



# $\beta$ -blockers in pulmonary arterial hypertension: evolving concepts of right heart failure

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**Beta-blockers can be used safely by some PAH patients with comorbidities such as arrhythmias or hypertension** <http://ow.ly/P2JHg>

Current guidelines advise against the use of  $\beta$ -blockers in pulmonary arterial hypertension (PAH) to avoid systemic hypotension [1]. In addition, PAH patients have a fixed stroke volume, and are therefore highly dependent on heart rate to increase their cardiac output [2–4]. Indeed, PROVENCHER *et al.* [5] showed that withdrawal of  $\beta$ -blockers significantly improved exercise capacity in portopulmonary hypertension. PEACOCK and ROSS [6] described another case of portopulmonary hypertension, in which the use of a  $\beta$ -blocker to treat a supraventricular tachycardia in an already haemodynamically unstable patient was nearly fatal.

Interestingly, patients with left heart failure also have a relatively fixed stroke volume [3, 7]. However, in this case,  $\beta$ -blocker therapy (together with angiotensin-converting enzyme (ACE) inhibition) is considered the cornerstone of treatment [8]. How can we explain this discrepancy?

PACKER [9] elegantly described the change in perspective on heart failure over the past 50 years. Until the 1960s, heart failure was solely regarded as an oedematous disorder, and the use of diuretics was central in the treatment. In the 1980s this view was extended with the cardiocirculatory model, in which heart failure was also viewed as a haemodynamic disorder. This led to the use of peripheral vasodilators and the development of positive inotropic agents. Although these agents effectively reduced symptoms, later it was consistently demonstrated that they increased mortality. Therefore, the conceptual view was adjusted again in the 1990s, and nowadays heart failure is also considered a neurohormonal disorder. This is the basis for the treatment with  $\beta$ -blockers and ACE inhibitors.

We see a similar pattern emerging when looking at PAH-induced right heart failure, where more and more evidence is accumulating that might shift our conceptual framework from a solely haemodynamic to also a neurohormonal perspective. We have previously summarised the pathophysiological relevance of the neurohormonal axis in PAH [10, 11]. In short, in PAH patients, sympathetic nervous system activity is increased and correlates with prognosis [12–17]. In addition, local changes in  $\beta$ -adrenergic receptor signalling of the right ventricular myocardium of PAH patients have been demonstrated [18–20]. Furthermore, in experimental PAH-models,  $\beta$ -blocker therapy reversed cardiac remodelling and improved outcome [21–23].

Whereas it is much too early to advocate  $\beta$ -blockers treatment to reverse right heart failure in patients, signals are emerging that the dangers of  $\beta$ -blockers in PAH patients are much smaller than previously thought. In this issue of the *European Respiratory Journal*, BANDYOPADHYAY *et al.* [24] describe the outcomes of  $\beta$ -blocker use in the largest PAH cohort thus far. Most patients received  $\beta$ -blockers for treatment of arrhythmias, presumed congestive cardiac failure or hypertension. Main reasons to

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discontinue  $\beta$ -blockers were systemic hypotension, shortness of breath or volume overload. In this retrospective analysis, they did not find detrimental effects on survival or time-to-clinical worsening, when comparing  $\beta$ -blockers use *versus* no  $\beta$ -blocker use. The authors are to be commended for providing unique long-term follow-up data. The overall findings are consistent with other retrospective reports [25–27], but are in contrast to earlier case series [5]. This may be explained by the difference in patient population (portopulmonary hypertension *versus* idiopathic PAH or PAH secondary to connective tissue disease) and the more frequent use of third generation  $\beta$ -blockers (propranolol *versus* metoprolol/carvedilol). Interestingly, the data at 10-year follow-up even suggest a little survival benefit, although this could be a type I error. The dataset was too small for a meaningful comparison between the different types of  $\beta$ -blockers. One could argue that based on these data, there is no reason to discontinue  $\beta$ -blockers, when prescribed for other indications than PAH. This fits to the perspective of PAH-induced right heart failure that neurohormonal factors may play a role.

The study by BANDYOPADHYAY *et al.* [24] has taught us that when comorbidities exist, such as arrhythmias or hypertension,  $\beta$ -blockers can be used relatively safely in a considerable number of PAH patients. However, clinical evidence that  $\beta$ -blockers are to be used for the treatment of right heart failure in these patients is currently lacking. Two small pilot studies have provided some interesting signals [28, 29], but an adequately powered randomised clinical trial is urgently needed.

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