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Ivabradine in Cardiovascular Disease: Heart Rate Isn't Everything

Arthur M. Feldman, MD, PhD

The funny or hyperpolarization-activated cyclic nucleotide-gated channel (HCN) modulates cardiac excitability and heart rate by regulating the I_f or I_{Kf} current in sinoatrial cells.[1] The 4 HCN channel isoforms (HCN1–4) are unique in that they are activated by both cyclic adenosine monophosphate (AMP) and hyperpolarized membrane channels. Thus, sympathetic activation of β-adrenergic receptors (β-AR) on the cardiac sarcolemma and the resultant increase in cellular levels of cyclic AMP shift the activation potential of the channel thereby increasing heart rate. Channel activity is also modified by phosphoinositides including phosphatidylinositol-4,5-bisphosphate and by Src kinase–mediated phosphorylation in an isoform-specific manner.[2] HCN channels also play a role in regulating excitability in neurons, and changes in channel activity have been associated with the development of epilepsy and seizures.[3]

Much of what we know about HCN channels in the heart comes from studies in which the channels were knocked out. For example, animals in which HCN1 had been knocked out had sinus pauses and reduced cardiac output,[4,5] whereas mice with knockout of HCN3 had abnormal action potentials.[6] Global knockout of HCN4 was lethal, presumably because of a profound decrease in heart rate, whereas conditional deletion of HCN2 and HCN4 was associated with an increase in ventricular arrhythmias.[2,7–9] Although adult ventricular myoctes do not express appreciable levels of HCN channels under normal conditions, HCN expression is increased in cardiac hypertrophy and failure although the physiological relevance is uncertain.[10–16] Either pharmacologic blockage of the HCN channels or selective knockdown of HCN2 or 4 channels affected cardiac remodeling or ventricular function during the development of cardiac hypertrophy[17] and a loss of function mutation in HCN4 in families with bradycardia was also associated with structural abnormalities of the myocardium.[18] Therefore, in aggregate, these results suggested that any salutary benefits of HCN inhibition were likely because of an effect on heart rate and not on the biology of the myocardium.

Despite the lack of basic science data supporting a role for cardiac HCN channels in the pathobiology of left ventricular dysfunction, the recognition that there was an inverse relationship between heart rate and survival in patients with cardiovascular disease led to the development of the selective sinus note I_f channel inhibitor ivabradine.[19,20] Ivabradine has been evaluated in large multicenter trials assessing its efficacy in the treatment of a variety of cardiovascular disease including stable coronary artery disease with left ventricular dysfunction, chronic heart failure, and stable coronary artery disease without clinical heart failure.[21–23] The BEAUTIFUL (morbidity–mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) trial randomized 10,917 patients with stable coronary disease and a left ventricular ejection fraction of <40% to receive either ivabridine or placebo after a 14-day run-in period.[21] The starting dose of ivabradine was uptitrated if the resting heart rate was 60 beats per minute (bpm) or greater. Not surprisingly, ivabradine reduced heart rate; however, it had no effect on the primary end point of cardiovascular death or admission to a hospital for new-onset or worsening heart failure. In a subgroup of patients with a heart rate of 70 bpm or greater, ivabradine treatment reduced the secondary end points of admission to a hospital for a fatal or nonfatal myocardial infarction and coronary revascularization. In a substudy of only 426 subjects, the investigators reported a significant decrease in the primary end point of left ventricular end-systolic volume index assessed by echocardiography.[24]

From the Department of Medicine, Temple University School of Medicine, Philadelphia, PA.

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Reprints: Arthur M. Feldman, MD, PhD, Temple University School of Medicine, 3500 N. Broad St, Suite 1150, Philadelphia, PA 19140 (e-mail: arthur.feldman@tuhs.temple.edu).

However, they were not able to show a change in the left ventricular end-diastolic index, and there was no change in the levels of brain natriuretic peptide.

Ivabradine was then evaluated in the SHIFT trial (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial). Similar to BEAUTIFUL, 6,558 patients were randomized to either ivabradine or placebo, and the study drug was titrated based on heart rate.[22] By design, the investigators enrolled patients who were receiving at least 50% of the target daily dose of a β-blocker as defined by the European Society of Cardiology guidelines; however, the dose of β-blocker was not titrated regardless of heart rate. Ivabradine improved the primary end point of death or hospitalization for worsening heart failure. However, in a prespecified subgroup of f patients receiving at least 50% of the evidence-based target daily dose of a β-blocker, ivabradine did not significantly affect the primary end point, and the mortality component was not significantly reduced. Importantly, 18% of the placebo-treated patients were receiving less than 50% of the recommended dose of a β-blocker, the mean daily doses of β-blockers were less than guideline-mandated levels, and a significant number of patients were receiving metoprolol tartrate, a drug formulation that is not approved for the treatment of heart failure in the United States because the primary end point was not met in a single clinical trial.[25]

Finally, in a recent randomized, double-blind, and placebo-controlled trial in 19,102 patients who had stable coronary artery disease without clinical heart failure and a heart rate of 70 bpm or greater, ivabradine, failed to affect the primary end point of death from cardiovascular causes of nonfatal myocardial infarction.[23] In fact, ivabradine was associated with an increase in the incidence of the primary end point among patients whose activity was limited by angina. As with earlier ivabradine trials, patients in both groups were receiving suboptimal doses of β-blocker. Although the 3 trials did not point to atrial fibrillation as a potential side effect of ivabradine use, the most recent study reported a highly significant increase in the frequency of atrial fibrillation (5.3% vs. 3.8%) in the ivabradine group, and a meta-analysis reported a 15% increase in the risk of atrial fibrillation with ivabradine—an effect that warrants attention.[26–28]

In this issue of the Journal, Saggu et al[29] present data from a study that was designed to evaluate the cardiovascular effects of ivabradine as compared with metoprolol in patients with mild to moderate mitral stenosis. Although the study population was small, the results are more informative than the much larger multicenter studies because by using a crossover design and by titrating the doses of both ivabradine and metoprolol to a heart rate end point, the investigators eliminated the bias that occurred in the large trials because ivabradine was titrated to heart rate in the treatment group but the dose of the β-blocker was not titrated in the placebo group. Saggu reported no difference between ivabradine and metoprolol in lowering heart rate, improving symptoms, or improving cardiac hemodynamics. Thus, in the context of mild to moderate mitral stenosis, there is only a role for ivabradine in patients who are intolerant of a β-blocker or in whom a β-blocker is contraindicated.

The fact that the large clinical trials failed to titrate β-blocker dosing to the levels that were used in the clinical trials that demonstrated their effectiveness biased the results but more importantly failed to account for the effects of β-blocker therapy over and above simply controlling heart rate. β-blockade attenuates the β1/β2-AR–adenylyl cyclase–cyclic AMP signaling pathway that increases heart rate through inhibition of HCN channel activity but also decreases short-term cardiac function by decreasing the ability of protein kinase A to phosphorylate proteins that regulate Ca^{2+} handling and that modulate the contractile apparatus. However, a large body of recent work has demonstrated that the beneficial effects of β-blockers in patients with cardiovascular disease and heart failure are due to far more than simply decreasing heart rate. For example, β-blockers attenuate β-AR–mediated Ca^{2+} overload, apoptosis, activation of the fetal gene program, calmodulin kinase II–mediated hypertrophy, and protein kinase A–initiated myocardial arrhythmias while at the same time increasing cardiac levels of antioxidants.[30,31] Studies have also shown that nonselective β-blockers can act as inverse agonists and stimulate Gs-dependent adenylate cyclase activity.[32,33] Perhaps, the most important role of β-blockers (carvedilol, bucindolol, propranolol) is that they can act as biased ligands. Although they block harmful G protein–mediated signaling, they also actively recruit β-arrestin with subsequent activation of a signaling cascade that includes activation of epidermal growth factor receptors, phosphorylation of extracellular signal–regulated kinase 1/2, and cardioprotection.[34] β-adrenergic agonists can therefore improve intrinsic systolic function by regressing pathological hypertrophy and reversing maladaptive cardiac remodeling.[31]

Our understanding of the complex signaling pathways that regulate cardiac contractility, remodeling, hypertrophy, and homeostatic regulation is increasing at an exponential pace as our ability to rapidly and effectively dissect these pathways has been enhanced by technological advances. Therefore, it is imperative that the development of new drugs and biologics takes full advantage of this new information. The plethora of drugs available for the treatment of heart failure and/or angina can make it difficult to design studies to evaluate new drugs or biologics; however, a thorough understanding of the workings of existing drugs and a systematic evaluation of the mechanisms responsible for the putative benefits of new drugs must be merged to create a trial design that does not bias the overall results. Had the sponsor and investigator of the large clinical trials assessing the efficacy of ivabradine taken the approach of Sugga et al, we might know far more about the potential role of this new pharmacologic agent. In an era when bending the cost curve for chronic diseases such as heart failure is a primary concern, it is of critical importance that we do not replace existing and inexpensive pharmacologic agents with new ones without carefully assessing the unique attributes of each in an unbiased and transparent manner.

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