

# Can $I_f$ inhibition help in congestive heart failure?

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*Ivabradine is a selective inhibitor of the  $I_f$  pacemaker current, and as such decreases heart rate without inducing any negative inotropic effects. Experimental and clinical evidence suggests that the beneficial effects of  $\beta$ -blockers in heart failure are mediated by a reduction in heart rate. Long-term heart rate reduction with ivabradine in a rat model of heart failure elicited an improvement in left ventricular function and a positive effect on cardiac remodeling, leading to a decrease in collagen density and an increase in capillary density. In addition, recent evidence indicates that the  $I_f$  current may be reexpressed in animal and human ventricular myocytes from failing hearts and may have an arrhythmogenic role.  $I_f$  inhibition would thus exert an antiarrhythmic effect in heart failure, but this hypothesis remains to be proven in the clinical setting.*

**Keywords:** heart failure; heart rate;  $I_f$  inhibition; electrophysiology; ventricular myocyte; electrophysiological remodeling; ivabradine

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Ivabradine is a novel pharmacological agent developed for the treatment of stable angina pectoris. It is a specific, dose-dependent, inhibitor of the sinoatrial pacemaker  $I_f$  current and a selective heart rate-lowering agent, which decreases heart rate at rest and during exercise, and which has no negative inotropic effect and no effect on atrioventricular conduction.<sup>1</sup>

## POTENTIAL CLINICAL EFFECTS OF $I_f$ CURRENT MODULATION IN HEART FAILURE

In patients with chronic stable angina pectoris, ivabradine reduces heart rate and the rate-pressure product (heart rate  $\times$  systolic blood pressure), resulting in a reduction in cardiac workload and myocardial oxygen consumption. However, its heart rate-lowering effect, by reducing the energy cost of overall myocardial contractile activity and prolonging ventricular diastolic filling, could also be beneficial in patients with left ventricular dysfunction and heart failure. Mortality trials using phosphodiesterase inhibitors, hydralazine-nitrate, angiotensin-converting enzyme inhibitors, and  $\beta$ -blockers in heart failure patients have shown a relationship between changes in resting heart rate and mortality reduction (*Figure 1*).<sup>2</sup> Two studies in patients with severe heart failure treated with enalapril<sup>3</sup> and amiodarone,<sup>4</sup> respectively, showed that baseline heart rate was an im-

portant determinant of the response to treatment. In these studies, the benefit of treatment in terms of survival was restricted to patients with a raised baseline heart rate and was associated with a significant heart rate reduction.

Nagatsu et al reported evidence that the benefit of  $\beta$ -blockade on left ventricular contractility in experimental heart failure associated with elevation in baseline heart rate is mediated by heart rate reduction.<sup>5</sup> These authors showed that chronic administration of atenolol in dogs with heart failure induced by creating severe mitral regurgitation resulted in a significant improvement in left ventricular con-

### SELECTED ABBREVIATIONS AND ACRONYMS

<b>CIBIS II</b>	Second Cardiac Insufficiency Bisoprolol Study
<b>DCM</b>	dilated cardiomyopathy
<b>HCN</b>	hyperpolarization-activated cyclic nucleotide-gated cation channel
<b>ICM</b>	ischemic cardiomyopathy
<b>LVH</b>	left ventricular hypertrophy
<b>MERIT-HF</b>	MEtoprolol controlled-release Randomized Intervention Trial in Heart Failure
<b>SHR</b>	spontaneously hypertensive rat



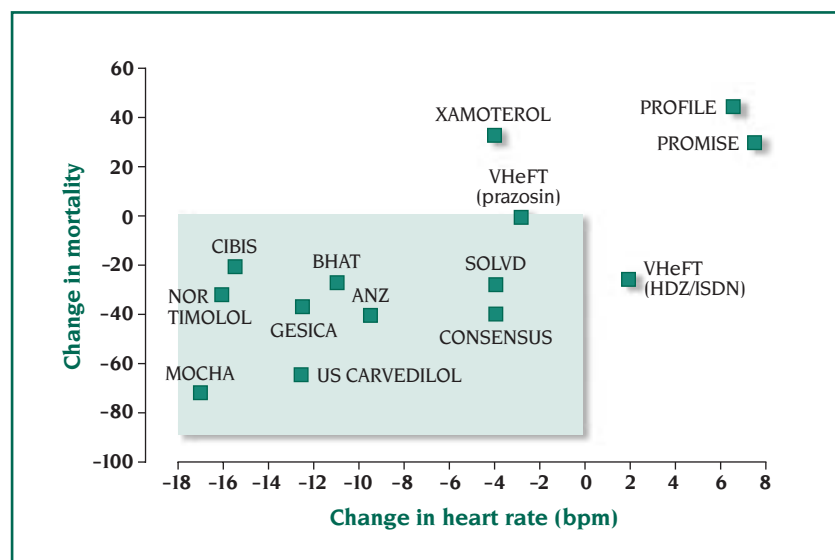
tractility. This improvement was completely prevented by chronic pacing at a rate equal to the pre-treatment heart rate.

The importance of heart rate reduction per se was evaluated in post-hoc analyses of the major clinical trials testing the effects of  $\beta$ -blockers in heart failure. In the METoprolol controlled-release Randomized Intervention Trial in Heart Failure (MERIT-HF), two dosage subgroups were compared, one receiving more than 100 mg metoprolol CR/X twice

The Second Cardiac Insufficiency Bisoprolol Study (CIBIS II) evaluated the relationship between baseline heart rate changes 2 months after the beginning of treatment and outcomes (mortality and hospitalization for heart failure).<sup>7</sup> Multivariate analyses showed that, in addition to  $\beta$ -blocker treatment, both baseline heart rate and changes at 2 months significantly correlated with survival and hospitalization for worsening of heart failure. Furthermore, the lowest baseline heart rate and the greatest heart rate reduction

not significant in patients with atrial fibrillation. It was observed that among these patients, those treated with  $\beta$ -blockers and who subsequently died, had a more important decrease in blood pressure, suggesting that the marked decrease in blood pressure induced by  $\beta$ -blocker treatment may be deleterious. This effect is not expected with drugs inhibiting the  $I_f$  channels.

Conflicting results have been reported in studies investigating the effects of carvedilol in heart failure patients. Post-hoc stratification of patients in the US-Carvedilol heart failure program into groups above and below the mean baseline heart rate showed that the mortality benefit of carvedilol compared with placebo was only significant in the group with a high baseline heart rate.<sup>9</sup> Others have not found such a relationship. In a retrospective, observational, single-center study aimed at determining whether the process of reverse remodeling in response to carvedilol in heart failure patients was dependent on baseline heart rate and on  $\beta$ -blockade-induced heart rate reduction, no relationship was found between left ventricular size and left ventricular function and heart rate, either at baseline or after  $\beta$ -blockade.<sup>10</sup> This suggests that the remodeling process may also be controlled by mechanisms other than heart rate.



**Figure 1.** Relationship between changes in heart rate and mortality in congestive heart failure (CHF). In patients with heart failure changes in mortality with a variety of drug regimens in different trials are related to changes in heart rate. Only trials in the lower left quadrant had reduced heart rate and mortality.

Adapted from reference 2: Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. *Eur Heart J.* 1999;1(suppl H):H64-H69. Copyright © 1999, Oxford University Press.

daily (n=1202) and the other receiving 100 mg or less (n=412) during the first 3 months of follow-up.<sup>6</sup> Heart rate was reduced to a similar degree in both groups. The reduction in total mortality with metoprolol CR/XL versus placebo was similar in both groups (38%). This may indicate a higher sensitivity to  $\beta$ -blockade in the low-dose group, but it may also suggest that the main benefit of  $\beta$ -blockade resulted from its effect on heart rate.

were associated with better survival and a greater reduction in hospital admissions. These results were interpreted as confirming the hypothesis that heart rate reduction per se in patients with heart failure is associated with improved survival. This result is possibly the consequence of the induced reduction in ischemia, which is present to different degrees in dilated ventricles even in the absence of coronary artery disease.<sup>8</sup> The benefit of bisoprolol was

Recent experimental and clinical findings consistently indicate that the heart rate reduction induced by ivabradine may be beneficial in patients with left ventricular dysfunction. The effects of long-term heart rate reduction on left ventricular function and remodeling was investigated in a rat model of heart failure.<sup>11</sup> The animals randomized to ivabradine, exhibited long-term (90 days) heart rate reduction. In these animals, treatment with ivabradine

resulted in improved left ventricular function compared with placebo, and stroke volume was increased, thereby preserving cardiac output. Changes in ventricular structure were also reported, with a decrease in left ventricular collagen density and an increase in capillary density, without any change in left ventricular weight. The mechanisms of these structural and functional cardiac changes are still speculative. Heart beating is metabolically costly. Moreover, elevated heart rate shortens the diastolic intervals during which the coronary blood flow perfuses the myocardium and provides the myocytes with nutrients and oxygen and carries away the terminal products of cellular metabolism. Relative hypoxia in the subendocardial layers can also induce endothelial dysfunction, triggering the release of cytokines and free radicals.

In a 3-month randomized double-blind placebo-controlled clinical study,<sup>12</sup> ivabradine was administered at a dosage of 10 mg twice daily on top of conventional therapy (except  $\beta$ -blockers) to 56 patients with coronary artery disease and mild-to-moderate congestive heart failure. Patients with the highest degree of left ventricular systolic dysfunction (echographic left ventricular ejection fraction [EF] <35%) demonstrated a mean 5% increase in EF with ivabradine, compared with a mean 0.5% decrease in patients receiving placebo.

Several data support ivabradine's safety in the elderly population. A pharmacokinetic analysis performed in elderly patients showed that there were no differences in pharmacokinetics (AUC and  $C_{max}$ ) between elderly (>65 years) and very elderly patients (>75 years) and the overall population.<sup>13</sup> In contrast,  $\beta$ -blockers are contraindicated in patients with obstructive lung dis-

eases, decompensated conditions, hypotension, and atrioventricular conduction disturbances, as listed by a retrospective study assessing  $\beta$ -blocker utilization patterns in clinical practice setting.<sup>14</sup> Similar findings were observed in a nationwide observational study performed in Italy.<sup>15</sup> Moreover, in patients in whom  $\beta$ -blocker therapy needed to be uptitrated to the maximum tolerated dose, the dose administered was frequently lower than the recommended dose.<sup>16,17</sup>  $\beta$ -Blocker use may also be hampered by the occurrence of fatigue, hypotension, dizziness, and dyspnea, requiring discontinuation of treatment. Thus, though  $\beta$ -blockers are very effective in heart failure patients, a number of contraindications and poor tolerability may in practice restrict their use at the full dosage proven to be effective in clinical trials.

Ivabradine can be combined with all the drugs currently recommended for use in heart failure patients without any risk of untoward drug interactions developing. Thus, no kinetic or dynamic interactions with ivabradine were observed in patients of pivotal phase 3 studies receiving angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, aspirin, digoxin, amiodarone, or cholesterol-lowering agents. No clinically significant changes in atrioventricular conduction, QT interval, and myocardial contractility have been reported. Therefore, combination of ivabradine and  $\beta$ -blockers or other heart rate-lowering agents does not pose specific problems. Thus, it appears that patients with coronary artery disease and left ventricular systolic dysfunction may benefit from heart rate reduction with ivabradine whatever the background therapy, including or not  $\beta$ -blockers. Ivabradine is currently being tested in a large international phase 3 trial—the

Morbidity-mortality Evaluation of the  $I_f$  inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL).

### POTENTIAL CLINICAL EFFECTS OF $I_f$ INHIBITION IN NONPACEMAKER CARDIAC CELLS

In addition to the benefit of  $I_f$  inhibition in regard of the pacemaker cells of the atrioventricular node, discussed above,  $I_f$  inhibition may also be of benefit in heart failure through a different mechanism of action, by acting on the reexpression of the  $I_f$  current in the *ventricular cells* of the failing heart.

Whereas the role of  $I_f$  in the generation of spontaneous sinus node activity and in the control of heart rate is widely documented and has been known for a long time,<sup>18,19</sup> the presence of  $I_f$  in ventricular myocytes is a more recent and quite intriguing finding. First of all, it must be stressed that the presence of  $I_f$  in ventricular myocytes relates to pathophysiology rather than physiology. The first recording of  $I_f$  in ventricular cardiomyocytes was reported in 1993 in the normal guinea pig. The characteristics of this  $I_f$  current were such that they ruled out any possible physiological role in the ventricle, because it was much smaller than the  $I_f$  current recorded in pacemaker cells, and was activated at negative voltages far below the values of normal resting potentials, (ie, more negative than -100 mV).<sup>20</sup> However, in the setting of heart disease, the situation is very different. This is because, in various animal models of cardiac hypertrophy and failure,  $I_f$  has been shown to be upregulated,<sup>21-23</sup> to the extent that it may assume a functional role. It was found that during the recording of the intracel-



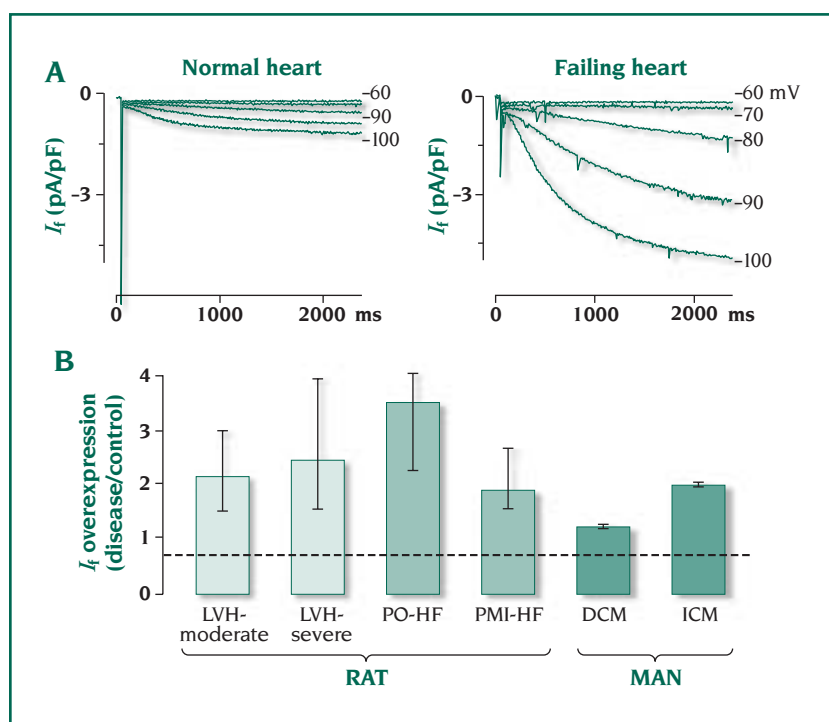
lular electrical activity of papillary muscles isolated from 18-month-old spontaneously hypertensive rats (SHR), ie, rats with a severe cardiac hypertrophy, the diastolic phase was not flat but a "sort" of diastolic depolarization could be detected between two driven action potentials.<sup>24</sup> The papillary muscles isolated from old SHR were also particularly sensitive to the arrhythmic action of isoprenaline, a  $\beta$ -adrenergic agonist. It seemed obvious to conclude that one of the reasons for this enhanced susceptibility to the arrhythmogenic action of the catecholamines could be due to the "unusual" presence of that "unusual" diastolic depolarization. The presence of  $I_f$  was subsequently documented in ventricular myocytes isolated from the heart of animals with different degrees of cardiac hypertrophy. The degree of hypertrophy was positively correlated with an increased  $I_f$  density,<sup>22</sup> and changes in expression levels were most pronounced in those cardiac regions with the highest overload,<sup>25,26</sup> indicating that the processes leading to hypertrophy directly affected the level of hyperpolarization-activated cyclic nucleotide-gated cation channel (HCN) expression, which are the molecular components of native f-channels.<sup>27</sup> Four HCN genes were identified, encoding different proteins, which assemble to form tetrameric (homomeric or, likely, heteromeric) compounds.

Figure 2A shows  $I_f$  current recordings obtained in ventricular myocytes isolated from normal human heart (human donor heart not used for transplantation because of technical problems) and in myocytes isolated from a human heart explanted because of terminal failure. Figure 2B summarizes the relative increase in "current density," comparing diseased vs control ventricular cardiomyocytes, in several rat

models of cardiomyopathies and in human ischemic and dilated cardiomyopathies. "Current density" designates a current amplitude that is normalized with respect to cell size: since the cardiomyocytes are "hypertrophic," ie, enlarged, in cardiomyopathies, it is absolutely nec-

essary to correct the current amplitude for cell dimensions.  $I_f$  density is markedly increased in left ventricular cardiomyocytes from rats with moderate or severe cardiac hypertrophy (LVH) caused by pressure overload (PO), and is even greater in rats with overt heart failure (HF) consequent to high blood

pressure (PO) or post-myocardial infarction (PMI). In addition to electrophysiological data, molecular biology techniques allowed to demonstrate a parallel upregulation of the HCN2 and HCN4 mRNA levels, which are the predominant isoforms underlying ventricular  $I_f$ .<sup>28</sup>



**Figure 2.** Ventricular  $I_f$  expression is increased in cardiomyopathies. **Panel A:** Typical example of  $I_f$  recorded in ventricular myocytes isolated from normal or failing heart. **Panel B:** Each histogram represents the ratio between current density measured in ventricular cardiomyocytes from rat or human diseased hearts, and respective controls (indicated by the dashed line); bars are confidence intervals (95%). LVH-moderate and LVH-severe: relative increase in  $I_f$  in rats with moderate or severe left ventricular hypertrophy caused by aortic banding<sup>23</sup> or long-lasting pressure overload (PO),<sup>22</sup> respectively. PO-HF, PMI-HF: relative increase of  $I_f$  in rats with overt heart failure (HF), resulting from uncompensated hypertrophy due to pressure overload (PO-HF)<sup>22</sup> or post-myocardial infarction (PMI-HF) due to coronary ligation,<sup>25,26</sup> respectively. DCM, ICM: relative increase of  $I_f$  in left ventricular myocytes isolated from the explanted heart of patients undergoing cardiac transplantation for terminal dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM).<sup>34</sup> For all conditions, the relative increase in  $I_f$  density was statistically significant versus controls, ie, normotensive rats, sham-operated rats, or nondiseased donor hearts not transplanted for technical reasons, with the exception of DCM patients (NS: not significant).

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Recordings of  $I_f$  in ventricular myocytes show electrophysiological properties (voltage-dependence, kinetics of activation, Na/K permeability ratio) qualitatively similar to those described 20 years ago by DiFrancesco (as reviewed in reference 29) for primary and subsidiary pacemakers. It has been proposed

that mislocalized expression and/or overexpression of cardiac HCN channels may represent an example of a general phenomenon, called cardiac remodeling, which consists namely in the reexpression of fetal proteins: in fact, f-channels are present in fetal or neonatal ventricular myocytes,<sup>30,31</sup> which lose their capacities of generating spontaneous activity during electrophysiological maturation toward adult phenotype. However, from a clinical point of view, the most interesting aspect of this phenomenon is that  $I_f$  may represent an arrhythmogenic mechanism in heart failure, which is a condition associated with high risk for sudden cardiac death. Further support for this hypothesis comes from the evidence of  $I_f$  expression in the failing human ventricle from explanted hearts.<sup>32,33</sup> Correlation with the severity of cardiac disease was obviously impossible in this setting, as all patients had terminal heart failure. However, a fascinating finding was that changes in  $I_f$  density correlated with the etiology of the disease, and, for example,  $I_f$  overexpression was greater in ischemic cardiomyopathy (ICM) than in idiopathic dilated cardiomyopathy (DCM) (Figure 2).<sup>34</sup> Recent molecular findings have shown that HCN2 and HCN4 expression at both mRNA and protein levels is markedly increased in samples obtained from hearts explanted from patients with ICM, providing a molecular explanation for the functional up-regulation of  $I_f$  in heart failure.<sup>35</sup> The signaling pathways leading to enhancement of  $I_f$  in nonautomatic regions of the heart are not fully clarified, but the renin-angiotensin system seems to play a pivotal role.<sup>36,37</sup> Overall, these studies represent the first evidence in favor of an altered  $I_f$  expression in cardiac diseases and suggest its potential role in the associated abnormal electrical activity.

## CONCLUSIONS

The molecular identification of HCN subunits and their functional/molecular detection in the diseased ventricle have resulted in an unforeseeable surge of interest for pacemaker channels. Based on these new findings, it appears that selective f-channel inhibitors such as ivabradine, in addition to selective heart rate reduction (which in itself may be beneficial in patients with left ventricular dysfunction and heart failure), may also block the  $I_f$  current expressed in ventricular myocytes of the failing heart (where it may represent an arrhythmogenic trigger), and thus reduce the risk of sudden death—an exciting prospect that still awaits clinical confirmation.

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