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Review Article

Heart rate and cardiovascular protection

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ABSTRACT

Recent large epidemiological studies have confirmed that an elevated resting heart rate is an independent predictor of cardiovascular and overall mortality in the general population as well as in patients with hypertension, coronary heart disease and chronic heart failure. Pathophysiological studies indicate that a higher heart rate has detrimental effects that favor myocardial ischemia, ventricular arrhythmias, as well as an increase in vascular oxidative stress, endothelial dysfunction and atherosclerosis progression. Benefits of heart rate lowering drugs, such as beta-blockers and ivabradine, in reducing overall and cardiovascular-related mortality, have been demonstrated particularly in patients with coronary heart disease and heart failure. However, despite these evidences, resting heart rate is still an overlooked cardiovascular risk factor.

1. Introduction

With the exception of human species, mammals present a linear inverse semi-logarithmic relationship between life expectancy and heart rate: smaller mammals have higher heart rates and shorter life spans than larger members of their class [1].

Heart rate is a simple and accessible cardiovascular parameter. A significant association between resting heart rate (RHR) and all-cause and cardiovascular mortality has been recently reported in many epidemiologic studies. Nevertheless, despite its inclusion in the Cooper Clinic risk index for overall mortality, RHR is not yet contemplated in more widely known indices for evaluation of global cardiac risk, namely the European SCORE, the Framingham Score Assessment and the PROCAM Risk Score [2]. The aim of this article is to make a literature review of the importance of heart rate lowering on cardiovascular protection. We performed an electronic library search (Pubmed) using "resting heart rate", "heart rate variability", "cardiovascular risk factors", "endothelial dysfunction", "atherosclerosis" and "autonomic dysfunction" as keywords. We identified the most cited articles between 1990 and 2013.

2. Epidemiological data

An elevated RHR correlates with cardiovascular mortality and is an independent risk factor for cardiovascular (CV) disease, comparable to smoking, hypertension and dyslipidemia [3,4].

In the CORDIS trial, Kristal-Boneh at al. [5] studied 3527 men over the age of 25 over a follow-up period of 8 years. The subjects had no known diagnosis of CV disease and were not receiving chronic medication affecting heart rate. A statistically significantly positive correlation was found ($p < 0.05$) between a higher RHR and age, body mass index (BMI), total serum cholesterol, smoking and systolic blood pressure. Both all-cause and CV disease-related mortality was higher with the increase in RHR ($p < 0.0001$ and $p < 0.0006$, respectively). When adjusting for traditional CV risk factors (age, BMI, total serum cholesterol, exercise and smoking), RHR was strongly associated with all-cause mortality [RHR 70–79 beats/min (bpm): relative risk (RR) with 95% confidence interval (CI) 0.94 (0.6–1.5); HR ≥90 bpm: RR 2.08 (1.3–3.4); $p = 0.001$] and with CV mortality [RHR 70–79 bpm: RR 0.53 (0.2–1.2); HR ≥90 bpm: RR 1.95 (1.1–3.8); $p = 0.011$].

Endorsing this data, Benetos et al., in the French IPC trial [6], evaluated the effects of RHR on mortality, over a 20-year follow-up period, in 12,123 men and 7263 women aged between 40 and 64 years. In

Abbreviations: RHR, resting heart rate; CV, cardiovascular; CHD, coronary heart disease; RR, relative risk; CI, confidence interval; MI, myocardial infarction; CHF, chronic heart failure; HRV, heart rate variability; NN, intervals between consecutive normal heart beats or normal R wave peaks; SDNN, standard deviation of all NN intervals; SDANN, standard deviation of NN intervals for each 5 minute period; pNN50, percentage of adjacent cycles >50 ms apart; RMSSD, square root of the mean squared difference of successive NN intervals; TP, total power spectrum; ULF, ultra low frequency; VFL, very low frequency; LF, low frequency; HF, high frequency; BRS, baroreflex sensitivity; NSTV, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VFT, ventricular fibrillation threshold; VSMC, vascular smooth muscular cell; IMT, intima–media thickness; ET-1, endothelin; IFN, interferon; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; PAI-I, plasminogen activator inhibitor; ROS, reactive oxygen species; PGI2, prostacyclin; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

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men, all-cause, non-CV, CV and coronary heart disease (CHD)-related mortality was significantly higher in the groups with an increased RHR ($p < 0.001$), whereas in women only all-cause and non-CV disease-related mortality were significantly associated with a higher RHR ($p < 0.003$). Those findings were also true in both genders, when adjusting the RR of mortality for traditional CV risk factors. However the impact of gender and race, when evaluating the relationship between RHR and outcome, is not consensual. In the NHANES I Epidemiologic follow-up study, 5136 white and 859 black men and women with no history of CV disease, aged between 45 and 74 years old at baseline, were studied [7]. In women the risk of death from all causes was higher with an increase in RHR, but this difference was not statistically significant. However the risk of death related to CV disease was significantly associated with an increase in RHR [RR with 95% CI: 1.53 (1.10–2.14)], even after adjusting for other CV risk factors (smoking, age, diabetes). In black women there was a significant association between an elevated RHR and the all-cause mortality rate [RR 1.95 (1.16–3.27)], as well as that due to CV diseases [RR 3.03 (1.46–6.28)]. These associations were also observed in black and white men.

A higher RHR in patients with hypertension also correlates with both CV and all-cause related mortality. In the Framingham Study, 4530 patients between 35 and 74 years old, with systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg, who were not treated with antihypertensive drugs, were studied. The odds ratio (OD) with 95% CI for each increment of 40 bpm in RHR (comparison of 100 bpm and 60 bpm), adjusted for age and systolic blood pressure were: for all-cause mortality OD 2.18 (CI 1.68–2.38) in men and OD 2.14 (CI 1.59–2.88) in women; for CV-related mortality OD 1.68 (CI 1.19–2.37) in men and OD 1.70 (CI 1.08–2.67) in women [8].

In patients with CHD at baseline, the RHR is also an independent risk factor for all-cause and CV-related mortality. In the CASS Study, 24,913 patients with suspected or proven coronary heart disease (CHD), were followed for a median period of 14.7 years. After adjusting for traditional CV risk factors, there was a significantly higher risk for all-cause mortality in patients with higher RHR (≥83 bpm): hazard ratio (HZR) with 95% CI 1.32 (1.15–1.48), $p < 0.0001$; and for CV-related mortality (≥83 bpm): HZR 1.31 (1.15–1.48), $p < 0.0001$. The RHR was also an independent predictor of the time to the first re-hospitalization due to any cardiovascular event (RHR ≥ 83 bpm: HZR 1.4 (CI 1.02–1.27), $p < 0.0001$) [9].

In the context of acute myocardial infarction (MI), a higher RHR is also an independent predictor of in-hospital and one year post-discharge mortality. Disegni et al. [10] studied 1044 patients admitted for MI. In-hospital mortality was 5.2% ($n = 294$) for RHR < 70 bpm, 9.5% ($n = 532$) for RHR 70–89 bpm and 15.1% ($n = 323$) for RHA ≥90 bpm ($p < 0.01$). A difference of 15 bpm increase in the RHR at admission was associated with an estimated increase of 36% in in-hospital mortality [OD with 95% CI 1.36 (1.08–1.72)] and with a 45% increase in mortality one year after discharge [OD 1.45 (1.15–1.84)], even after adjusting for traditional CV risk factors The importance of RHR on the outcome was also proved in patients with CHF. Lechat et al., in the CIBIS II trial [11], confirmed that RHR is an independent predictor of mortality and re-hospitalization in patients with chronic heart failure (CHF). In this trial 2184 patients with chronic heart failure (New York Heart Association [NYHA] functional class III/IV) were treated for 2 months with bisoprolol. The baseline RHR and RHR reduction after 2 months of treatment were both significantly related to mortality [risk ratio 1.015 ($p = 0.0012$) and 0.98 ($p = 0.0049$), respectively] and to re-hospitalization [risk ratio 1.018 ($p = 0.0001$) and 0.982 ($p = 0.0001$), respectively], with the best prognosis being achieved with the lowest baseline RHR and the greatest RHR reduction.

These data, collected in a wide variety of clinical and epidemiologic studies, although not indicating a causality, seem to confirm that a higher RHR is an independent predictor of CV and overall mortality in subjects without CV disease, regardless of gender or race, but especially in white men and in black men and women. These findings were also true for patients with hypertension, CHD and CHF [2,4].

3. Heart rate variability

RHR is determined by the sinus node activity, which is influenced by the interaction of sympathetic and vagal activities. A high RHR may therefore result from sympathetic overactivity or from a decrease in vagal activity (sympathovagal imbalance) [12].

Reflecting this balance in cardiac autonomic function, heart rate variability (HRV) is a measure of the cyclic variations of beat-to-beat (NN) intervals [13]. It is influenced by physiologic factors such as age, postural changes and time of day, and by pathologic conditions such as congestive heart failure, CHD and diabetic neuropathy [14].

The most widely used methods for HRV analysis are derived from 24 h electrocardiograph recordings and are classified as time-domain and frequency-domain methods (Table 1) [15].

In the time domain methods, instantaneous heart rate and the intervals between successive normal complexes are measured. The calculated time domain variables may be divided into two classes: variables derived from direct measurement of the NN intervals or from instantaneous heart rate (SDNN and SDANN), and variables derived from the differences between NN intervals (pNN50 and RMSSD) [16]. The SDNN (standard deviation of all NN intervals) is a global index of HRV, reflecting all the cyclic components responsible for variability over the period of recording. The pNN50 and RMSSD estimate high-frequency variations in heart rate and reflect variations in autonomic tone vagally mediated [16,17].

The frequency domain methods describe periodic oscillations of the heart rate signal decomposed at different frequencies and amplitudes, and result from spectral analysis of HRV, commonly by fast Fourier transform [12,17]. Using this technique, individual NN intervals are transformed into bands with different spectral frequencies [17].

The total power spectrum (TP) ranges from 0 to 0.5 Hz and represents the total variance, reflecting the sum of the four bands (HF, LF, VLF and ULF) [17].

The HF is a marker of vagal modulation and is synchronized to the respiratory rhythm, while the LF component is modulated by both the sympathetic and vagal systems [18]. The index between LF and HF (LF/HF ratio) reflects global sympathovagal balance [12]. In a healthy human adult this index is generally between 1 and 2 [17]. Correlations between time and frequency domains are well established: pNN50 and RMSSD correlate with HF, reflecting vagal activity; SDANN is considered equivalent to ULF and VLF in the frequency domain; and SDNN is a measure of total variability, reflecting ULF, VLF, LF and HF [19].

Fluctuations of the cardiac autonomic input (vagal withdrawal and/or sympathetic overactivity) lead to a decrease in these HRV indices and to a reduced HRV [12,17], which has been shown to be related to a higher risk of cardiac events [12,13].

Table 1
Heart rate variability indices.

Variable	Definition
Time-domain	
NN	Mean value of all normal-to-normal inter-beat intervals
SDNN	Standard deviation of all NN intervals
SDANN	Standard deviation of NN intervals for each 5 minute period
pNN50	Percentage of adjacent cycles >50 ms apart
RMSSD	Square root of the mean squared difference of successive NN intervals
Frequency-domain	
TP	Total power (0.0–0.5 Hz)
ULF	Ultra low frequency (<0.033 Hz)
VLF	Very low frequency (0.033–0.04 Hz)
LF	Low frequency (0.04–0.15 Hz)
HF	High frequency (0.15–0.40 Hz)
LF/HF	Ratio low to high frequency