Editorial Commentary

Heart Rate Reduction
An Old and Novel Candidate Heart Failure Therapy

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See related article, pp 949–957

Acumulating evidence suggests that increased resting heart rate is an independent risk and prognostic factor for heart failure (HF). For every 5-bpm increase in heart rate, the combined risk of cardiovascular death or hospital admission for worsening HF increases by 16%. Selective heart rate reduction strongly relates to decreased energy expenditure by decreasing contraction numbers and increased blood supply and improved force-frequency associations by extending diastole.1 Although an increase in heart rate mediated by β-adrenergic receptor activation of the sympathetic system is common in HF, the mechanisms linking heart rate and HF are unclear. In this issue of Hypertension, Moritz Becher et al2 investigated the effect of lowering heart rate, either by I,K channel or β-receptor blockade, on angiotensin II–induced HF. Despite similar heart rate reductions, ivabradine, a selective inhibitor of the I,K channel, showed a more positive impact on remodeling of the left ventricle (LV) than metoprolol, a β-receptor blocker. Ivabradine attenuated systolic and diastolic dysfunction and reduced LV hypertrophy, fibrosis, inflammation, and apoptosis. In contrast, this study failed to demonstrate that metoprolol could prevent the development of dysfunction and adverse remodeling of the LV, despite similar reductions in heart rate and inflammatory responses, as well as lower systolic blood pressure.

Ivabradine selectively reduces heart rate by directly inhibiting the I,K channel current, which governs the electric pacemaker activity in the sinoatrial node. Ivabradine does not affect intramyocardial conduction or myocardial contractility, even in patients with compromised ejection fraction.3 Metoprolol blocks sympathetic nervous system action by blocking the β-adrenergic receptor and reducing sympathetic activity to reduce heart rate. Unlike ivabradine, metoprolol also reduces myocyte contractility, which may create a mismatch between metabolic demand and perfusion.4 Based on the findings of the study by Moritz Becher et al,2 heart rate reduction is important for the prevention of angiotensin II–induced HF, but it is not likely the major theme. The beneficial roles played by ivabradine may be attributable to antiapoptotic, antifibrotic, and antihypertrophic effects, as well as an improved hemodynamic profile (Figure).

Inflammation is markedly amplified in failing hearts of animals and patients and is involved in the development and progression of HF. In this study, angiotensin II infusion induced the upregulation of proinflammatory cytokines interleukin 1β, interleukin 6, and tumor necrosis factor-α and increased the recruitment of leukocytes, all of which were reduced to values similar to controls by both ivabradine and metoprolol. The decreased inflammation by both treatments has also been confirmed in other studies.5–7 Ivabradine inhibits chemokine-induced CD4+ lymphocyte migration by suppressing phosphatidylinositol 3-kinase and small GTPase activity and myosin light chain phosphorylation.5 Ivabradine also reduces oxidative stress and monocyte chemotactic protein 1 expression in atherosclerotic plaques.6 Metoprolol offers anti-inflammatory and cardioprotective roles in lethal endotoxemia by reducing interleukin 18 and monocyte chemotactic protein 1.7 That both agents show similar influences on inflammation indicates that the explanation for the different outcomes does not lie with different effects on inflammation.

Hyperpolarization-activated channels and atrial natriuretic peptide play crucial roles in cardiac hypertrophy. Ivabradine but not metoprolol significantly decreased hyperpolarization-activated channel 2 and atrial natriuretic peptide mRNA expression and reduced the LV mass:body weight ratio (a marker for LV hypertrophy). Increased apoptosis by angiotensin II infusion was also attenuated by ivabradine but not by metoprolol. This raises the possibility that hyperpolarization-activated channels are candidate targets for ivabradine. The difference in hypertrophy and apoptotic responses may explain the distinct effects of the 2 agents.

Chronic infusion of angiotensin II upregulates extracellular matrix and matrix metalloproteinases, which stimulate cardiac fibrosis, adverse remodeling, and cardiac dysfunction. The upregulated mRNA and protein expression of collagen I and III after angiotensin II infusion were both blocked by ivabradine but not by metoprolol. Increased expression of α-smooth muscle actin (a marker for myofibroblasts and

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Increasing the number of c-kit attenuate adverse remodeling postmyocardial infarction by nase 9, or tissue inhibitor of metalloproteinase 1 expres-
did not affect collagen deposition, matrix metalloprotei-
plasma angiotensin II levels. This link bridges ivabradine
hypercholesterolemic rabbits, accompanied by decreased
alleviated diastolic dysfunction and cardiac fibrosis in
accepts that overlap in the 2 agents are denoted in the gray ellipse.
whether ivabradine directly affects the
receptor blocker
metoprolol only reduced
response, as evidenced by a decrease in afterload in
implying that heart rate reduction in the prevention of HF. Ivabradine showed a more beneficial effect than metoprolol in the angiotensin II–infused HF model. In the large-scale clinical Ivabradine and Outcomes in Chronic Heart Failure Trial, ivabradine significantly reduced adverse clinical outcomes related to HF and improved health-related quality of life when added to guideline based treatment. The benefit was most pronounced in patients with high baseline heart rates. Ivabradine may be a good choice for patients who do not tolerate β-blockers, but quality studies need to be done to determine whether the benefit will be seen without previous use of β-blockers. Additional randomized, double-blind, placebo-controlled, multicenter trials are needed before translating this therapy to first-line use.

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