HEART RATE AS A RISK FACTOR IN CARDIAC DISEASE

ABSTRACT:
There is a lot of evidence that elevated heart rate is an independent risk factor for mortality and morbidity in healthy individuals with and without hypertension and in patients with coronary artery disease (CAD), acute myocardial infarction (AMI), and heart failure. Several large placebo-controlled trials of patients with AMI or heart failure have demonstrated that beta-blockers reduce mortality and morbidity. The effects seem to be more marked in patients with higher pre-treatment heart rates. Selective heart rate reduction by the novel sinus node inhibitor Ivabradine is promising for a variety of conditions ranging from stable angina to heart failure. Heart rate should be considered as an important cardiac risk factor and patients with elevated resting heart rate at risk of CAD or with established CAD should be treated the available agents to reduce their heart rate to a normal level.

INTRODUCTION
CAD is the single largest cause of death in the United Kingdom. Statistics show that more than 1.4 million people in England suffer from angina and out of these approximately 275,000 people suffer from AMI annually. Overall, CAD contributes to 110,000 deaths each year. For many years, cardiac risk factors such as smoking, diabetes, cholesterol and hypertension have been the highlight of aggressive management by physicians in patients with CAD. Recently heart rate has been identified as an independent cardiovascular risk factor and there is a growing body of evidence to support this. Clinical studies have shown an increased risk of morbidity and mortality in patients with an increased heart rate and underlying cardiovascular disease.

ELEVATED HEART RATE AS AN INDEPENDENT CARDIOVASCULAR RISK FACTOR:
A study showed that across all animal species there is a predetermined number of heart beats in a life time. Life expectancy across the animal kingdom varies and there is evidence to suggest that it is in fact heart rate that determines life expectancy. It is not clear what constitutes a cut-off value for a safe resting heart rate. Data from different studies reveals normal heart rate values between 60 and 80 beats/minute and tachycardia as greater than 100 beats/minute. It is also not clear at what heart rate the risk starts to increase. A few studies indicate values below 70 beats/minute as to be safe, although no definitive information can be derived from the available and conflicting results. The clinical scenarios with respect to heart rate and risk of cardiac disease as discussed below.

Normal population and Hypertension: Many epidemiological studies on long-term follow-up of healthy individuals have shown an independent association between elevated heart rate and cardiovascular mortality and morbidity with the first study more than half a century back revealing increased risk of hypertension with elevated resting heart rates. About 40 studies, including the Framingham study have shown that heart rate is independently associated with cardiovascular and all-cause mortality. The association between heart rate and cardiovascular events is present at all ages and even in elderly subjects older than 70 years. The evidence spans across patients with and without cardiovascular complications and appears to be independent of other risk factors for the atherosclerotic disease and is as consistent as the association between other “classic” risk factors and cardiovascular disease.

Heart rate has been shown to have a positive relationship with other “conventional” risk factors like blood pressure readings, body weight, triglycerides, insulin and glucose metabolism. It is not sure if the relationship between heart rate and the cardiac risk is linear. This indicates the rather non-specific role of this variable in predicting cardiovascular events. In the 30 year follow up from Framingham study (n = 5070), of healthy men and women, the increase in the overall mortality as a consequence of elevated resting heart rate was more marked among men than women, younger and older individuals. Another study on healthy subjects aged 25–74 years with 6 and 13 years (n = 5995) of follow up revealed that elevated resting heart rate was an independent risk factor for CAD incidence or death among white and black men and women. In several studies of healthy men and women, it has been found that elevated resting heart rate is not only a predictor of all-cause mortality, but also an independent risk predictor of sudden cardiac death. The European Society of Hypertension has recently reviewed the evidence for the role of heart rate in patients with hypertension and commented that: “We strongly believe that the onus of ‘innocence’ should be removed from high heart rate and hope that in due time a fast heart rate will
be universally accepted as a strong predictor of cardiovascular events."

**Patients with CAD:** In CAD patients at baseline, elevated heart rate is an independent risk predictor for major ischemic coronary events, cardiovascular mortality, and sudden cardiac death, similar to that seen in healthy/hypertensive individuals. In CASS registry, with 24913 men and women with suspected or proven CAD and a median follow-up time of 14.7 years, resting heart rate was found to be a predictor of overall and cardiovascular mortality. Further subgroup analysis, and the association between heart rate and total mortality was consistent in all analysed subgroups regardless of sex, age, hypertension, cardiac function, body weight, presence of diabetes, or use of beta-blockers. Heart rate was also a predictor of time to first re-hospitalization because of congestive heart failure. Another study revealed heart rate to be a predictor of major ischemic heart disease events, cardiovascular mortality, and sudden cardiac death, both in patients with CAD and in the normal population with or without hypertension.

Resting heart rate is a very useful indicator in angina. Baseline heart rate, before a heart rate increase is directly linked to the likelihood of developing ischemia. In a study of patients with stable coronary artery disease, patients with a resting heart rate above 80 beats/minute (bpm), were twice as likely to develop ischemia as those below 60bpm. More than 80% of episodes of ambulatory ischemia are associated with substantial increases in heart rate. In a study analysing 68 ischemic episodes the hour leading up to an event was accompanied by an increase in heart rate. Ischemia was measured by ST segment depression using 48hr ambulatory ECG monitoring.

In patients with AMI, the resting heart rate on arrival in the emergency and the average heart rate during the hospital stay or at the time of discharge are independent and highly significant predictors of later death. In a study from hospitals in San Diego (n=1807), heart rate was found to be a more powerful predictor of later mortality than assessment of left ventricular function after arrival in hospital. Similar observations were made in the GISSI-3 study (n=11020) with patients with AMI, which showed that elevated heart rate at discharge was highly significant and independently correlated with 6-month mortality. The positive effects on infarct size with HR reduction are also reflected in the overall effect on cardiac death. In a meta-regression analysis of 14 trials in the post-MI setting with beta-blockers, there was a strong correlation between the heart rate lowering effect of beta-blockers and their effect on reducing cardiac death. The greater the heart rate lowering effect in beta-blocker trials the lower the relative risk of cardiac death.

**Heart Failure:** Large trials on patients with congestive heart failure have demonstrated that baseline heart rate is an independent risk predictor of all-cause mortality, cardiovascular mortality, and hospitalization for congestive heart failure. This was seen in MERIT-HF trial (n=3991), but only in the placebo-treated patients. This trial clarified that heart failure patients with a higher heart rate are very different from those with a lower heart rate; in general, patients with a higher heart rate have more risk factors. Even when adjusting for these differences, heart rate is an independent risk predictor of prognosis. Similar results were seen in the CIBIS-II trial (n=2539), which revealed that heart rate was a strong predictor of 1-year mortality. The benefits from heart rate reduction in heart failure can't be over-emphasized. The impact of selective heart rate reduction with sinus node inhibitor ivabradine in heart failure is discussed separately in this review.

**PATHOPHYSIOLOGICAL ASPECTS:**

There is good experimental and clinical evidence that high heart rate is of importance in the development and progression of atherosclerosis, myocardial ischemia, acute ischemic events, and sudden cardiac death, and that a reduction in heart rate has beneficial effects. In context of CAD, angina pectoris is caused by ischemia of the myocardium as a result of an imbalance of oxygen supply to cardiac muscle and myocardial perfusion. An elevated heart rate hence increases oxygen demand and reduces myocardial perfusion. High resting heart rate reflects an imbalance of the autonomic nervous system, with increased sympathetic activity and/or reduced vagal activity. Heart rate is a major determinant of myocardial oxygen consumption and energy utilization; furthermore, an increase in heart rate reduces the diastolic coronary perfusion time. With these two mechanisms, an increase in heart rate may trigger ischemic events. An increase in sympathetic activity and/or lowering of vagal activity are known to increase the risk of ventricular fibrillation in experimental studies on myocardial ischemia. High heart rates have also been associated with coronary artery endothelial dysfunction in experimental studies. It is well known that psychosocial stress-associated increases in heart rate can trigger the onset of AMI, in addition to sudden cardiac death. Elevated heart rate during mental stress may play a key role in the development of sudden cardiac death.

It is well recognized that the incidence of sudden cardiac death among patients with hypertension, myocardial infarction, or congestive heart failure is reduced by beta-blockers and the magnitude of heart rate reduction is strongly correlated to its effect on cardiovascular mortality. The link between heart rate and CAD seems largely due to the impact on atherosclerotic plaques, whether it is favouring conditions that lead to atherosclerotic lesions or conditions that lead to plaque rupture. Interestingly the relationship between heart rate and mortality holds regardless of whether a patient is on beta-blocker treatment or not.

In summary, out of the several mechanisms proposed for explaining the relationship between an elevated heart rate and cardiovascular risk, two have been confirmed on experimental and clinical studies. The first one represents the heart rate as an integrated index of autonomic cardiovascular function and elevated heart rate values indicate adrenergic overdrive, leading to or worsening ischemia with risk of acute coronary syndromes (ACS), fatal or non-fatal arrhythmias or heart failure. Secondly, the elevated heart rate exerts mechanical effects on the cardiac...
vasculature leading to increased shear stress, impaired arterial compliance and favours the development of atherosclerotic vascular lesions.

There are no clear cut indicators regarding heart rate variability and increased cardiac risk. Very few studies have systematically compared the prognostic value of clinic versus “out-of-office” heart rate, with conflicting results. Even though the high variability of heart rate values during day and night may mean that a 24-hour average heart rate would provide a better prognostic estimation of risk than traditional “office heart rate”, no significant difference was found with regards to either of the approaches in the Syst-Eur study and the PAMELA study.

**THERAPEUTIC IMPLICATIONS:**

Lowering heart rate by therapeutic interventions has shown favourable prognostic benefits, but most of the data so far is retrospective, and limited to AMI and heart failure with beta blocker treatment. No such information is available regarding benefits of the heart rate reduction in hypertension, making it difficult to give practical recommendations. The 2006 Consensus Document from the European Society of Hypertension suggests that, despite the lack of conclusive data, “heart rate reduction by antihypertensive agents may have beneficial effects”. This has strong therapeutic implications, especially for post-AMI and heart failure patients.

The three beta blocker trials in AMI showed reduction in all-cause mortality, cardiovascular and sudden cardiac death, and hospitalization and revealed that patients with a heart rate above the median at baseline had a higher mortality during follow-up and that the effect of the beta-blockers was most marked in the patients with the highest heart rate at baseline. Other benefits include reduction in all-cause mortality, sudden cardiac death, ventricular fibrillation, infarct development, and enzyme-estimated infarct size. It has been proposed that there is a significant relationship between the reduction in resting heart rate and the decrease in all-cause mortality. In survivors of AMI, similar benefits have been seen over long term follow up in a meta-analysis.

Similar relationship between heart rate reduction and all-cause mortality in patients with heart failure have been found with beta-blockers. In the two large trials CIBIS-II and MERIT-HF, patients with a higher heart rate at baseline had the highest mortality, and among these patients, there was a more marked effect of the beta-blockers.

**Selective heart rate reduction:** This is a novel and recent therapeutic concept, and is based on the fact that many patients with cardiac disease have limitations with rate limiting drugs (i.e. beta blockers or calcium blockers) due to various reasons like co-morbidities (e.g. Asthma), hemodynamic side effects, contraindications, other side effects limiting drug tolerance and sub-optimal rate control. Selective heart rate reduction can be achieved by sinus node inhibition without any hemodynamic consequences. Ivabradine, a selective sinus node inhibitor, has been shown to be beneficial in many clinical scenarios. Ivabradine was the first antianginal treatment demonstrated to reduce the risk of myocardial infarction and revascularization in stable coronary patients, even when they were receiving optimal preventive therapy. It can be used in stable angina as monotherapy or in addition to beta blocker for additional rate reduction. The ASSOCIATE study established that it was safe to combine Ivabradine with a beta blocker for additional heart rate reduction in stable angina patients.

The benefits of selective heart rate reduction have also been clearly demonstrated in the heart failure. In the recently published results from the BEAUTIFUL study, Ivabradine reduced myocardial infarction (fatal or nonfatal) and revascularization in coronary patients with elevated heart rate in a total of 10 917 patients with CAD and left ventricular dysfunction who were followed up for a median duration of 19 months and a maximum duration of 35 months. The primary composite end point of the study (mortality) did not reach statistical significance. The BEAUTIFUL study is the first prospective study to demonstrate that coronary patients with a baseline heart rate ≥70 bpm have a significantly higher risk of cardiovascular events, independently of other comorbidities or treatments. BEAUTIFUL has also shown that in patients with a heart rate more than 70 bpm, Ivabradine significantly reduces the risk of coronary events by 22%, fatal and nonfatal myocardial infarction by 36%, and coronary revascularization by 30%, respectively. Results are awaited from the SHIFT trial, which will throw further light on this issue whether selective heart rate reduction with Ivabradine improves cardiovascular mortality and hospitalisations in patients with moderate to severe heart failure.

**LIMITATIONS AND SUMMARY:**

Heart rate is a key determinant of ischemia and there is reasonable evidence that it is an independent risk predictor of the onset of acute coronary events, including all-cause mortality, cardiovascular mortality, sudden cardiac death. Despite being quite simple to measure in routine practice, it remains a neglected and under-measured parameter and its importance underestimated by physicians worldwide. The data on prognostic benefits with heart rate reduction are still not clear apart from in AMI and heart failure with beta blockers. There is no data in hypertensive population regarding benefit with heart rate reduction. Effects due to increased heart rate and the benefits with treatment seem to work in conjunction with other factors, raising questions about heart rate as a sole and independent risk factor. There is lack of convincing data for both genders, all ages or ethnic groups and all co-morbidities, with respect to heart rate. These unaddressed questions as of today prevent inclusion of heart rate in the routine assessment of total cardiovascular risk. However, Recent guidelines of the European Society of Cardiology and the European Society of Hypertension mention that an accelerated heart rate is considered as an independent risk factor and potentially as a target for pharmacologic therapies, especially in high-risk patients and it’s expected to become a well recognised “frontline” cardiac risk factor for patient assessment soon in the
future. It is anticipated that more than half of CAD patients have a resting heart rate ≥ 70 bpm, and they could certainly benefit from a reduction of coronary events with rate limiting agents with beta/calcium channel blocker without Ivabradine. The increase in the cardiovascular risk, associated with the acceleration of heart rate, is thought to be comparable to the increase in risk observed with high blood pressure. It has been shown that an increase in heart rate by 10 beats per minute was associated with an increase in the risk of cardiac death by at least 20%, and this increase in the risk is similar to the one observed with an increase in systolic blood pressure by 10 mm Hg.

Measurement of heart rate is recommended routinely in patients with or without established CAD and it should be treated at par with other risk factors, e.g. high blood pressure and cholesterol, smoking, cardiac dysfunction, and diabetes. It is known that hypertension, smoking, heart failure and diabetes are all associated with an elevated heart rate and benefit from treatment, symptom or prognosis wise. With the data so far, physicians should aim to achieve ideal heart rates (around 60 beats/minute) in stable angina, ACS, heart failure using different treatment strategies. In AMI or chronic heart failure, beta-blockers have shown more marked effects on mortality in patients with higher pre-treatment heart rates. Selective heart rate reduction with Ivabradine has been shown to reduce angina, myocardial infarction and revascularization rates. The effect of selective heart rate reduction on the ultimate marker of prognosis (mortality) in CAD and left ventricular systolic dysfunction (LVSD) still remains to be seen.

REFERENCES:


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