Editorial Focus

The 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 (PVR), frequently leading to right heart failure and premature death. PH is defined as a mean PAP ≥25 mmHg at rest by right heart catheterization (10). The classification of PH includes 5 major categories of the disorder (10). Group 1 or pulmonary arterial hypertension (PAH), is a clinical condition defined as mean PAP ≥25 mmHg and pulmonary capillary wedge pressure ≤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 been progressed, such as prostaglandin I_2 (1), endothelin-recepter antagonists (9), phosphodiesterase-V inhibitors (14), and soluble guanylate cyclase activators (11), PAH still remains a fatal disease mainly due to right heart failure. Thus, the novel therapy for PAH with right heart failure remain 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 the right ventricle (RV) have a distinct embryonic origin, 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 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 due to their possible negative effects on hemodynamics and exercise capacity. Especially, the negative inotropic and hypotensive effects of β-blockers are important issues because PH patients are likely to be hypotensive with vasodilator treatments. It has been 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-recepter

agonists (17). A recent study 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 (19). Another study reported that cardiac index and exercise capacity were decreased with β-blockers compared with those without them, while RV ejection fraction was comparable between the two groups (20). 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 (**Figure**). 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 dysfunctions through HR reduction by adrenergic recepter blockade. It is also known that PH causes not only RV disfunction but also LV dysfuntion (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 β1-blocker, had direct protective effects on the right heart myocardium in the pressure-volume curve analysis. (6) While PH causes not only RV disfunction but also LV dysfunction (18), carvedilol improved dysfunctions of the both ventricles through inhbition of TGF-β1 signaling, fibrosis and apoptosis (15). However, in those studies, it was unclear to which extent the effects of HR reduction was involved in the beneficial effects of β-blockers in PH.

In this issue of the Journal, Gomez et al. reported that HR reduction, but not adrenergic recepter blockade, is invloved in the beneficial effects of carvedilol to improve biventricular dysfunctions in monoclotaline-induced PH rats (12). Importantly, they showed that not only carvedirol but also ivabradine, a selective inhibitor of the sinoatrial If current, improved biventricular dysfunctions, although pulmonary arterial pressure and Fulton ratio were unaltered with these drugs in the PH rats. The animals showed prolonged biventricular isovolumic

contraction times (ICT), delayed RV peak-radial motion, and impaired early relaxation. In this study, both carvedilol and ivabradine shortened biventricular ICT 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 dP/dT minimum (12). These results demonstrate that pharmacological HR reduction, but not adrenergic recepter blockade, increased cardiac output and improved biventricular functions (**Figure**).

The present study by Gomez et al. demonstrates that ivabradine may be useful to improve biventricular dysfunctions 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 monoclotalin-induced PH rats (12), in line with the clinical study in PAH patients (5). In this clinical study, ivabradine was administered to 10 PAH patients with HR >100 beats/min for 3 months, and along with the significant reduction in HR, exercise tolerance and mean NYHA functional class were significanly improved, while pulmonary arterial pressure 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 the current ESC/ERS 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 present experimenal study by Gomez et al. suggests that β-blockers or ivabradine may be useful for the treatment of biventricular dysfuntions in PAH patients, this notion remains to be examined in randomized clinical trials in future studies.

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Figure legend

Potential effects of β-blockers and ivabradine in pulmonary arterial hypertension

EF, ejection fraction; LV, left ventricle; PAEC, pulmonary arterial endothelial cells; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cells; RV, right ventricle

Figure