mechanical circulatory support or death) Secondary: QoL test, 6MWD, clinical status at three months.	Early termination due to increased mortality of HF patients in the treatment group
Kalra et al.[87]	n = 1613 LVEF < 35% NYHA IIIb – IV	Bosentan versus placebo	All-cause mortality or HF hospitalization	Worsening HF andincreased risk for hospitalization
Packer et al.[88]	n = 370 LVEF < 35% NYHA II-IV	Bosentan (slow titration) versus Bosentan (rapid titration) versus placebo	Primary: change in clinical status after 26 weeks Secondary: combined all-cause mortality and worsening heart failure	Increased risk for HF during the first month
Vachiery et al.[89]	n = 63 LVEF > 35% NYHA II-IV CpcPH criteria	Macitentan versus placebo	Primary: safety and tolerability Secondary: changes in hemodynamics, 6MWTD and N-terminal proBNP	Greater fluid retention in the macitentan group compared to placebo. No differences in secondary outcomes
Lewis et al.[90]	n = 13 LVEF > 35% NYHA III	Sildenafil	Primary: improvement in exercise capacity and exercise hemodynamics	Reduction in exercise mPAP and PVR as well as O_2 consumption
Jabbour et al.[91]	n = 6 Heart transplantation waiting list patients TPG > 15 mmHg	Sildenafil	Changes in central venous pressure, mean PAP, PVR, TPG, PAWP, systemic pressure and vascular resistance, and CO	Reduction in PAWP of 5.5 mmHg and TPG < 15 mmHg in four patients
Guazzi et al.[92]	n = 45 LVEF > 50% NYHA II-IV Systolic PAP by echo > 40 mmH	Sildenafil versus placebo	Primary: changes in TAPSE and pulmonary hemodynamics Secondary: Quality of life	Reduction in mPAP, PAWP, PVR and right atrial pressure. Improvement in RV function and quality of life
Redfield et al.[93]	n = 216 LVEF 50% NYHA II-IV	Sildenafil versus placebo	Primary: change in peak oxygen consumption Secondary: change in 6MWTD and a three-tier hierarchical composite clinical status score	No significant differences
Hoendermis et al.[94]	n = 52 LVEF > 45%	Sildenafil versus placebo	Change in PAWP, CO, mean PAP and peak VO_2	No differences between groups
Bermejo et al.[95]	n = 200 mean PAP > 30 mmHg Mitral/aortic valve replacement at least one year before	Sildenafilo vs Placebo	Primary: combined outcome score (NYHA class + quality of life + death or HF) Secondary: clinical score components, BNP, 6MWTD echocardiographic parameters	Worsening clinical status and higher HF hospitalizations
Lewis et al.[96]	n = 34 LVEF <40% NYHA II-IV	Sildenafil vs Placebo	Primary: Change in VO_2 Secondary: change in PVR and 6MWTD	Positive for both primary and secondary outcomes
Kramer et al.[97]	n = 40 HFpEF and CpcPH WHO FC II-III	Sildenafil or Tadalafil	Improvement in N-terminal proBNP, clinical, functional, and echocardiographic variables	Improvement in 6MWTD, WHO functional class, N-terminal proBNP and TAPSE

(Continued)

Table 2. Main studies regarding the use of pulmonary vasodilators in pulmonary hypertension due to left heart disease *(continuation)*

Author	Population characteristics	Drug	Outcomes	Result
Belyavskiy et al.[98]	n = 50 HFpEF and CpcPH	Sildenafil versus placebo	Primary: change in 6MWTD Secondary: change in NYHA functional class, exercise duration and maximal achieved workload during cycle ergometry, mitral E/e' ratio and systolic PAP both at rest and during diastolic stress	50 meters increase in the 6MWTD as well as improvement in secondary outcomes
Monzo et al.[99]	*n* = 22 LVEF < 40% In consideration for heart transplant	Sildenafil	Acute changes in pulmonary hemodynamics, RV ejection fraction	RV afterload reduction, improved RV ejection fraction, reduced RV volumes and lower PAWP
Bonderman et al.[101]	n = 201 LVEF < 40%, NYHA II-IV	Riociguat versus Placebo	Primary: mean PAP Secondary: other hemodynamic parameters	No significant differences in mean PAP Increase in cardiac index and reduction in PVR in the treatment group
Bonderman et al.[102]	n = 39 LVEF > 50% Symptomatic HF	Riociguat versus Placebo	Primary: peak decrease in mean PAP from baseline to 6 h Secondary: additional hemodynamic and echocardiographic parameters, biomarker levels, safety variables, and pharmacokinetics	No significant differences in mean PAP

BNP: brain natriuretic peptide; CO: cardiac output; CpcPH: combined pre- and postcapillary pulmonary hypertension; HF: heart failure; HFpEF: heart failure preserved ejection fraction; HFrEF: heart failure reduced ejection fraction; NYHA: New York heart association functional class; LVEF: left ventricular ejection fraction; PAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistances; QoL: quality of life; RV: right ventricle; TAPSE: Tricuspid annular plane systolic excursion; TPG: transpulmonary gradient; VO2: oxygen consumption; WHO: World Health Organization. 6MWTD: 6 minutes walking test distance.

Despite this recommendation, some groups have continued to investigate the effect of sildenafil in specific groups of patients with PH-LHD based on some favourable results[92,96]. Thereby, Kramer et al.[97] published in 2019 an observation study showing the evolution of 40 patients with CpcPH due to HFpEF reporting an improvement in functional class and quality of life. The same target population was evaluated Belyavskiy et al.[98] in a small pilot randomized clinical trial published in 2020. Patients receiving sildenafil presented an increase in 6-minute walking test distance (6MWTD) and improvement in pulmonary hemodynamics and RV function. More recently, Monzo et al.[99] studied the acute effect of sildenafil on PA-RV coupling and load-independent RV contractility in patients with advanced HF and associated CpcPH, finding a reduction in PAWP an RV volume and better RV ejection fraction. In this line, our group also demonstrated a significant improvement in RV function associated with a reduction in myocardial apoptosis in an experimental model of postcapillary PH[100].

In summary, we have robust evidence against the use of prostanoids and endothelin receptor antagonists in PH-LHD[86-88], but further research is still needed to identify if a specific subgroup of PH-LHD patients, very well characterized, could benefit from sildenafil. Finally, the use of riociguat, a soluble guanylate cyclase stimulator, resulted neutral for the primary outcome (mean PAP) both in PH secondary to HFrEF[101] and HFpEF[102], although

differences in PVR and cardiac output significantly favoured riociguat[94]. The following section is devoted to vericiguat, a member of the same family of drugs.

Vericiguat

Vericiguat is a new soluble guanylate cyclase stimulator recently tested in patients with HFrEF regardless of the presence of PH. The VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction (VICTORIA) trial randomized 5050 symptomatic patients with LV ejection fraction < 45% and at least one previous hospitalization six months before the enrolment or use of intravenous diuretic treatment in the last three months to vericiguat versus placebo. At one-year follow-up, vericiguat reduced in a 10% the primary outcome (cardiovascular death or hospitalization for HF), mainly achieved through a reduction in HF hospitalizations[103]. Vericiguat has been recently approved by the EMA and recommended by the latest European guidelines of HF for symptomatic HF patients (NYHA functional class III-IV) and a previous hospitalization despite optimized HF treatment. Considering some hemodynamic benefits (in PVR and cardiac output) observed with riociguat in the pilot study[101], an additional beneficial effect on pulmonary hemodynamics with vericiguat might be speculated.

Sodium glucose co-transporter 2 inhibitors (ISLGT2)

ISGLT2 have become a mainstay in the treatment of HFrEF[104] and a promising therapy in HFpEF, after the recent publication of the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Preserved ejection fraction (EMPEROR-PRESERVED)-trial[105]. These large trials did not incorporate hemodynamic evaluation, so the direct effect of these drugs on pulmonary hemodynamics was not available. However, a recent small clinical trial randomizing 78 diabetes to dapagliflozin or placebo for six months observed a significant reduction of the primary outcome RV systolic pressure during exercise[106]. Also, in the experimental field, treatment with empagliflozin significantly reduced RV systolic pressure and pulmonary arterial remodelling in the model of PH induced by monocrotaline in rats[107]. Further preclinical and clinical studies evaluating the efficacy of iSGLT2 in PH-LHD are needed.

β3 adrenoreceptor agonists

β3 adrenoreceptors (β3AR) are expressed in human myocardium and vessels and have been described to be upregulated in LHD[108]. They are coupled to G proteins and the downstream activated pathways include NOS, nitric oxide-activated guanylyl cyclase and cyclic guanylyl monophosphate synthesis, directly related to PH pathogenesis[109]. It is known that cyclic nucleotides exert several favourable effects on pulmonary vasculature, including vasodilatation, inhibition of smooth muscle cell proliferation, and prevention of platelet aggregation[110]. Due to these characteristics, this receptor emerged as a new possible therapeutic target for PH.

Our group was the first to study the effect of β3AR agonists on PH. In a porcine model of postcapillary PH, β3AR agonism was associated with a significant reduction of PVR and pulmonary vascular remodelling and an

improvement in RV performance. Also, its administration in human pulmonary smooth muscle cells culture caused a reduction in cell proliferation by a nitric oxide-mediated mechanism[111]. These promising results and the evidence of a good safety profile of mirabegron, a selective oral β3AR agonist used for the treatment of overactive bladder syndrome, both in urological[112] and HF patients[106]encouraged us to evaluate its use in patients with PH-LHD. The Beta3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure (SPHERE-HF) trial (NCT02775539)[114] is a multicentre clinical trial that has randomized 81 patients presenting CpcPH to mirabegron versus placebo for 16 weeks. Patients have followed complete characterization by RHC, echocardiography, CMR (or computed tomography in case of contraindication), blood analysis and 6MWTD, at baseline and after the 16-week treatment period. The main outcome is PVR at the end of treatment whereas the pre-specified secondary outcomes include clinical, biochemical and RV performance parameters. Data is currently under analysis and results will be published soon and will hopefully shed some light regarding the use of β3AR as a potential treatment for PH.

Interventional strategies

Percutaneous treatment of valvular heart disease

Mitral valve regurgitation is a major cause of PH-LHD as the high pressure in the LV during systole is freely transmitted backwards. Its surgical correction has been demonstrated long ago to reduce PVR and LA pressure[115] despite a recurrence during the follow-up in a considerable percentage of patients[116]. Also relevant, PH is associated with an increased risk of mortality after mitral valve surgery for mitral regurgitation[117].

Nowadays, less invasive reparation by a percutaneous approach is available. In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial, the MitraClip device significantly reduced two-year mortality and HF hospitalizations compared to medical therapy[118]. In a sensitivity analysis published later[119], the primary outcome was reduced irrespective of baseline systolic PAP although in general, patients with systolic PAP ≥ 50 mmHg before intervention had higher two-year rates of death or hospitalization compared to those with systolic PAP < 50 mmHg (68.8% versus 49.1%, p = 0.002). In another study of patients following MitraClip implantation[120], systolic PAP significantly decreased in patients with severe PH, but surprisingly remained unchanged in those with mild PH, and even increased in patients without PH at baseline. In-hospital outcomes did not vary significantly according to pre-existing PH in another observational study of 1037 patients undergoing MitraClip procedure[121]. However, in a larger multicentre cohort including 4071 patients undergoing MitraClip implantation, there was a clear association between preprocedural PH severity and one-year mortality and admissions for HF, even after multivariable adjustment (HR per 5 mmHg of mean PAP increase = 1.05, 95% CI, 1.01-1.09, p = 0.02)[122]. In summary, evidence suggests that pre-existing PH is associated with increased mortality and readmissions for HF

in patients undergoing MitraClip system for severe mitral regurgitation, while it is true that in survivors the severity of PH tends to improve after the procedure. Finally, in a small series of cases recently published in end-stage HF patients previously excluded for HT due to PH, the use of MitraClip reduced PAP enough to redeem patients eligible for transplantation. This is of course an off-label indication of this device and further evidence is needed to confirm the potential benefit in this scenario[123].

Left ventricular assist devices

HT is the gold standard treatment for end-stage HF[104] but severe fixed PH is considered a contraindication. In this scenario, the implantation of an LVAD reduces LV filling pressures and PVR and increases PAC in a few weeks after its implantation[58] and has become a good alternative for end-stage HF patients not eligible for HT. However, pre-existent RV dysfunction due to PH can cause irreversible RV failure after LVAD implantation. In this regard, preprocedural evaluation of morphology and function of the RV and pulmonary hemodynamics are essential to select candidates for LVAD support. The already commented PAC[57], PAPi and RV stroke work index are the most commonly used techniques for this purpose[52].

Pulmonary arterial denervation

PA denervation (PADN) targets directly the sympathetic stimulus over the pulmonary vasculature and has emerged as a promising therapeutical option for PH. During the past decade, multiple studies have been published both in the experimental field and clinical arena with controversial results (for an extensive review see a dedicated paper[124]). Overall, a beneficial effect with PADN has been observed in experimental models of acute PH[125,126] and chronic PH induced by monocrotaline[127-129], and also in patients with PAH. Nevertheless, the scientific evidence continues to be limited as there is only one randomized clinical trial[130], with a small sample size and significant methodologic shortcomings. Another trial has recently demonstrated a beneficial effect of PADN in chronic thromboembolic PH[131].

Regarding PH-LHD, our group performed an experimental study to assess the effect of PADN with bipolar clamps in a porcine model of postcapillary PH[132]. In this experiment, transmural PADN produced no benefit in terms of PA hemodynamics, and a trend towards increased biventricular volumes and RV mass evaluated by CMR and histology. These results contrast with those coming from clinical observations. Zhang et al.[133] randomized 98 patients suffering from CpcPH to PADN or sildenafil plus a sham PADN. At 6 months, patients in the procedural arm presented a significantly reduction in PVR and an increase in the 6MWTD compared to sildenafil plus control procedure[133]. However, the results were confusing as there is no solid evidence for the use of sildenafil in CpcPH to be used as a comparator; indeed systemic hypotension in the control arm might have precluded the up-titration of HF-specific medications accounting for a worse evolution. In summary, we have some preliminary positive data suggesting that PADN could be an effective therapy for chronic PH, with more

convincing data for PAH than PH-LHD. Nevertheless, there are still important gaps of knowledge regarding the mechanism of action, the best technique for the application, the durability of the effect (due the possibility of autonomic reinnervation) and the absence of a potential deleterious effect on cardiac remodelling and function. Currently there are two ongoing event-driven trials with PADN in PAH (PADN-PAH, NCT02284737 and PADN-CDFA, NCT03282266) and a pilot trial on ultrasound PADN for patients with PH-LHD (TROPHY-II, NCT03611270) that will shed light on the future of this therapy.

Remote monitoring devices

In the current connected era, and even more after the COVID19 pandemic, remote monitoring of patients has emerged essential. Based on the distortion of a piezoelectric membrane included in a small device that can be implanted in the PA through a femoral vein catheterization, remote methods for PAP monitoring have been developed. The first of these devices was the Cardiomems system. The first study to demonstrate its safety and efficacity was the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial (CHAMPION) trial[134]. In this study, the device presented a very low complication rate of 1.4% and a reduction in HF hospitalizations of 37% in a cohort of patients suffering HF NYHA functional class III and at least one HF hospitalization in the previous 12 months[128]. The extension of this trial showed that this benefit persisted in time[135]. A more recent study performed in Europe in a similar cohort of HF NYHA class III patients (the CardioMEMS European Monitoring Study for Heart Failure [MEMS-HF] trial), reported even better reduction in HF hospitalizations (62% reduction) and increase in quality of life[136]. Moreover, results from daily clinical practice using this device are encouraging as well[137]. However, no differences were observed in the combined outcome of mortality and total HF events in the very recently published randomized clinical trial Hemodynamic-GUIDEd management of Heart Failure (GUIDE-HF)[138]. Nevertheless, it should be noted that the trial concurred with the COVID19 pandemic which could have affected the results, as a sensitivity analysis indicated a possible benefit of hemodynamic-guided management on the primary outcome in the pre-COVID19 period, primarily driven by a lower HF hospitalization rate compared with the control group. There are ongoing relevant trials aiming to assess the cost-effectiveness of hemodynamic monitoring by CardioMEMS in addition to standard HF care[139].

New devices focused on direct measurement of LA pressure are in development. The V-LAP system (Vectorious Medical Technologies, Tel Aviv, Israel) has proved its utility in a first-in-man reported case during the COVID19 pandemic[140.] The ongoing VECTOR-HF trial (NCT03775161) will evaluate its safety and performance in patients with NYHA functional class II HF.

CONCLUSIONS

PH-LHD remains a clinical need due to its high prevalence, bad prognosis, and lack of therapeutic options. The recognition of common aspects between CpcPH and PAH, the

role of the LA, genetics or the microbiome move towards a better understanding and characterization of this entity. For this aim, hemodynamics and imaging techniques remain key. The treatment of this currently orphan entity will probably evolve by using treatments currently available in specific carefully studied subgroups and/or the development of new therapeutic targets.

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CONFLICTS OF INTEREST

There are no conflicts of interest regarding this work other than that Ana García-Álvarez is co-inventor of a patent for the use of beta-3 agonists for the treatment of pulmonary hypertension.

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