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Lessons from the left heart in developing novel therapeutic options for right heart failure in pulmonary arterial hypertension

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ABSTRACT

In pulmonary arterial hypertension, right heart function is the most important indicator of prognosis (PAH). As we will show in this post, there are currently no medicines available that directly target the right ventricle.

When analysed using the pump-function graph, a meta-analysis of clinical trials in PAH found that current PAH treatment appears to have minimal cardiac-specific effects. We investigated the clinical potential of left heart failure (LHF) therapy for PAH based on currently available data, driven by the idea that "left" and "right" heart failure may share fundamental underlying pathophysiological mechanisms.

The sympathetic nervous system and the renin–angiotension–aldosterone system are both significantly active in PAH, just as they are in LHF. We know from LHF that interfering with this process, such as by inhibiting angiotensin-converting enzyme or blocking b-blockade, is helpful in the long run. As a result, these drugs may be effective in the treatment of PAH. In addition, implantable cardioverter-defibrillators may minimise the risk of sudden cardiac death in PAH patients. Finally, pilot trials have shown that interventricular dyssynchrony, which is common in end-stage PAH, can benefit from cardiac resynchronization therapy.

Finally, treatments for LHF could be useful in the treatment of PAH. However, before they can be used to treat PAH, they must first be tested for safety and efficacy in well-designed clinical trials.

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

INTRODUCTION

Excessive pulmonary vascular remodelling causes pulmonary arterial hypertension (PAH), resulting in a significant increase in right ventricular (RV) afterload. To counteract the typically four-fold increase in pressure in PAH, the thin-walled, crescent-shaped right ventricle must be remodelled into a thick-walled, more spherical-shaped high-pressure pump. Right heart failure arises when the right ventricle is unable to deal with the increased strain [1, 2]. Despite the

effective introduction of various new pulmonary-selective vasodilating treatments over the last decade, PAH patients' prognosis remains poor [3, 4].

The link between RV afterload (which is primarily dictated by PVR and pulmonary arterial compliance [5]) and RV dysfunction is not straightforward. Patients with PAH caused by systemic sclerosis (low load/low pressure) have a worse prognosis than those with idiopathic PAH, but patients with PAH caused by congenital heart disease (high load/high pressure) have a better prognosis [6]. In PAH, mean pulmonary artery pressure (P pa) and PVR are of limited prognostic value, whereas 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) are the strongest predictors of survival [8–10].Thus, it is not the load *per se*, but the failing right ventricle itself that leads to death.

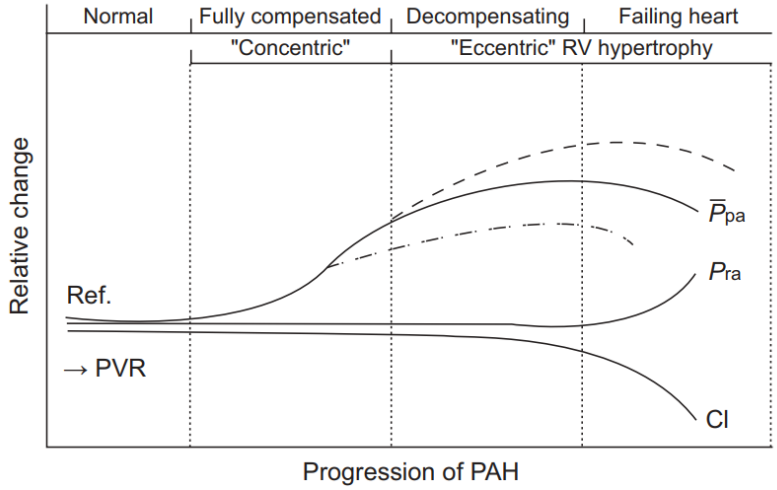

FIGURE 1; Haemodynamic changes during the progression of pulmonary arterial hypertension (PAH). The continuous rise in pulmonary vascular resistance (PVR) during the progression of PAH is initially compensated by concentric remodelling of the right ventricle (RV). Right atrial pressure (*P*ra) remains normal and there is a steep increase in mean pulmonary artery pressure (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 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, 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 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 itsafterload. Ref.: reference/normal value.

Current PAH treatment (prostacyclines, endothelin receptor blockers, phosphodiesterase (PDE)-5 inhibitors, and calcium antagonists) focuses on reducing RV load by managing the excessive vascular remodelling seen in PAH [11]. Their cardiac-specific effects on RV adaptation and remodelling have yet to be investigated, but as we will see later, they are most likely of limited clinical value. As a result, there is still untapped potential for medicines that target the right ventricle directly [12].

It is well known that, regardless of the initial cardiac event, the process of cardiac remodelling itself, while compensatory at initially, is deleterious in the long run in left heart failure (LHF) [13]. In patients with LHF, there is now solid evidence that interfering in the remodelling process decreases morbidity and death significantly [14, 15]. We believe that the RV remodelling seen in PAH patients and the cardiac remodelling seen in LHF patients share

important pathophysiological underpinnings. This suggests that the negative RV remodelling might be treated with the same well-established LHF treatments.

Clinically distinguishing cardiac-specific effects of treatment from their effects on load (pulmonary vasodilation), which also indirectly influence the heart, is critical for gaining a better understanding of the processes involved. As a result, we will address how this separation of effects might be explored in the first half of this review, as well as evaluate the cardiac-specific effects of current PAH medications. We will look at the potential relevance of current evidence-based LHF therapy (table 1) for right heart failure secondary to PAH in the second half of the review.

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

Functionally, the right ventricle and the pulmonary vascular bed are linked [1, 2]. As a result, using normal diagnostic methods to separate cardiac-specific effects from pulmonary-specific effects of an intervention is difficult (i.e. right heart catheterisation or echocardiography). Bosentan medication, for example, has been demonstrated to partially restore cardiac dimensions and function: as compared to placebo, bosentan treatment improved cardiac output (0.4 Lmin-1m-2, p0.01) and the RV/LV diastolic area ratio (-0.64, p0.01) [16].These benefits, however, are most likely due to a reduction in RV load (difference in PVR reduction, bosentan therapy against placebo: -41599 dyn?s?cm-5; p,0.001) [17] and are not cardiac specific. Epoprostenol, sildenafil, and successful pulmonary endarterectomy or lung transplantation have all been linked to similar results.

This difficulty can be avoided in an experimental context by utilising models with a fixed RV afterload (e.g. pulmonary arterial banding). Two strategies are described here that can also be used in a clinical context.

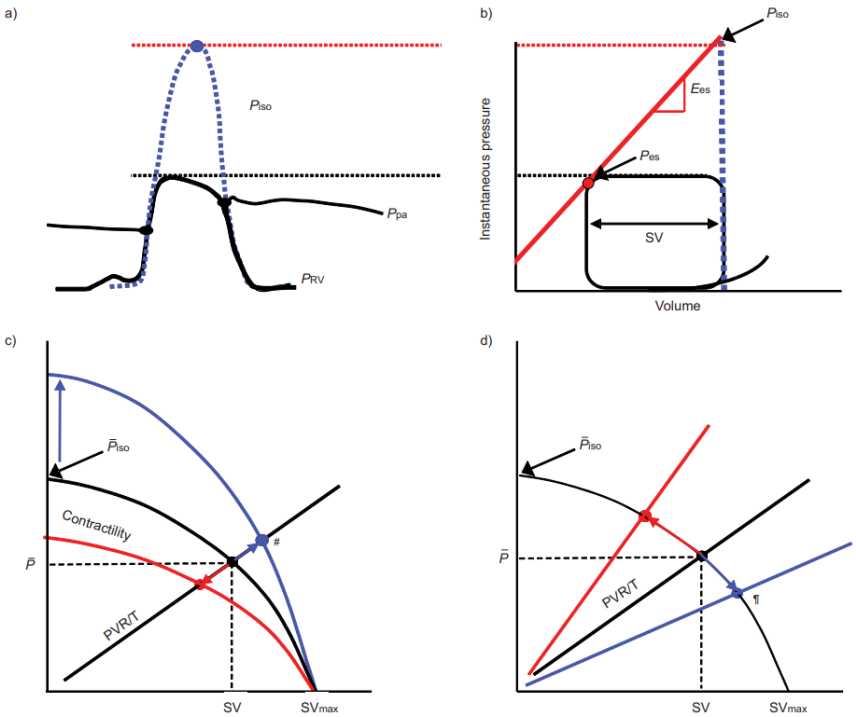

FIGURE 2: Distinguishing cardiac-specific from pulmonary-specific effects in pulmonary hypertension (PAH) patients. a) Pressure curves of the right ventricle (RV) and the main pulmonary artery are shown. Maximal isovolumic pressure is estimated (*P*iso) by sine wave fit [18]. b) Pressure–volume loops can be constructed from instantaneous pressure and volume measurements by use of conductance catheters. End-systolic elastance (Ees) 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 SVmax remains unchanged; the new working point has moves 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 known that cardiac function and contractility characteristics can be determined from combined ventricular pressure and volume measures that are independent of arterial load. The end-systolic elastance (Ees or Emax), which is assessed by the slope of the fitted line linking end-systolic pressure volume points, is an example of a load-independent systolic function parameter (fig. 2b). Furthermore, load-independent diastolic function parameters can be calculated [21, 22]. This technique has been successfully utilised to describe LV performance in a variety of disease situations [23], and its use in PAH patients for the right ventricle has just been validated [24].Pressure–volume loops require simultaneous measurements of instantaneous pressure and volume signals (fig. 2a and b), which can only be acquired with specialised equipment (e.g. conductance catheters). Furthermore, varying cardiac load (typically via a transient partial blockage of the inferior vena cava) is required to precisely determine Ees, which may be unacceptably risky in patients with haemodynamic impairment, such as PAH patients. Fortunately, mathematical procedures have been devised (e.g. single-beat estimation) that allow good calculation of Ees with only a high-quality RV pressure curve and a valid stroke volume (SV) measurement during steady state [18, 19].The pressure–volume relationship (including single-beat estimation) has been shown to be effective in recent investigations comparing the separate cardiac and pulmonary effects of norepinephrine, dobutamine, and levosimendan in an experimental model for right heart failure [25, 26].

PUMP-FUNCTION GRAPH

The pump-function graph [20, 22] is an attractive alternative for examining cardiac-specific versus pulmonary-specific effects. This method has the benefit of requiring only immediate pressure and average flow measurements, and it does not require instantaneous volume signals for analysis. A pump-function graph can be generated by plotting average RV pressure against SV (the working point) and using the same single-beat estimation as previously stated (fig. 2c and d). Improved cardiac contractility is indicated by an increase in mean isovolumic pressure while SVmax remains unchanged (fig. 2): in this scenario, the new working point advances to the upper right (fig. 2c).When cardiac load falls due to pulmonary vasodilation (but ventricular contractility stays intact), the working point shifts to the lower right. We recently observed reduced cardiac contractility in systemic sclerosis-associated PAH compared to idiopathic PAH using the pump-function graph, which could explain the patients' worse prognosis despite lower PVR [7].

Due to RV remodelling, both approaches (pressure–volume loops and pump–function graph) may be insufficient for evaluating chronic (as opposed to acute) impacts of an intervention. They can, however, be refined further by include measures of RV remodelling (RV wall thickness and diameter) in the analysis, in which case RV wall stress (s) is employed instead

of RV pressure (calculated using Laplace's law) [22]. We conclude that distinguishing the cardiac-specific from the pulmonary-specific effects of an intervention in PAH patients can be done using an integrated strategy [22].
It's often difficult to tell the difference between cardiac and pulmonary effects of PAH medication in patients. The pressure–volume loop and the pump-function graph were created for this reason. The pump-function graph across the pressure–volume loop is recommended because it is more easily obtained in individuals undergoing routine RV catheterization.

CARDIAC EFFECTS OF CURRENT PAH MEDICATION

Only a few studies have looked into the cardiac-specific effects of current PAH medicines, as opposed to their pulmonary-vasodilating effects. First, we'll go over the few pertinent experimental experiments.

EXPERIMENTAL STUDIES

Using pressure–volume analysis, ZIERER et al. [27] studied the effects of diltiazem (a calcium-channel blocker) on RV function in a chronic model of RV pressure overload. Diltiazem administration during constant RV afterload decreased cardiac output, which was mostly due to decreased right atrial function and RV filling. KERBAUL et al. [28] used pressure–volume analysis to explore the effects of prostacyclines in an acute model of RV pressure overload. Epoprostenol increased cardiac output, which was explained by a significant reduction in RV afterload with no changes in RV contractility. REX et al. [29] have corroborated these observations.Two recent articles [30, 31] investigated the effects of chronic sildenafil administration in a model of RV pressure overload generated by pulmonary artery banding. Both investigations found that sildenafil causes an increase in RV hypertrophy and/or improves RV function, implying that sildenafil has a direct effect on the heart. NAGENDRAN et al. [32] previously observed PDE-5 overexpression in hypertrophied, but not normal, rat and human RV myocardium, as well as acute inotropic effects of sildenafil in the isolated Langendorff-perfused heart. In conclusion, experimental data suggest that calcium-channel blockers have acutely negative effects on RV function and remodelling, while prostacyclines have a neutral effect and sildenafil has perhaps favourable cardiac-specific effects on RV function and remodelling.There are currently no (experimental) data on the effects of endothelin receptor blockers on the right ventricle in the context of PAH. Until now, these compounds have only been studied in models where the RV afterload was not fixed.

META-ANALYSIS OF CLINICAL STUDIES

There are no clinical studies that have precisely separated the cardiac and pulmonary effects of current PAH treatments that we are aware of. As a result, we used the pump-function graph to re-evaluate all placebo-controlled randomised clinical trials in PAH that contained serial invasive haemodynamic data, as recently summarised by GALIE et al. [33]. (fig. 3). P pa was utilised as a substitute for mean RV pressure, and SVi was recalculated by dividing cardiac output by heart rate and body surface area (estimated as 1.82 m2 if not reported).The pump-function graph's simultaneous evaluation of the haemodynamic changes in P pa and SVi throughout a typical study period of 12 weeks (range 8 weeks to 12 months) reveals that current PAH treatments mostly have pulmonary vasodilating effects. When comparing figure 3 to the situation in figure 2d, this becomes clear. Although more research into this issue is needed, this finding shows that there is a compelling case to be made for creating innovative PAH medications that particularly target the right ventricle [12].
The key determinant of prognosis in PAH is right heart function. Current drugs (endothelin receptor blockers, PDE-5 inhibitors, and prostacyclines) appear to have only little effects on

the heart (when analysed by an RV pump-function graph). Novel treatments that improve right heart function in PAH patients are required.

RELEVANCE OF LHF THERAPIES FOR PAH-RELATED RIGHT HEART FAILURE

(Loop)diuretics, a b-blocker, and angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers if ACE inhibitors are not tolerated, are the foundations of modern (systolic) LHF therapy (table 1). If the patient's renal function allows, an aldosterone antagonist or angiotensin blocker is administered if the symptoms persist. Exercise training is recognised as a complementary treatment. For selected LHF patients, an implantable cardioverter-defibrillator and/or

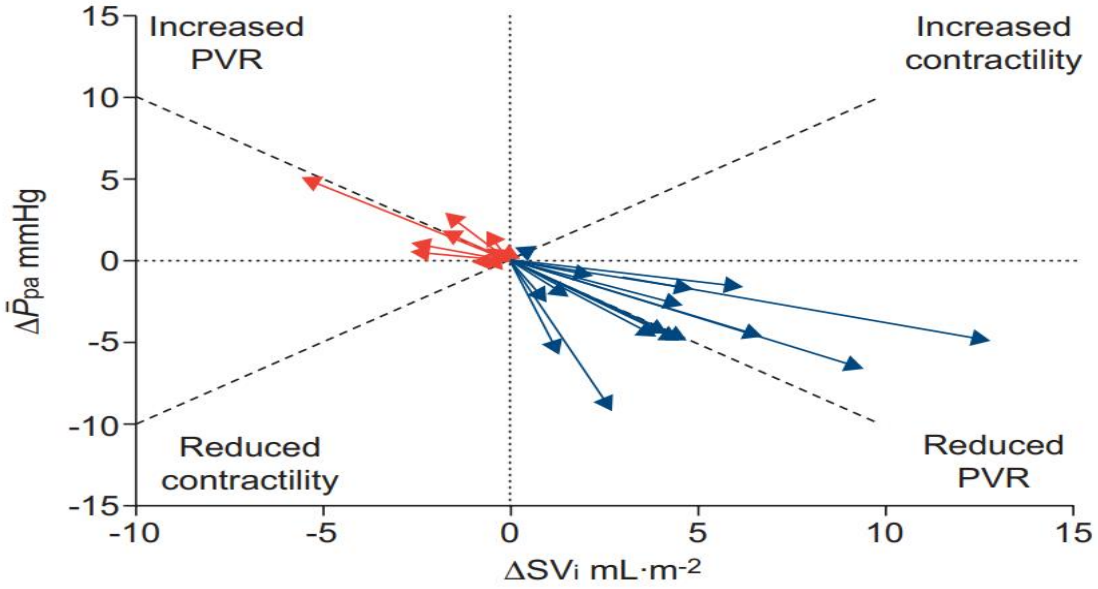

FIGURE 3. Meta-analysis of pulmonary arterial hypertension (PAH) trials by pump function. Each arrow shows the general absolute change in indexed stroke volume (DSVi) and mean pulmonary artery pressure (D$\bar{P}$pa; as a surrogate measure for mean right ventricle pressure) per study group of all placebo 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 treatments are well-known and have been shown in a number of well-designed randomised controlled trials (more details on current LHF therapy can be found in current guidelines [14, 15]). It's worth noting that clinical benefit was found in these trials regardless of the cause of LHF. This confirms the current theory that, following the initial shock, the process of cardiac remodelling is comparable and unaffected by the cause (e.g., ischaemia or hypertension) [13]. However, it has been shown that therapeutic efficacy in systolic and diastolic heart failure (different LHF phenotypes) may differ [34].As a result, only these recommendations will be reviewed in this paper, as the cardiac remodelling seen in PAH patients with right heart failure is comparable to that seen in systolic LHF (lower ejection fraction and ventricular dilatation) [10].

Even though there are significant structural, functional, and developmental variations between the left and right ventricles, it is tempting to apply the LHF recommendations to right heart failure [1, 2]. Nonetheless, there is considerable overlap in recommendations between the LHF and PAH guidelines [3, 4, 14, 15], implying that, at least from a treatment standpoint, there may be some fascinating parallels. Loop diuretics, for example, are commonly utilised to achieve rapid symptomatic relief in both PAH and LHF. Furthermore, for PAH patients who are clinically stable and receiving adequate pharmacological treatment, moderate exercise training is now acknowledged as an adjuvant therapy [35–37].

We won't go into detail on loop diuretics or exercise training because they're already part of the existing PAH guidelines' recommendations. We also won't talk about LHF treatments that are currently in the early stages of development. Instead, this review will concentrate on the clinical potential of: 1) b-blockers as sympathetic nervous system modulators; 2) ACE inhibitors, angiotensin blockers, and aldosterone antagonists as RAAS modulators; and 3) the potential of electrical cardiac interventions, such as implantable cardioverter-defibrillators and cardiac resynchronization therapy, as novel PAH add-on therapies (fig. 4).We will primarily focus on the significance of the underlying pathophysiological mechanisms for PAH that are altered by these interventions because there are few prospective controlled data that evaluate the relevance of various LHF therapy in PAH.

NEUROHUMORAL ACTIVATION AND PAH

In addition to symptomatic treatment with loop diuretics, the combination of a b-blocker (more specifically bisoprolol, carvedilol, or sustained released metoprolol) with either an ACE inhibitor, angiotensin blocker, and/or an aldosterone antagonist significantly reduces morbidity and mortality in LHF [14, 15]. These drugs affect the underlying "neuro- humoral activation," which is now thought to be patho- gical in the long run since it promotes cardiac remodelling and disease development [13, 38].In LHF, neurohumoral activation is defined as a situation in which the neurological and hormonal systems designed to maintain appropriate organ perfusion are overactive. From a therapeutic standpoint, the sympathetic nervous system and RAAS are the most important components of this activation [14, 15, 38].

SYMPATHETIC NERVOUS SYSTEM

Early on in the course of LHF, autonomic dysbalance with sympathetic system dominance ensues [39], which is mostly due to diminished baroreceptor discharge. Mechanical stretch triggers baroreceptors, which are mostly found in the aortic arch, carotid arteries, and the left ventricle, and they respond by tonically suppressing central sympathetic neuronal outflow. Both systemic arterial pressures and baroreceptor sensitivity are lowered in LHF patients. Overstimulation and selective downregulation of cardiac-specific b1-adrenergic receptors in the left ventricle originate from sympathetic overdrive, which causes chronically increased norepinephrine levels. This stimulus increases heart mechanical stress (through inotropic, chronotropic, and vasoconstrictive effects), as well as having direct cardiotoxic consequences [40].As a result, LV remodelling continues, resulting in additional functional decline [38]. By antagonising the b-adrenergic receptor, b-blockers can break the vicious cycle of heart failure [41]. Digoxin's therapeutic effects are now linked not just to its mild inotropic effects, but also to its minor neurohumoral effects: digoxin indirectly sensitises the cardiac baroreceptor, reducing sympathetic outflow in the central nervous system [42].

Several approaches have been devised to establish sympathetic overdrive in LHF patients, despite the fact that sympathetic activity is difficult to detect in the clinical situation [39]. Regional norepinephrine spill-over measurements or microneurography (which directly measures post-ganglionic muscular sympathetic nerve activity (MSNA)) are the most accurate ways to evaluate sympathetic activity. The use of 123I-MIBG tracers provides a sophisticated

noninvasive option (heart-to-mediastinum ratio falls when the sympathetic nervous system is chronically activated). The assessment of heart rate variability is a cruder yet simple method (which is reduced when the sympathetic nervous system is over-activated).

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The RAAS [43] is another important system in this context, as it is strongly linked to the sympathetic nervous system. Reduced cardiac output causes decreased renal perfusion, which activates this mechanism. The juxtaglomular cells in the kidneys react by secreting renin in this circumstance. Renin raises angiotensin I levels, which ACE converts to angiotensin II (abundantly present in the lung endothelium). Multiple functions are mediated by angiotensin II, which is a powerful vasoconstrictor with inotropic, natriuretic, and antidiuretic effects. All cause cardiac stress in the setting of LHF and are harmful in the long run.Angiotensin II, like norepinephrine, excessively stimulates and selectively down-regulates its angiotensin II type 1 (AT1)-receptor in the left ventricle, causing cardiac remodelling directly. Angiotensin II also increases the production of aldosterone and vasopressin (also called antidiuretic hormone). Both have natriuretic and antidiuretic properties, as well as promoting heart remodelling directly. By decreasing certain components of the RAAS, ACE inhibitors, angiotensin blockers, and aldosterone antagonists interfere with this mechanism [14, 15].

The activity of the RAAS can be measured directly in plasma by measuring renin or angiotensin II activity. The assessment of hyponatremia [38] is a straightforward but indirect way to measure chronically activated RAAS.

Over-activation of the sympathetic nervous system in PAH

Given that the fundamental source of neurohumoral activation in LHF (decrease in cardiac output) is also a key clinical characteristic in PAH, the sympathetic nervous system and RAAS are likely to be substantially activated in PAH. Indeed, sympathetic and RAAS activation assessments in PAH are equivalent to those in LHF [44, 45].

Measurements in PAH patients revealed higher norepinephrine levels in plasma, similar to those seen in LHF patients [46, 47], albeit this was not consistently found in other research [48]. In PAH patients, increased MSNA [48], reduced cardiac uptake of 123I-MIBG [49], reduced heart rate variability [50], and selective down-regulation of b1-adrenergic receptors in the right (but not left) ventricle have all been observed, all of which are indicators of increased sympathetic activity affecting the right ventricle [51]. Furthermore, these findings were linked to the severity of the condition.

In PAH-induced right heart failure, RAAS is also involved. Hyponatremia was recently reported by FORFIA et al. [52], implying that RAAS activation is a significant independent prognostic factor in PAH. In PAH patients, parameters that more directly assess RAAS activation (increased renin activity, raised levels of angiotensin II, aldosterone, and/or vasopressin) have yet to be studied. Nonetheless, in patients with right heart failure owing to hypoxic pulmonary hypertension (cor pulmonale) [53] and in different experimental models of PAH-induced right heart failure [54], enhanced renin activity and raised aldosterone levels in plasma have been shown. Furthermore, specific AT1-receptor down-regulation in the right ventricle has been found in PAH patients [55].

These findings imply that in PAH, the sympathetic nervous system and the RAAS are both significantly active. However, unlike LHF, only a few clinical investigations have looked into the therapeutic potential of neurohumoral modulation. RICH et al. [56] studied the effect of i.v. digoxin administration in PAH patients and discovered an immediate increase in cardiac output with a concurrent decrease in norepinephrine levels, similar to the digoxin effect in LHF. Surprisingly, no clinical investigation on the effects of b-blockers, which have a stronger effect on the sympathetic nervous system than digoxin, has been conducted in PAH-induced right heart failure. B-blocker use is even contraindicated, according to medical opinion.

PROVENCHER et al[57] .'s work corroborates this frequently. In a limited group of patients with portopulmonary hypertension, they found considerable functional improvement two months after stopping the b-blocker. However, all of the patients were given high-dose propanolol or atenolol to prevent variceal haemorrhage. In compared to newer b-blockers, these older b-blockers are contraindicated for LHF because of their significant myocardial depression and vasoconstrictive effects [41].Furthermore, LHF has long known that acute functional benefits do not always translate to long-term positive changes, and that overall good effects of b-blockers can normally be predicted after o3 months of chronic treatment [41].

The need of maintaining RV systolic function is another (related) rationale opposing b-blocker use in PAH. Acute b-blocker medication has been shown to aggravate dyspnea, most likely due to negative inotropic effects that cause instant ventriculo-arterial uncoupling [18]. However, as seen in LHF patients [14, 15], this transitory effect may be better tolerated with judicious administration of selective b-blockers ("start low, go slow").

Although it goes against current consensus, we believe that the sympathetic nervous system is stimulated to pathological levels in PAH, just as it is in LHF, and that this can be normalisedwith judicious b-blocker treatment. More (pre-clinical) study is needed to see if a low-dose of a newer selective b-blocker could be a tolerable option for eliminating the negative consequences of sympathetic overdrive in PAH.

ACTIVATION OF RAAS IN PAH

The involvement of RAAS in pulmonary vascular remodelling and pulmonary vasoconstriction has long been recognised [58, 59]. When captopril (the first ACE inhibitor) became commercially available, it was avidly tried in PAH patients for whom there was no effective treatment at the time. Four short case series (a total of 26 patients) on the haemodynamic effects of captopril in PAH were published in the 1980s. Three of the investigations were encouraging, with significant improvements in cardiac output and exercise capacity [60, 61]. However, one study [63] found no haemodynamic alterations, either positive or negative.Surprisingly, no more clinical trials have been published since then. Since the discovery of ACE2, an isoform of ACE with anti-inflammatory (protective) properties [64, 65], there has been renewed interest in RAAS. The heart's potential benefit from ACE inhibitors, angiotensin blockers, and/or aldosteron antagonists has yet to be tested in patients with PAH.

Preclinical investigations utilising several models of PAH and right heart failure, on the other hand, have proven that taking an ACE inhibitor or angiotensin blocker lowers RV remodelling and improves cardiac function and/or mortality [66–69]. We conclude that pharmacological interference in the RAAS could (partially) reverse pulmonary and cardiac remodelling in PAH, indicating the need for a prospective controlled clinical trial of the effects of ACE inhibitors, angiotensin blockers, and/or aldosterone antagonists in PAH.

The sympathetic nervous system and the RAAS are significantly active in PAH, just as they are in LHF. As a result, well-established pharmaceutical therapies for LHF may be applicable for PAH as well. ACE inhibitors, angiotensin II blockers, and selective b-blockers, on the other hand, have not been studied in PAH, and clinical trials evaluating their potential are urgently needed. Nonetheless, routine use of these neurohumoral modulators, particularly b-blockers, is not currently recommended in PAH unless further trials show that their usage is safe and effective in PAH.

ELECTRICAL REMODELLINGAND PAH

In the treatment of LHF, implantable cardioverter-defibrillators and cardiac resynchronization therapy are relatively novel therapeutic methods. Since 2001, major heart failure guidelines have included recommendations for implanted cardioverter-defibrillator use, but only since 2005 have recommendations for resynchronization treatment been included. In addition to the

beneficial effect of optimal pharmacological LHF treatment, it is now widely accepted that resynchronisation therapy significantly reduces morbidity and that both cardioverter-defibrillators and resynchronisation therapy significantly reduce mortality in certain LHF patient groups [14, 15].

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

A cardioverter-defibrillator detects and terminates life-threatening and malignant ventricular arrhythmias before they cause abrupt cardiac death. With the advancement of LHF, the risk of ventricular arrhythmias rises. As a result, the use of an implantable cardioverter-defibrillator is now recommended as a secondary prevention for sudden cardiac death in LHF patients with a (suspected) history of ventricular arrhythmia, or as a primary prevention in LHF patients with a severely reduced left ventricular ejection fraction. LHF patients must have a realistic prospect of survival with a functional status of >1 year in both instances [14, 15]. After 24 months, the clinical trials on which these guidelines are based indicated a 30 percent relative decrease in all-cause mortality and a 5% absolute risk reduction [70, 71], implying a number-needed-to-treat of 20 patients.

Shocking cardiac death, apparently caused by malignant ventricular arrhythmias, has also been identified as a significant clinical risk in PAH patients [72]. Markers for a "electrically instable heart," such as extended QTc-intervals and greater QT dispersion determined from ECG [73], neurohumoral abnormalities (as previously addressed), and a rise in cardiac fibrosis [74], have been established in PAH patients, much as they have in LHF patients. In contrast to LHF, however, the actual incidence of ventricular arrhythmia-related events in PAH is thought to be modest.However, the reported percentages of PAH mortality due to ventricular arrhythmias range from 8% to 26% [8, 75], and the real numbers may change significantly for 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]). Furthermore, these figures are based on retrospective research and were compiled in part prior to the introduction of PAH medicines. To precisely determine the current prevalence of sudden cardiac fatalities in different subgroups of PAH, systematic prospective clinical investigations are required.By calculating the number-needed-to-treat, this data will give a rough estimate of the clinical potential of cardioverter-defibrillators in PAH (extrapolating the effect of cardioverter-defibrillators in LHF). Implantable cardioverter-defibrillators (or pharmacological anti-arrhythmic drugs) are not widely suggested as a (main) preventive measure for sudden cardiac death in PAH patients until that time comes [4, 72].

SUPRAVENTRICULAR TACHYARRHYTHMIAS

Supraventricular arrhythmias appear to be substantially more common than ventricular arrhythmias, and they are thought to be a major cause of clinical worsening in PAH patients. An annual incidence of supraventricular tachyarrhythmias in PAH was reported to be,3% in a retrospective study [77], with atrial fibrillation and atrial flutter being equally prevalent. Persistent atrial fibrillation was linked to a poor prognosis in this study (nine out of 11 PAH patients died within 24 months), which could be explained by a decline in RV function caused by the loss of atrial "kick" to ventricular filling. As a result, maintaining sinus rhythm is now considered an important therapy target in PAH [4].The clinical experience with LHF, on the other hand, contradicts this. Rhythm-control treatment had no better survival results than rate-control treatment (acceptance of atrial fibrillation and decrease of the ventricular response rate in combination with sufficient anticoagulation) but needed more hospitalisation due to the requirement for repeated cardioversion [78, 79]. Due to a paucity of prospective and controlled data, we completely accept existing recommendations to restore and maintain sinus rhythm in

PAH patients if possible. Future trials, on the other hand, will be required to determine the efficacy of this therapeutic plan.

CARDIAC RESYNCHRONISATION THERAPY

Cardiac dyssynchrony in LHF is defined by localised variations in the left ventricle's electrical and/or mechanical activity (usually a delay in activation of the LV free wall in relation to the interventricular septum). Dyssynchrony causes ineffective left ventricle pumping, which leads to additional clinical deterioration. Cardiac resynchronization therapy can quickly restore LV contraction synchrony, resulting in improved overall LV (systolic) performance. In the long run, resynchronization therapy causes cardiac remodelling to reverse, resulting in even better LV performance.Despite the fact that the current clinical selection criteria for resynchronization therapy (wide QRS complex on ECG) under-predict clinical benefit for the individual LHF patient, resynchronization therapy has been shown to reduce morbidity and mortality in LHF patients and is now a well-established treatment modality [14, 15].

Ventricular dyssynchrony is frequently seen when PAH-induced right heart failure progresses [80, 81]. Mechanical interventricular dyssynchrony in PAH is associated with poor RV systolic function (as seen by the paradoxical bulging of the interventricular septum). Ventricular dyssynchrony is also hypothesised to compromise LV diastolic performance by septum bulging [82, 83]. Resynchronization of the right ventricle may thus be beneficial in the treatment of PAH. We recently showed, however, that LV and RV dyssynchrony are fundamentally different: Regional changes in the duration of the contraction, rather than regional abnormalities in the initiation of the contraction (e.g. due to a conductance delay), are the source of PAH-related ventricular dyssynchrony, which is strongly afterload dependent [83, 84].

Previously, cardiac resynchronization therapy has been shown to be effective in patients with PAH who also have congenital heart disease [85]. These individuals, however, have a "LHF-like" dyssynchrony as a result of a total right bundle branch block as a (late) consequence of cardiac surgery, and so are not indicative of the PAH community as a whole. In the absence of conduction abnormalities, we recently investigated the therapeutic potential of resynchronization therapy in an animal model of PAH-induced right heart failure [84]. Pre-excitation of the RV free wall improved RV systolic function and reduced unfavourable LV diastolic interaction, according to our findings.HARDZIYENKA et al. [86] recently corroborated similar findings in a research with patients suffering from right heart failure and ventricular dyssynchrony due to chronic thrombo-embolic pulmonary hypertension. Standard tissue-Doppler echocardiography was used to examine a group of 67 patients prior to surgery, and seven individuals were chosen for a temporary pacing strategy due to the presence of substantial diastolic interventricular delay (as a quantification of PAH-related ventricular dyssynchrony).Resynchronization therapy improved cardiac synchrony, RV contractility, and LV diastolic filling, and resulted in a.10 percent improvement in SV. These encouraging findings call for more research into cardiac resynchronization therapy as a novel treatment for right heart failure caused by PAH [12], with a focus on long-term effects and the development of robust selection criteria for PAH patients who would benefit the most from cardiac resynchronization therapy.

The incidence of malignant ventricular arrhythmias is thought to be low in PAH, although this discovery has to be confirmed in the future. Implantable cardioverter-defibrillators are not yet suggested for PAH patients. Clinical worsening is common with supraventricular tachyarrhythmias. Maintaining sinus rhythm is an important treatment goal based on retrospective evidence, but this preference for rhythm control over rate control needs to be supported in prospective controlled research, especially because this is in contrast to the experiences in left heart failure. Cardiac resynchronization therapy (CRT) appears to be a

potential new treatment option. To examine its long-term impacts and identify rigorous selection criteria, prospective controlled studies are required.

CONCLUSIONS

The possible application of current LHF therapy for the treatment of PAH-induced right heart failure was explored in this review. We conclude, based on the available research, that LHF and right heart failure share fundamental underlying pathophysiological pathways that are treatable (fig. 4); nevertheless, clinical experience with current LHF therapies in the setting of PAH is very limited.

This disparity is perplexing, and we can only hypothesise as to why it exists. For starters, it's difficult to distinguish between cardiac and pulmonary consequences of treatment therapies in PAH patients. We propose using the pump-function graph as a solution. Second, PAH is still a rare condition, despite the fact that many more clinical trials have been conducted in the last two decades [33]. Third, right heart failure was once thought to be an unavoidable end result of PAH, but now the right ventricle is being looked at as a potential therapeutic target [12].

So, where do we go from here? Before LHF therapy can be used to treat PAH, solid clinical proof is required. As a result, phase I/II trials must be carried out initially, in order to gain insight into the safety, tolerability, and efficacy of LHF therapy in PAH. Following that, randomised clinical trials comparing current PAH therapy with and without add-on LHF medication should be conducted. The length of the trial is also important: the LHF experience suggests that reversing cardiac remodelling will take longer than the standard 12-week trial period.Furthermore, in these types of investigations, the question of which end-point to chose remains unanswered: Traditional PAH endpoints, such as 6-minute walking distance, may be insufficiently sensitive, and direct assessments of RV remodelling and function may be more relevant. The most optimal end-point, however, mortality, may be overly stringent and require the inclusion of an unrealistically large number of patients [87].

To sum up, well-designed clinical studies are necessary because they may give evidence for the adoption of novel therapeutic modalities that are reasonably easy to come by in the treatment of this severe disease. If travelling "left" is a step in the "correct" direction, more research will be needed.

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