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REVIEW

Pulmonary hypertension in chronic heart failure: definitions, advances, and unanswered issues

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Abstract

Pulmonary hypertension (PH) is a common and severe complication of heart failure (HF). Consequently, HF is the leading cause of PH. For many years, specialists have attempted to better understand the pathophysiology of PH in HF, to define its prevalence and its impact on prognosis in order to improve the therapeutic management of these patients. Nowadays, despite the recent guidelines published on the subject, several points remain unclear or debated, and until now, no study has demonstrated the efficacy of any treatment. The aim of this review is to report the evolution of the concepts on post-capillary PH (diagnosis, prevalence, prognosis, and therapeutics). The main issues are raised, focusing especially on the link between structural alterations and haemodynamic abnormalities, to discuss the possible reasons for treatment failures and future potential targets.

Keywords Heart failure; Pulmonary hypertension; Pathophysiology; Classification; Diagnosis; Treatment; Heart transplantation

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Introduction

Heart failure (HF) affects 23 million individuals worldwide. Despite many therapeutic advances, the prognosis of HF remains poor.[1–4] Pulmonary hypertension (PH) is a major determinant of unfavourable outcome in chronic HF (CHF).[5–10]

The most common mechanism of PH in HF (referred to as 'post-capillary PH', also called WHO Group 2 PH) is pulmonary vascular congestion due to increased pulmonary venous pressure resulting from the chronically increased left-heart filling pressure (LHFP). A total or partial reversibility of PH is expected after restoring a normal LHFP by reducing blood volume and/or improving left-heart function. The second mechanism is pulmonary arterial vasoconstriction and remodelling associated with increased pulmonary vascular resistances (PVR)[11–13] partly due to an imbalance between a decreased nitric oxide (NO) availability and an increased endothelin expression, as described in the 'mitral lung'.[14] In this case, reversibility of PH is uncertain, even after restoring normal left-heart haemodynamics.[15]

Chronic PH induces right ventricular (RV) remodelling and might lead to RV failure, which has been shown to be an important prognostic factor in HF.[10,16–19] At the late stage of HF, an elevated PVR has been considered a contraindication to heart transplantation as it may induce RV graft failure.[20]

Despite the recent guidelines published on PH, several points remain unclear or debated, and until now, no study has demonstrated the efficacy of any treatment.The aim of this review is to report the evolution of the concepts on post-capillary PH (diagnosis, prevalence, prognosis, and therapeutics). The main issues are raised, focusing especially on the link between structural alterations and haemodynamic abnormalities, to discuss the possible reasons for treatment failures and to propose future potential targets.

How is/was post-capillary pulmonary hypertension defined in heart failure and why did pulmonary hypertension definition change over the last 10 years?

Pulmonary hypertension is defined by an increase in the resting mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg measured by right heart catheterization (RHC). Post-capillary PH is defined by an mPAP $\geq$ 25 mmHg and a pulmonary arterial wedge pressure (PAWP) $>$ 15 mmHg.

Over the years, different definitions of PH have been used. The aim of these definitions was to discriminate the two mechanisms of post-capillary PH also called WHO Group 2 PH described in the Introduction (*Table 1*).

Several haemodynamic parameters were proposed to estimate the amount of pulmonary vascular remodelling contributing to increase pulmonary pressures. The first definition used the PVR [Wood units (WU)]. The diagnostic value of the PVR was found to be limited by its strong and non-linear correlation with the cardiac output (CO). 'Fixed' PVR may be overestimated in low CO as a consequence of under-recruited pulmonary vasculature, which is a transient phenomenon related to the low output state leading to overestimation. For this reason, even if the PVR remains part of the definition of PH, it has been supplemented with other parameters in order to improve the diagnostic accuracy.

The difference between mPAP and PAWP referred to as 'the transpulmonary gradient (TPG)' was added in the second definition: Post-capillary PH with TPG $\leq$ 12 mmHg was defined as 'passive' or due to pulmonary vascular congestion and $>$12 mmHg as 'reactive', 'out-of-proportion', or 'mixed' PH.[21] However, the TPG depends on loading conditions, which explains at least in part its limited prognostic value.[22–24]

The difference between the diastolic PAP and the PAWP, known as the diastolic pressure gradient (DPG), was found to be less dependent on loading conditions. Subsequently, the DPG was proposed as a new diagnostic tool showing an increased prognostic value[25] and was included in the updated PH definition of the European Society of Cardiology and the European Respiratory Society. Post-capillary PH is now defined as isolated post-capillary PH if the DPG is $<$7 mmHg and/or the PVR is $\leq$3 WU, or as combined post-capillary and pre-capillary PH if the DPG is $\geq$7 mmHg or the PVR is $>$3 WU.[26] However, several publications did not confirm the incremental prognostic value of this promising parameter.[22–24,27]

The current definition of the RV afterload includes a resistive component characterized by the PVR, and a dynamic component characterized by the stroke volume/pulmonary pulse pressure ratio, referred to as pulmonary vascular capacitance (PVC). This parameter reflects the blood flow pulsatility and wave reflections within the entire pulmonary circulation. Recent publications have proposed to use the PVC as a new pathophysiological and prognostic parameter in post-capillary PH.[28–30] However, this parameter is also strongly influenced by the CO, heart rate, and loading conditions, suggesting that it may depend not only on pulmonary vessels but also on cardiac pump function. Ventricle-independent measures of right heart afterload such as arterial elastance exist but may not be suitable for widespread clinical adoption.[31]

Table 1 Changes in pulmonary hypertension definitions over time

PH groups based on the classification	Date of revised definition	PH terminology	Hemodynamic parameters and threshold				
			mPAP (mmHg)	PAWP (mmHg)	PVR (WU)	TPG (mmHg)	DPG (mmHg) and/or PVR (WU)
Post-capillary PH or 'WHO Group 2 PH'	Before 2009	Unfixed	$\geq$25	$>$15	$<$6	—	—
		Fixed	$\geq$25	$>$15	$>$6		
	2009–2015	Pulmonary venous hypertension Passive PH	$\geq$25	$>$15		$<$12	—
		Mixed PH or out-of-proportion PH Reactive PH	$\geq$25	$>$15		$\geq$12	—
	$>$2015	Isolated (Ipc-PH)	$\geq$25	$>$15	—		$<$7 and/or $\leq$3
		Combined PH (Cpc-PH)	$\geq$25	$>$15	—		$\geq$7 or $>$3

Cpc-PH, combined post-capillary and pre-capillary PH; DPG, diastolic pressure gradient; Ipc-PH, isolated post-capillary-PH, mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; WU, Wood units.

Do the various definitions of post-capillary pulmonary hypertension in chronic heart failure meet their objectives?

Impact of post-capillary pulmonary hypertension definitions on the pathophysiological understanding of the disease

The definitions proposed for Group 2 PH are based on invasive haemodynamic measurements assumed to entirely reflect the underlying pulmonary vascular disease. They do not include an anatomical characterization of the pulmonary vasculature through a histopathological examination or the use of imaging techniques. Studies supporting a close and proportional relationship between the vascular remodelling and haemodynamic measurements are limited in HF. In mitral valve disease, several historical studies have shown a significant pulmonary arterial remodelling without determining whether it was related to disease duration, the severity of the valvular dysfunction, or an abnormal LHFP.[14,32] More recently, Delgado and colleagues studied vascular lesions in pulmonary arteries of 17 heart transplant recipients with preoperative PH who died shortly after transplantation.[13] Correlation between preoperative haemodynamic PH data and morphological changes showed that medial hypertrophy of pulmonary arterioles was common, severe, and constantly present, even in patients with normal TPG and/or PVR. However, those patients died shortly after transplant, so the extrapolation of Delgado's work, to a post-transplant population wherein most patients do not die, might suffer from a significant selection bias that impacts the ability to meaningfully extrapolate data. This observation points out the limits of haemodynamic measurements to characterize pulmonary arteriolar remodelling in CHF. This result contrasts with the subanalysis of the Gerges study in which nine patients with elevated TPG/elevated DPG, compared with the nine other patients with elevated TPG/normal DPG, showed a more pronounced pulmonary vascular remodelling, suggesting that elevated DPG has the potential to help to identify pulmonary arteriolar remodelling.[25] In this study, the limited number of patients with available pulmonary histology may have weakened the conclusions. Taken together, these studies illustrate the difficulties to investigate pulmonary vascular remodelling in CHF owing to the limited availability of lung samples. Considering PH as a fixed pulmonary arteriolar remodelling phenomenon (with the possibility of reverse remodelling) is a questionable paradigm. Most elevation in PVR resolves relatively quickly after left ventricular assist device (LVAD) placement, suggesting that combined post-capillary and pre-capillary PH (Cpc-PH) or fixed remodelling is relatively uncommon.[33] This suggests that the current definitions may overstate the value of haemodynamic parameters that is not really proven (*Table 2*).

Several other questions remain:

(1) Which genetic, biochemical, and environmental factors may significantly impact PH development by modifying

Table 2 Supposed mechanisms of combined pulmonary hypertension in chronic heart failure current

Chronology	Mechanisms	Consequences	Further effects
1st	Systolic and/or diastolic dysfunction Decrease in LA compliance Exercise-induced mitral regurgitation Increased pulmonary venous pressure and capillary pulsatile load	Passive increased mPAP	Pulmonary oedema
2nd	Pulmonary endothelial dysfunction and vasoconstriction	Vascular remodelling added to passive increased mPAP	Reduced risk of pulmonary oedema, increase in right ventricular pressure
3rd	Vascular remodelling, decreased vascular compliance	Severe pulmonary vascular disease, right ventricle dilatation and failure	Increase in right atrial pressure, decrease in cardiac output Death

LA, left atrial; mPAP, mean pulmonary artery pressure.

NO availability, endothelin expression, collagen deposition, and other mechanisms involved in pulmonary arteriolar dysfunction and remodelling?

(2) Are there substantial structural and functional differences between pulmonary arteriolar remodelling and PH in HF with reduced left ventricular ejection fraction, HF with preserved left ventricular ejection fraction (HFpEF), or mitral stenosis?

(3) What is the time course of pulmonary arteriolar remodelling in the different left-heart diseases?

(4) Which PH phenotype is associated with reversible pulmonary arteriolar remodelling, and how do we measure reversibility? It is a clinically relevant problem and a very controversial issue in the literature (Which drugs are used in vasodilator challenge? Which doses? What are the haemodynamic objectives of these tests? etc.); furthermore, it is unknown whether the vasodilator challenge has a clinical or prognostic significance in the general population of HF patients.

Most PH-HF studies assumed that pulmonary arteriolar vasoconstriction and remodelling occur secondarily to chronically elevated pressures in the left heart, called the 'vascular theory'. However, the RV distribution system is a continuum ending with the left atrium, and the left atrial (LA) reservoir function is therefore a critical component of the total RV afterload. Blood entering in a non-compliant left atrium results in a steep pressure rise and a prominent V wave, increasing the systolic PAP (sPAP). Indeed, LA dysfunction is increasingly recognized as a major determinant of PH-HF.[34] Recently, an impaired echocardiographic LA-strain response at exercise in HF patients has been found to be a key haemodynamic trigger for RV–pulmonary artery (RV–PA) uncoupling and exercise ventilation inefficiency.[35]

A fundamental component of right heart distribution system is the right ventricle. It is now largely demonstrated that RV dysfunction is common in HF and that its presence contributes to increased morbidity and mortality RV distribution system.[16–19] As a matter of fact, the poor prognosis in PH-HF could not be the direct consequence to the remodelling of the pulmonary circulation, but it could be attributed to the detrimental consequence that PH exerts on the right ventricle. Although more work can clearly be carried out specific to WHO Group 2 PH, there is ample evidence to suggest that right heart afterload alone is not poorly prognostic, but instead, it is RV coupling to the right heart afterload and pulsatile load at rest and at exercise that should be considered as the main determinant of the course of the disease.[31]

Impact of post-capillary pulmonary hypertension definitions on disease prevalence and prognosis

Although post-capillary PH is undoubtedly the most common form of PH, its exact prevalence is challenging to assess. Indeed, the prevalence of PH-HF reported in the literature varies by up to 100% depending on the type of studied population (acute HF or CHF, reduced or preserved ejection fraction), the measurement method (echocardiography, RHC, wireless system), and the parameters used (sPAP, mPAP, PVR, TPG, DPG).[7,21,36,37] RHC is usually performed in a non-representative cohort of selected patients with advanced left-heart disease who are candidates for heart transplantation or mechanical circulatory support, or in case of diagnostic difficulties. Consequently, the prevalence of PH in these cohorts is particularly high and cannot be extrapolated to the overall population of HF patients.[33] Regarding the prevalence of increased DPG, it is estimated to range between 12% and 38% in HF patients.[23,25,38] Cpc-PH is rare in CHF and characterized by younger age, chronic obstructive pulmonary disease, and worse RV–PA coupling. Prognostic information may be more related with worsening of RV–PA coupling than haemodynamic phenotyping.[31] An important concept to be taken into account is that these parameters vary over time. This was clearly demonstrated in the CHAMPION study in which pressure measurements were carried out daily using a wireless system.[39] However, because high-fidelity measurement of the wedge was not performed day to day, it does not inform a hypothesis over whether the DPG, TPG, and PVR undergo the same degree of variability (*Tables 3* and *S1*).

Table 3 Relationship between commonly used haemodynamic parameters and various issues in post-capillary pulmonary hypertension

Observed parameter	Epidemiological value	Prognostic value	Determining pathophysiological mechanisms contributing to PH	Independence from other parameters	Transplant recipient selection
Increased PAP	well demonstrated/useful	well demonstrated/useful	not demonstrated/useless	equivocally demonstrated/uncertain	well demonstrated/useful
Increased PVR	not demonstrated/useless	equivocally demonstrated/uncertain	equivocally demonstrated/uncertain	not demonstrated/useless	well demonstrated/useful
Increased TPG	not demonstrated/useless	equivocally demonstrated/uncertain	equivocally demonstrated/uncertain	equivocally demonstrated/uncertain	well demonstrated/useful
Increased DPG	not demonstrated/useless	equivocally demonstrated/uncertain	equivocally demonstrated/uncertain	well demonstrated/useful	not demonstrated/useless
Decreased capacitance	not demonstrated/useless	equivocally demonstrated/uncertain	equivocally demonstrated/uncertain	equivocally demonstrated/uncertain	not demonstrated/useless

DPG, diastolic pressure gradient; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

well demonstrated/useful; equivocally demonstrated/uncertain; not demonstrated/useless.

Many studies agree that PH in HF is a marker of poor outcome.[5,6,9,21,37,38,40] However, several factors interfere with the assessment of PH-HF. First, all haemodynamic parameters measured by RHC, including PAP, are dependent on blood pressure, cardiac function (CO, LV, and RV function), and blood volume. Second, neither the TPG nor the DPG has clearly shown any incremental prognostic value (rehospitalization and cardiovascular death).[22,23,25,38] Third, PVC and PVRs seem to be the two most interesting parameters, but they are strongly related to the CO and therefore cannot be interpreted independently.[28–30]

Finally, it is also unclear how PH definition truly impacts prognosis. Moreover, it is already unknown if it is PH itself and haemodynamic phenotype or its detrimental consequence on the right ventricle and the RV coupling to the right heart afterload that lead to worse prognosis.[31]

Which parameter is important for the treatment of heart failure and pulmonary hypertension?

Medical interventions

To date, the consensual treatment of post-capillary PH is still based on blood volume optimization with diuretics and sodium and fluid restriction, in addition to the optimal medical treatment of HF.

Over the last decade, more specific therapeutic targets have emerged such as the control of the pulmonary arteriolar tone and the alveolo-capillary membrane permeability. Several molecules have been tested in this innovative field, yielding inconsistent results (*Table 3*). Indeed, different inclusion criteria and primary outcome measurements (clinical, biological, and/or haemodynamic parameters) were used in these studies, making comparisons difficult. One possible reason of treatment failure is that in most clinical trials with pulmonary arterial hypertension (PAH) therapies (except MELODY-1), patients were not included on the basis of haemodynamics using the Cpc-PH definition (*Table S2*).

Phosphodiesterase type 5 inhibitors (PDE5-I) appeared to be one of the most promising pharmacological approach. In a recent registry including patients with normal LV function and mPAP $\geq$ 25 mmHg, PDE5-I treatment was associated with improved exercise capacity and decreased natriuretic peptide level in idiopathic PH and in atypical PAH (i.e. PAH with $\geq$3 risk factors for left-heart disease).[41] Another registry showed that the use of sildenafil improved haemodynamics in HF patients with post-capillary PH before heart transplantation.[42] However, the most important randomized trial that tested the administration of PDE5-I (sildenafil) in 216 patients with HFpEF for 24 weeks did not show any improvement in exercise capacity or clinical status.[43] Recently, the SIOVAC trial results reported worse outcomes with sildenafil in patients with persistent PH after correction of valvular disease.[44] These last two studies suggest that sildenafil's induced lung vasodilatation increased pulmonary venous return and LV filling pressure causing haemodynamic damage to a flow-sensitive failing heart. Furthermore, sildenafil might also lead to hypoxemia in CHF by increasing ventilation–perfusion mismatching.[45] The other pharmacological approaches are inconclusive. In the MELODY-1 trial, including 63 patients with Cpc-PH, macitentan showed numerically more frequent adverse events and fluid retention than did placebo and did not improve any exploratory endpoints (PVR, pulmonary capillary wedge pressure, cardiac index, and NT-pro-BNP), suggesting that macitentan may be harmful in WHO Group 2 PH as well.[46] Endothelin receptor antagonists and prostacyclin analogues have been studied in post-capillary PH. While short-term changes in haemodynamics have been seen, there has been either no clinical benefit or the suggestion for harm. In these studies, patients were not included on the basis of the haemodynamic variables PVR, DPG, and TPG except in the MELODY-1 trial that shows negative results (*Tables S1* and *S2*). This underscores the uncertainty of conceptualizing post-capillary PH as a disease of pulmonary vascular remodelling. Several other treatments (guanylate cyclase activators, endothelin 1 blockers, inorganic nitrate, etc.) are currently being studied to answer this question. Finally, one possible reason of treatment failure is that in the clinical trials with PAH therapies, patients were not included on the basis of haemodynamic definition of PH [i.e. Isolated post-capillary-PH (Ipc-PH) or Cpc-PH]. The main target remains to improve the left function and to give reflex tracks with an RV phenotype that would be candidate for a specific treatment. The evaluation not only can be haemodynamic but also must integrate the evaluation of the right function and the RV–PA coupling. We should focus on the way to decrease left atrial pressure (LAP).

Heart transplantation and left ventricular assist devices

In case of advanced HF, elevated PVR has long been a contraindication to heart transplantation because the important increase in RV afterload was considered prohibitive for RV graft, not adapted to withstand a significantly increased pulmonary resistance. Different haemodynamic parameters were used to predict the post-transplant survival mainly on the basis of the baseline PVR with or without reversibility test. More recently, the DPG did not show any predictive potential with regard to the post-transplant survival.[23] The recent 2016 guidelines for heart transplantation of the International Society for Heart and Lung Transplantation recommend to perform RHC before heart transplantation in order to measure the mPAP and PVR as they are determinants of post-transplantation outcome.[43]

Several recent studies have shown that implanted LVADs in cardiac transplantation candidates with severe PH and elevated PVR allow increasing CO and decreasing LV filling

pressure, mPAP, and PVR,[47,48] thus enabling heart transplant with reduced risk of RV failure. Most elevation in PVR resolved quickly after LVAD replacement, suggesting that 'fixed' remodelling is relatively uncommon.[33] Thus, the use of LVADs questioned the concept of 'fixed PH'. In other words, PH-HF previously classified as irreversible shows a significant potential of reversibility.[49] Consequently, the diagnostic usefulness of combined PH-HF markers (PVR, DPG, and TPG) remains limited for patient selection for heart transplantation and for the prediction of graft failure. The use of RHC in a pre-transplant situation is useful for mPAP and right ventricular pressure evaluation.

However, a persistently elevated PVR and reduced pulmonary compliance can still be observed in a small subset of patients after heart transplantation or with LVADs.[47,48] Thus, predicting reversible pulmonary vascular damage remains a clinical challenge in the transplantation setting, not resolved with the RHC parameters currently used.

Which questions should be answered to improve pulmonary hypertension management in heart failure?

What would be the characteristics of an ideal pulmonary hypertension marker?

An ideal PH marker should be a guide for diagnosis, monitoring, and therapy. It should be easy to measure and to be reproduced over time. It should help to differentiate between pre-capillary and post-capillary PH. This marker would also help to distinguish the mechanisms of post-capillary PH to target the therapeutic actions: congestion and passive increase in venous pressures vs. pulmonary vascular remodelling.

Right heart catheterization is actually the gold standard to define PH. However, RHC is invasive, and its use is limited in HF clinical practice. This may lead to PH misdiagnosis or late diagnosis and also to a bias in PH prevalence estimation. Echocardiography is commonly used and allows a reliable assessment of the PAP with measurement of the maximal velocity of the tricuspid regurgitation. It may also evaluate RV dilation and function and explore left-side disease, which is of major importance for analysing the consequences and the aetiologies of PH. However, the Vmax may be reliably recorded in only 60% of cases.[50–52] More recently, the CardioMEMS, a wireless PAP monitoring system implanted with a microelectromechanical system-based PAP sensor during RHC, has appeared as an interesting but invasive monitoring device. Recent advances in cardiac tomography (CT) (dual-energy) or lung perfusion magnetic resonance imaging (MRI) might allow in the future the direct or indirect assessment of pulmonary vascular disease.[53] In pilot studies, dynamic contrast-enhanced CT was able to distinguish patients with and without PH with a specificity and sensitivity of 100% by measuring the speed and time propagation of the contrast material bolus in the pulmonary arteries (i.e. the time difference was correlated with mPAP[54]) whereas automated MRI-based 3D volumetry of central pulmonary artery measurement was also able to discriminate patients with or without PH.[55] However, none of these new techniques have shown any added diagnostic value neither in terms of the prediction of reversibility, nor in terms of RV post-transplant failure prediction, nor in terms of morbidity/mortality.

Should pulmonary hypertension and pulmonary vascular remodelling only be considered as detrimental in heart failure?

Vascular remodelling and vasoconstriction reflect a chronic increase in PH, which is itself secondary to an increase in LHFP that exceeds the 'buffer' capacity of the left atrium. On the one hand, pulmonary vascular remodelling and/or vasoconstriction may contribute to prevent pulmonary oedema, especially by maintaining an effective CO. On the other hand, the persistence of hypervolemia is a marker of poor prognosis that physicians must manage at all stages of the disease. This mechanism is completely different from that of pre-capillary PH, where the primary cause is the pathological remodelling of the pulmonary capillary, which then becomes a real therapeutic target. Finally, physiopathologically, vascular remodelling, or vasoconstriction resulting from the chronic increase in LAP is intended to preserve alveolo-capillary haematosis and maintain the right CO. Suppressing the mechanism with a vasodilator means suppressing the last protection against increased pressures and congestion. Moreover, in the worst case, pulmonary vasodilation could lead to pulmonary oedema. Vascular remodelling could be a kind of 'alveolar protective mechanism' with a major detrimental consequence that PH exerts on the right ventricle and that leads to worse prognosis.

One question persists: Should pulmonary vascular remodelling/vasoconstriction be targeted or should we focus on the way to specifically decrease the LAP[56–58]?

Conclusions

Pulmonary hypertension is an important prognostic marker in CHF, and its precise prevalence remains unknown. The exact pathophysiology of PH in HF is still only partially understood. RHC allows accurate measurement of mPAP and main pulmonary artery haemodynamic parameters, but it

has limitations leading to several changes in post-capillary PH definition during the last decade that illustrates the complexity of identifying a good marker and surrogate of post-capillary PH.

Furthermore, in post-capillary PH trials, new therapeutics targeting pulmonary pressure/remodelling were inconclusive except for the indisputable control of hypervolemia. Ultimately, the question to raise is whether post-capillary PH is more a risk marker or a therapeutic target. Further studies are needed to answer these questions and identify a (biological, morphological, or haemodynamic) parameter that could better characterize the adaptability of the circulatory system to face chronic pressure elevation in CHF. Studying RV coupling and LA functional capacity seems a promising approach.

Conflict of Interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of the most recent hemodynamic studies in heart failure with prognosis and main results.

Table S2. Selected studies assessing the effect of drugs on cardiopulmonary hemodynamics and clinical endpoints in HF classified according to the studied drug.[34–42]

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