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CURRENT OPINION

Ivabradine: Cardioprotection By and Beyond Heart Rate Reduction

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Abstract Ivabradine inhibits hyperpolarization-activated cyclic nucleotide-gated channels in the sinus node, thereby reducing heart rate, and heart rate reduction improves regional myocardial blood flow and contractile function in ischemic myocardium. Accordingly, ivabradine reduces anginal symptoms in patients with stable coronary artery disease but does not improve their clinical outcome. Heart rate reduction with ivabradine in patients with symptomatic heart failure reduces symptoms, attenuates remodeling, and improves clinical outcome. In pigs and mice, ivabradine reduces infarct size from myocardial ischemia/reperfusion, even when heart rate reduction is abrogated by atrial pacing. Improved viability is also observed in isolated ventricular cardiomyocytes subjected to simulated ischemia/reperfusion. These beneficial effects are attributed to reduced reactive oxygen species formation from the mitochondria. There is also evidence for a heart rate-independent benefit from ivabradine in the vasculature of mice and humans, and in left ventricular contractile function of pigs. Finally, in mice, ivabradine also has anti-aging potential.

Key Points

Ivabradine reduces symptoms but does not improve clinical outcome in patients with chronic stable angina; however, it reduces symptoms and improves clinical outcome in patients with heart failure.

The beneficial effects of ivabradine are related to heart rate reduction, but ivabradine also has pleiotropic effects that are related to attenuated formation of reactive oxygen species in cardiomyocyte mitochondria.

1 Introduction

Ivabradine reduces heart rate by inhibition of hyperpolarization-activated cyclic nucleotide-gated channels and their I_f current in the sinus node [1, 2]. It is clinically used in the treatment of chronic stable angina and heart failure [3, 4].

2 The Role of Heart Rate in Myocardial Ischemia/Reperfusion

Increased heart rate results in proportionate increases in myocardial oxygen consumption [5–7]. Concomitantly, diastolic duration is overproportionately reduced [8]. With healthy coronary circulation, metabolic vasodilation is powerful enough to compensate for the decreased diastolic duration and accommodate the increased oxygen demand with increased oxygen supply [8, 9]. However, in the

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presence of atherosclerotic narrowing/stenosis of an epicardial coronary artery and coronary microvascular dysfunction, the scenario is very different: increased heart rate increases the hemodynamic severity of the coronary stenosis [9], and eventually the potential for coronary vasodilation distal to the stenosis is largely exhausted to compensate for the stenosis and maintain normal coronary blood flow at rest, but further vasodilation to increase coronary blood flow in response to increased heart rate is no longer possible [9]. On the contrary, the decreased diastolic duration now even reduces coronary blood flow. The reduction in coronary blood flow with increased heart rate particularly affects the more vulnerable subendocardial layers of the myocardium [10, 11]. In this scenario, collateral blood flow from the adjacent myocardium is also reduced with increased heart rate because the driving pressure gradient for collateral blood flow is reduced. On the one hand, metabolic vasodilation in the intact donor coronary circulation decreases perfusion pressure at the origin of collaterals. On the other hand, pressure at the orifice of collaterals into the post-stenotic coronary circulation is increased since the post-stenotic coronary vascular bed is already maximally dilated in compensation for the stenosis, and decreased diastolic duration then reduces coronary blood flow or, conversely, increases coronary resistance [12].

Reduction in heart rate by ivabradine reverses the above unfavorable blood flow redistribution and improves both regional blood flow and regional contractile function in ischemic myocardium [13]. In contrast to β-blockade, which also reduces heart rate and improves blood flow to the ischemic myocardium [14], ivabradine has no negative inotropic effect. Importantly, in contrast to β-blockade, ivabradine does not unmask α-adrenergic coronary vasoconstriction [15–18] during sympathetic activation, e.g. by exercise [19] and, thereby, unlike β-blockade [20], does not reduce coronary blood flow in the absence of heart rate reduction.

The effects of β-blockade and the unmasking of α-adrenergic coronary vasoconstriction by β-blockade have been discussed controversially. In fact, β-blockade reduces oxygen consumption in non-ischemic myocardium more than ivabradine at equivalent heart rate reduction [21]. As long as heart rate is reduced, β-blockade also induces a favorable blood flow redistribution towards the ischemic myocardium during sympathetic activation [22, 23] but, in the absence of heart rate reduction, β-blockade reduces regional myocardial blood flow and contractile function in exercise-induced myocardial ischemia [20]. α-Adrenergic coronary vasoconstriction during sympathetic activation has been proposed to maintain a uniform transmural blood flow distribution [24], but this idea remains contentious [25]. α-Adrenergic coronary vasoconstriction during sympathetic activation has also been proposed to cause a more favorable blood flow distribution towards the ischemic myocardium [26], but again this idea is contentious [16]. The available clinical studies all support a deleterious role for α-adrenergic coronary vasoconstriction in myocardial ischemia [18, 27–31], and therefore lack of α-adrenergic coronary vasoconstriction is an advantage of ivabradine.

3 Ivabradine in Chronic Stable Angina

Several smaller proof-of-concept trials demonstrated symptomatic efficacy of ivabradine in terms of reduced anginal pain and better exercise tolerance [32–36]. In the large BEAUTIFUL (Morbidity-mortality evaluation of the IF inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) trial in patients with stable coronary artery disease and left ventricular systolic dysfunction, ivabradine did not reduce the primary composite endpoint of cardiovascular death or hospitalization for new-onset or worsening heart failure [37]. In a subsequent subgroup analysis of BEAUTIFUL, ivabradine reduced hospitalization for myocardial infarction and coronary revascularization, particularly in patients with angina at baseline and a resting heart rate $\geq$70 per min [38]. The reduction of these endpoints (75 % reduction in hospitalization for myocardial infarction and 59 % reduction in coronary revascularizations) appeared largely out of proportion for the small placebo-corrected heart rate reduction (by 7 beats per min) [39]. In the more recent, large SIGNIFY (Study assessing the morbidity-mortality benefits of the IF inhibitor ivabradine in patients with coronary artery disease) trial in patients with stable coronary artery disease without clinical heart failure, ivabradine did not reduce the primary composite endpoint of death from cardiovascular causes or non-fatal myocardial infarction [40]. In patients with activity-limiting angina, ivabradine even increased the incidence of the primary endpoint. It is unclear whether or not the excess of primary endpoints in patients with symptomatic angina with ivabradine relates to its failure to blunt adrenergic responses. Clearly, in the future, patients who may benefit from ivabradine must be carefully selected, and it is possibly worthwhile to consider a combination of β-blockade and ivabradine. Thus, heart rate reduction with ivabradine appears to improve symptoms, but not clinical outcome, in patients with stable coronary artery disease; this is also true for all other antianginal drugs on the market.

4 The Role of Heart Rate in Heart Failure

Increased heart rate results in increased contractile function—the so-called Treppe or Bowditch effect. The Treppe phenomenon varies among species and reflects improved excitation–contraction coupling kinetics that are not clear in detail [41–43], but includes interaction with β-adrenergic activation [44, 45]. Interestingly, increased contraction

frequency is associated with increased formation of reactive oxygen species in isolated adult rat ventricular cardiomyocytes [46]. In preparations from failing myocardium, the Treppe is reversed [43], such that contractile function decreases with increased heart rate. The relationship between d*P*/d*t*(max) and heart rate is positive in healthy human hearts but flat in failing human hearts [47]. Sustained increases in heart rate by atrial or ventricular pacing induce left ventricular dysfunction and the clinical symptoms of heart failure (dyspnea, cachexia, congestion, exercise intolerance) [41, 48–50], and pacing-induced heart failure is an established animal model for the study of heart failure [51]. Sustained tachyarrhythmias also induce heart failure in patients [52–54].

5 Ivabradine in Heart Failure

Resting heart rate is an independent predictor of all-cause mortality in the general population [55]. In the SHIFT (Systolic heart failure treatment with the IF inhibitor ivabradine trial) trial, an increase in heart rate increased the primary composite endpoint of cardiovascular death or hospitalization for worsening heart failure in patients with symptomatic heart failure [56]. Previous large trials in patients with symptomatic heart failure using a variety of drugs had suggested an association of mortality reduction with heart rate reduction [57, 58]. In the SHIFT trial in patients with symptomatic heart failure and resting heart rate $\geq$70 min, ivabradine reduced the primary composite endpoint of cardiovascular death or hospitalization for worsening heart failure, largely through reduced hospitalization for heart failure and death from heart failure [59]. In the echocardiographic substudy of the SHIFT trial, ivabradine reversed left ventricular remodeling [60]. Thus, ivabradine in patients with symptomatic heart failure not only reduced symptoms but also improved clinical outcomes. When comparing the effects of heart rate reduction by ivabradine in coronary artery disease and heart failure, it has to be kept in mind that mortality in stable coronary artery disease is much less than in heart failure, and that associations of heart rate with mortality may be stronger in heart failure than in coronary artery disease. In fact, in the general population, heart rate is an independent predictor of all-cause mortality, but not for coronary events [55].

6 Pleiotropic Action of Ivabradine

In parallel with the BEAUTIFUL trial, we conducted an experimental study in anesthetized open-chest pigs with 90 min severe hypoperfusion of the left anterior descending coronary artery and 120 min reperfusion, which mimics the clinical situation of an acute coronary syndrome [13]. Regional myocardial blood flow was measured with microspheres, regional contractile function was measured with sonomicrometry, and infarct size was measured with triphenyl tetrazolium staining. When administered before ischemia, ivabradine reduced heart rate, improved ischemic regional myocardial blood flow and contractile function, and reduced infarct size. The improvements of ischemic regional myocardial blood flow and contractile function were reversed by atrial pacing, which abrogated any heart rate reduction. Surprisingly, the reduction of infarct size largely persisted in the absence of heart rate reduction. Similar findings were observed when ivabradine was administered only 15–20 min after the onset of myocardial ischemia. Infarct size was still reduced, even when ivabradine was administered only immediately before reperfusion and when heart rate reduction is abrogated by atrial pacing (Fig. 1). These data suggested that ivabradine improved ischemic regional blood flow and contractile function through reduction

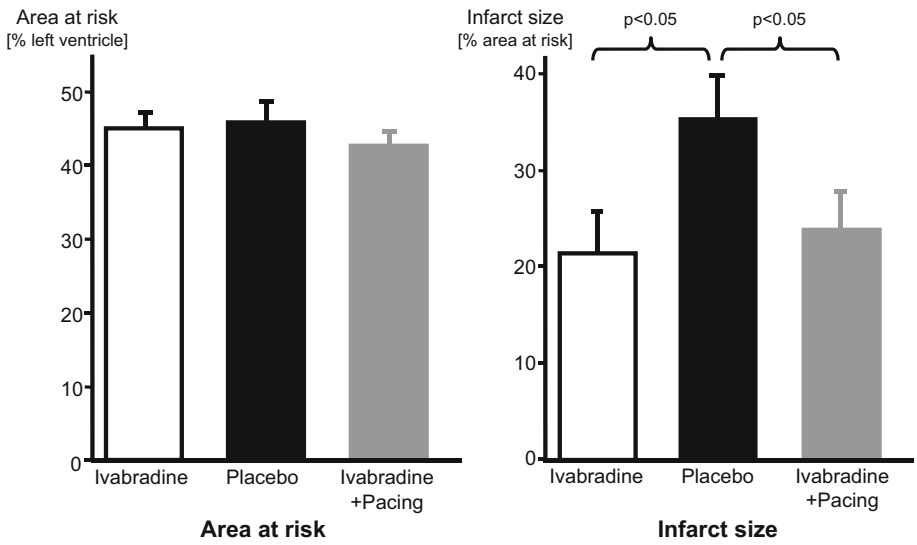

Fig. 1 Area at risk and infarct size in pigs with 90 min myocardial ischemia and 120 min reperfusion. Ivabradine, when administered 5 min before reperfusion, reduced infarct size along with heart rate reduction, and also in the absence of heart rate reduction. From Heusch and Yoshimoto [13]

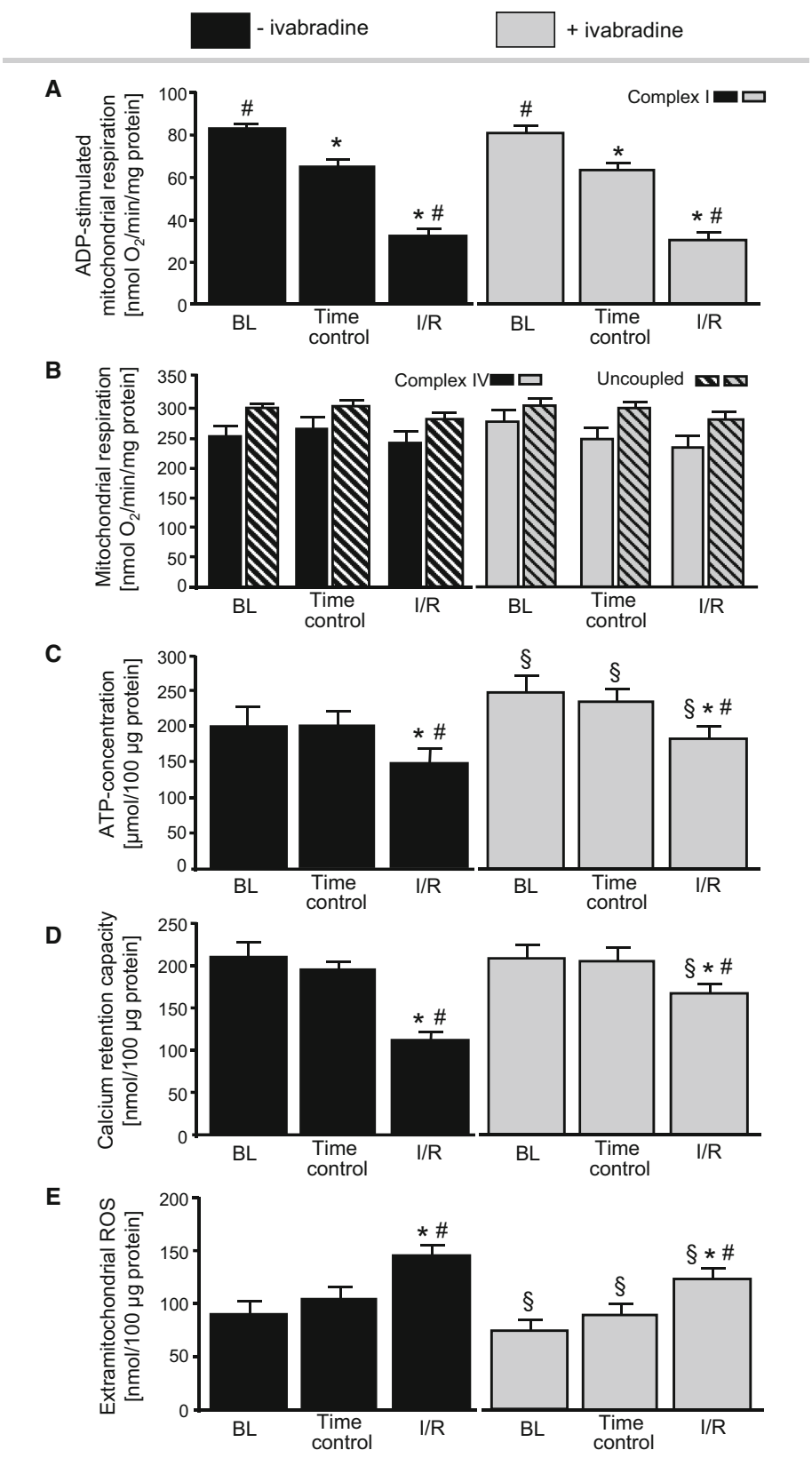

Fig. 2 Effects of simulated I/R vs. BL and a time-matched control in the absence and presence of ivabradine on ADP-stimulated complex I respiration, complex IV and uncoupled respiration, ATP concentration, calcium retention capacity, and ROS formation. I/R reduced ADP-stimulated complex I respiration, ATP concentration and calcium retention capacity, and increased ROS formation. Ivabradine improved ATP concentration and calcium retention capacity and attenuated ROS formation. *I/R* ischemia/reperfusion, *BL* baseline, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *ANOVA* analysis of variance, *ROS* reactive oxygen species. $^{*}p < 0.05$ vs. BL; $^{\S}p < 0.05$ vs. without (−) vs. with (+) ivabradine; $^{\#}p < 0.05$ vs. time control, using two-way ANOVA for repeated measures and Fisher's post hoc tests. From Kleinbongard et al. [62]

in heart rate, but that the reduction of infarct size was through a heart-rate-independent effect on reperfusion injury. This cardioprotective effect was called pleiotropic, and was speculatively attributed to reduced reactive oxygen species formation [61]. In a subsequent experimental study in anesthetized, open-chest mice with 30 min coronary occlusion and 120 min reperfusion, the heart-rate-independent reduction of infarct size by ivabradine was confirmed [62]. Ivabradine also improved the viability of freshly isolated adult murine ventricular cardiomyocytes that were exposed to simulated ischemia/reperfusion, and also reduced the formation of reactive oxygen species. To determine the source of reactive oxygen species formation that was sensitive to ivabradine, we isolated mitochondria from mouse hearts and measured their respiration at complex I, adenosine triphosphate (ATP) production, reactive oxygen species formation, and calcium retention capacity. Ivabradine had no impact on complex I respiration but reduced reactive oxygen species formation and improved ATP production and calcium retention capacity (Fig. 2). Actions of ivabradine through hyperpolarization-activated cyclic nucleotide-gated channels in ventricular cardiomyocytes rather than specific sinus node cells have been previously reported [63, 64], particularly in failing human hearts [65, 66]. Thus, in our model of an acute coronary syndrome, ivabradine reduced infarct size, most likely through attenuated formation of reactive oxygen species in cardiomyocyte mitochondria.

In the VIVIFY (Evaluation of the intravenous IF inhibitor ivabradine after ST-segment elevation myocardial infarction) trial, ivabradine, when administered during reperfusion to patients with acute ST-segment elevation infarction, did not reduce biomarkers reflecting infarct size (creatine kinase muscle-brain or troponin *I* or *T*), but the drug was administered "at least 1 h after the end of the percutaneous coronary intervention", and thus too late to exert cardioprotection [67–69].

Ivabradine also improved left ventricular function in conscious pigs with chronic hypertension, even when heart rate reduction was abrogated by atrial pacing [70]. The attenuation of stunning in conscious dogs with exercise-induced myocardial ischemia [71], and in patients with stable coronary artery disease following exercise-induced myocardial ischemia by ivabradine [72], might also be due, in part, to reduced formation of reactive oxygen species which play a causal role in stunning [73].

Reduced reactive oxygen species formation in the vascular wall of atherosclerotic apolipoprotein E-deficient mice has also been previously reported, but was attributed to reduced NADPH oxidase activity secondary to reduced shear stress at reduced heart rate [74]. Improved vascular function has also been reported in dyslipidemic mice chronically treated with ivabradine when endothelium-mediated vasodilation was determined ex vivo, i.e. in the absence of concomitant heart rate reduction [75]. Finally, improved coronary flow velocity reserve was reported with ivabradine in patients with stable coronary artery disease when heart rate reduction was abrogated by atrial pacing [76]. In another study in patients with stable coronary artery disease, ivabradine and bisoprolol reduced heart rate to the same extent, but ivabradine improved coronary flow velocity reserve to a significantly greater extent, again supporting the notion of a pleiotropic action of ivabradine on the coronary circulation [77].

We realize that in the above experimental studies supporting a pleiotropic action of ivabradine, the dose of ivabradine was substantially higher than in clinical trials or in clinical practice where heart rate is reduced by no more than 10 beats/min. It remains to be seen whether or not the reported pleiotropic effects of ivabradine in the above experimental and clinical studies have clinical relevance.

7 Anti-Aging Effect of Ivabradine

There is the long-held popular belief that there is a fixed number of heart beats for each individual throughout its life, and indeed there is an inverse relation between

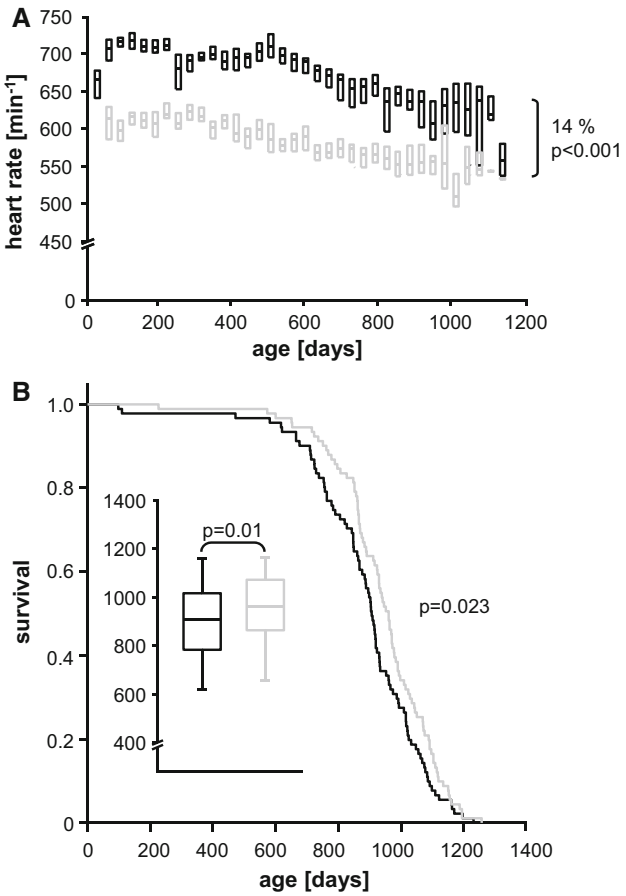

Fig. 3 Life-long treatment with ivabradine in mice reduced heart rate by 14 % and prolonged lifespan by 6.2 %. From Gent et al. [79]

lifespan and heart rate across different species [78]. We tested the idea by comparing survival curves of placebo-treated mice and mice chronically treated with ivabradine, and found a 14 % chronic heart rate reduction associated with a 6.2 % increased lifespan; the mechanistic role of heart rate reduction versus the pleiotropic actions of ivabradine in this study is not clear [79]. Our study confirms a prior study in mice in which a heart rate reduction of approximately 50 % with digoxin had enhanced lifespan by 20 %, but digoxin also reduced body weight to the same extent [80], such that an effect through caloric restriction, which also prolongs lifespan [81], could not be excluded. We realize that a mouse model, with its relatively short lifespan and its high heart rate, is quite remote from the human situation (Fig. 3).

8 Conclusions and Perspective

In myocardial ischemia/reperfusion, as expected from hemodynamics, heart rate reduction by ivabradine improves regional myocardial blood flow and contractile function and attenuates anginal symptoms, but, surprisingly, does not improve clinical outcomes. Careful selection of patients with stable coronary artery disease who may benefit from ivabradine is mandatory. In contrast, in heart failure, ivabradine not only reduces symptoms but also improves clinical outcomes in close association with heart rate reduction, although the (sub)cellular mechanisms of this benefit are not clear in detail. In the experiment, ivabradine reduces infarct size in the absence of heart rate reduction, and this benefit is attributed to reduced formation of reactive oxygen species from the mitochondria. Heart-rate-independent effects that are possibly also related to reduced formation of reactive oxygen species are also observed in vascular function and left ventricular function in a few studies, but further studies are needed to determine the sources and exact nature of reactive oxygen species, the precise targets for ivabradine, and their sensitivity at clinically used concentrations. For the effect of ivabradine on mitochondrial function, it remains to be determined whether it occurs through inhibition of mitochondrial hyperpolarization-activated cyclic nucleotide-gated channels, for which molecular biology and/or electrophysiological studies are needed. In addition, a clinical trial to look at the effects of ivabradine on myocardial ischemia/reperfusion injury appears worthwhile, i.e. in patients with ST-segment myocardial infarction undergoing primary percutaneous coronary interventions, or in patients undergoing cardiac surgery under cardiopulmonary bypass with ischemic cardioplegic arrest. In such a scenario, blood and tissue samples could probably be taken to substantiate a potential effect of ivabradine on reactive oxygen species.

Compliance with Ethical Standards

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