CONTEMPORARY REVIEW

The rationale for repurposing funny current inhibition for management of ventricular arrhythmia

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Management of ventricular arrhythmia in structural heart disease is complicated by the toxicity of the limited antiarrhythmic options available. In others, proarrhythmia and deleterious hemodynamic and noncardiac effects prevent practical use. This necessitates new thinking in therapeutic agents for ventricular arrhythmia in structural heart disease. Ivabradine, a funny current (I_f) inhibitor, has proven safety in heart failure, angina, and inappropriate sinus tachycardia. Although it is commonly known that funny channels are primarily expressed in the sinoatrial node, atrioventricular node, and conducting system of the ventricle, ivabradine is known to exert effects on metabolism, ion homeostasis, and membrane electrophysiology of remodeled ventricular myocardium. This review considers novel concepts and evidence from clinical and experimental studies regarding this paradigm, with a potential role of ivabradine in ventricular arrhythmia.

KEYWORDS Funny current; HCN; I_f; Ivabradine; Ventricular arrhythmia

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Introduction

Ventricular arrhythmias in myopathic hearts

Ischemic and nonischemic cardiomyopathies are the most common structural heart diseases associated with ventricular arrhythmia (VA). Despite prompt revascularization and initiation of β-adrenergic antagonists, a significant percentage of patients is still affected by VA in the early phase of myocardial infarction (MI).[1] There is substantial increase in the risk of life-threatening VAs over time, and sudden cardiac death accounts for one-half of all deaths in these patients.[2] In patients with heart failure, VA is associated with sudden death, hemodynamic decompensation, and pump failure death.[3] Although insertion of an implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy–defibrillator protects against sudden cardiac death and heart failure symptoms,[4,5] inhibition of recurrent VA is essential to prevent recurrent ICD therapy and maintain adequate biventricular pacing.[6]

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Antiarrhythmic approach in myopathic ventricle

Traditional ion channel modulation approaches usually are targeted at modifications of arrhythmia substrate (ie, conduction velocity and refractory period). These approaches have largely failed in myopathic ventricle due to complex structural and electrophysiological remodeling that predispose the ventricular myocardium vulnerable to the proarrhythmic effects of sodium channel blockers.[7–9] Some class I agents are poorly tolerated due to negative inotropic effects.[10] Long-term utilization of most class III agents is limited by increased torsadogenic risk.[11] A meta-analysis of class III agents demonstrated significant VA suppression by amiodarone in patients with structural diseases.[12] However, the antiarrhythmic efficacy of amiodarone is offset by noncardiac side effects, and long-term treatment increases in all-cause mortality.[13,14] The iodine component of amiodarone is postulated to be responsible for noncardiac toxicities, and dronedarone lacks the iodine component. However, dronedarone use in the heart failure population is associated with increased mortality.[15] β-Adrenergic antagonists modify both trigger and substrate of VA; however, the optimum dose of β-blocker is not tolerated by a significant number of at-risk patients due to detrimental effects on borderline hemodynamic conditions.[16] Considering the limitations of ion channel modulation in the myopathic ventricle and the fact that a drug that was developed as an antianginal and multi-ion

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channel modulator (amiodarone) is practically useful,[17] pursuing another drug with such pleiotropic effect is worthwhile.

Repurposing heart failure therapy as candidate drug

Ivabradine, an inhibitor of the hyperpolarization-activated cyclic nucleotide-gated (HCN) current, also known as the funny current (I_f), reduces the rate of spontaneous diastolic depolarization and spontaneous action potential firing in the sinoatrial node (SAN) of the heart. Despite the nonphysiological presence of I_f in ventricular myocardium, ivabradine has mortality benefits in the heart failure population.[18] Heart rate reduction and improvement of the diastolic interval are considered major mechanisms of clinical benefit.[18] However, studies suggest that funny channels are up-regulated in ventricular myocardium during remodeling of ischemia, hypertrophy, or heart failure.[19] Ivabradine is also demonstrated to exert a host of metabolic and electrophysiological effects other than funny channel inhibition.[20,21] Being a pure negative chronotropic agent, it does not affect myocardial contractility, vascular resistance, or blood pressure.[22] The present narrative review aims to re-evaluate the experimental and clinical data available regarding the potential role of ivabradine for modifications of trigger and substrate for VAs. The objective was to review the limited clinical data on VA, the experimental data supporting utility for VA, the basic concepts of I_f and potential mechanistic impact of ivabradine on the substrate, multi-ion channel modulation effect, and triggers of VA. We conclude the review by proposing a pathway to rigorously test the clinical utility.

Funny channels and ivabradine

The pacemaker function of the SAN is dependent on spontaneous, slow, and positive increase of membrane potential at the end of the previous action potential. When this diastolic depolarization reaches the threshold potential, generation of the subsequent action potential takes place. Activity of HCN channels generates a key membrane associated current (I_f) involved in the initiation of diastolic depolarization.[23] This pore-loop cation channel consists of 4 subunits, and each subunit contains 6 transmembrane segments (S1–S6) (Figure 1). The ion conducting pore is located between the S5 and S6 segments, and the positively charged S4 segment acts as a voltage sensor.[24] These channels are reported to conduct sodium, potassium, and calcium ions.[24,25] However, conductance of inward Na^+ current plays a major role in the generation of diastolic depolarization in physiological conditions.[24] Cyclic adenosine monophosphate (cAMP) binds to the cyclic nucleotide-binding domain (CNBD) in the cytosolic C-terminal portion of HCN channels, shifting the voltage-dependence of activation to more positive voltages and enhancing channel opening .[26] Four HCN channels isoforms are known (HCN1–HCN4), with HCN1, HCN2, and HCN4 being expressed in the SAN. Different HCN channel isoforms differ in activation voltage and activation kinetics. HCN4 is a dominant isoform in human SAN, atrioventricular node, and Purkinje fibers. HCN1 and HCN2 also contribute to I_f generation in the SAN. Apart from 4 homotetramers, several different heterotetrameric isoforms are described in different pathophysiological conditions.[19,27] Adrenergic stimulation and phosphodiesterase inhibitors can increase the intracellular cAMP level and thus the activity of I_f leading to an increase in the slope of diastolic depolarization resulting in tachycardia (Figure 1). Ivabradine, a nonselective HCN channel inhibitor, binds with open state of the channel and prevents cationic conduction.[28,29] This leads to a dose-dependent reduction in the slope of diastolic depolarization and a decrease in sinus rate (Figure 1). Apart from inhibition of I_f, ivabradine also reduces the expression of HCN channels.[30]

Ivabradine and clinical VA

In patients with chronic heart failure and reduced ejection fraction, the SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) study demonstrated a significant reduction in hospitalization and death from heart failure with ivabradine therapy.[18] However, VA burden was not monitored, and arrhythmic death was not a prespecified endpoint in the SHIFT trial.[18] Patients with high VA burden (history of ventricular tachycardia or ICD-ICD shock within 6 months before randomization) were excluded from the study, and only 3% of patients in the study group had ICD insertion.[18] Lethal VA contributes to HF hospitalization and pump failure death in the heart failure population, and sometimes it is difficult to distinguish the mode of death in this patient population.[31,32] Heart rate reduction leading to hemodynamic improvement and reversal of structural remodeling is one postulated mechanism of reduction of heart failure outcomes in the SHIFT trial.[33] However, in the experimental model, VA suppression by ivabradine is independent of the change of heart rate or structural remodeling.[34] There is a paucity of published clinical data on the utility of this agent in VA. Case reports on suppression of VA burden in heart failure and catecholaminergic polymorphic ventricular tachycardia have been published.[35,36]

Rationale for considering ivabradine in VA

Despite the relative paucity of clinical data, ivabradine suppresses VA in the spectra of experimental models including ischemic and nonischemic cardiomyopathy.[30,34,37] In a mouse model of dilated cardiomyopathy, ivabradine suppressed premature ventricular complexes (PVCs) and sustained VA as well as to improve survival.[34] However, ivabradine failed to modulate the electrophysiological substrate or autonomic balance in this model. In another murine model of nonperfused acute MI, ivabradine reduced spontaneous VA episodes, arrhythmic death, and total mortality.[30] Arrhythmia suppressions were observed in both the early and late phases of MI. A significant effect on heart rate, cytosolic calcium handling, and regional action

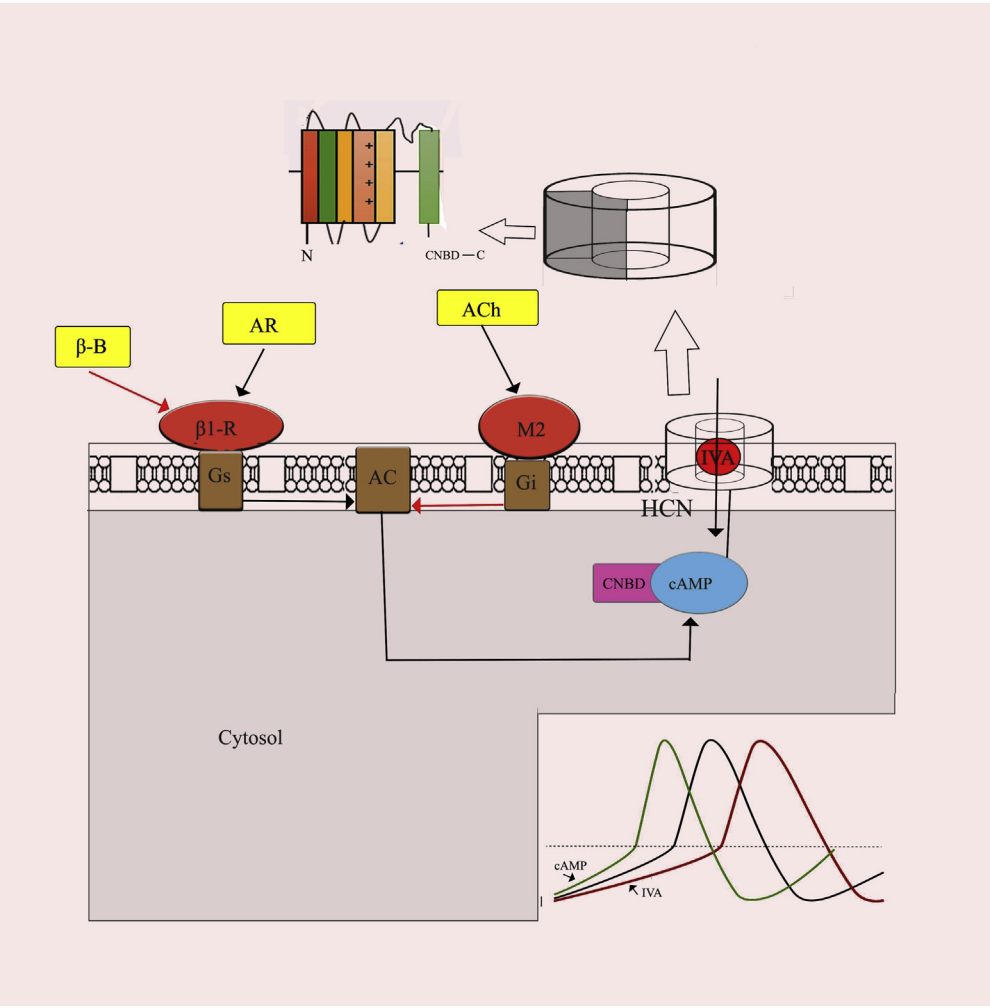

Figure 1 Ivabradine (IVA) and funny channel. Four protein subunits are organized around the pore. Each subunit contains 6 membrane-spanning segments. S1 *(red circle)* is the N-terminal segment, and S6 *(green circle)* is the C-terminal segment. The pore is located between S5 and S6. The S4 contains plenty of positively charged (+) amino acids. Hyperpolarization-dependent migration of positive charges toward a specific direction leads to conformational changes and opening of the channel. Opening of the channel leads to a flow of depolarizing current and diastolic depolarization (phase 4), followed by action potential (**inset:** *black curve*). A cyclic nucleotide-binding domain (CNBD) is located after S6 in the cytosol close to the C-terminal. Binding of cyclic adenosine monophosphate (cAMP) to CNBD causes a leftward shift of slope of phase 4 (**inset:** *green curve*). Binding of IVA to the hyperpolarization-activated cyclic nucleotide-gated channel (HCN) leads to channel inhibition and a rightward shift of phase 4 slope (**inset:** *red curve*). Adenylate cyclase (AC) is responsible for intracellular cAMP synthesis. β1-adrenergic receptor (β1-R) activation by adrenaline (AR) causes activation of AC by stimulatory and β1-adrenergic receptor antagonist (β-B) inhibits this stimulation. Activation of muscarinic receptor (M2) by acetylcholine (Ach) leads to inhibition of AC. Gi = inhibitory G-protein; Gs = stimulatory G-protein.

potential duration (APD) heterogeneity was also noted. Beneficial effects on autonomic balance due to hemodynamic improvement are also reported post-MI.[38] Transgenic mice with overexpression of HCN2 channel (HCN2-Tg) demonstrated an increased propensity to VA in response to chronic β-adrenergic stimulation without any change in ventricular structure or mechanical function.[34] Ventricular myocytes isolated from this model demonstrated generation spontaneous action potentials with isoproterenol treatment, and ivabradine inhibited isoproterenol-induced spontaneous diastolic depolarization, thus indicating the role of funny current (I_f) in the generation of VA in this model. Ivabradine reduces digitalis-induced VA without affecting the QT interval or APD.[37] However, prolongation of the effective refractory period was observed, suggesting the role of postrepolarization refractoriness (PRR). In this review we describe the possible molecular mechanisms by which ivabradine can modify VA trigger and substrate

Ivabradine in the modification of metabolic remodeling

Growing evidence supports the linking between deranged cardiac metabolism and formation of the arrhythmogenic milieu in cardiac pathologies.[39] This metabolic remodeling precedes electrophysiological and structural remodeling.[40–42] The metabolic aberrations contribute to arrhythmogenesis by altering cytosolic calcium handling and function of ion channels and transporters.[39] Posttranslational protein modification by O-linked N-acetylglucosamine is reported

in the remodeled ventricular myocardium.[43,44] O-linked N-acetylglucosamination (*O*-GlcNAc) of Ca^{2+}/calmodulin–dependent protein kinase II (CaMKII) and phospholamban (PLB) modulates calcium handling by ryanodine receptors (RyR2) and sarcoplasmic reticulum calcium ATPase type 2a (SERCA2a) (Figure 2). The effects of *O*-GlcNAC is independent of the phosphorylation status of CaMKII and PLB. *O*-GlcNAc of transcription factor sp1 also leads to a reduction of expression of SERCA2a. Abnormal calcium transients and trigger generation due to dysfunction of RyR2 and SERCA2a is associated with posttranslational *O*-GlcNAc of regulatory proteins.[45–47] UDP-GlcNAc, the glucosamine donor for *O*-GlcNAc, is generated from glucose via the hexosamine biosynthetic pathway. Ivabradine reduces the utilization of glucose in the hexosamine biosynthetic pathway, and increases glucose utilization in glycolysis and energy generation in normal and abnormal heart.[21,48] The metabolic benefit is independent of heart rate reduction.[21] Reduction of *O*-GlcNAc by ivabradine may be responsible for favorable cytosolic calcium dynamics (Figure 2) and explain the inhibition of

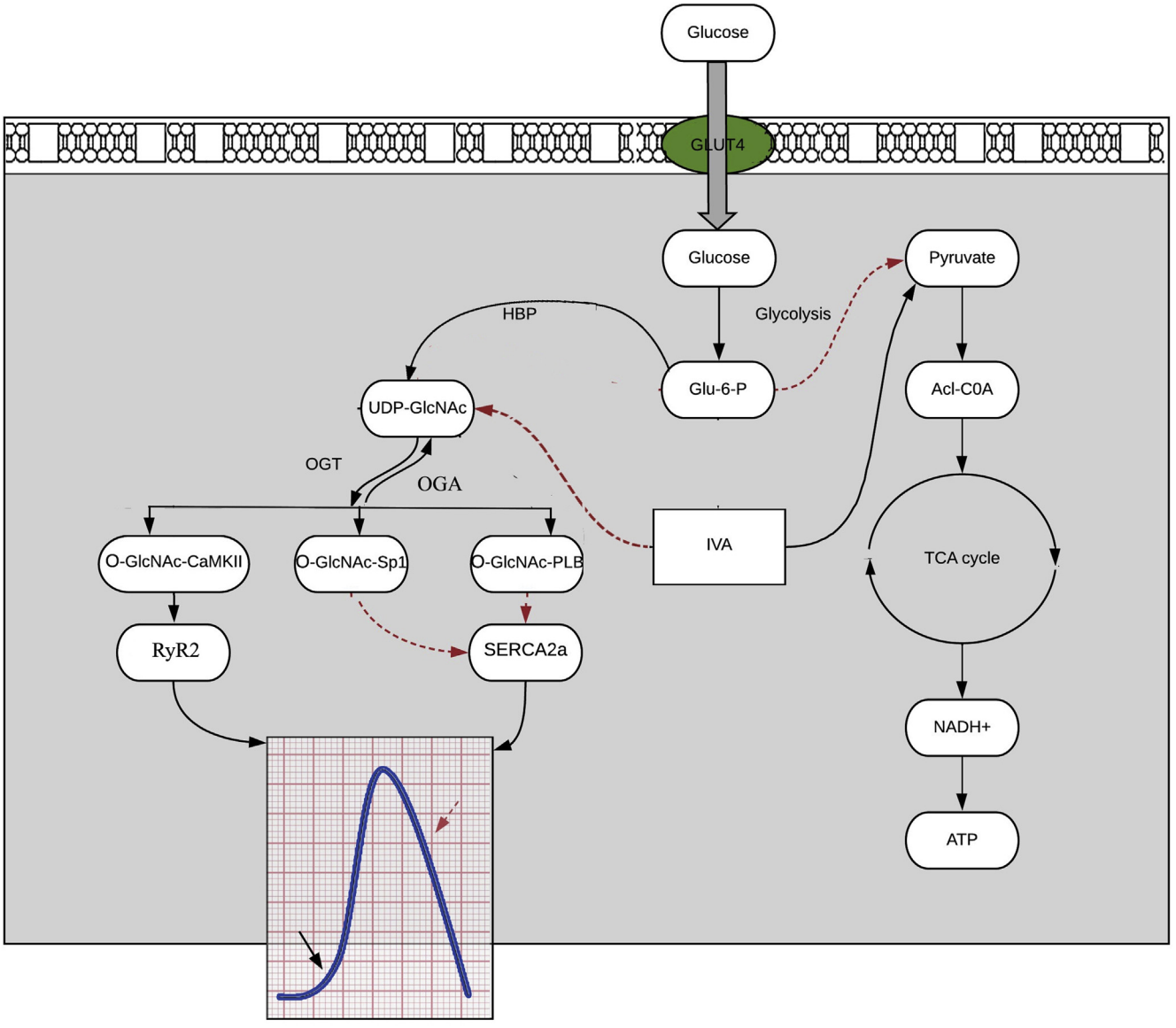

Figure 2 Ivabradine (IVA), metabolic remodeling, and cytosolic calcium dynamics. Following receptor-mediated (glucose transporter type 4 [GLUT4]) uptake, glucose is metabolized to glucose-6-phosphate (Glu-6-P). Glu-6-P is subsequently metabolized by glycolysis and the hexosamine biosynthetic pathway (HBP). UDP-GlcNAc is generated via HBP. UDP-GlcNAc is the substrate for O-linked N-acetylglucosamination (*O*-GlcNAc) of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), phospholamban (PLB), and transcription factor sp1. O-GlcNAc-CaMKII causes abnormal diastolic leak through the ryanodine receptor (RyR2). O-GlcNAc-Sp1 inhibits SERCA2a expression and O-GlcNAc-PLB disrupts the association of PLB to SERCA, leading to impaired Ca^{2+} uptake and diastolic calcium overload. Metabolic remodeling is associated with inhibition *(red dashed arrow)* of glycolysis and stimulation *(black arrow)* of HBP. IVA causes stimulation of glycolysis *(black arrow)* and inhibition *(red dashed arrow)* of HBP. **Inset:** Cytosolic calcium transient curve *(blue)*. Abnormal diastolic leak *(black arrow)* and impaired diastolic clearance *(red dashed arrow)* due to metabolic remodeling. Acl-COA = acetyl coenzyme A; ATP = adenosine trisphosphate; NADH = nicotinamide adenine dinucleotide; OGA = O-β-N-acetylglucosaminidase hexosaminidase; O-GlcNAc = O-linked N-acetylglucosamine; OGT = O-β-N-acetyl glucosaminyltransferase; SERCA2a = sarcoplasmic reticulum calcium ATPase type 2a; TCA = tricarboxylic acid.

proarrhythmic diastolic Ca^{2+} leak after MI in the absence of alteration of CaMKII phosphorylation.[30]

Potential role of ivabradine in preventing VA trigger

In experimental models, ivabradine modified both calcium-dependent and independent triggers of VA. Presence of HCN channels and I_f current-induced diastolic impulse generation has been documented in fetal ventricular myocardium.[49,50] Maturation leads to quantitative and qualitative changes in ventricular $I_{f,}$[50] and in adult heart these channels are mainly localized in the SAN and other regions of the conducting system.[19] Working ventricular myocardium in the adult heart is thought to contain a nonsignificant amount of HCN channels for any demonstrable physiological function, although it has been reported that HCN3 channels are functional in mouse ventricular myocardium where they affect action potential morphology.[51] Furthermore, like other fetal phenotypes, HCN is also demonstrated to be expressed in remodeled myocardium.[52] Neurohormonal activation can contribute to up-regulation of ventricular HCN.[53] The density of HCN channels in ventricular myocardium correlates with the severity of pathologic remodeling[54] and is greater in ischemic than in nonischemic heart.[55] This pathology-dependent functional expression of funny current may explain the higher propensity of VA in ischemic cardiomyopathy. Although increased expression of both HCN4 and HCN2 is noted, HCN4 is the predominant isoform in failed human ventricular myocardium.[56] Altered HCN expression is associated with increased density funny current and generation of spontaneous diastolic depolarization in the ventricle.[56–58] The funny current in diseased ventricular myocardium is of larger amplitude, is activated in less hyperpolarized membrane potential, deactivates slowly, and is more sensitive to adrenergic stimulation compared to cardiomyocytes from control heart.[56] The combination of quantitative and qualitative changes of HCN channels during ventricular remodeling likely predisposes the ventricle to abnormal automaticity (Figure 3).[52] Generation of ventricular spontaneous diastolic depolarization from active HCN channels can lead to PVC formation, and the PVC may act as a trigger for VA.[34] Increased sensitivity of funny current to adrenergic stimulants can explain the role of catecholamine in VA in the remodeled ventricle.[34,56] β-Adrenergic antagonists can inhibit I_f-induced trigger by decreasing cytosolic cAMP. Reduction of cytosolic cAMP by activation of muscarinic receptors (M2) may explain the protective role of the parasympathetic system against VA in heart failure.[59] Treatment with ivabradine is associated with a reduction of ventricular I_f current density and ventricular spontaneous diastolic depolarization, which is translated to reduced PVC burden in the animal model.[30,34,38,60] Ivabradine-induced reduction in ventricular HCN protein expression can also contribute to the reduction of I_f current.[30,60] Apart from reducing funny current–mediated automaticity, ivabradine also modulates Ca^{2+}-induced triggered activity in ischemic myocardium (Figure 3).[30] Reduction of abnormal diastolic calcium leak through RyR2 without any change in the phosphorylation status of CaMKII has been reported.[30] The exact mechanism is not known, and decreased Ca^{2+} sensitivity of RyR2 by ivabradine is postulated.[30] As described earlier, the metabolic effect of ivabradine can play a significant role in the modulation of cytosolic calcium dynamics. Besides inhibition of I_f-dependent and Ca^{2+}-dependent triggers, sodium channel blockade by ivabradine, as described earlier, may also contribute to reduction of VA burden by suppressing initiation of extrasystole.[20]

Potential role of ivabradine in modulation of VA substrate

Ivabradine inhibits a host of ion channels other than HCN, and multiple ion channel modulation can influence the VA substrate by modifying action potential configuration of ventricular myocardium (Figure 3). In cardiomyocytes separated from normal rabbit, canine, or human ventricle, ivabradine consistently inhibited the rapid component of delayed rectifier potassium current (I_{Kr}) due to structural homology between HCN and hERG (ether-a-go-go related gene) channels.[20,61,62] Despite significant inhibition of repolarization current, ivabradine induces only modest prolongation of APD[20,61,62] and heart rate–corrected QT interval (QTc).[63] Concurrent inhibition of the late component of the inward sodium current (I_{Na}) during the plateau phase of repolarization, as documented in the human-induced pluripotent stem cell–derived cardiomyocyte model, may compensate for the APD-prolonging effect of hERG inhibition.[61] Frequency- and dose-dependent reductions of maximum upstroke velocity (Vmax) of phase 0 of the action potential are reported with ivabradine on canine ventricular myocytes and myocytes from the normal human ventricle.[20] Inhibition of the fast component of the sodium current (I_{Na}) is postulated to be responsible for this effect.[20] An increase in PRR in digoxin-treated hearts can also be explained by sodium channel blockade.[37,64] Up-regulation of HCN channels can lead to a reduction of repolarization reserve by increasing depolarizing I_f current during the plateau phase of the cardiac action potential in remodeled myocardium.[65] The reduction of repolarization reserve plays a crucial role in proarrhythmic electrophysiological remodeling in these conditions.[65,66] Spatial dispersion of HCN channel expression between the left and right ventricles may also contribute to regional repolarization heterogeneity in the remodeled heart.[67,68] Dual inhibition of funny current and sodium current in this setting may be responsible for the improvement of repolarization reserve and regional dispersion of repolarization.[20,65] Funny current is described to be responsible for prolongation of phase 2 of the repolarization of the epicardial surface of the ventricle in structurally normal heart.[51,69] Inhibition of I_f by ivabradine in epicardium in the absence of any change in endocardium can contribute to modulation of transmural ventricular repolarization heterogeneity in a normal heart.[62] Contrary to normal myocardium, in the acute MI model,

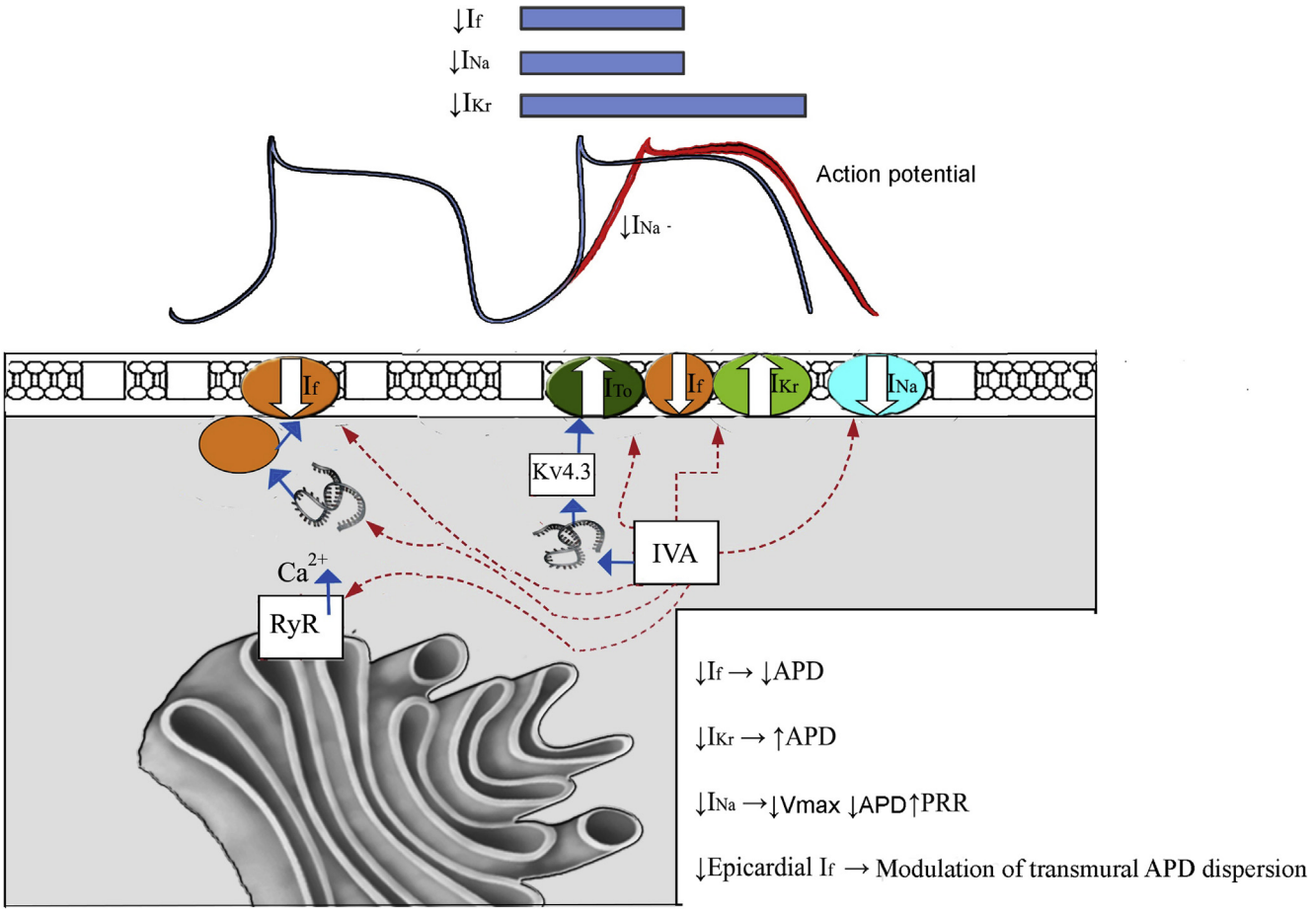

Figure 3 Effects of ivabradine (IVA) on ventricular depolarization and repolarization. Besides inhibition of I_f, IVA reduces expression of the hyperpolarization-activated cyclic nucleotide-gated channel (HCN), and inhibits rapid rectifier K^+ current (I_{Kr}) and sodium current (I_{Na}) in ventricular myocardium. Inhibition of phase 4 of diastolic depolarization leads to inhibition of trigger formation from remodeled myocardium. The effect of IVA on repolarization is dependent on the pathophysiological condition of the ventricular myocardium **(inset)**. Inhibition of I_{Kr} leads to prolongation of action potential duration (APD). Inhibition of the fast component of I_{Na} causes a reduction of maximum upstroke velocity (Vmax) of phase 0 of the action potential (AP) (*red line* in AP curve), which can lead to suppression of initiation of ventricular extrasystole. Inhibition of the slow component of I_{Na} during repolarization compensates for the APD prolongation by I_{Kr} and leads to prolongation of postrepolarization refractoriness. Inhibition of inward I_f current during phase 2 of the AP leads to improvement of repolarization reserve by IVA in hypertrophy failure remodeling. Late remodeling after myocardial infarction is associated with down-regulation of Kv4.3 and prolongation of APD. IVA prevents down-regulation of Kv4.3, leading to normalization of APD. In ischemic myocardium, IVA can also reduce diastolic calcium leak from the ryanodine receptor (RyR). Epicardium but not endocardium of normal ventricle contains scanty HCN3 channels. Funny current through these channels can contribute to the depolarization current of phase 2. Inhibition of this current can lead to modulation of transmural APD dispersion. *Red dashed arrows* indicate inhibitory signals. *Blue solid arrows* indicate stimulatory signals.

ivabradine reduces the regional dispersion of repolarization in the early and late phase after MI.[30] Improved perfusion, due to an increase in the diastolic interval, leading to less activation of ATP-activated K^+ channels in the border zone, is postulated to be responsible for the reduction of APD dispersion in the early phase of MI.[30,70] However, prevention of reduction of repolarizing current by ivabradine in the border zone may be responsible for the same in the late phase of MI.[30,71] Remodeling after MI is associated with a reduction of expression of repolarizing Kv4.3 or transient outward potassium current (I_{Kto}) channels in the infarct border zone leading to prolongation of APD in this area. At the same time, expression of KChip2 (auxiliary subunit I_{Kto}) is augmented in remote areas, leading to increased functional activity of the same channel and abbreviation of APD in remote areas. Different effects of ischemia on the action of I_{Kto} in 2 different areas (border zone vs remote areas) create repolarization heterogeneity in the ventricle. Treatment with ivabradine prevents the reduction of Kv4.3 expression and augmentation of KChip2 expression in the border zone and remote zone, respectively.[71] The effects mentioned can lead to reduction of APD dispersion in the ischemic ventricle.[30,71] Favorable action of ivabradine on APD dispersion in remodeled myocardium can explain the lower propensity to produce torsades de pointes arrhythmia despite QT prolongation.[72]

Summary

Management of VA in myopathic ventricle is challenging due to proarrhythmia and hemodynamic side effects of commonly used antiarrhythmic agents. Experimental data suggest that funny current in remodeled ventricular

myocardium is responsible for the generation of the trigger of VA. The overall effects of ivabradine on remodeled ventricle include inhibition of calcium-dependent and independent triggers and modification of arrhythmia substrate. Another advantage of ivabradine is the lack of effect on blood pressure and myocardial contractility.[22] Despite prolongation of QT, clinically significant torsades de pointes is not reported in the absence of concurrent drug administration.[72] Although sinus bradycardia, atrial fibrillation, and transient visual disturbances are reported side effects, these conditions rarely require discontinuation of therapy.[18,29] While reviewing the potential mechanisms of action of ivabradine on ventricular metabolic and electrophysiological remodeling, we have extrapolated concepts from animal models in which it has been investigated extensively. Ventricular electrophysiology in animal cardiomyocytes is different from that in humans in many aspects, so we caution readers to use the pieces of evidence from experimental studies as concept-generating only. In conclusion, ivabradine, originally developed as a heart rate–lowering agent to treat angina pectoris, demonstrates multi-ion channel modulating and metabolic pleiotropic effects on remodeled ventricular myocardium, which has been translated into a reduction of VA burden in experimental models. Unlike conventional antiarrhythmic agents, this drug can be used safely in cardiomyopathies without any significant concern of worsening mortality. Postulates discussed in this article need to be validated in large prospective clinical trials with a prespecified endpoint of VA reduction to establish the efficacy of this concept.

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