Neurohormonal modulation as therapeutic avenue for right ventricular dysfunction in pulmonary artery hypertension: till the dawn, waiting

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Contributions: (I) Conception and design: TH Le Jemtel, A Jaiswal; (II) Administrative support: None (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Neuro-hormonal activation may lead to or be associated with pulmonary arterial hypertension (PAH) and right ventricular dysfunction. Notwithstanding whether it is the cause or the consequence of PAH-related right ventricle (RV) dysfunction neurohormonal activation contributes to significant morbidity and mortality in patients with PAH and the progression of RV dysfunction. Experimental data regarding the use of beta adrenergic blockade and renin-angiotensin aldosterone system modulation are encouraging. However, clinical studies have largely been negative or neutral; and, neuro-hormonal modulation is discouraged in patients with PAH related RV dysfunction for fear of systemic hypotension. Herein, we summarize the pathophysiological background that supports the potential role of neuro-hormonal modulation in the management of PAH related RV dysfunction; also present current clinical experience; and, discuss the need for controlled studies to move forward. Lastly, we review potential non- pharmacological modalities for neuro-hormonal modulations in PAH patients with RV dysfunction.

Keywords: Right ventricle (RV); heart failure; right ventricular dysfunction; beta blocker; angiotensin converting enzyme inhibitor; aldosterone inhibitor

Submitted May 11, 2018. Accepted for publication May 31, 2018.
doi: 10.21037/atm.2018.06.04
View this article at: http://dx.doi.org/10.21037/atm.2018.06.04

Introduction

Pulmonary arterial hypertension (PAH) remains a fatal condition despite emerging and promising therapeutic options (1,2). Right ventricle (RV) function is the major determinant of prognosis in all types of PAH (3,4). As with the left ventricular dysfunction, RV dysfunction is associated with neuro-hormonal activation (5-8). The progression of RV dysfunction could be independent from that of pulmonary vascular resistances (4). Despite growing evidence supporting the role of neuro-hormonal activation in the pathogenesis of PAH related RV dysfunction, patients with PAH and RV dysfunction are not receiving neuro-hormonal modulators including beta adrenergic blockers (BB) and renin-angiotensin-aldosterone system (RAAS) inhibitors due to the fear of side effects (9).

This review highlights neuro-hormonal modulation as a prospective therapeutic avenue for the management of RV dysfunction in PAH and the need of further studies.

Why patients with PAH and RV dysfunction are not receiving neurohormonal blockade?

Evidence against the use of BB in PAH stems from

Table 1 Status of clinical trials evaluating neurohormonal modulation in PAH and RV dysfunction

Study Identifier	Description	Treatment	Status	Enrolled/target
NCT 02120339	B-blocker safety and efficacy in PAH and RV dysfunction	Carvedilol	Stopped due to low enrollment	5 pts
NCT01723371	Beta blockers for treatment of pulmonary arterial hypertension in children	Carvedilol	Stopped due to low enrollment	0 pts
NCT02507011	Beta-blockers in pulmonary arterial hypertension	Carvedilol	Recruiting	26 pts
NCT01712620	Spironolactone for pulmonary arterial hypertension	Spironolactone	Recruiting	70 pts
NCT00964678	Safety of carvedilol in PAH and RV dysfunction	Carvedilol	Concluded	10 pts
NCT01468571	Effects of spironolactone on collagen metabolism in pulmonary arterial hypertension	Spironolactone	Withdrawn	–
NCT01586156	Pulmonary arterial hypertension treatment with carvedilol for heart failure (Carvedilol) (PAHTCH)	Carvedilol	Concluded	30 pts
NCT00240656	Spironolactone combined with captopril and carvedilol for the treatment of pulmonary arterial hypertension		Completed/no results	Unknown
NCT00811486	Body volume regulation in pulmonary arterial hypertension with right ventricular failure	Spironolactone/ conivaptan	Withdrawn due to lack of enrollment	0 pts
NCT03344159	Spironolactone therapy in chronic stable right HF trial (STAR-HF)	Spironolactone	Recruiting	30 pts
NCT01246037	Beta-blockers in i-PAH	Bisoprolol	Withdrawn due to lack of enrollment	30 pts
NCT00519870	Losartan therapy in pulmonary hypertension	Losartan	Completed/no results	Unknown
NCT01181284	Modulating effects of lisinopril on sildenafil activity in pulmonary arterial hypertension (PAH) (MELISSA)	Lisinopril	Completed/no results	24 pts

experiences gathered in small PAH cohorts (10,11). Provencher *et al.* reported improved exercise capacity after withdrawal of propranolol which was used for prophylaxis for variceal bleeding in 10 patients with moderate-to-severe portopulmonary hypertension. An increase in heart rate after withdrawal of propranolol was thought to mediate the improvement in cardiac output and functional capacity (10). Cardiac output may largely depend on heart rate as PAH-related longstanding pressure overload steadily reduces RV myocardial contractility (9).

More recent observations indicate that patients with PAH can tolerate BB therapy. A single center experience with long term follow up (20 months) of 94 adult PAH patients (28% of patients were receiving mostly selective BBs for cardiac comorbidities) reported no detrimental effect on clinical, functional and hemodynamic outcomes including mortality (12). Tolerance to BB was confirmed over a period of 5 years by a USA-based PAH registry of 564 patients with 13% of them receiving cardio-selective BB agents (13). Lastly, Bandyopadhyay *et al.* showed that BB therapy was not associated with any deleterious effects for up to 78 months in PAH patients (14).

Notwithstanding their small patient populations, recent prospective studies provide proof of concept for the use of BB in PAH patients with RV dysfunction (15). A pilot study of 12 PAH patients demonstrated improvement in RV size and function after treatment with nebivolol—a third generation BB (16). Similarly, carvedilol-a third generation BB was well tolerated and improved RV function in an open label study of six type 1 PAH patients with baseline RV dysfunction (17). In a cohort of congenital heart disease patients with RV failure, Bouallal *et al.* demonstrated beneficial effects of BB therapy with improvement of RV ejection fraction and NYHA functional class (18). Several controlled clinical studies were undertaken to evaluate the impact of BB in PAH, however, only few patients were enrolled (*Table 1*). The only double blind, placebo controlled, randomized trial-PAHTCH examined the safety and benefits of carvedilol in 30 PAH patients (19). Carvedilol was well tolerated, did not affect functional

capacity, and improved RV function as well as expression of beta-1 adrenergic receptor in a dose dependent manner.

Several reasons may explain the discordant findings between older and recent studies of BB therapy in RV dysfunction: small study population and detrimental effect of propranolol on cardiac function might have contributed to the functional and hemodynamic improvement after discontinuation of propranolol (20-22). Additionally, propranolol may increase RV afterload as beta-2 adrenergic receptor blockade heightens pulmonary vascular resistance (23). The dose of metoprolol-a second generation cardioselective BB may have been excessive as noted to occur in patients with LV dysfunction who received a high initial dose of BB (21). Left ventricular systolic function declines at initiation of BB therapy in patients with heart failure with reduced ejection fraction (HFrEF). Thus one avoids initiation of BB therapy in decompensated HFrEF patients and starts at a low BB dose when have returned to a compensated state (24,25).

Experience with RAAS modulation is scarce in patients with PAH. It consists of few small uncontrolled studies that were carried out decades ago. Captopril significantly reduced pulmonary vascular resistance and pulmonary artery pressure along with improvement in RV performance independent of changes in LV systolic dysfunction (26). Improvement in RV function occurred within 4 days of captopril therapy in PAH patients (27). Although systemic arterial pressure fell, cardiac output and heart rate did not change. Stumpe *et al.* later on documented the sustained hemodynamic and clinical benefits of captopril in PAH patients (28). More recently, functional capacity was shown to improve after initiation of dual therapy with endothelin and mineralocorticoid receptor blockade in PAH patients (29). Use of RAAS inhibitors is not consistently effective in all PAH patients as some patients don't derive benefits while some others may develop significant hypotension (27,30). However, the precise phenotype of such patients remains uncharacterized.

Pathophysiological basis for neurohormonal blockade in PAH with RV dysfunction

Experimental data provide clear evidence of neurohormonal activation and beneficial effects of neurohormonal modulation in PAH and RV dysfunction. Usui *et al.* have shown biventricular increase in local Angiotensin II, and norepinephrine reactivation of fetal gene program and hypertrophy in rats with PAH (31). Treatment with valsartan and carvedilol improved short term survival. However, due to a short follow up one does not know whether the short-term survival benefit was associated with delayed progression of PAH. Bogaard *et al.* provided a longer follow up and reported improved survival in rats with PAH with RV dysfunction after treatment with carvedilol. In addition, carvedilol led to improvements in exercise endurance, cardiac output and RV function (8,32). The RV functional improvement was associated with increased capillary density, lower rates of cardiomyocyte death, decreased fibrosis, and reduced pulmonary arteriolar hypertrophy and reduced pulmonary pressures. Bogaard *et al.* also reported the beneficial effect of beta-1 adrenergic receptor blockade with metoprolol in PAH rats. Interestingly, selective beta-1 adrenergic receptor blockade with metoprolol had a comparable effect to carvedilol, except for a lower reduction in RV hypertrophy (RVH) and dilatation; and the absence of pulmonary vascular remodeling. Thus, beta-1 adrenergic receptor blockade may prevent RVH but does not affect pulmonary vascular function. Similar findings were reported by de Man *et al.* using another beta-1 receptor adrenergic selective blocker-bisoprolol (33). Bunazosin hydrochloride, an alpha adrenergic blocker, may attenuate the elevation of RV systolic pressure, but not RVH in rats (34). Indeed, alpha and predominantly beta-2 receptors are found in pulmonary vasculature which might have role in PAH (23,35,36).

Overall, non-selective alpha and beta adrenergic receptor blockade may be preferred for slowing down or reversal of pulmonary vascular remodeling and prevention and progression of RV hypertrophy. The alpha and beta adrenergic receptor blocker arotinolol—an experimental drug prevented the progression of MCT-induced PAH and RVH in rat (37).

Zakheim *et al.* were the first to note reductions in pulmonary vascular resistance and RVH after treatment with angiotensin enzyme inhibitor (ACEI) in a hypoxia induced PAH model in rats (38). Subsequently, RAAS modulation with ACEI, angiotensin receptor blocker, mineralocorticoid receptor antagonist and ACE-2 agonist has been consistently shown to improve hemodynamics, decreased RV afterload, and reduce pulmonary vascular remodeling with arrest of pulmonary arterial smooth muscle proliferation in the absence of systemic side effects (39-46).

In summary, few clinical studies of utilizing BB and RAAS blockade/inhibition have been reported. However, a wealth of experimental data argues in favor of neurohormonal modulation for the treatment of PAH and RV

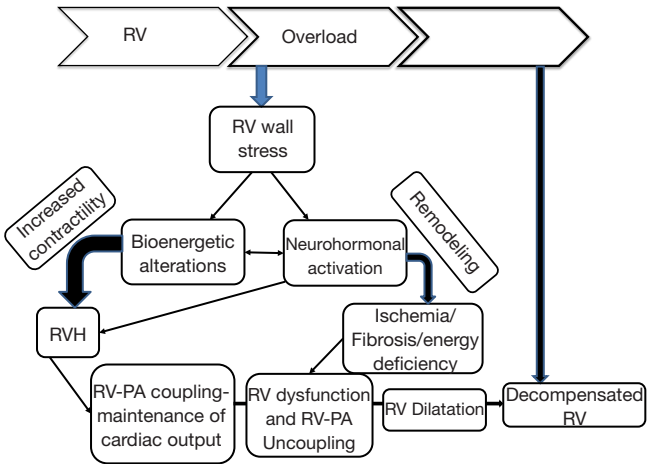

Figure 1 RV remodeling in PAH. PA, pulmonary artery; RV, right ventricle; RVH, right ventricular hypertrophy.

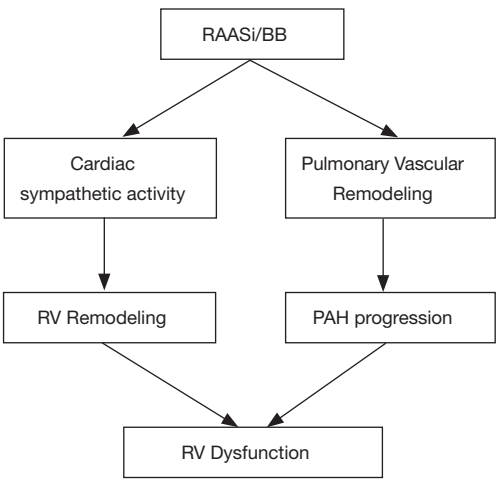

Figure 2 Role neurohormonal modulation in PAH and RV dysfunction. BB, beta blocker; PAH, pulmonary artery hypertension; RAASi, renin angiotensin aldosterone system inhibitor; RV, right ventricle.

dysfunction. Thus, human studies are needed to evaluate the role of BB and RAAS inhibition/blockade in the management of PAH with RV dysfunction.

Future directions

Even with differences between the RV and the LV including embryological origin, shape, structure, and circulatory milieu, the RV remodels similarly to the LV when subjected to increased afterload and neuro-hormonal activation (*Figure 1*) (47). Thus, neuro-hormonal modulation is likely to benefit patients with PAH and RV dysfunction as suggested by preclinical studies (*Figure 2*) (vide supra). Accordingly, a comprehensive approach to neuro-hormonal modulation akin to that used for LV dysfunction is warranted in patients with PAH and RV dysfunction. Lessons learnt from the use of pharmacological agents in HFrEF should be applied to the RV dysfunction management (19,25).

Although earlier studies utilizing non-selective first-generation BB concluded to adverse events in patients with PAH, the recent use of second and third generation BBs did not show any adverse effects and suggested positive effects on RV function and PAH progression. Definite evidence awaits controlled clinical studies. Slow enrollment has thwarted such attempts, National registries that include centers actively engaged in the management of pulmonary hypertension may uncover the benefits of BB/RAAS blockade/inhibition in PAH patients with RV dysfunction.

The preferred BB agent for PAH and RV dysfunction may be selective to pressure beta-2 adrenergic activation in the pulmonary and skeletal muscle vasculature. While metoprolol which does not affect peripheral alpha and vascular beta-2 adrenergic receptors may be better tolerated, however, carvedilol or nebivolol have vasodilatory and anti-inflammatory properties that make them attractive for the treatment of PAH with RV dysfunction. Both ACEI and ARB carry the risk of systemic arterial hypotension. However, selective angiotensin-1-receptor blockade may be more appropriate in patients with PAH and RV dysfunction who are at risk for systemic hypotension (48).

In addition to pharmacotherapy, device-based interventions directed at modulation of autonomic tone needs to be investigated. Whether or not modulation of neuro-hormonal activation shows benefits in patients with PAH and RV dysfunction, device-based modulation of autonomic tone has shown promises in the management of HFrEF (49).

Apart from heightened sympathetic activity, reduced parasympathetic activity relative to sympathetic activation contributes to morbidity and mortality, and therapeutic interventions improve clinical outcomes in HFrEF (50-52). Such approach may be desirable as reduction in sympathetic activity could be limited due to side effects of hypotension and decreased cardiac output seen with pharmacologic agents (53). Moreover, parasympathetic activation might provide additional myocardial benefits when added to the background sympathetic nervous system (SNS) and RAAS

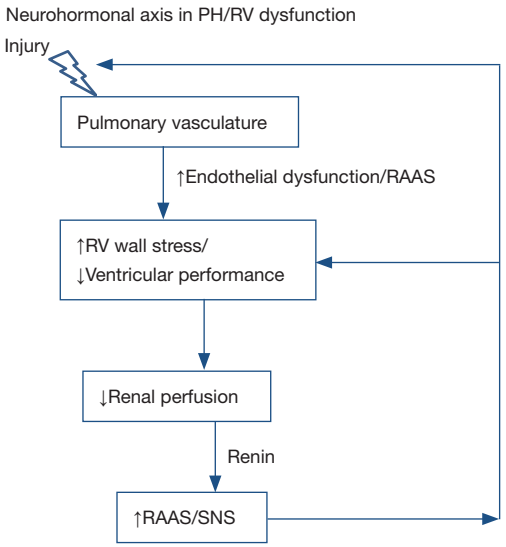

Figure 3 Injury of pulmonary endothelium results in local increase in ACE activity resulting in increased angiotensin II. Increase in Ang II preferentially facilitates vasoconstriction, proliferation and fibrosis over vasodilation due to downstream up regulation of AT1 receptors and a concomitant down regulation of vasodilatory ACE-2 and Angioten1-7. Moreover, endothelial dysfunction promotes local aldosterone promotion which in turn further augments pulmonary vascular remodeling. The pulmonary vascular remodeling results in increased RV afterload which consequentially results in increased RV wall stress and decreased myocardial function. In succession, these RV changes promote local and systemic release of norepinephrine and Ang II which acutely promotes RV contractility and induces hypertrophy for chronic compensation. Similar to HFrEF, chronic neurohormonal up-regulation results in down-regulation of the B1-adrenergic receptors impairing inotropic, chronotropic and lusitropic responsiveness of RV, to the similar extent. This creates a vicious cycle of decreased cardiac output and neurohormonal hyper stimulation. Decreased cardiac output and increased venous congestion impair renal perfusion which triggers the release of renin, activating RAAS and SNS. RV, right ventricle; HRrEF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

modulators (54). Restoration or augmentation of vagal tone can be achieved by electrical stimulation of vagal nerve, pharmacological approach, and exercise strategies.

Moreover, in addition to the management of established RV dysfunction in PAH, the neuro-hormonal modulation may be more effective in early PAH stages for prevention of RV dysfunction as SNS and RAAS activation are involved early in the pathogenesis of RV dysfunction (*Figure 3*).

Conclusions

Neuro-hormonal activation is common in PAH and RV dysfunction. Whether this activation is the cause or the result of RV dysfunction remains uncertain. Experimental models support neuro-hormonal modulation in pressure overload RV failure. However, clinical experience is inconclusive and suffers from methodological limitations. Neuro-hormonal modulation has evolved from being contraindicated to now being the back bone of HFrEF management. One needs to systematically evaluate the clinical impact of neurohormonal modulation in patients with PAH and RV dysfunction.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Emanuel R, Chichra A, Patel N, Le Jemtel TH, Jaiswal A. Neurohormonal modulation as therapeutic avenue for right ventricular dysfunction in pulmonary artery hypertension: till the dawn, waiting. Ann Transl Med 2018;6(15):301. doi: 10.21037/atm.2018.06.04

