



REVIEW

Perspectives on novel therapeutic strategies for right heart failure in pulmonary arterial hypertension: lessons from the left heart

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ABSTRACT: Right heart function is the main determinant of prognosis in pulmonary arterial hypertension (PAH). At present, no treatments are currently available that directly target the right ventricle, as we will demonstrate in this article.

Meta-analysis of clinical trials in PAH revealed that current PAH medication seems to have limited cardiac-specific effects when analysed by the pump-function graph. Driven by the hypothesis that “left” and right heart failure might share important underlying pathophysiological mechanisms, we evaluated the clinical potential of left heart failure (LHF) therapies for PAH, based on currently available literature.

As in LHF, the sympathetic nervous system and the renin–angiotension–aldosterone system are highly activated in PAH. From LHF we know that intervening in this process, e.g. by angiotensin-converting enzyme inhibition or β -blockade, is beneficial in the long run. Therefore, these medications could be also beneficial in PAH. Furthermore, the incidence of sudden cardiac death in PAH could be reduced by implantable cardioverter-defibrillators. Finally, pilot studies have demonstrated that interventricular dyssynchrony, present at end-stage PAH, responded favourably to cardiac resynchronisation therapy as well.

In conclusion, therapies for LHF might be relevant for PAH. However, before they can be implemented in PAH management, safety and efficacy should be evaluated first in well-designed clinical trials.

KEYWORDS: Adrenergic β -antagonists, artificial cardiac pacing, implantable defibrillators, pulmonary heart disease, rennin-angiotensin system, right ventricular dysfunction

Pulmonary arterial hypertension (PAH) is characterised by excessive pulmonary vascular remodelling, resulting in a marked increase in right ventricular (RV) afterload. The thin-walled, crescent-shaped right ventricle in the normal situation needs to remodel to a thick-walled, more spherical-shaped high-pressure pump to overcome the often four-fold increase in pressure in the case of PAH. Eventually, the right ventricle is not able to cope with the increase in load and right heart failure develops [1, 2]. Despite the successful introduction of several new pulmonary-selective vasodilating therapies in the last 10 yrs, the prognosis of PAH patients remains poor [3, 4].

The relationship between RV afterload (mainly determined by pulmonary vascular resistance

(PVR) and pulmonary arterial compliance [5]) and RV dysfunction is not straightforward. Patients with systemic sclerosis associated-PAH (relatively low load/low pressure) have a worse prognosis compared with patients with idiopathic PAH, whereas patients with PAH associated with congenital heart disease (high load/high pressure) have a relatively good prognosis [6]. Also in PAH, mean pulmonary artery pressure (\bar{P}_{pa}) and PVR are of limited prognostic value, while the strongest predictors of survival are reflections of RV (mal)adaptation to its increased load (cardiac index, right atrial pressure, tricuspid annular plane systolic excursion and N-terminal pro-brain natriuretic plasma levels) (fig. 1) [8–10]. Thus, it is not the load *per se*, but the failing right ventricle itself that leads to death.

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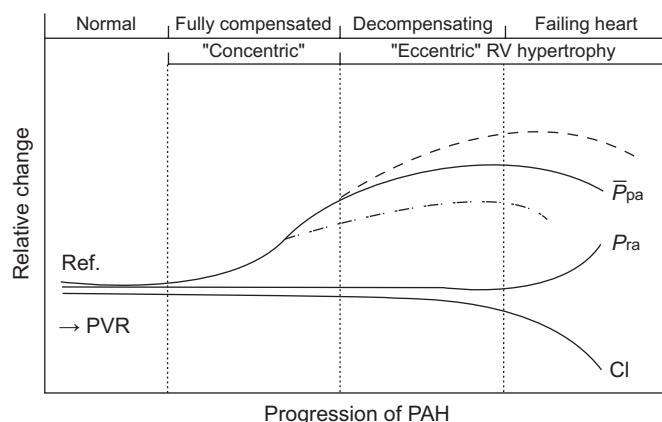


FIGURE 1. Haemodynamic changes during the progression of pulmonary arterial hypertension (PAH). The continuous rise in pulmonary vascular resistance (PVR) during the progression of PAH is initially compensated by concentric remodelling of the right ventricle (RV). Right atrial pressure (P_{ra}) remains normal and there is a steep increase in mean pulmonary artery pressure (\bar{P}_{pa}) as cardiac index (CI) at rest is preserved. In the next stage, the RV is not able to fully compensate for the further increase of PVR and starts to decompensate; eccentric RV remodelling is observed. There is a modest rise in \bar{P}_{pa} as CI also starts to fall. At this stage P_{ra} remains at near normal levels. In the final stage of overt right heart failure there is a severe drop in CI, a steep rise in P_{ra} and, even though PVR still increases, \bar{P}_{pa} drops due to the low output state. Changes in RV function fit to the different disease stages in PAH and explain the prognostic importance of CI and P_{ra} over \bar{P}_{pa} . In systemic sclerosis associated-PAH (-----), the ability of the RV to adapt to the increasing PVR appears limited, therefore, the heart fails at lower PVR [7]. The aim of specific RV-therapies (- - -) is to improve the ability of the heart to adapt to its afterload. Ref.: reference/normal value.

Current PAH medication (prostacyclines, endothelin receptor blockers, phosphodiesterase (PDE)-5 inhibitors and calcium antagonists) focuses on controlling the excessive vascular remodelling typical for PAH, resulting in a reduction in RV load [11]. Their cardiac-specific effects on RV adaptation and remodelling have not really been studied yet, but they are most probably of limited clinical relevance as we will demonstrate later. Therefore, there is still unexploited potential for therapies that directly target the right ventricle [12].

In left heart failure (LHF) it is well accepted that the process of cardiac remodelling itself, regardless of the initial cardiac

event, is, although compensatory at first, detrimental in the long run [13]. There is now convincing evidence that intervening in the process of remodelling importantly reduces morbidity and mortality in patients with LHF [14, 15]. We hypothesise that the RV remodelling observed in PAH patients shares important pathophysiological mechanisms with the cardiac remodelling observed in LHF patients. This implies that the adverse RV remodelling could possibly be treated with the same well-established therapies for LHF.

To get better insight into the processes involved, it is essential to clinically distinguish cardiac-specific effects of treatment from their effects on load (pulmonary vasodilation), which also indirectly affect the heart. Therefore, in the first part of this review we will discuss how this separation of effects can be studied, and will evaluate the cardiac-specific effects of current PAH treatments. In the second part of the review we will explore the potential relevance of current evidence-based LHF therapy (table 1) for right heart failure secondary to PAH.

HOW CAN WE DISTINGUISH THE CARDIAC-SPECIFIC EFFECTS OF PAH THERAPY FROM THE PULMONARY VASODILATING EFFECTS?

The right ventricle and the pulmonary vascular bed are functionally coupled [1, 2]. As a result, it is difficult to distinguish cardiac-specific effects from pulmonary-specific effects of an intervention with the use of standard diagnostic tools (*i.e.* right heart catheterisation or echocardiography). For example, bosentan treatment has been shown to partially restore cardiac dimensions and function: compared with placebo, bosentan treatment improved cardiac output ($0.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, $p < 0.01$) and RV/left ventricular (LV) diastolic area ratio (-0.64 , $p < 0.01$) [16]. However, these effects are most probably the result of the decrease in RV load (difference in PVR reduction, bosentan treatment *versus* placebo: $-415 \pm 99 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$; $p < 0.001$) [17] and are, therefore, not cardiac specific. Similar observations have been reported for epoprostenol, sildenafil and after successful pulmonary endarterectomy or lung transplantation.

In an experimental setting, this problem can be circumvented by using models with a fixed RV afterload (*e.g.* pulmonary arterial banding). Herein we describe two methods that are also applicable in a clinical setting.

TABLE 1 Summary of current left (systolic) heart failure therapy

1. Treat underlying cause when possible, *e.g.* coronary artery disease and arterial hypertension
2. General measurements, self-care management (avoid drugs that adversely affect the clinical status whenever possible)
3. Diuretics (and moderate salt restriction)
4. **β -blockers (initiated in very low doses, followed by gradual increment)**
5. **Angiotension-converting enzyme inhibitors (or angiotensin II receptor blockers, if intolerant for angiotension-converting enzyme inhibitors)**
6. **Aldosterone antagonists (only when renal function is preserved and closely monitored)**
7. Exercise training (adjunct to optimal medical therapy)
8. **Implantable cardioverter-defibrillator (patients at high-risk for life-threatening arrhythmic disorders)**
9. **Cardiac resynchronisation therapy (symptomatic heart failure patients despite optimal medical treatment, with signs of cardiac dyssynchrony): digoxin, hydralazine/nitrate, left ventricle assist devices, heart transplantation**

The therapies marked in bold are not standard in current pulmonary arterial hypertension management. Data taken from [14, 15].

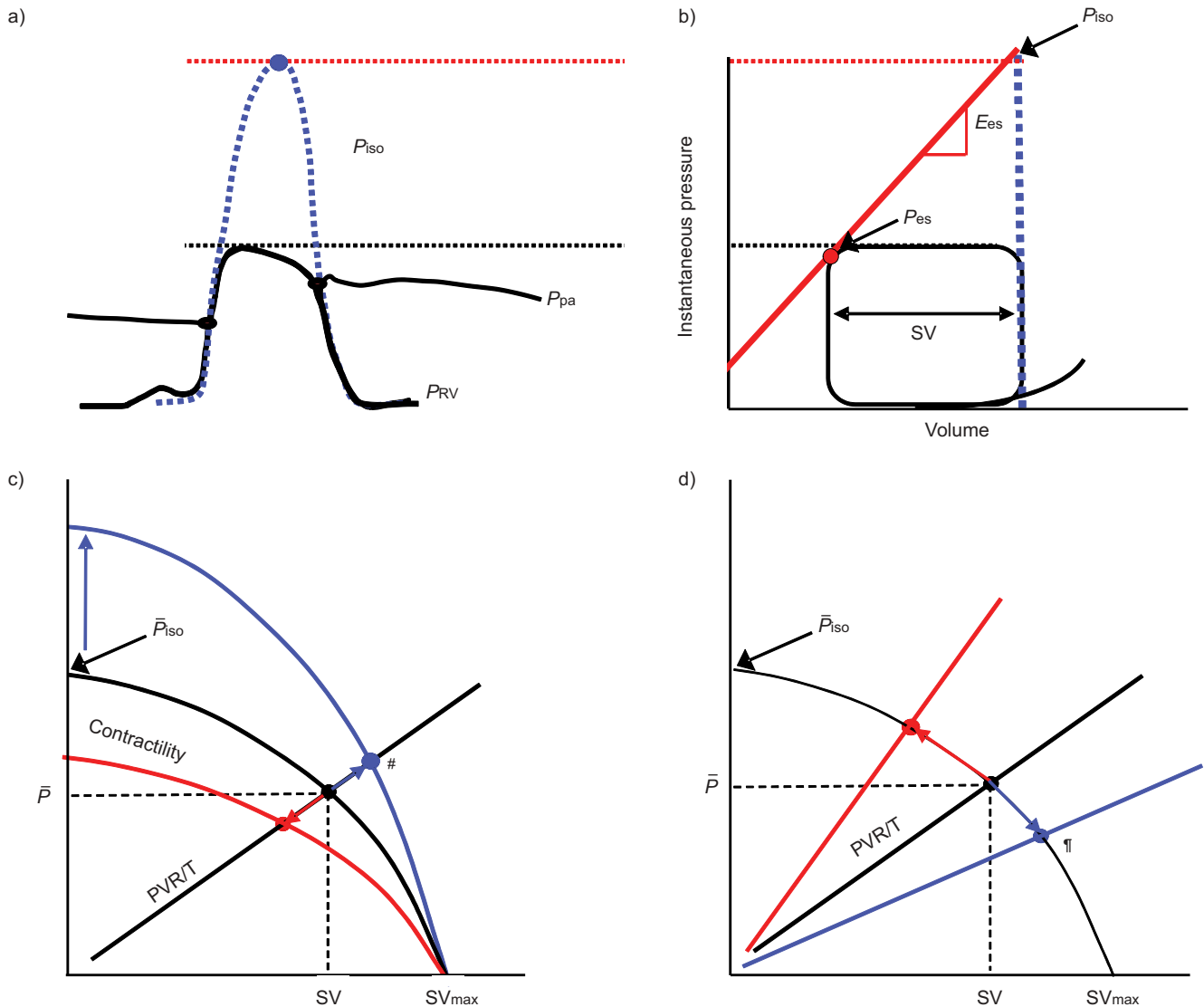


FIGURE 2. Distinguishing cardiac-specific from pulmonary-specific effects in pulmonary hypertension (PAH) patients. a) Pressure curves of the right ventricle (RV) and the main pulmonary artery are shown. Maximal isovolumic pressure is estimated (P_{ISO}) by sine wave fit [18]. b) Pressure–volume loops can be constructed from instantaneous pressure and volume measurements by use of conductance catheters. End-systolic elastance (E_{ES}) is considered a load-independent measure of RV contractility and is measured from the slope of the connecting line between end-systolic pressure (P_{ES}) and P_{ISO} [19]. c) Increase in contractility. d) Decrease in pulmonary vascular resistance (PVR). An alternative approach for describing heart function is the pump-function graph [20]. Here, average RV pressure *versus* stroke volume (SV) at steady state are plotted (the working point) and by the same single-beat estimation (\bar{P}_{ISO}), a pump-function graph is constructed (—). The slope of the line from the origin through the working point is a measure for PVR divided by heart period (PVR/T) and, therefore, a measure for RV afterload. When RV contractility increases (c), this is observed in the pump-function graph by increased \bar{P}_{ISO} while SV_{max} remains unchanged; the new working point has moved to the upper right (#). When RV afterload is reduced (PVR/T decreases; d), the pump-function graph remains unchanged, while the new working point moves to the lower right (¶). \bar{P} : mean pressure; P_{pa} : pulmonary artery pressure; P_{RV} : RV pressure curve.

Pressure–volume relationship

It is well accepted that from combined ventricular pressure and volume measurements, parameters of cardiac function and contractility can be derived that are independent of the arterial load. An example of a load-independent parameter of systolic function is the end-systolic elastance (E_{ES} or E_{max}), which is measured by the slope of the fitted line connecting end-systolic pressure volume points (fig. 2b). In addition, load-independent parameters of diastolic function can be derived [21, 22]. This method has been used successfully in describing LV performance in multiple disease conditions [23], and more

recently its use has been validated in PAH patients for the right ventricle as well [24]. The construction of pressure–volume loops requires simultaneous measurements of instantaneous pressure- and volume-signals (fig. 2a and b), which can only be obtained using specialised equipment (*e.g.* conductance catheters). Moreover, to accurately determine E_{ES} , it is necessary to vary cardiac load (usually by a temporary partial occlusion of the inferior vena cava), which might be unacceptable in patients that are haemodynamically compromised, such as PAH patients. Fortunately, mathematical techniques (*e.g.* single-beat estimation) have been developed that allow

reasonable estimation of E_{es} and only require a high-quality RV pressure curve and a reliable stroke volume (SV) measurement during steady state [18, 19]. Recent studies that compared the separate cardiac and pulmonary effects of norepinephrine, dobutamine and levosimendan in an experimental model for right heart failure are examples of the usefulness of the pressure–volume relationship (including single-beat estimation) [25, 26].

Pump-function graph

An interesting alternative for studying cardiac-specific *versus* pulmonary-specific effects is the pump-function graph [20, 22]. A major advantage of this method is that only instantaneous pressure and average flow measurements suffice, and that its analysis does not require instantaneous volume signals. Average RV pressure is plotted against SV (the working point) and, using the same single-beat estimation as discussed above, a pump-function graph can be constructed (fig. 2c and d). An increase in mean isovolumic pressure while SV_{max} remains unchanged (fig. 2) indicates improved cardiac contractility: in this case the new working point moves to the upper right (fig. 2c). A change in cardiac load has a different effect: when load decreases by pulmonary vasodilation (and cardiac contractility remains unchanged) the working point moves to the lower right. With the use of the pump-function graph, we recently demonstrated lower cardiac contractility in systemic sclerosis-associated PAH compared with idiopathic PAH, which could well explain the patients' worse prognosis despite lower PVR [7].

When studying chronic (as opposed to acute) effects of an intervention, both methods (pressure–volume loops and pump-function graph) may be insufficient due to RV remodelling. However, they can be further refined by incorporating measures of RV remodelling (RV wall thickness and RV diameter) in the analysis, in which case RV wall stress (σ ; estimated by Laplace's law) is used instead of RV pressure [22]. We conclude that by an integral approach, it is certainly possible to distinguish the cardiac-specific from the pulmonary-specific effects of an intervention in PAH patients [22].

Often, it is very difficult to distinguish the cardiac- from the pulmonary-specific effects of PAH therapy in patients. For this purpose, the pressure–volume loop and the pump-function graph have been developed. We propose the use of the pump-function graph over the pressure–volume loop as it is more easily obtained in patients using routine RV catheterisation.

CARDIAC EFFECTS OF CURRENT PAH MEDICATION

The cardiac-specific effects of current PAH therapies, in contrast to their pulmonary-vasodilating effects, have only been investigated in a small number of studies. The few relevant experimental studies are discussed first.

Experimental studies

ZIERER *et al.* [27] investigated the effects of diltiazem (a calcium-channel blocker) on RV function in a chronic model of RV pressure overload, using pressure–volume analysis. Administration of diltiazem during constant RV afterload acutely depressed cardiac output, and this was mainly related to depressed right atrial function and RV filling. KERBAUL *et al.* [28] investigated the effects of prostacyclines in an acute model

of RV pressure overload, also using pressure–volume analysis. Epoprostenol improved cardiac output, and this was explained by a marked decrease in RV afterload without detectable changes in RV contractility. These observations have been confirmed by REX *et al.* [29]. Two recent papers studied the effects of chronic treatment of sildenafil in a model where RV pressure overload was induced by pulmonary artery banding [30, 31]. Both studies reported an increase in RV hypertrophy and/or improvement of RV function, which implies that there is a direct effect of sildenafil on the heart. Prior to this, NAGENDRAN *et al.* [32] reported upregulation of PDE-5 in hypertrophied, but not in normal, rat and human RV myocardium and also demonstrated acute inotropic effects of sildenafil in the isolated Langendorff-perfused heart. In summary, experimental data suggest acute detrimental effects of calcium-channel blockers, a neutral effect of prostacyclines and possibly beneficial cardiac-specific effects of sildenafil on RV function and RV remodelling. Currently, no (experimental) data is available on the cardiac-specific effects of endothelin receptor blockers on the right ventricle in the setting of PAH. To date, these substances have only been evaluated in models in which RV afterload was not fixed.

Meta-analysis of clinical studies

To the best of our knowledge, no clinical studies exist that specifically separated the cardiac from pulmonary effects of current PAH therapies. Therefore, we re-evaluated all placebo-controlled randomised clinical trials in PAH that included serial invasive haemodynamic data, recently summarised by GALIE *et al.* [33], by use of the pump-function graph (fig. 3). \bar{P}_{pa} was used as a surrogate measure for mean RV pressure, SV indexed for body surface area (SV_i) was recalculated by dividing cardiac output by heart rate and body surface area (estimated as 1.82 m^2 if not reported). Concomitant evaluation of the haemodynamic changes in \bar{P}_{pa} and SV_i by the pump-function graph, during a typical study period of 12 weeks (range 8 weeks to 12 months), suggests that current PAH therapies have predominantly pulmonary vasodilating effects. This is highlighted by comparing figure 3 with the situation in figure 2d. Although future clinical studies specifically designed to address this issue are necessary, this observation demonstrates that there is a strong rationale for developing novel PAH therapies that specifically target the right ventricle [12].

Right heart function is the main determinant of prognosis in PAH. Current medication (endothelin receptor blockers, PDE-5 inhibitors and prostacyclines) appears to have limited cardiac-specific effects (when analysed by an RV pump-function graph). Novel therapies that specifically improve right heart function in PAH are needed.

RELEVANCE OF LHF THERAPIES FOR PAH-RELATED RIGHT HEART FAILURE

The cornerstones of current (systolic) LHF therapy are: (loop)diuretics; a β -blocker; and angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers if ACE inhibitors are not tolerated (table 1). In case of persisting symptoms, an aldosterone antagonist or an angiotensin blocker is added, if the patient's renal function permits. Exercise training is regarded an adjuvant therapy. For selected LHF patients, an implantable cardioverter-defibrillator and/or

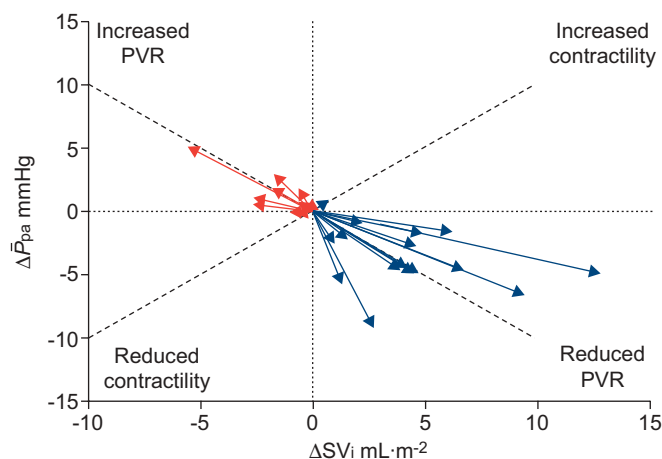


FIGURE 3. Meta-analysis of pulmonary arterial hypertension (PAH) trials by pump function. Each arrow shows the general absolute change in indexed stroke volume (ΔSV_i) and mean pulmonary artery pressure (ΔP_{pa} ; as a surrogate measure for mean right ventricle pressure) per study group of all placebo controlled randomised clinical trials in PAH reporting serial haemodynamic measurements [33]. A decrease in SVi was always accompanied by an increase in \bar{P}_{pa} in the placebo group (red arrows), implying an increase in pulmonary vascular resistance (PVR) without relevant changes in cardiac contractility. For the intervention groups (blue arrows), an increase in SVi was always accompanied by a decrease in \bar{P}_{pa} , implying reduction in PVR without important changes in cardiac contractility. Therefore, current PAH medications predominantly have pulmonary vasodilating effects with only limited cardiac-specific effects.

cardiac resynchronisation therapy can be considered. These therapies are well-established and are based on numerous well-designed randomised controlled trials (more details on current LHF therapy can be found in current guidelines [14, 15]). Of note, clinical benefit in these trials was demonstrated irrespective of the aetiology of LHF. This supports the current idea that the process of cardiac remodelling, after the initial hit, is similar and independent of its cause (e.g. ischaemia or hypertension) [13]. However, it has been argued that therapy efficacy might be different in systolic *versus* diastolic heart failure (different LHF phenotype) [34]. Therefore, as the cardiac remodelling observed in PAH patients with right heart failure is comparable to that of systolic LHF (reduced ejection fraction and ventricular dilatation) [10], only these recommendations will be discussed in this article.

It is tempting to extrapolate the LHF recommendations to right heart failure, even though there are important structural, functional and developmental differences between the left and right ventricle [1, 2]. Nevertheless, there is already some overlap in recommendations between the LHF and PAH guidelines [3, 4, 14, 15], which suggests that, at least from a therapeutic perspective, there might be some interesting similarities. For example, loop diuretics are widely used to achieve fast symptomatic relief, both in PAH as well as in LHF. In addition, nowadays, moderate exercise training is accepted as an adjuvant therapy for PAH patients that are clinically stable and under optimal medical treatment [35–37].

Since loop diuretics and exercise training are already part of the recommendations of current PAH guidelines, we will not discuss these therapeutic modalities any further here. We will

also not discuss therapies for LHF that are still experimental. Instead, this review will focus on the clinical potential of: 1) β -blockers as modulators of the sympathetic nervous system; 2) ACE inhibitors, angiotensin blockers and aldosterone antagonists as modulators of the renin–angiotensin–aldosterone system (RAAS); and 3) the potential of electrical cardiac interventions, such as implantable cardioverter-defibrillators and cardiac resynchronisation therapy, as novel add-on therapies for PAH (fig. 4). Because there are hardly any prospective controlled data available that investigated the relevance of these LHF therapies in PAH, we will mainly focus on the relevance of the underlying pathophysiological mechanisms for PAH that are affected by these interventions.

NEUROHUMORAL ACTIVATION AND PAH

The combined use of a β -blocker (more specifically bisoprolol, carvedilol or sustained released metoprolol) with either an ACE inhibitor, angiotensin blocker and/or an aldosterone antagonist, in addition to symptomatic treatment by loop diuretics, significantly reduces morbidity and mortality in LHF [14, 15]. These medications modulate the underlying “neurohumoral activation”, which is nowadays considered pathological in the long run, as they promote cardiac remodelling and progression of the disease [13, 38]. Neurohumoral activation in LHF can be seen as a state in which neural and hormonal systems designed to maintain adequate organ perfusion are increased to excessively high levels. This activation includes many components, of which the sympathetic nervous system and RAAS are, from a therapeutic perspective, the most relevant [14, 15, 38].

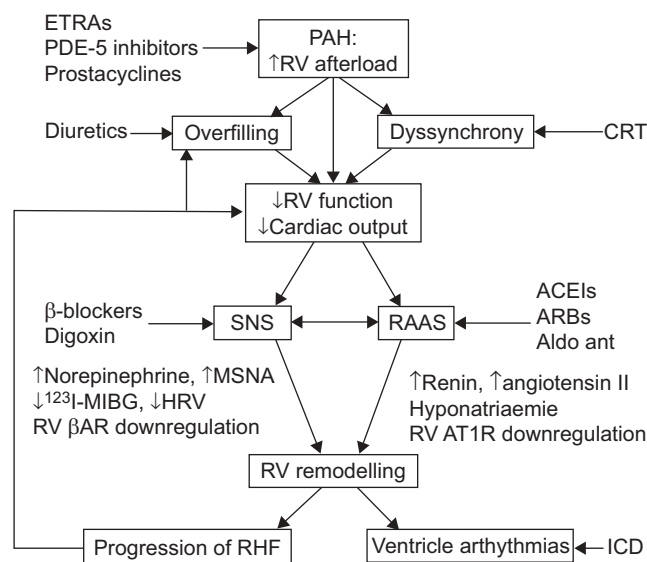


FIGURE 4. Schematic diagram showing as yet unexplored pathophysiological mechanisms in pulmonary arterial hypertension (PAH). RV: right ventricular; ETRAs: endothelin receptor antagonists; PDE-5: phosphodiesterase-5; CRT: cardiac resynchronisation therapy; SNS: sympathetic nervous system; RAAS: renin–angiotensin–aldosterone system; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; MSNA: muscle sympathetic nervous activity; HRV: heart rate variability; β AR: cardiomyocyte β_1 -adrenergic receptor; AT1R: cardiomyocyte angiotensin type 1 receptor; Aldo ant: aldosterone antagonist; RHF: right heart failure; ICD: implantable cardioverter defibrillator.

Sympathetic nervous system

Autonomic dysbalance with dominance of the sympathetic system already occurs at early stages of LHF [39], and is mainly attributed to reduced baroreceptor discharge. Baroreceptors, mainly located in the aortic arch, carotid arteries and the left ventricle, are normally triggered by mechanical stretch and respond by tonically inhibiting the central sympathetic neural outflow. In the case of LHF, both systemic arterial pressures and baroreceptor sensitivity are reduced. Sympathetic overdrive leads to chronically elevated levels of norepinephrine, resulting in overstimulation and selective downregulation of the cardiac-specific β_1 -adrenergic receptors in the left ventricle. This stimulus not only leads to increased cardiac mechanical stress (by inotropic, chronotropic and vasoconstrictive effects), but also has direct cardiotoxic effects [40]. As a result, LV remodelling progresses with further functional deterioration [38]. β -blockers are able to stop this vicious circle of heart failure by antagonising the β -adrenergic receptor [41]. Of interest, the therapeutic effects of digoxin are no longer solely attributed to its weak inotropic effects, but also to its modest neurohumoral effects: digoxin indirectly sensitises the cardiac baroreceptor, and in this way reduces sympathetic outflow of the central nervous system [42].

Although sympathetic activity is difficult to measure in the clinical setting, several methods have been developed to demonstrate sympathetic overdrive in LHF patients [39]. Of these, measurements of regional norepinephrine spill-over or microneurography (which directly measures post-ganglionic muscle sympathetic nerve activity (MSNA)) quantify sympathetic activity best. A sophisticated noninvasive alternative is the use of ^{123}I -MIBG tracers (heart-to-mediastinum ratio falls when the sympathetic nervous system is chronically activated). A cruder but easy method is the assessment of heart rate variability (which is reduced when the sympathetic nervous system is over-activated).

Renin-angiotensin-aldosterone system

Another relevant system in this context, closely interrelated with the sympathetic nervous system, is the RAAS [43]. This system is triggered by impaired renal perfusion due to reduced cardiac output. In this case, the juxtaglomerular cells in the kidneys react by secreting renin. Renin increases angiotensin I levels, from which angiotensin II is formed by ACE (abundantly present in the lung endothelium). Angiotensin II mediates multiple processes: it is a potent vasoconstrictor and it has inotropic, natriuretic and antidiuretic properties. In the setting of LHF, all impose cardiac stress and are detrimental in the long run. Like norepinephrine, elevated levels of angiotensin II over stimulate and selectively down-regulate its angiotensin II type 1 (AT_1)-receptor in the left ventricle, directly promoting cardiac remodelling. Furthermore, angiotensin II stimulates the secretion of aldosterone as well as vasopressin (also called antidiuretic hormone). Both have natriuretic and antidiuretic effects and also directly promote cardiac remodelling. ACE inhibitors, angiotensin blockers and aldosterone antagonists interfere in this process by suppressing specific components of RAAS [14, 15].

RAAS activity is relatively easily quantified by directly measuring renin or angiotensin II activity in plasma. A simple

but indirect alternative to measure chronically activated RAAS is the assessment of hyponatremia [38].

Over-activation of the sympathetic nervous system in PAH

Since the primary trigger of neurohumoral activation in LHF (reduction in cardiac output) is also an important clinical feature in PAH, one would expect that the sympathetic nervous system and RAAS are highly activated in PAH as well. Indeed, measurements of the sympathetic and RAAS activation in PAH are comparable to those in LHF [44, 45].

Measurements in PAH patients, as in LHF, revealed elevated levels of norepinephrine in plasma [46, 47], although this was not consistently found in other studies [48]. Furthermore, increased MSNA [48] reduced cardiac uptake of ^{123}I -MIBG [49], reduced heart rate variability [50], and selective down-regulation the β_1 -adrenergic receptors in the right (but not left) ventricle have been observed in PAH patients [51], which are all indicators of increased sympathetic activity affecting the right ventricle. Moreover, these findings were correlated with disease severity.

RAAS is also involved in PAH-induced right heart failure. FORFIA *et al.* [52] recently identified hyponatremia, which indirectly indicates RAAS activation as an important independent prognostic factor in PAH. Parameters that more directly measure RAAS activation (increased renin activity, elevated levels of angiotensin II, aldosterone and/or vasopressin) have not been systematically investigated in PAH patients yet. Nevertheless, increased renin activity and elevated aldosterone levels in plasma have been demonstrated in patients with right heart failure due to hypoxic pulmonary hypertension (cor pulmonale) [53], and in different experimental models of PAH-induced right heart failure [54]. In addition, selective down-regulation of the AT_1 -receptor in the right ventricle has been observed in PAH patients [55].

Taken together, these studies suggest that the sympathetic nervous system and RAAS are highly activated in PAH. But in contrast to LHF, there are only a few clinical studies that have explored the therapeutic potential of neurohumoral modulation. RICH *et al.* [56] investigated the effect of *i.v.* administration of digoxin in PAH patients and found acute improvement in cardiac output with concomitant reduction in norepinephrine levels, comparable to the digoxin effect in LHF.

Interestingly, no clinical trial exists in PAH-induced right heart failure on the effects of β -blockers, which have more potent effects on the sympathetic nervous system than digoxin. By common clinical consensus, β -blocker use is even contraindicated. Often this is substantiated by the study of PROVENCHER *et al.* [57]. They reported significant functional improvement, 2 months after β -blocker withdrawal in a small series of patients with porto-pulmonary hypertension. However, all patients (treated for prophylaxis of variceal bleeding) were receiving high-dose propranolol or atenolol. These old β -blockers are also contraindicated for LHF because of their profound myocardial depressive and vasoconstrictive effects, in comparison to newer β -blockers [41]. Moreover, it is well-known from LHF that acute functional improvements do not invariably lead to favourable changes long-term, and that overall beneficial effects of β -blockers can typically be expected after chronic use of ≥ 3 months [41].

Another (related) argument against β -blocker use in PAH is the importance of maintenance of RV systolic function. Acute administration of a β -blocker is known to exacerbate dyspnoea, most likely due to its negative inotropic effects, leading to instant ventriculo-arterial uncoupling [18]. However, this temporary effect might be better tolerated by careful use of selective β -blockers (“start low, go slow”), as is successfully demonstrated in LHF-patients [14, 15].

Although this is against present consensus, we would like to argue that, like in LHF, the sympathetic nervous system is activated to pathological levels in PAH, and that this could be normalised by careful β -blocker use. Further (pre-clinical) research is necessary to investigate whether a low-dose of a newer selective β -blocker might be a tolerable option to abolish the detrimental effects of sympathetic overdrive in PAH.

Activation of RAAS in PAH

RAAS has long been recognised to play an important role in pulmonary vascular remodelling and pulmonary vasoconstriction [58, 59]. Therefore, when captopril (the first ACE inhibitor) became commercially available, this new drug was eagerly tested in PAH patients, for whom no effective treatment existed at that time. In the 1980s, four small case-series (26 patients in total) reported on the haemodynamic effects of captopril in PAH. Three of the studies were positive and found a significant increase in cardiac output [60, 61] and exercise capacity [62]. One study, however, did not observe any haemodynamic changes, neither positive nor negative [63]. Surprisingly, no additional clinical studies have been published since. Currently, there is renewed interest in RAAS since the discovery of ACE2, an isoform of ACE with counteractive (protective) actions [64, 65]. The theoretical beneficial effects of ACE inhibitors, angiotensin blockers and/or aldosterone antagonists on the heart in PAH have not been addressed in patients yet.

Pre-clinical studies using different models of PAH and right heart failure, however confirmed that the use of ACE inhibitors or angiotensin blockers significantly reduces RV remodelling and improves cardiac function and/or survival [66–69]. We conclude that in PAH, pharmacological interference in RAAS could (partially) reverse pulmonary and cardiac remodelling, which warrants a prospective controlled clinical study of the effects of ACE inhibitors, angiotensin blockers and/or aldosterone antagonists.

There is convincing evidence that, as in LHF, the sympathetic nervous system and RAAS in PAH are highly activated. Well-established pharmacological interventions for LHF could, therefore, be relevant for PAH as well. However, ACE inhibitors, angiotensin II blockers and selective β -blockade have not been explored in PAH, and clinical investigations of the potential of these drugs are urgently needed. Nevertheless, routine use of these neurohumoral modulators and, in particular, the use of β -blockers are currently not recommended in PAH, unless future studies can prove that their use in PAH is safe and beneficial.

ELECTRICAL REMODELLING AND PAH

Implantable cardioverter-defibrillators and cardiac resynchronisation therapy are relatively new therapeutic modalities in LHF

management. Major heart failure guidelines contain recommendations on implantable cardioverter-defibrillator use since 2001, but recommendations on resynchronisation therapy have only been incorporated since 2005. For selected LHF patient groups, it is now well-accepted that resynchronisation therapy significantly reduce morbidity, and both cardioverter-defibrillators and resynchronisation therapy significantly reduce mortality, in addition to the beneficial effect of optimal pharmacological LHF treatment [14, 15].

Implantable cardioverter-defibrillator

A cardioverter-defibrillator detects and prematurely terminates malignant and life-threatening ventricular arrhythmias, preventing sudden cardiac death. The incidence of ventricular arrhythmias increases with the progression of LHF. Therefore, implantable cardioverter-defibrillator use is currently recommended as secondary prevention for sudden cardiac death in LHF patients with a (presumed) history of ventricular arrhythmia, or as primary prevention in LHF patients with a severely reduced left ventricular-ejection fraction. In both cases LHF patients must have a reasonable expectation of survival with acceptable functional status of >1 yr [14, 15]. The clinical trials, on which these recommendations are based, reported a relative reduction of all-cause mortality after 24 months of ~30% and an absolute risk reduction of ~5% [70, 71], which implies a number-needed-to-treat of ~20 patients.

Also in PAH, sudden cardiac death, presumably due to malignant ventricular arrhythmias, has been recognised as an important clinical risk for these patients [72]. As in LHF, markers for an “electrically instable heart”, such as prolonged QTc-intervals and increased QT dispersion derived by ECG [73], neurohumoral disturbances (as discussed previously) and increase in cardiac fibrosis [74], have been demonstrated in PAH patients. However, in contrast to LHF, the actual incidence of events related to ventricular arrhythmias in PAH is considered to be low. However, the reported percentages of deaths in PAH attributed to ventricular arrhythmias vary widely, from 8 to 26% [8, 75], and the actual numbers might importantly differ for the different PAH subgroups (*e.g.* higher for PAH associated with congenital heart disease, which might be related to the presence of surgical cardiac scars [76]). Moreover, these numbers are based on retrospective studies and were partially obtained before the introduction of PAH specific medications. Systematic prospective clinical studies are necessary to accurately determine the current incidence of sudden cardiac deaths in different subgroups of PAH. These data will allow a crude estimation of the clinical potential of cardioverter-defibrillators in PAH, by calculation of the number-needed-to-treat (extrapolating the effect of cardioverter-defibrillators in LHF). Until then, implantable cardioverter-defibrillators (or pharmacological anti-arrhythmic agents) are generally not recommended as a (primary) preventive measure for sudden cardiac death in PAH patients [4, 72].

Supraventricular tachyarrhythmias

In contrast to ventricular arrhythmias, the incidence of supraventricular arrhythmias seems to be much higher, and they are considered to be an important cause of clinical deterioration in PAH patients. In a retrospective analysis [77],

an annual incidence of supraventricular tachyarrhythmias in PAH of ~3% was found: atrial fibrillation and atrial flutter were equally common. In this study, persistent atrial fibrillation was associated with a very poor prognosis (nine out of 11 PAH patients died within 24 months), which may be explained by worsening of RV function due to the loss of atrial “kick” to ventricular filling. Maintenance of sinus rhythm is, therefore, currently considered an important treatment goal in PAH [4]. However, this is in contrast to the clinical experience in LHF. The treatment strategy of rhythm-control, compared with rate-control (which is acceptance of atrium fibrillation and lowering of the ventricular response-rate in combination with adequate anticoagulation), had no superior effect on survival, whereas it required more hospitalisation because of the need for repeated cardioversion [78, 79]. We fully support current recommendations to restore and maintain sinus rhythm in PAH patients if possible, by lack of prospective and controlled data. Future trials, however, are necessary to test the validity of this treatment strategy.

Cardiac resynchronisation therapy

Cardiac dyssynchrony in LHF is characterised by regional differences in electrical and/or mechanical activation of the left ventricle (usually a delay in activation of the LV free wall in relation to the interventricular septum). Dyssynchrony results in inefficient pumping of the left ventricle, and further clinical deterioration. Cardiac resynchronisation therapy can acutely restore synchrony of LV contraction, thereby improving overall LV (systolic) performance. In the long run, resynchronisation therapy leads to reversed cardiac remodelling, resulting in an even further improvement of LV performance. Although the current clinical selection criteria for resynchronisation therapy (wide QRS complex on ECG) sub-optimally predict clinical benefit for the individual LHF patient, resynchronisation therapy has been shown to significantly reduce morbidity and mortality, and is now a well-established treatment modality in LHF [14, 15].

Ventricular dyssynchrony is often also observed in progressive stages of PAH-induced right heart failure [80, 81]. Mechanical interventricular dyssynchrony in PAH (which is clinically easily recognised by the paradoxical bulging of the interventricular septum) is associated with impaired RV systolic function. Furthermore, through septum bulging, ventricular dyssynchrony is thought to impair LV diastolic function as well [82, 83]. Resynchronisation of the right ventricle could, therefore, be of clinical benefit in PAH. However, we recently demonstrated that LV and RV dyssynchrony are essentially different: the origin of PAH-related ventricular dyssynchrony lies in regional differences in the duration of the contraction, rather than regional differences in onset of the contraction (*e.g.* due to a conductance delay); and is highly afterload dependent [83, 84].

Previously, successful application of cardiac resynchronisation therapy has been demonstrated in patients with PAH associated with congenital heart disease [85]. However, these patients display a “LHF-like” dyssynchrony due to a complete right bundle branch block as a (late) complication of cardiac surgery and are, therefore, not representative for the PAH population in general. We recently explored the clinical potential of resynchronisation therapy in an experimental model of PAH-induced right heart failure, in the absence of

conduction disturbances [84]. We found that pre-excitation of the RV free wall resulted in improved RV systolic function and reduced adverse LV diastolic interaction. Interestingly, these findings have recently been confirmed by HARDZIYENKA *et al.* [86] in a study with patients suffering from right heart failure and ventricular dyssynchrony secondary to chronic thromboembolic pulmonary hypertension. A cohort of 67 patients was pre-operatively screened by standard tissue-Doppler echocardiography and seven patients were selected for a temporary pacing protocol, based on the presence of large diastolic interventricular delay (as a quantification of PAH-related ventricular dyssynchrony). Resynchronisation therapy acutely reduced ventricular dyssynchrony, enhanced RV contractility and LV diastolic filling, and resulted in an improvement of SV of >10%. These promising results warrant further investigations of cardiac resynchronisation therapy as a novel treatment for right heart failure secondary to PAH [12], that should focus on its long-term effects, and on the identification of robust selection criteria for PAH patients that could profit most from cardiac resynchronisation therapy.

In PAH, the incidence of malignant ventricular arrhythmias is considered low, but this observation needs prospective validation. For now, the use of implantable cardioverter-defibrillators is not recommended for PAH patients. Supraventricular tachyarrhythmias often lead to clinical deterioration. Based on retrospective data, maintenance of sinus rhythm is an important treatment goal, but this preference of rhythm- over rate-control needs be confirmed in prospective controlled studies, especially because this is opposite to the experiences in left heart failure. Cardiac resynchronisation therapy emerges as a promising new treatment modality. Prospective controlled trials are necessary to study its long-term effects and to identify robust selection criteria.

CONCLUSIONS AND FUTURE DIRECTIONS

In this review we investigated the potential applicability of current LHF therapy for the treatment of PAH-induced right heart failure. Based on available literature, we conclude that: LHF and right heart failure share important underlying pathophysiological mechanisms that are amenable for treatment (fig. 4); however, clinical experience with current LHF treatments in the setting of PAH is very limited.

This discrepancy is intriguing, and we can only speculate about its reasons. First, it is difficult to separate cardiac- from pulmonary-specific effects of therapeutic interventions in PAH patients. As a solution, we propose the use of the pump-function graph. Secondly, PAH remains a rare disease where many other clinical trials have been undertaken in the last two 20 yrs [33]. Thirdly, until recently right heart failure was regarded as an inevitable final consequence of PAH, whereas it is now the right ventricle which is considered a potential therapeutic target [12].

So, how do we move forward? Solid clinical evidence is essential before LHF therapy can be implemented in PAH management. Therefore, phase I/II trials need to be conducted first, which must provide insights in safety, tolerability and efficacy of LHF therapy in PAH. Subsequently, randomised clinical trials should be performed that compare current PAH

therapy with and without add-on LHF therapy. An important aspect is sufficient duration of the trial: the experiences in LHF would predict that reversal of cardiac remodelling requires more than the typical 12-week trial duration. In addition, the question remains as to which end-point to choose in these types of studies: classical end-points in PAH trials, such as 6-min walking distance, might not be sensitive enough, and direct measures for RV remodelling and function are possibly more appropriate. However, the most ideal end-point, mortality, might be too stringent and will require inclusion of unrealistically high numbers of patients [87].

To conclude, well-designed clinical studies are warranted, as they might provide supporting evidence for the use of novel therapeutic modalities that are relatively easily available to treat this devastating disease. Future investigations will reveal whether going “left” is a step in the “right” direction.

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