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EDITORIAL FOCUS

Effect of heart rate reduction in pulmonary arterial hypertension

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Pulmonary hypertension (PH) is a fatal disease caused by small pulmonary artery obstruction by vascular proliferation and remodeling (10). PH is characterized by elevated pulmonary arterial pressure (PAP) and increased pulmonary vascular resistance, frequently leading to right heart failure and premature death. PH is defined as a mean PAP of ≥25 mmHg at rest by right heart catheterization (10). The classification of PH includes five major categories of the disorder (10). Group 1, or pulmonary arterial hypertension (PAH), is a clinical condition defined as a mean PAP of ≥25 mmHg and pulmonary capillary wedge pressure of ≤15 mmHg without other causes of PH, such as PH due to chronic obstructive pulmonary disease, chronic thromboembolism, or other rare diseases. Although the treatment of PAH has progressed, with such treatments as PGI_2 (1), endothelin receptor antagonists (9), phosphodiesterase V inhibitors (14), and soluble guanylate cyclase activators (11), PAH still remains a fatal disease mainly because of right heart failure. Thus, a novel therapy for PAH with right heart failure remains to be developed.

Since lower heart rate (HR) at rest is favorable for long-term prognosis of patients with left heart failure, β-blockers are commonly used to improve the prognosis of those patients. However, it is unclear whether β-blockers also improve long-term prognosis of patients with right heart failure because the left ventricle (LV) and right ventricle (RV) have distinct embryonic origins, have different metabolisms, and have distinct adaption mechanisms to pressure overload (4). Furthermore, although higher HR at rest was associated with worse prognosis in PAH patients in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) study (2), it is unclear whether HR reduction with drugs, such as β-blockers or ivabradine, improves the long-term prognosis of PAH patients with right heart failure. Indeed, β-blockers have been considered relatively contraindicated for PH patients, mainly because of their possible negative effects on hemodynamics and exercise capacity. The negative inotropic and hypotensive effects of β-blockers are especially important issues because PH patients are likely to be hypotensive with vasodilator treatments. It has been previously reported that PH patients have an increased basal level of sympathetic activity (7). Indeed, PH patients are in a hyperadrenergic state, and their exercise tolerance is improved with β-receptor agonists (17). A recent study (19) with propensity score analysis showed that the prognosis and adverse outcome of PAH patients treated with β-blockers were not different from those without them. Another study (20) reported that cardiac index and exercise capacity were decreased with β-blockers compared with those without them, whereas RV ejection fraction was comparable between the two groups. β-Blockers have also been shown to improve RV function and prevent RV remodeling in animal models of PH (3) and PAH patients (13).

There are two possible mechanisms for the improvement of prognosis of PH patients with β-blockers (Fig. 1). One possible mechanism is their direct effects on the pulmonary artery. Indeed, β-blockers inhibit proliferation of pulmonary arterial smooth muscle cells from PAH patients (8) and improve dysfunction of pulmonary artery endothelial cells in PAH patients (16). Another possible mechanism is the effect of the improvement of biventricular dysfunction through HR reduction by adrenergic receptor blockade. It is also known that PH causes not only RV dysfunction but also LV dysfunction (18). Carvedilol reversed established RV dysfunction in monocrotaline-induced PH rats, where the beneficial effects of carvedilol were mediated by reversal of pulmonary vascular remodeling (3). Moreover, bisoprolol, a selective β_1-blocker, had direct protective effects on the right heart myocardium in pressure-volume curve analysis (6). While PH causes not only RV dysfunction but also LV dysfunction (18), carvedilol improved dysfunction of both ventricles through inhibition of transforming growth factor-β_1 signaling, fibrosis, and apoptosis (15). However, in those studies, it was unclear to what extent the effects of HR reduction were involved in the beneficial effects of β-blockers in PH.

In a recent article published in the *American Journal of Physiology-Heart and Circulatory Physiology*, Gomez et al. (12) reported that HR reduction, but not adrenergic receptor blockade, is involved in the beneficial effects of carvedilol to improve biventricular dysfunction in monocrotaline-induced PH rats. Importantly, they showed that not only carvedilol but also ivabradine, a selective inhibitor of sinoatrial current (I_f), improved biventricular dysfunction, although PAP and the Fulton ratio were unaltered with these drugs in PH rats. The animals showed prolonged biventricular isovolumic contraction times, delayed RV peak radial motion, and impaired early relaxation. In this study, both carvedilol and ivabradine shortened biventricular isovolumic contraction time and time to biventricular peak radial motion, improved RV relaxation, and increased early diastolic LV filling through improvement of interventricular interaction and improved timing. Furthermore, the authors showed that both carvedilol and ivabradine improved the parameters of RV and LV contractility and relaxation, such as pressure-volume loop-derived end-systolic elastance, time constant of RV relaxation, and the maximal rates of ventricular pressure decay (12). These results demonstrate that pharmacological HR reduction, but not adrenergic receptor

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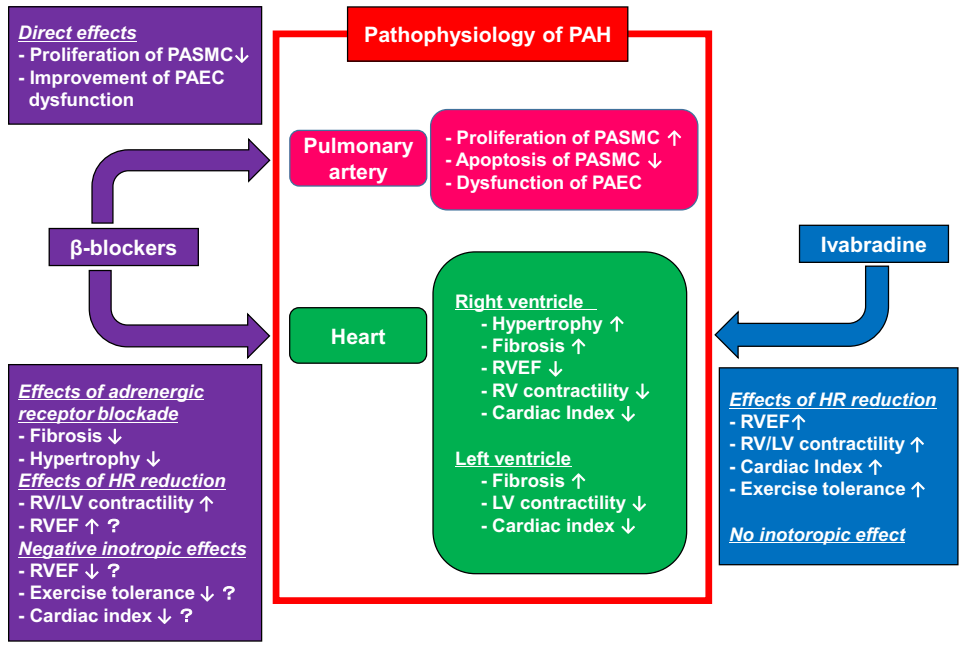

Fig. 1. Potential effects of β-blockers and ivabradine in pulmonary arterial hypertension. HR, heart rate; LV, left ventricle; PAEC, pulmonary arterial endothelial cells; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cells; RV, right ventricle; RVEF, RV ejection fraction.

blockade, increased cardiac output and improved biventricular function (Fig. 1).

The study by Gomez et al. (12) demonstrates that ivabradine may be useful to improve biventricular dysfunction in PAH. Ivabradine can reduce HR without any negative inotropic or lusitropic effects on the heart. Thus, ivabradine may reduce HR in PAH patients without any negative inotropic effects of β-blockers such as hypotension or reduction in cardiac output. Indeed, the authors reported that cardiac output did not decrease with ivabradine treatment in monocrotaline-induced PH rats (12), in line with a clinical study in PAH patients (5). In this clinical study, ivabradine was administered to 10 PAH patients with HRs of >100 beats/min for 3 mo, and along with a significant reduction in HR, exercise tolerance and mean New York Heart Association functional class were significantly improved, whereas PAP remained unchanged.

At this moment, it remains to be fully examined whether β-blockers or ivabradine are useful for the treatment of PAH patients. Indeed, in current European Society of Cardiology-European Respiratory Society PH guidelines, the use of β-blockers for PAH patients is not recommended unless required by comorbidities, and no statement has been made on the use of ivabradine (10). Although the experimental study by Gomez et al. (12) suggests that β-blockers or ivabradine may be useful for the treatment of biventricular dysfunction in PAH patients, this notion remains to be examined in randomized clinical trials in future studies.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

N.Y. and H.S. drafted manuscript; N.Y. and H.S. edited and revised manuscript; N.Y. and H.S. approved final version of manuscript.

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