Heart Rate Reduction by Ivabradine: Slowly but Surely?

Pulmonary arterial hypertension (PAH) is a disease characterized by pulmonary vascular remodeling and increased pulmonary vascular resistance, finally culminating in right ventricular (RV) hypertrophy and failure (1). Although changes in the pulmonary vasculature are the primary cause of PAH, it is well accepted that the RV function is the most important determinant of survival in patients with PAH (2). Although it is increasingly recognized that, in addition to the pulmonary vasculature, the right heart is a viable therapeutic target for the treatment of pulmonary hypertension (PH) (3), there are still no approved therapies targeting the right ventricle in PH. In this issue of the *Journal*, it is against this background that Ishii and colleagues (pp. 843–855) address one important aspect of right ventricle–targeting therapy in PH (4).

It has previously been reported that sympathetic nervous system activation is an independent predictor of clinical deterioration in PAH (5), and a strong linear relationship between heart rate (HR) and mean pulmonary arterial pressure has been described (6), suggesting that targeting sympathetic and/or parasympathetic nervous system activity might be beneficial in the treatment of patients with PAH. Indeed, therapies targeting HR have been extensively studied in patients with left ventricular heart failure over the past few decades. It was shown that in patients with left ventricular heart failure, a higher resting HR is associated with higher morbidity and mortality. This finding was explained by the fact that an elevated HR plays an important role in the development of myocardial ischemia because of increased myocardial oxygen demand and a reduction in diastolic perfusion time (7, 8).

Blocking β-adrenergic receptors suppresses sympathetic nervous system activity in the heart and subsequently reduces HR. Therefore, β-adrenergic receptor blockers are considered as part of the first-choice treatment strategy in patients with left ventricular heart failure. Although a beneficial effect of β-adrenergic receptor blockade on RV function in experimental PH has been shown (9, 10), clinical results in patients with PH remain unconvincing (11). Moreover, side effects of β-adrenergic receptor blockers, such as systemic hypotension, fatigue, and exacerbation of chronic obstructive pulmonary disease, limit their use in patients with PH.

Ivabradine selectively inhibits the pacemaker current in the sinus node of the heart by binding to the hyperpolarization-activated, cyclic nucleotide–gated channels from the intracellular side of the membrane of pacemaker cells. Ivabradine was approved by the U.S. Food and Drug Administration to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure who have a left ventricular ejection fraction $\leqslant 35\%$, who have a sinus rhythm with a resting HR $\geqslant 70$ beats/min, and who either receive maximally tolerated doses of β-blockers or have a contraindication to β-blocker use (12).

Recently published data demonstrate that HR reduction by ivabradine as supportive treatment to the well-established therapy in patients with PH led to improvement of cardiac function, 6-minute walk distance, and New York Heart Association functional class (13) and even reduced rehospitalization for worsening heart failure (14). Thereafter, Gomez and coauthors demonstrated that HR reduction by ivabradine improves RV filling and biventricular hemodynamics through the realignment of RV–left ventricular cardiac cycle events and improves interventricular interactions in monocrotaline-induced PH in rats (15).

In the current issue of the *Journal*, Ishii and coauthors greatly extended these data and describe the effect of ivabradine on RV function in three comprehensive animal models of PH and RV hypertrophy and failure (4). The authors show that despite persistently severe PH or RV pressure overload, HR reduction with ivabradine improved the RV TGF-β1 pathway signaling, fibrosis, and extracellular matrix remodeling in association with improved RV systolic and diastolic function and exercise capacity, which might be mediated by improved cardiac myocyte Ca^{2+} handling and relaxation, as demonstrated by an *in vitro* approach (4). They describe HR reduction in rats with RV pressure overload in response to ivabradine during echocardiographic examination. A similar HR reduction was not observed, however, using invasive hemodynamic measurements. One explanation for this discrepancy is that the authors performed open-chest catheterization, which causes loss of intrathoracic pressure, changes of myocardial integrity, and trauma, which can affect all measured variables, including HR. Indeed, closed-chest catheterization is difficult to perform in rodents, but in future studies, this issue should be addressed (16).

Nonetheless, the authors addressed one of the important aspects of the right ventricle–targeting therapy in PH in animal models of RV pressure overload: Will improvement of cardiac contractility without affecting pulmonary vascular tone and/or remodeling be beneficial in PH and RV heart failure? The authors stated, "Despite persistent PH, heart rate reduction (HRR) with ivabradine was associated with improved exercise tolerance and, despite a mildly lower heart-rate, increased cardiac output through increased stroke volume. This may be attributable to HRR effects on improved contractility and diastolic performance." Indeed, improvement in cardiac output and subsequent mild reduction in pulmonary vascular resistance might improve exercise capacity in animal models of PH as well as in patients with PH. However, in this regard, the right ventricle still needs to work against high pulmonary arterial pressure, and it might lead to further worsening

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of RV function. Therefore, combination therapy by using two or more classes of drugs, which target both the pulmonary vasculature and (right) heart function, is preferable and more appropriate in patients with PAH.

Thus, ivabradine demonstrates beneficial effects in animal models of PH and RV hypertrophy and failure (4, 15), as well as in patients with PH, as a treatment supporting the basic therapy (13, 14). However, further preclinical studies will most likely be needed to investigate the effect of ivabradine and its combination with other approved therapies on cardiac function, myocardial perfusion, and metabolic changes in the right ventricle before conducting a study in a large cohort of patients with PH. ■

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Baktybek Kojonazarov, M.D., Ph.D.
Institute for Lung Health
Justus-Liebig University of Giessen
Giessen, Germany

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