Heart failure (HF) affects ≈2% to 3% of the population in many industrialized countries and is a major cause of mortality. Although widely used treatments such as β-blockers and renin-angiotensin system antagonists have largely improved outcomes in the past 2 decades, prognosis remains poor. Accumulating data collected in >200,000 individuals in various epidemiological studies support that an elevated heart rate (HR) is a risk marker for future cardiovascular outcomes (including sudden cardiac death) in the general population, in patients with risk factors for coronary artery disease (CAD), and in those with established CAD (both stable and unstable), as well as an established risk factor in those with HF, as discussed below. HR reduction is particularly beneficial in chronic HF, and novel therapeutic approaches that selectively target HR have been recently proposed and raise new hopes for the treatment of HF.

HR generation relies on different molecular mechanisms, including the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Figure 1). The HCN family of channels is involved in numerous physiological functions in the central nervous system and heart where they are responsible for the IF current in the sinoatrial node (SAN). HCN channels have been shown to be involved in the pathophysiology of neurological disorders, including epilepsy (reviewed by Lewis and Chetkovich) and chronic pain, as well as in retinal physiology (see Table 1 for a summary of HCN functions in extracardiac pathophysiology). HCN channels have also emerged as interesting targets for the development of drugs that lower HR.

In this review, we first briefly highlight the current knowledge of the biophysical properties of HCN channels. We then discuss the molecular mechanisms underlying the regulation and function of HCN channels as revealed through studies in different animal models. Finally, we present their role in human diseases by focusing on HF and arrhythmias through data from recent clinical studies with the HCN channel inhibitor ivabradine.

The HCN Channel Family

HCN channels belong to the superfamily of voltage-gated pore-loop cation channels. Four isoforms (HCN1–HCN4) with a high homology have been cloned and share common biophysical properties. They have a reverse voltage dependence leading to activation on hyperpolarization, a unique mechanism among vertebrate voltage-gated ion channels. HCN channels are constituted of 4 subunits, forming a tetramer. Each monomer is composed of 6 transmembrane α-helical segments, named S1 to S6, with S4 being the putative voltage sensor (Figure 2). In the C terminus, a cyclic nucleotide-binding domain is connected to the channel core via the C linker. The selectivity filter and the pore region are formed between the S5 and S6 segments, following tetramer assembly. Two major structural modules are usually distinguished: the transmembrane core harboring the gating machinery and the conducting pore with the cytosolic domains conferring modulations.

When first described in the rabbit cardiac SAN, the current resulting from the activation of HCN channels was called funny (IF) because it is activated by hyperpolarization, unlike other voltage-dependent currents, displaying a characteristic sigmoidal time course following membrane hyperpolarization (for a complete historical description of IF origin and discovery, see References 18 and 19). This unique voltage dependency is attributable to an inverted gating between the movements of the voltage-sensor/S4 segment; they seem to sense correctly the transmembrane depolarization and displace in the same direction compared with those of the shaker potassium channels. Despite extensive efforts to address this question, the exact mechanism at the origin of this inverted voltage dependency is not completely understood. The most recent work shows that among the structural particularity of HCN channels, a leucine-zipper motif between the S5 and S6 segments seems to be involved by stabilizing the closed state at depolarized potentials. As stated above, the IF current is voltage dependent (activated by hyperpolarization; see Figure 2). An unusual property of HCN channels involves the permeability to both Na+ and K+ (higher permeability to K+ ions than to Na+ ions). During diastole, the inward current is carried mainly by Na+ and K+, with a permeability ratio of 1:4, leading to a slow depolarization phase, ie, the pacemaker activity. Although K+ is the most easily conducted ion, followed by Na+, a small passage of Ca2+ ions also seems possible, whereas the inward current is blocked by Cs+. However, despite the preference for K+ conductance, under physiological conditions, HCN channels carry mainly an inward Na+ current. HCN channel isoforms differ from each other in their voltage dependency, activation kinetics, and response to cAMP.
Expression Patterns of HCN Channels

There are 4 isoforms of HCN channels, and the expression of all of them has been reported in the myocardium, albeit at low levels for HCN3. The relative expression profiles of HCN channel isoforms show regional differences.

HCN expression is highly regulated during embryonic development. In the mouse heart, the transcription profiles of the 4 HCN genes from embryonic stage to postnatal day 120 vary significantly. The consistently low HCN transcription in adult myocardium may be required to prevent atrial and ventricular arrhythmogenesis. HCN N-glycosylation has been observed in the embryonic heart and could be involved in membrane localization.

In the adult SAN, HCN4 seems to be the major isoform found at the mRNA level in rabbits, mice, and humans. In mice, HCN2 mRNA is expressed in the SAN and myocardium, whereas HCN1 is found only in the SAN and atrioventricular node at lower levels. HCN3 is only weakly detected. HCN expression patterns were also studied in rats by laser capture microdissection of the inferior nodal extension, a specific area located in the atrioventricular junction area. HCN4 mRNA expression was high in the inferior nodal extension, atrioventricular node, and SAN, with low expression levels observed in Purkinje fibres. Although the expression of HCN1 was low in the rat heart, it was observed in the inferior nodal extension, atrioventricular node, and SAN. HCN2 was expressed at higher levels in working myocytes than in nodal tissues.

Aging also affects the expression of HCN genes in the SAN. In rats, an age-dependent decrease in HCN1, HCN2, and HCN4 transcription has been observed. The effect of Cs+ on pacemaker activity was consistently reduced with age. Because aging is associated with deteriorating SAN function, the transcription and relative function of HCN channels may contribute to the decline of function in aged rats. In humans, higher expression of HCN4 and HCN1 mRNAs was observed in the SAN compared with the right atrium.

Regulation of HCN Channel Function

HCN channels are involved in the regulatory pathways of SAN activity. HCN channels are regulated by many pathways, and complex models have been used to describe their gating. Modulation by cAMP appears to be a common mechanism because the cyclic nucleotide-binding domain region is conserved in all 4 HCN channels (schematically presented in Figure 2). cAMP (or cGMP) accelerates the opening kinetics by binding to the C terminus of HCN4 and HCN2 isoforms and shifts their open probability toward more depolarized voltages, whereas HCN1 and HCN3 are almost unaffected. Regulation by cAMP can be influenced by the composition of the milieu or the parameters of the experimental conditions. Through cAMP regulation, modulation of HCN channel activity supports physiologically driven control of HR. The sympathetic and parasympathetic neurotransmitters control the cytosolic concentration of the second messenger cAMP (through activation of β-adrenergic [mainly β2 but also β1]

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Table 1. HCN Channels in Noncardiac Physiology or Pathophysiology: Central Nervous System and Retina

<table>
<thead>
<tr>
<th>Findings</th>
<th>Potential Clinical Interest</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior, Rewarding effects of ethanol</td>
<td>Fight alcohol</td>
<td>10</td>
</tr>
<tr>
<td>targeting HCN genes expressed in dopaminergic ne...</td>
<td>abuse and addiction</td>
<td></td>
</tr>
<tr>
<td>Pain, Neuropathic pain is initiated by HCN2-driven action</td>
<td>New medications</td>
<td>8</td>
</tr>
<tr>
<td>potential firing in Na(V) 1.8-expressing nociceptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy, Genetic HCN variants could predispose to sudden death in epilepsy</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>HCN2-deficient mice exhibit spontaneous absence seizures and sinus dysrhythmia</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Dendritic HCN1 subunit facilitates epileptogenesis</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Febrile seizure, Febrile seizures modulate the expression of different HCN genes, thus altering the neuronal HCN phenotype; seizure-induced augmentation of HCN2 expression</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Retina, HCN channels are involved in retinal physiology because they could modulate the function of photoreceptors</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Retina, Phosphophanes and troubled vision</td>
<td>Limiting side effects</td>
<td>15</td>
</tr>
</tbody>
</table>
and muscarinic M2 receptors, respectively). Because cAMP concentration determines the open probability of the HCN channel, sympathetic/parasympathetic control of intracellular cAMP is able to induce an increase/decrease of the net inward current during diastolic depolarization and thereby an increase/decrease of firing rate. HR regulation through cAMP levels could be mediated rapidly by direct binding of cAMP to the C-terminus of the HCN channel, shifting its activation curve to more depolarized voltages, thus increasing the current. cAMP directly opens the HCN channel, leading to activation of the I\(f\) current and diastolic depolarization of the cell. Ivabradine is shown (small molecule) blocking the I\(f\) current from the internal side of the HCN channel. Many regulatory pathways can intervene at the extracellular and intracellular levels and through interactions with both membrane and extracellular/intracellular proteins. Gi and Gs indicate Gi and Gs proteins coupled with receptors; KCR1, K+ channel regulator-1; MIRP1, MinK-related protein-1; \(\beta\), phosphorylation status; PIP\(_2\), phosphatidylinositol-4,5-bisphosphate; and PLC, phospholipase C.

**Figure 2.** Schematic structure of the hyperpolarization-activated cyclic nucleotide-gated (HCN)-channel and its main regulatory pathways. HCN channels are tetramers; only 2 of the subunits are shown here. Each subunit is composed of 6 transmembrane helixes (S1–S6). S4 is the putative voltage sensor, rich in basic amino acids. In the C-terminal region, the cyclic nucleotide-binding domain (CNBD) is connected to the channel core and can host the cAMP molecule product of adenylate cyclase (AC) under regulation from \(\beta_1\) and \(\beta_2\) adrenergic receptors (\(\beta\)-AR1 and \(\beta\)-AR2, respectively), as well as the muscarinic receptor (M2). Acetylcholine, which is released from cardiac vagal nerves, acts on muscarinic receptors to inhibit the formation of cAMP. In contrast, norepinephrine, which is released from cardiac sympathetic nerves, acts on \(\beta\)-adrenergic receptors to increase the formation of cAMP. cAMP directly binds to the C-terminus of the HCN channel, shifting its activation curve to more depolarized voltages, thus increasing the current. cAMP directly opens the HCN channel, leading to activation of the \(I_f\) current and diastolic depolarization of the cell. Ivabradine is shown (small molecule) blocking the \(I_f\) current from the internal side of the HCN channel. Many regulatory pathways can intervene at the extracellular and intracellular levels and through interactions with both membrane and extracellular/intracellular proteins. Gi and Gs indicate Gi and Gs proteins coupled with receptors; KCR1, K+ channel regulator-1; MIRP1, MinK-related protein-1; \(\beta\), phosphorylation status; PIP\(_2\) (PIP\(_2\)), phosphatidylinositol-4,5-bisphosphate; and PLC, phospholipase C.

**Table 2. Involvement of Different HCN Channels in Cardiac Pathophysiology**

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Expression in the Heart</th>
<th>Knockout Mouse Phenotype</th>
<th>Additional Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCN1</td>
<td>Conduction system(^{25})</td>
<td>Neuronal dysfunction(^{44}); no cardiac phenotype described</td>
<td>Decreased in old rats(^{29})</td>
</tr>
<tr>
<td>HCN2</td>
<td>Ubiquitous, mainly in SAN(^{25})</td>
<td>Sinus arrhythmia(^{12})</td>
<td></td>
</tr>
<tr>
<td>HCN3</td>
<td>Left ventricle(^{27})</td>
<td>Defects in ventricular late repolarization(^{56})</td>
<td></td>
</tr>
<tr>
<td>HCN4</td>
<td>Ubiquitous, the isoform most expressed in SAN(^{31,55,57}) but also present in AVN(^{28}) (and His-Purkinje fibers)</td>
<td>Varying (mild to marked) effects on cardiac automaticity(^{40,51,52}); embryonic lethality(^{49})</td>
<td>Main HCN channel involved in the generation of sinus rhythm</td>
</tr>
</tbody>
</table>

AVN indicates atrioventricular node; HCN, hyperpolarization-activated cyclic nucleotide-gated; and SAN sinoatrial node.
Both extracellular and intracellular protons regulate HCN channel function. Intracellular acidosis seems to inhibit HCN activation, which is important during cardiac ischemia and HF, whereas extracellular acidosis activates the channel. Numerous auxiliary proteins have been shown to regulate HCN function by controlling the fine electrophysiological regulation or the subcellular compartment trafficking: K+ channel regulator-1, Tamalin, c-Src, scaffold proteins such as Mint2 and synaptic scaffolding molecule (which positively regulates cell-membrane localization), caveolin-3 (which could provide a pathway for the β2-AR regulation of HCN by clustering HCN4 in caveolae), and potassium voltage-gated channel subfamily E member-2 (also known as MinK-related protein). Posttranslational modifications such as phosphorylation were shown to account for the function of HCN channels in specific cells. All these interacting proteins and modifications affect HCN function, as well as the abundance of HCN channels in the membrane (the number of functional pores) and their subcellular localization.

HCN Function and Disease

Genetic mice models are available for all 4 HCN channels. Constitutive cardiac deletion of HCN4 results in embryonic lethality, highlighting the role of HCN4 for SAN action potential formation. In some nonconstitutive knockout models, only mild effects on cardiac automaticity were observed with reductions of both the Ic current, leading to selective heart rate reduction. Reproduced from DiFrancesco and Camm with permission from the publisher. Copyright © 2004, Springer Science+Media BV.

Electrophysiological remodeling has been described for many channels, including the HCN channels, in humans and in a canine model of ventricular tachypacing. In the canine model of tachypacing-induced HF, HCN4 was the dominant subunit in the SAN and right atrium; downregulation of HCN4 and HCN2 expression contributed to HF-induced sinus node dysfunction, whereas upregulation of atrial HCN4 was proposed to promote atrial arrhythmia formation. In contrast, analysis in human hearts showed that the expression of both HCN2 and HCN4 was significantly increased in failing ventricles. Studies have suggested that HCN upregulation may play a role in serious ventricular arrhythmias.

HCN Channel Inhibition With Ivabradine

Although some nonspecific compounds can block the function of HCN channels, specific inhibitors have emerged; currently, only ivabradine (3-(3-[[((7-chloro-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino)propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride \([C_27H_36N_2\cdot3\cdot2H\cdot3\cdot3\cdot7\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\cdot8\·...)

\[\text{HCN4} \text{ gene lacking the cAMP-binding site in mice resulted in basal bradycardia and reduced isoprenaline-induced tachycardia, further corroborating the crucial role of HCN4 for the generation of basal pacemaker activity and maximal firing rate. Ablation of the other HCN channels had only subtle effects (Table 2). HCN mutations in humans lead to detectable changes in HCN function (reviewed elsewhere). The search for human channelopathies related to HCN mutations confirmed that HCN4 is crucial in normal physiology. Four loss-of-function mutations of HCN4 have been described and were all associated with idiopathic sinus bradycardia, accompanied in 1 case by more complex arrhythmias.

Electrophysiological remodeling has been described for many channels, including the HCN channels, in humans and in a canine model of ventricular tachypacing. In the canine model of tachypacing-induced HF, HCN4 was the dominant subunit in the SAN and right atrium; downregulation of HCN4 and HCN2 expression contributed to HF-induced sinus node dysfunction, whereas upregulation of atrial HCN4 was proposed to promote atrial arrhythmia formation. In contrast, analysis in human hearts showed that the expression of both HCN2 and HCN4 was significantly increased in failing ventricles. Studies have suggested that HCN upregulation may play a role in serious ventricular arrhythmias.

The pharmacokinetic properties of ivabradine have previously been described. It is rapidly absorbed (tmax=0.75–1.5 hours) with a bioavailability of 37% to 49%. Ivabradine has extensive tissue distribution with 70% protein binding. It is extensively metabolized by the cytochrome P450 3A4 into several metabolites, including the N-demethylated derivate, which is the major active metabolite. The elimination process occurs by both fecal and urinary pathways. The main half-life of ivabradine is 2 hours, whereas that of its N-demethylated metabolite is 13 hours.

In vitro, ivabradine reduces the spontaneous beating rate in an isolated SAN cell from rabbit using patch clamp technique (see Figure 3). In patch-clamp experiments, ivabradine has been shown to block the pacemaker current of isolated SAN cells of rabbits in the low-micromolar range, with minimal or no effects on other potassium and calcium currents. In a study of healthy volunteers assessing the correlation between bradycardic activity and plasma levels of the parent compound and its metabolite, ivabradine was found to exert a dose-dependent HR-reducing effect, partly through its N-demethylated metabolite. The maximal reductions of HR during exercise were 11±4% (10 mg) and 18±6% (20 mg) after single oral doses and 18±4% (10 mg twice daily) and 27±6% (20 mg twice daily) after repeated doses. Maximal reduction of
resting HR was 16±18% after the single 10-mg oral dose and 24±16% after the 10-mg twice-daily repeated dose.

In patch-clamp experiments, ivabradine induced a use-dependent inhibition of heterologously expressed HCN4 with an IC50 of 0.5 μmol/L; the development of the progressive blocking action on the current was related on channel openings during the activating pulses rather than time itself. This property results from the fact that ivabradine is an open channel blocker and exhibits a current-dependent release of block, rendering its action sensitive to the number of pulses and the voltage at which HCN channels are activated.

Additionally, the use dependence of ivabradine may be at the origin of the frequency dependency that is observed in vitro in SAN preparations from different species. Such a frequency-dependent property could, at least partly, explain its increased effectiveness in species with rapid SAN pacemaker activity and supports its greater impact in patients with elevated HR. In contrast, patients with low HR are less responsive, reducing the risk of clinically significant bradycardia.

Importantly, ivabradine has been shown to bind only weakly to other ionic channels. In a patch-clamp model in rabbit cells, the risk of clinically significant bradycardia. In contrast, patients with low HR are less responsive, reducing the risk of clinically significant bradycardia.

Effects on cardiac Na+ channels and on Kv1.5 potassium channels were reported only in vitro at very high concentrations (30–100 μmol/L), so these nonspecific effects seem unlikely to arise at therapeutically relevant concentrations, as in clinical practice. The electrophysiological effects of a single intravenous administration of ivabradine were studied in patients with normal baseline electrophysiology. An intravenous dose of ivabradine does not prolong the corrected QT interval or modify the conductivity and refractoriness of the atria, atrioventricular node, His-Purkinje system, and ventricles. Ivabradine also does not cause detrimental effects on coronary vasomotion.

The clinical effects of ivabradine appear to be mediated by HR reduction. An analysis of the Systolic Heart Failure Treatment With I, Inhibitor Ivabradine Trial (SHIFT) study underlined that HR reduction by itself explains the positive impact of ivabradine in HF. Other beneficial effects of ivabradine on endothelial function, oxidative stress, and atherosclerosis severity in mice are also probably mediated through HR reduction. There is no other known pharmacological target for the effect of ivabradine. In patients with stable CAD, ivabradine was shown in the phase 3 INternational TRial on the Treatment of angina with IVabradinE vs. atenolol (INITIATIVE) trial (n=939) not to be inferior to the β-blocker atenolol in terms of its antianginal and anti-ischemic effects. Furthermore, ivabradine (5 mg twice daily for 2 months followed by 7.5 mg twice daily for 2 additional months) provided additional antianginal and anti-ischemic efficacy in patients with residual symptoms despite β-blocker treatment, as demonstrated in the evaluation of the Antianginal efficacy and Safety of the A ssociation Of the If Current Inhibitor ivAbradine with a beTa-blockEr (ASSOCIATE) study (n=889).

HCN Channels and HF

HCN Blockade in Animal Models

The efficacy of ivabradine in HF has been shown in various animal models. In a rat model of myocardial infarction leading to HF, ivabradine significantly reduced left ventricular (LV) end-systolic but not end-diastolic diameter, which preserved cardiac output. Ivabradine also reduced LV diastolic dysfunction and both atrial and ventricular fibrosis in hypercholesterolemic rabbits. Angiotensin II and aldosterone levels after treatment with ivabradine were correlated with HR in that study. This beneficial impact of ivabradine on diastolic dysfunction was recently corroborated in another model. In a mouse model of angiotensin II–induced HF, both ivabradine and metoprolol led to a similar reduction in HR, but only ivabradine led to a significant improvement in LV systolic and diastolic function. This effect was associated with reductions in cardiac hypertrophy, fibrosis, inflammation, and apoptosis. Colin et al investigated the effects of ivabradine and atenolol on LV isovolumetric relaxation at rest and during treadmill exercise in chronically instrumented dogs. For a similar reduction in HR at rest and during exercise, ivabradine, in contrast to atenolol, did not exert any negative lusitropic effects.

In a rat myocardial infarction model, metoprolol (250 mg·kg−1·d−1) and ivabradine (10 mg·kg−1·d−1) had similar effects on HR reduction, and both treatments partially prevented deterioration of LV ejection fraction and reduced LV wall stress. Metoprolol partially prevented LV dilation, whereas ivabradine potentiated LV hypertrophy. However, in another study in severe post–myocardial infarction chronic HF in rats, ivabradine prevented the worsening of LV dysfunction and remodeling, and this was associated with a downregulation of cardiac renin-angiotensin-aldosterone system transcripts. Ivabradine has also been shown to induce reverse electrophysiological remodeling in a myocardial infarction model of HF in rats, underlining the importance of transcriptional and posttranscriptional mechanisms. The increase in I, after myocardial infarction was attenuated by ivabradine, and reduced HCN4 expression was associated with increases in both the microRNAs miR-1 and miR-133, which regulate the HCN2 and HCN4 genes. Finally, in a dog model of coronary stenosis and exercise leading to myocardial stunning, ivabradine reduced ineffective postsystolic LV wall thickening and modified it into ejectional thickening, thereby improving ventricular efficiency.

HCN Blockade in Patients With HF

The effect of a single intravenous dose of ivabradine on LV function was studied in patients with systolic dysfunction with echocardiography. The LV ejection fraction did not significantly decrease with ivabradine (0.2%) compared with placebo (1.7%). Other echocardiographic parameters such as fractional shortening and stroke volume were also unchanged after the intravenous administration of ivabradine. In a small study of 10 patients with advanced HF and severe LV systolic dysfunction (mean ejection fraction, 21%), intravenous administration of ivabradine reduced HR by 27%, increased stroke volume, and preserved cardiac output.
The first large trial of ivabradine dedicated to patients with LV systolic dysfunction and HF was the SHIFT study. This randomized, double-blind, placebo-controlled study included 6558 patients with symptomatic HF (equally distributed between classes II and III), with an LV ejection fraction ≤ 35% (mean ejection fraction at baseline, 29%), and in sinus rhythm with an HR of 70 bpm. These patients were admitted to hospital for HF within the previous year and were on stable contemporary background treatment, including a β-blocker if tolerated (89% were actually treated with a β-blocker). The placebo-corrected reduction in HR with ivabradine was 9.1 bpm at 1 year. Over a median follow-up of 22.9 months (interquartile range, 18–28 months), ivabradine led to an 18% relative risk reduction in the primary composite end point of cardiovascular death or hospitalization for worsening of heart failure (A), on hospitalization for worsening of heart failure (B), on death from heart failure (C), and on cardiovascular death (D). The placebo-corrected reduction in HR with ivabradine was 9.1 bpm at 1 year. Over a median follow-up of 22.9 months (interquartile range, 18–28 months), ivabradine led to an 18% relative risk reduction in the primary composite end point of cardiovascular death or hospital admission for worsening HF (hazard ratio, 0.82; 95% confidence interval, 0.75–0.90; P = 0.0001; 793 patients (24%) in the ivabradine group and 937 patients (29%) in the placebo group indeed experienced a primary clinical event during the study (Figure 4A). Iubradine was associated with relative risk reductions of 26% for both hospitalizations for worsening HF (672 [21%] placebo versus 514 [16%] ivabradine; hazard ratio, 0.74; 95% confidence interval, 0.66–0.83; P = 0.0001; see Figure 4B) and deaths caused by HF (151 [5%] versus 113 [3%]; hazard ratio, 0.74; 95% confidence interval, 0.58–0.94; P = 0.014; see Figure 4C). The reduction in cardiovascular deaths with ivabradine did not reach statistical significance (see Figure 4D).

In the placebo group of SHIFT, the risk of suffering a primary composite end point event increased by 3% with every beat increase in baseline HR. In the ivabradine group, there was a direct association between HR achieved at 28 days and subsequent cardiovascular outcomes. Patients with HR < 60 bpm at 28 days on treatment had fewer primary events during the study (event rate, 17.4%) than did patients with higher HR. The benefit of ivabradine was accounted for by the HR reduction, as shown by the neutralization of the treatment effect after adjustment for change in HR.

The effects of ivabradine on quality of life were evaluated in a subset of 1944 patients with HF in SHIFT. The reduction in HR with ivabradine was associated with improved health-related quality of life. Furthermore, the magnitude of HR reduction was related to the extent of improvement of quality of life. An echocardiographic substudy was also conducted in 411 patients with HF in SHIFT. Iubradine improved both LV end-systolic and end-diastolic volume indexes compared with placebo by −5.8 and −5.5 mL/m² (P < 0.001 and P = 0.002, respectively) from baseline to the 8-month follow-up, which translate into placebo-corrected reductions of 11 mL in both nonindexed LV end-systolic and end-diastolic volumes (Figure 5A and 5B). Iubradine also improved LV ejection fraction by a mean of 2.7% when corrected for placebo (P < 0.001). Thus, ivabradine induces reverse LV remodeling in patients with HF and LV systolic dysfunction.
Clinical Use and Side Effects of Ivabradine

The results mentioned above have been taken into consideration in the new European Society of Cardiology guidelines on HF, leading to a recommendation for ivabradine in patients with chronic heart failure and systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 35%) who were in sinus rhythm and had resting heart rate ≥ 70 bpm. A total of 411 patients with chronic heart failure and systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 35%) who were in sinus rhythm and had resting heart rate ≥ 70 bpm were randomly allocated to ivabradine or placebo. Complete echocardiographic data at baseline and 8 months are presented.

A. Treatment with ivabradine reduced left ventricular end-systolic volume index (primary substudy end point) vs placebo (−7.0 ± 16.3 vs −0.9 ± 17.1 mL/m²; difference, −5.1 mL/m²; SE, 1.6 mL/m²; 95% confidence interval, −8.8 to −2.7; P < 0.001). B. Left ventricular end-diastolic volume index was improved in the ivabradine group vs placebo (−7.9 ± 18.9 vs −1.8 ± 19.0 mL/m²; P = 0.002). Ivabradine also increased LVEF (2.4 ± 7.7% vs −0.1 ± 8.0% vs placebo; P < 0.001; not shown).

Clinical Use and Side Effects of Ivabradine

Bradycardia and phosphenes (transient enhanced brightness in a limited region of the visual field) are the most common side effects associated with the pharmacological action of ivabradine. The cardiac safety of ivabradine was specifically evaluated in the Holter substudy of morbidity-mortality EvAlUaTion of the IF inhibitor ivabradine in patients with CAD and left ventricular dysfunction (BEAUTIFUL), which included 840 patients. Although 93% of patients received concomitant β-blockers, the incidence of episodes of HR < 30 bpm during waking hours or during sleep was ≤ 1% in the ivabradine and placebo groups. No between-group difference in episode severity was observed, despite the fact that there were more patients with HR < 40 or < 50 bpm with ivabradine than with placebo (eg, asleep, 22% versus 5% for < 40 bpm and 77% versus 50% for < 50 bpm, respectively). Furthermore, there was no increase in the incidence of conduction or rhythm disturbances.

Phosphenes are related to the effect of ivabradine on related h channels in the retina. These visual symptoms are transient, do not interfere with quality of life, and have led to few withdrawals (24 of 2545 patients [< 1%] in a safety study). These visual side effects have been shown typically to resolve during treatment, as previously reported. In the BEAUTIFUL study of 10917 patients, < 1% of patients discontinued the treatment because of visual symptoms. Eosinophilia has been reported by the European Medicines Agency to occur uncommonly with ivabradine.

In the large SHIFT study in 6558 HF patients, fewer serious adverse events occurred in the ivabradine group than in the placebo group. The total number of serious adverse events, including cardiac and noncardiac serious events, was 3388 in the ivabradine group and 3847 in the placebo group (P = 0.025). Symptomatic bradycardia occurred in 150 patients (5%) in the ivabradine group and 38 patients (1%) in the placebo group (P = 0.001). Bradycardia led to permanent withdrawal from the study in 55 patients (2% in the ivabradine group and 1% in the placebo group).
the study in 48 patients (1%) on ivabradine and 10 patients (<1%) in the placebo group. Visual side effects were reported by 89 patients (3%) on ivabradine and 17 patients (1%) on placebo (P<0.0001), and <1% of patients withdrew from ivabradine because of them. There were no between-group differences in laboratory parameters. The good tolerability of ivabradine was also recently demonstrated in patients with asthma and chronic obstructive pulmonary disease, with no alteration in respiratory function or symptoms.97

HCN Channels and Arrhythmias

Human genetic and animal studies have highlighted the involvement of HCN channels in the pathophysiology of arrhythmias.98 In a canine model, upregulation of atrial HCN4 has been shown to promote atrial arrhythmias.99 Furthermore, overexpression of the human mineralocorticoid receptor in embryonic stem cells resulted in increased expression of HCN4 and other ion channels.100 In dogs undergoing atrial tachypacing and with evidence of impaired sinoatrial function, SAN HCN2 and HCN4 mRNA expression and HCN-related current densities were reduced (perhaps because of a lack of need owing to pacing).

HCN modulation could be of interest for therapeutic purposes when HCN channels are either upregulated (mainly in HF, as previously detailed, or in inappropriate sinus tachycardia) or downregulated (mainly in SAN disease). The best example of restoring HCN channel activity to treat an arrhythmia is provided by research on bioartificial pacemakers, which underline several important factors involved in arrhythmias, including the HCN channels, the ratio between \( I_{K1} \) and \( I_{K2} \) currents,98 and the distribution of different HCN subtypes among the cells.100 Strategies to restore biological activity of a deficient pacemaker involve either fusion of cells expressing large amounts of HCN1101 or HCN gene-based therapy.102 In terms of gene therapy, overexpression of an engineered HCN construct via somatic gene transfer has been used to fine-tune cardiac pacing in vivo.102 Focal transduction of this construct, a shorted S3-S4 linker to favor channel opening, in the left atrium of animals with sick sinus syndrome reproducibly induced a stable, catecholamine-responsive in vivo bioartificial node.

On the other hand, the best example of a therapeutic decrease in HCN channel activity (ie, blocking the \( I_{K1} \) current) for the treatment of an arrhythmia is the management of the inappropriate sinus tachycardia syndrome. Many case reports have suggested the efficacy and tolerability of the treatment of inappropriate sinus tachycardia with ivabradine. In addition, a study of 18 patients with a typical history of inappropriate sinus tachycardia showed that HR was significantly reduced by ivabradine and that tolerance to physical activity was increased, with a progressive rise in maximal load reached.103 Ivabradine has also been suggested to alleviate symptoms related to the postural orthostatic tachycardia syndrome. In a retrospective study of 18 patients, 8 patients reported reduced tachycardia and fatigue, 4 patients reported only reduced tachycardia, and 6 patients did not experience benefits.104

The safety of ivabradine in terms of its effects on arrhythmias was evaluated in the BEAUTIFUL study, a randomized, placebo-controlled trial of 10917 patients with stable CAD and an LV ejection fraction <40%.95 The primary composite end point in BEAUTIFUL was not affected significantly, although a hypothesis-generating analysis revealed that patients with a resting HR of ≥70 bpm at baseline appeared to benefit from ivabradine. The Holter substudy in BEAUTIFUL involved 840 patients who underwent 24-hour ambulatory ECG monitoring at baseline and 1 and 6 months.97 There was no increase in the incidence of conduction and rhythm disturbances with ivabradine.

Finally, HCN channels could be considered a common point between \( \beta \)-blockers and ivabradine. Ivabradine is a selective HCN channel antagonist, providing pure HR reduction, hence its usefulness in cardiovascular disease, including HF. The use of \( \beta \)-blockers is associated with side effects because of their actions on the neurohormonal system or effects on other targets. On the other hand, the impact of \( \beta \)-blockers on neurohormonal imbalance remains of interest against ventricular arrhythmias. \( \beta \)-Blockers are likely to be more effective in treating ventricular arrhythmias (eg, generated in areas of myocardial scarring) compared with HCN blockade, the effect of which is focused on the SAN. Therefore, \( \beta \)-blockers and ivabradine can be considered complementary drugs.

Conclusions

HR is a prognostic marker in a wide spectrum of individuals, including patients with HF, in whom it has been shown to be a risk factor for future cardiovascular clinical events. HCN channels play a significant role in cardiac pacemaker activity in animals and humans, and ivabradine is the only drug currently available clinically that specifically blocks HCN channels. HR reduction with the HCN channel blocker ivabradine reduces hospital admissions for worsening HF and deaths resulting from HF in patients with an LV ejection fraction <35%, HF, and an HR of at least 70 bpm (in sinus rhythm). Ivabradine has gained approval for the treatment of HF and angina in several regions of the world. The Study assessing the morbidity–mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease (SIGNIFY) trial (n=19000) is currently testing whether the HCN channel blocker ivabradine will also improve clinical outcomes of patients with stable CAD, without HF, and with a resting HR of ≥70 bpm.

Acknowledgments

Dr Tardif holds the Canada Research Chair (tier 1) in translational and personalized medicine and the Université de Montréal endowed research chair in atherosclerosis. We thank Dr Ekaterini Kritikou for her editing of and advice on the manuscript.

Source of Funding

This work was supported by grants from the Fédération Française de Cardiologie (Dr Roubille).

Disclosures

Servier has provided support for the research activities of Drs Roubille and Tardif. Drs Roubille and Tardif have received honoraria from Servier for lectures. Dr Tardif is cited as a coauthor in 1 patent on ivabradine.

References

Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29:2388–2442.


**Key Words:** arrhythmias | HCN channels | heart failure | heart rate | ivabradine
New Therapeutic Targets in Cardiology: Heart Failure and Arrhythmia: HCN Channels
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doi: 10.1161/CIRCULATIONAHA.112.000145

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