Heart rate: a strong predictor of mortality in subjects with coronary artery disease

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This editorial refers to 'Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease† by A. Diaz et al., on page 967

Risk stratification is important for determining the prognosis of subjects at moderate to high cardiovascular risk and various attempts have been made to integrate several clinical variables into a user-friendly risk model. Recently, the ESC has developed a model called SCORE which incorporates age, gender, smoking, systolic blood pressure, and total cholesterol (or total cholesterol/HDL-cholesterol ratio). This model does not take into account several other risk factors for cardiovascular disease, which may be relevant for modulating the disease risk, on the grounds that their impact on risk estimation is still uncertain. In the SCORE project article, resting heart rate was not even included in the list of the risk factors still under scrutiny. Yet, a large number of studies have shown that high heart rate is prospectively related to the development of cardiovascular morbidity and mortality, an association which was independent of other risk factors for atherosclerosis. The predictive power of heart rate for cardiovascular disease was observed in general populations, in elderly subjects, in hypertensive cohorts, and in patients with myocardial infarction. Further evidence in this respect is provided in the excellent article by Diaz et al., who studied the prognostic importance of resting heart rate for total and cardiovascular mortality in a large cohort of patients with stable coronary artery disease from the Coronary Artery Surgery Study (CASS) during a 15 year follow-up. In this study, subjects of the top heart rate quintile had a significantly higher risk for either all-cause mortality (HR = 1.32, CI = 1.19–1.47) or cardiovascular mortality (HR = 1.31, CI = 1.15–1.48) than subjects of the bottom quintile. High heart rate was also an independent predictor of time to rehospitalization. The strong predictive power of heart rate for mortality was found after adjustment for several other clinical variables and risk factors including hypertension, diabetes, smoking, number of diseased coronary vessels, and left ventricular function. It might be argued that in subjects with ischaemic heart disease the fast heart rate reflects a degree of left ventricular dysfunction. According to this view, the higher mortality rate among subjects with tachycardia would merely reflect congestive heart failure. However, in the Diaz et al. study, heart rate was an important predictor of all-cause and cardiovascular mortality in both subjects with and without left ventricular dysfunction. The better prognosis of the subjects with low heart rate was not due to a protective effect of beta-blockers, because the predictive value of heart rate for mortality was found also in the subjects not taking beta-blockers.

Another important finding of this study is that the predictive power of heart rate for mortality was equally strong in men and women. A gender-related difference in the association between heart rate and mortality has been found in some studies conducted either in subjects from general populations or in patients with myocardial infarction. In particular, in most studies high heart rate appeared to be a weak predictor of death from coronary artery disease in the female gender. The study by Diaz et al. performed in patients with stable coronary artery disease indicates that tachycardia can be deleterious also in the female gender and that also women might benefit from pharmacological cardiac slowing in this clinical setting.

A potential limitation of this as well as of other analyses which focused on heart rate as a risk factor for cardiovascular events is that resting heart rate was estimated from a single measurement. The authors themselves recognize that assessment of a patient’s heart rate...
rate with a single measurement is relatively crude and that their results may have underestimated the true relationship between heart rate and cardiovascular outcome. However, in the CASTEL study, we found that a single heart rate measurement was as good a predictor of outcome as a mean of three measurements.\(^5\) In the Diaz et al. study,\(^7\) heart rate measurement was based on a fairly good number of cardiac cycles, as the heartbeats included in a minute were averaged out. This may explain why a single casual heart rate measurement remained a strong predictor of future events. The association between heart rate and mortality was particularly strong for a heart rate $\geq 83$ bpm which corresponded to the lower limit of the top heart rate quintile. Although there are no objective data for establishing normal limits for this clinical variable, in studies performed in general populations or hypertensive subjects a value between 80 and 85 bpm has been considered as a reasonable cut-off level between normal and high heart rate.\(^8\) The 83 bpm cut-off identified by Diaz et al.\(^7\) is in keeping with previous results obtained in different clinical settings and confirm that values $> 80-85$ bpm should not be considered normal for resting heart rate. This implies that subjects with heart rate above that level could gain benefit from pharmacological interventions aimed at reducing heart rate.

Up to now, the effect of heart rate reduction by drug therapy in humans has been studied only in retrospective analyses using results from beta-blocker trials carried out in survivors of acute myocardial infarction or in patients with congestive heart failure.\(^8\) In both clinical settings, beta-blocking therapy was effective only in subjects with high heart rate at the baseline and was completely ineffective in those with low heart rate. In post-myocardial infarction patients, a favourable effect on cardiovascular mortality has been found also for non-dihydropyridine calcium antagonists and the data in the literature appear to establish that the efficacy of calcium channel blockers in these patients depends essentially on their effect on the sympathetic nervous system and heart rate.\(^8\) For calcium antagonists which increase the heart rate there was a trend toward increased mortality, while for those which decrease the heart rate the trend was toward a decrease in mortality, at least in the patients with normal left ventricular function and no evidence of pulmonary congestion.

Unfortunately, the effect of drugs with cardiac slowing properties has never been dealt with in randomised clinical trials performed in different clinical settings such as stable coronary artery disease or hypertension. Consequently, there is no evidence to show that reduction of high heart rate in these clinical conditions can confer additional benefit to that provided by standard treatment. However, the haemodynamic stress produced by an increase in heart rate causes a pronounced increase in cardiac work and oxygen consumption, a situation that is especially detrimental in individuals with ischaemic heart disease. A heart rate $> 80$ bpm was shown to facilitate the disruption of a coronary plaque whereas beta-blocking therapy exerted a protective effect.\(^9\) It is, thus, legitimate to assume that reduction of both components of the haemodynamic stress (heart rate and blood pressure) can be highly beneficial in the coronary patient. In spite of the above evidence, heart rate measurement has not yet become daily routine. Doctors are still reluctant to rely on a parameter that they consider "soft" for two main reasons: first, because heart rate is considered a poorly reproducible clinical variable, and secondly, because it is considered a mere marker of sympathetic activity rather than a cardiovascular risk factor \textit{per se}. That is why in the whole strategy of cardiovascular risk detection, little attention has been paid to the measurement of heart rate. However, the notion that tachycardia is transient has not been substantiated. Records of subjects with "hyperkinetic" circulation diagnosed at average age of 32 years in the Tecumseh study, show that they had reproducible tachycardia at 6 and 22 years of age.\(^10\) Today, a large body of evidence substantiates the concept that tachycardia is not only a marker of other cardiovascular risk factors but that increased frequency of cardiac beats causes additional cardiovascular damage mechanically. The results of the study by Diaz et al.\(^7\) suggest that this can occur also in subjects with ischaemic heart disease. In times of major health care budget burden, heart rate can be utilized with no additional costs to further stratify patients into risk categories who may benefit to a greater extent by preventive treatments.

References


