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

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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-blokers 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[1]. 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[2]. 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[3].

Beta-blockers constitute a cornerstone in left heart failure treatment, as it has shown to reduce mortality, hospital admissions and prevent cardiac remodeling[4,5]. 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[6] (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[7]. 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[8,9]. With respect to adaptation and heart

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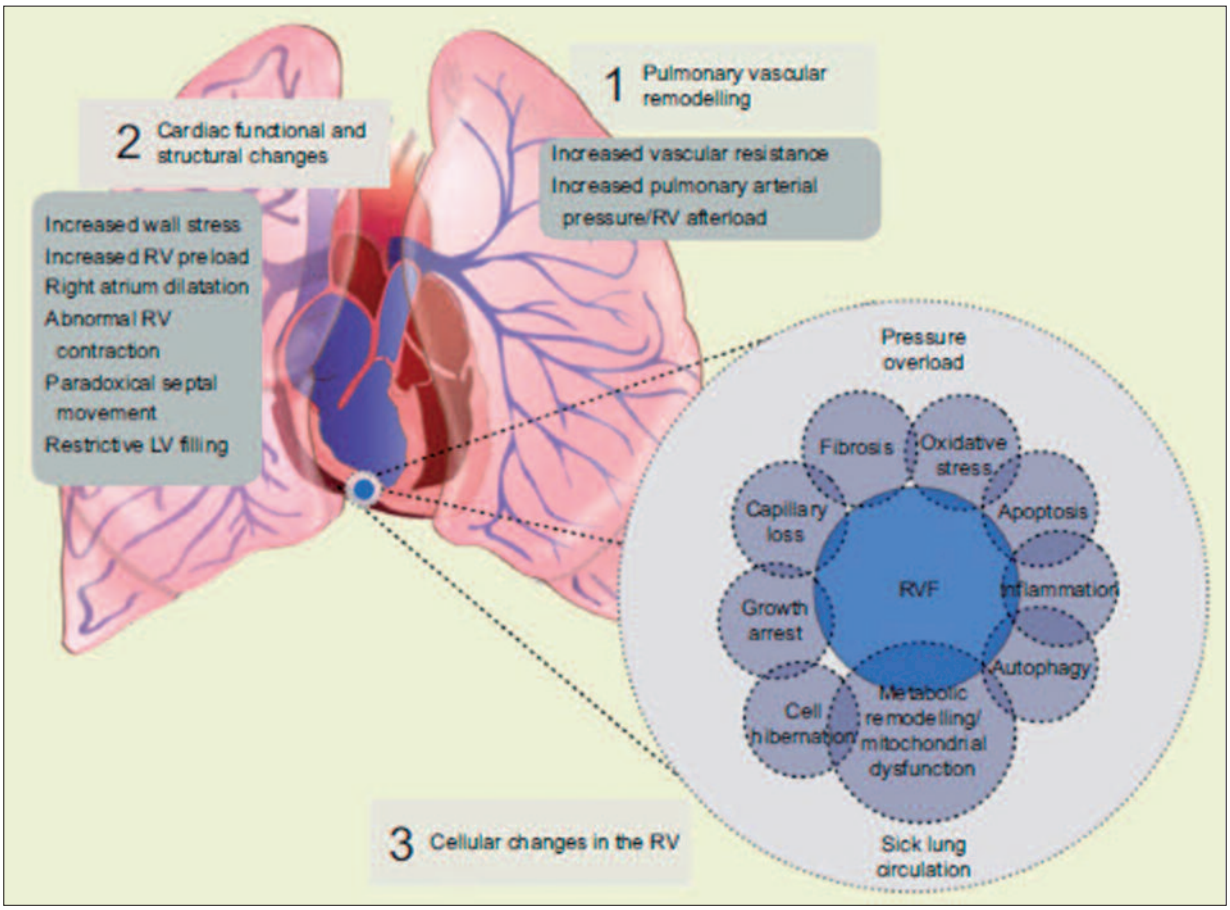

Figure 1. Pulmonary hypertension causes a series of events called as sick lung circulation–right heart failure axis that contains pulmonary vascular remodeling (1), functional and structural changes on right heart (2), and right heart failure (3). Reproduced from Voelkel NF et al[6] with permission. Pathobiology of pulmonary arterial hypertension and right ventricular failure. Eur Respir J 2012; 40: 1555-1565.

failure, studies in rat models have shown that while α-1 adrenergic agonists increase the contraction of the LV, the RV responds by a reduction of contractile force. Moreover, while the LV responds to long-term infusion of norepinephrine with hypertrophy, the RV does not[10,11].

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[12].

RV hypertrophy involving the papillary muscles, trabeculations and IVS, asymmetric septal hypertrophy
Progressive RV dilatation until it becomes the dominant, apex-forming ventricle
Abnormal IVS motion
Tricuspid regurgitation as a consequence of RV dilatation and stretching of the valve annulus
IAS becomes convex leftwards reflecting elevated RA pressures
Dilated RA and plethoric vena cavae
Pericardial effusion

Abbreviations: IAS: Interatrial Septum; IVS: Interventricular Septum; RA: Right Atrium; RV: Right Ventricular. Adapted from Bradlow et al[12] with permission. Cardiovascular magnetic resonance in pulmonary hypertension. J Cardiovasc Magn Reson 2012; 14: 1-12.

Table II. Molecular and genetic changes in the right heart and vessels in pulmonary hypertension.

Impaired energy efficiency and low PCr/ATP ratio[13]
Increased sympathetic tone[14]
Loss in circadian rhythm associated heart rate variability[15]
Down regulation of β-adrenergic receptors[16]
RV neuronal noradrenaline transporter density and activity[17]
Increased formation of AT 1–7 from both AT-I and -II[18]
Upregulation of angiotensinase[18]
Increase in ACE-binding sites and down-regulation of the AT-II type-I receptor[18]
Increased BNP production[19,20]
Increased expression ET receptor[21]
Upregulation and increased activity of the ERK1/2 cascade[23]
Prolongation of isovolumic contraction correlated with prolongation of intracellular Ca^{2+}, indicating a reduced rate of sequestration[22]
Type-III and -V collagens increase relative to type-I collagen[24,25]
Upregulation of gelatinase MMP-9 and stromelysin MMP-3[26]
Re-expression of the fetal genes MHC- β[27]
Increased expression of ANP, CTGF, and Rcan1 and fibrosis-controlling proteins such as TGF-β1, TGF- β2, Smad4, MAPK-3, and forkhead box A2[28]
Increased expression of IGF-1 mRNA and Klf5 during RV hypertrophy stage[28]
Reduced expression of IGF-1 mRNA during RV failure stage[28]
Elevated expression of genes encoding glycolytic enzymes such as hexokinase-1, phosphofructokinase and mitochondrial Ucp2 and decreased expression of alcohol dehydrogenase 7[28]
HIF-1 α expression associated with cardiac hypertrophy[29]
Reduced AT-1, apelin, and VEGF mRNA associated with capillary rarefication[30]
Alterations in NO bioavailability[31]
Ion channel dysfunction[32]

Abbreviations: ACE: Angiotensin Converting Enzyme; ANP: Atrial Natriuretic Peptide; AT: angiotensin; ATP: Adenosine Three Phosphate, BNP: brain natriuretic peptide; CTGF: Connective Tissue Growth Factor, ERK 1/2: extracellular signal-regulated kinase 1/2; ET: Endothelin; HIF-1 α: Hypoxia Inducible Factor1α; IGF-1: Insulin-like Growth Factor-1; Klf5: Kruppel-Like Factor 5; MAPK: Mitogen-Activated Protein Kinase; MHC: Myosin Heavy Chain; MMP: Matrix Metalloproteinase, mRNA: Messenger Ribonucleic Acid; NO: Nitric Oxide; PCr: Phosphocreatine; Rcan: Regulator of Calcineurin; RV: Right Ventricular; TGF: Transforming Growth Factor; Ucp-2: Uncoupling Protein-2; VEGF: Vascular Endothelial Growth Factor.

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 β-adrenergic receptors, there is a hyperadrenergic state. This down-regulation leads α1, β1, 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[39] showed in a prospective study involving 94 PH patients,

Table III. The randomized and double blinded ongoing trials.

	Trial	Description	Estimated completion date
1	Beta-blockers in I-PAH	30 I-PAH patients will be randomized to either bisoprolol- or placebo-treatment in a double-blinded fashion. A cross-over trial design will be used to increase the power of the study and to assess long-term effects of bisoprolol-treatment and -withdrawal. The medication will be given in an escalating dose regimen	April 2014
2	PAH treatment with carvedilol for heart failure	A double-blinded, randomized placebo controlled study looking at carvedilol in class-I PAH patients, stable on their PAH medications, between ages 18-65	July 2018
3	Pilot study of the safety and efficacy of carvedilol in PAH	The purpose of this study is to determine whether carvedilol treatment of patients with PAH and associated RHF is safe and results in an improved function of the right heart	September 2013

Abbreviations: I-PAH: Idiopathic Pulmonary Arterial Hypertension; PAH: Pulmonary Arterial Hypertension; RHF: Right Heart Failure. Adapted from clinical trials.gov.

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 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.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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