REVIEW

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Resting Heart Rate: Risk Indicator and Emerging Risk Factor in Cardiovascular Disease

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ABSTRACT

Resting heart rate is central to cardiac output and is influenced by changes occurring in numerous diseases. It predicts longevity and cardiovascular diseases, and current evidence suggests that it is also an important marker of outcome in cardiovascular disease, including heart failure. Beta-blockers improve outcomes in heart failure; however, they have effects outside reducing heart rate. Ivabradine has demonstrated efficacy in reducing rehospitalizations and mortality in heart failure and in improving exercise tolerance and reducing angina attacks in patients with coronary artery disease, whereas selective heart rate reduction may also prove to be beneficial in therapeutic areas outside those in which ivabradine has already demonstrated clinical efficacy. This review provides an update on the associations between heart rate and cardiovascular outcomes in various conditions, the experimental effects of heart rate reduction with ivabradine, and the potential new indications in cardiovascular disease.

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Heart rate is a physical sign that is easily and noninvasively measured without special training or equipment. It is a determinant of myocardial oxygen demand, coronary blood flow, and myocardial performance and is central to the adaptation of cardiac output to metabolic needs. Heart rate is regulated by the autonomic nervous system and, consequently, can be affected easily by various disease conditions.[1] Heart rate has become an established biomarker strongly prognostic of cardiovascular outcomes. In some disease states, such as heart failure, heart rate has evolved from a biomarker to a true modifiable risk factor, because its reduction can confer benefits on outcomes.[1-4] However, its role as a risk factor and therapeutic target is unclear in some areas because cardiovascular fitness might confound these associations.[5] The development of specific heart rate-reducing agents without any other known cardiovascular effects, such as the f-channel blocker ivabradine, enables the precise study of outcomes of heart rate modification without other confounding influences. Since the discovery in 1979 of the nonspecific cation I_f current responsible for modulation of the spontaneous diastolic depolarization of sinus nodal cells,[6] characterization of its 4 isoforms,[3] and, finally, the development of a clinically available inhibitor (ivabradine),[7] researchers have had a physiologic basis and pharmacologic tool to study the association of heart rate and risk reduction.

HEALTHY INDIVIDUALS AND PATIENTS WITH CARDIOVASCULAR RISK FACTORS

Epidemiologic studies involving >100,000 subjects and follow-up intervals of 5 to 36 years have demonstrated that heart rate is directly associated with survival in the general population and in individuals with cardiovascular conditions,[8-11] and that this association is inverse (higher heart rates indicate lower survival) and independent of background risk.[10,12] In turn, heart rate has been associated with incident cardiovascular risk factors, such as impaired

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glucose metabolism, obesity, and diabetes mellitus.[13,14] Of note, in a long-term follow-up of mainly young men returning from World War I, a positive association was observed between cardiovascular mortality and transient hypertension and episodic heart rate increases.[15] In hypertension, large trials have demonstrated that an increase in heart rate during follow-up, in addition to high heart rates at baseline, is associated with mortality risk, whereas a decrease in heart rate over time is associated with lower cardiovascular mortality.[16,17] In addition, among patients with left ventricular hypertrophy, increasing heart rate adds to cardiovascular mortality risk of hypertension,[18] whereas it differentiates between high- and low-risk patients in situations in which acute elevations in blood pressure are observed.[19]

CLINICAL SIGNIFICANCE

- Heart rate is associated with cardiovascular outcomes and hypertension, coronary artery disease, and heart failure.
- Heart rate reduction therapy with ivabradine produces antianginal effects and an improvement of heart failure.
- Conditions such as cognitive decline, renal impairment, and endothelial dysfunction are associated with high heart rates. Therefore, heart rate, in addition to blood pressure, provides an easy measure to judge outcomes and is a potential therapy target.

ATHEROSCLEROSIS

In animal models of atherosclerosis, plaque formation is associated with heart rate, which in turn is related directly to oxidative stress, vascular stiffness, and endothelial dysfunction.[20] Its reduction with ivabradine in apolipoprotein E knockout mice[21] led to a reduction of atherosclerosis and an improvement of endothelial dysfunction.[21-24] Endothelial dysfunction, oxidative stress, and plaque load were all significantly diminished after treatment with ivabradine (**Figure 1**).[18-21,23,24]

In humans, high heart rates are associated with markers of endothelial dysfunction[25,26] and with carotid and aortic arterial stiffness.[27] In mice and monkeys, abnormal shear stress and enhanced pulsatile stress act in concert to promote atherosclerosis.[28-30] However, a prospective study with the beta-blocker atenolol failed to reduce endothelial dysfunction in individuals with diabetes mellitus.[31] The reason for this lack of efficacy might be enhanced pulse-wave reflection by beta-blockers, which may be minimized beneficially when selective heart rate reduction with ivabradine is achieved.[32]

CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION

Heart rate is associated with the severity of coronary atherosclerosis in young patients after myocardial infarction[33] and with coronary atherosclerosis progression.[34] In the contemporary population of patients with coronary artery disease with left ventricular dysfunction studied in the Morbidity-Mortality Evaluation of the If-Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial,[35,36] heart rates >70 beats/min were associated with higher cardiovascular mortality, hospitalization for myocardial infarction, and need for coronary revascularizations[35] compared with heart rates ≤70 beats/min. In the BEAUTIFUL trial, cardiovascular death and vascular events were not significantly reduced by ivabradine; however, there was a significant reduction in the need for revascularization and myocardial infarction after ivabradine in the prespecified subgroup of patients with a resting heart rate >70 beats/min.[36] In the pre-beta-blocker era,[37] heart rate during the course of hospitalization and at hospital discharge was associated with increased mortality rate. However, heart rate reduction with beta-blockers failed to show a clear benefit in patients with low-risk myocardial infarction.[38] Nonetheless, high-risk patients with unstable plaques may potentially benefit, because plaque ruptures are associated with high heart rates.[39]

After stroke or myocardial infarction, or in proven vascular disease, heart rate is associated directly with cardiovascular death, stroke, and heart failure hospitalization; however, after all adjustments, the association with myocardial infarction is not significant.[40] These data suggest that the association of heart rate with outcomes may differ among populations of different risk and different antecedent events. With this issue requiring clarification, a trial in 19,000 patients (Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease) recently reported on whether ivabradine reduces events in patients with stable coronary artery disease without left ventricular systolic dysfunction or clinical heart failure.[41] Ivabradine was not able to reduce a composite end point of cardiovascular death and nonfatal myocardial infarction in patients with known coronary artery disease at a heart rate of >70 beats/min in sinus rhythm. In this situation, heart rate is more a risk indicator and not a risk factor.

After myocardial infarction, patients may have angina, which requires antianginal therapies.[42,43] Heart rate reduction has a significant impact on the relation of myocardial oxygen consumption to oxygen supply,[44] the imbalance of which, putatively, is the primary cause of angina. Ivabradine has been investigated in patients with angina pectoris in the absence of beta-blocker therapy[45] and in patients treated with atenolol[46] or amlodipine.[47] In these trials, heart rate reduction resulted in improved exercise tolerance measured as time to ST-segment depression and onset of angina symptoms,[46,47] and the drug was well tolerated.[46,47] On the basis of these data, ivabradine is recommended in the