The adrenergic nervous system as a therapeutic target in pulmonary arterial hypertension: a cautionary tale

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A study of beta-adrenergic blockade in patients with PAH demonstrated no benefit but some serious adverse effects http://ow.ly/xeJy302c69b

While the role of the adrenergic nervous system in the progression of left ventricular failure has been well established, its contribution to the pathogenesis of pulmonary arterial hypertension (PAH) and the resultant right ventricular failure is far less clear. The earliest attempts to treat PAH included drugs that were α-adrenergic agonists such as tolazoline [1] and isoproterenol [2]; unfortunately, their administration usually resulted in systemic hypotension and little evidence of a beneficial effect on pulmonary circulatory or right ventricular dynamics. More recently, interest has shifted towards targeting the β-adrenergic pathway as a therapeutic strategy for PAH. Nebivolol, a β_1 antagonist and β_{2-3} agonist, inhibits proliferation of pulmonary vascular cells and produces endothelial and nitric oxide-dependent relaxation of pulmonary artery rings [3]; both nebivolol and pulmonary artery sympathetic denervation (PADN) attenuate vascular remodelling in monocrotaline-treated rats [3, 4], and single-centre preliminary results of PADN in PAH patients are of considerable interest [5]. In this issue of the *European Respiratory Journal*, van Campen *et al.* [6] report the results of their single-centre study of the effects of β-adrenergic blockade in patients with PAH. Their results reinforce the notion that the pulmonary and systemic circulations and their respective ventricles behave very differently both in the pathogenesis of disease states and in response to targeted therapies.

Using a cross-over design, van Campen *et al.* [6] evaluated 17 PAH subjects treated with bisoprolol. Bisoprolol produced no improvement in right ventricular ejection fraction measured by magnetic resonance imaging, but did result in a statistically (and clinically) significant decrease in both heart rate and cardiac index, and a trend toward reducing exercise capacity. One patient developed worsening right heart failure while receiving bisoprolol that required hospitalisation and treatment with intravenous diuretics, and systemic hypotension in several other subjects precluded further incremental dosing.

The study by van Campen *et al.* [6] suffers from a numbers of limitations. 1) The choice of bisoprolol, a selective β_1 antagonist and potent antihypertensive agent, is questionable, and the results do not preclude a therapeutic benefit using other β-adrenergic agents with more complex actions on other receptors. 2) The study was powered based on an anticipated change of 3% in right ventricular ejection fraction with bisoprolol, although the clinical meaningfulness of this change is unclear. 3) Bisoprolol dosing appears to have been based solely on tolerability, leaving unknown whether doses that produce a lesser degree of heart rate reduction might be beneficial or equally harmful. 4) The highly ambitious nature of the study compromised enrolment. Thus, instead of having a more interpretable and focused set of parameters to analyse, we have a less robust and broad set of results to ponder.

While the study by van Campen *et al.* [6] is far from definitive, it is nevertheless informative. It should serve as a cautionary tale for those who may wish to try bisoprolol or similar drugs to treat PAH outside of a

Received: July 05 2016 | Accepted: July 06 2016

Conflict of interest: None declared.

clinical trial, and to consider alternative drugs when PAH coexists with other conditions such as systemic hypertension or supraventricular arrhythmias. In addition, it highlights pitfalls that would be best avoided if any future trials of drugs that target the β-adrenergic pathway in the setting of PAH are under consideration.

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DOI: 10.1183/13993003.01333-2016