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REVIEW TOPIC OF THE WEEK

When an Increase in Central Systolic Pressure Overrides the Benefits of Heart Rate Lowering

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ABSTRACT

An elevated resting heart rate has been unequivocally linked to adverse cardiovascular events. Conversely, a physiologically low heart rate may confer longevity benefits. Moreover, pharmacological heart rate lowering reduces cardiovascular outcomes in patients with heart failure, with the magnitude of the reduction associated with survival benefit. In contrast, pharmacological heart rate lowering paradoxically increases cardiovascular events in hypertension, possibly because it elicits a ventricular-vascular mismatch, leading to increased central systolic blood pressure (BP). By the same hemodynamic mechanism, pharmacological heart rate lowering also engenders an increase in central (aortic) BP in coronary heart disease and, as a consequence, fails to decrease myocardial oxygen consumption. Whether in heart failure, hypertension, or coronary heart disease, or even athletes, heart rate lowering consistently increases central systolic pressure. The increase in central systolic BP is prone to abolish the potential benefits of heart rate lowering interventions, possibly accounting for failure to reduce outcomes in patients with hypertension and coronary artery disease. (J Am Coll Cardiol 2016;68:754–62) © 2016 by the American College of Cardiology Foundation.

Ever since the Framingham Study identified resting heart rate (RHR) as a powerful independent risk factor for cardiovascular morbidity and mortality more than a quarter of a century ago (1), numerous epidemiological studies have linked RHR to myocardial infarction, stroke, and death in healthy people (2–5) as well as in patients with hypertension (6,7), coronary artery disease (CAD), and heart failure (8,9). A spate of recent reviews has thoroughly analyzed this link and found an inverse linear relationship between RHR and survival in the general population as well as in patients with cardiovascular disease (9–12). In their thorough review, Palatini et al. (10) compiled 43 papers encompassing the results of 39 studies on the risk of elevated heart rate for cardiovascular and/or all-cause mortality. All but 2 of these studies reported a significant association between all-cause mortality and RHR (10).

However, these findings indicate that RHR should be viewed in the same light as other well-identified risk factors, such as blood pressure (BP), low-density lipoprotein cholesterol, smoking, diabetes, or ejection fraction. Although RHR as a prognostic

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factor and potential therapeutic target remains underappreciated, most clinicians believe that an increased RHR should no longer be viewed as an innocent clinical feature. Conversely, the data on the benefits of heart rate lowering therapies remain controversial. In the current article, we review the data linking heart rate to cardiovascular outcomes and examine potential mechanisms accounting for the paradoxical effects of RHR reduction in hypertension and the absence of a benefit in patients with CAD.

PATHOPHYSIOLOGIC LINK BETWEEN RHR AND OUTCOME

There are several possible reasons for increased RHR to be a powerful cardiovascular risk factor.

1. An increased RHR may simply be a marker for excessive activity of the sympathetic nervous system (13–15). An increase in RHR reflects decreased parasympathetic tone and/or increased sympathetic tone. The heightened sympathetic tone underlying fast RHR can predispose to lethal ventricular arrhythmias (16). Cardiovascular risk factors, such as hypertension, diabetes, obesity, dyslipidemia, smoking, and sedentary life-style, are, at least to some extent, also related to sympathetic activity (17–20). Patients with increased RHR have significantly more cardiovascular risk factors than subjects with a normal or slow RHR (4–6,21,22).
2. An elevated RHR increases the hemodynamic burden of the left ventricle by both greater myocardial oxygen consumption and decreased myocardial perfusion. The apparent inverse relation between lifespan and RHR may be related to the sustained burden imposed by a faster RHR. The greater the hemodynamic burden, the faster the heart may wear out. As shown by Levine (23) and Azbel et al. (24), despite extreme differences in body weight, heart weight, stroke volume, and total blood volume pumped throughout life, the total number of heartbeats per lifespan remains remarkably constant from species to species, with an inverse semilogarithmic relationship between RHR and life expectancy.
3. Heart rate correlates with the severity and the progression of atherosclerosis on coronary angiography among men with myocardial infarction at a young age (25,26). An elevated RHR has also been associated with an increased risk of coronary plaque disruption, which may be due to increased shear stress on the vasculature (27).

Thus, there is solid experimental and clinical evidence that an increased RHR is detrimental and facilitates atherosclerosis with its clinical manifestations.

BENEFITS OF A LOW HEART RATE

Levine (23) had estimated that a reduction in mean heart rate from 70 to 60 beats/min throughout life could increase lifespan from 80.0 to 93.3 years of age. Indeed, the Framingham cohort reported that physiologically lower RHR was associated with survival to 75 years of age in men (28). Similarly, Benetos et al. showed, in a large French population, that accelerated RHR was an independent predictor of noncardiovascular mortality in both sexes, and of cardiovascular mortality in men, independent of age and the presence of hypertension (4). The probability of reaching 85 years of age in men with a RHR >80 beats/min was reduced by more than 40% compared with men of the same age with a low heart rate (<60 beats/min) (29).

BENEFITS OF HEART RATE LOWERING

If RHR proves to be a determinant of lifespan, one may ask whether measures that reduce RHR have the potential to prolong life. Experimental data demonstrated that reduction in RHR can delay the progression of coronary atherosclerosis in cynomolgus monkeys (30–32). Beere et al. (33) showed that these primates subjected to sinus node ablation or with innately low RHR had significantly less coronary atherosclerosis than those with higher RHR. These findings suggest that heart rate in itself may contribute to the mechanisms by which behavioral patterns and physical training influence CAD. Similarly, in "behaviorally predisposed" (using psychosocial manipulations) male cynomolgus monkeys fed an atherogenic diet, heart rate lowering with propranolol was shown to inhibit coronary atherosclerosis (31).

More than 25 years ago, Kjekshus (34) documented the importance of RHR in determining beta-blocker efficacy in acute and long-term myocardial infarction intervention trials: the greater the decrease in heart rate, the better the short- and long-term prognoses. Heart rate lowering became the standard by which beta-blocker efficacy was assessed in the postmyocardial infarction patient population. Presumably, a decrease in RHR and BP reduced myocardial workload, thereby acutely diminishing infarct size and, over the long term, preventing remodeling of the left ventricle. Similarly, there are ironclad data in heart failure patients showing that

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CAD = coronary artery disease
RHR = resting heart rate

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