Use of β-Blockers in Pulmonary Hypertension

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Abstract—Contrasting with the major attention that left heart failure has received, right heart failure remains understudied both at the preclinical and clinical levels. However, right ventricle failure is a major predictor of outcomes in patients with precapillary pulmonary hypertension because of pulmonary arterial hypertension, and in patients with postcapillary pulmonary hypertension because of left heart disease. In pulmonary hypertension, the status of the right ventricle is one of the most important predictors of both morbidity and mortality. Paradoxically, there are currently no approved therapies targeting the right ventricle in pulmonary hypertension. By analogy with the key role of β-blockers in the management of left heart failure, some authors have proposed to use these agents to support the right ventricle function in pulmonary hypertension. In this review, we summarize the current knowledge on the use of β-blockers in pulmonary hypertension. **(*Circ Heart Fail*. 2017;10:e003703. DOI: 10.1161/CIRCHEARTFAILURE.116.003703.)**

Key Words: β-blocker ■ heart failure ■ heart ventricles ■ hypertension, pulmonary ■ receptors, adrenergic ■ sympathetic nervous system

Pulmonary hypertension (PH) is defined by an increase in mean pulmonary arterial pressure ≥25 mm Hg at rest as assessed by right heart catheterization. PH has been classified into 5 clinical subgroups.[1] PH results from an increase in pulmonary vascular resistance, which is because of either an active remodeling of distal pulmonary arteries (pulmonary arterial hypertension [PAH]: group 1 of the PH classification), a consequence of passive back stream elevation in left heart pressures with elevated pulmonary artery wedge pressure (PH complicating left heart disease [LHD-PH]: group 2) or lung parenchymal changes and consequent capillary bed reduction resulting in chronic alveolar hypoxia, pulmonary vasoconstriction, and remodeling of distal pulmonary arteries (PH caused by lung diseases: group 3). Other PHs include PH caused by chronic thromboembolic pulmonary disease (group 4) and miscellaneous/complex disorders (group 5). In this review, we focus on the use of β-blockers in groups 1 and 2, which is the best documented and relevant use of these molecules in PH.

PAH therapies targeting endothelial dysfunction have been successfully developed in recent years in PAH,[2] whereas LHD-PH and PH caused by lung diseases should be managed by treating the cardiopulmonary causal condition.[1] Because right heart failure (RHF) is the leading cause of death in PH, some authors have hypothesized to support right ventricular (RV) function with β-blockers, by analogy with the key role of β-blockers in the management of left heart failure (LHF).[3,4] However, this is certainly an oversimplification. Indeed, the left ventricle (LV) and the RV have a distinct embryological origin, critical differences in their metabolism, vascularity or response to pressure overload.[5,6] Overall the RV seems to be less able to adapt to pressure overload than the LV. Thus, it is not possible to extrapolate knowledge-derived from the studies on LV to the studies on RV.[5,6]

Evidence for β-blocker use in PH is currently lacking. β-blocker use remains contraindicated in PAH unless required by comorbidity.[1] Moreover, the proportion of PH cases in the randomized controlled trials with β-blockers in patients with LHD has not been reported and limited data exist about the efficacy of β-blockers in PH caused by lung diseases. In this review, we report and discuss the data on the use of β-blockers in human PH (groups 1 and 2) and experimental animal models of PH. We propose a comprehensive overview on this contemporary, controversial, and translational topic, to guide further experimental and clinical research according to PH groups.

Preclinical Data

Preclinical studies have shown benefit of β-blocker therapy in experimental PH and associated RHF. The first studies were

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performed in the monocrotaline and Sugen-hypoxia rat models to induce PH and RHF. Ishikawa et al[7] showed that the development of RHF in monocrotaline rats could be prevented when using the mixed α- and β-blocker arotinolol. Bogaard et al[8] showed that carvedilol, another nonselective α- and β-blockers, reversed established RHF in monocrotaline and Sugen-hypoxia rats. In this study, carvedilol but not metoprolol mitigated pulmonary vascular media thickening in monocrotaline rats. Neither carvedilol nor metoprolol modified pulmonary vascular morphology in Sugen-hypoxia rats, but treatment with both drugs resulted in decreased fibrosis, apoptosis, and capillary rarefaction in the pressure-overloaded RV. These improvements were associated with enhanced activity of the cardioprotective protein kinase G. Although in those first studies there was a signal to suggest that some of the beneficial effects, at least in the monocrotaline model, were mediated through reversal of pulmonary vascular remodeling, de Man et al[9] used pressure–volume loop analysis to prove that the selective β-blocker bisoprolol had direct protective effects on the right heart myocardium, independent from changes in afterload. A transcriptional analysis indicated that the cardioprotective effects of β-blockers were associated with expression changes of genes encoding pathways of hypertrophy, protein ubiquitination, and mitochondrial function.[10] In contrast to these favorable studies, negative results were reported in a study with bisoprolol in a pulmonary artery banding rat model.[11] In this experiment of pure mechanical pressure overload in the context of a normal pulmonary vasculature, neither losartan nor bisoprolol changed hypertrophy or load-independent indices of RV function.

Although the direct protective effects of β-blockade on the pressure-overloaded RV remain controversial, Perros et al[12] recently reported favorable effects of nebivolol on pulmonary artery endothelial cells from patients with PAH. In this study, a comparison was made between the effects of nebivolol and metoprolol on cultured human pulmonary artery endothelial cells from patients with PAH and control subjects. Nebivolol, but not metoprolol, dose-dependently reduced proliferation and vasoactive and proinflammatory factor production. In addition, nebivolol improved endothelium-dependent and nitric oxide–dependent relaxation of pulmonary artery rings and reduced smooth muscle cell proliferation by affecting endothelial–smooth muscle cell cross talk. Nebivolol was also more potent than metoprolol in improving cardiac function, pulmonary vascular remodeling, and inflammation in rats with monocrotaline-induced PH. In the aggregate, preclinical studies suggest that β-blocking drugs, in particular carvedilol, bisoprolol, and nebivolol, might have therapeutic potential in the presence of PH. However, existing animal models mimicking PAH all have limitations and therefore these preclinical results do not justify β-blocker treatment of patients with PAH before appropriate clinical testing.

β-Blockers in PAH

The activity of the sympathetic nerve system is greatly augmented in patients with PAH, and this sympathetic overactivity is associated with increased mortality.[13] Although this finding may suggest a benefit of β-blocker treatment in patients with PAH,[14–16] current guidelines advise against their use.[1,17] This advice is based on reports of negative inotropic and chronotropic effects of β-blockers resulting in systemic hypotension and a decreased exercise capacity.[18,19] Withdrawal of propranolol and atenolol in patients with porto-PH resulted in an increase in exercise capacity and improvement in cardiac output.[18] Similarly, Peacock et al[19] reported negative consequences of β-blocker therapy in a porto-PH patient with acute heart failure and supraventricular tachycardia.

Despite the current recommendation to avoid β-blocker therapy in patients with PAH, β-blocker use is in fact not uncommon in this aging population with significant cardiovascular comorbidities. PAH registries have demonstrated that ≈1 in 4 Canadian patients with PAH is treated with β-blockers.[20] On the basis of unpublished data provided by GlaxoSmithKline and Pfizer, we calculated that in ARIES (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2),[21] the SUPER-1 study (Sildenafil Use in Pulmonary Arterial Hypertension),[22] and PACES-1 (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil),[23] respectively, 14%, 12%, and 6% of patients with PAH were treated with β-blockers. It is unclear whether the reported negative findings of β-blocker use in PAH can be translated to the use of all β-blockers. In fact, a survival benefit on propranolol or atenolol use was never tested in LHF. Moreover, it is questionable whether these observations would also apply to patients with relatively stable PAH. For example, registry data reported by Bandyopadhyay et al[24] indicated no change in survival or time to clinical worsening in patients with PAH on β-blocker therapy although they did have a tendency toward a shorter walking distance. Finally, a report by Thenappan et al[25] has suggested that careful administration of β-blocker therapy in patients with PAH if required by comorbidities is not associated with adverse outcomes. Therefore, the use of different types and doses of β-blockers and differences in patients' characteristics might explain some of the controversial results reported in the medical literature. In LHF, more favorable results are obtained using carvedilol, nebivolol, metoprolol, and bisoprolol. Grinnan et al[26] published a small pilot study of 6 patients with PAH indicating that the use of carvedilol may result in a significant improvement in RV ejection fraction, whereas no negative effects on exercise capacity were observed. Hypothesizing that positive effects on myocardial remodeling and oxygen efficiency can counteract possible acute negative inotropic and chronotropic effects, we recently undertook a randomized, placebo-controlled, crossover, single-center study on chronic β-blocker treatment in PAH.[27] The aim of the study was to explore the safety and efficacy of bisoprolol treatment in patients with idiopathic PAH. Bisoprolol treatment led to significant reductions of heart rate and cardiac index and a statistically near-significant deterioration in 6-minute walking distance. No improvement in RV ejection fraction was found.[27] Cautious uptitration of bisoprolol treatment did not result in fluid retention, systemic hypotension, or a change in quality of life. Fifteen of 17 patients (88%) tolerated bisoprolol treatment, a figure that is comparable to the 85% reported in LHF.[27] The significant reduction in heart rate was associated with decreased myocardial oxygen consumption. However, in contrast to LHF studies,[28,29] bisoprolol did

Table 1. Clinical Studies of β-Blocker Use in Patients With PAH

Population	β-Blocker Used	Effect on End Point(s) Tested	Comments	References
PAH associated with portopulmonary hypertension (n=10)	Propranolol, atenolol	Reduced exercise capacity and reduced cardiac output	Withdrawal of β-blocker after chronic use was associated with improved exercise capacity. No second- or third-generation β-blockers with known beneficial effects on survival in LHD were tested	18
PAH associated with portopulmonary hypertension (single case)	Metoprolol	Circulatory collapse 30 min after administration of single dose of 25-mg metoprolol	Unstable patient with supraventricular tachycardia, immediate circulatory collapse, reversible after administration of isoprenaline	19
Ottawa Heart Institute PAH registry (n=94 mostly idiopathic PAH; 1 in 4 using β-blockers)	All types	No differences in clinical survival, hospitalizations, exercise capacity, echo parameters	Congenital heart disease and portopulmonary hypertension slightly over-represented and connective tissue disease under-represented in patients on β-blockers. β-blockers mostly prescribed for hypertension, atrial fibrillation, and coronary artery disease	20
Cleveland Clinic PAH registry (n=508 with IPAH and CTD-PAH; one quarter of patients using β-blockers)	All types	No difference in survival of clinical outcomes between users and nonusers of β-blockers	β-blockers mainly prescribed for atrial fibrillation. Trend of lower 6MWD and higher BNP levels in β-blocker users	24
University Medical School Registry of patients with PAH (n=564, 71 of whom on β-blockers)	All types	No difference in mortality between those with and without β-blockers	β-blocker users were older, had higher prevalence of comorbidities, and were more often on diuretics, digoxin, and angiotensin-converting enzyme inhibitors. Severity of PAH and right ventricular failure was similar between those with and without β-blocker use	25
6 patients with PAH (idiopathic, hereditary, and scleroderma related)	Carvedilol	Improvement in RVEF, no effect on exercise capacity	Open-label proof-of-concept study. Slow titration necessary because of fatigue and hypotension; significant increase in NT-proBNP that was correlated to increase in RVEF	26
18 idiopathic patients with PAH	Bisoprolol	No change in RVEF, significant decrease in cardiac index and exercise tolerance	Double-blind, placebo-controlled, crossover study. Bisoprolol was relatively well tolerated although 1 patient had to be treated with iv diuretics. Significant reduction in heart rate could be achieved	27

6MWD indicates six-minute walk distance; BNP, B-type natriuretic peptide; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; LHD, left heart disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; and RVEF, right ventricular ejection fraction.

not improve cardiac efficiency. Table 1 succinctly recapitulates the clinical studies on β-blockers in patients with PAH.

In summary, to date, no clear demonstration of a favorable benefit:risk ratio of the use of β-blockers in patients with PAH is provided. Therefore, the use of β-blockers is not recommended in this setting unless required by comorbidities (ie, high blood pressure, coronary artery disease, or LHF).

β-Blockers in PH Complicating Left Heart Disease

LHD-PH accounts for a large group of PH cases.[30] Group 2 of the PH clinical classification includes heart failure with reduced LV ejection fraction (HFrEF) or with preserved LV ejection fraction (HFpEF) or with left heart valvular disease.[1] From the hemodynamic point of view, LHD-PH is postcapillary (pulmonary artery wedge pressure >15 mm Hg) and further classified in isolated postcapillary or postcapillary combined with a precapillary component according to the diastolic pressure gradient and the pulmonary vascular resistance.[1]

Although targeting the increased adrenergic activation with β-adrenergic receptor-blocking agents is considered the single most effective drug therapy for patients with HFrEF,[31,32] the same evidence has not been demonstrated in HFpEF or in left heart valvular disease.[33–35] Although rate-lowering drugs are thought to improve LV filling by lengthening the diastolic period thus increasing stroke volume and cardiac output, it is not clear why β-blockers seem to be not effective and even detrimental in HFpEF. Long-term studies using modern diagnostic criteria for HFpEF are urgently needed to establish whether β-blocker therapy exerts significant clinical benefit in this setting.

The favorable effects of β-blockers in LHD may require specific pathophysiological conditions including marked reduction of myocardial contractility such as in HFrEF. No reliable data are available on the efficacy and safety of β-blockers treatment in conditions with predominant increase of loading conditions either diastolic such as in HFpEF or systolic such as in aortic stenosis when the contractility of the LV is not compromised. These findings need to be taken into consideration when the β-blocker therapy is proposed for conditions with predominant afterload mismatch and preserved or even increased contractility such as PAH.[36] The incidence of PH in the randomized controlled trials with β-blockers in patients with HFrEF or HFpEF has not been reported even if it is conceivable that a proportion of them may have been affected by this complication. This is particularly true in studies including patients with HFpEF because of the relatively high incidence of PH in this condition.[37] Therefore, the benefit:risk ratio of β-blockers in the presence of heart failure complicated by PH remains unclear. The recent European Society of Cardiology/European Respiratory

Society PH guidelines suggest to use optimized medical therapy in LHD-PH, and this may include β-blockers in particular in HFrEF indicating the level of evidence as expert opinion.[1] Interestingly, LV assist devices are able to normalize cardiopulmonary hemodynamics at rest after 6 weeks, including post-capillary PH combined with a pre-capillary component in cardiac transplant candidates with HFrEF.[38]

Discussion

In this review, we highlighted the evidence of adrenergic system involvement in PH and reported the beneficial and detrimental effects of β-blockers use in this condition, and the current recommendations on their prescription in clinical practice in PAH and LHD-PH (Figure). The take-home message of our review is that although several mechanisms of action of β-blockers might support their use in PH, their limited and sometimes adverse effects observed in clinical practice make them currently not recommended in PAH, while further studies are needed to determine the benefit:risk ratio of β-blockers in LHD-PH. However, we recently pointed out that β-blockers are a heterogeneous group of molecules. β-blockers differ in terms of β-adrenergic receptors selectivity, adjunctive effects on α-receptors, and effects on oxidative stress and inflammation (Table 2).[39–41] Different clinical, functional, and hemodynamic responses may exist between the different types of β-blockers in PH, and it is currently unclear whether some β-blockers may have beneficial effects in subgroups of PH patients.[39,42] In particular, last-generation NO-stimulating β-blockers may show promising therapeutic effects beyond heart failure management. Using human cultured pulmonary vascular cell from explanted patients, it has recently been demonstrated that nebivolol, a β_1-antagonist and $\beta_{2,3}$-agonist, abrogates PAH-associated pulmonary endothelial dysfunction.[12] It also produces endothelial and nitric oxide–dependent relaxation of pulmonary artery rings and attenuates vascular remodeling and inflammation in monocrotaline-treated rats. Recently, another study performed on human pulmonary endothelial cells demonstrated that blockade of protein kinase C activity by β-blocker restored NO formation by PAH cells, supporting further the hypothesis that β-blockers may benefit PAH through recovery of endothelial functions.[43]

In PH, we face a cardiopulmonary syndrome, in which both organs, heart and lungs, are innervated and functionally regulated by the sympathetic system. Interestingly, the innervation of the pulmonary artery is predominantly sympathetic,[44] and pulmonary artery denervation was recently tested in 2 preliminary studies in patients with PAH from the same center.[45,46] The benefit shown by pulmonary artery denervation was remarkable, but because of methodological and ethical questions (including concerns about the withdrawal of targeted-approved therapies) surrounding these studies, there is a clear need for confirmation of these data by other groups.[47] The immediate changes in pulmonary artery pressure observed in clinical studies of pulmonary artery denervation cannot be explained by reversal of vascular remodeling of

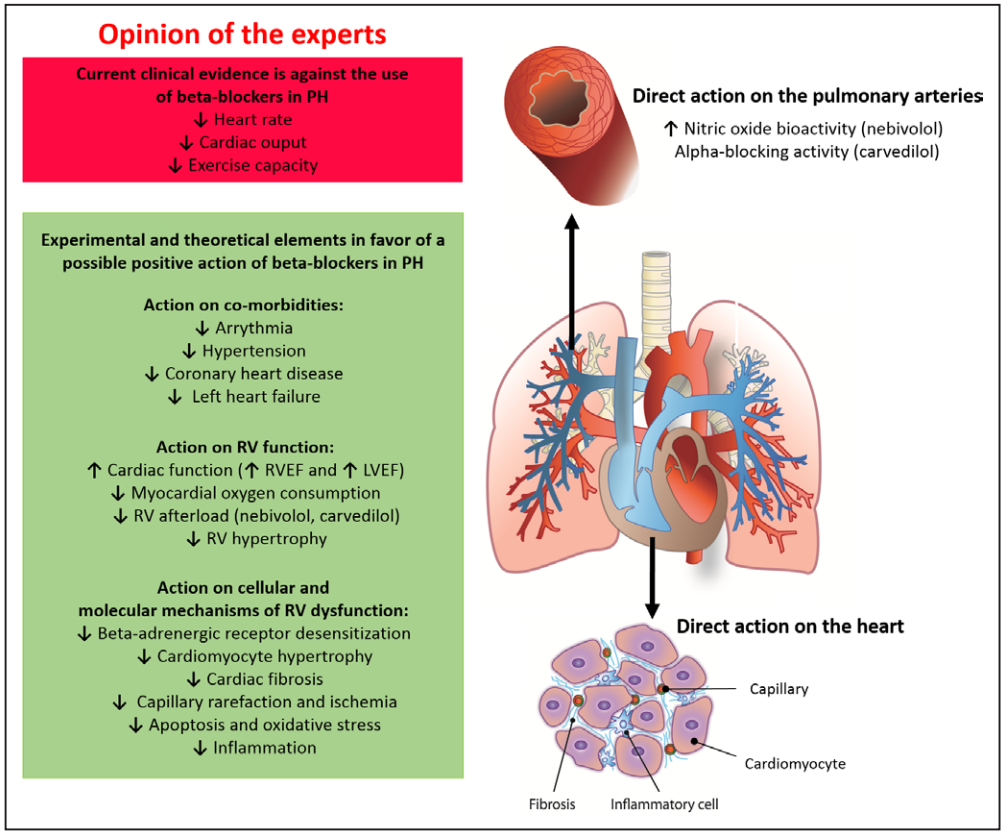

Figure. Potential effects of β-blockers in pulmonary hypertension based on theoretical/experimental data because the clinical experience (randomized controlled trials) with β-blockers remains limited in this setting. LVEF indicates left ventricular ejection fraction; RV, right ventricle; and RVEF, right ventricular ejection fraction.

Table 2. Specificity of β-Blockers (Based on Bristow[40] and Helfand et al[41])

β-Blocker	Half-Life, h	Lipophilicity	Excretion	β1/β2 Cardioselectivity	α-Antagonistic Effect	NO-Mediated Vasodilation
Atenolol	6–9	No	Renal	Yes (74)	No	No
Propranolol	3–4	Yes	Hepatic	No (2.1)	No	No
Metoprolol	3–7	Yes	Hepatic	Yes (74)	No	No
Bisoprolol	9–12	Yes	Hepatic/renal	Yes (119)	No	No
Carvedilol	7–10	Yes	Hepatic	No (7.3)	Yes	Yes
Nebivolol	12–19	Yes	Hepatic	Yes (293)	No	Yes

the distal pulmonary arteries and are more likely to reflect an improvement in pulmonary artery compliance. The predominant decrease in systolic pulmonary artery pressure associated with minor changes in diastolic pressure reinforces this hypothesis.[48,49] Renal sympathetic denervation was also investigated as a way to reduce neurohormonal activation in a dog model of PH.[50] The fact that α1-adrenergic receptors are present on the small- and medium-sized pulmonary arteries[51] and that sympathetic nerve fibers of the human pulmonary artery possess α2-adrenoceptors[52] suggests to test in future studies β-blocker with α-antagonistic effect like carvedilol.[31] Of note, approved PAH therapies may interfere with β-blocker effects. For instance, sildenafil causes a marked increase in sympathetic activation.[53,54] Alpha-adrenergic–mediated vasoconstriction may compensate for vasodilation during phosphodiesterase type 5 inhibition and may explain the significant hypotension observed in patients taking α-blockers with sildenafil.[53] It was also suggested that sildenafil may have direct central effects on sympathetic outflow.[54] Moreover, studies in dogs, rats, and mice have demonstrated that phosphodiesterase type 5 regulates β-adrenergic receptor signaling in cardiac response[55,56] and sildenafil can potently suppress adrenergic-stimulated contractility in the intact human heart.[57] From a mechanistic point of view, Isidori et al[58] recently demonstrated that inhibition of phosphodiesterase type 5 counteracts β2-adrenergic signaling in beating cardiomyocytes, decreasing β-adrenergic–dependent contraction rate. Evidence also exists in favor of an interaction between the endothelin pathway and the adrenergic receptor system.[59]

Perspectives

In light of the current review, we can define 4 future directions for further experimental and clinical research:

1. To delineate the specific safety and potential efficacy of different classes of β-blocker in PAH, and in particular of β-blockers with NO-activating property (eg, nebivolol or carvedilol), in sufficiently powered prospective or retrospective studies or meta-analyses.
2. To provide more data about the efficacy and safety of β-blockers treatment in LHD-PH in the context of HFrEF or HFpEF.
3. To investigate in preclinical studies, the impact of β-3 adrenergic agonists, either pure β-3 agonists (eg, BRL37344 or mirabegron)[60] or β-blockers with a β3-adrenergic agonist activity (eg, nebivolol),[12] on pulmonary vascular resistance and RV performance in animal models of PAH.
4. To bring clinical validation of multicenter randomized trials for pulmonary artery and renal sympathetic denervation as an additional methods for targeting the negative consequences of chronic sympathetic nerve activation in PAH.

Conclusions

There is a long way to go before finding the clinical evidence for efficacy and a final consensus on the use of β-blockers in PH. The specificity of each β-blocker and possible interactions with PAH therapies have to be taken into consideration. As stated in recent European PH guidelines, the use of β-blockers is not recommended in patients with PAH/PH unless required by comorbidities (ie, high blood pressure, coronary artery disease, or LHF). Pulmonary artery and renal sympathetic denervation are additional methods for targeting the negative consequences of chronic sympathetic nerve activation, but they require the clinical validation of multicenter randomized trials.

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