

## REVIEW ARTICLES

# Heart Rate – An Emerging Cardiovascular Risk Factor

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### Abstract:

*The development of cardiovascular disease (CVD) is usually caused by multiple risk factors, which interact to produce an individuals total CVD risk. Therefore the guidelines on the prevention of CVD recommend the preventive measures be based on individual's levels of total CVD risk so that the most intensive risk factor management can be directed towards those at highest risk. Elevated resting heart rate is a known independent cardiovascular risk factor but is not included in any risk estimating system-Coronary risk chart or SCORE(Systematic Coronary Risk Evaluation),which are used for estimation of individuals 10 year risk of a CVD event based on gender, age, total cholesterol, smoking status and systolic blood pressure. The findings several epidemiological studies showed an association between elevated heart rate an increased risk of all-cause mortality and morbidity in general population ,hypertensives,diabetics and those with CAD.*

**Key words-** Heart rate ,Emerging cardiovascular risk factor

The development of cardiovascular disease (CVD) is usually caused by multiple risk factors, which interact to produce an individuals total CVD risk .Therefore the guidelines on the prevention of CVD recommend the preventive measures be based on individual's levels of total CVD risk so that the most intensive risk factor management can be directed towards those at highest risk.<sup>1</sup>

Individuals with established CVD have already categorized as high risk. Similarly individuals with established type 2 or type 1 diabetes with microalbuminuria or markedly elevated levels of single risk factors are automatically considered as high risk. For other asymptomatic individuals an assessment of risk level is necessary.

Recently ,much attention has focused on many other risk factors (*Lipid*: Lipoprotein remnant particles-Lipoprotein (á),HDL sub species, Apolipoprotein -A, Apolipoprotein-B, Total-C/HDL-C ratio and *Non lipid*: Inflammatory markers – hs CRP, ICAM-1, Fibrinogen, Homocysteine-Hyperhomocysteinemia ,Impaired fasting Glucose etc) are not also included in the above mentioned risk estimating system.

Heart rate (HR) is a simple and easily measurable clinical parameter has been found to be a risk predictor of mortality and morbidity in various populations. Heart rate has already appeared in European guidelines on CVD prevention.<sup>2</sup>

Elevated resting heart rate is a known emerging independent cardiovascular risk factor but is not included in any risk estimating system – Framingham's risk score chart of AHA/ACC or SCORE (Systematic Coronary Risk Evaluation)of ESC -which are used for estimation of individuals 10 year risk of a CVD event based on gender, age, total cholesterol, smoking status and systolic blood pressure.

Resting heart rate both contributes to and reflects cardiac pathology. Increased heart rate due to imbalances of the autonomic nervous system with increased sympathetic activity or reduced parasympathetic activity/ vagal tone, has an impact on perfusion-contraction, which is the dynamic that regulates myocardial blood supply and function. In the healthy heart, increased metabolism as a result of increased contractile function results in increased myocardial blood flow and, to a lesser degree, increased oxygen extraction. In the presence of coronary artery disease, perfusion-contraction mismatching is localized to areas of inadequate blood supply. When coronary artery inflow is inadequate to meet demands, contractile and diastolic functions in that affected area are correspondingly reduced .<sup>3</sup> An increase in heart rate results not only in an increase in myocardial oxygen demands, but also a potential impairment of supply resulting from a reduction of collateral perfusion pressure and collateral flow .<sup>3</sup>

Pathophysiological mechanisms promoted by increased heart rate- This imbalance may promote ischemia, arrhythmias and ventricular dysfunction, as well as acute coronary syndromes, heart failure or sudden death.

With increased heart rate, diastolic perfusion time lessens while myocardial oxygen demand increases. Peak coronary flow increases markedly during diastole, subjecting the coronary arteries to enhanced endothelial shear stress and pulsatile wall stress. The stressed endothelium releases growth hormones (eg, transforming growth factor-beta and insulin-like growth factor-1) and vasoconstrictor peptides (eg, endothelin), and is associated with increased platelet aggregation and a relative deficiency of nitric oxide synthesis. Rapid pulsatile changes appear to increase mechanical damage on the already stressed endothelium. All of these factors encourage the development of atherosclerotic lesions, especially at arterial branches.<sup>4</sup>

Prolonged elevated heart rates cause cardiac noradrenalin synthesis to increase and circulating plasma noradrenalin levels to rise. This increase in sympathetic activity and myocardial oxygen requirements may have a direct cytotoxic effect on myocytes, increasing apoptosis with deleterious effects on ventricular remodeling. Elasticity of the larger arteries is reduced by elevated heart rates, resulting in a greater pulsatile arterial load on the heart, consequently increasing the myocardial energy requirements.<sup>4</sup> In addition, prolonged elevated heart rates may also cause or exacerbate heart failure.

The present paper reviews the evidences for elevated heart rate as a cardiovascular risk factor and some of the current clinical trials testing this hypothesis.

A large European prospective study in more than 21,000 patients without a history of coronary heart disease, angina or heart failure found an increase of 15 beats per minute in RHR increased the risk of cardiovascular mortality by 24% in men and 32% in women after 12 years. This study also showed "Resting heart rates greater than 90 beats/min have been shown to be associated with at least a doubling of risk – a similar effect to smoking. The study also showed the "strong, graded, independent relationship" remained after adjusting for age, gender, cholesterol, physical activity, blood pressure and BMI.<sup>5</sup>

A 2010 Danish population study among current, former and never smokers found that for every 10-beats-per-minute increase in resting heart rate, the risk of all-cause mortality rose 6 percent in never smokers, 11 percent in former smokers, and 13 percent in current smokers. The average difference in survival between study subjects in

the lowest RHR range evaluated (less than 65 beats per minute) and the highest RHR range evaluated (more than 80 beats per minute) was 4.7 years in men and 3.6 years in women.<sup>6</sup>

A recent research study reported that middle-aged men who achieved at least a 4-beats-per-minute reduction in resting heart rate within a five-year period of their initial RHR reading reduced their all-cause mortality risk by 14 percent.<sup>7</sup>

In a 2011 study published in the *European Journal of Cardiovascular Prevention and Rehabilitation*, showed - in a large French population, accelerated resting HR represents an independent predictor of noncardiovascular mortality in both genders, and of cardiovascular mortality in men, independent of age and the presence of hypertension. Further investigations are needed to explain the complex interactions between HR, pulse pressure, and cardiovascular complications.<sup>8</sup>

One study showed obese subjects had values of resting heart rate 7.8% higher than nonobese (P = .001). Hypertensive children and adolescents also had elevated values of resting heart rate (P = .001). When the sample was stratified in nonobese and obese, the higher quartile of resting heart rate was associated with hypertension in both groups of children and adolescents.<sup>9</sup>

*In an observational study, elevated resting heart rate was significantly associated with high blood pressure — independent of obesity — in male children and adolescents.* Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy adults, but what is the association in children? Researchers in Brazil conducted a cross-sectional study of 358 healthy male children and adolescents (age range, 8–18 years; 65% white) who were not taking any medications. This study confirms an association between elevated resting heart rate and high blood pressure in a pediatric population. Surprisingly, the association was independent of obesity, ethnicity, and age. Therefore, the results suggest that measurement of resting heart rate in children and adolescents can provide insight into a child's future cardiovascular health, regardless of body fat.

The findings several epidemiological studies showed an association between elevated heart rate an increased risk of all-cause mortality and morbidity in general population, ,hypertensives,diabetics and those with CAD.<sup>10</sup>

Elevated resting heart rate is a significant indicator for all-cause and cardiovascular mortality in general population and patients with cardiovascular disease.<sup>11</sup>

More specifically increased heart rate is a significant predictor death and cardiovascular death /hospitalization in heart failure patients.<sup>12</sup>

Moreover, some studies show a biological gradient – a continuous and graded association between heart rate and cardiovascular risk.<sup>13,14</sup>

**Role of heart rate in atherosclerosis and coronary events-**  
A considerable number of epidemiological studies have reported a strong association between elevated heart rate and cardiovascular risk, and this association appears to be independent of other major risk factors for atherosclerosis.<sup>15</sup> This association has been consistent and was observed in healthy populations among men and women,<sup>16-18</sup> (although in some studies the association is less robust in women, various races,<sup>16-18</sup> hypertensive subjects,<sup>13,19</sup> patients with coronary artery disease,<sup>20,21</sup> and in those with heart failure.<sup>22</sup>

The most common coronary presentations of atherosclerotic patients are stable angina pectoris and acute coronary syndromes. Stable coronary disease can be asymptomatic (silent ischaemia) or symptomatic (effort angina). Both angina pectoris and silent ischaemia are associated with an increased risk of cardiovascular events.<sup>23</sup>

**Role of heart rate in myocardial ischaemia in patients with stable angina and those who suffer from myocardial infarction** is well known. The likelihood of myocardial ischaemia is related to baseline resting heart rate and is two times higher in patients in patients with heart rate of 60 bpm.<sup>24</sup>

To definitively establish heart rate as a cardiovascular risk factor, evidence that lowering heart rate reduces cardiovascular risk is required. To date, such evidence is available retrospectively from studies of beta-blocker use after myocardial infarction.<sup>24,25</sup> and heart failure.<sup>26-29</sup>

In addition to lowering heart rate and blood pressure, beta-blockers have other actions that may also account for their benefits.

A new class of agents is now available that acts selectively on the sinoatrial node and lowers heart rate without affecting other pathways. Ongoing trials with these agents will more directly test the role of heart rate as a true cardiovascular risk factor. Ongoing trials with a new class of drug, selective  $I_f$  inhibitors, Ivabradine - a 'pure' heart rate-reducing medication confirming the causal link between elevated heart rate and cardiovascular outcomes.

Three studies of normal populations with and without hypertension – the Paris Prospective Study I,<sup>30</sup> Hypertension Ambulatory Recording VEnetia Study (HARVEST)<sup>31</sup> and a review by Aboyens and Criqui<sup>32</sup> had a combined sample of nearly 180,000 people. They all showed that cardiovascular mortality significantly increases as resting heart rate increases.<sup>14</sup>

The Framingham study<sup>17</sup> (5070 healthy subjects) measured its subjects' heart rates every two years. Investigators reported that, in both sexes and at all ages, all-cause, cardiovascular and coronary mortality rates increased progressively in relation to antecedent heart rates; this was, however, more marked in men than in women.

The National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study<sup>18</sup> (5995 healthy subjects) concluded that elevated resting heart rate was an independent risk factor for coronary artery disease incidence or death among white and black men and women.

The British Regional Heart Study<sup>21</sup> looked at a mixed (healthy and unhealthy) population of 7735 men aged 40 to 59 years over a period of eight years. In men with no evidence of ischemic heart disease, there was a strong positive association between resting heart rate and age-adjusted rates of all major ischemic heart disease events (fatal and nonfatal), ischemic heart disease-related deaths and sudden cardiac death. After adjustment for age, systolic blood pressure, blood cholesterol, smoking, social class, heavy drinking and physical activity, this association was still significant. In men with pre-existing ischemic heart disease, the association also held but its effect was less pronounced. Investigators noted that elevated heart rate (90 beats/min or greater) is a risk factor, particularly for sudden cardiac death; it is independent of other established coronary risk factors and is most clearly seen in men with no pre-existing ischemic heart disease at the time of the initial examination.

Over the past 30 years, at least 38 studies have looked at the connection between heart rate and cardiovascular or all-cause mortality.<sup>22</sup> These studies have covered a wide variety of populations: men and women, black and white, healthy and diseased, and younger and older. After adjusting for risk factors and lifestyle, at least 32 studies show that elevated heart rate is an independent risk factor for mortality and morbidity in healthy people with and without hypertension; it is also an independent risk factor in patients with coronary artery disease, myocardial infarction and heart failure.<sup>32,14</sup>

The Coronary Artery Surgery Study (CASS)<sup>22</sup> looked at 24,913 men and women with stable coronary artery disease and one or several clinical variables such as hypertension, diabetes, dyslipidemia and high body mass index. Among the subjects, 4.3% took lipid-lowering drugs, 33.2% smoked while enrolled and 34.8% had sedentary lifestyles. They ranged in age from 50 to 73 years. After 14.7 years (median) of follow-up, the investigators determined that, even after adjusting for those many clinical variables, a resting heart rate of 83 beats/min or greater at baseline conferred significantly higher risk for all-cause and cardiovascular mortality.

The male and female subjects (n=2599, age 50 to 73 years) in the Carvedilol or Metoprolol European Trial (COMET)<sup>33</sup> were patients with heart failure, and they were prescribed beta-blockers with the dose titrated up over several weeks. Most subjects were on a steady maintenance dose at evaluation (four months after enrollment). Heart rate was related to mortality, both at rest and after therapy, although, after multivariate regression, only post-treatment heart rate (at four-month follow-up on maintenance therapy) had prognostic value for all-cause mortality.

Mehta et al<sup>34</sup> recently showed that patients presenting with acute myocardial infarction and shock, and with heart rate greater than 100 beats/min and systolic blood pressure 80 mmHg or less, had 30-day death rates greater than 90%; the authors suggested that this information might be used when determining treatment strategy and counseling patients about their risks.

The Cardiac Insufficiency Bisoprolol Study (CIBIS)<sup>28</sup> showed that heart rate change over time had the highest predictive value for survival in patients with LV systolic dysfunction, and that bisoprolol promotes preservation of LV function.

The CIBIS II trial<sup>35</sup> examined the relationships between baseline heart rate (BHR), heart rate changes at two months (HRC) and outcomes (mortality and hospitalization for heart failure) in a large (n=2539) sample of patients with mild to moderate symptomatic heart failure. BHR and HRC were significantly related to prognosis, the lowest BHR and the greatest HRC being associated with best survival and reduction of hospital admissions.

It has been shown, for heart failure patients, that greater heart rate reduction is associated with better outcomes; in addition, patients with persistently elevated heart rates derive additional benefit from higher beta-blocker doses.<sup>36</sup> The Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure

(MERIT-HF) investigators<sup>37</sup> have recommended aiming for the target beta-blocker dose rather than a target heart rate. Current practice when prescribing heart failure medications is thus to titrate doses up to the maximum recommended unless symptoms impose limits.

Taken together, above mentioned studies on heart failure patients suggest that agents that reduce heart rate – in these cases, beta-blockers (atenolol, carvedilol, metoprolol, bisoprolol) – are clinically useful for heart failure irrespective of patient age or LV ejection fraction, and they are recommended in current national heart failure guidelines.<sup>38,39.</sup>

### Conclusion:

There were several studies conducted over the past several years that revealed the diagnostic value of resting heart rate as a predictor of all-cause mortality and cardiovascular disease risk. These studies had evaluated resting heart rate in healthy middle-aged adults, the elderly, smokers, diabetics, people with heart disease and other population samples. All of them had demonstrated “the resting heart rate is a significant predictor of all-cause mortality”. Many of them had found similar predictive value when it came to cardiovascular disease risk. So all these studies also support a conclusion that heart rate is a reliable prognostic indicator in both the healthy population and in those with cardiovascular disease and elevated heart rate could be an emerging risk factor for cardiovascular diseases and specifically for coronary artery disease.

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