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Heart Rate Slowing by I_f Current Inhibition

Editors
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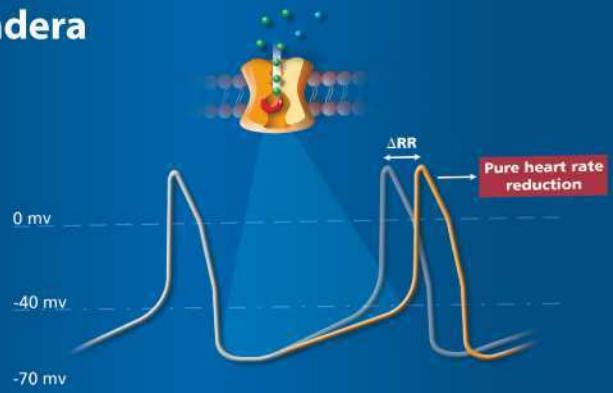

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Heart Rate Slowing by I_f Current Inhibition

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Volume Editors

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Contents

Foreword

Those animals that live long lives tend to have slower heart rates. Several plausible theories suggest that this may not be a chance association but that the slower heart rate may have a causal relationship to the longer life. Many large population studies have also shown that a slower heart rate is associated with a longer life in the general population, in elderly subjects, and in patients with stable coronary artery disease, hypertension, or myocardial infarction. Similarly, slowing the heart rate with β-blockers in patients after myocardial infarction or when presenting with heart failure extends life in proportion to the degree by which the heart rate is slowed.

The normal heart rate at rest is usually defined as 60–100 beats per minute. Much evidence suggests that the human resting heart rate should certainly be less than 90 beats per minute. However, the optimum has not been defined. A faster heart rate may be a sign of inappropriate autonomic balance with hazardous sympathetic tone outweighing protective parasympathetic effects. Sinus tachycardia is seen in those that are unfit and those that have disease. The arrhythmia may particularly reflect underlying cardiac disease. It may also cause heart disease by damaging atherosclerotic plaques, by provoking myocardial ischemia or by inducing inefficient cardiac hemodynamics.

A variety of medications may be utilized to slow the heart rate for therapeutic purposes. β-Adrenergic blocking agents are the most commonly used, but the nondihydropyridine calcium channel antagonists also slow the pulse. About a decade ago, a new class of potential pharmaceuticals emerged which inhibited the I_f transmembrane current which is specifically responsible for the diastolic depolarization of pacemaker cells within the sinus node. Initial

attempts to develop a medicinal product with this mechanism of action were thwarted by unwanted effects such as hypotension and QT prolongation (due to I_{Kr} blockade). Recently, ivabradine, which selectively inhibits the I_f current and has virtually no other demonstrable effect on the heart, has been successfully developed and approved for clinical use in patients in sinus rhythm who have angina, and in whom ß-blockade is contraindicated or poorly tolerated.

The ability to slow the heart rate is a cornerstone therapy for the symptomatic management of angina pectoris since decreased cardiac systole reduces the oxygen demand whilst at the same time longer cardiac diastole increases the supply of oxygenated blood to the myocardium. Titrating the heart rate with an agent which only affects the discharge frequency of the sinus node provides a simple method to mitigate angina without encountering unwanted adverse events. The results of the development program for ivabradine demonstrate impressive antianginal efficacy and only few complications from therapy. Not surprisingly, more new molecules with I_f inhibition activity are now being actively investigated.

As yet, there is no information about the potential prognostic value of pure heart rate reduction such as that which might be achieved with I_f inhibition. However, several studies are now underway to evaluate the effect of ivabradine on the survival of patients with coronary artery disease and poor left ventricular function or significant left ventricular failure. Whether lowering heart rate per se will prolong life is not yet known but it may offer a new and important life saving strategy.

In this volume, experts in the investigation of cardiac pathophysiology and the management of heart disease discuss the new and exciting development of I_f inhibition for the control of angina pectoris and potentially for the prolongation of life.

A. John Camm
Michal Tendera

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Heart Rate: A Risk Factor for Cardiac Diseases and Outcomes?

Pathophysiology of Cardiac Diseases and the Potential Role of Heart Rate Slowing

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Abstract

Several cohort studies have shown that increasing heart rate (HR) is a predictor of cardiovascular mortality in apparently healthy subjects, independent of several other potential coronary risk factors. Increased resting HR is also a well-known negative prognostic sign in patients with acute myocardial infarction (MI) and in those with heart failure. The predictive value of HR in MI patients extends at long-term follow-up, is independent of most clinical parameters, including left ventricular function, and seems maintained in the modern era of aggressive reperfusion treatment. In accordance with these data, numerous clinical studies have demonstrated that β-blockade, which decreases HR, has significant favorable clinical effects in patients with a history of acute MI or heart failure. Although the unfavorable prognostic effect of HR may reflect the deleterious effect of a sympathovagal imbalance, characterized by sympathetic predominance and vagal depression, several data suggest that HR may by itself cause negative effects on cardiovascular function, inducing an increase in cardiac work and myocardial oxygen consumption and a reduction of the diastolic time, with a reduction of time of myocardial blood supply, both conditions favoring the development of myocardial ischemia, besides facilitating arrhythmias in myocardial ischemic areas, by reentry mechanisms. Thus, a reduction of HR might have direct beneficial clinical effects, as also suggested by experimental findings.

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Heart rate (HR) is one of the physiological parameters most frequently assessed by physicians in daily practice. Its simple measurement by pulse palpation may indeed provide important clinical information. For instance, an accelerated pulse rate may be a clue to several cardiac and noncardiac diseases.

Accordingly, a large number of cohort studies in the past years have tried to establish whether HR measurement may portend significant prognostic implications in cardiac patients or even in apparently healthy subjects.

Prognostic Role of Heart Rate

Heart Rate in Asymptomatic Subjects

Several studies have shown that increasing HR is predictive of clinical events in asymptomatic subjects. Dyer et al. [1] examined the associations between HR and survival in three groups of middle-aged white males in Chicago, followed from 5 to 17 years. Mortality from both cardiovascular and noncardiovascular causes increased with increasing HR. Furthermore, HR was independently associated with all-cause mortality after adjustment for age and with sudden coronary artery disease (CAD) death and noncardiovascular death in 2 of 3 studies after adjusting for age, blood pressure, cholesterol, smoking and weight, whereas the association with other cardiovascular deaths and with nonsudden CAD death appeared to be secondary to the associations with other cardiovascular risk factors.

Analyzing data from the NHANES-I Epidemiologic Follow-Up Study, Gillum et al. [2], over a follow-up period of 6–13 years, found associations between HR and risk of ischemic heart disease and of cardiac and noncardiac death, even after adjustment for multiple risk factors. Risk-adjusted cardiovascular mortality for HR >84 bpm versus HR <74 bpm was 1.44 [95% confidence interval (CI), 1.08–1.92] and 1.52 (95% CI, 0.86–2.7) in white and black men, respectively, and 1.26 (95% CI, 0.89–1.76) and 3.03 (95% CI, 1.46–6.28) in white and black women, respectively. The association with cardiovascular death was particularly striking in black women.

Similar results were also reported in European populations. In a Swedish cohort of 10,004 men, the risk of cardiovascular mortality increased with the increase of HR [3]. In a French population of 19,386 subjects, aged 40–69 years, men with an HR of 60–80, an HR of 81–100, and an HR >100 bpm had a risk of cardiovascular mortality, after adjustment for other risk factors, of 1.35 (95% CI, 1.01–1.80), 1.44 (95% CI, 1.04–2.00), and 2.18 (95% CI, 1.37–3.47), respectively, compared to subjects with an HR <60 bpm. In women, HR did not influence cardiovascular mortality [4] (fig. 1). However, HR was a significant predictor of noncardiovascular mortality in both sexes.

Seccareccia et al. [5], in the MATISS project, tested the role of HR in the prediction of mortality in a low-risk population of 2,533 Italian men, aged 40–69 years. During a follow-up of 4–17 years, 393 men died. Age-adjusted total mortality (RR for each HR increment, 1.52; 95% CI, 1.29–1.78), and both

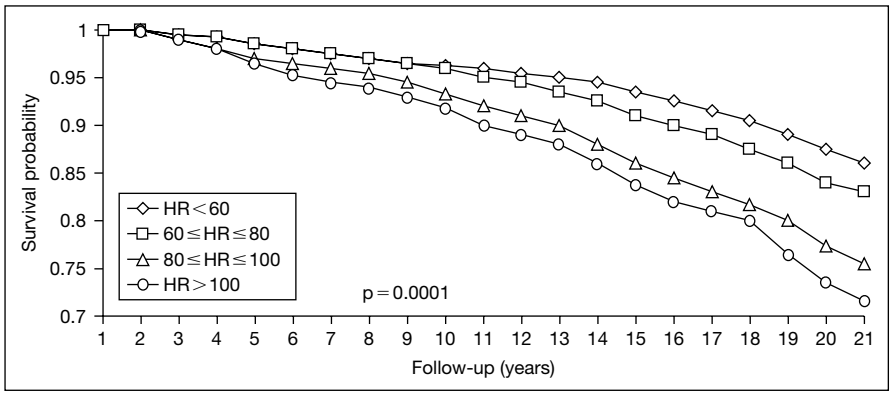

Fig. 1. Long-term survival curves in a large population of normal subjects according to HR at rest (modified from Benetos et al. [4]).

cardiovascular mortality (RR, 1.63; 95% CI, 1.26–2.10) and noncardiovascular mortality (RR, 1.47; 95% CI, 1.19–1.80) increased for increasing values of HR.

Notably, in a Japanese population (573 male participants, aged 40–64, followed for 18 years), Fujiura et al. [6] found that HR measured on resting ECG was the strongest predictor of all-cause mortality after adjustment for age and was significantly associated with death in a multivariate model, together with age, elevated blood pressure, antihypertensive medications, uric acid, vital capacity and serum cholesterol (inversely). Mortality was 14.3% in patients with a resting HR <60 bpm and 38.2% in those with an HR ≥ 90 bpm. A continuous model suggested a graded increase in risk from <70 to ≥ 90 bpm ($p < 0.01$).

Finally, expanding previous data from the PARIS-1 study, Jouven et al. [7] have recently reported data from 5,713 asymptomatic working men (aged 42–53 years), who underwent standardized graded exercise testing. During a 23-year follow-up period, resting HR >75 bpm was associated with a significant increase in all-cause mortality (adjusted risk, 1.89; 95% CI, 1.60–2.24; $p < 0.001$) and, even more, with the occurrence of sudden death from acute myocardial infarction (MI) (RR, 3.46; 95% CI, 1.60–7.44).

A similar prognostic value for HR has also been reported in asymptomatic patients with hypertension. Analyzing data from the Framingham population, Gillman et al. [8] showed that total and cardiovascular mortality increased significantly with HR, in particular for HR ≥ 85 bpm (fig. 2).

Heart Rate in Acute Myocardial Infarction

Increased resting HR (>100 bpm) is a well-known ominous sign in the acute phase of MI [9]. Notably, HR on admission and/or at discharge has also been recognized to be associated with increased long-term mortality in MI

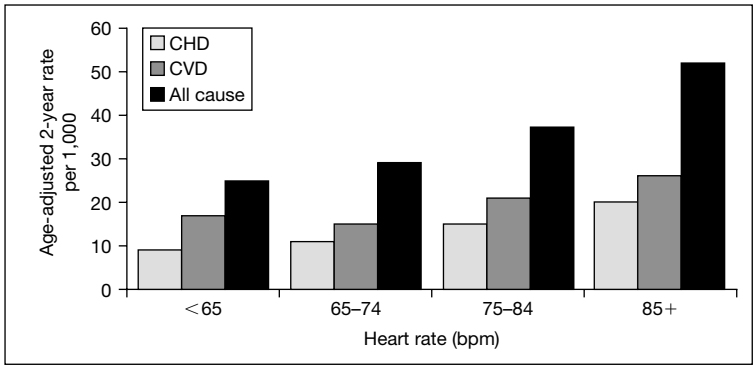

Fig. 2. Two-year rate of coronary, cardiovascular and total mortality adjusted for age in the hypertensive population enrolled in the Framingham Study according to the basal value of heart rate (data from Gillman et al. [8]). CHD = Coronary heart disease; CVD = cardiovascular disease.

patients, and several data suggest that this association can be largely independent of other risk factors, including heart failure or left ventricular (LV) dysfunction.

In the prethrombolytic era, Hjalmarson et al. [10], in 1,807 patients with acute MI, showed that both in-hospital and postdischarge mortality increased with increasing admission HR. At 1-year follow-up, mortality was 15% in patients with admission HR <60 bpm, but about 30% for HR around 90 bpm and >45% in those with HR >100 bpm, respectively. Resting HR measured at discharge yielded similar prognostic information for postdischarge mortality. Although in patients with overt congestive heart failure (CHF) mortality was high regardless of HR, in those with moderate CHF mortality was over twice as frequent in those with an HR ≥90 bpm compared to patients with an HR <90 bpm (39 vs. 18%, respectively). The prognostic implication of increased HR was evident independently of β-blocker therapy.

Similar data were reported by Disegni et al. [11] in 1,044 MI patients enrolled in the SPRINT-2 study. In this study, in-hospital mortality was 5.2% in patients with an HR <70 bpm, 9.5% in those with an HR of 70–89 bpm and 15.1% in those with an HR ≥90 bpm ($p < 0.01$). Furthermore, postdischarge mortality at 1-year follow-up was 4.3, 8.7 and 11.8% in the three HR groups, respectively ($p < 0.01$). Admission HR was an independent risk factor for in-hospital and postdischarge mortality in multivariate analysis and showed a more significant association with mortality in patients with mild CHF ($p = 0.02$) than in those with no CHF ($p = 0.06$).

The prognostic implications of increased HR in acute MI patients have been confirmed in the thrombolytic era. Zuanetti et al. [12] measured HR on surface ECG on admission and at discharge in 8,915 patients with acute MI

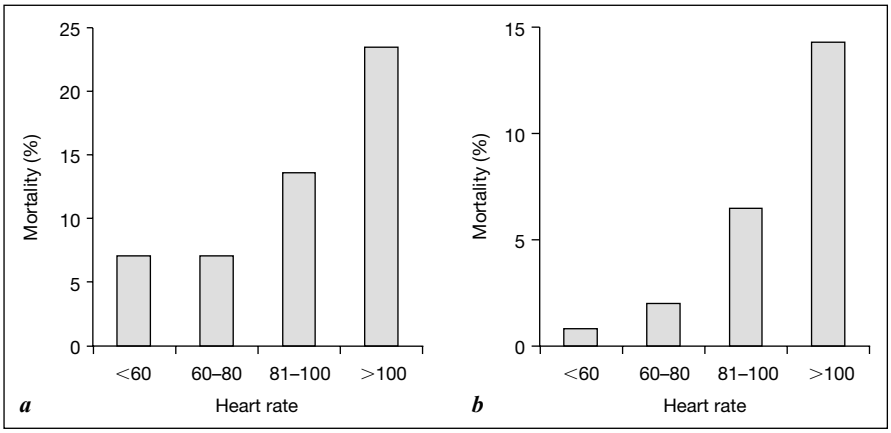

Fig. 3. Relation between HR on admission and in-hospital mortality (***a***) and between HR at discharge and 6-month mortality (***b***) in a population of patients with acute MI treated by systemic thrombolysis (data from Lee et al. [13]).

enrolled in the GISSI-2 study. In-hospital mortality increased progressively with increasing HR (from 7.1% for HR <60 bpm to 23.4% for HR >100 bpm). A progressive increase in HR at discharge was also associated with increasing 6-month mortality (from 0.8% for HR <60 bpm to 14.3% for HR >100 bpm). HR >100 bpm was an independent predictor of in-hospital mortality (RR, 2.24; 95% CI, 1.76–2.85) and the strongest predictor of 6-month mortality (RR, 4.54; 95% CI, 2.21–9.30) at multivariate analysis (fig. 3).

Similarly, in a study involving 41,021 patients enrolled in the GUSTO-I trial, Lee et al. [13] reported that elevated HR ($p < 0.0001$) was an independent predictor of mortality on multivariable analysis, together with age, lower systolic blood pressure, Killip class and anterior MI.

Increased HR seems to maintain a significant predictive value even in the modern era of primary percutaneous coronary interventions (PCI) in acute MI patients. Steffenino et al. [14] assessed the prognostic role of HR in 2,227 high-risk patients with acute MI treated with primary PCI (n = 721), systemic thrombolysis (n = 1,090) or no reperfusion treatment (n = 416). At multivariate analysis, a high HR was an independent predictor of the clinical endpoint (death, nonfatal reinfarction and stroke) both during hospital stay (OR, 1.01; 95% CI, 1.0–1.02; $p = 0.008$) and at 1-year follow-up (OR, 1.01; 95% CI, 1.0–1.01; $p = 0.0001$), together with older age, anterior infarction, Killip class >1 and low systolic blood pressure.

More recently, Mauss et al. [15] have reported the predictive power of HR measured on ECG or on Holter ECG recordings at hospital discharge in

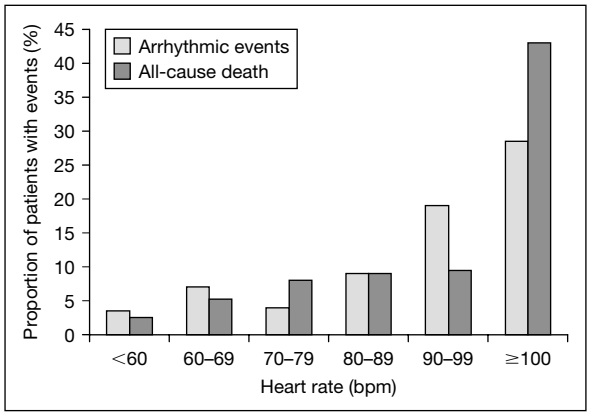

Fig. 4. Relation between HR on admission and long-term mortality and occurrence of arrhythmic events in a population of patients with acute MI treated by systemic thrombolysis or primary PCI (data from Mauss et al. [15]).

432 survivors of acute MI treated by primary PCI or thrombolysis. At an average follow-up of 41 months, HR at rest was a risk predictor of survival in general and after arrhythmic events (fig. 4), even at multivariate analysis ($p = 0.008$), together with LV ejection fraction ($p = 0.0007$) and age ($p = 0.02$). In particular, HR ≥75 bpm on resting ECG was associated with a hazard ratio of 2.17 (95% CI, 1.2–3.7; $p = 0.005$) and HR ≥75 bpm on Holter ECG was associated with a hazard ratio of 1.83 (95% CI, 1.0–3.2; $p = 0.03$).

Thus, in summary, there is growing evidence that increased resting HR in patients with acute MI is an important predictor of fatal events. The predictive value extends at long-term follow-up, is independent of most clinical parameters and seems to be maintained in the modern era of aggressive reperfusion treatment.

Besides acute MI, a predictive prognostic value for HR has also been reported in patients with evidence of stable CAD. In a recent study, Diaz et al. [16] reported long-term follow-up data (14.7 years) in a total of 24,913 patients with suspected or proven CAD included in the Coronary Artery Surgery Study registry. All-cause and cardiovascular mortality increased with increasing HR ($p < 0.0001$). In particular, patients with a resting HR ≥83 bpm had a significantly higher total mortality (hazard ratio, 1.32; 95% CI, 1.19–1.47; $p < 0.0001$) and cardiovascular mortality (hazard ratio, 1.31; 95% CI, 1.15–1.48; $p < 0.0001$) compared to the reference group (HR <62 bpm), after adjustment for multiple clinical variables (fig. 5).

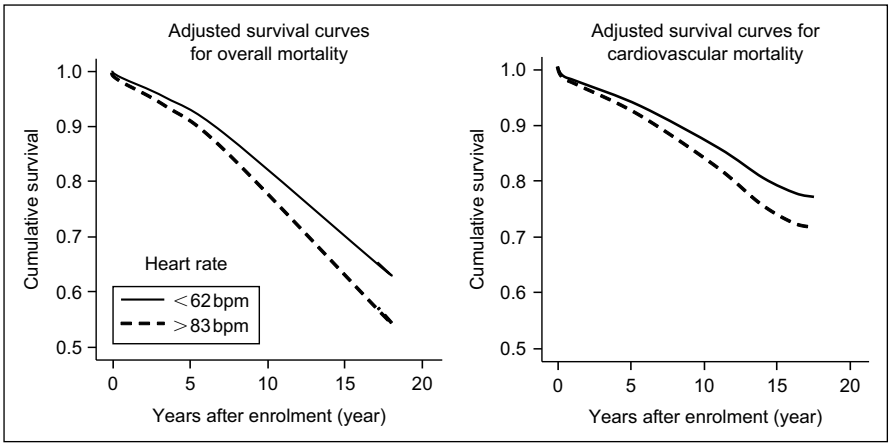

Fig. 5. Relation between HR and long-term mortality and adjusted survival curves for overall mortality and for cardiovascular deaths in a population of patients with stable forms of CAD (data from Diaz et al. [16]).

Heart Rate in Congestive Heart Failure

The association between HR and clinical outcome has also been confirmed in patients with CHF. In a study on 268 ambulatory patients with advanced CHF, indeed, Aaronson et al. [17] found that resting HR was the best predictor of an adverse outcome.

In the CIBIS-II study, which assessed the effect of bisoprolol therapy in patients with New York Heart Association (NYHA) class III–IV and LV ejection fraction ≤35%, multivariate analysis showed that HR at enrolment was a significant predictor of death, independently of several clinical variables and of β-blocking treatment ($p = 0.0012$) [18].

The association between increased HR and worse outcome in CHF was also confirmed in a substudy of the MERIT-HF study, which assessed the effect of metoprolol therapy in CHF patients with functional NYHA class II–IV and LV ejection fraction <40% [19]. In this substudy, the risk of events at follow-up was similar in patients with a resting HR in the lower 4 quintiles (<90 bpm) but increased significantly in the highest HR quintile.

Effects of β-Blockade on Prognosis

As increased HR is associated with increased risk of cardiovascular mortality and events, a potential beneficial effect on clinical outcome could be expected

from interventions aimed at decreasing resting HR. Accordingly, numerous clinical studies in the 1980s and 1990s have demonstrated that β-blockade may have significant favorable effects in several groups of cardiac patients.

β-Blockade in Acute Myocardial Infarction

The beneficial effect of lowering HR in MI patients by β-blockade therapy has been demonstrated by several clinical trials in the prethrombolytic and in the thrombolytic era. β-Blocker therapy has consistently been shown to improve short- and long-term prognosis after acute MI, thus becoming a cornerstone treatment in this setting.

In a Norwegian trial (a multicenter double-blind randomized study), timolol (10 mg twice daily) or placebo was given to 1,884 patients surviving MI, starting 7–28 days after the acute event [20]. At a mean follow-up of 17 months, there were 152 deaths in the placebo group and 98 in the timolol group ($p < 0.001$). When considering deaths occurring during treatment or within 28 days of withdrawal, the sudden death rate over 33 months was 13.9% in the placebo group and 7.7% in the timolol group (a reduction of 44.6%, $p = 0.0001$). Notably, in this study, the reinfarction rate was also lower in patients randomized to timolol compared to those randomized to placebo (14.4 vs. 20.1%, $p = 0.0006$).

In the multicenter, double-blind BHAT study, 3,837 patients were randomized to propranolol hydrochloride (180–240 mg/day) or placebo, starting 5–21 days after the acute event [21]. The trial was stopped 9 months ahead of schedule as active treatment was clearly effective in improving survival. Indeed, during an average follow-up of 24 months, total mortality was 7.2% in patients randomized to propranolol and 9.8% in those randomized to placebo (a reduction of 26%, $p < 0.005$). Similarly, CAD mortality was 6.2 and 8.5%, and sudden cardiac death was 3.3 and 4.6% in the two groups, respectively.

These studies showed that β-blocking agents could safely be used in the vast majority of MI patients, serious side effects being uncommon. Most importantly, they showed clear long-term survival benefits by β-blockade in MI patients, thus pointing out that, unless contraindicated or not tolerated, β-blocking therapy has to be instituted in all patients with a recent MI for secondary prevention.

Subsequent studies were directed to analyze if an early administration of β-blockers could be as safe and effective as a later administration in MI patients.

In the MIAMI trial, 5,778 patients admitted to hospital because of suspected acute MI (definite acute MI confirmed in 4,127 patients) were randomized to receive intravenous metoprolol (15 mg) or placebo shortly after patient's arrival, followed by oral treatment with metoprolol (200 mg daily) or placebo for a study period of 15 days [22]. Mortality was 4.9% in the placebo group and 4.3% in the metoprolol group (a nonsignificant difference of 13%, $p = 0.29$).

However, in a predefined high-risk group, including approximately 30% of randomized patients, the mortality rate was 29% lower in the metoprolol-treated group than in the placebo group. No significant effect by metoprolol was observed on ventricular fibrillation, although the number of episodes tended to be lower in the metoprolol-treated patients during the later phase.

In the randomized ISIS-1 trial, atenolol (5–10 mg i.v. immediately followed by 100 mg/day orally for 7 days) or placebo was given to 16,027 patients with suspected acute MI at a mean of 5.0 h from symptom onset. Cardiovascular mortality during the treatment period was significantly lower in the treated group (3.9 vs. 4.6%, $p < 0.04$) [23]. Actuarial cardiovascular mortality at 1-year follow-up was also significantly lower in atenolol-treated patients (10.7 vs. 12.0%, $p < 0.01$), but not at the latest follow-up (crude figures: 12.5 vs. 13.4%; $p < 0.07$). Slightly fewer nonfatal cardiac arrests and reinfarctions were recorded in atenolol-treated patients, but neither difference was significant.

A direct comparison of immediate versus deferred β-blockade administration in patients with acute MI was done in a subgroup of 1,434 patients enrolled in the TIMI II-B study [24]. In one group, metoprolol was given within 2 h of initiating rt-PA (a total intravenous dose of 15 mg, followed by a target oral dose of 100 mg every 12 h). In the other group, oral metoprolol was started on day 6 (target dose 100 mg twice a day). Overall, there was no difference in mortality between the two groups. However, the incidence of reinfarction at 6 days was lower (2.7 vs. 5.1%, $p = 0.02$) in patients randomized to immediate metoprolol administration.

Overall, these studies showed that early administration of β-blocking agents is advisable in acute MI patients. Indeed, they are well tolerated (when used appropriately) and their use is associated with an improvement of survival and with a significant reduction of major cardiac events compared to later administration.

A review of fatal and of nonfatal events in all randomized trials of intravenous β-blockade by ISIS-1 researchers suggested that treatment reduces mortality in the first week by about 15% and results in the avoidance of 1 reinfarction, 1 arrest, and 1 death during days 0–7 in every 200 treated patients ($p < 0.0002$) [23].

β-Blockade in Congestive Heart Failure

After being considered potentially harmful and contraindicated in patients with depressed LV function for several years, β-blockers have now become a cornerstone form of treatment in patients with CHF after several trials have consistently found beneficial effects on survival (fig. 6).

In the MERIT-HF (in a randomized double-blind study), controlled/extended-release metoprolol or placebo, in addition to standard therapy, was given to 3,991 patients with CHF (NYHA functional class II–IV) and low LV ejection fraction (≤0.40) [19]. The study was stopped early, at a mean

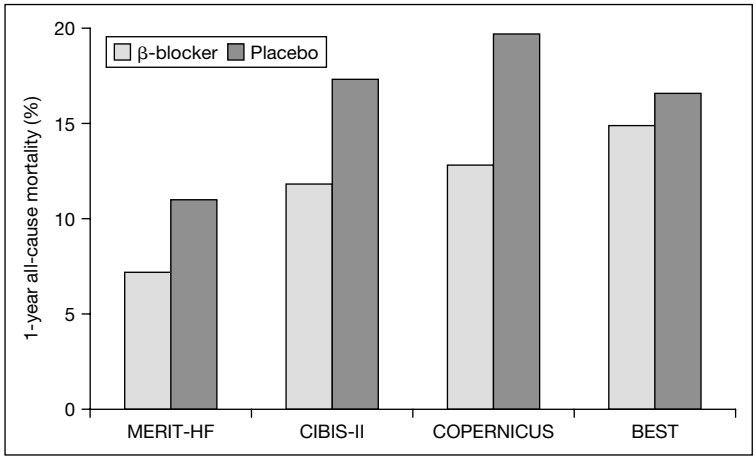

Fig. 6. Effect of β-blocking therapy on 1-year mortality in controlled trials on patients with CHF. Consistent beneficial effects have been reported by all clinical studies, although the difference in mortality did not achieve statistical significance in the BEST trial (data derived from the MERIT-HF Study Group [19], Norwegian Multicentre Study Group [20], Packer et al. [26], and Beta-Blocker Evaluation of Survival Trial Investigators [27]).

follow-up time of 1 year, as all-cause mortality was clearly lower in metoprolol-treated patients than in placebo-treated patients (7.2% patient-year vs. 11.0%; RR, 0.66; 95% CI, 0.53–0.81; $p = 0.0062$ adjusted for interim analyses). Notably, the rate of sudden death (RR, 0.59; 95% CI, 0.45–0.78; $p = 0.0002$) and of deaths from worsening heart failure (RR, 0.51; 95% CI, 0.33–0.79; $p = 0.0023$) were both lower in metoprolol-treated than in placebo-treated patients.

In the double-blind CIBIS study [25], 641 patients with CHF (NYHA class III–IV) and LV ejection fraction <40%, on optimal medical therapy, were randomized to bisoprolol, a selective β_1-blocker, or placebo. At a mean follow-up of 9 months, there was no significant difference in mortality between the two groups (67 placebo-treated patients, 53 bisoprolol-treated patients, $p = 0.22$; RR, 0.80; 95% CI, 0.56–1.15) and no significant difference was observed either in sudden death rate, although fewer patients in the bisoprolol group required hospitalization for cardiac decompensation ($p < 0.01$) and more patients improved by at least one NYHA functional class ($p = 0.04$).

The effect of bisoprolol on survival from CHF was reassessed in the CIBIS-II study [18]. A total of 2,647 CHF patients (NYHA class III–IV) with LV ejection fraction ≤35% receiving standard therapy were randomized to bisoprolol (target dose 10 mg/day) or placebo. The study was stopped early after

a mean follow-up of 1.3 years, because bisoprolol clearly improved survival. All-cause mortality was indeed 11.8% with bisoprolol versus 17.3% with placebo (RR, 0.66; 95% CI, 0.54–0.81; $p < 0.0001$), with also fewer sudden deaths among patients on bisoprolol than in those on placebo (3.6 vs. 6.3%; RR, 0.56; 95% CI, 0.39–0.80; $p = 0.0011$). The effects of treatment were independent of the severity or cause of heart failure.

In the double-blind COPERNICUS trial, 2,289 patients with symptoms of CHF at rest or on minimal exertion during standard therapy and with LV ejection fraction <25% were randomized to carvedilol or placebo [26]. The study was stopped early, after a mean period of 10.4 months. There were 190 deaths in the placebo group and 130 deaths in the carvedilol group (a 35% decrease with carvedilol; 95% CI, 19–48; $p = 0.0014$, adjusted for interim analyses). The favorable effect was seen consistently in all the subgroups examined. Fewer patients in the carvedilol group than in the placebo group withdrew because of adverse effects or for other reasons ($p = 0.02$).

Finally, in the BEST study, 2,708 patients with CHF (NYHA functional class III–IV and LV ejection fraction ≤35%) were randomly assigned to double-blind treatment with bucindolol or placebo [27]. The study was stopped early due to the evidence of significant effects of β-blockade on CHF reported by other trials. At that time, there was no significant difference in mortality between the two groups (unadjusted $p = 0.16$). At an average follow-up of 2.0 years, mortality was 33% in the placebo group and 30% in the bucindolol group (adjusted $p = 0.13$). The risk of death from cardiovascular causes, however, was lower in the bucindolol group (RR, 0.86; 95% CI, 0.74–0.99).

Thus, these clinical trials have consistently shown that β-blockers improve survival in patients with advanced CHF taking optimal diuretic/vasodilator therapy and that, therefore, they should be given to all patients who tolerate them.

Relation between Heart Rate Reduction and Prognosis

Although the use of β-blockade has been associated with improved prognosis in patients with acute MI and those with CHF, and although its major and more evident effect is the reduction of HR, the relationship between the effect of β-blockade on HR and an improved clinical outcome has only sporadically been investigated.

In acute MI patients, however, the observation that β-blocking agents with a limited effect on HR, such as those with intrinsic sympathomimetic activity (e.g. oxprenolol, pindolol), were not found to have significant effects on survival [28], in contrast with pure β-blocking agents, suggests that the effect of β-blockers on HR might be of importance in determining their efficacy.

A direct evidence of this relation was found in the CIBIS-II trial, in which the pharmacologic reduction of HR was associated with the greatest improvement of survival. Indeed, the higher tertile of HR change, compared to the middle and bottom tertiles, was associated with a lower mortality (RR, 0.51; 95% CI, 0.39–0.66; $p < 0.001$) [29].

Pathophysiologic Mechanisms

HR is the result of the combination of several factors influencing the activity of the sinus node, the leading cardiac pacemaker. Sinus node activity is mainly determined by the interaction of sympathergic and vagal activity, which have stimulating and depressing effects, respectively. Thus, HR mainly reflects the sympathovagal balance, although it cannot allow to distinguish between the relative effects of the two sections of the autonomic nervous system.

A sympathovagal imbalance, characterized by sympathetic predominance and vagal depression, has been shown to be associated with increased mortality [30, 31]. For instance, it is well known that depressed vagal activity and enhanced adrenergic activity increase the risk of life-threatening arrhythmic events and sudden death, in particular during myocardial ischemia and in the presence of depressed LV function [32, 33].

Thus, the association between autonomic imbalance and arrhythmic risk explains the relationship between increased HR and sudden death in patients with depressed LV function.

An open question is whether autonomic imbalance may favor atherosclerosis and acute coronary events. In fact, recently, sympathovagal imbalance has been associated with increased indexes of inflammation. Thus, conditions which lead to sympathovagal imbalance may result in an increased inflammatory state [34], which predisposes to atherosclerosis and coronary plaque complications [35], thus also explaining the reported relationship between increased HR and development of atherosclerosis in experimental studies.

However, several studies suggest that increased HR is associated with increased cardiovascular risk not only because it is a marker of autonomic imbalance, but because it may have detrimental effects on cardiovascular function.

In CAD patients, direct negative effects of an increased HR are, for instance, an increase of cardiac work, which increases myocardial oxygen consumption, and a reduction of the diastolic time, which decreases coronary blood flow, both conditions favoring the development of myocardial ischemia. Furthermore, an increased HR may also facilitate arrhythmias in myocardial ischemic areas by favoring reentry mechanisms.

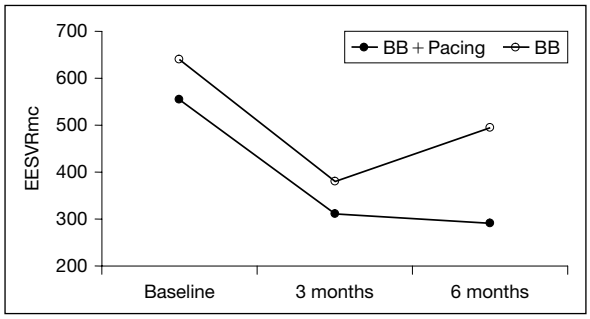

Fig. 7. Effect of HR on the mass-corrected slope of the end-ejection stress-volume relationship (EESVRmc), a measure of myocardial contractile function, in dogs with mitral regurgitation. In this study, after 3 months of mitral regurgitation, dogs were treated with a β-blocker (BB) alone or a BB and atrial pacing to prevent bradycardia (BB + Pacing). Myocardial function did not improve in the latter group of animals, whereas it showed a significant improvement in those treated by BB alone (data from Nagatsu et al. [36]).

Thus, a reduction of HR might have direct beneficial clinical effects. This contention is supported by experimental findings. In a model of LV dysfunction in dogs, HR reduction was demonstrated to be a major mechanism by which β-blockade was effective in the restoration of contractile function [36]; indeed, among β-blockade dogs, LV function improved more significantly in those in which bradycardia was not prevented by atrial pacing (fig. 7).

Experimental data obtained from isolated myocardial strips and the intact heart of a rat model of ischemic heart failure also suggested that a decrease in HR can directly improve left systolic function (fig. 8) [37]. Indeed, in a study, long-term treatment with ivabradine, a pure bradycardia-inducing agent which acts by inhibiting the inward Na^+/K^+ I_f current of sinus node cells, resulted in sustained improvement of LV function, with reduction of the LV end-systolic diameter and increase in cardiac output, as a result of an increase of stroke volume.

Moreover, some data suggest that increased HR may by itself also have negative effects on the vascular function. Thus, in a study comparing 6 monkeys that underwent sinus node ablation with 8 control monkeys, all treated with a highly atherogenic diet, coronary atherosclerosis after 6 months was much more evident in the control group, thus suggesting that increased HR may favor atherogenesis in the presence of coronary risk factors [38].

Furthermore, Heidland and Strauer [39], analyzing coronary angiographies of 106 CAD patients who underwent 2 coronary angiographic procedures within 6 months, found that an HR >80 bpm was an independent predictor of plaque disruption at the time of the second coronary angiography.

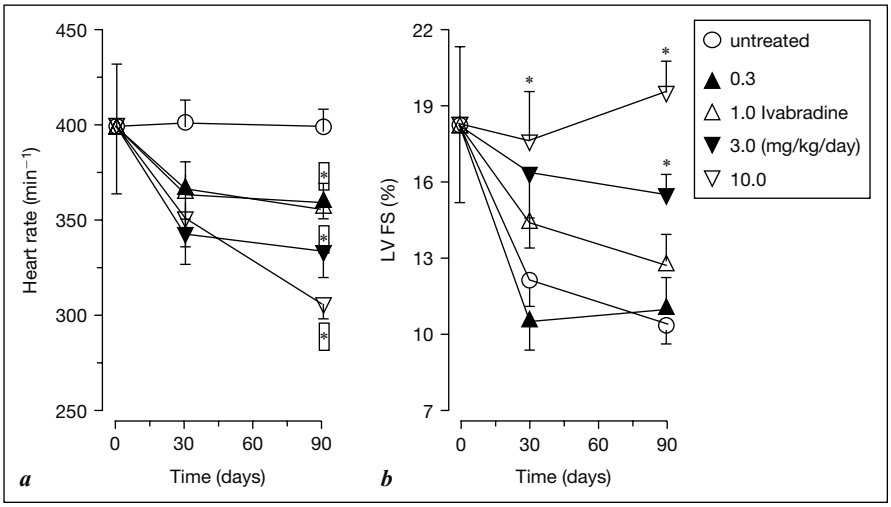

Fig. 8. Effect of various doses of ivabradine, a selective inhibitor of the I_f current of the sinus node, on HR (***a***) and LV fractional shortening (LV FS) (***b***) in a model of rats with CHF. Together with a bradycardic effect, ivabradine administration also induced an improvement of LV function, thus suggesting favorable effects of HR slowing on myocardial contractility (data from Mulder et al. [37]).

Taken together, these data suggest that hemodynamic forces, related to the increased HR, may play an important role in vascular damage, favoring both atherogenetic mechanisms and complications of atherosclerotic plaques responsible for acute coronary events.

In conclusion, a simple reduction of HR might have direct beneficial effects on vascular function and clinical outcome in patients with CAD. Thus, trials with drugs which affect HR only are warranted to test this intriguing working hypothesis.

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I_f Current Inhibition: Cellular Basis and Physiology

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Abstract

The slow diastolic depolarization phase in cardiac pacemaker cells is the electrical basis of cardiac automaticity. The hyperpolarization-activated current (I_f) is one of the key mechanisms underling diastolic depolarization. Particularly, I_f is unique in being activated on membrane hyperpolarization following the repolarization phase of the action potential. I_f has adapted biophysical properties and voltage-dependent gating to initiate pacemaker activity. I_f possibly constitutes the first voltage-dependent trigger of the diastolic depolarization. For these reasons, I_f is a natural pharmacological target for controlling heart rate in cardiovascular disease. In this view, I_f inhibitors have been developed in the past, yet the only molecule to have reached the clinical development is ivabradine. At the cellular level, the remarkable success of ivabradine is to be ascribed to its relatively high affinity for f-channels. Furthermore, ivabradine is the most I_f-specific inhibitor known to date, since moderate inhibition of other voltage-dependent ionic currents involved in automaticity can be observed only at very high concentrations of ivabradine, more than one order of magnitude from that inhibiting I_f. Finally, the mechanism of block of f-channels by ivabradine has particularly favorable properties in light of controlling heart rate under variable physiological conditions. In this article, we will discuss how I_f inhibition by ivabradine can lead to reduction of heart rate. To this aim, we will comment on the role of I_f in cardiac automaticity and on the mechanism of action of ivabradine on f-channels. Some aspects of the cardiac pacemaker mechanism that improve the degree of security of ivabradine will also be highlighted.

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Pharmacological Inhibition of I_f as Therapeutically Effective Tool

Controlling heart rate in cardiovascular disease is one of the major goals to limit cardiac ischemia, ameliorate patient's everyday life and improve long-term survival. The main challenge in this approach is to reduce heart rate in the

absence of negative side effects on cardiac contractility. Even if heart chronotropic and inotropic mechanisms are anatomically and functionally separated, the possibility of modulating heart rate in a specific way has long been limited by the lack of knowledge about the physiological mechanisms underlying cardiac automaticity. However, during the last 20 years, electrophysiology of cardiac pacemaker cells has put into evidence the relevance of ionic channels in cardiac automaticity and particularly, the specific role of the 'pacemaker' current I_f in the genesis and autonomic regulation of heart automaticity [1]. The possibility of targeting I_f for controlling heart rate has thus become a new concept in the pharmacological treatment of cardiac ischemic disease. By the theoretical point of view, a specific heart-rate-reducing agent should influence only the duration of the diastole with no effect on either heart contractility or repolarization.

Ivabradine has been shown to fulfill all these requirements and can constitute a new reference molecule for further development of heart-rate-reducing agents. Ivabradine is a heart-rate-reducing agent developed for the treatment of stable angina pectoris (for a review, see DiFrancesco and Camm [2]). It specifically inhibits I_f and limits exercise-induced tachycardia in the absence of inotropic [3] or dromotropic effects in all animal models tested thus far [4]. Ivabradine administered at pharmacological doses to experimental animals does not affect the corrected QT interval [5]. As expected from a pure effect on the diastolic phase of the cardiac cycle, the consequence of heart rate reduction is an improved balance between myocardial oxygen demand and supply [6]. At the cellular level, ivabradine induces negative chronotropism in pacemaker cells by decreasing the rate of diastolic depolarization [7]. Here we will discuss the cellular mechanism of action of ivabradine with respect to the functional role of I_f in pacemaking and put into evidence the importance of I_f inhibition for modulating heart rate.

Properties and Expression of I_f in Automatic Cells

I_f is a mixed cationic current carried by Na^+ and K^+ ions [8]. However, the main current through f-channels is due to Na^+ ions which have higher permeability than K^+ [9]. In sinoatrial node (SAN) pacemaker cells, I_f reverses nearly -20 mV [10]. Consequently, I_f is inward during the diastolic depolarization and switches to the outward direction during the upstroke and repolarization phase of the action potential. I_f is activated upon membrane hyperpolarization and supplies inward current in the voltage range corresponding to the diastolic depolarization [11]. I_f is regulated in opposite ways by catecholamines and acetylcholine (ACh). Indeed, activation of the β-adrenergic receptor stimulates I_f [12], while muscarinic receptor activation inhibits I_f [13]. Most of the autonomic

regulation of I_f is due to activation of f-channels by intracellular cAMP [14]. Particularly, cAMP accelerates activation of f-channels and facilitates opening at a given voltage [15]. Recent work has shown that f-channels are concentrated in membrane lipid rafts [16]. It is thus tempting to speculate that regulation of f-channels by cAMP can take place in a local submembrane compartment constituted by lipid rafts [16].

I_f current is the electrophysiological marker of cardiac automatic cells. Indeed, I_f has been found in all spontaneously beating mammalian heart cells coming from the SAN and the cardiac conduction system (CCS) [17]. I_f is strongly expressed in the SAN [12, 18]. Particularly, the density of I_f is higher in the periphery of the SAN [19]. I_f is also detectable in the working myocardium, even if at low density [20]. In the ventricle, I_f displays a very negative activation range [21]. Hypertension, chronic atrial fibrillation and heart failure have been shown to enhance I_f expression and to positively shift current activation in the myocardium of animal models and humans [22–26]. As to action of ivabradine on heart rate, we will discuss some possible implications of I_f expression in the myocardium in what follows.

Molecular Basis of f-Channels

A gene family coding for I_f channels has been cloned from the mouse [27, 28] and humans [29–31]. Four isoforms named HCN1–4 (hyperpolarization-activated cyclic nucleotide-gated cation) have been cloned and expressed in heterologous systems and differ in their voltage dependence for activation and relative sensitivity to cAMP [32].

The primary sequence of HCN isoforms is similar to that of voltage-dependent K^+ channels (K_v). Indeed, a 6-transmembrane domain motif (S1–S6) is present and a high level of homology is conserved ($\geq$80% identity) between HCN isoforms (fig. 1). A typical S4 transmembrane domain coding for the channel voltage sensor (S4) is identical in all HCN isoforms and is defined by ten regularly spaced consecutive positive-charged amino acids (for a review, see Baruscotti et al. [1]). The pore sequence is predicted to contain a GYG sequence [33]. HCN channels also contain the specific cyclic nucleotide binding domain at the C-terminus [27, 28]. The intracellular N- and C-termini also display significant homology between the 4 isoforms, even if to a moderate extent compared to the pore region [34, 35].

HCN1 channels have fast activation and low sensitivity to cAMP [27, 28], while HCN4 channels have slow activation kinetics and strong sensitivity to cAMP [30]. As to HCN2 channels, they display intermediate gating properties between HCN1 and HCN4 channels [30, 36]. These differential properties

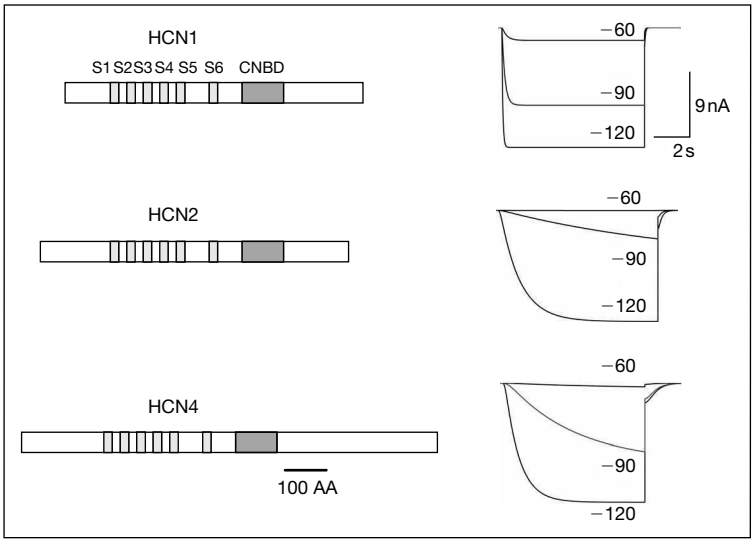

Fig. 1. Primary structure (left panels) and corresponding kinetics (right panels) of HCN channel isoforms expressed in the heart. Sample current traces have been obtained by numerical simulations of recombinant HCN currents. Channel gating has been calculated according to the allosteric model by Altomare et al. [37].

between HCN isoforms have been successfully explained by an allosteric model of HCN channel regulation by voltage and cAMP [37] (fig. 1). Also the kinetics of HCN channels can be regulated under some experimental conditions by the short transmembrane protein KCNE2 [38, 39]. In the heart, HCN4 constitutes the major isoform coding for I_f in the SAN [40] and the atrioventricular node [41]. HCN1 and HCN2 mRNA have been found in the SAN [40–42]. The working myocardium seems to express moderate levels of HCN2 and HCN4 mRNA [40, 41]. The robust SAN expression of mRNA coding for HCN4 channels, together with the strong sensitivity of native f-channels to cAMP [15], indicates that HCN4 is a major molecular determinant of native I_f. Nevertheless, the exact subunit composition of f-channels in the SAN has not been elucidated.

I_f and Cardiac Pacemaking

Heart automaticity is generated by a small population of modified myocytes located in the SAN. Automaticity in pacemaker cells is due to the diastolic depolarization (also named pacemaker potential), a slow depolarizing phase of the action potential, which leads the membrane potential at the end of

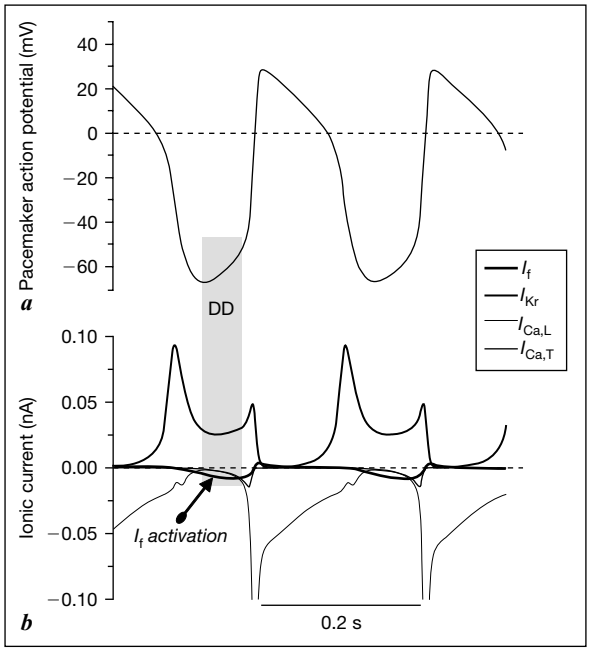

Fig. 2. Numerical modelling of SAN pacemaker activity shows activation of I_f during the diastolic depolarization (DD). ***a*** Pacemaker action potential and diastolic depolarization. ***b*** Time-dependent activation of ionic currents ($I_{Ca,L}$, $I_{Ca,T}$ and I_{Kr}) compared to that of I_f. Other ionic currents have been neglected for clarity. Note that I_f is the first voltage-dependent current to activate upon hyperpolarization even slightly before the maximum diastolic potential to counterbalance deactivating I_{Kr}. I_f activation then increases throughout the diastolic depolarization and deactivates during the first half of the repolarization phase.

an action potential to the threshold of the following action potential (fig. 2). Diastolic depolarization develops during the diastole of the cardiac contraction cycle and is a hallmark of cardiac automatic cells. The atrioventricular node and the Purkinje fiber network can also generate viable pacemaker activity. However, due to its intrinsic higher firing rate, the SAN suppresses pacemaking of the CCS and controls the overall heart rate. Even if pacemaker activity of the conduction system in vivo is normally suppressed by the dominant firing frequency of the SAN, it can become dominant in case of SAN failure or block of the atrioventricular conduction [43].

I_f is associated with the genesis of automaticity throughout the heart development. Indeed, it is important to note that in the embryo, before the development of the CCS, myocardial cells generate their own pacemaker activity. For example, during the development of the mouse heart, I_f is expressed in the

whole myocardial tissue and is associated with automaticity [44]. After the development of the CCS, the working myocardium loses its pacemaking properties and the SAN takes over the chronotropic control of the heartbeat [45]. The expression of I_f is drastically downregulated in the myocardium at the end of the development and becomes restricted to the mature CCS. It would be interesting to know at which point of the heart development I_f becomes important for pacemaking since early candidate precursors of pacemaker cells beat in the absence of functional voltage-dependent ionic channels [46]. In this respect, one of the most intriguing finding in embryonic hearts lacking HCN4 channels is the lack of mature differentiated pacemaker cells in the heart. Indeed, only cells showing early embryonic pacemaking can be found in HCN4-deficient hearts. This observation is suggestive of a key contribution of HCN4 channels in the development of the pacemaker cells and the CCS [44].

In contrast to early precursor pacemaker cells, automaticity in mature pacemaker cells is generated by the association of different classes of ionic channels (fig. 2). Indeed, pacemaker activity in the adult can be viewed as the sum of the activity of different classes of ionic channels playing specific physiological roles [47]. Since biological evolution has based the mammalian cardiac pacemaker on a concerted ionic mechanism, it is possible to target I_f for controlling heart rate without impairing automaticity per se.

Numerical simulations of pacemaker activity such as in figure 2 can illustrate this point in a visually pleasant way. From this simulation of mouse SAN pacemaker activity [Mangoni et al., unpubl. results], it can be viewed that I_f is activated in the diastolic depolarization range and supplies inward current which contributes to counterbalancing the decaying fast component of the delayed rectifier (I_{Kr}) close to the maximum diastolic potential, as experimentally shown in rabbit pacemaker cells [11]. Beside I_f, the T- and L-type Ca^{2+} currents ($I_{Ca,L}$ and $I_{Ca,T}$) activate during diastolic depolarization and contribute to the setting of the pacing rate. $I_{Ca,L}$ is also responsible for the upstroke phase of the action potential and regulates the action potential duration by opposing to the repolarizing action of I_{Kr}.

The fundamental importance of I_f is thus linked to its property of being activated upon hyperpolarization. Thanks to this, I_f is the first voltage-dependent mechanism which opposes to I_{Kr} after the repolarization phase, thereby initiating diastolic depolarization and allowing the proper recruitment of $I_{Ca,T}$, $I_{Ca,L}$ as well as other voltage-dependent channels which are all activated upon depolarization. This is the reason why specific pharmacological inhibition of I_f reduces the slope of the early and late diastolic depolarization phase (fig. 3). I_f also constitutes a safety guard mechanism in pacemaker tissue that naturally opposes to membrane hyperpolarization induced by muscarinic K^+ channels (I_{KACh}) or in ischemic conditions [48]. Consistent with this view, all known pharmacological inhibitors

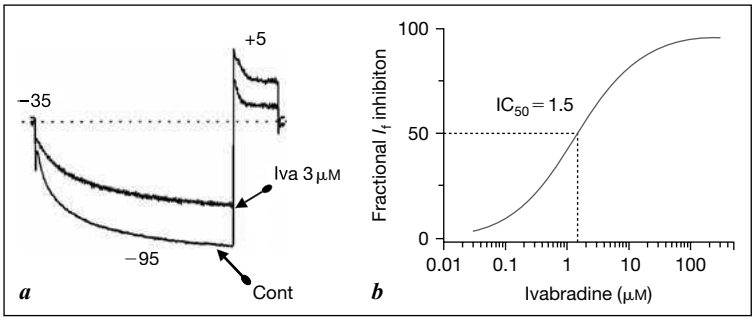

Fig. 3. ***a*** I_f inhibition by 3 μM ivabradine in mouse SAN pacemaker cells [Mangoni, unpubl. results]. ***b*** Dose-response of I_f to ivabradine in rabbit SAN pacemaker cells. The grey line represents fitting of averaged data from studies in Bois et al. [60] and Bucchi et al. [61].

of f-channels, including ivabradine, induce moderate negative chronotropism in both intact SAN tissue and in isolated pacemaker cells [19, 49]. Consistently, the heterogeneous regional distribution of I_f influences the sensitivity to different f-channel blockers of pacemaker activity in the center and in the periphery of the SAN. For example, the negative chronotropic effect of Cs^+ and UL-FS 49 is more pronounced in the periphery of the SAN than in the dominant center region [19].

The capability of I_f to set the heart rate is also strikingly demonstrated by genetic evidence. Indeed, in a large-scale mutagenesis study in zebrafish, a study in which mutant strains were selected for mutations affecting the cardiovascular system, a mutant named '*slow mo*' *(smo)* was identified by virtue of the reduced heart rate observed in embryos [50]. More precisely, isolated heart cells from *smo* embryos have downregulated I_f due to abolition of its fast kinetic component [50]. The functional association between abolition of the fast component of I_f and bradycardia in *smo* zebrafish mutants constitutes strong evidence of the importance of f-channels in the determination of heart rate.

Finally, the capability of f-channels to initiate automaticity constitutes the basis of the development of so-called 'biological pacemakers' [51]. This approach is based on the observation that overexpression of HCN2 or HCN4 channels in cultured neonatal ventricular myocytes strongly enhances automaticity [52]. Consistent with the view that I_f initiates pacemaking in these myocytes, suppression of HCN channel expression by a dominant negative HCN2 subunit abolished automaticity [52]. It has been shown that adenoviral gene transfer of HCN2 channels in vivo in the canine left atrium induces expression of I_f in atrial myocytes and is able to generate viable supraventricular rhythms [53]. This strategy has now been modified to obtain a specific gene transfer in the CCS, rather than in the myocardial tissue [54].

Importance of I_f in the Autonomic Regulation of Pacemaker Activity

I_f is also one of the major effectors for promoting autonomic control of pacemaker activity [17, 55]. For our purposes, it is important to keep in mind that I_f has the capability to respond to a small increase/decrease in intracellular cAMP by positively or negatively shifting its voltage dependence [17]. As a consequence, even small changes in the cAMP concentration can result in significant changes in the rate of pacemaking. In this respect, it has been proposed that I_f constitutes the major mechanism to both reduce the heart rate at low parasympathetic tone and to quicken the heartbeat under moderate activation of the β-adrenergic receptor [56, 57]. This proposal is based on the observation that low doses of ACh or of the β-adrenergic agonist isoproterenol specifically decrease and increase the slope of the diastolic depolarization in the absence of an effect on the action potential shape [17]. We can thus think to f-channels as both an accelerator and brake of the heart rate in the everyday life of the individual.

The importance of f-channels in the autonomic regulation of the heart rate has recently been confirmed in a human subject carrying mutations in the HCN4 gene. This mutation (named 573X) generates a truncation at the C-terminal part of the channel protein and induces a loss of the exercise-induced increase in heart rate [58]. Another mutation in the human HCN4 gene is associated with familial asymptomatic bradycardia [59]. Affected HCN4 channels are normally responsive to cAMP, but activate for more negative voltages than wild-type channels. Interestingly, this mutation induces a moderate reduction of the basal heart rate leading the authors to propose that this mutation has functional effects similar to that of low doses of ACh [59]. These observations are consistent with the view that manipulations of the activity of f-channels can effectively regulate heart rate without disrupting the pacemaker mechanism or inducing life-threatening arrhythmias.

Action of Ivabradine at the Cellular Level

Evidence of the action of ivabradine on cardiac automaticity came from in vitro studies in isolated spontaneously beating rat right atria [7]. Indeed, ivabradine reduced the rate of pacing of these preparations in a dose-dependent way. This result was strongly suggestive of an effect of the drug on SAN automaticity and prompted further in vitro studies on rabbit SAN tissue preparations [49] and isolated pacemaker cells [2]. Particularly, using isolated rabbit SAN pacemaker cells, it has been demonstrated that ivabradine reduces pacemaker activity by decreasing the slope of the diastolic depolarization, without significantly affecting

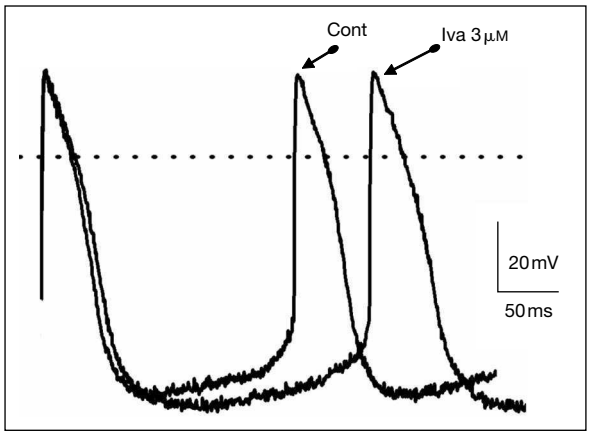

Fig. 4. Pacemaker rate reduction and slowing of the diastolic depolarization by 3 μM ivabradine in mouse SAN pacemaker cells [Mangoni, unpubl. results].

the cell maximum diastolic potential [2]. Dose-dependent reduction of the slope of the diastolic depolarization is paralleled by progressive inhibition of I_f in a similar range of concentrations of ivabradine. Indeed, the IC_{50} for reduction of pacemaker activity and I_f inhibition are consistent between 1.5 and 3 μM (fig. 3) [60, 61]. These observations on isolated rabbit SAN cells have recently been confirmed also in mouse SAN cells (fig. 4). For concentrations close to the IC_{50} for I_f, no effect was observed on $I_{Ca,L}$, $I_{Ca,T}$ and I_{Kr} [60]. Moderate inhibition of $I_{Ca,L}$ (16%) and I_{Kr} (18%) have been observed at 10 μM ivabradine, when I_f is blocked at about 90%. Such moderate effects on $I_{Ca,L}$ and I_{Kr} at high doses of ivabradine are unlikely to have any supplementary impact on pacemaker activity, since numerical simulations of rabbit SAN pacemaking indicate that no alterations of the action potential waveform are observed when these effects are included in calculations [Mangoni et al., unpubl. obs.]. These data demonstrate the specificity of ivabradine action on f-channels in pacemaker cells.

Mechanism of Action of Ivabradine on f-Channels

Electrophysiological recordings on isolated SAN pacemaker cells using the patch-clamp technique have demonstrated use- and current-dependent inhibition of I_f by ivabradine [61]. In this respect, the action of ivabradine on f-channels differs from that of other I_f blockers such as UL-FS49 [62, 63]. Indeed, I_f inhibition by UL-FS49 is also use dependent, but block does not depend on the current driving force [64].

Ivabradine reduces the total I_f conductance without affecting its voltage dependence, indicating that the drug does not alter the capability of the gating mechanism to sense the membrane voltage [61]. Ivabradine enters the f-channel mouth by the intracellular side of the membrane thereby interfering with transmembrane ionic flux. Consistent with this view, native SAN f-channels must be in the open state for being blocked by ivabradine. The current-dependent block of I_f by ivabradine is an interesting phenomenon. Particularly, current dependency of block reveals competition of occupancy in the pore of the f-channel between Na^+ and K^+ ions and ivabradine. Consequently, when both Na^+ and K^+ permeate the channel from outside the membrane at negative voltages below the K^+ equilibrium potential, ivabradine will be effectively 'pulled out' from the channel inner mouth. Inversely, when net outward current flows through f-channels, the efficacy of block by ivabradine will be maximal [61]. In the pacemaker cycle, ivabradine will thus preferentially inhibit I_f at positive voltages, during the diastolic depolarization and repolarization when f-channels deactivate. Use dependency of block will also favor I_f inhibition at a high pacing rate, when control of heart rate is more useful. Importantly, release of f-channel block at lower heart rates or when the maximum diastolic potential undergoes spontaneous hyperpolarization (e.g. during enhanced vagal tone) can constitute a supplementary safety mechanism to counteract excessive slowing of heart rate. We can expect that ivabradine might also be useful in the diseased myocardium in conditions where I_f expression is enhanced and has been proposed to have potential proarrhythmic effects [24]. Indeed, it could be possible that block of I_f in the atria might prevent the onset of atrial fibrillation [24]. Future clinical observations will help confirm this hypothesis.

Conclusions

In conclusion, after 10 years of extensive research, it is now well established that I_f constitutes both the target and the physiological effector of ivabradine. The specificity of action of ivabradine on I_f has also recently been confirmed in spontaneously beating cardiac embryonic bodies. In these experiments, ivabradine was able to reduce the beating rate of embryonic bodies only after functional expression of I_f [46]. Indeed, I_f was not recorded in very early precursor cells and ivabradine did not affect pacemaker activity [46].

Affinity of ivabradine for I_f underlies its peculiarity of being a pure heart-rate-reducing agent. Furthermore, the specificity of ivabradine for I_f ensures safety with respect to other currents involved in automaticity (e.g. $I_{Ca,L}$, $I_{Ca,T}$), as well as currents involved in the repolarization phase of the cardiac action potential [64]. The mode of action of ivabradine on f-channels has particularly

favorable properties to enhance the drug effect when necessary (e.g. elevated heart rate), but also to reduce it in case of slowing of pacemaking for additional causes (e.g. muscarinic receptor activation or SAN dysfunction). Also, expression of I_f in the atrioventricular node and Purkinje fibers cannot affect conduction (no dromotropic effect), since pacemaking in the CCS is suppressed under SAN rhythm.

f-Channels are the first ionic channels underlying pacemaking to be targeted by a therapeutically active drug. Other channel classes, such as $Ca_v1.3$ [65] and $Ca_v3.1$ [66] channels, might constitute future targets for the development of new molecules which specifically regulate heart rate in the absence of concomitant negative inotropism.

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Heart Rate Reduction by Pharmacological I_f Current Inhibition

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Abstract

Heart rate reduction is becoming a new strategy to treat coronary patients. The development of heart-rate-lowering drugs, with a more specific activity than β-blockers, coincides with the detection of the sinoatrial pacemaker I_f current. The first selective I_f inhibitor that has been approved for clinical use is ivabradine. Ivabradine has been shown to reduce heart rate, preserve myocardial contractility, increase diastolic filling and maintain both small and large coronary artery vasodilation, whatever the level of exercise, thus ensuring adequate endocardial blood perfusion during exercise. Furthermore ivabradine decreases myocardial oxygen consumption and improves myocardial energetics, protecting the myocardium during acute ischemic conditions and showing favorable antiremodelling properties in patients with chronic ischemic disease.

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Recognition that β-blockade not only reduces heart rate but also the myocardial inotropic state, unmasks α-adrenergic coronary vasoconstriction and exerts several side effects has prompted the development of more specific heart-rate-lowering drugs, namely the selective I_f inhibitors.

Their development coincides with the detection of the sinoatrial pacemaker I_f current by DiFrancesco et al. [1, 2]. The cellular characteristics and the physiological role of the I_f current have been extensively described in the precedent article and will not be reviewed here.

The first drug advocated as I_f inhibitor is alinidine, a clonidine derivative. In conscious dogs and anesthetized pigs with coronary stenosis, alinidine decreases heart rate, causes a favorable redistribution of myocardial blood flow into the post-stenotic subendocardium and attenuates ischemic contractile

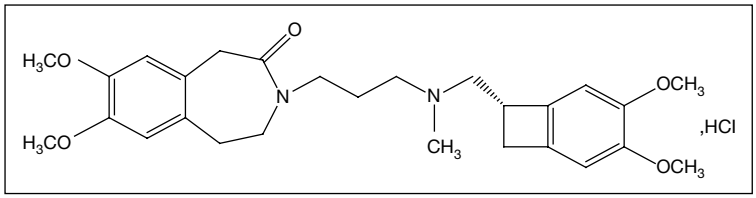

Fig. 1. Structural formula of ivabradine.

dysfunction. All these positive effects, however, occur at the expense of a significant negative inotropic effect, suggesting that alinidine is not a selective I_f current inhibitor. For this and other reasons, alinidine was not further developed [3–7].

ULFS-49 is a benzazepinone acting on the I_f current. As alinidine, in conscious chronically instrumented dogs with coronary stenosis, ULFS-49 reduces heart rate, both at rest and during exercise, improves post-stenotic blood flow and attenuates ischemic contractile dysfunction. These beneficial effects are achieved in the absence of negative inotropic actions. However, despite its favorable anti-ischemic profile, ULFS-49 resulted in frequent adverse events and has never been developed further for clinical use [8].

The first selective I_f inhibitor that has been approved for clinical use is ivabradine.

Pharmacokinetic and Pharmacodynamic Profile of Ivabradine

Figure 1 indicates that ivabradine contains two ring systems: a benzazepinone and a benzocyclobutane moiety. These two cycles are linked with an azapentane chain. Ivabradine in healthy volunteers exhibits linear pharmacokinetics over single oral doses ranging from 0.5 to 40 mg, and single intravenous bolus doses from 1 to 24 mg.

After oral administration, absorption is rapid (EPAR). The plasma peak is obtained in about 1 h, irrespective of dosage. The food intake slightly delays t_{max} by approximately 1 h, and increases plasma exposure by 20–30%. Oral bioavailability is close to 40%, irrespective of the dose. Crossing of the intestinal barrier has been shown to be passive. The average volume of distribution is estimated about 1.4 l/kg in patients.

Plasma protein binding is approximately 70%, irrespective of plasma concentration, and the blood/plasma ratio is about 0.7. The average plasma

concentration is 10 ng/ml at steady state. Ivabradine is extensively metabolized; the metabolism takes place in the liver, through cytochrome CYP450 3A4. Interaction studies show that ivabradine does not exert any inhibitory effect on other substrates for CYP3A4. The coadministration of the potent CYP3A4 inhibitor ketoconazole with ivabradine results in an increase in C_{max}, and plasma exposure to ivabradine. Consequently, maximal heart rate reduction at peak exercise is increased, but QTc is unchanged.

On the contrary, interaction between ivabradine and CYP3A4 inducers results in a reduction of the plasma exposure to ivabradine without any change of the electrocardiographic parameters.

In vivo, the main half-life of ivabradine under conditions of chronic administration is about 2 h, and the effective half-life reaches 11 h, which is consistent with a twice-daily administration.

Ivabradine is rapidly eliminated and equally excreted in urine and feces. Less than 10% of the administered dose is found unchanged in the urine after oral administration. There is no accumulation at steady state, which is reached within 24 h.

Pharmacology of Ivabradine: Effects on the f-Channels

Ivabradine has been shown to inhibit, in a concentration-dependent manner, I_f current in various experimental settings [9] (fig. 2).

Ivabradine binds specifically to the f-channels on the intracellular side of the plasma membrane of the pacemaker cells in the sinoatrial node, thereby inhibiting the I_f current. This is a consequence of the finding that no binding is detected when the membrane potential is maintained at –35 mV and the I_f channel is maintained in the closed state. On the contrary, at a more negative potential, when the f-channel is in the open configuration, ivabradine gets inside and binds to an intracellular site of the channel [10]. This finding also implies that binding of ivabradine occurs when there is an actual ion flow inward across the channel itself. This can be visualized by describing that ivabradine is 'kicked into' the channel by the ion flux until it reaches the binding site and blocks the channel. It follows that the potency of f-channel blocking depends on the driving force of ion flow across the channel pore (fig. 3). This has an important therapeutic implication as ivabradine would be more effective at a faster heart rate, when heart rate reduction is necessary [11].

The direct electrophysiological consequence of the inhibition of the f-channel is a reduction in the slope of the spontaneous diastolic depolarization curve, leading to an increase in the time interval between successive action potentials and, therefore, to a decrease in heart rate [12].

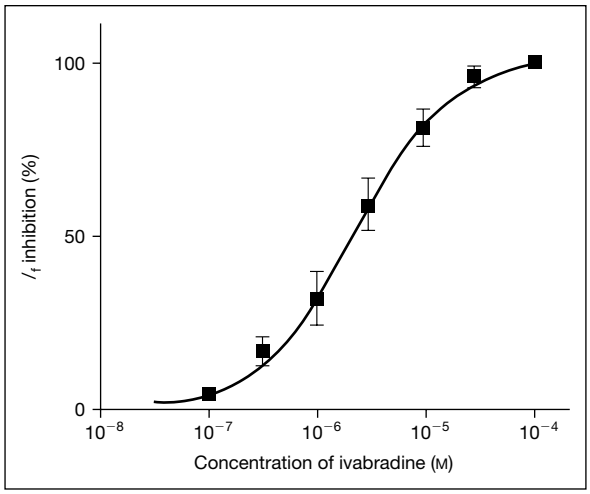

Fig. 2. Dose-dependent I_f current inhibition with ivabradine.

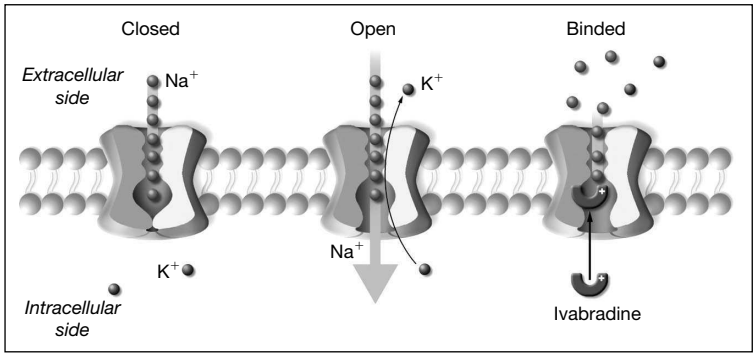

Fig. 3. Ivabradine specifically binds to the f-channel when the channel is in the open state.

In addition to I_f current, the action of ivabradine on other ion currents was assessed, including mainly I_K and $I_{Ca,T}$, and $I_{Ca,L}$ at concentrations of 3 and 10 μM, which represent 140–470 times the average therapeutic plasma concentration.

Two types of calcium currents are involved in the sinus node action potential, the T- and the L-type calcium channels. No detectable blockade of the

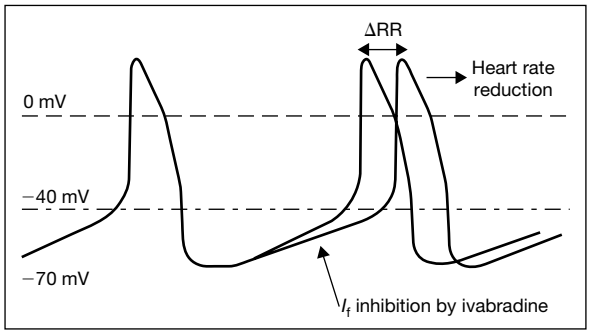

Fig. 4. Ivabradine significantly reduces the diastolic depolarization phase, providing pure heart rate reduction.

T-type calcium channel was recorded, at any concentration of ivabradine, up to 10 μM. Slight inhibition of L-type Ca^{2+} channels (18%) was observed with ivabradine10 μM. This relative lack of effect of ivabradine on the L-type Ca^{2+} current suggests the absence of negative inotropy induced by ivabradine. No significant effect on Na^+ or K^+ currents by ivabradine is reported. At therapeutic concentrations and even at 3 μM, ivabradine has no effect on the outward potassium current I_K, indicating that ivabradine is unlikely to affect the action potential duration [13]. Thus, all these electrophysiological investigations confirm that ivabradine is a specific and selective inhibitor of the I_f pacemaker current [14].

Effects on Heart Rate

As just mentioned, there is a direct correlation between I_f current and pacemaker activity, indicating the importance of I_f as a determinant of heart rate through modulation of the diastolic depolarization slope. The mode of action of ivabradine has received confirmation from a study with direct recording in sinus node cells [5]. It has been shown that the specific binding of ivabradine to the f-channels and the selective I_f current inhibition allows ivabradine to reduce the diastolic depolarization slope without affecting maximal diastolic potential. This effect results in an increase in the time to action potential firing resulting in heart rate reduction and preserves the amplitude of the action potential, thus providing pure heart rate reduction, with no alteration of electrophysiological parameters [5] (fig. 4).

Hemodynamic Effects

Unlike β-blockers, ivabradine exerts no significant effect on myocardial contractility, either at rest or during exercise. Comparison of the systemic hemodynamic effect of ivabradine and propranolol in pigs showed that, while ivabradine preserves global myocardial contractility [left ventricular pressure gradient versus time (LVdP/dt)] at rest and does not interfere with the increase in LVdP/dt consecutive to exercise, propranolol significantly reduces LVdP/dt at rest and considerably limits the increase in LVdP/dt consecutive to the myocardial adaptation to exercise [15].

The preservation of myocardial contractility and reduction of heart rate result in a marked increase in cardiac stroke volume, thus maintaining cardiac output.

Another important hemodynamic action of ivabradine is the increase in diastolic perfusion time. Diastolic time has a direct impact on left ventricular filling and coronary perfusion, and is therefore a major determinant of anti-ischemic properties. In conscious dogs, heart rate reduction induced by increasing doses of ivabradine results from simultaneous prolongation of both systolic and diastolic times. This effect has clinically relevant implications during myocardial ischemia [16].

Since improvement in oxygen supply is a key target in the treatment of ischemic coronary disease, it is important to assess the impact of ivabradine on coronary artery adaptation to exercise. A study comparing ivabradine and propranolol, both versus saline solution, shows that, in contrast to propranolol, ivabradine preserves the exercise-induced increase in mean coronary artery diameter observed with saline solution. The slight, but nonsignificant, decrease in mean coronary artery diameter is the direct consequence of heart rate reduction. In contrast, propranolol, like many β-blockers, maintains a significant vasoconstriction, thereby increasing coronary resistance, and strongly decreases coronary blood flow velocity. In contrast, coronary blood flow is not affected with ivabradine [17].

To conclude, ivabradine reduces heart rate, preserves contractility, increases diastolic filling and maintains both small and large coronary artery vasodilation, whatever the level of exercise, thus ensuring adequate endocardial blood perfusion during exercise.

Anti-Ischemic Effects

The anti-ischemic effect of ivabradine depends, although not exclusively, on its ability to reduce heart rate and therefore to reduce myocardial energy expenditure on the one hand and to improve perfusion of the ischemic myocardium on the other hand.

Adenosine triphosphate (ATP) is the primary source of energy in the heart and is used for electrical excitation, contraction, relaxation, and recovery of the resting electrochemical gradients across membranes.

Even though the heart may suddenly increase its output up to sixfold, thus requiring a huge amount of energy, unlike other tissues, it only stores low quantities of ATP, just sufficient to support a few beats. However, the low ATP levels in the heart are counterbalanced by a higher level of creatine phosphate which permits availability of ATP from the adenosine diphosphate, through a phosphorylation reaction catalyzed by creatine kinase [18]. In the heart, ATP is synthesized in the mitochondria from a variety of aerobic substrates [19]. At rest, ATP is mainly generated from fatty acid β-oxidation (60–70%) and carbohydrate catabolism (30%) including exogenous glucose and lactate catabolism. Amino acids and ketone bodies are utilized as substrates, however, less frequently.

Thus, heart rate reduction at the cellular level is pivotal for cardiac protection [9] because oxygen delivery in the heart mainly occurs during diastole, through the coronary flow. It is clear that the deleterious consequences resulting from conditions in which the heart is damaged and oxygen delivery is impaired, such as ischemic heart disease and certain types of heart failure, will be improved when agents able to decrease heart rate are administered [20–23]. Because heart rate is a major determinant of oxygen consumption and metabolic demand, heart rate reduction would be beneficial.

Often under ischemic conditions, stenotic coronary arteries are connected via collaterals to intact or less severely stenotic arteries. This causes a typical redistribution of coronary flow with a possible steal phenomenon.

Any increase in heart rate would be deleterious as it would further reduce diastolic perfusion, increase stealing from the ischemic zone, and impair the flow at the ischemic obstruction, which, in turn, further compromises coronary flow. Reduction of heart rate under these circumstances is therefore highly beneficial.

Main Pharmacological Results for Cardiac Protection with Ivabradine

The effect of ivabradine on coronary perfusion has been investigated in resting and exercising conscious dogs and compared with the β-blocker propranolol [17]. Ivabradine reduced resting and exercising heart rate in a dose-dependent manner and preserved coronary artery vasodilatation during exercise without any negative inotropic effects. In contrast, for the same heart rate reduction, propranolol caused vasoconstriction of the coronary arteries and a negative inotropic effect.

The same study showed that ivabradine does not alter the increased cardiac output and stroke volume upon exercise, which were significantly decreased by propranolol. Finally, this study proved that the coronary and systemic effects of ivabradine were exclusively due to its effect on heart rate as they were abolished by atrial pacing [17]. Therefore, ivabradine reduces heart rate, preserves coronary vasodilatation upon exercise, i.e. myocardial perfusion, with no negative inotropic effects and maintenance of cardiac contractility.

Ivabradine's anti-ischemic properties also effectively ensure a better cardiac recovery upon reperfusion. In a recent study in our laboratories, we have shown that administration of ivabradine preserves tissue ATP levels in the isolated perfused rabbit heart during ischemia and reperfusion. This cardioprotection is dependent on ivabradine's heart-rate-lowering activity because it disappears upon atrial pacing and it is dose dependent. These results confirm previously reported findings in another experimental model study with a β-blocker [24].

Equally, ivabradine decreases, in a dose-dependent manner, myocardial oxygen consumption assessed in experimental studies by measuring the difference in quantity of oxygen between aortic and coronary sinus blood. In addition, ivabradine does not affect the ratio between oxygen delivery-consumption, thus preserving coronary artery dilatation.

The protection of the ischemic myocardium by heart rate reduction has been tested for ivabradine and atenolol in an animal model of exercise-induced ischemia and stunning [24]. Ivabradine and atenolol reduced heart rate to the same extent at rest and during exercise.

During exercise, ivabradine improved left ventricular wall thickening (anti-ischemic effect) and reduced the subsequent myocardial stunning compared with saline. The β-blocker also improved left ventricular wall thickening, but had no effect on stunning (fig. 5). The effect of ivabradine disappeared upon atrial pacing, proving that it is solely due to ivabradine's heart-rate-reducing properties [24] and can be linked to the improvement in myocardial contractility. Atenolol appeared to be rather deleterious on stunning [24].

Ivabradine has also been shown to improve left ventricular dysfunction in congestive heart failure and to reduce remodelling subsequent to myocardial infarction. In postmyocardial infarction rats, heart rate reduction with ivabradine decreased left ventricular collagen density and increased left ventricular capillary density, without modifying left ventricular weight, indicating that heart rate reduction improves left ventricular function, increases stroke volume, and preserves cardiac output (fig. 6). This improvement in cardiac function was related not only to the heart rate reduction per se but also to the modification of the extracellular matrix and the function of the myocytes as a result of the long-term reduction in heart rate [25]. These observations have been tested clinically using ivabradine in coronary artery disease patients with left ventricular

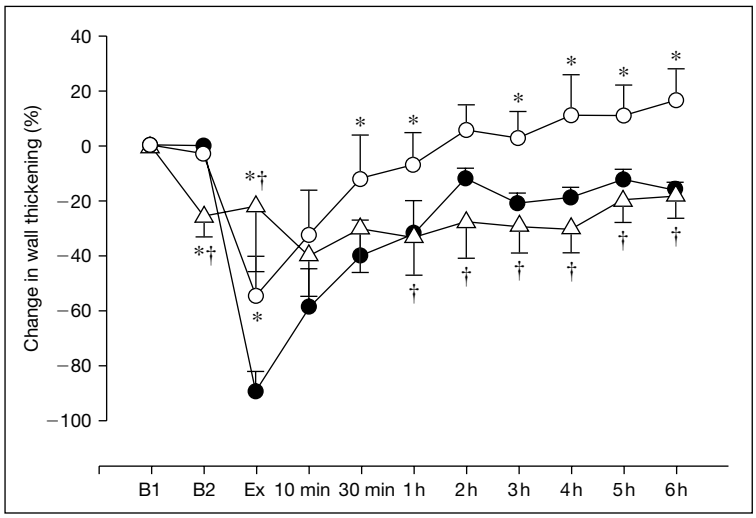

Fig. 5. Evolution of wall thickening percent change from (base 1) in the ischemic zone as measured before (B1) and after (B2) administration of saline (●), ivabradine (○), or atenolol (△). *$p < 0.05$, significantly different from saline; †$p < 0.05$, atenolol significantly different from ivabradine. Ex = Treadmill exercise test. Reproduced from Monnet et al. [24].

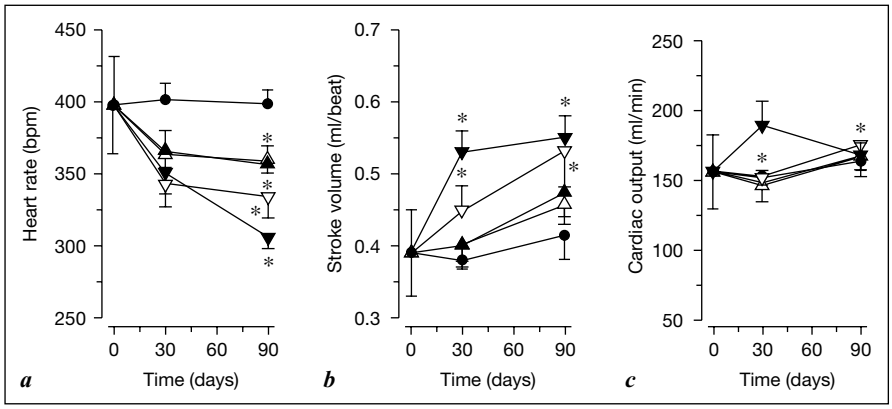

Fig. 6. Heart rate (***a***), stroke volume (***b***), and cardiac output (***c***) measures in anesthetized rats with congestive heart failure, either untreated (●) or treated by ivabradine at a dose of 0.3 (△), 1 (▲), 3.0 (▽), or 10.0 (▼) mg/kg/day (n = 8–19 per group). *$p < 0.05$ vs. untreated congestive heart failure. Reproduced from Mulder et al. [25].

dysfunction (ejection fraction <40%) with promising results [26]. These results may be linked to modifications of left ventricular structure.

Increased heart rate and hemodynamic forces may play a role in plaque disruption. Plaque rupture is the main pathophysiological mechanism underlying acute coronary syndromes and the progression of coronary atherosclerosis [27]. The role of hemodynamic forces, i.e. heart rate, has been investigated in 106 patients who underwent two coronary angiographic procedures within 6 months [28]. This study identified positive associations between plaque rupture, left ventricular muscle mass >270 g, and mean heart rate >80 bpm and a negative association with heart-rate-reducing treatment.

Potential Pharmacological Benefits of I_f Inhibition beyond Heart Rate Control

f-channels have been identified not only in the sinus node but also in the diseased ventricle of experimental animals with heart failure or in ventricular biopsies of patients transplanted for ischemic or dilated cardiomyopathies.

The presence of f-channels in ventricular myocytes is intriguing, and relates to pathophysiology rather than to physiology. In fact, the first recordings of the I_f current in normal guinea pig ventricular cardiomyocytes (VCMs) ruled out any possible physiological role for this current, which was much smaller than in the sinus node, and activated at voltages far from normal resting potentials (i.e. more negative than −100 mV) [29]. The situation, however, appears to be quite different in heart disease, since f-channels are upregulated in a variety of animal models of cardiac hypertrophy and failure [30–33]; in those circumstances, a functional role becomes apparent and a clear-cut diastolic depolarization can be detected in ventricular myocytes isolated from the diseased ventricles of those animals [30]. Figure 7 shows the relative increase in current density (diseased vs. control VCMs) in several rat models of cardiomyopathies as well as in human ischemic and dilated cardiomyopathies. Current density is a convenient way to normalize current amplitude with respect to cell size, as cardiomyocytes are ‘hypertrophic’. f-channels were at least doubled in left VCMs from rats with mild or severe cardiac hypertrophy caused by pressure overload, and in rats with overt heart failure caused by high blood pressure or postmyocardial infarction. The degree of hypertrophy positively correlated with an increased f-channel density [30] and changes in expression levels were most pronounced in those cardiac regions with highest overload (a finding that was confirmed in our lab), indicating that the processes leading to hypertrophy directly affected the level of hyperpolarization-activated cyclic nucleotide-gated channel expression. In addition to electrophysiological data, molecular

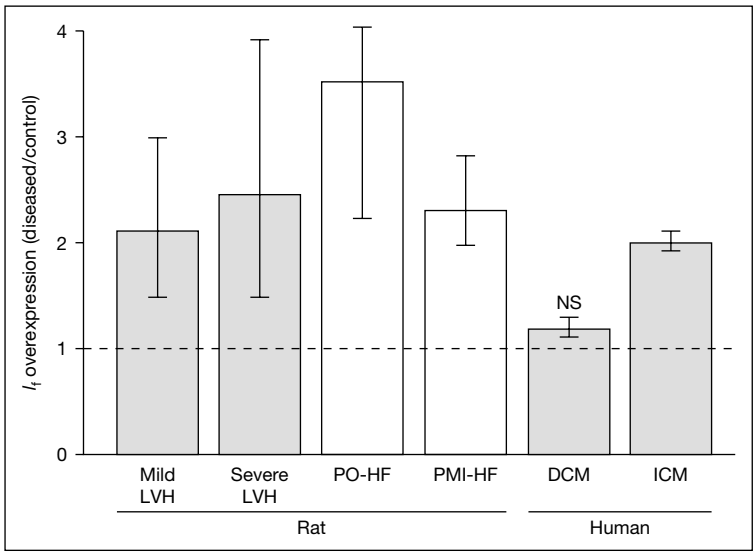

Fig. 7. Ventricular I_f expression is increased in cardiomyopathies. Each histogram represents the ratio between current density measured in VCMs from rat or human diseased hearts, and respective controls (indicated by the dashed line); bars are confidence intervals (95%). Mild LVH, severe LVH: relative increase in I_f in rats with mild or severe left ventricular hypertrophy caused by aortic banding or long-lasting pressure overload, respectively. PO-HF, PMI-HF: relative increase in I_f in rats with overt heart failure, resulting from uncompensated hypertrophy due to pressure overload or following myocardial ischemia due to coronary ligation, respectively. DCM, ICM: relative increase in I_f in patients undergoing cardiac transplantation for terminal dilated or ischemic cardiomyopathy, respectively. For all conditions, the relative increase in I_f density was statistically significant versus controls, that is normotensive rats, sham-operated rats, or undiseased donor heart not transplanted for technical reasons, with the exception of DCM patients. NS = Not significant.

biology techniques have evidenced a parallel upregulation of mRNA levels, of isoforms underlying ventricular channels [34] not only in the diseased rat heart [35] but also in the hypertrophied hearts of mice overexpressing β_2-adrenoceptors [36].

I_f recorded in nonpacemaker regions of the heart shows electrophysiological properties (voltage dependence, kinetics of activation, Na/K permeability ratio) qualitatively similar to those described 20 years ago by DiFrancesco et al. [as reviewed in reference 1] for primary and subsidiary pacemakers.

It was proposed that mislocalized expression and/or overexpression of cardiac f-channels may represent an example of a general phenomenon, termed cardiac remodelling, which also consists in the re-expression of fetal proteins. In fact, f-channels are present in fetal and neonatal ventricular myocytes

[37, 38] and lose their capacity for generating spontaneous activity during electrophysiological maturation toward adult phenotype. From a clinical point of view, the most interesting aspect of this phenomenon is that the I_f current may represent an arrhythmogenic mechanism in heart failure, a condition associated with high risk of sudden cardiac death. Another possibility is that the I_f current is implied in determining the transition from the adult to the embryonic genetic program, leading to reinstatement of cardiac apoptosis and subsequent remodelling of the ventricle.

Conclusion

We can expect a number of clinical benefits from pure heart reduction in coronary patients. Pure heart rate reduction by specific and selective I_f inhibition decreases oxygen demand and improves myocardial energetics; it increases diastolic perfusion time and preserves myocardial contractility and coronary vasodilatation during exercise. Ivabradine also protects the myocardium in acute ischemic conditions and has favorable antiremodelling properties in the long term. There is clinical proof of the antianginal and anti-ischemic effects of ivabradine in stable angina. Pure heart rate reduction with chronic treatment with ivabradine is therefore of clear clinical benefit in patients with chronic ischemic disease.

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Clinical Perspectives of Heart Rate Slowing for Coronary Event Reduction and Heart Failure

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Abstract

Heart rate is a major determinant of myocardial oxygen consumption. There is ample evidence of an association between high heart rate and poor outcome in numerous clinical settings. Experimental studies in monkeys have shown a link between increased heart rate and development of atherosclerosis. In the clinical setting, increased heart rate has been found associated with coronary plaque rupture. A causal relationship is further supported by the fact that β-blockers have a well-documented efficacy after myocardial infarction, although the other properties of these agents may also participate in their protective effect. Beyond the potential benefits of heart rate lowering in patients with coronary artery disease, medications capable of decreasing heart rate without altering left ventricular function, such as the I_f current inhibitor ivabradine, might prove particularly helpful in patients with chronic heart failure associated with coronary artery disease, but also in heart failure without systolic dysfunction, or in patients needing inotropic support for acute heart failure.

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Numerous epidemiologic studies have found strong correlations between resting heart rate and long-term outcomes, both in normal populations and in coronary disease patients [1–4]. But beyond these observational findings, there are many reasons to believe that heart rate reduction might prove beneficial in coronary artery disease patients. Obviously, the larger part of coronary perfusion takes place during diastole, where wall stress is considerably less than during systole, and the role of a lower heart rate in prolonging the diastolic time is patent. This article reviews some of the available evidence linking heart rate with the presence and evolution of coronary artery disease, and the possible clinical perspectives of heart rate reduction for treating coronary artery disease and heart failure.

Role of Heart Rate in the Clinical Course of Coronary Artery Disease

In the past, experimental data suggested a link between heart rate and the development of coronary artery atherosclerosis [5, 6]. Similarly, in experiments also using simian models, it was shown that the animals with the lowest heart rate had a less pronounced development of carotid atherosclerosis [7], while another study showed that the thickness of aortic or iliac plaques was correlated with the rate-pressure product [8], suggesting that heart rate might impact on the development of coronary as well as extracoronary atherosclerosis.

In man, the relationship between heart rate and coronary vasomotion was examined by Nabel et al. [9]. Coronary dilatation and coronary blood flow were studied in relation to increases in heart rate induced by pacing in a group of 15 patients, according to the presence and severity of coronary artery narrowings. The results observed in patients with normal coronary angiograms were compared with those in patients with mild plaques ($<$30% reduction) or with tight stenoses ($>$70%). In patients with normal coronary arteries, there was a rate-dependent increase in coronary artery cross-sectional area (up to +31%) and blood flow (up to +137%, at a rate of 150 beats per minute). In contrast, patients with mild plaques had a slight decrease in coronary artery area (about −10%), and a slight increase in coronary blood flow (+10%), and patients with tight stenoses exhibited a strong vasoconstriction (−73% coronary area) and a strong decrease (−70%) in coronary blood flow. From the results of this study, it appears that increased heart rate is likely to have devastating consequences in patients with advanced coronary artery disease, in whom it will aggravate the degree, and therefore the hemodynamic consequences, of the tightest stenoses.

The role of heart rate variations, however, may not be as straightforward as it may seem. In presumably healthy subjects, the failure to adequately *increase* heart rate during stress or exercise (chronotropic incompetence) appears clearly deleterious. In the Framingham offspring cohort, 1,570 men receiving no β-blocker therapy underwent exercise testing and were able to reach or go beyond Bruce stage 2 [10]. Their chronotropic response was evaluated using three different indices: failure to achieve 85% of maximal predicted workload, increase in heart rate from baseline to maximal exercise, and chronotropic response index (calculated as the ratio of heart rate reserve/metabolic reserve at Bruce stage 2). All 3 indices were significantly correlated with the occurrence of a coronary event during follow-up. They also independently (i.e. using multivariate analyses) predicted the occurrence of coronary events in patients who had no events during the first 2 years of follow-up.

Chronotropic incompetence and inadequate recovery of heart rate after exercise were also found to have a deleterious prognostic impact, irrespective of

the severity of coronary artery disease and of left ventricular function [11, 12]. Similarly, it was found in a prospective cohort of nearly 6,000 working men followed for 23 years that both chronotropic incompetence during exercise and a lower return to normal after exercise were predictors of sudden death [13].

From these data, it appears that a lower heart rate at baseline is beneficial, but that the heart must keep at least part of its capacity to increase its rate in situations of increased metabolic demand.

Beyond its beneficial effects in terms of myocardial perfusion, a lower heart rate might also help avoid complications of coronary artery disease. In this regard, a recent angiographic study suggests a possible explanation: a lower heart rate might bring protection against the risk of coronary plaque rupture [14]. In this study, 53 patients having undergone two coronary angiograms 6 months apart and showing evidence of rupture of an initially smooth atherosclerotic plaque on the second angiogram were matched on age and sex with 53 patients without signs of plaque rupture. The 2 best independent predictors of plaque rupture were an increased left ventricular mass >270 g (odds ratio: 4.92, 95% confidence interval: 1.83–13.2) and a mean resting heart rate over 24 h at the time of the first angiogram >80 beats per minute (odds ratio: 3.19; 95% confidence interval: 1.15–8.85). In addition, treatment with β-blockers was associated with a significant independent reduction in the risk of plaque rupture, similarly, treatment with angiotensin-converting enzyme inhibitors or statins was associated with a strong trend toward a reduction in the risk of plaque rupture ($p = 0.06$).

Inducing Changes in Heart Rate: A Therapeutic Target?

Nonpharmacological Intervention

Among the different therapeutic possibilities in patients with coronary artery disease, myocardial revascularization, either using coronary bypass surgery or percutaneous coronary interventions, is not expected to decrease heart rate. In contrast, nonpharmacological interventions such as physical training and cardiac rehabilitation can lower heart rate, both at baseline and during exercise, resulting in an increase in exercise capacity. Malfatto et al. [15] studied 53 patients with stable coronary artery disease and a recent myocardial infarction. Three groups were examined: 14 patients who received β-blocking agents and did not participate in the rehabilitation program (group 1), 19 patients who participated in the rehabilitation program but received no β-blockers (group 2), and 20 patients who both underwent cardiac rehabilitation and received β-blockers (group 3). At baseline, exercise duration, maximal workload, and rate-pressure product were similar in all 3 groups. After 3 months, however, exercise duration and maximal workload increased and the rate-pressure product decreased in a

similar way in groups 2 and 3, while all 3 variables remained unchanged in the group which received β-blocking agents but did not participate in the rehabilitation program. Such benefits of physical training may result in definite clinical improvement, both in terms of symptoms and coronary events.

Physical training was compared to percutaneous coronary interventions in a controlled trial including 101 patients ≤70 years of age with stable coronary artery disease and an index coronary artery stenosis amenable to percutaneous intervention [16]. Patients in the exercise training group first had a 2-week hospital program of physical training, and were then asked to exercise daily (20 min of bicycle ergometry per day). At 2 years of follow-up, resting heart rate decreased from 71 to 65 beats per minute in the exercise training group, but was unchanged in the percutaneous coronary intervention group. There was an equivalent improvement in the Canadian classification of angina. Maximal exercise tolerance increased in the exercise training group but remained unchanged in the percutaneous coronary intervention group. Event-free survival was higher in the rehabilitation group (88 vs. 70%, $p = 0.02$), mainly because of reinterventions in the groups having undergone coronary angioplasty.

β-Blocking Agents

Among medications with a potential to lower heart rate, some of the calcium antagonists have shown a trend to improved clinical outcomes after acute coronary syndromes, at least in the absence of marked left ventricular dysfunction. But the class of anti-ischemic medications with the most important impact on heart rate is obviously that of β-blocking agents. In the recent past, data have suggested that β-blockers might have additional efficacy, compared with other antianginal medications having similar direct anti-ischemic properties. In a series of 352 patients with stable coronary artery disease having undergone thallium single photon emission computed tomography, Marie et al. [17] analyzed the influence of therapeutic changes immediately after the exercise test. The presence of myocardial ischemia documented by thallium single photon emission computed tomography was a strong predictor of major coronary events in the whole population; in patients who received β-blocking agents after the test, however, the prognostic impact of exercise ischemia was no longer found, whereas it remained present in patients who received additional antianginal medications when these medications did not include β-blockers. Whether the additional protection conferred by β-blockers might be partially or totally related to their heart-rate-lowering capacity remains speculative. Concordant data, however, suggest that heart rate reduction with β-blockers might be one of the main reasons for their efficacy. After myocardial infarction, there is ample evidence that β-blocking agents improve long-term prognosis. In the meta-analysis by Freemantle et al. [18], administration of β-blockers was associated

with a 23% reduction in the risk of death over the following years. When β-blockers were classified according to their pharmacologic properties, however, those with an intrinsic sympathomimetic activity appeared to have a lesser efficacy compared with those without intrinsic sympathomimetic activity (odds ratio: 1.19; 95% confidence interval: 0.96–1.47). Likewise, a very strong correlation is found between the reduction in mortality with β-blockers and the decrease in heart rate observed in the randomized trials carried out with different β-blocking agents in the postmyocardial infarction setting [19]. In the CIBIS-II trial, which assessed the role of β-blockade with bisoprolol in patients with congestive heart failure [20], changes in heart rate were recorded in patients alive 2 months after inclusion in the trial and their impact on long-term survival was assessed. Using multivariate analyses, both a lower baseline heart rate and a higher degree of heart rate reduction during the first 2 months were independently correlated with late mortality. In patients with sinus rhythm at baseline, treatment with bisoprolol was an additional predictor of improved survival, independently of baseline heart rate and of heart rate reduction, suggesting independent roles for heart rate reduction and use of the β-blocking agent bisoprolol in this setting.

Experiments in nonatherosclerotic dogs also suggest that the anti-ischemic efficacy of β-blockers is not solely due to their heart rate reduction properties, but also to their negative inotropic effects. Colin et al. [21] compared myocardial oxygen consumption in a series of 8 instrumented dogs under saline, atenolol or ivabradine infusion. Both atenolol and ivabradine decreased oxygen consumption at maximal workload, though the β-blocker had a more profound effect. When the dogs were paced, however, ivabradine failed to improve oxygen consumption, while atenolol still had an impact, suggesting that, in this model, the anti-ischemic effect of atenolol was equally due to its action on heart rate and inotropism. Conversely, Aupetit et al. [22] analyzed the impact of propranolol on the fibrillation threshold, in pigs subjected to increasing periods of ischemia. Under spontaneous heart rate conditions, propranolol significantly increased the fibrillation threshold at all durations of coronary occlusion. When the animals were paced, however, the antifibrillatory effect of propranolol completely disappeared, suggesting that this major protective property of β-blocking agents might be solely related to their impact on heart rate.

Potential Applications in Heart Failure: Diastolic Heart Failure, Acute Heart Failure

With the constant ageing of patient populations in industrialized countries, heart failure with preserved left ventricular systolic function represents an

increasingly frequent cause of cardiac failure. The therapeutic management of these patients is complex, as only very few patients with diastolic heart failure were enrolled in the large randomized trials. As stated by the Task Force of the European Society of Cardiology for the Diagnosis and Treatment of Chronic Heart Failure [23, 24], therapeutic recommendations therefore remain largely speculative. Nevertheless, because of the pathophysiologic mechanisms of diastolic dysfunction, medications that improve relaxation by reducing heart rate and increasing the diastolic period are recommended. To date, these medications are mainly represented by β-blockers and verapamil-type calcium antagonists, which were recommended as first-rank therapy by the European Task Force. In support of this concept, an ancillary study of the Metoprolol in Dilated Cardiomyopathy Trial [25], which included 77 patients with congestive heart failure undergoing repeated Doppler echocardiographic measurements over 1 year, showed that the evolution of E-wave deceleration time, a marker of diastolic function, reflected the evolution of heart rate, both in patients on placebo and in those receiving metoprolol: a lower heart rate was accompanied by increased E-wave deceleration time, reflecting improved diastolic function in these patients otherwise presenting with impaired left ventricular systolic function; conversely, when heart rate increased in patients on placebo, E-wave deceleration time decreased. Ivabradine, the selective and specific I_f current inhibitor, prolongs the diastolic period without impairing ventricular contractility, which might be particularly helpful in the specific setting of diastolic heart failure. Colin et al. [26] examined left ventricular relaxation in response to saline infusion, atenolol or ivabradine in dogs at rest and during exercise. Under saline, heart rate increased from 108 to 220 beats per minute, and the relaxation constant τ_{BF} decreased from 22 to 14 ms. Both atenolol and ivabradine significantly limited the increase in heart rate during exercise to about 150 beats per minute. Concomitantly, atenolol prevented the decrease in τ_{BF} (23 ms), while ivabradine did not (15 ms). In brief, ivabradine limited exercise-induced tachycardia, without simultaneously altering the exercise-induced acceleration of the rate of left ventricular relaxation; in contrast, for the same levels of limitation of heart rate during exercise, atenolol did prevent the acceleration of the rate of ventricular relaxation.

Lastly, ivabradine has the unique property to decrease heart rate without depressing left ventricular function. In acute situations such as the acute stage of myocardial infarction, a higher heart rate on admission is a strong correlate of mortality. In a prospective registry of patients admitted for acute myocardial infarction in France in 2000, heart rate >90 beats per minute on admission was associated with a 76% increase in the risk of in-hospital mortality after multivariate adjustment [27]. In such situations, the capacity to decrease heart rate without altering cardiac contractility would appear particularly useful. In such

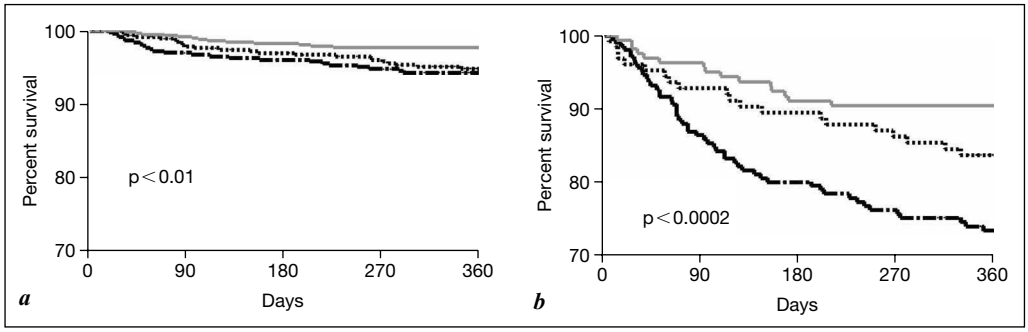

Fig. 1. Impact of admission heart rate. In patients surviving an acute myocardial infarction, the prognostic significance of admission heart rate (represented here as tertiles) is much less when patients are subsequently treated with β-blockers. After multivariate adjustment, increased heart rate is no longer an independent predictor of 1-year mortality in patients discharged on β-blockers. ***a*** Patients on β-blockers. ***b*** Patients without β-blockers. Data from the French USIC 2000 registry. Black curve = highest tertile, dotted line = middle tertile, grey line = lower tertile.

patients, the long-term prognostic significance of increased admission heart rate was much less when the patients subsequently received β-blocking agents (fig. 1) and was no longer an independent predictor of long-term mortality in multivariate analyses. In addition, in the case of acute heart failure complicating acute myocardial infarction, but also in patients with acute decompensation of chronic heart failure, the use of sympathomimetic agents such as dobutamine or dopamine is usually warranted. However, in clinical practice, the increase in heart rate caused by dobutamine often constitutes a limitation for its use, particularly at high dosages. The combined use of heart-rate-controlling medications might prove particularly helpful, provided these medications do not cause any additional impairment in left ventricular function. There is experimental evidence, in a rat model of myocardial stunning caused by a sequence of ischemia and reperfusion, that the concomitant use of dobutamine and ivabradine permits to avoid the tachycardia generated by dobutamine, without impairing mean arterial pressure, nor the recovery of left ventricular wall thickening and left ventricular fractional shortening obtained with dobutamine [Richard, pers. commun.].

Conclusion

Heart rate is a major determinant of myocardial oxygen consumption. There is ample evidence of an association between high heart rate and poor

outcome in numerous clinical settings. A causal relationship is reinforced by the fact that β-blockers have a well-documented efficacy in secondary prevention after myocardial infarction, although the other properties of these agents may also participate in their protective effect. Likewise, nonpharmacologic measures that cause heart rate reduction, such as programs of regular exercise training, also have beneficial clinical effects. Beyond the potential benefits of heart rate lowering in patients with coronary artery disease, medications capable of decreasing heart rate without altering left ventricular function might prove particularly helpful in patients with diastolic heart failure, or in patients needing inotropic support for acute heart failure. Ivabradine, a selective inhibitor of the I_f current, has demonstrated an anti-ischemic efficacy that is similar to that of β-blockers in man. Whether this medication, capable of decreasing heart rate without concomitant hemodynamic properties, will have, at least in some clinical situations, an efficacy similar or even superior to that of β-blockers in terms of secondary prevention remains to be studied.

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Clinical Effect of 'Pure' Heart Rate Slowing with a Prototype I_f Current Inhibitor: Placebo-Controlled Experience with Ivabradine

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Abstract

Heart rate slowing is generally accepted as effective for angina prevention but this approach has not been rigorously evaluated as no pure heart rate slowing treatment has been available. With the identification of the I_f current, the primary modulator of heart rate, and use of this as a target for drug development, the role of isolated heart rate slowing can be elucidated. More than 4,000 patients now have been studied in angina prevention trials with ivabradine, a prototype I_f current inhibitor devoid of other cardiovascular effects. These studies demonstrate the efficacy of isolated heart rate slowing for angina prevention. Indeed, in one direct comparison with atenolol involving 939 patients, ivabradine not only was non inferior to the β-blocker but nominally appeared to be more efficient in angina prevention. Moreover, since ivabradine is devoid of most of the adverse effects of β-blockers (and of calcium channel blockers), it is a suitable alternative when these established drugs are not adequately tolerated. Additional studies now must assess other potential actions in patients with coronary disease.

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This article reviews and interprets the results of placebo-controlled clinical trials of ivabradine in patients with angina pectoris to enable conclusions about the efficacy of pure heart rate reduction in the prevention of the symptom. Though heart rate slowing is universally recognized as an effective strategy for angina prevention, it has been difficult to evaluate the utility of this approach, particularly in comparison with multidrug therapy aimed at several pathophysiological

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targets. The reason for this difficulty is that no heart rate slowing treatment has been devoid of effects on other cardiovascular characteristics that may confound interpretation of the importance of isolated heart rate slowing. β-Blocking drugs, originally developed primarily because of the theoretical benefits of heart rate slowing associated with their use [1], actually have complex pharmacological effects that include vasoactivity (either vasoconstriction or vasodilatation depending on the degree of selectivity of the drug for specific β-receptor subtypes), negative inotropy, and interference with normal atrioventricular and even intraventricular conduction of electrical impulses, all at doses that are employed clinically and all potentially involved in generating adverse effects that limit tolerability of the heart-rate-reducing benefit [2]. Moreover, each of these effects can modulate the likelihood and severity of angina, precluding conclusions about the relative therapeutic importance of heart rate slowing alone. Even the carotid sinus nerve stimulator, developed several decades ago specifically for heart rate reduction [3], had the potential for additional vasodepressive effects. The role of isolated heart rate slowing for angina prevention can be optimally elucidated only by application of a pure heart rate slowing therapy. The development of ivabradine has provided a prototype drug that is well suited for exploring the pathophysiological importance of heart rate in the development of angina and the relative utility of pure heart rate slowing for its prevention [4]; concomitantly, the absence of other cardiovascular effects enables the resolution of the relation of heart rate slowing to certain adverse effects of other heart-rate-slowing drugs (β-blockers, nondihydropyridine calcium channel blockers) that have been ascribed to heart rate slowing but for which other possible pharmacological effects may also be responsible. Thus, information needed to support I_f inhibition for application in patients with angina can be gained only from appropriately designed clinical trials of a drug manifesting this pharmacological effect [5].

The pharmacology of ivabradine is presented elsewhere in this volume and will not be reviewed here. However, to evaluate and interpret the results of the clinical trials, it is important to emphasize that, while hyperpolarization-activated cyclic nucleotide-gated channels exist in several parts of the heart and in other tissues, and blockade of these channels may be associated with pharmacological effects not yet identified or understood, current evidence suggests that these channels are not physiologically active in the heart except in the sinoatrial node. Thus, at the ivabradine doses used for heart rate slowing, no other cardiovascular effects of I_f inhibition are apparent, rendering ivabradine uniquely useful in efforts to understand the effects of pure heart rate slowing [4]. Specifically, the drug does not suppress myocardial inotropy [6–9], does not independently impact on electrocardiographic (ECG) QT interval duration [10] (though, of course, this parameter is related to heart rate), does not affect the cardiac conduction system and does not cause vasoconstriction or vasodilatation [11].

Placebo-Controlled Clinical Trials with Ivabradine for Angina Prevention

More than 4,000 patients with coronary artery disease and chronic stable angina [4] have been studied as part of the formal clinical development of ivabradine for angina prevention. This is by far the largest antianginal drug development effort reported to date. Additional large trials are now ongoing to assess the impact of heart rate slowing with ivabradine on mortality and major morbid events among patients with coronary artery disease, and on various manifestations of heart failure with and without coronary disease [12]. The first placebo-controlled trial of ivabradine as monotherapy (of sufficient duration to be considered as a basis for approval by drug regulatory agencies) was sufficiently large to provide useful estimates of the magnitude of the antianginal effect resulting from pure heart rate slowing [13].

The trial design featured an initial 2- to 7-day placebo 'washout and run-in phase' (duration depending on the time-action characteristics of the drugs employed prior to the trial) followed by a 2-week parallel-arm 'dose-ranging' comparison of placebo versus ivabradine administered as either 2.5 mg orally twice daily, 5 mg twice daily or 10 mg twice daily; treatment assignment was randomized and double blinded. Importantly, neither another long-acting antianginal drug therapy nor another cardioactive treatment that might affect membrane activity (and, hence, ECG responses) could be employed during the trial. Only short-acting nitroglycerin was allowed to treat patients when angina occurred. Multiple centers in several different countries provided the 360 patients initially entered into the trial (intent-to-treat population). After the 2-week parallel-arm phase, all patients were to receive ivabradine 10 mg twice daily, open label, for 2–3 months (participation voluntary), followed by a placebo-controlled withdrawal (sudden cessation of ivabradine in half the patients, maintenance of 10 mg twice daily in the others) for 1 week or unless limiting angina supervened earlier. Bicycle ergometric exercise testing (one of the approaches routinely employed to standardize angina-inducing stresses to achieve drug approval for marketing [14]), with ECG monitoring to assess ischemia, was performed at several intervals, including prior to randomization, immediately prior to all regimen changes and at study conclusion, as well as at some intermediate times. Early withdrawals and/or protocol violations affected 103 patients; therefore, 257 patients comprised the 'per-protocol' subset for purposes of analysis (fig. 1). In addition, local legal and other constraints, as well as patient choice, precluded participation of some patients in the randomized withdrawal phase and dictated whether the open-label phase could be 2 or 3 months. Insofar as can be ascertained, these exclusions were nonbiasing.

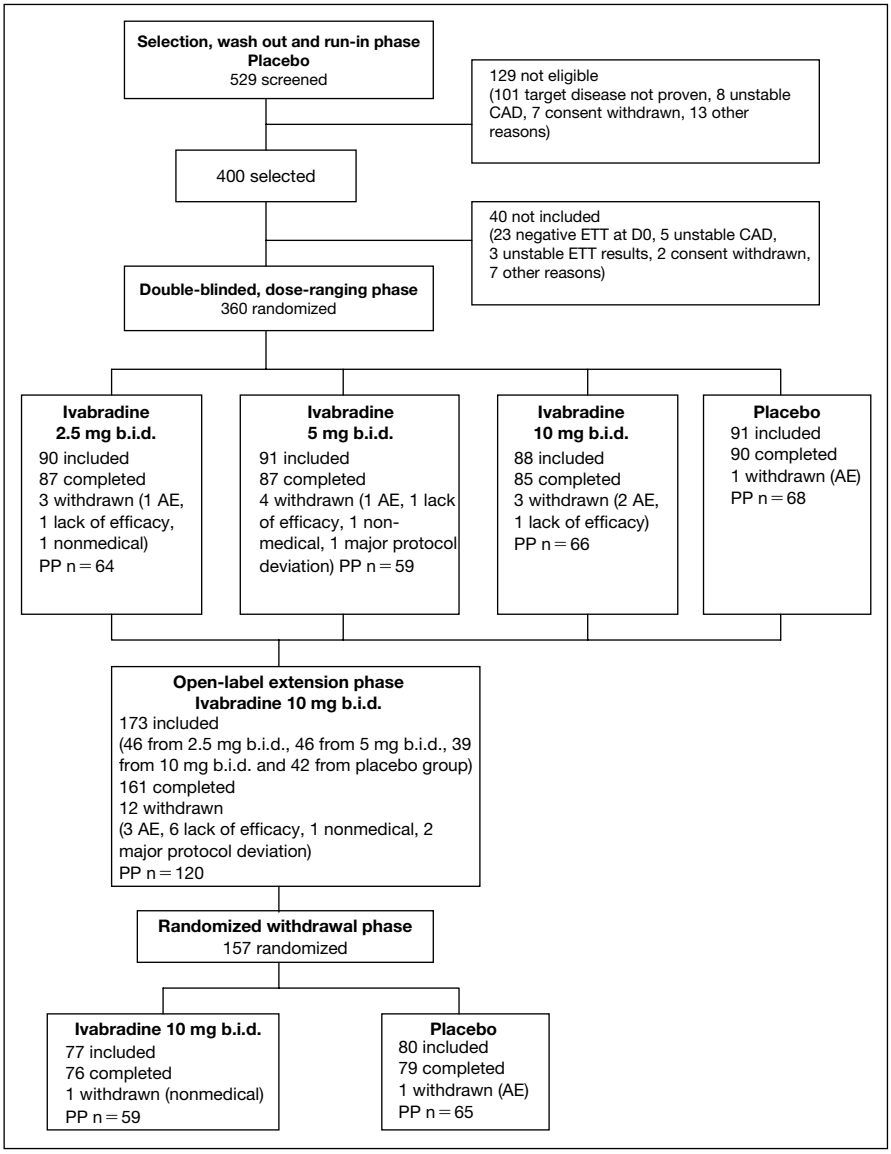

Fig. 1. Design of the trial of ivabradine as monotherapy. AE = Adverse event; CAD = coronary artery disease; ETT = exercise tolerance test; PP = per-protocol population. (Reprinted from Borer [13], with permission from the American Heart Association, Dallas, Tex., USA.)

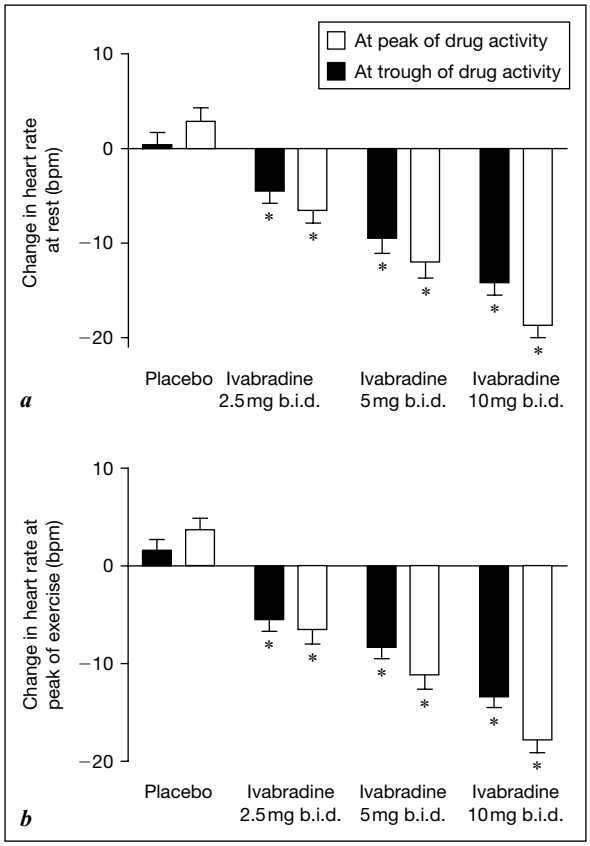

Fig. 2. Changes in heart rate at rest (***a***) and at peak exercise (***b***) in the different treatment groups during double-blinded dose ranging of ivabradine. Error bars = Standard error of the mean. *$p < 0.05$ versus placebo in pairwise comparison. (Reprinted from Borer [13], with permission from the American Heart Association, Dallas, Tex., USA.)

The initial outcome of importance was the effect of ivabradine on heart rate. This was dose related, was apparent both at rest and during exercise and, at the doses employed, was similar to that expected with therapeutic doses of β-blockers for angina prevention (and greater than usually achieved with relevant, nondihydropyridine calcium channel blockers). At the trough of drug activity, placebo-subtracted heart rate reduction at rest ranged from an average of approximately 13 beats/min at the highest dose to approximately 3 beats/min at the lowest and, during exercise, from approximately 12 beats/min to approximately 4 beats/min (fig. 2). This effect appeared to be related solely to drug, with no apparent influence of reflex or compensatory responses to other pharmacological changes:

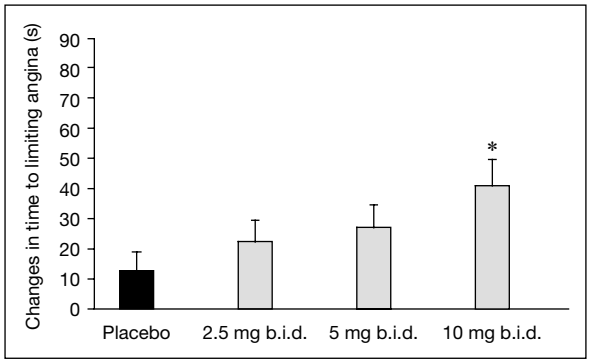

Fig. 3. Effect of ivabradine, at the trough of drug activity, on time to angina sufficient to limit continued bicycle exercise among 257 protocol-compliant patients with coronary artery disease. Measurements were obtained after 2 weeks of double-blinded randomized therapy. A dose-response relation is apparent and the dose of 10 mg b.i.d. is significantly more effective than placebo (*$p < 0.05$). Between-dose comparison was significant at $p = 0.049$. (Reprinted from Borer [15] with permission.)

neither blood pressure reduction nor other functional changes were observed with ivabradine. Thus, in this trial, heart rate slowing was the primary and, insofar as can be determined, only cardiovascular effect of therapy.

Ivabradine-mediated heart rate slowing resulted both in prolonged exercise tolerance before angina development (or total preclusion of angina), reduction (or preclusion) of exercise-mediated ischemia and reduction in angina reported during ambient activity, as compared with placebo treatment. (Reduction in ischemia in association with angina reduction is important both from a pathophysiological perspective and in terms of approval and labeling of antianginal modalities by duly constituted regulatory authorities in the United States and Europe; it is important to exclude the possibility that treatment is 'masking' angina through an analgesic effect, possibly allowing patients to exercise to dangerous ischemia, sufficient to cause infarction or worse, without symptomatic warning.)

Thus, data from the per-protocol population, analyzed immediately after the 2-week parallel-arm phase, indicate an increase in time to limiting angina with all doses of drug compared with placebo [13], though the comparison reached statistical significance only with the highest dose (greatest heart rate reduction) (fig. 3); however, a dose-effect relation was apparent across all doses, with between-group comparison reaching statistical significance ($p = 0.049$). Results in the intent-to-treat population (i.e. including protocol violators and early withdrawals) were similar to those of the per-protocol population but, as might be expected, were somewhat less consistent, reaching a p value of 0.058. During

open-label extension, all patients not receiving 10 mg twice daily (including those previously receiving placebo, 2.5 or 5 mg ivabradine twice daily) increased their dose to match that of the approximately one quarter of patients who had been randomized to and continued on this dose. Further slowing of heart rate in these patients was associated with increase in exercise capacity to match that of the patients initially receiving the maximal drug dose (fig. 4). When half the patients were withdrawn at random (and in blinded fashion) to placebo after the open-label phase, time to limiting angina fell significantly in patients reassigned to placebo but was unaltered among patients maintained on ivabradine 10 mg twice daily (between-group difference: $p = 0.018$) [13].

Simultaneously with improvement in exercise tolerance, exercise-induced ischemia was significantly mitigated by drug-mediated heart rate slowing [13]. Time to 1 mm ST segment depression was significantly lengthened by ivabradine 5 mg twice daily and 10 mg twice daily; a dose-response relation was apparent for the anti-ischemic effect of heart rate slowing across all doses. Ambient angina attack rate and nitroglycerin use were significantly reduced by chronic heart rate slowing, and were increased by randomized withdrawal to placebo [13].

Heart rate slowing with ivabradine was associated neither with syncope nor untoward hypotension nor heart failure. Indeed, adverse events, except those associated with vision, were similar in the placebo and ivabradine groups [13].

Visual symptoms, including mainly phosphenes, were more frequent in patients receiving ivabradine than placebo, were dose related, were rarely sufficiently bothersome to cause voluntary withdrawal from drug and were invariably reversible with drug cessation, consistent with the absence of irreversible retinal effects reported in preclinical studies. There is no basis for attributing the visual symptoms to heart rate slowing; rather, these are likely related to the presence of ion channels in the retina that are very similar to those in the sinoatrial node. [The retina appears to be among the few places (perhaps the only place) in the body, other than the sinoatrial node, where such channels are physiologically functional. From data gathered from the full ivabradine development program, visual side effects occur in 2–15% of patients receiving 2.5–10 mg twice daily; they were sufficiently bothersome to result in drug withdrawal in $<1\%$ of patients [11].]

Clearly, since heart rate slowing with ivabradine results from activity of the drug directly and solely on the sinoatrial node, this drug cannot be used to achieve the desired goal (or the resulting angina prevention) in patients with atrial fibrillation; further, patients with bradycardia due to intrinsic sinus node disease (‘sick sinus syndrome’) should not receive ivabradine because of concern about excessive rate reduction; such patients were not included in the ivabradine development trials.

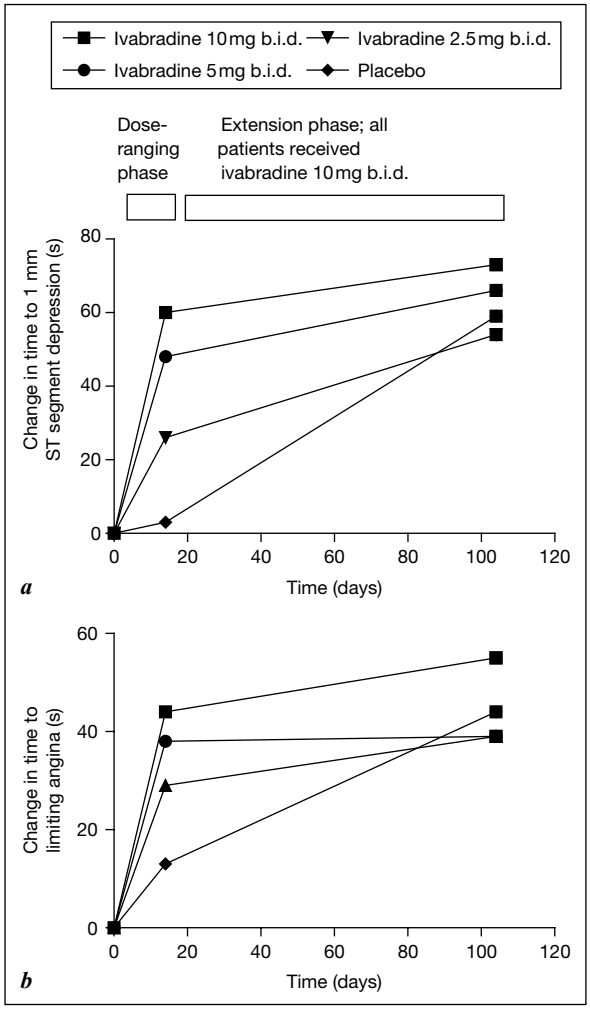

Fig. 4. Changes in time to 1 mm ST segment depression (***a***) and in time to limiting angina (***b***) measured during the exercise tolerance test at the trough of drug activity, in 'per-protocol' patients continuing in the open-label extension, identified by their treatment group during the double-blinded phase. Data for the approximately. 10% of patients for whom the open-label extension ended after 2 months were pooled with those for whom the extension ended after 3 months. (Reprinted from Borer [13], with permission from the American Heart Association, Dallas, Tex., USA.)

One additional placebo-controlled trial of heart rate slowing with ivabradine has been performed. Design and results of this study have been presented publicly at the European Society of Cardiology Annual Scientific Session, but have not been published in full or abstract form. Therefore, details of this study cannot be presented here. However, in summary, the second trial involved randomization to oral treatment with either placebo, ivabradine 5 mg twice daily, or ivabradine 7.5 mg twice daily, each administered on a background of amlodipine 10 mg daily. As amlodipine is a direct vasodilating dihydropyridine calcium channel blocker devoid of direct effects on heart rate, the use of this drug would not be expected to alter the effects of ivabradine on heart rate. The study was carried out during a 3-month period of randomized, double-blinded drug administration, in 728 patients with chronic, stable coronary artery disease and angina. Preliminary assessment indicates significant heart rate slowing with ivabradine and, in association with this pharmacological effect, statistically significant superiority of ivabradine versus placebo for both doses at peak drug effect, with nominal superiority at trough.

Additional insight into the relative importance of heart rate slowing can be gained from a trial that compared ivabradine and atenolol without a placebo arm. In this study, presented preliminarily in abstract form and recently published in full [16], 939 patients received either ivabradine or atenolol. For 4 weeks, atenolol 50 mg daily was compared with ivabradine 5 mg twice daily; during the next 3 months, atenolol 100 mg daily was compared with one of 2 ivabradine dose regimens, 7.5 mg twice daily or 10 mg twice daily. Antianginal and anti-ischemic measures were statistically indistinguishable among the comparisons, though ivabradine was nominally superior to atenolol in comparisons at all doses, despite the nominally greater heart rate reduction with atenolol than with the corresponding doses of ivabradine. Thus, formal noninferiority testing indicated that ivabradine was not inferior to atenolol at these doses ($p < 0.0001$), but also suggested that the antianginal effect of heart rate slowing, alone, may be slightly mitigated by other effects of the β-blocker. Though this hypothesis must be retested and confirmed by other studies before it can be accepted, this possibility raises important pathophysiological and pharmacological issues regarding the role of heart rate and its modulation. In addition, fatigue was more prominent with atenolol than with ivabradine, suggesting that heart rate, itself, is not the only possible cause of this adverse event with currently approved heart-rate-slowing antianginal drugs.

Elucidation of the impact of heart rate slowing is also provided by another non-placebo-controlled, but randomized and double-blinded comparison of 2 doses of ivabradine (ivabradine 5 mg twice daily or ivabradine 7.5 mg twice daily) administered for 1 year to 386 patients [17]. At the conclusion of the study, heart rate was compared with that recorded at baseline prior to treatment and was substantially reduced, as in earlier studies. Once again, heart rate slowing

was associated with a reduction in angina frequency, measured only as ambient episodes, with no untoward effects related specifically to heart rate slowing.

Conclusions

Placebo-controlled clinical trials involving ivabradine, supported by comparative studies not involving placebo, are consistent with the importance of heart rate in determining the frequency of angina and the severity of underlying ischemia. As a practical matter, these studies are most important in supporting the value of pure heart rate modulation in preventing angina and minimizing underlying ischemia. The data further suggest that heart rate slowing, by itself, is relatively well tolerated, and that the adverse effects of other heart-rate-slowing antianginals, including β-blockers and nondihydropyridine calcium channel blockers, are most likely due to other pharmacological effects of these drugs. These adverse effects are important in determining the tolerability of therapy. They include, for β-blockers (generally the first choice for angina prevention), exacerbation of claudication from associated peripheral arterial occlusive disease [1], of symptoms of obstructive lung diseases [18], of sequelae of intrinsic atrioventricular node disease [19], of hypotension of nonspecific causes and of difficulty in managing metabolic disorders (diabetes mellitus [20] or hyperlipidemia [21]), and potential production or exacerbation of sexual dysfunction in men and depression in both sexes. For calcium channel blockers, potentially avoidable adverse effects include atrioventicular node dysfunction, unmasking of congestive heart failure [22], peripheral edema, gingival hyperplasia and constipation (a particular problem in the elderly). For long-acting nitrates [23], adverse effects that may be avoidable with substitution of pure heart rate modulation for angina prevention include headaches or light-headedness (direct results of the beneficial pharmacological effects of nitrates); also intermittent use of nitrates may result in rebound angina and vasoconstriction. The studies with ivabradine, a pure heart-rate-slowing agent, indicate that these adverse effects, if encountered, may be avoided without sacrificing angina prevention by depending on pure heart rate reduction.

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Heart Rate Slowing versus Other Pharmacological Antianginal Strategies

Results of Comparative Studies

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Abstract

Relieving the symptoms of angina and improving the quality of life and functional status are important objectives in the management of patients with chronic stable angina. A high heart rate induces or exacerbates myocardial ischemia and angina because it both increases oxygen demand and decreases myocardial perfusion. β-Blockers are effective at reducing anginal symptoms largely by decreasing heart rate. Physician use and patient compliance may be limited by the side effects of β-blockers which include fatigue, depression and sexual dysfunction. Heart rate reduction can also be obtained by the calcium antagonists verapamil and diltiazem and by the new selective heart-rate-reducing agent ivabradine. Ivabradine (Procoralan) is a selective and specific I_f inhibitor that acts on one of the most important ionic currents for the regulation of the pacemaker activity of sinoatrial node cells. Ivabradine has demonstrated dose-dependent anti-ischemic and antianginal effects in a placebo-controlled study. The INITIATIVE trial is a large multicenter trial in which 939 patients with stable angina were randomized to ivabradine or atenolol. The noninferiority of ivabradine was shown in the INITIATIVE trial at all doses and for all criteria including time to limiting angina. The number of angina attacks per week was decreased by two thirds with both ivabradine and atenolol. In another trial of 1,195 patients, time to 1 mm ST segment depression was increased by 45 s with ivabradine 7.5 mg b.i.d. and by 40 s with amlodipine 10 mg daily. Unlike β-blockers, ivabradine is devoid of intrinsic negative inotropic effects and does not affect coronary vasomotion. A whole range of patients with angina may benefit from exclusive heart rate reduction with ivabradine, including those with contraindications or intolerance to the use of β-blockers and patients that are insufficiently controlled by β-blockers or calcium channel blockers.

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Chronic stable angina is a common and disabling condition, affecting 30,000–40,000 per 1 million people in Europe and the United States. Angina results when myocardial perfusion is insufficient to meet metabolic demand.

Individuals with typical chronic stable angina usually have significant narrowing of at least one major epicardial vessel and experience pain which is related to an increase in physical activity or psychological stress. Heart rate is one of the most important determinants of myocardial oxygen demand. A high heart rate induces or exacerbates myocardial ischemia and subsequent angina since it both increases myocardial oxygen demand and decreases myocardial perfusion, the latter by shortening the duration of diastole.

Relieving the symptoms of angina and improving the quality of life and functional status are an integral part of the management of patients with chronic stable angina [1]. β-Blockers are effective at reducing anginal symptoms largely by decreasing heart rate [2] and they have usually been preferred as initial therapy in the absence of contraindications [3]. Despite the demonstrated safety and effectiveness of β-blockers, physician use and patient compliance may be somewhat limited by the side effects of this class of agents which include fatigue, sexual dysfunction, depression, cold extremities, light-headedness, gastrointestinal disturbances, bronchospasm and atrioventricular block [4–7]. β-Blockade can also increase coronary resistance and limit exercise-induced increase in coronary arterial flow [8, 9]. In addition, β-blockers can reduce left ventricular (LV) contractility and have negative lusitropic effects [10]. Finally, this class of agents can have detrimental effects on carbohydrate and lipid metabolism [11, 12].

Heart rate reduction can also be obtained by a few other antianginal agents that do not cause β-adrenergic receptor blockade, namely the calcium channel blockers verapamil and diltiazem and the new pure heart-rate-lowering agent ivabradine. This article reviews the results of studies comparing heart-rate-slowing agents and other pharmacological antianginal strategies.

β-Blockers versus Calcium Channel Blockers

The majority of the clinical trials that have compared β-blockers and calcium antagonists in patients with stable angina were crossover in design and the mean length of the studies was only 8 weeks [13]. Most of these studies required the documentation of coronary artery disease or the presence of myocardial ischemia. More than 80% of patients involved in these trials were men, approximately 35% had a history of myocardial infarction and a minority of patients (11%) had diabetes. When comparing β-blockers to long-acting calcium antagonists, there were no significant differences between groups in terms of the number of angina episodes per week (mean difference: 0.08 episode per week, 95% CI: −0.75 to 0.91) and nitroglycerin use per week (mean difference: −0.14 per week, 95% CI: −0.41 to 0.32). Likewise, exercise time to 1 mm ST segment

depression was similar for the β-blocker and the calcium antagonist arms in the 20 clinical studies in which it was evaluated.

There have been 2 studies that have compared β-blockers with the calcium channel blockers diltiazem (the TIBET trial) [14] and verapamil (the APSIS trial) [15] for more than 6 months in patients with stable angina. There was no significant difference in the rates of cardiac death and myocardial infarction, with an overall odds ratio of 0.98 for risk with β-blockers (95% CI: 0.66–1.47). Similar findings were obtained for cardiac death and myocardial infarction when combining these 2 trials with 59 short-term studies comparing β-blockers and calcium antagonists (odds ratio: 0.97) [13].

β-Blockers versus Long-Acting Nitrates

A meta-analysis of 6 studies comparing β-blockers and long-acting nitrates in patients with stable angina has been done. The baseline characteristics of patients included in these studies were similar to those in trials comparing β-blockers and calcium antagonists. Approximately 80% of patients were men, the mean age was 57 years, 39% of patients had had a myocardial infarction in the past, and 24% of patients had diabetes. Trends favoring β-blockers over long-acting nitrates were observed for time to 1 mm ST segment depression and total exercise duration, but the very small number of patients studied (less than 30 patients treated in either study arm) did not provide sufficient power to demonstrate statistically significant differences. Nevertheless, there was a strong trend for reduced nitroglycerin use per week with β-blockers versus long-acting nitrates (-1.90 per week, $p = 0.08$), as well as a nonsignificant reduction in the number of anginal episodes per week.

Pharmacological Properties of the I_f Inhibitor Ivabradine

Ivabradine (Procoralan) is a selective and specific I_f inhibitor and represents a new approach in pure heart rate reduction. Ivabradine specifically binds to the f-channel, and selectively inhibits the I_f current involved in the pacemaker activity of sinoatrial node cells. I_f is a mixed sodium-potassium inward current activated by hyperpolarization and modulated by the autonomic nervous system and is one of the most important ionic currents for the regulation of pacemaker depolarization. The N-demethylated metabolite of ivabradine, S 18982, has also shown heart rate reduction activity in animals as well as in humans. La Veille et al. [16–19] and Resplandy et al. [20] reported the complete profile of the pharmacokinetic properties of ivabradine. This novel agent is

rapidly and well absorbed (t_{max} = 0.75–1.5 h) and has good bioavailability (around 40%). Ivabradine has extensive tissue distribution with limited protein binding. It is metabolized exclusively by the cytochrome P450 3A4 to its active metabolite. The latter is eliminated by fecal and urinary pathways. Ivabradine is eliminated with a half-life of 2 h in plasma, and an effective half-life of 11 h. In a study of healthy volunteers assessing the correlation between bradycardic activity and plasma levels of the parent compound and its metabolite, it was found that ivabradine exerts a dose-dependent heart-rate-reducing effect, to which its N-demethylated metabolite contributes [19]. In this study, the maximal reductions of heart rate during exercise were 11 ± 4% (10 mg), 18 ± 6% (20 mg) after single oral doses ($p < 0.05$) and 18 ± 4% (10 mg) and 27 ± 6% (20 mg) after repeated doses ($p < 0.01$) [21]. Maximum heart rate reduction after an intravenous bolus of ivabradine was 19 ± 4%.

The electrophysiological effects of a single intravenous administration of ivabradine were studied by Camm and Lau [22] in patients with normal baseline electrophysiology. They observed that an intravenous dose of ivabradine does not prolong the corrected QT interval or modify conductivity and refractoriness of the atria, atrioventricular node, His-Purkinje system, and ventricles. In addition, Manz et al. [23] studied with echocardiography the impact of a single intravenous dose of ivabradine on LV function in patients with systolic dysfunction. 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. LV relaxation is as crucial for optimal LV function as is contractility. The negative lusitropic effect of β-blockers could therefore be potentially deleterious. Colin et al. [10] 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 heart rate at rest and during exercise, ivabradine, in contrast to atenolol, did not exert any negative lusitropic effect. In addition, in contrast to β-blockers, ivabradine does not cause detrimental effects on coronary vasomotion [24].

The I_f Inhibitor Ivabradine versus Placebo

The antianginal and anti-ischemic effects of ivabradine have first been studied in a randomized, double-blind, multicenter, placebo-controlled trial [25]. In this elegantly designed clinical trial, 360 patients with a history of at least 3 months of chronic stable angina and documented coronary artery disease (by way of angiography or previous myocardial infarction at least 3 months

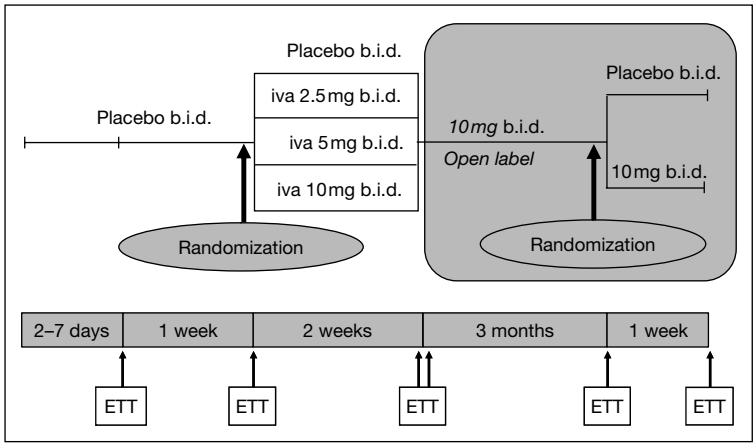

Fig. 1. Design features of a multicenter, double-blind, placebo-controlled, dose-ranging study of ivabradine (iva) in 360 patients with documented coronary artery disease [25].

before randomization) were randomly assigned, after a washout period of antianginal medications, to receive 1 of 3 doses of ivabradine (2.5, 5 or 10 mg b.i.d.) or placebo for 2 weeks (fig. 1). This was followed by an open-label 2-month or 3-month extension phase during which all patients received ivabradine 10 mg b.i.d. Patients were then randomly assigned to continue on ivabradine 10 mg b.i.d. or to withdraw to placebo for 1 week. The primary efficacy endpoints were the changes from baseline in time to 1 mm ST segment depression and time to limiting angina during bicycle exercise tolerance tests (ETT) performed at the trough of drug activity.

Between the start and end of the double-blind dose-ranging phase, resting heart rate and maximal heart rate during exercise significantly decreased compared to placebo in all 3 active treatment groups (fig. 2). Ivabradine 10 mg b.i.d. reduced both resting heart rate and maximal heart rate by 12–13 beats per minute ($p < 0.05$). Time to 1 mm ST segment depression during ETT improved with ivabradine treatment in a dose-related fashion and the increase was significant in the 5-mg and 10-mg b.i.d. groups ($p < 0.005$, fig. 3). Time to limiting angina increased significantly in comparison to placebo in the 10-mg b.i.d. group (mean increase: 41 s, $p < 0.05$). Ivabradine-mediated improvements in time to 1 mm ST segment depression and time to limiting angina in the double-blind phase were maintained in the open-label phase. In addition, angina attacks were reduced from a mean of approximately 4 attacks per week at baseline to less than 1 attack per week at the end of the open-label extension ($p < 0.001$). During the double-blind randomized withdrawal period, patients who were continued on ivabradine 10 mg b.i.d. maintained the benefits on heart rate, time to

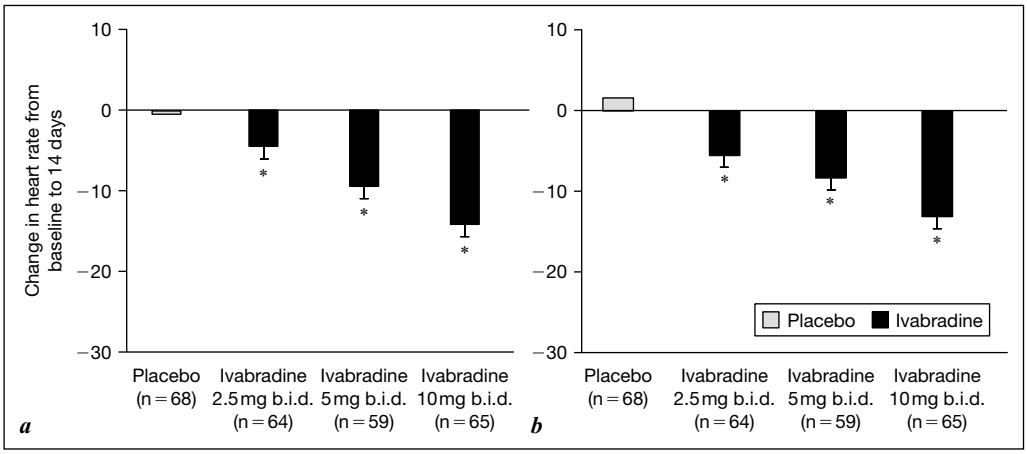

Fig. 2. Changes from baseline in heart rate at rest (***a***) and at the peak of exercise (***b***) in the different treatment groups, at the trough of drug activity at the end of the double-blind dose-ranging phase [25]. *$p < 0.001$.

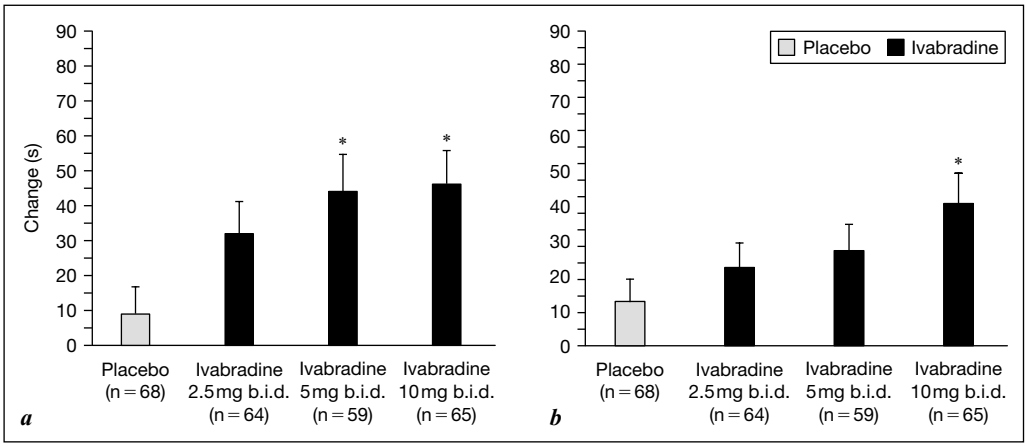

Fig. 3. Changes in ETT criteria at the trough of drug activity during the double-blind, dose-ranging phase [25]. ***a*** Time to 1 mm ST segment depression (*$p = 0.016$). ***b*** Time to limiting angina (*$p = 0.049$).

1 mm ST segment depression and time to limiting angina, whereas ETT parameters deteriorated in patients withdrawn to placebo (fig. 4). Importantly, no rebound phenomena were observed on treatment cessation. In summary, ivabradine demonstrated dose-dependent anti-ischemic and antianginal effects at the doses of 5 and 10 mg b.i.d. in this placebo-controlled study [25].

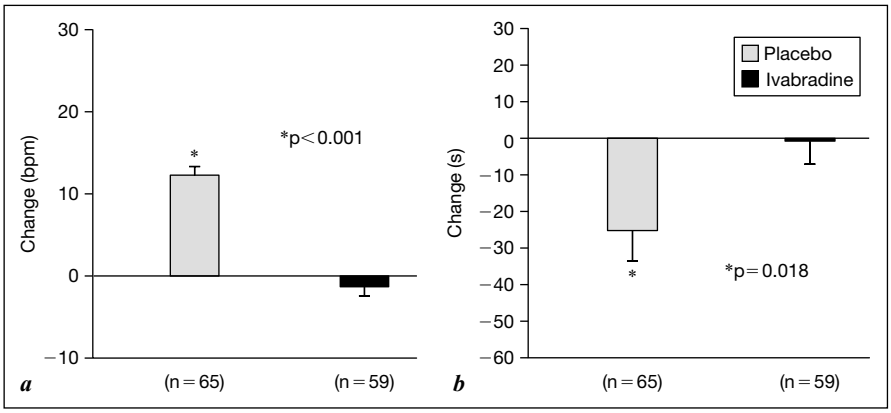

Fig. 4. Changes in maximal heart rate (***a***) and increase in time to limiting angina (***b***) during the double-blind randomized withdrawal period. Patients withdrawn to placebo had significant deteriorations in exercise test parameters [25].

Ivabradine versus β-Adrenergic Receptor Blockers

The INITIATIVE trial was a randomized, double-blind, multicenter study of 144 centers in 21 countries evaluating the antianginal and anti-ischemic effects of ivabradine versus the β-blocker atenolol in 939 patients with chronic stable angina [26]. The primary objective of the INITIATIVE trial was to demonstrate the noninferiority of ivabradine in improving exercise capacity compared to atenolol. Patients with a history of at least 3 months of chronic stable angina were selected. Additional entry criteria were: (1) evidence of underlying coronary artery disease manifested by at least 1 of the following 5 criteria: a history of myocardial infarction confirmed by Q wave and/or cardiac enzyme elevation ≥3 months before study entry, coronary angioplasty performed ≥6 months before study entry, bypass surgery performed ≥3 months before study entry, a coronary angiogram showing a diameter stenosis ≥50% in the proximal two thirds of ≥1 of the major coronary arteries, or scintigraphic or echocardiographic evidence of exercise-induced reversible myocardial ischemia; (2) 2 positive exercise treadmill tests, and (3) time to 1 mm ST segment depression within 20% or 1 min of the previous exercise test.

Trial protocol and medication dosages are shown in figure 5. After placebo washout of all antianginal medications that lasted 2–7 days depending on the previously administered treatment (≥5 half-lives), patients were randomized into 1 of 3 treatment groups: ivabradine 5 mg b.i.d. for 4 weeks increasing to 7.5 mg b.i.d. for 12 weeks; ivabradine 5 mg b.i.d. for 4 weeks increasing to 10 mg b.i.d. for 12 weeks, or atenolol 50 mg o.d. for 4 weeks increasing to 100 mg o.d.

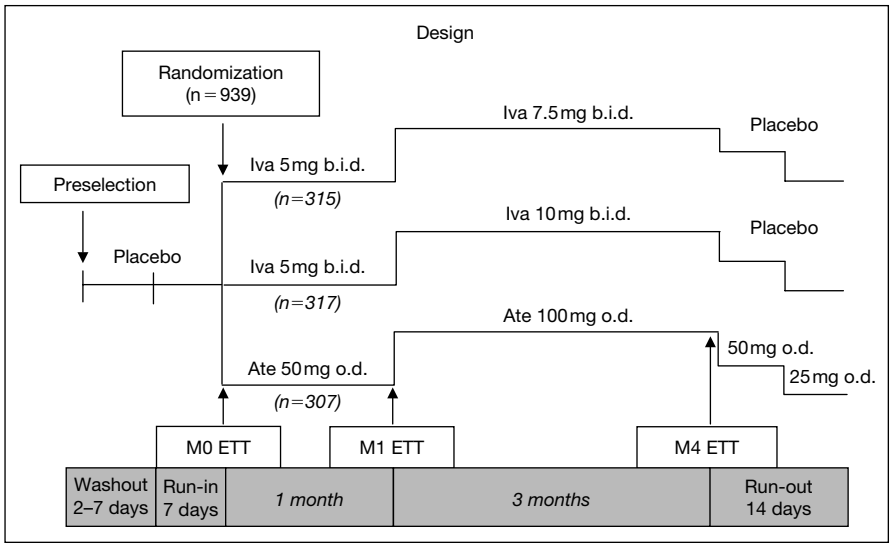

Fig. 5. Study design of the INITIATIVE trial. Ate = atenolol; iva = ivabradine.

for the following 12 weeks (fig. 5). The primary efficacy endpoint was the change from baseline to end of treatment (16 weeks) in total exercise duration during treadmill ETT performed according to a modified Bruce protocol at the trough of drug activity. Secondary endpoints included changes in time to limiting angina, time to onset of angina, and time to 1 mm ST segment depression, both at the trough and peak of drug activity. Angina attack frequency and short-acting nitrate consumption were also evaluated from patient's diaries.

Patients were on average 61 years of age and more than 80% were men. Approximately 70% of patients had class 2 angina, 54% had a prior history of myocardial infarction, 19% had previously undergone percutaneous coronary interventions and 18% coronary artery bypass graft surgery. Total exercise duration at the trough of drug activity increased from inclusion to end of treatment (16 weeks of therapy) by 86.8 ± 129.0 s with ivabradine 7.5 mg b.i.d., 91.7 ± 118.8 s with ivabradine 10 mg b.i.d., and 78.8 ± 133.4 s with atenolol 100 mg o.d. The mean differences when compared to atenolol 100 mg were 10.3 ± 9.4 and 15.7 ± 9.5 s in favor of ivabradine 7.5 and 10 mg (p values for noninferiority <0.001) (fig. 6). No significant difference was observed between the ivabradine groups, with an adjusted estimated difference of 5.4 s (95% CI: −12.9 to 23.8). Time to 1 mm ST segment depression increased by 98.0 ± 153.7 s with ivabradine 7.5 mg b.i.d., 86.9 ± 128.2 s with ivabradine 10 mg b.i.d., and 95.6 ± 147.5 s with atenolol 100 mg o.d. ($p < 0.001$ and $p = 0.002$ for noninferiority of ivabradine 7.5 and 10 mg versus atenolol 100 mg, respectively). This increase in time to 1 mm ST segment depression by approximately 1.5 min with

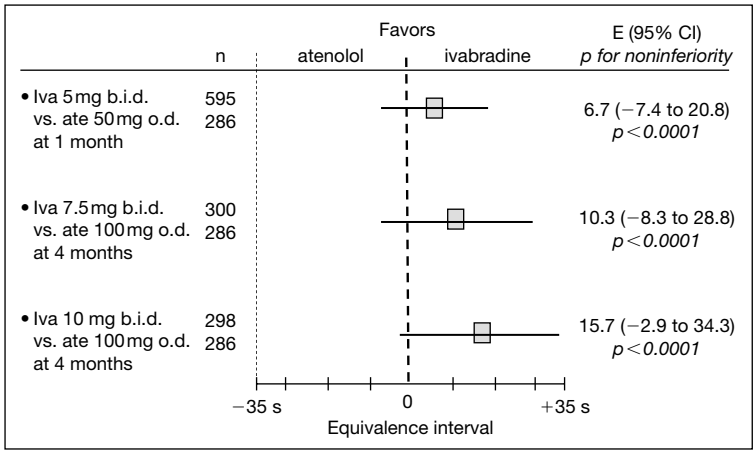

Fig. 6. Differences in the change in total exercise duration at the trough of drug activity for ivabradine (iva) versus atenolol (ate).

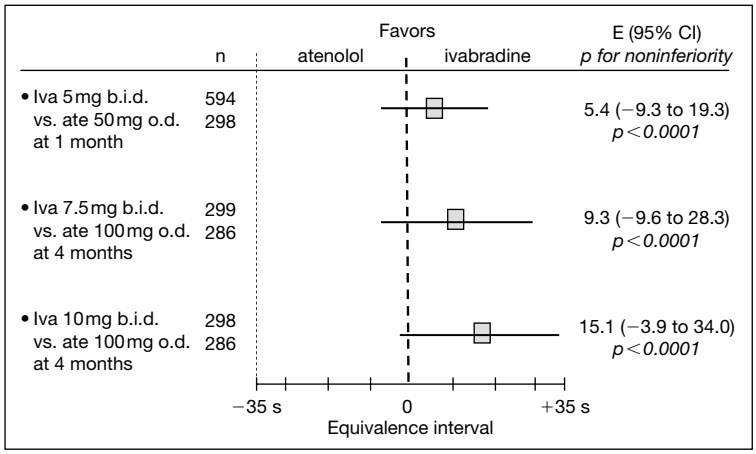

Fig. 7. Differences in the change in time to limiting angina at the trough of drug activity in the study groups. Ate = Atenolol; iva = ivabradine.

ivabradine indicates that the improvement in total exercise capacity was mediated by a relevant anti-ischemic effect. Total exercise duration after 4 weeks of therapy improved by 64.2 ± 104.0 s with ivabradine 5 mg and by 60.0 ± 114.4 s with atenolol 50 mg ($p < 0.001$ for noninferiority). Noninferiority of ivabradine was shown at all doses and for all criteria including time to limiting angina, in both the intent-to-treat and per-protocol populations (fig. 7).

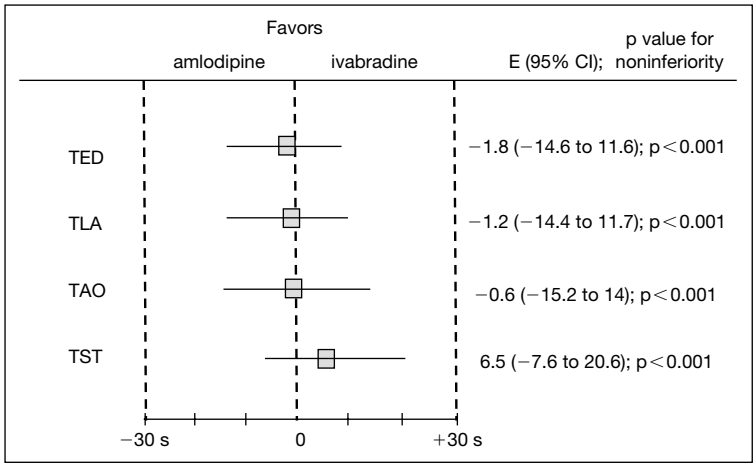

Fig. 8. Changes in the ETT parameters in the ivabradine 7.5 mg b.i.d. group versus the amlodipine 10 mg o.d. group. TAO = Time to angina onset; TED = total exercise duration; TLA = time to limiting angina; TST = time to 1 mm ST segment depression.

Compared to baseline, heart rate and rate-pressure product were reduced at the end of the treatment period, at rest as well as at the peak of exercise. At the peak of exercise, the decrease in heart rate was greater in patients treated with atenolol (14.0 beats per minute) than in those with ivabradine (8.6 and 10.3 beats per minute with 7.5 and 10 mg, respectively), showing that ivabradine induced a similar or greater improvement in exercise capacity compared to the atenolol group for a comparatively lower rate-pressure product and heart rate reduction. The number of angina attacks per week was decreased by two thirds over the 4-month treatment period with both ivabradine and atenolol, to approximately 1 attack per week. Thus, the INITIATIVE trial has shown that ivabradine is as effective as the β-blocker atenolol for the treatment of stable angina [26].

Ivabradine versus the Calcium Channel Blocker Amlodipine

A large randomized clinical trial was conducted to demonstrate the noninferiority of ivabradine versus the calcium channel blocker amlodipine. Ivabradine at doses of 7.5 mg b.i.d. and 10 mg b.i.d. was compared to amlodipine 10 mg o.d. during 3 months of therapy in a randomized trial that involved 1,195 patients with chronic stable angina and documented coronary artery disease. In that study, ivabradine 7.5 mg b.i.d. was found to have efficacy indistinguishable from that of amlodipine 10 mg o.d. for all measured bicycle exercise test parameters (fig. 8). Total exercise duration was increased by 27.6 ± 91.7 s and

31.2 ± 92.0 s with ivabradine 7.5 mg b.i.d. and amlodipine 10 mg o.d., respectively (95% CI: −14.6 to +11.6 seconds, $p < 0.001$ for noninferiority). Time to 1 mm ST segment depression, time to limiting angina, and time to angina onset were also consistently increased. Formal statistical testing also revealed that ivabradine is noninferior to amlodipine ($p < 0.0001$) in preventing angina attacks. As previously observed in large clinical trials, ivabradine significantly decreased the number of angina attacks by two thirds and reduced the short-acting nitrate consumption.

Tolerability of Ivabradine

Ivabradine has demonstrated a very good safety profile throughout its large clinical development program including the large multicenter INITIATIVE [26] study. A total of 5,000 patients have been included in this clinical program, with 3,500 patients treated with ivabradine and 1,200 of these patients treated for more than 1 year. The most frequent adverse drug reactions have been visual symptoms, the majority being phosphenes that were transient and nonserious in nature. These symptoms consisted of transient enhanced brightness in limited areas of the visual field that were commonly associated with abrupt changes in light intensity [27]. The visual symptoms were dose dependent and they were generally mild and well tolerated, causing less than 1% of patients to withdraw from treatment. They may be related to the action of ivabradine at HCN (hyperpolarization-activated, cyclic nucleotide-gated cation currents) channels known to be present in the retina [28]. All visual symptoms resolved spontaneously during therapy or after drug discontinuation. Importantly, the abrupt discontinuation of ivabradine has not resulted in a rebound angina phenomenon. In summary, the clinical tolerability of ivabradine was documented in a large population of patients with coronary artery disease and stable angina and drug-related adverse events had minimal impact on acceptability.

Combination Antianginal Therapy

Considerable evidence suggests that combination therapy may be more effective than monotherapy for the treatment of angina pectoris [1, 3]. The efficacy and safety of a combination therapy must be established through well-designed clinical trials. Patients with stable angina treated with a β-blocker but insufficiently controlled by this treatment might benefit from the heart-rate-lowering effect of ivabradine. One study intends to establish the efficacy and safety of ivabradine when combined with atenolol in 750 patients with stable

angina. Another multicenter randomized trial of 728 patients has already confirmed the antianginal and anti-ischemic effects of ivabradine at doses of 5 and 7.5 mg b.i.d. when given in addition to amlodipine 10 mg o.d., as assessed by treadmill ETT at the peak of drug activity [EPAR].

Potential Antiatherosclerotic Effects of Heart Rate Reduction

The relationship between resting heart rate and cardiovascular events has been documented in numerous epidemiological studies in different populations including elderly patients and those with hypertension or the metabolic syndrome. Experimental data have demonstrated that a reduction in heart rate can delay the progression of coronary and carotid atherosclerosis in animal models [29, 30]. This association between heart rate and atherosclerosis has also been observed in humans [31, 32], where disease progression was predicted independently by minimum heart rate in a study of 56 men who had developed myocardial infarction at a young age. Coronary artery endothelial cell dysfunction associated with high heart rates may represent an important mechanism for this increased atherogenesis [33, 34]. More recently, positive associations have been identified between plaque disruption, an elevated LV mass, and a mean heart rate >80 bpm, and a negative association with the use of β-blockers has also been demonstrated [35]. These observations are supported by results from the BCAPS study that demonstrated reduction of the rate of progression of carotid intima-media thickness with the use of a β-blocker in asymptomatic patients [36]. In addition to its antianginal properties, this plausible effect on the atherosclerotic plaque may represent a potentially important target for the heart-rate-reducing agent ivabradine.

Conclusion

Heart rate slowing is an integral part of an optimal pharmacological antianginal strategy. β-Blockers have traditionally been considered as a first-line therapy for stable angina, but their use may be limited by side effects including fatigue, depression and sexual dysfunction. Bronchospasm and atrioventricular block represent other limitations of β-blockers. Ivabradine is a selective and specific I_f inhibitor with antianginal and anti-ischemic effects that have been shown to be noninferior to those of the β-blocker atenolol and the calcium channel blocker amlodipine. Unlike β-blockers, ivabradine is devoid of intrinsic negative inotropic effects and does not affect coronary vasomotion. A whole range of patients with angina may benefit from exclusive heart rate

reduction with ivabradine, including those with contraindications or intolerance to the use of β-blockers.

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Novel I_f Current Inhibitor Ivabradine: Safety Considerations

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Abstract

Ivabradine is a novel heart-rate-lowering agent that acts specifically on the sinoatrial node by selectively inhibiting the I_f current, which is the current predominantly responsible for the slow diastolic depolarization of pacemaker cells. Unlike many rate-lowering agents, ivabradine reduces heart rate in a dose-dependent manner both at rest and during exercise without producing any negative inotropic or vasoconstrictor effect. The bradycardic effect of ivabradine is proportional to the resting heart rate, such that the effect tends to plateau. Thus, extreme sinus bradycardia is uncommon. Less than 1% of patients withdrew from therapy because of untoward sinus bradycardia. The QT interval is expectedly prolonged with the reduction in heart rate, but after appropriate correction for heart rate and in direct comparisons of the QT interval when the influence of the heart rate was controlled by atrial pacing, no significant effect of ivabradine on ventricular repolarization duration was demonstrated. Consequently, ivabradine has no direct torsadogenic potential, although, for obvious reasons, the specific bradycardic drug should not be administered with agents which have known rate-lowering and/or QT-prolonging effects. Ivabradine has little effect on the atrioventricular node and ventricular refractoriness, but because of its effect on the sinus node, it should be avoided in patients with sick sinus syndrome. The physiological significance of upregulation of the I_f current in the His-Purkinje system and ventricular myocardium due to ionic remodeling in pathophysiological conditions, such as end-stage heart failure, and the effects of ivabradine have yet to be explored. Because ivabradine also binds to hyperpolarization voltage-gated channels which carry the I_h current in the eye, transient, dose-dependent changes of the electroretinogram resulting in mild to moderate visual side effects (phenomes) may occur in approximately 15% of patients exposed to ivabradine. Ivabradine does not cross the blood-brain barrier and therefore, has no effect on the I_h current in central nervous system neurons. The safety of ivabradine has been assessed in a development program that enrolled over 3,500 patients and 800 healthy volunteers in 36 countries from Europe, North and South America, Africa, Asia and Australia, 1,200 of whom were exposed to ivabradine for over 1 year. Ivabradine has been associated with a good safety profile during its clinical development and its safety will be further assessed by postmarketing surveillance and during on-going clinical trials.

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Table 1. Percentage of inhibition of sinus node ion currents by ivabradine in rabbit sinoatrial cells using the patch-clamp technique

Ion current	Concentration of ivabradine (μM)				
	0.03	0.3	1	3	10
I_f	5.5 ± 1.0	19.5 ± 2.2	32 ± 3	59 ± 2	80 ± 2
$I_{Ca,T}$	0	0	0	0	0
$I_{Ca,L}$	0	0	0	0	18 ± 1
I_K	0	0	0	0	16 ± 1

$I_{Ca,L}$ = Long-lasting calcium current; $I_{Ca,T}$ = transient calcium current; I_f = current carried by HCN channels; I_K = potassium current. Reproduced from [2].

Ivabradine has two major pharmacological effects: it selectively inhibits two currents that utilize hyperpolarization-activated, cyclic nucleotide-gated cation (HCN) channels in the heart and the eye, which carry the I_f and I_h currents, respectively. Selective inhibition of the I_f current is associated with prolongation of spontaneous slow diastolic depolarization of the sinus node, which leads to heart rate slowing, the primary mechanism of action for the antianginal effect of ivabradine. Ivabradine and its main active metabolite, S 18982, have high affinity for the HCN4 isoform of HCN channels, which is the main isoform in the heart; the IC_{50} for the I_f current carried by HCN4 channels is in the range of 1.5–3 mM [1]. At concentrations associated with a high therapeutic dose of 7.5 mg twice daily (mean C_{max} of approximately 0.1 μM) in humans, ivabradine is highly selective for the I_f current, with no effect on L- and T-type calcium currents and the delayed rectifier potassium current I_K (table 1) [2]. Ivabradine does not interact with β-adrenergic or muscarinic receptors. Because ivabradine has no or little direct electrophysiological and cardiovascular effects, its safety and adverse-effect profile should be discussed in the context of its specific I_f and I_h blockade. Ivabradine does not cross the blood-brain barrier and therefore, has no effect on the I_h current in central nervous system neurons.

The safety of ivabradine has been assessed in a development program that enrolled over 3,500 patients and 800 healthy volunteers in 36 countries from Europe, North and South America, Africa, Asia and Australia, 1,200 of whom were exposed to ivabradine for over 1 year. The mean age of patients was 60 years. Approximately 34% of the patients were 65 years or older; 17% were women, and about 94% were Caucasians. All patients had a history of coronary artery disease and 53% had a previous myocardial infarction. Ivabradine demonstrated a good overall cardiac safety profile compared with traditional

Table 2. Overall cardiac safety of ivabradine compared with atenolol and amlodipine in patients with coronary artery disease

Event rate, %	Ivabradine (n = 1,651)	Atenolol (n = 408)	Amlodipine (n = 404)
Angina pectoris aggrevated	2.0	1.7	1.0
Angina unstable	2.0	0.2	1.2
Myocardial ischemia	1.2	1.5	0.5
Sinus bradycardia	3.2	5.1	1.7

Data from EPAR.

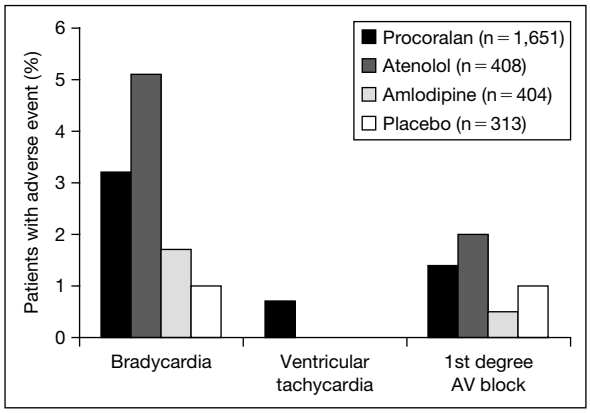

Fig. 1. Cardiac adverse events associated with therapy with ivabradine. AV = Atrioventricular. Data from EPAR.

antianginal drugs, such as atenolol and amlodipine (table 2). The most common adverse events that are likely to relate to specific bradycardic action of ivabradine are presented in figure 1.

Bradycardia

Sinus bradycardia is an expected pharmacological effect of ivabradine and is seen both in resting conditions and during exercise. Selective I_f inhibition and the resulting slowing of the sinus node discharge rate is proportional to the resting heart rate. In the safety and efficacy studies, sinus bradycardia ≤55 beats per minute was reported in 3.2% of patients receiving ivabradine compared with 1.0% receiving placebo and 1.0 and 5.1% of patients treated with the

Table 3. Incidence of bradycardia-related symptoms in patients treated with atenolol and ivabradine

Bradycardia-related symptoms[1]	Atenolol	Ivabradine
Number of patients	32	164
Number of patient-years	17	71
Mean lowest heart rate, bpm	41.3 ± 2.4	42.0 ± 2.0
Heart rate range, bpm	35–44	35–44
Hypotension, %	0.0	2.8
Dizziness, %	6.5	5.7
Syncope, %	6.6	0.0
Fatigue, %	19.4	2.8
Dyspnea, %	19.4	1.4

[1]Rates per 100 patient-years exposure; bradycardia is defined as a heart rate <45 beats per minute. Savelieva I, Camm AJ, data on file.

active comparators amlodipine and atenolol, respectively. The frequency of bradycardia increased with an increase in dose and was 2.8 and 4.0% in patients receiving 5 and 7.5 mg of ivabradine twice daily, respectively, with nearly half the cases having been reported during the first month of treatment.

However, bradycardia is well tolerated and is not associated with any deleterious arrhythmia. Only 0.2% of patients experienced severe sinus bradycardia compared with 0.9% in the atenolol group, and less than 1% of patients withdrew from therapy because of untoward bradycardia. Overall, the proportion of patients with heart rate below 40 beats per minute did not exceed 0.3% in the whole population. In patients with slow heart rates (<45 beats per minute) on treatment, bradycardia-related symptoms such as hypotension and dizziness were not different in patients treated with ivabradine and patients treated with atenolol, whereas syncope occurred only in the atenolol arm (table 3).

A low proportion of patients who developed clinically significant bradycardia can be explained by a plateau dose-response, use-dependent effect of ivabradine on heart rate. Ivabradine binding to HCN channels is restricted to the open-channel state and the drug-channel interaction is controlled by the balance between the open and close state. Since the pacemaker potential is modulated by several (at least 10) ion channel mechanisms, 100% block of the I_f current would be expected to cause only a 25–30% reduction in heart rate [1, 2].

To minimize the risk of inappropriately low heart rates during therapy with ivabradine, treatment should only be initiated when baseline resting heart rate is 60 beats per minute or higher and the dose should be reduced if the heart rate slows below 50 beats per minute or when a symptomatic sinus bradycardia

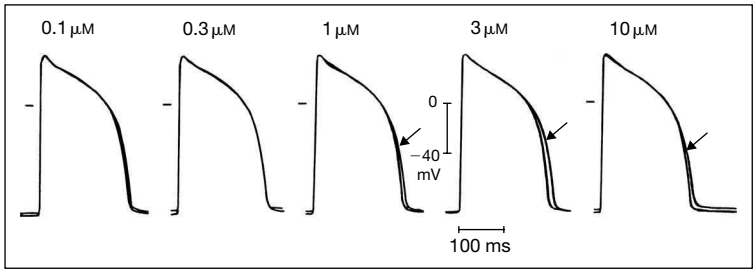

Fig. 2. Ivabradine at doses of 0.1–10 μM did not prolong action potential duration in guinea pig papillary muscles after a 30-min exposure. Representative recordings of action potentials showing maximal effects of ivabradine (arrows) superimposed on respective action potential recordings at baseline. The preparations were driven at 1 Hz. Modified from Thollon et al. [3].

occurs. In patients older that 75 years, the initial dose should be 2.5 mg twice daily. The concomitant use of potent cytochrome P450 CYP3A4 enzyme inhibitors such as azole antifungals, retroviral drugs, and macrolide antibiotics is contraindicated. The association of ivabradine with nondihydropyridine calcium antagonists (diltiazem and verapamil) is not recommended. Ivabradine does not inhibit the CYP3A4 enzyme system and coadministration of agents which depend on CYP3A4 metabolism does not lead to an increase in the maximum concentration of the drug.

The effects of ivabradine on nodal and ventricular escape rhythms have not been studied in patients with congenital or acquired heart block. The therapeutic benefit from rate lowering may not be present in patients with atrial or ventricular pacemakers. However, patients whose heart rate is controlled predominantly by the sinus node, despite an implanted pacemaker set at a low escape rate, may benefit from therapy with ivabradine.

QT Interval Prolongation

In preclinical studies, ivabradine was not a potent blocker of the human ether-a-go-go-related gene channel and therefore did not affect the duration of cardiac repolarization directly. In vitro, ivabradine blocks the I_{Kr} current with an IC_{50} of 4.9 μM, which is approximately 75-fold higher than the mean total plasma concentration C_{max} in patients treated with 7.5 mg of ivabradine twice daily and 250-fold higher when considering the unbound plasma fraction (approximately 30%), that is, well above the commonly accepted 30-fold safety margin. In guinea pig papillary muscles, no prolongation of action potential duration was observed at concentrations up to 10 μM [3] (fig. 2). In conscious

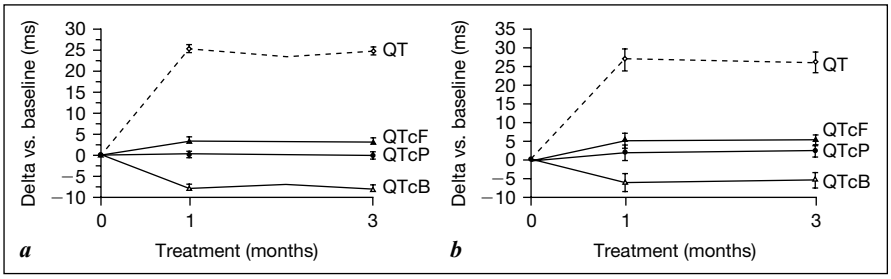

Fig. 3. Comparison of the effects of ivabradine 5–10 mg twice daily (***a***) and atenolol 100 mg once daily (***b***) on the QT interval during 3 months of treatment using Bazett's (QTcB), Fridericia's (QTcF), and the population-specific correction formula (QTcP). Modified from Savelieva et al. [4].

dogs, long-term (up to 1 year) exposure to oral ivabradine at doses sufficient to produce C_{max} values 135-fold the C_{max} achieved by human dosing with 7.5 mg twice daily did not affect the QTc interval.

Slowing of the heart rate by ivabradine is associated with prolongation of the QT interval by 18–30 ms. This effect is dose dependent. However, no changes in the duration of ventricular repolarization were observed when the QT interval was appropriately corrected for heart rate. Using a population-specific rate correction formula, an increase in the QT interval with ivabradine did not exceed 2 ms [4] (fig. 3). The threshold level of regulatory concern is QT prolongation by 5 ms. The consensus of the International Conference on Harmonization on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs is that drugs that prolong the QT/QTc interval by around 5 ms or less do not appear to be torsadogenic [5]. Furthermore, direct comparisons of the uncorrected QT interval when heart rate was controlled by atrial pacing at a series of identical rates showed that ivabradine had no direct effect on ventricular repolarization and did not alter the electrophysiological properties of the heart [6].

The incidence of drug-induced QT interval prolongation of potential concern, i.e. ≥500 or ≥60 ms from baseline, was reported in the range of 0.2–1.6% for ivabradine 5–10 mg twice daily compared with 0% for atenolol 100 mg once daily. After appropriate correction for heart rate, there was only 1 case of QTc prolongation ≥500 ms (0.2%) in 447 taking ivabradine 7.5 mg twice daily (or 0.1% of the total ivabradine group of 1,140 patients) and 1 case (1.1%) in 91 patients receiving atenolol. In the long term, the proportion of patients with QTc prolongation ≥500 ms was approximately 1% in both the ivabradine and atenolol groups.

Therefore, the torsadogenic potential of ivabradine determined by its effect on ventricular repolarization is probably low and other than for QT prolongation directly consequent on bradycardia, ivabradine does not appear to have any direct proarrhythmic effect. However, the potential importance of a prolonged uncorrected QT value is not clear and may give rise to arrhythmia in patients at high risk of drug-induced torsades de pointes, e.g. patients with congenital long QT syndrome or individuals with acquired long QT syndrome due to other QT-prolonging drugs.

Ventricular Tachyarrhythmias

Bradycardia is a risk factor for ventricular tachyarrhythmias because of the reverse use dependency of several of the ion channels that are responsible for ventricular repolarization. Thus, bradycardia is associated with QT lengthening and the possibility of torsades de pointes ventricular tachycardia.

Treatment with ivabradine, even when significant bradycardia results, has not been associated with an excess of ventricular proarrhythmias. The incidence of ventricular premature beats recorded on the 12-lead electrocardiogram and during 24-hour ambulatory Holter monitoring or noted during an exercise stress test did not differ in patients receiving ivabradine, amlodipine, atenolol or placebo (2.8, 2.7, 1.4 and 1.3%, respectively). The occurrence of rhythm abnormalities during 24-hour Holter monitoring, including atrioventricular block, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia and ventricular extrasystoles, was similar in the ivabradine and comparator groups. There were 11 documented cases of ventricular tachycardia in 2,907 patients treated with ivabradine; the overall incidence of ventricular tachycardia that occurred in association with ivabradine and atenolol was 0.38 and 0.2%, respectively. However, in the development program, there were 2 cases of documented nonsustained polymorphic ventricular tachycardia which were unlikely to be related to ivabradine directly, but merely bradycardia unmasked previously unrecognized long QT syndrome or the severe form of low repolarization reserve. Furthermore, patients with risk factors for drug-induced ventricular proarrhythmias, that is female gender, elderly age, left ventricular hypertrophy, congestive heart failure, and hypokalemia, did not appear to experience more ventricular arrhythmias with ivabradine than amlodipine or atenolol (fig. 4).

Electrophysiological Effects

The electrophysiological studies with ivabradine have shown that it has no or little effect on the antioventricular node, His-Purkinje system, and atrial and

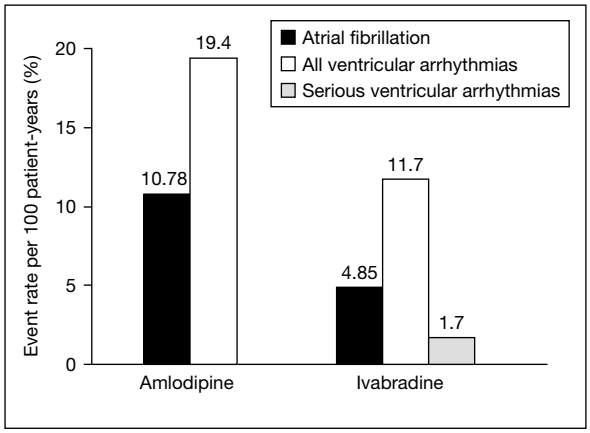

Fig. 4. Incidence of atrial fibrillation and ventricular arrhythmias in patients with one or more risk factors for arrhythmias (female gender, older age, left ventricular hypertrophy, heart failure, left ventricular dysfunction, severe angina, electrolyte disturbances). Data from EPAR.

Table 4. Electrophysiological effects of a single intravenous bolus of ivabradine in 36 patients undergoing electrophysiological study

Parameter	Baseline	30 min	60 min
Heart rate, bpm	80 ± 14	65 ± 11*	65 ± 11*
QT interval, ms	367 ± 42	392 ± 52*	397 ± 53
QTc interval, ms	418 ± 30	404 ± 30	407 ± 38
PR interval, ms	148 ± 20	155 ± 25	156 ± 24
QRS complex, ms	89 ± 19	88 ± 20	92 ± 19
Corrected SNRT, ms	253 ± 97	353 ± 122*	377 ± 140*
SACT, ms	144 ± 59	178 ± 78	177 ± 88
IACT, ms	44 ± 36	43 ± 29	46 ± 34
AH interval, ms	77 ± 19	80 ± 21	81 ± 21
HV interval, ms	44 ± 12	48 ± 13	47 ± 13
WHR, bpm	180 ± 32	178 ± 35	175 ± 36

IACT = Intra-atrial conduction time; QTc = corrected QT interval using Bazett's formula for rate correction; WHR = heart rate at which 1:1 atrioventricular conduction not possible (Wenckebach point). *$p < 0.05$ versus baseline.

ventricular refractoriness (table 4). The effects of a single intravenous bolus of ivabradine (0.2 mg/kg over 15 s) were assessed in an open-label study of 14 subjects who underwent an electrophysiological study and had normal baseline electrophysiology [7, 8]. Heart rate decreased significantly, but most electrophysiological

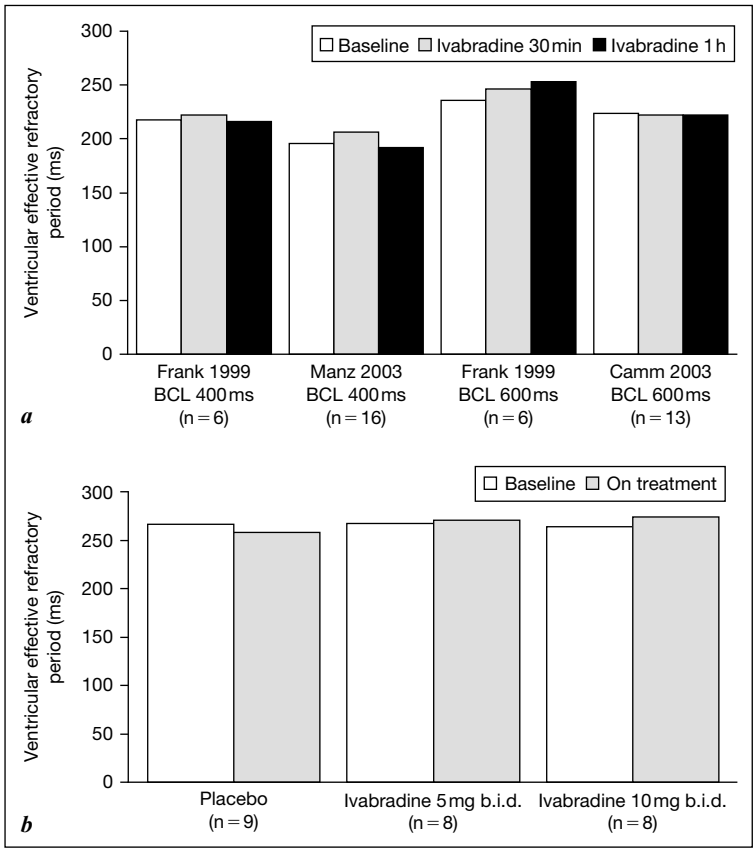

Fig. 5. Effects on ventricular refractoriness of a single intravenous bolus of ivabradine 0.2 mg/kg at 30 min and 1 h after infusion (***a***) and of oral therapy with ivabradine 5 and 10 mg twice daily for 3 1/2 days (BCL 550 ms) (***b***). BCL = Basic cycle. Modified from Savelieva et al. [6] and Camm et al. [7].

parameters including intra-atrial, atrioventricular, and intraventricular conduction times were unaffected. In another series of 16 patients studied in the electrophysiological laboratory setting [unpublished data], a slight prolongation of the AH and HV intervals was present following infusion of 0.2 mg/kg ivabradine, which may be due to the individual variability of the measurements. Acute intravenous studies involving a total of 36 subjects and a short-term study with ivabradine administered orally to 25 patients with permanent pacemakers fitted with the telemetric programmed stimulation facility demonstrated no clinically significant effect of the drug on the ventricular effective refractory period (fig. 5). In phase III randomized clinical studies, the incidence of heart block, QRS prolongation or bundle branch

block was low in all treatment groups and placebo and was likely to reflect naturally occurring events in a large patient population with coronary artery disease and previous myocardial infarction.

Ivabradine prolonged corrected sinus node recovery time (SNRT) by approximately 90–120 ms at 30 min and 1 h after drug administration. In the Non-Invasive Electrophysiological Study of Ivabradine (NESI) of 25 patients, therapy with ivabradine 10 mg twice daily administered orally for 3 days was associated with a 200-ms increase in uncorrected SNRT in subjects who were implanted with a permanent pacemaker for sinus node disease [6]. At a lower dose of 5 mg twice daily, ivabradine produced no effect on SNRT. However, these changes were not consistent at different pacing rates and were also observed in the placebo group. The effects of ivabradine on SNRT are a consequence of a slower rate of depolarization in the sinoatrial region resulting from inhibition of the I_f current and are not of any significant safety concern.

Atrial Fibrillation

In vitro, ivabradine produced a concentration-dependent block of human cloned hKv1.5 channels which are similar to channels responsible for the ultrarapid delayed rectifier current (I_{Kur}) recorded in human atrial myocytes [9]. This block was also voltage dependent and increased steeply between −30 and 0 mV, which corresponded to the voltage range for I_{Kur} channel opening. There is evidence that the I_f current may play a role in causing abnormal diastolic depolarization of atrial myocardium and that the expression of mRNA of the HCN channels is upregulated in the presence of atrial fibrillation [10]. The presence of the I_f current and spontaneous diastolic depolarizations were demonstrated in human atrial myocytes, which could be suppressed by pharmacological interventions, such as stimulation of adenosine and muscarinic receptors and administration of class IC antiarrhythmic agent propafenone [11, 12]. Activation of the I_f current in atrial myocytes was observed at more negative potentials and exhibited different kinetic properties than the I_f current in pacemaker cells within the sinus node and its contribution to arrhythmogenesis has yet to be investigated.

These observations suggest that ivabradine may potentially prolong action potential duration of the atrial myocytes and prevent atrial fibrillation. However, the electrophysiological studies with ivabradine showed no effect on the effective refractory period of the atria [7, 8]. In the clinical setting, the incidence of atrial fibrillation was similar with amlodipine and ivabradine (1.2 and 1%, respectively), although a trend towards a decrease in atrial fibrillation rates per 100 person-years was observed during treatment with ivabradine (fig. 4). Because ivabradine has no blocking effect on the atrioventricular node and the

I_f current is no longer fully operational in atrial fibrillation, ivabradine is ineffective at reducing heart rate in patients with permanent atrial fibrillation. Its use should probably be avoided in such patients as well as in patients with frequent episodes of paroxysmal or persistent atrial fibrillation.

Effects on Left Ventricular Function

Ivabradine has no direct effect on myocardial contractility and relaxation, cardiac output, coronary flow, blood pressure, and peripheral vascular resistance. In Langendorff-perfused preparations and animal experiments, ivabradine shifted the ventricular systolic pressure-volume curve leftwards and reduced collagen accumulation. Experimental studies using a chronic heart failure model in rats have demonstrated that ivabradine effectively reduced heart rate, decreased the left ventricular systolic diameter and improved myocardial contractility [13]. Ivabradine does not affect vascular relaxation or increase peripheral vascular resistance and has been shown to produce an antihypertrophic effect on the aorta in rats with spontaneous hypertension [14, 15]. In a canine model of exercise-induced myocardial stunning, pretreatment with ivabradine consistently accelerated the recovery of stunned myocardium by 50% compared with atenolol [16]. This trend was distinguished more clearly when agents were administered after the induction of stunning.

Subsequent studies in healthy subjects and patients with and without ventricular systolic impairment have shown lack of the effects of ivabradine on myocardial contractility [17, 18]. In healthy individuals, the decrease in the rate-pressure product and cardiac index during sympathetic stimulation as seen with exercise was less significant with ivabradine 30 mg than propranolol, despite a similar reduction in heart rates [17]. Intravenous administration of ivabradine 0.25 mg/kg in patients with ischemic cardiomyopathy reduced heart rate by 18%, but did not influence left ventricular ejection fraction, fractional shortening, and stroke volume [18]. The mean maximum decrease in ejection fraction and fractional shortening was 0.2 and 0.7%, respectively, with ivabradine compared with 1.7% each on placebo. The stroke volume decreased by only 2.4 ml in the ivabradine group as opposed to 12.2 ml in the placebo group. Ivabradine produced no negative inotropic effect irrespective of the presence of global or regional impairment of the systolic function.

The incidence of new-onset heart failure in patients with coronary artery disease and preserved left ventricular systolic function at baseline was 0.3% during long-term therapy with ivabradine and 0.5% during therapy with atenolol or amlodipine. In patients with an ejection fraction less than 40% and NYHA class II heart failure, therapy with ivabradine resulted in the reduction in

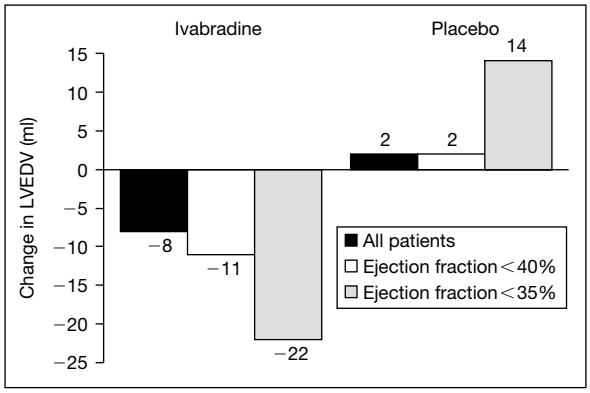

Fig. 6. Effects of ivabradine on left ventricular diastolic volume (LVEDV) in patients with impaired systolic function. Modified from [20].

left ventricular volumes after 3 months compared with placebo. The effect was more apparent in patients with significantly impaired systolic function and those with an ejection fraction less than 35% (fig. 6) [19].

However, the clinical experience in patients with more advanced ventricular dysfunction is insufficient. Although HCN channels are expressed in the His-Purkinje system and ventricular myocardium and generate the I_f current in neonatal and embryonic cardiac tissue, they are functionally inactive in adults. Therefore, the I_f current does not contribute to action potentials of His-Purkinje fibers and ventricular myocardium. In failing hearts, the density of HCN channels and the I_f current are increased as part of complex ionic remodeling which may have important potential implications regarding ventricular arrhythmogenesis, particularly related to triggered activity [20–22]. Changes in autonomic regulation with a shift towards a higher sympathetic tone associated with end-stage heart failure may also influence the I_f current expression in ventricular myocardium.

The on-going BEAUTIFUL (morbidity-mortality evaluation of the I_f inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction) study is designed to investigate whether ivabradine confers a benefit on survival free of death and major cardiovascular events in over 10,000 patients with a left ventricular ejection fraction equal to or less than 39%.

Visual Effects

Block of HCN1 channels carrying the I_h current in the eye is associated with changes in the electroretinogram, mainly in the cone system responses of

the retina. The I_h current is responsible for retinal responses to bright light stimuli, possibly by curtailing the hyperpolarizing response to light; it plays a minor role in the response to dim light stimuli [23, 24]. Visual effects that may result from the I_h inhibition in retinal neurons include the appearance of bright areas in the visual field (phosphenes) and are often triggered by changes in luminosity from dark to light. In long-term studies in dogs exposed to concentrations of ivabradine 40-fold higher than those observed with 20 mg of ivabradine daily in humans, no histological or ultrastructural changes in the retina were observed.

The visual side effects (mainly phosphenes) in humans were observed in 14.5% of patients receiving ivabradine compared with 3.4% on placebo and 4.5–6.4% of patients treated with amlodipine or atenolol, respectively. These included luminous phenomena such as photopsia, luminous flashes, laser effects, luminous or flashing spots (phosphenes), starry aspects or, less commonly, stroboscopic vision [25, 27]. The visual effects occurred on average after 25 days of treatment, were dose dependent, and their frequency was 2.2, 9.2, and 15.9%, in the ivabradine 2.5, 5, and 7.5 mg twice daily dose groups, respectively. The most frequently identified triggering factor was 'light variation' (abrupt change in light intensity). In such situations, the sensitivity of the retina is high, and small increases in neuronal responses to light would be more likely to reach a threshold for perception. Conversely, most events occurred at times of low ambient light intensity, e.g. in the evening (nearly half the events), in the early morning (16%) or at night (22%).

In 80–90% of cases, symptoms were mild, and in the majority of cases the visual disturbance disappeared even though treatment continued. Visual acuity, color vision, and visual fields were unaffected and visual symptoms did not interfere with driving. Rarely, visual disturbances persisted leading to treatment discontinuation in 24 (4.4%) of patients with visual symptoms, which constituted only 0.96% out of all patients exposed to ivabradine (n = 2,907). In 78% of patients, symptoms resolved before or within 48 h after the last drug intake. Very few patients, 16 out of 2,545, or 0.6%, reported visual symptoms when driving, and only 4 patients (0.1%) stopped the treatment for this reason.

The effect of ivabradine on retinal function was assessed by electroretinography in a subset of 426 patients, many of whom also had a concomitant condition that carried a risk of ophthalmic complications, including hypertension (60%), diabetes (16%), and/or a history of ophthalmic disease (20–30%), mainly cataract, dyschromatopsia, and glaucoma. Ivabradine caused a 4–5% reduction in cone responses, i.e. a decrease in b-wave amplitudes, which reflect currents in Müller glial cells, and an increase in visual evoked latency by 2–4 ms. Although the proportion of patients with a bilateral change in the electroretinogram was higher in the ivabradine group (9.1%) than in the atenolol group (0%), these

Table 5. Deaths per 100 patient-years after treatment exposure in the ivabradine, amlodipine, atenolol, and placebo groups

	Ivabradine (n = 2,907)	Placebo (n = 313)	Atenolol (n = 435)	Amlodipine (n = 404)
Patient-years	1,107.2	65.2	210.9	95.9
Deaths per 100 patient-years, %	2.44	3.07	0.50	2.09

Data from EPAR.

changes are mild and reversible and are not likely to be of potential clinical concern. Furthermore, none of the patients showed retinal degeneration or other permanent alteration of retinal function or morphology that could not be explained by an underlying condition. Long-term follow-up does not give rise to any concern either. In the majority of patients, the ophthalmic changes improved or resolved at subsequent investigations.

Effects on Driving Performance

The effects of visual disturbances on driving associated with therapy with ivabradine were studied using a driving simulator in 90 subjects aged between 18 and 45 years, 75 of whom received ivabradine 10–15 mg twice daily and 15 received placebo (EPAR). There were no significant differences in absolute speed, deviation from the speed limit, deviation from the ideal route, and the number of collisions in different light conditions between subjects receiving placebo and subjects with and without visual symptoms after 14 days of ivabradine exposure.

Mortality

All-cause mortality rates per 100 patient-years were similar in the ivabradine, placebo and amlodipine groups, and lowest in the atenolol group (table 5). Two patients who died in the ivabradine group also received amlodipine, as were both patients who died in the placebo group. Most deaths were cardiovascular and 16 were sudden death. Overall, all-cause mortality with ivabradine did not differ from what was predicted for patient populations with stable coronary artery disease (2–3% per year). Although atenolol was associated with lower all-cause mortality, this trend was not statistically significant.

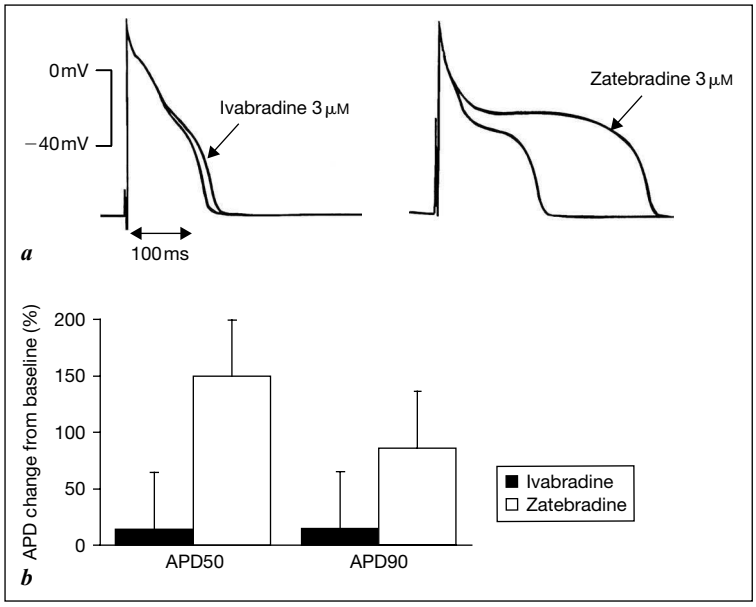

Fig. 7. ***a*** Comparative effects of ivabradine and zatebradine at 3 μM on action potential duration of rabbit Purkinje fibers at 50 and 90% of repolarization (APD50 and APD90, respectively) after a 40-min exposure to each agent. ***b*** Representative recordings of action potentials showing maximal effects of ivabradine and zatebradine superimposed on action potential recordings at baseline. The preparations were driven at 0.25 Hz. Modified from Thollon et al. [3].

Other Specific Bradycardic Agents

Specific heart-rate-lowering agents include alinidine (ST567), falipamil (AQ-A39), zatebradine (UL-FS49), cilobradine (DK-AH269), and ZD-7288 [27]. Other experimental and investigational agents with a similar mode of action are under development or at different stages of clinical investigation. Alinidine (N-allyl-clonidine), the first member of the family of specific bradycardic agents with little inotropic effects, is an imidazoline compound derived from the antihypertensive drug clonidine. Alinidine was abandoned because its selectivity for HCN4 channels in the heart was limited and prolongation of action potential duration was observed at moderate drug concentrations (0.3 μg/ml). It also had significant central nervous system adverse effects, including hypotension and negative inotropic effects accounted for by its metabolism in the liver to clonidine [28]. High affinity to block the I_h current in the eye associated with irreversible visual disturbances at low concentrations (1 μM), substantial inhibition of the I_h current in

neurons in the central nervous system (hippocampal, thalamocortical, and substantia nigra neurons), and the potential to prolong the QT interval and cause torsades-de-pointes-like ventricular tachycardia were the reasons for termination of phase II clinical trials with ZD-7288 about 5 years ago [27]. In contrast, ivabradine does not cross the blood-brain barrier and has no effect on the I_h current in central nervous system neurons. Falipamil and its more potent, longer-acting and more specific descendant zatebradine were found to block the T-type and L-type calcium currents ($I_{Ca,T}$ and $I_{Ca,L}$) and the delayed rectifier potassium current I_K increasing the risk of QT prolongation and torsades de pointes [29]. In contrast to ivabradine, zatebradine markedly prolonged the action potential within the range of concentrations needed to produce clinical bradycardic action and posed increased risk of proarrhythmia at slow heart rates (fig. 7) [3, 29]. The proarrhythmic potential of zatebradine, along with the side effects from I_h blockade in the eye and lack of effect on exercise tolerance or prevention of angina limited its use in the clinical entity. Clobradine (Boehringer Ingelheim) is proposed for treatment of heart failure and is still in its early phase of investigation [30].

Conclusions

Ivabradine is currently the most advanced selective inhibitor of the I_f current which is proven to be effective for prevention of angina in patients with stable coronary artery disease. The general safety of ivabradine with regard to the incidence of adverse events is in line with what was observed in the other treatment groups. No further adverse events (other than visual disturbances and sinus bradycardia) were identified as related to ivabradine, and there was no evidence of excess in mortality with ivabradine. There are several on-going studies, including the large randomized BEAUTIFUL trial, of the effects of ivabradine on all-cause death and cardiovascular morbidity and mortality in patients with left ventricular dysfunction, and studies in patients with severe heart failure, as well as an open-label 5-year extension safety study in 558 patients.

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Heart Rate Slowing for Myocardial Dysfunction/Heart Failure

Rationale and Preclinical Studies

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Abstract

Heart failure is a major health problem, and is one of the few cardiovascular diseases that increased its prevalence over the last decade. Increased heart rate, generally observed in patients with heart failure, is involved in the deterioration of cardiac pump function. However, the effects of 'pure' heart rate reduction on the progression of heart failure are unknown. In a rat model of heart failure, ivabradine, a blocker of I_f channels reduces dose-dependently heart rate without modification of blood pressure. This heart rate reduction is associated with an improvement in cardiac function. After chronic administration, this improvement of cardiac function persists after ivabradine withdrawal, revealing an improvement in intrinsic myocardial function. This beneficial effect could be explained by direct effects of heart rate reduction induced by ivabradine, i.e. improved myocardial oxygen supply to demand ratio, and/or myocardial tissular effects induced by chronic decrease in heart rate such, i.e. decreased extracellular collagen accumulation, increased myocardial microcirculation. In conclusion, 'pure' chronic heart rate reduction can be beneficial in heart failure.

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Rationale

Enhancement of heart rate, due to increased sympathetic nervous activity, is one of the mechanisms that attenuate the impairment of cardiac output in patients with congestive heart failure (CHF). However, the increase in cardiac output induced by an enhancement of heart rate is associated with an impairment of left ventricular filling, a decrease in myocardial perfusion and an increase in myocardial O_2 consumption. Moreover, these phenomena are known to be involved in the development of left ventricular dysfunction and/or CHF observed after persistent tachycardia [1, 2], and it has been shown that an

enhancement of heart rate reduces long-term survival [3]. Thus, heart rate slowing should, in theory, be beneficial in CHF.

Indeed, large-scale clinical trials conducted with β-blockers in CHF suggest such an essential role of heart rate slowing, since the effects of β-blockers on cardiac function and survival are correlated with the magnitude of the heart rate slowing [3–5]. Furthermore, pacing abolishes the increase of left ventricular contractile function in a dog model of CHF after long-term β-blocker treatment [6]. These data support the hypothesis of an essential role of heart rate slowing in the beneficial effects observed after long-term β-blockade in heart failure, even if other mechanisms, such as prevention of β-receptor downregulation and/or direct myocardial damage caused by catecholamines [7], are potentially involved and cannot be excluded.

Preclinical Studies

Until the development of selective inhibitors of the cardiac pacemaker I_f current, or sinoatrial node modulators, such as zatebradine and ivabradine [8], the possible beneficial effects of 'pure' heart rate slowing in CHF remained hypothetical. In contrast with other heart-rate-slowing drugs, I_f current inhibitors induce, in humans and animals, a selective and dose-dependent heart rate reduction [9–11] without modifying the atrioventricular, intraventricular conduction and/or contractility [12]. It must be stressed that this heart-rate-slowing effect is independent of the physiopathological status, i.e. reduced myocardial relaxation/contraction, since the heart rate reduction induced by I_f current inhibitors observed in humans and animals with CHF is similar to that in healthy volunteers and normal rats [9]. Moreover, the heart-rate-slowing effect does not seem to be due to tachyphylaxy, since in rats with CHF, the magnitude of the heart rate slowing observed after 4, 30 or 90 days is similar (fig. 1).

Both after short- and long-term treatment, the reduction in heart rate is associated with an increase in stroke volume resulting in a preservation of the cardiac output, despite the heart rate reduction (figs. 2, 3). Moreover, several mechanisms seem implicated in the increase in stroke volume observed after short- or long-term treatment. Indeed, after short-term heart rate slowing, i.e. 4 days, the increase in stroke volume is related with an increase in the left ventricular diastolic diameter without modification of the left ventricular systolic diameter. In contrast, after long-term heart rate slowing, i.e. 90 days, the increase in stroke volume is associated with a decrease in the left ventricular systolic diameter without modification of the left ventricular diastolic diameter. Thus, while the preservation of cardiac output after short-term heart rate slowing mainly involves the Frank-Starling mechanism, the preservation of stroke volume after long-term heart rate slowing might be partially related to a modification of

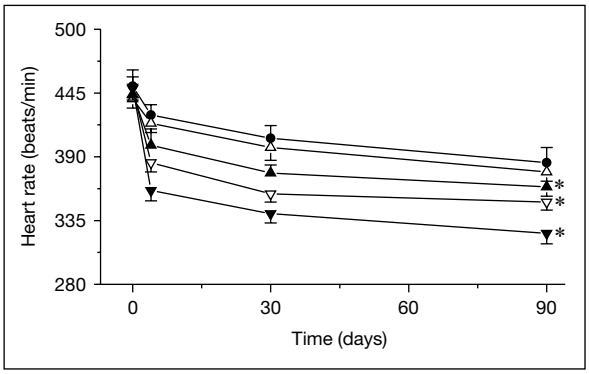

Fig. 1. Heart rate measured in rats with chronic heart failure, either untreated (●) or treated per os by the I_f current blocker ivabradine at a dose of 0.3 (△), 1 (▲), 3 (▽) or 10 mg/kg/day (▼). Treatment with ivabradine dose-dependently reduces heart rate reaching a plateau as early as 4 days after initiating treatment, illustrating the absence of tachyphylaxy (adapted from Mulder et al. [15]). *$p < 0.05$ vs. untreated CHF.

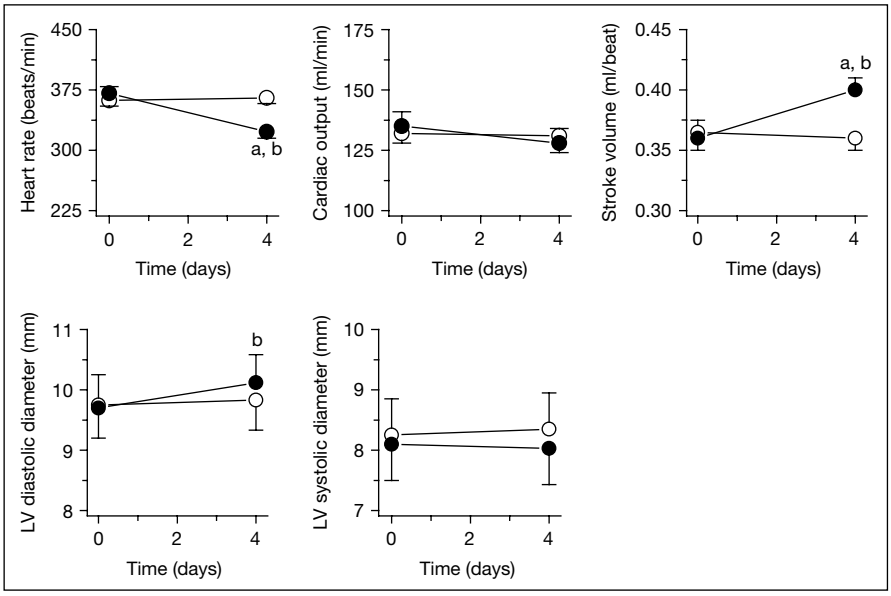

Fig. 2. Heart rate, cardiac output, stroke volume and left ventricular (LV) diastolic as well as systolic diameters determined in anesthetized rats with chronic heart failure, either untreated (○) or treated per os for 4 days by ivabradine at a dose of 10 mg/kg/day (●). Four days of ivabradine treatment induces a significant heart rate slowing and preserves cardiac output due to an increase in stroke volume. The latter is the result of a significant increase in

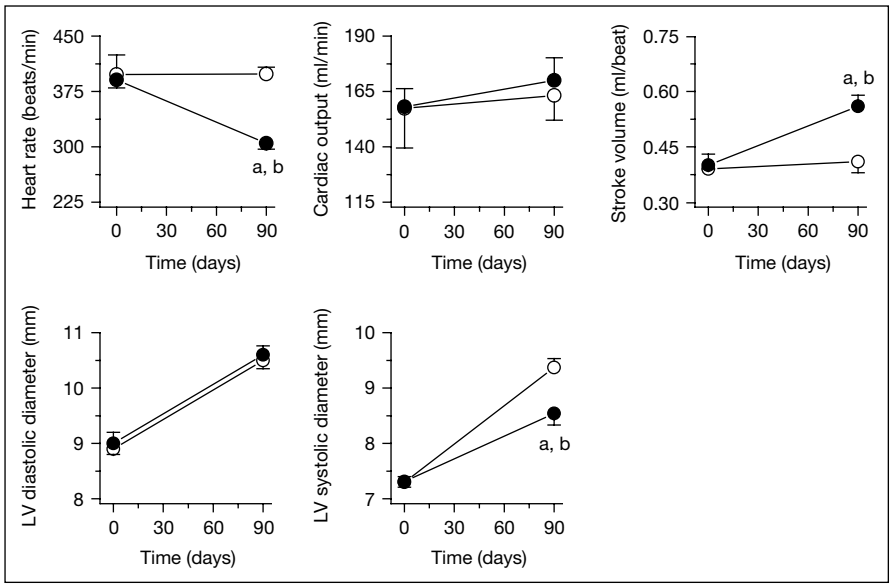

Fig. 3. Heart rate, cardiac output, stroke volume and left ventricular (LV) diastolic as well as systolic diameters determined in anesthetized rats with chronic heart failure, either untreated (○) or treated per os for 90 days by ivabradine at a dose of 10 mg/kg/day (●). Ninety days of ivabradine treatment induces a significant heart rate slowing and preserves cardiac output due to an increase in stroke volume. The latter is the result of a significantly smaller LV systolic cavity diameter without any modification of the LV diastolic cavity diameter (adapted from Mulder et al. [15]). $^{a}p < 0.05$ vs. time-matched untreated chronic heart failure; $^{b}p < 0.05$ vs. pretreatment value.

the left ventricular structure and/or myocyte properties. Indeed in the context of an impaired contractility, the chronic heart rate slowing induced by I_f current inhibitors results in an enhancement of the left ventricular contractile force, illustrated in vivo by the decrease in the left ventricular systolic diameter (fig. 4) and in vitro by the higher left ventricular systolic pressure-volume relation in the Langendorff experiments (fig. 5). Moreover, the fact that normalization of heart rate due to interruption of long-term ivabradine treatment does not abrogate the beneficial effect on stroke volume (fig. 4) or left ventricular systolic pressure-volume relation (fig. 5) further strengthens the hypothesis that

the LV diastolic cavity diameter without any modification of the LV systolic cavity diameter [unpubl. data]. $^{a}p < 0.05$ vs. time-matched untreated chronic heart failure; $^{b}p < 0.05$ vs. pretreatment value.

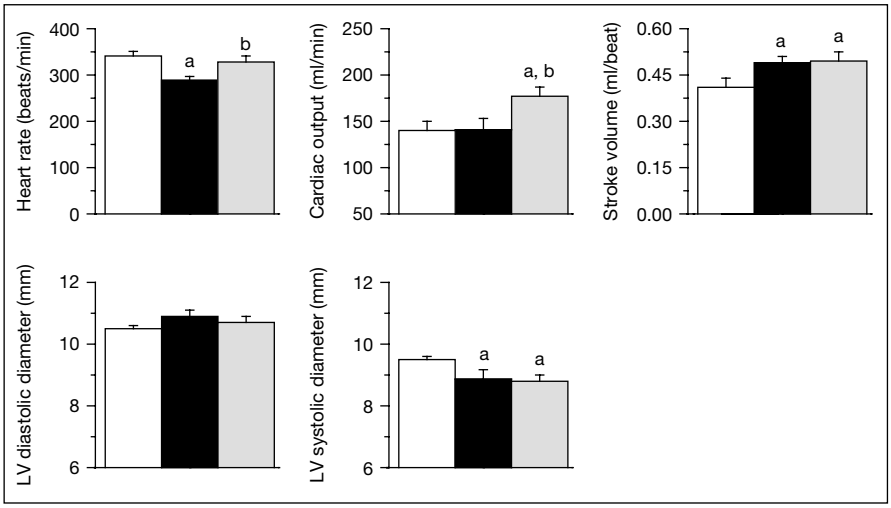

Fig. 4. Heart rate, cardiac output, stroke volume and left ventricular (LV) diastolic as well as systolic diameters determined in anesthetized rats with chronic heart failure, either untreated (□), treated for 90 days with ivabradine at a dose of 10 mg/kg/day (■), or 3 days after interruption of the 90-day ivabradine administration (▨). While interruption of long-term ivabradine treatment results in a return of heart rate to a level observed in untreated rats, cardiac output significantly increases, as a result of the preservation of stroke volume at a level observed in long-term ivabradine-treated animals. This is due to the persistent effect, i.e. smaller left ventricular systolic cavity diameter without any modification of the left ventricular diastolic cavity diameter, despite the interruption of treatment (adapted from Mulder et al. [15]). $^{a}p < 0.05$ vs. time-matched untreated chronic heart failure; $^{b}p < 0.05$ vs. ivabradine treatment.

long-term heart rate slowing induces a modification of the left ventricular structure and/or myocyte properties. Thus, long-term effects contrast with acute effects of ivabradine or zatebradine, since these drugs do not modify cardiac contractility after acute administration [9, 13, 14].

It should be stressed that, despite the marked heart rate slowing, I_f current inhibitors do not modify blood pressure. This, together with the fact that cardiac output is maintained, suggests that peripheral vascular resistance does not change, illustrating the absence of vascular tropism in terms of vascular relaxation or contraction [10], and cannot account for the beneficial effects of I_f current inhibitors on left ventricular function, i.e. stroke volume. Moreover, the improvement in left ventricular function does not appear to be related to modifications in the left ventricular workload or to circulating neurohumoral factors, since (1) heart rate slowing does not modify left ventricular hemodynamics [15, 16] and (2) improvement in left ventricular function is also observed in isolated heart preparation at fixed pre- and afterload.

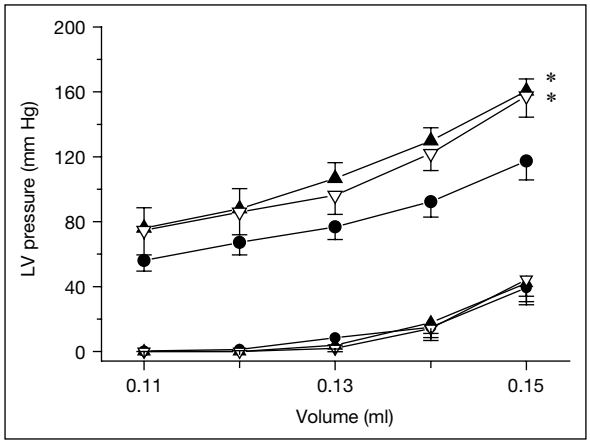

Fig. 5. Left ventricular (LV) systolic and diastolic pressures in response to increasing left ventricular volume in chronic heart failure rats, either untreated (●), treated for 90 days with ivabradine at a dose of 10 mg/kg/day (▲), or 3 days after interruption of the 90-day ivabradine administration (▽) in an isolated Langendorff heart preparation. While the LV diastolic pressure-volume relationship is not modified by long-term ivabradine treatment, the left ventricular systolic pressure-volume relationship is significantly shifted to the left, illustrating an improved contraction. The effect on the LV systolic pressure-volume relation is not modified in heart studies 3 days after interruption of ivabradine treatment, illustrating a persistent improvement in LV contractility (adapted from Mulder et al. [15]). *$p < 0.05$ vs. time-matched untreated chronic heart failure.

In contrast, heart rate slowing per se is beneficial in CHF in terms of oxygen demand and supply after short- as well as long-term treatment. Indeed, since heart rate plays a pivotal role in myocardial oxygen consumption, heart rate slowing will reduce oxygen demand, which is most likely beneficial in a setting of CHF. Furthermore, heart rate slowing will improve myocardial oxygen supply. Indeed, since the heart rate-diastolic time relation is nonlinear, a decrease in heart rate induced by I_f current inhibitors most likely results in an increase in the diastolic part of the cardiac cycle [17], leading to an increased coronary perfusion time and thus myocardial perfusion especially to the deeper layer [18].

However, the increase in coronary perfusion might be important for the long-term effects of heart rate slowing. Indeed, an increase in coronary perfusion due to heart rate slowing would prevent the development of coronary endothelial dysfunction provoked by the long-term decreased perfusion observed in CHF [19, 20]. Moreover, it could diminish, by preventing local hypoxia, the local production of cytokines, like IL-1, IL-6, or TNF-α [21], free radicals [22], and/or vasoconstrictors like endothelin [23], all factors implicated in the deterioration of left

ventricular function/remodeling as well as intrinsic tissue structure. Furthermore, in terms of myocardial O_2 demand and tissue-protective effects, the improvement in left ventricular filling induced by the decrease in heart rate diminishes sympathetic activity, as suggested by the decrease in noradrenaline plasma levels [15]. This probably limits downregulation of cardiac β-receptors as well as the direct toxic effect of noradrenaline, thus mimicking in part the effect of β-blockers. Finally, one of the most important structural effects of heart rate slowing is its effect on coronary rarefaction observed in CHF [24]. Indeed, long-term heart rate slowing not only induces myocardial angiogenesis in normal animals [25] but also prevents coronary rarefaction of the 'viable' part of the myocardium in rats with CHF [15, 16, 26]. We can only speculate upon the mechanism(s) involved in the prevention of coronary rarefaction, but augmented levels of hypoxia-inducible factor-1α and associated growth factors might be implicated. Indeed, the increase in the left ventricular diastolic diameter observed after acute heart rate slowing will increase myocardial stretch, which is a trigger for the increase in hypoxia-inducible factor-1α [27] and growth factors [26], like vascular endothelial growth factor, myocyte tumor growth factor-β, and basic fibroblast growth factor proteins, which all are involved in angiogenesis [25, 28].

Whatever the mechanism(s), all these direct and indirect myocardial effects, together with a reduced O_2 requirement induced by heart rate slowing [29], will improve the O_2 supply-oxygen demand ratio that is beneficial, in terms of 'coronary reserve' [16, 26], and thus prevents the progressive degradation of cardiac function in heart failure.

Conclusion

Long-term heart rate slowing induced by selective I_f inhibitors improves left ventricular function and increases stroke volume, resulting, despite the heart rate slowing, in a preserved cardiac output. This improvement in cardiac function is probably related to the heart rate slowing per se, but also to modifications of the left ventricular structure, myocyte properties and/or improved myocardial perfusion secondary to long-term heart rate slowing.

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Future Directions: What Data Do We Need?

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Abstract

Pure heart rate reduction by ivabradine during exercise results in the decrease in oxygen demand and the increase in oxygen supply through the prolongation of diastole. These properties are crucial for its beneficial effect in patients with chronic stable angina. The ability of ivabradine to reduce the heart rate at rest can also have a potential use in clinical practice. In fact, the new directions for future clinical research are focused on this property. Chronic coronary artery disease, acute coronary syndromes and heart failure represent the areas in which resting heart rate reduction may improve cardiovascular prognosis. Application of ivabradine in these conditions deserves full attention, with dedicated and properly powered outcome trials.

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The I_f current is responsible for heart rate (HR) regulation in the sinus node [1]. Ivabradine is a selective and specific inhibitor of this current, which has the ability to slow the HR both at rest and during exercise [1].

Limitation of HR increase during exercise has beneficial effects in stable angina. Pure HR reduction with ivabradine results in a decrease in oxygen demand and an increase in oxygen supply through the prolongation of diastole. These properties formed the basis for the registration of ivabradine for the treatment of chronic stable angina [2, 3].

The ability of ivabradine to reduce the resting HR can also have a potential use in clinical practice. In fact, the new directions for future clinical research with ivabradine are focused on this property.

Resting HR is a well-established indicator of cardiovascular risk [4]. Three areas in which pure HR reduction may improve the cardiovascular prognosis deserve full attention with dedicated and properly powered outcome clinical

trials: chronic coronary artery disease (CAD), acute coronary syndromes (ACS) and heart failure.

Chronic Coronary Artery Disease

CAD is a leading cause of death in industrialized countries. It is well known from epidemiological studies that high resting HR is associated with an increased total and cardiovascular mortality. Despite recent advances in the management of myocardial infarction (MI), patients with compromised left ventricular ejection fraction with or without heart failure still suffer from high mortality.

β-Blockers have been shown to reduce total mortality and sudden cardiac death in MI patients. It is believed that at least part of this benefit is related to their HR-lowering effect.

A multivariate analysis of the CIBIS II study – which aimed to demonstrate that β-adrenergic blockade using bisoprolol decreases mortality in chronic heart failure (CHF) – showed that the change in HR between baseline and the follow-up at 2 months after randomization was related to improved survival and less hospitalizations in patients with sinus rhythm [5]. However, despite the documented reduction in mortality and morbidity associated with β-blockade in patients with a history of MI and impaired left ventricular systolic function with or without clinical heart failure [6], β-blockers are still underused in this patient population. There may be at least two reasons for this phenomenon. First, β-blockers are contraindicated in patients with decompensated heart failure, chronic obstructive lung disease, severe peripheral arterial disease, hypotension or atrioventricular conduction defects. According to a retrospective study performed to assess the β-blocker utilization in clinical practice [7], contraindications account for about 25% of abstentions from treatment with β-blockers in patients with heart failure. Second, a threat of precipitation or progression of heart failure, related to the negative inotropic effect of β-blockers, although not documented in some studies [8], may be a reason why treatment is not initiated.

Ivabradine has no effect on cardiac inotropism and does not decrease left ventricular ejection fraction, even in patients with impaired left ventricular function [9]. On the contrary, ivabradine improves left ventricular function, increases stroke volume and maintains cardiac output [9]. These properties may result from modifications of the left ventricular structure as demonstrated by the reduction of cardiac collagen accumulation and the persistence of the improvement in left ventricular function after interruption of long-term treatment with ivabradine [10]. Potential benefits of ivabradine in patients with mild to moderate left ventricular dysfunction (left ventricular ejection fraction >30 and $<45\%$) were evidenced during a 3-month randomized double-blind placebo-controlled study [11]. Ivabradine

10 mg b.i.d. was administered to 53 patients on top of the standard therapy (except β-blockers). Preliminary results showed a trend towards an increase in ejection fraction in patients treated with ivabradine, compared to a trend towards a decrease in patients receiving placebo. These data suggest that ivabradine may exert a beneficial effect on left ventricular geometry in the presence of left ventricular dysfunction, and may improve the outcome of patients with stable CAD and depressed left ventricular ejection fraction, who are at high risk of death.

A study which compares ivabradine with placebo in patients with CAD and left ventricular systolic dysfunction is ongoing (BEAUTIFUL: morbidity-mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction). This study is the first opportunity to investigate whether a pure HR-lowering agent reduces cardiovascular events.

BEAUTIFUL is a randomized, double-blind, placebo-controlled, parallel-group international multicenter trial [12]. The study population will include about 10,000 patients with stable CAD and left ventricular systolic dysfunction, with normal sinus rhythm. These patients are at high risk of experiencing a cardiovascular event and are likely to benefit from the HR-lowering effect of ivabradine. The patients will be recruited in approximately 660 centers worldwide. The study is designed to demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality, hospital admission for acute MI, hospital admission for new onset or worsening heart failure (composite endpoint).

Acute Coronary Syndromes without Persistent ST Segment Elevation

Patients with unstable angina or an acute MI without persistent ST segment elevation may have an unfavorable outcome in spite of intensive medical therapy. Prognosis is defined primarily by the recurrence and severity of myocardial ischemia. Thus, the aim of treatment is to alleviate existing ischemia and to prevent its recurrence that might lead to the development of MI. This goal can be achieved using two approaches targeted at different mechanisms. Firstly, anticoagulants (unfractionated and low-molecular heparin) and antiplatelet agents (aspirin, clopidogrel) are administered to prevent thrombus formation or extension. Secondly, myocardial oxygen consumption is reduced, mostly using nitrates and β-blockers. These agents now have widespread acceptance as a first-line therapy in the management of ACS patients. Therapeutic benefit of β-blockers is mainly related to their effect on HR. Interestingly, the evidence for the beneficial effect of β-blockers in patients with unstable angina is based on limited data from randomized trials, as well as on pathophysiological considerations and extrapolation from the experience in stable angina and

acute MI. Moreover, the use of β-blockers in patients with ACS is limited to those without acute or exacerbated heart failure, atrioventricular conduction abnormalities or severe obstructive pulmonary disease. Accordingly, a selective sinus node inhibitor, which will reduce HR without interaction with β-adrenergic receptors, may be of theoretical advantage in many patients with ACS.

As the first step, the effect of pure HR reduction with ivabradine on silent and symptomatic ischemia in patients with ACS without persistent ST segment elevation should be assessed by continuous 24-hour, 12-lead ECG monitoring. Subsequently, the impact of this treatment on in-hospital and 30-day clinical outcome should be evaluated.

Heart Failure

The prevalence of CHF is increasing due to the aging of the population and to improved survival after acute MI. The patients who survive tend to have impaired left ventricular systolic function, which is likely to evolve into clinical heart failure. CHF is a very disabling condition, associated with repeated hospitalizations and a substantial reduction in the quality of life. Heart failure also presents a significant economic burden, since it consumes 1–2% of total health care expenditure in industrialized countries [13]. Despite the advances in the treatment of CHF over the past decade, the prognosis remains serious, with the annual mortality ranging from 8–10% to more than 20% in recent clinical trials involving patients with different severity of the disease presenting with impaired left ventricular systolic function [14–17]. For example, in the COMET trial [17] that included patients with mild to moderate CHF (NYHA classes II and III in equal proportions, and left ventricular ejection fraction $<$35%), more than 35% of patients died within the 5-year follow-up, despite optimal treatment. In the COMET trial, in which β-blockers were used in both treatment groups, this therapy was permanently discontinued in a large proportion of patients, i.e. in 32% in both groups. Thus, despite the beneficial effects of β-blockers, including HR reduction and its physiological consequences, such as neurohormonal modulation, reduction of inflammation and apoptosis, and prevention of left ventricular remodelling, in reality a large number of patients do not receive these drugs. The numbers are even higher in the community [18].

The adverse effects of β-blockers, contraindications to their use, and the relative difficulty in attaining optimal dosage have driven the interest to test the efficacy and safety of ivabradine as an alternative HR-lowering agent in patients with CHF.

Resting HR is inversely related to prognosis in many cardiovascular diseases and is thought to have an independent prognostic value in CHF, across a large

spectrum of severity of the disease [4]. Recent studies have suggested that lowering HR in patients with CHF might have a favorable effect on prognosis [5].

Patients with CHF at the highest ranges of resting HR have distinct clinical characteristics, for example they more often have diabetes, lower ejection fractions, and more severe symptoms (NYHA classes III–IV) [19]. Those variables are independent markers of a poor prognosis, but they are also related to an autonomic imbalance with increased sympathetic drive and reduced vagal activity. This imbalance has been proposed as the pathophysiological mechanism responsible for the relationship between high resting HR and poor prognosis. Increased cardiac sympathetic stimulation leads to an increase in myocardial metabolic rate, inducing ischemia and hypoxia at the cellular level. The increase in HR and plasma norepinephrine is also associated with reduced HR variability, the latter being correlated with a poor prognosis [20, 21]. The clinical consequences of sustained sympathetic stimulation include vasoconstriction, progressive impairment of left ventricular function and an increased risk of arrhythmias.

Preliminary preclinical and clinical data confirm the safety of ivabradine in heart failure, and the ability of the drug to reduce left ventricular size and improve systolic function in this condition.

Ivabradine improved left ventricular function and structure and increased stroke volume in a rat model of cardiac failure induced by coronary ligation [10]. In patients with heart failure due to systolic dysfunction, a single intravenous dose of ivabradine induced HR reduction, while preserving left ventricular function [9].

The rationale for adding a pure HR-lowering agent to a β-blocker is to further reduce the consequences of excessive sympathetic stimulation primarily at the myocardial level in those patients who, despite therapy with a β-blocker, still have a relatively high resting HR.

If a study, in patients with moderate to severe CHF and reduced left ventricular ejection fraction receiving optimal recommended therapy, comparing the effect of ivabradine with that of placebo on cardiovascular mortality and hospitalizations for worsening heart failure shows superiority of ivabradine, it will be consistent with the conclusion that HR is an independent prognostic factor in heart failure. Such a study will require recruitment of 5,000–6,000 patients in order to demonstrate a beneficial effect of further HR reduction in this setting.

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