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Review Article

Prognostic Role of Resting Heart Rate in Cardiovascular Diseases: Just a Risk Marker?

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Abstract

The prognostic influence of many risk factors, such as hypertension or hypercholesterolemia, in several cardiovascular disorders has been widely proved. It has appeared, growing knowledge about the role of resting s (HR) and its association to other known cardiovascular risk factors. Resting HR takes an important place in cardiovascular physiopathology. Oxygen supply-demand balance, endothelial function, atherosclerosis development and vascular stress leading to plaque disruption are all directly influenced by increasing resting HR. Information obtained from recent trials, specially performed in heart failure patients, demonstrate the great benefits of decreasing resting HR. In this field, every increase in baseline beats per minute (bpm) is associated to increasing mortality rates and elevated risk of adverse cardiovascular outcomes. This shows the role, not only as risk marker but also as important risk factor, in cardiac diseases. Furthermore there is no optimal and homogeneous cut-off value of baseline HR for the different cardiovascular disorders. Despite of this, it seems desirable to maintain patient HR as lower as possible, below 70 bpm, in order to minimize risk of adverse events. So lowering baseline heart rate is a target to achieve,to improve prognosis.

Introduction

Blood pressure is usually determined during physical examination and Heart Rate (HR) can be also easily obtained. HR must be measured by pulse palpation during two 30 second periods, performed in a sitting position after 5 minutes sitting in a quiet room [1]. HR has a clear circadian rhythm, with higher rates during waking hours, and it is known to decrease with age and to be higher in women compared with men [2]. Care must be taken not only to high blood pressure values but also to elevated resting HR. The knowledge about the pivotal role of resting HR in cardiovascular diseases has grown for the last years. This has led to several publications reporting the prognostic risk factor of HR in different cardiovascular areas. The aim of this article is to review the evidence showing the influence of resting HR in different cardiovascular disorders and its pathophysiological mechanism.

Heart Rate as Prognostic Factor in General Population

The predictive value of resting heart rate is been widely studied, for the past decades. Data extracted from observational studies, reveal the inverse semilogaritmic relationship between HR and life expectancy among mammals species, except humans. This affirmation is supported by the shorter life span that smaller mammals have compared with larger members of their class [3] (Figure 1). These observations suggest that the total number of heartbeats during a lifetime is constant among mammals. Biological research based on the energetic consumption/body atom per heart rate conffirms these findings and suggest HR as marker of metabolic rate [4]. First descriptions of the relationship between elevated heart rate and clinical prognosis were made by Levy et al. in 1945 [5]. This author concludes transient tachycardia alone or associated to transient hypertension is a prognostic risk factor in general population.

Several epidemiological studies [6-12] with large follow up including more tan 150000 patients, and reviews [13] have reported the association between resting heart rate and all-cause and cardiovascular mortality in previously healthy people. The analysis of the Framingham cohort deserves to be highlighted. In this large observational registry 5070 patients were followed during 30 years. In both sexes, at all ages, overall and cardiovascular mortality rates increased progressively with resting HR, with stronger association observed in men. After correction for age and several known cardiovascular risk factors such as hypertension, hypercholesterolemia, smoking, and left ventricular hypertrophy the association remained significant, suggesting HR as an independent predictor of mortality [7].

These findings have been probed valid in both genders, in the elderly and in different ethnicities. Elevated resting HR was found to be an independent risk factor of all cause mortality in both men and

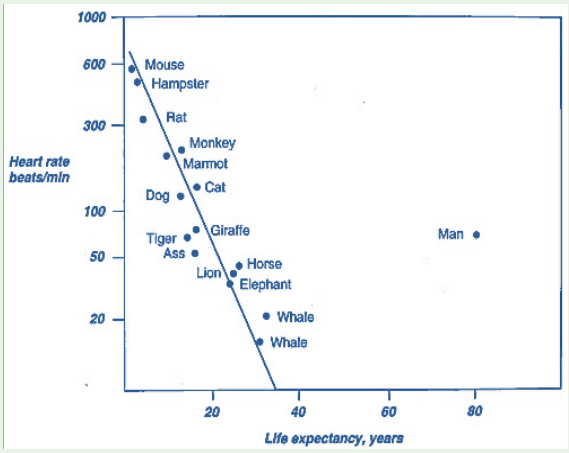

Figure 1: Inverse relationship between life expectancy and heart rate per minute among mammal species.The more HR/min the less years of expectancy. Note that humans do not satisfy this rule. Adapted from Levine et al. [3].

women over a large cohort of more than 19000 subjects by Benetos et al [9]. This author provided evidence of the same relationship in men over 65 years after a follow up of 16 to 20 years [14]. And finally resting HR was found an independent predictor of total and cardiovascular mortality in middle-aged Japanese population [12] demonstrating the same findings made in Western population.

Robust information was given by Jouven et al. studying 5713 middle-aged working men without proven or suspected cardiovascular disease[15]. They found resting HR of more than 83 beats per minute (bpm) to be in independent risk factor of all cause, non-sudden and sudden cardiac death from myocardial infarction even after adjusting for several confounding factors. The strongest relationship was observed between sudden death and resting HR over 83 bpm, with 3.5 times higher risk than in the lower quintile (people below 60 bpm).

Role of Heart Rate in Different Cardiovascular Disorders

Stable coronary arthery disease

Results obtained from the Coronary Artery Surgery Study (CASS) offered the greatest demonstration of the influence of HR in patients with proven coronary disease [16]. This study involved 24913 patients followed during a mean period of 14,7 years. All cause and cardiovascular mortality rates were related to increase resting HR, as cardiovascular rehospitalizations did too. The HR cut-off value of more than 83 bpm at study entry had a significant higher risk of total and cardiovascular death even after multivariate analysis including several known cardiovascular risk factors, Ejection Fraction (EF), number of affected vessels and treatment with diuretics, beta blockers, antiplatelets and lipid-lowering drugs (Figure 2).

More than 22000 patients with clinical coronary artery disease and hypertension enrolled in the International VErapamil-SR/trandolaprilSTudy (INVEST) were studied to prove the prognostic factor of resting HR [17]. Elevated baseline resting HR was associated with increased incidence of adverse outcomes (death, non-fatal myocardial infarction and non-fatal-stroke) with a two-fold increase among patients with resting HR >100 bpm (vs. those with<100 bpm). In the overall study population, mean follow-up resting HR was strongly associated with risk for adverse outcomes despite of excelent blood pressure control with the study drug and a J-shaped relationship was observed. An increase in follow-up HR from 70 to 80 bpm supposed a 31% of excess risk for adverse outcomes, giving the evidence of the independent effect of HR despite of good blood pressure control.

HR after an acute myocardial infarction (MI)

First published data demonstrating the influence of discharge HR after an acute MI and short-term mortality come from the fibrinolysis era. Hjalmarson et al. showed the independent relationship between both in hospital and discharge HR, and total mortality at 1 year follow up [18]. They found the association was also independent of the development of heart failure during in hospital hospitalization.

Several years before, informationof more than 20000 patients, extracted from the GISSI trials showed evidence of worse prognosis

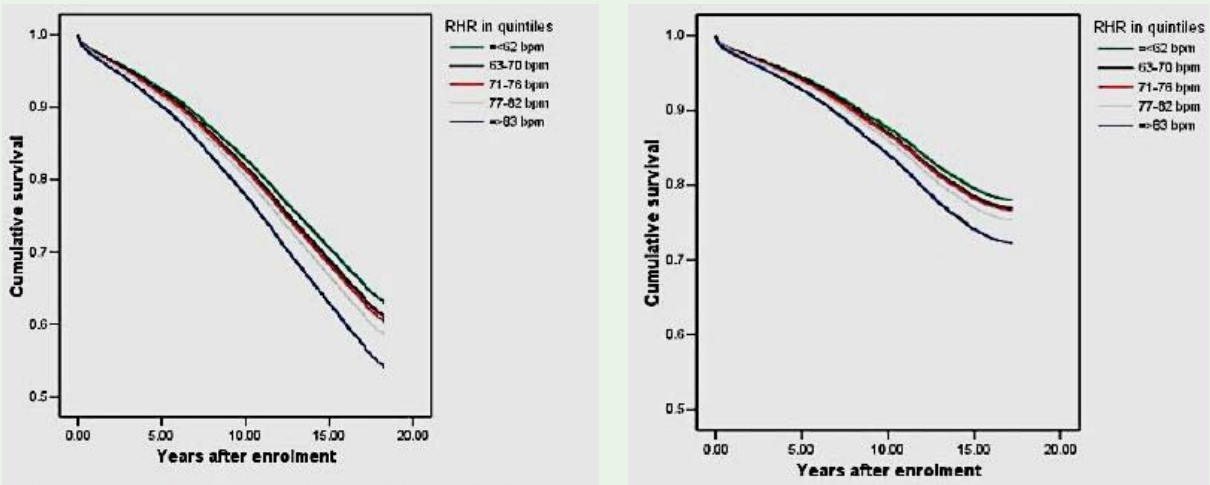

Figure 2: Adjusted survival curves for overall (left) and cardiovascular (right) mortality. The highest HR quintile (>83 bpm) correlates with worst survival. Adapted from Diaz et al. [16].

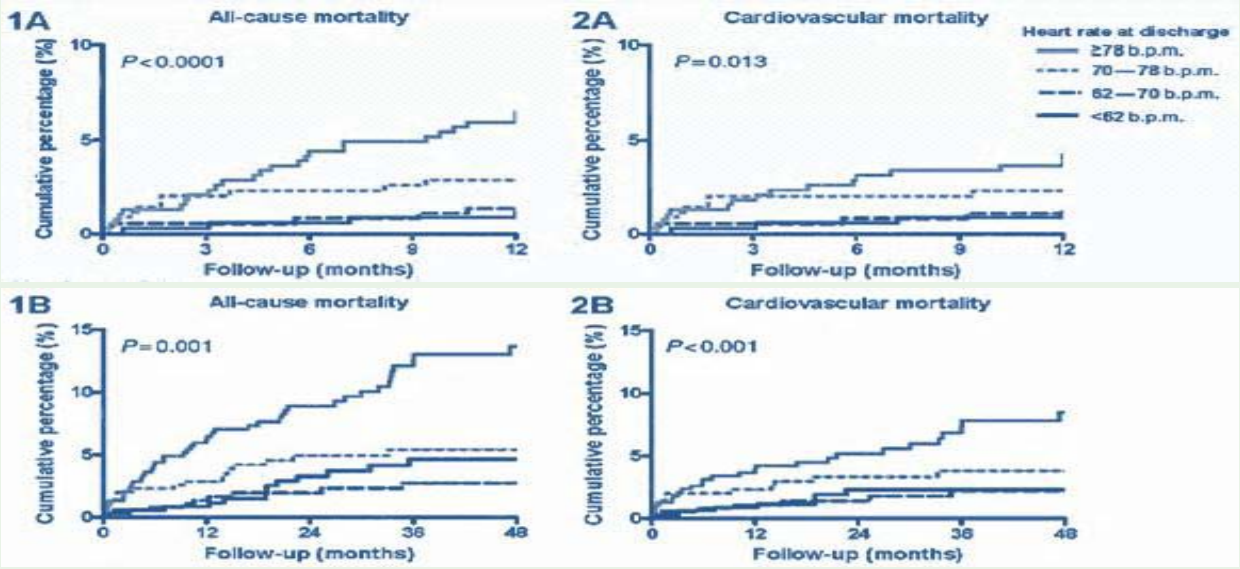

Figure 3: Kaplan-Meier time to event curves for HR at discharge divided by quartiles and all-cause mortality (1) and cardiovascular mortality (2) at 1-year (up row) and 4-year (down row) follow-up. Adapted from Antoni et al. [23].

in patients with HR of more than 100 bpm at discharge after an MI [19,20]. An elevated HR of more than 100 bpm was associated with 14.3% increase risk of 6 months mortalitycompared with patients with HR below 60 bpm.

After that, primary percutaneous coronary intervention (PCI) has been universalizated as the standard therapy in acute MI. Some initial reports pointed the prognosis risk factor of admission and delayed HR in early revascularizated patients after short term follow-up [21,22]. Important data, including long term follow-up, in this field has been recently published [23]. This study contains 1453 patients admitted with ST elevation myocardial infarction undergoing urgent PCI. It is needed to be highlighted the optimal therapy at discharge of this population. Rates of antiplatelets, betablockers, angiotensin convertingenzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and statins were more than 92% for each group, reaching 100% of population treated with antiplatelet drugs. Despite of all, all cause and cardiovascular mortality was significant higher in the quartile of patients with HR of more than 78 bpm at 1 year and remained an important predictor for adverse events at four years follow-up (Figure 3). Every increase in 5 bpm was related to an increased risk of 26% for allcause mortality and 24% for cardiovascular mortality even adjusting for infarct size, ejection fraction and development of heart failure.

Ischemic systolic disfunction and heart failure

In the last years important mortality and morbidity information has been derived from two large clinical trials [24,25].The first one is the BEAUTIFUL (morbiditymortalityevaluation of the if inhibitor ivabradine in patients with coronary disease and left ventriculardysfunction) study. This randomised, double-blind, placebo-controlled, parallel-group trial included 12473 patients with coronary heart disease and ejection fraction below 40%, none or mildly symptomatic. The subgroup analysis of the placebo arm (5438 patients untreated with the styudy drug) have extended our understanding of the prognostic importance of HR [26]. Despite of really good rates of medical treatment (including betablockers, antiplatelets, ACE inhibitors/ARB and statins), resting HR of more than 70 bpm at mean follow-up of 2 years was related to an increase risk of cardiovascular mortality and adverse outcomes (hospitalization due to heart failure, MI or revascularization). There was a 34% increase in the adjusted relative risk of cardiovascular death in patients with HR >70bpm versus HR lower than 70 bpm. This contrasts with the overall results of the BEAUTIFUL trial in which adition of ivabradine to optimal medical therapy failed to demonstrate improvement in cardiac outcomes [24].

Similar and even more interesting results appeared in the field of heart failure patient with the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine) trial. This randomised, double-blinded, placebo-controlled trial included 6505 ischemic heart failure patients with ejection fraction less than 35% and resting HR of more than 70 bpm. Important lessons about the prognostic role of HR can be taken from the placebo arm (>3200 patients). In this trial subgroup, analyses with heart rate as a continuous variable showed that for every beat increase in heart rate, risk of a primary composite endpoint event increased by 3% (p<0.0001). Similar increases in risk were shown for the components of the primary endpoint (3% for both hospital admission for worsening heart failure and cardiovascular death, both p<0.0001). For every 5-bpm increase in heart rate, the risk of the primary composite endpoint increased by 16%. [27]. As in the BEAUTIFUL trial, this population was under high rates of medical treatment,even including a small percentage of people with resynchronization therapy device. The increased risk for adverse outcomes remained significant after correction for several confounder factors.

Furthermore, ivabradine achieved the primary endpoint, in the overall study population, with a 18% relative risk reduction of cardiovascular death or hospital admission for worsening heart failure [25]. In the ivabradine group, there was a direct association between heart rate achieved at 28 days and subsequent cardiac outcomes. Patients with heart rate lower than 60 bpm at 28 days on treatment

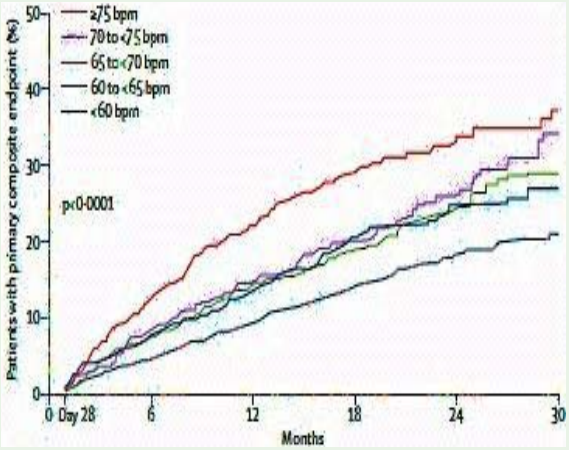

Figure 4: Kaplan-Meier event curves for the primary composite endpoint in the ivabradine group, according to groups defined by heart rate achieved at 28 days. Patients over 75 bpm remain at higher risk of events compared to the under-65 bpm quintile. Adapted from Böhm et al. [27].

had fewer primary composite endpoint events during the study. One important finding more is, that patients not achieving heart rates lower than 75 bpm despite of ivabradine treatment were at high risk of absolute adverse events (Figure 4). This supports that patients with heart rate of 70 bpm or higher remain at increased risk of events, and that there is also a continuous direct association between baseline heart rate and outcomes. HR is not only a risk marker in heart failure, but that it is also a risk factor and modification of heart rate also modifies risk.

Which are the Reasons for these Clinical Findings?

Myocardial oxygen supply, coronary blood flow and cardiac work are directly determined by HR [28]. The influence of HR in the different steps of cardiovascular pathology is resumed in the lines below.

Endothelial dysfunction

Endothelial dysfunction is the first step in the development of atherosclerotic disease [24]. The mechanism by which HR reduction improves endotelial function is decreasing vascular oxidative stress. This affirmation is supported by the improvement in endothelial function profile seen in different lipid-induced atherosclerosis animal models by lowering HR with ivabradine treatment [29-31].

Atherosclerosis

Pulsatile stress effect of HR over the artherial wall affects vascular endothelium homeostasis and is probably responsible of the predisposition to atherosclerosis development [32]. HR has been related to the extent of coronary and carotid atherosclerosis in several monkey models and, its reduction, with the decrease in areas covered by plaques [33,34]. In humans progression of focal coronary atherosclerosis has been independently associated to resting HR and HR variability [35].

Plaque disruption

Mechanical stress such as circunferential and repetitive tensile stress have been shown to affect plaque morphology precipitating inestabilization [36]. HR has been demonstrated as an important haemodynamic trigger facilitating coronary plaque disruption in humans. HR was related to plaque disruption in a logistic regression analysis done in 53 patients who underwent two coronary angiography 6 months apart. Those patients who developed plaque disruption by the time of the second angiography had a mean HR of more than 80 bpm [37].

Myocardial ischemia

The disbalance between myocardial demand and supply is directly influenced by HR control. Elevated HR increases oxygen demand and decreases oxygen supply by shortening diastolic fraction of cardiac cycle [38]. In patients with stable coronary artery disease, HR increases influence in exercise-induced myocardial isquemia [39] and the frequency of ambulatory ischemic episodes [40] with twice as often in patients with HR>80 bpm compared to patients with mean HR less than 70 bpm.

Heart Failure

The final common way of the processes mencioned above is myocardial suffering, left ventricular dysfunction and development of heart failure symptoms.HR reduction with betablocker therapy reduces oxygen demand and improves mechanical efficiency. Several meta-analysis including more than 20 betablockers trials in heart failure patients agree that the beneficial effect of these drugs is proportionally related to the magnitude of HR reduction [41,42]. These demonstrated benefits are abolished if HR is kept constant by atrial pacing [43], showing the pivotal effect of HR reduction in improving cardiovascular risk profile.

Conclusion

High heart rate is often found together with other cardiovascular risk factors like hypertension, dyslipidemia, diabetes and overweight [44] and also correlates with the number of them presenting in an individual. Therefore it is been widely accepted as a risk marker in many cardiovascular and non-cardiovascular disorders.Indeed resting HR is included in risk assessment indices for patients after acute coronary syndromes [45-47].

Nonetheless changes in HR can modify cardiovascular risk profile in healthy population and cardiac patients. In clinical trials and observational studies presented previously when adjusting for accepted cardiovascular risk factors, HR remained an independent risk predictor. Elevated resting HR not only has the ability to select healthy people at risk of developing adverse cardiac events and early mortality but also cardiovascular patients at high risk of worse clinical course. The cut-off values for elevated resting HR implying more risk of adverse outcomes are not the same between different epidemiologic studies. Although it is difficult to propose an optimal heart rate,the common link for high cardiovascular risk profile is an increased resting HR.

Information obtained from recent clinical trials studying the effect of selective HR lowering drug has confirmed the importance of decreasing HR in improving cardiovascular risk profile. Lowering HR correlates well with less risk of mortality and morbidity. Actually those patients with persistent high HR, even after decreasing baseline HR with different treatments, are still at high risk of cardiovascular events. So, as much as we can, it seems desirable to mantain resting HR lower than 70 bpm.

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