Pulmonary hypertension and beta blockers: where do we stand? Where are we going?

B. BUGAN, E.C. ROACH

Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, USA

Abstract. – Pulmonary hypertension (PH) is a chronic, progressive debilitating disease and associated with poor prognosis despite the novel numerous treatment options. Beta-blockers constitute a cornerstone in left heart failure treatment; however, we still don’t know the role of beta-blockers on PH and they are considered relatively contraindicated in patients with PH because of the possible negative effect on these patients’ hemodynamics and exercise capacity. On the other hand, animal models of PH and non-randomized clinical trials have shown that beta-blockers may improve right ventricular function and prevent remodeling in the heart muscle. As it is well-known, right heart function is the main prognostic determinants of the PH. The purpose of this chapter is to present the use of beta-blockers for the treatment of PH, the purported mechanisms of action, previously conducted animal studies and clinical trials.

Key Words: Beta-blockers, Pulmonary hypertension, Right heart function.

Introduction

Pulmonary hypertension (PH) is a chronic, progressive debilitating disease, which was first described in 1891. This disease essentially is a hemodynamic state defined by a resting pulmonary artery pressure at or above 25 mm Hg, or 30 mmHg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mmHg. This disease is characterized by progressive vascular remodeling and concomitant increased right ventricular afterload, which in turn, in time, transforms into right heart failure (RHF) which is the main determinant of mortality and morbidity.

Treatments in PH have in general, focused on vasodilatation of the pulmonary vasculature, to decrease the afterload, hence bringing about a relative increase in the ejection fraction. The available treatment options include prostaglandin analogues, calcium channel blockers, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. However, despite the numerous treatment options which are now available, the median survival time, as reported in a USA-based registry, is 3.6 years and the 1-, 3- and 5-year survival rates are 84, 67 and 58%, respectively.

Beta-blockers constitute a cornerstone in left heart failure treatment, as it has shown to reduce mortality, hospital admissions and prevent cardiac remodeling. However, the use of beta-blockers for the treatment of PH related RHF has been a subject of debate for the past few decades.

In this brief review, we aim to go over the logic behind suggesting the use of beta-blockers for the treatment of PH, the purported mechanisms of action, previously conducted animal studies and clinical trials. Afterwards, ongoing or planned clinical trials will be summarized.

Background: What Goes on in the Right Heart in Pulmonary Hypertension?

PH is the net result of a series of events which eventually lead to resistance in the pulmonary vasculature, increased afterload, and compensatory responses of the right ventricle (RV), followed by RHF (Figure 1). Right heart function is one the main prognostic determinants of the disease and together with progressive obstruction of the pulmonary circulation determines the outcome of the patient. Many articles regarding the incidents that take place in the right heart in PH have been published; they are summarized below.

The RV is different from the left ventricle (LV) both in embryological origin and in responses to diseases. While the primary heart field gives rise to the LV, the RV originates from the secondary heart field. With respect to adaptation and heart
Figure 1. Pulmonary hypertension causes a series of events called as sick lung circulation–right heart failure axis that contains pulmonary vascular remodeling (1), functional and structural changes on right heart (2), and right heart failure (3). Reproduced from Voelkel NF et al with permission. Pathobiology of pulmonary arterial hypertension and right ventricular failure. Eur Respir J 2012; 40: 1555-1565.

Many intracellular events take place in the heart during the course of the disease. The morphological, molecular and genetic changes in the right heart in PH, which have been identified so far in animal and/or human studies, are summarized in Table I and II, respectively.

Table I. Morphological changes in the right heart in pulmonary hypertension.

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<th>Change</th>
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<td>RV hypertrophy involving the papillary muscles, trabeculations and IVS, asymmetric septal hypertrophy</td>
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<td>Progressive RV dilatation until it becomes the dominant, apex-forming ventricle</td>
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<tr>
<td>Abnormal IVS motion</td>
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<td>Tricuspid regurgitation as a consequence of RV dilatation and stretching of the valve annulus</td>
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<tr>
<td>IAS becomes convex leftwards reflecting elevated RA pressures</td>
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<td>Dilated RA and plethoric vena cavae</td>
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<td>Pericardial effusion</td>
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The adrenergic system has great significance in PH. Previous studies have shown that patients with PH have an increased basal level of sympathetic activity\(^{14}\). Also, loss of heart rate variability with respect to circadian rhythm has been demonstrated\(^{15}\). In heart failure, despite the down-regulation of \(\beta\)-adrenergic receptors, there is a hyperadrenergic state. This down-regulation leads \(\alpha_1\), \(\beta_1\), and D1-receptor expression levels and receptor-dependent signal transduction limits RV contractile reserve, particularly in chronic RV failure\(^{33}\). The exact place of beta receptors and the neurohumoral system in pathological remodeling of the right heart remains to be elucidated.

Currently Ongoing and Past Clinical Trials Studying the Use of Beta Blockers in Pulmonary Hypertension

Beta-blockers are considered relatively contraindicated in PH, due to concerns for the possible negative effect on these patients’ hemodynamics and exercise capacity. This is based on a study involving 10 patients with portopulmonary hypertension, in whom withdrawal of propranolol was associated with improved exercise tolerance\(^{34}\). A case report described a patient with portopulmonary hypertension (PH with accompanying portal hypertension-increased blood pressure in the portal vein system, which drains the blood of organs in the abdomen) who suffered acute cardiovascular decompensation, after receiving a beta-blocker for supraventricular tachycardia\(^{35}\). In another study, patients with severe mitral stenosis and PH, undergoing valvuloplasty had increased pulmonary vascular resistance and decrease cardiac output when given atenolol, another beta blocker\(^{36}\).

On the other hand, beta-blockers have been shown to improve RV function and prevent remodeling in the heart muscle in animal models of PH\(^{28,37,38}\). In humans, So et al\(^{19}\) showed in a prospective study involving 94 PH patients,
among whom 28% were prescribed a variety of beta-blocker that there is no increased adverse clinical or hemodynamic consequences associated with the administration of those drug. The study had limitations in that it was non-randomized and there were differences in PH subtypes, exercise capacity, and accompanying diseases between groups treated with and without beta-blockers.

Currently, additional clinical trials, some of which are randomized and double blinded, are being carried out to further evaluate the use of beta blockers in PH. Their results are likely to have larger impact and help establish clinical practice guidelines (Table III).

### Conclusions

Beta blockers are an exciting new avenue, a new approach to PH management. Currently there are studies being carried out in large pulmonary vascular disease centers, both clinical and mechanistic, to establish to place of beta blockers in the management of this debilitating disease. Further validations in large multi-national multi-centric centers, might help beta blockers gain a position in PH management, as an affordable add-on therapy.

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**Conflict of Interest**

The Authors declare that there are no conflicts of interest.

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