Heart rate as a treatable cardiovascular risk factor

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Background: Although several epidemiological studies demonstrate the association between resting heart rate (HR) and cardiovascular morbidity and mortality, an elevated HR remains a neglected cardiovascular risk factor.

Sources of data: This review summarizes the results of published studies on the relationship between elevated HR and cardiovascular risk.

Areas of agreement: The role of HR in myocardial ischaemia in coronary patients is well known. Experimental data and clinical observations support the importance of HR in the pathophysiology of atherosclerosis and plaque rupture. A large body of evidence points to high resting HR as a risk factor for mortality in various populations, including coronary patients.

Areas of controversy: HR reduction is suggested to be a mechanism explaining the prognostic benefit of beta-blockers after myocardial infarction or in heart failure patients. However, it was unclear whether HR reduction per se directly affects cardiovascular prognosis. Treatment with ivabradine, a pure HR-reducing agent, provides an opportunity to assess the effects of selectively lowering HR without altering other aspects of cardiac function.

Growing points: The results of the recent Morbidity–Mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction study underline the importance of HR reduction in the management of stable coronary artery disease. The prospective analysis of data from the placebo arm demonstrated that elevated resting HR (≥70 bpm) is a strong independent predictor of clinical outcomes. Consistent with these data, ivabradine significantly improved coronary outcomes in patients with a HR of 70 bpm or more.

Areas timely for development: These data support the importance of HR in the management of stable coronary artery disease to assess prognosis and to guide optimal therapy.

Keywords: heart rate/risk factors/cardiovascular disease/coronary artery disease
Introduction

Coronary artery disease (CAD) represents a major cause of morbidity and mortality in industrialized countries and its prevalence makes it a public health problem worldwide.\(^1\) Despite modern therapy including intensive pharmacological treatment and interventional revascularization procedures, affected patients still suffer high event rates, including angina pectoris, myocardial infarction (MI), heart failure (HF) and cardiovascular death.\(^2\) Patients with left ventricular dysfunction or ischaemic cardiomyopathy are even at a higher risk of ischaemic events and/or cardiovascular death. Therefore, identification and treatment of risk factors are essential for improving the prognosis and quality of life of coronary patients.

Heart rate (HR), a simple and easily measurable clinical parameter, has been found to be a risk predictor of mortality and morbidity in various populations. The aim of this paper is to review the value of HR as a prognostic factor of mortality and morbidity and the effect of HR reduction on the prognosis of patients with CAD. Although HR reduction can be achieved with beta-blocker or non-dihydropyridine calcium antagonists, the recent development of the \(I_f\) current inhibitor ivabradine capable of achieving pure HR reduction is important to consider in light of the recently published results of the BEAUTIFUL (morBidity–mortality EvAlUaTion of the \(I_f\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) trial.

HR as a risk factor of cardiovascular and all-cause mortality

Epidemiological studies have consistently shown that resting HR is a predictive factor of all-cause mortality and cardiovascular mortality.\(^3\)–\(^6\) Dyer et al.\(^7\) observed statistically significant relationships between resting HR and both cardiovascular mortality and total mortality in men followed for 15 years in the Chicago People Gas Company study and for 17 and 5 years, respectively, in the Chicago Western Electric Company \((n = 1899)\) and Chicago Heart Association Detection Project \((n = 5784)\). HR was also an independent risk predictor of sudden coronary death, even when other CAD risk factors, such as age, blood pressure, total blood cholesterol, smoking and body weight, were taken into account in a multivariate analysis. A significant relationship was also found in the Framingham study between a high resting HR and increased rates of cardiovascular mortality, coronary heart disease and sudden coronary death both in men and women followed for 30 years.\(^8\) In a study of 19 386 French “white collar” employees...
followed for more than 20 years, Benetos et al. assessed cardiovascular mortality and non-cardiovascular mortality in four groups of HR based on the electrocardiogram: HR1 was <60 bpm, HR2 between 60 and 80 bpm, HR3 between 81 and 100 bpm and HR4 >100 bpm. In men, the relative risks of cardiovascular mortality in groups with resting HR of 60–80 bpm, 81–100 bpm and >100 bpm were 1.35, 1.44 and 2.18, respectively, as compared with the group with an HR of <60 bpm. HR was an independent risk factor in men, independent of age, hypertension, total cholesterol level, body mass index, smoking and level of exercise activity. In this cohort of women, HR did not influence cardiovascular mortality.

The Malattie Cardiovascolari Aterosclerotiche Istituto Superiore di Sanita (MATISS) study included 2533 men aged 40–69 years followed for a total of 24 457 subject-years and showed that HR was an independent predictive factor for total mortality and cardiovascular mortality. In a French population of 7079 subjects aged 42–53 years and followed for an average 23 years, there were 603 cardiovascular deaths including 118 sudden deaths and 192 following MI. The risk of sudden death increased linearly with the level of resting HR in men. Taking into account age, body mass index, systolic blood pressure, tobacco consumption, parental history of MI and parental history of sudden death, cholesterol level, diabetic status and sport activity, an elevated HR remained an independent risk factor for sudden death.

The latest data in this French population of healthy men showed that resting HR and its change over 5 years were both predictors of death, independent of the standard cardiovascular risk factors. This observational study followed up 5139 asymptomatic men (aged 42–53 years) who had their HR measured at rest in standardized conditions every year for 5 consecutive years. Subjects were divided into following tertiles of HR changes: decrease >4 bpm, unchanged (from −4 to +3 bpm) or increase >3 bpm. After adjustments were made for confounding factors, including baseline HR at rest, and compared with subjects with unchanged HR, those with HR that decreased during the 5 years had a 14% decrease in mortality risk (P = 0.05), whereas men whose HR increased over 5 years had a 19% increase in mortality risk (P < 0.012). The association between high resting HR and mortality is consistent with the published data from a number of epidemiological studies in the general population, but the study provides the first observation that change in HR over a 5-year period conferred additional information beyond HR at rest and was an independent predictor of mortality in middle-aged men.

In the 4530 hypertensive patients (defined as a systolic blood pressure ≥140 mm Hg or a diastolic ≥90 mm Hg) of the Framingham study (age 35–74 years) who were not on antihypertensive medications, an
increment of HR of 40 bpm was associated with an odds ratio for total mortality of 2.18 (95% CI: 1.68–2.83) for men and 2.14 (95% CI: 1.59–2.88) in women. For cardiovascular mortality, the odds ratios were 1.68 (1.19, 2.37) for men and 1.70 (1.08, 2.67) for women. It was therefore concluded that HR is an independent risk marker of cardiovascular death in patients with hypertension.

In patients with CAD, increased HR is a well-known precipitating factor of myocardial ischaemia and of angina. Tardif and his colleagues from the Montreal Heart Institute analysed a registry of 24,913 patients with suspected or proven CAD referred for coronary angiography and followed for an average of 14.1 years. They found that resting HR is an independent risk factor for total and cardiovascular mortality both in men and women. Commenting on this study, Palatini pointed out that the better prognosis observed in patients with lower resting HR was not due to beta-blockers as this was also observed in patients not receiving this therapy. The prognostic value of HR held true when controlling for hypertension, diabetes and smoking as well as powerful markers such as the left ventricular ejection fraction and the number of diseased coronary vessels. Patients with an HR of ≥83 bpm also had a significantly higher risk of hospital admissions for cardiovascular causes than those with an HR of ≤62 bpm.

Hjalmarson et al. characterized, in 1,807 patients with acute MI, the relationship between HR on hospital admission and after discharge from hospital and respectively total mortality from admission to discharge and mortality at 1 year. In-hospital mortality and post-discharge mortality increased with increasing HR on admission. Total mortality was 15% for patients with an admission HR ranging between 50 and 60 bpm, 41% for HR >90 bpm and 48% for HR ≥110 bpm. Mortality from hospital discharge to 1 year was also related to the maximal HR observed in the coronary care unit and to HR at discharge. In patients with moderate HF, the cumulative mortality for patients with an admission HR of ≥90 bpm was more than twice that of patients with an admission HR of <90 bpm (39% versus 18%). A similar relationship was observed in patients with mild or no HF (18% versus 10%).

The prognostic significance of HR was also assessed in 8,915 patients with acute MI of the GISSI-2 study and treated with fibrinolytic therapy. In this study, increased HR on admission was associated with a progressive increase in in-hospital mortality (from 7.1% for HR <60 bpm to 23.4% for HR >100 bpm). HR at discharge from the hospital was available in 7,831 patients. A progressive increase of 6-month mortality was noted with increasing HR (from 0.8% for HR <60 bpm to 14.3% for HR >100 bpm). Multivariate analysis showed that HR was an independent prognostic factor of mortality. Similar
results were observed in the Secondary Prevention Reinfarction Israeli Nifedipine trial, performed before the thrombolytic era, which showed that HR on admission in the coronary care unit was related to total mortality and to the occurrence of complications. In the CIBIS II trial, which randomized patients with HF to bisoprolol or placebo, the relationships between baseline HR, HR changes and outcomes, such as mortality and hospitalization for HF, were evaluated in the placebo group. Multivariate analysis showed that baseline HR and HR changes were both significantly related to survival and hospitalization for worsening HF. The lowest baseline HR and the largest HR changes were associated in the placebo group with the best survival and with a reduction of hospital admissions. Bisoprolol further improved survival at any level of baseline HR or HR changes to a similar extent. In the International Verapamil-SR/Trandolapril study, the relationships between resting HR at baseline and at follow-up and adverse outcomes (all-cause death, non-fatal MI and non-fatal stroke) were evaluated in 22,192 patients with hypertension and CAD treated either with verapamil or atenolol. Resting HR was found in this study to predict adverse events, and on-treatment HR was even more predictive than baseline resting HR.

Role of HR in the development of atherosclerosis and coronary events

Risk factors can trigger a complex chain of events leading to the continuum of cardiovascular diseases. Any modification along this chain of events may interrupt the pathological process, conferring cardiovascular protection. The most common coronary manifestations of atherosclerosis are stable angina pectoris and acute coronary syndromes. Experimental evidence support the role of HR in endothelial dysfunction and the progression of atherosclerotic lesions. Briefly, pressure wave-derived vascular stress sensed by mechanoreceptors triggers a cascade of signalling molecules. Elevated tensile stress is thought to induce direct endothelial injury and to increase endothelial permeability to LDL particles and to circulating inflammatory mediators.

The role of HR in myocardial ischaemia as seen in patients with stable angina and those who suffer a MI is well known (Fig. 1). An increased HR contributes to an imbalance between myocardial oxygen demand and supply, by causing both an increase in myocardial oxygen demand and a decrease in coronary blood supply (the latter via a shorter duration of diastole, the period during which most of the myocardial perfusion occurs). An increased HR may also be involved at the later stages of atherosclerosis including plaque rupture resulting in
coronary thrombosis (Fig. 2). Therefore, HR reduction may play an important role in the cardiovascular disease continuum.

HR reduction and decreased cardiovascular risk

Several studies have shown that beta-blockers are able to reduce total mortality and sudden cardiac death after MI. These beneficial effects have been ascribed at least in part to the reduction of HR.
Furthermore, a recent meta-regression of randomized clinical trials of beta-blockers and calcium channel blockers in post-acute MI patients strongly suggest that the beneficial effects of these agents are proportionally related to the reduction of resting HR.\textsuperscript{25} A statistically significant relationship was found between resting HR reduction and decreases in cardiac death, all-cause death, sudden death and non-fatal MI recurrence. This meta-regression strongly suggests that resting HR reduction could be a major determinant of the clinical benefits seen in these trials. This hypothesis was also tested more recently in randomized controlled trials of beta-blockers in HF due to left ventricular systolic dysfunction. There was a close relation between all-cause annualized mortality rate and HR in these studies, and a strong correlation between change in HR and change in left ventricular ejection fraction was also observed.\textsuperscript{26} Beta-blockers are a cornerstone of HF treatment, but their efficacy in elderly patients is less known as such patients are often excluded from clinical trials. According to recent findings from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure Registry, beta-blocker therapy reduces mortality and rates of re-hospitalization among elderly patients with HF who have left ventricular systolic dysfunction, but does not appear to have any beneficial effects in those with preserved systolic function.\textsuperscript{27}

In contrast to the beneficial effect of beta-blockers on mortality in post-MI and HF settings, Messerli\textsuperscript{28} has recently described an inverse relationship between HR reduction with beta-blockers and cardiovascular end points in patients with hypertension. However, this hypertension paradox observed with beta-blockers (mainly atenolol) cannot be explained solely by pharmacological HR slowing, and findings should not be extrapolated to pharmacological interventions aiming at pure HR reduction. Beta-blockers not only reduce HR, but also have a number of other effects. The novel specific HR-lowering agent ivabradine therefore provides an opportunity to assess the effects of lowering HR without directly altering other aspects of cardiac function. Ivabradine is the first of a new class of agents that act specifically on the sinoatrial node by inhibiting the $I_f$ current of cardiac pacemaker cells without affecting other cardiac ionic currents at therapeutic concentrations. Ivabradine is a new medication that has HR-lowering properties without other direct cardiovascular effects.\textsuperscript{29} A double-blind, placebo-controlled study in patients with chronic stable angina showed that ivabradine produces dose-dependent improvements in exercise tolerance and time to development of exercise-induced ischaemia.\textsuperscript{30} Ivabradine was also compared with the $\beta$-adrenoceptor antagonist atenolol in the International Trial of the Antianginal effect of Ivabradine study compared with atenolol.\textsuperscript{31} Ivabradine 7.5 mg twice
daily resulted in substantial and consistent HR reduction at rest that was fairly similar to that of beta-blockade. No relevant between-group differences were observed at rest. At peak exercise, HR decrease from baseline to end-of-study was less pronounced in both ivabradine groups than in the atenolol 100 mg o.d. group. Although atenolol showed greater HR reduction, ivabradine was non-inferior to the beta-blocker in terms of prolonging total exercise duration (primary end point) as well as time to limiting angina and time to angina onset during exercise tolerance testing. Thus, ivabradine induced a similar or greater improvement in exercise capacity while causing less reduction in rate-pressure product and HR when compared with atenolol. According to these findings, ivabradine increased exercise capacity to a greater extent for every beat of HR reduction. This might be linked to ivabradine’s lack of negative inotropic, peripheral vascular or coronary vasoconstrictor effect as well as the greater prolongation of diastole obtained with ivabradine compared with a beta-blocker. Data from the recently published assessment of efficacy and safety of oral ivabradine compared to placebo on top of atenolol (ASSOCIATE) study demonstrate that addition of ivabradine 7.5 mg bid to atenolol at the dose commonly used in clinical practice in patients with chronic stable angina pectoris produced additional HR reduction and further improvement in all exercise testing parameters, with no untoward effect on safety or tolerability.32

Ivabradine was also found to have beneficial effects on cardiac remodelling, capillary density and left ventricular dysfunction. In a rat model of congestive HF, Mulder et al.33 showed that chronic administration of ivabradine induced a dose-dependent reduction in HR without modification in systemic haemodynamics. Cardiac output was preserved despite the decrease in HR because stroke volume was increased owing to a decrease in left ventricular end-systolic diameter. In animals with dyslipidaemia, selective HR reduction with ivabradine decreases markers of vascular oxidative stress, improves endothelial function and reduces atherosclerotic plaque formation.34 Therefore, these data support the potential of HR reduction as an intervention to improve endothelial function, to attenuate progression of atherosclerosis and ultimately to prevent coronary events. Whether lowering HR with ivabradine in patients with stable CAD receiving optimal background therapy could result in reduction of cardiovascular events had to be demonstrated. This prompted the BEAUTIFUL study, the results of which have been recently reported.35 BEAUTIFUL is a large, international, randomized, placebo-controlled morbidity–mortality trial in a high-risk population of patients with CAD and left ventricular systolic dysfunction (ejection fraction <40%), conducted between December 2004 and December 2006. The study enrolled 10 917
eligible patients. About 5479 patients were randomized to receive the initial dose of 5 mg of ivabradine bid, with the aim to reach the target dose of 7.5 mg bid on top of conventional cardiovascular treatments as recommended by guidelines, and 5438 patients were randomly assigned to the placebo group. The mean age of the study patients was 65 years. The mean HR at baseline was 71.6 bpm and the mean left ventricular ejection fraction was 32.4%. The use of background evidence-based therapy was very high (including 87% of patients for beta-blockers).

The BEAUTIFUL investigators have added substantially to current knowledge concerning the prognostic value of elevated HR by also conducting a prospective analysis of the data from the placebo arm of the study to assess the association of HR with different clinical outcomes. Patients with an HR of 70 bpm or more had increased risks of cardiovascular death (34%, \( P = 0.0041 \), Fig. 3), admission to hospital for HF (53%, \( P < 0.0001 \)), admission to hospital for MI (46%, \( P = 0.0066 \)) and coronary revascularization (38%, \( P = 0.037 \)) after adjustment for other predictors of outcome.

Although the primary end point of the study (composite of cardiovascular mortality, admission to hospital for acute MI and admission to hospital for new onset or worsening HF) was not met in the overall population, ivabradine reduced the risk of coronary events by 22% (\( P = 0.023 \)), fatal and non-fatal MI by 36% (\( P = 0.001 \), Fig. 4) and coronary revascularization by 30% (\( P = 0.016 \)) in the pre-specified subgroup of patients with baseline HR ≥70 bpm. These benefits were observed despite the fact that 84% of these patients received beta-blockers.

Ongoing and future clinical studies will provide further evidence on the presence and extent of cardioprotective benefits of HR lowering...
with ivabradine in patients with cardiovascular disease. The Systolic Heart failure study with the If inhibitor ivabradine trial, which is currently investigating the effects of ivabradine in congestive HF, will provide important information concerning the importance of pure HR reduction in this patient population. This large-scale, randomized, placebo-controlled trial has recruited over 7000 patients with moderate to severe HF and resting HR \(\geq 70\) bpm. Throughout the study, all patients have continued their current standard treatments for HF and any other cardiovascular conditions. The aim is to evaluate the effects of adding treatment with ivabradine versus placebo in terms of reduction in cardiovascular events in HF.

**Applying current knowledge to practice**

In spite of the large body of evidence on the evaluation of cardiovascular risk, little attention has been paid to the measurement of HR for cardiovascular risk assessment in daily practice. There might be two main reasons for this: first, HR has been considered to be a poorly reproducible clinical variable, and, second, HR has been seen as a mere marker of sympathetic activity rather than a cardiovascular risk factor *per se*.

Recent evidence has fuelled the concept that increased resting HR is probably an independent cardiovascular risk factor. The new evidence from the BEAUTIFUL study constitutes the first prospective demonstration that an elevated resting HR \((\geq 70\) bpm) places coronary

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**Fig. 4** In stable CAD patients with left ventricular systolic dysfunction and an elevated resting HR \((\geq 70\) bpm), ivabradine reduced the risk of hospitalization for myocardial infarction in BEAUTIFUL. RRR = relative risk reduction.
patients at risk for cardiovascular events, even if they are well treated according to current guidelines including treatment with beta-blockers. Thus, resting HR should be considered in every patient with CAD, especially since it is an easily measurable parameter. To standardize measurement of resting HR, a consensus meeting and recent Guidelines for the Management of Arterial Hypertension recommended measurement of HR by pulse palpation during two 30-s periods, performed in a sitting position, after 5 min sitting in a quiet room.37,38

There are several methods for HR measurement. ECG is the most routinely used technique in clinical settings. Whether more precise measurement of HR with ECG translates into more meaningful data is not clear. According to Erikssen and Rodahl,39 these two types of measurement are highly correlated (R > 0.9) and provide similar information. Data on the prognostic value of home or 24-h HR measurement performed with electrocardiographic Holter recording are currently lacking. In a study by Aronow et al.,40 the risk of death increased by 14% for each 5 bpm increase in mean 24-h HR in both men and women, but no comparison with clinical HR was provided. Hozawa et al.41 reported a 17% increase in the risk of mortality for a 5 bpm increase in home HR, but their study failed to compare the predictive power of out-of-office HR with that of outpatient clinic HR. There is no available evidence demonstrating an advantage of HR measured out of the office over outpatient clinic HR. In times of major health care burden, HR measurement can be utilized with no additional cost in the overall strategy of cardiovascular risk assessment in daily practice.

HR has already appeared in European guidelines for the prevention of cardiovascular disease.42 The idea that high HR places patients at risk is by no means new, but previous studies generally confined themselves to comparing quartiles or quintiles of high versus low HR values. The BEAUTIFUL study has lowered the cutoff at which HR may pose a risk to 70 bpm. Resting HR is easy and inexpensive to measure in the clinic, and this should clearly become a component of the risk stratification of patients with stable CAD. Thus, the important implication of BEAUTIFUL is that HR >70 bpm is deleterious in patients with stable CAD and this issue needs to be addressed.

Conclusions

A large body of evidence supports high resting HR as a risk factor for total mortality and cardiovascular mortality in various populations including patients with CAD. Experimental evidence supports the role of high HR in endothelial dysfunction and atherosclerosis progression.
Recent evidence has extended current knowledge of the role of HR as a potential risk factor in CAD. Elevated HR (≥70 bpm) increases cardiovascular risk and this measurement should be used to guide optimal therapy in coronary patients.

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**References**


