Journal of Cardiology 62 (2013) 183–187

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Heart rate: A global target for cardiovascular disease and therapy along the cardiovascular disease continuum

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ARTICLE INFO

Article history:
Received 1 February 2013
Accepted 4 February 2013
Available online 24 June 2013

Keywords:
Heart rate
Cardiovascular disease continuum
I(f) current inhibition
Risk reduction

ABSTRACT

Heart rate is a predictor of cardiovascular and all-cause mortality in the general population and in patients with cardiovascular disease. Increased resting heart rate multiplies risk and interferes at all stages of the cardiovascular disease continuum initiating from endothelial dysfunction and continuing via atherosclerotic lesion formation and plaque rupture to end-stage cardiovascular disease. As a therapeutic target, heart rate is accessible via numerous pharmacological interventions. The concept of selective heart rate reduction by the *I(f)* current inhibitor ivabradine provides an option to intervene effectively along the chain of events and to define the specific and prognostic role of heart rate for patients with coronary artery disease and heart failure. Future interventional studies will further clarify the significance of heart rate and targeted heart rate reduction for primary and secondary prevention in cardiovascular and cerebrovascular events.

Introduction

Based on the evidence from epidemiological and clinical studies resting heart rate developed from an ordinary clinical variable to a relevant cardiovascular risk marker. The impact of increased resting heart rate on prognosis is validated in the general population, in patients with hypertension, coronary artery disease (CAD), or heart failure and exists irrespective of age, cardiovascular risk factors, or comorbidities [1–7]. The cardiovascular disease continuum includes risk factors initiating a process leading to tissue damage and a subsequent chain of events resulting in end-stage cardiovascular disease [8]. From vascular risk factors to cardiovascular events and heart failure, heart rate affects basically all stages of the cardiovascular continuum and has therefore evolved as a relevant risk marker and goal of therapy in cardiovascular prevention and disease [1,9]. The aim of the following article is to elucidate the close connection and the impact of heart rate on the different entities of the cardiovascular continuum and how a targeted reduction of heart rate may prevent cardiovascular events (Fig. 1).

Resting heart rate and outcome in patients with risk factors

Many epidemiological and clinical studies investigated the association between resting heart rate and outcomes in populations with and without existing cardiovascular risk factors. In the Framingham study, cardiovascular mortality increased progressively with resting heart rate in a population free from cardiovascular disease. The effect of heart rate on mortality was independent of other cardiovascular risk factors [2] and risk further increases with additional risk factors such as arterial hypertension [3]. Prospective studies in healthy populations showed that increased resting heart rate may predispose to the development of impaired glucose metabolism, obesity, and diabetes mellitus [10,11].

A fundamental association between heart rate and development of arterial hypertension was already shown in a retrospective analysis of military personnel following combat during World War I [12]. Since then a relevant association between cardiovascular mortality and resting heart rate in patients with hypertension was shown by several investigations. The HARVEST study established a strong link between higher heart rates and increases in blood pressure in a cohort of stage 1 hypertensive patients [13]. Patients in this cohort whose heart rate was persistently elevated during the study period of 6.4 years had a doubled fully adjusted risk of developing fixed hypertension compared with individuals with normal heart rates. In hypertensive persons of the Framingham cohort the rate of complications caused by cardiovascular events as well as the total mortality increased by about 100% when heart rate increased by 40 beats/min [3]. In patients with arterial hypertension, microalbuminuria increases cardiovascular risk and may be regarded as a marker of generalized vascular injury [14]. A potential connection between the prevalence of microalbuminuria and heart rate in hypertensive patients was analyzed in I-SEARCH [15]. In this outpatient cohort, heart rate was found to be a strong predictor

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0914-5087/$ – see front matter
http://dx.doi.org/10.1016/j.jjcc.2013.02.018

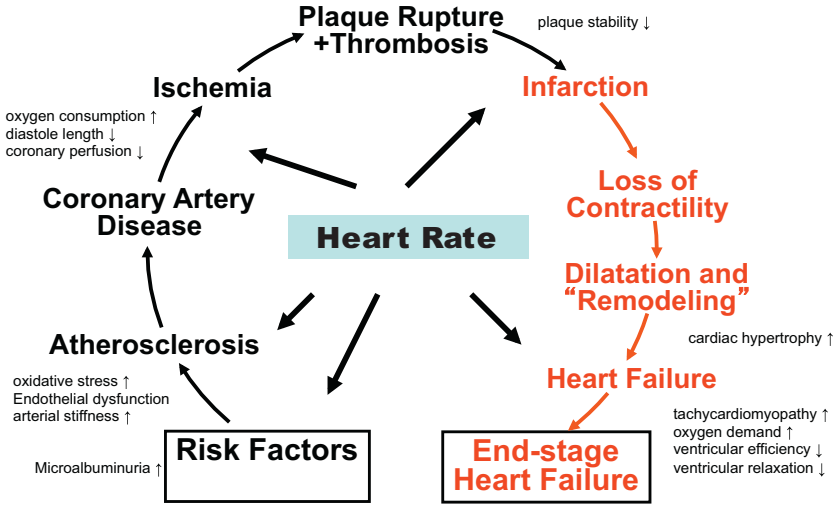

Fig. 1. Pathophysiological effects of heart rate on the cardiovascular disease continuum.

for the prevalence of microalbuminuria, even after adjustment for hypertension and risk factors such as pre-existing cardiac disease, diabetes mellitus, age, and sex. A consecutive analysis showed that the prevalence of microalbuminuria is even higher in hypertensive patients with a history of atrial fibrillation [16].

Heart rate promotes atherosclerosis

Experimental and clinical data suggest that sustained elevation of heart rate – independent of the underlying trigger – contributes to the pathogenesis of vascular disease. In animal studies, accelerated heart rate was associated with vascular oxidative stress, endothelial dysfunction, acceleration of atherogenesis, and vascular stiffness [1]. Since the early 1980s a broad range of animal studies investigated effects of selective heart rate reduction on vascular phenotypes in several animal models. Heart rate reduction by electrophysiological (sinus node ablation) and pharmacological [$I(f)$ current inhibition] interventions reduced atherosclerosis in monkeys and dyslipidemic mice [17,18]. Treatment with the $I(f)$ current inhibitor ivabradine reduced vascular oxidative stress and inflammation, restored endothelial function, and augmented vascular compliance in ApoE$^{-/-}$ mice [19–24].

In humans, accelerated resting heart rate was shown to be closely linked to systemic inflammation and markers of endothelial dysfunction [25,26]. However, despite extensive experimental evidence, clinical data investigating the effects of heart rate reduction on endothelial function are not yet conclusive. While heart rate was positively associated with brachial artery flow-mediated dilation (FMD) in a Framingham cohort [27], a prospective study in patients with diabetes mellitus did not show a positive effect of heart rate reduction induced by ivabradine on FMD [28].

Beyond the classical factors perturbing endothelial function like oxidative stress or inflammation vascular integrity may be affected by local hemodynamic characteristics defined by heart rate such as endothelial shear stress [29] or cyclic tensile stress [30]. As an integral component of cyclic stress (pulse pressure × heart rate), heart rate controls vascular function and defines transmural force imposed by pulsatile blood flow. Accelerated heart rate may promote low and oscillatory endothelial shear stress. Disturbed shear stress and enhanced tensile stress may synergistically promote atherogenesis and vascular stiffness [31]. However as heart rate dependent effects on atherosclerosis are discussed by several authors, experimental evidence on the exact rate-dependent changes of the local hemodynamic environment and the subsequent molecular signaling is sparse and still has to be characterized.

Heart rate in coronary heart disease and myocardial infarction

The prognostic importance of resting heart rate for morbidity and mortality in patients without cardiovascular disease also applies to populations with established CAD and after myocardial infarction. Studies such as CASS and BEAUTIFUL demonstrated a positive association between increased resting heart rate and cardiovascular mortality [4,32]. In BEAUTIFUL, patients with CAD and left ventricular systolic dysfunction and a resting heart rate >70 bpm displayed increased cardiovascular mortality as well as an increased risk for hospitalization due to heart failure, myocardial infarction, or need for coronary revascularization. Moreover, increased resting heart rate was associated with coronary vascular events [33]. This finding may be explained by increased occurrence of coronary plaque disruption since heart rate is a predictor for instability of coronary plaque [34]. Prognosis of patients after a myocardial infarction is closely linked to heart rate. Patients with myocardial infarction exhibit an increased resting heart rate and in particular the heart rate assessed at hospital discharge correlates with an increase in mortality rate after 1 year [6]. Metaanalyses of the GISSI-2 and 3 trials including about 20,000 patients demonstrated that in-hospital mortality rate of patients after myocardial infarction significantly rises from 3.3% to 10.1% when patients with heart rates <60 bpm were compared with those with heart rates >100 bpm on admission [35]. The GISSI-trials showed that even patients without heart failure and an elevated heart rate had a worse long-term survival prognosis [35].

Heart rate is a major determinant of myocardial oxygen demand and coronary blood flow [36]. In CAD, heart rate becomes relevant affecting both sides of myocardial oxygen balance. An increased heart rate contributes to an imbalance by both decreasing supply and increasing demand thereby leading to myocardial ischemia and subsequent angina. Since the advent of beta-blockers, pharmacological heart rate reduction may be seen as a cornerstone of symptomatic (anti-anginal) treatment of CAD patients. Today beta-blockade remains the standard of care for CAD patients particularly after a myocardial infarction [37,38]. However, as recently published data from the REACH registry show, beta-blocker use in patients with CAD (+/− myocardial infarction) was not associated with a lower event rate [39]. Data from the prospective

CLARIFY registry show that in outpatients with stable CAD despite a widespread use of beta-blockers, patients often have resting HR ≥70 bpm, which is associated with an overall worse health status, more frequent angina, and ischemia [40]. With the concept of *I*(*f*) current inhibition, a new treatment option expanded anti-anginal drug treatment. Ivabradine, an *I*(*f*) current inhibitor, induces a sustained and dose-dependent reduction of heart rate at rest and during exercise, without relevant effects on left ventricular (LV) contractility, blood pressure, and atrioventricular conduction [41]. The anti-anginal and anti-ischemic efficacy of ivabradine – in monotherapy or in combination with a beta-blocker – has been demonstrated by several clinical trials [42–44]. As a consequence, the substance evolved as an alternative strategy especially for patients in whom the use of beta-blockers is limited due to side effects or patients who remain symptomatic despite beta-blockade. Regarding the above-mentioned registry based results, further research is necessary to identify patients with CAD and after myocardial infarction who may benefit from co-treatment with ivabradine.

Resting heart rate and outcome in heart failure

In patients with heart failure increased sympathetic activity is associated with a positive chronotropic stimulation leading to accelerated resting heart rate [45]. Heart rate may directly affect myocardial performance by alteration of oxygen consumption, reduction of diastolic filling and coronary perfusion by impairment of relaxation, and finally by pro-arrhythmic effects [46]. Furthermore, high heart rates per se can cause heart failure [47]. The significance of heart rate on mortality was retrospectively addressed in sub-analyses of several heart failure trials which enrolled a total of almost 10,000 patients with advanced systolic heart failure (New York Heart Association class II–IV). The general trend of these trials clearly demonstrates that high heart rate at rest contributes to poor survival and represents a negative prognostic predictor [48]. In the CIBIS and CIBIS II trials (Cardiac Insufficiency Bisoprolol Study), heart rate and heart rate change both were significant predictors of mortality [49,50]. However, it remains currently unknown whether or to what extent the benefit from beta-blockers in patients with heart failure is due to heart rate reduction per se or other beneficial effects deriving from interruption of maladaptive beta-signaling pathways. Two metaanalyses investigated whether the survival benefits of beta-blockade in heart failure are associated with the magnitude of heart rate reduction or the beta-blocker dose. Both showed a close relation of outcome with the extent of rate reduction rather than with the achieved dosage [48,51]. In view of these findings interventional trials pursuing a concept of "selective" heart rate reduction seemed a logical consequence to provide further information on the prognostic role of heart rate in chronic heart failure. Post hoc analyses of two large scale prospective trials – the BEAUTIFUL and the SHIFT trials – investigating the effects of selective heart rate reduction with ivabradine identified heart rate as a modifiable risk factor in patients with heart failure [5,32,33,52]. In BEAUTIFUL, elevated heart rate (70 bpm or more) was a strong independent risk factor in patients with CAD and LV dysfunction a finding that was confirmed by the SHIFT cohort in patients with an LV ejection fraction of <35% and a heart rate of 70 bpm or higher.

Whereas both trials established a strong prognostic role for heart rate in heart failure, the results of the primary analyses turned out differently. Treatment with ivabradine on top of standard medication did not reduce the primary composite endpoint in patients with stable angina, left ventricular dysfunction (ejection fraction <40%), and heart rate ≥60 bpm in the BEAUTIFUL trial. However, it did reduce secondary endpoints (admission to hospital for fatal and non-fatal myocardial infarction, coronary revascularization) in a subgroup of patients with heart rate of 70 bpm or greater. The SHIFT trial included patients with left ventricular dysfunction (ejection fraction ≤35%), both ischemic (68%) and non-ischemic (32%) and a heart rate ≥70 bpm. Heart rate reduction by ivabradine reduced the risk for the primary composite endpoint by 18% (Fig. 2). This result was mainly driven by hospital admissions for worsening heart failure and occurred within the first 3 months after start of treatment. Moreover heart rate reduction with ivabradine reduced death from heart failure and hospital admissions for worsening heart failure and any other cardiovascular hospital admissions. A recently published secondary analysis of the SHIFT study showed that the effect of ivabradine on outcomes was most pronounced in patients with a baseline heart rate of ≥75 bpm. Risk reduction depended on heart rate with the best protection for heart rates <60 bpm or reductions >10 bpm on treatment with ivabradine. On the basis of this evidence the current ESC guidelines acknowledge the prognostic relevance of heart rate and consider ivabradine as add-on therapy in patients with severe left ventricular dysfunction (ejection fraction <35%) and a heart rate above 70 bpm despite treatment with a beta-blocker.

Resting heart rate and neurological outcomes

Whereas the intrinsic heart rate at rest is predictive for cardiovascular morbidity and mortality in the general population and in patients with cardiovascular disease no such association is known for neurological disease and ischemic stroke. As a consequence of a broad range of experimental data demonstrating a close link between heart rate and vascular function and phenotype recent studies focused on the effects of heart rate reduction on the cerebral vasculature and circulation. Conservation of endothelial homeostasis represents a prerequisite and a basic mechanism of stroke protection in mice, as shown by experimental studies [53,54]. In a model of mice subjected to chronic mental stress, stressed animals displayed higher resting heart rates, impaired endothelial function, and an increase in experimental stroke size. In turn a reduction of resting heart rate with ivabradine in stressed mice restored endothelial function and protected from ischemic brain injury via reduction of stroke size [55]. In a model of dyslipidemic mice chronic heart rate reduction via ivabradine maintained cerebral endothelial function and prevented cerebral artery remodeling [24]. Inspired by these findings a post hoc analysis of the PROFESS (The Prevention Regimen for Effectively Avoiding Second Stroke) trial aimed at evaluating associations of the resting heart rate at baseline with cardiovascular and neurological outcomes among patients who experienced an ischemic stroke [56]. Patients after a first stroke and a baseline heart rate ≥76 bpm had a higher risk

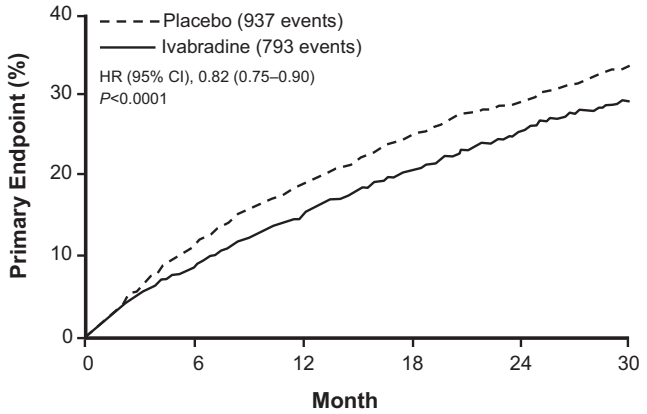

Fig. 2. Primary combined endpoint* of the SHIFT trial [52] (*composite of cardiovascular death or hospital admission for worsening heart failure).

of total death, vascular death, and non-vascular death. No significant association was found with recurrent stroke, myocardial infarction, and new onset or worsening congestive heart failure. A striking finding was a significant association between heart rate and functional neurological outcomes after a recurrent stroke. Poor functional independence according to the Barthel index score and cognitive decline according to the Mini-Mental State Examination (MMSE) score were significantly associated with an increasing resting heart rate. Low resting heart rate was associated with a better functional outcome and less cognitive decline (Fig. 3). Although preliminary and hypothesis-generating these results identify heart rate as mediator of cerebrovascular effects and may suggest heart rate as a potential novel target of intervention for improvement in cerebrovascular function after ischemic events.

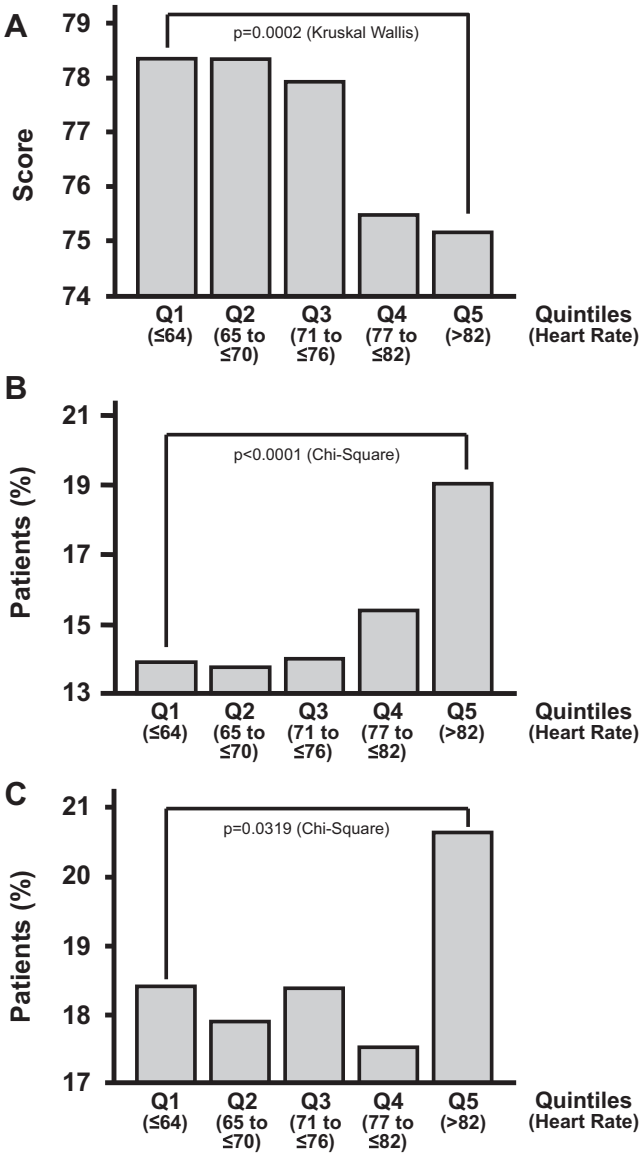

Fig. 3. Effects of resting heart rate on daily life activities and cognitive function in the PROFESS trial. (A) Barthel index [daily life activities and independence; 3 months after first stroke; scores ranging from 0 (complete dependence) to 100 (independence)]. (B) Mini-Mental State Examination (MMSE) from month 1 to penultimate visit (score from 0 to 30, lower scores indicative of a greater degree of cognitive impairment with 27.6 points as evidence for being cognitively intact and a score of 24 points or lower indicative of some degrees of cognitive impairment). (C) Patients with ≥2 points decrease in MMSE, from month 1 to the penultimate visit.

Summary

Increased resting heart rate interferes at all stages of the cardiovascular disease continuum. Heart rate may add to the pathogenesis of arterial hypertension or diabetes, increase the cardiovascular risk in patients with these diseases, and define mortality and morbidity in patients with CAD and heart failure. Heart rate reduction improves vascular function and prevents atherosclerosis in an experimental setting and is thus characterized as a potential modifiable risk factor by some authors. However an essential prerequisite to meet the criteria as a risk factor – interventional studies demonstrating a modulation of risk by heart rate reduction – are still lacking. If heart rate reduction may reduce risk in patients with established risk factors remains an open question. As a therapeutic target heart rate is accessible via pharmacological interventions. Beyond long established substances such as beta-blockers the concept of "pure" heart rate reduction via inhibition of $I(f)$ currents in the sinoatrial node was implemented in recent years. A multitude of interventional studies tested the concept of selective heart rate reduction by ivabradine both for symptomatic and prognostic treatment in CAD and in heart failure. In patients with coronary artery disease, heart rate reduction with the $I(f)$ current inhibitor ivabradine potently prevents angina and ischemia at rest and during exercise and today expands the armamentarium for the symptomatic treatment of chronic CAD. Although selective heart rate reduction with ivabradine led to some beneficial effects in patients with stable angina and left ventricular dysfunction, a clear prognostic benefit could not be established. Whereas in patients with chronic heart failure and a more severe reduction in left ventricular function (ejection fraction <35%) treatment with ivabradine improved clinical outcomes and established a role for heart rate as a modifiable risk factor in chronic heart failure. Although not a primary component of the cardiovascular continuum, cerebrovascular ischemic events and stroke share a large part of the underlying mechanisms contributing to cardiovascular events. Results obtained in animal models demonstrate beneficial effects of pharmacological heart rate reduction with ivabradine on vascular function and stroke size. Post hoc analyses of patients after a first stroke demonstrate an association between functional neurological outcomes and resting heart rate. Thus, selective heart rate reduction may play a future role in secondary prevention after cerebrovascular events.

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