Resting heart rate and cardiovascular events: risk factor or risk marker?

Ker JA, MBChB, MMed(Int), MD
Faculty of Health Sciences, University of Pretoria
Correspondence to: Prof James Ker, e-mail: james.ker@up.ac.za

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Heart rate in epidemiological studies

Over the last 25 years numerous reports demonstrated a significant association between resting heart rate and all-cause mortality in addition to cardiovascular mortality.

Observational studies, such as the Framingham Heart study or the French IPC study showed that a high resting heart rate is associated with an increase in cardiovascular mortality in the general population[1,2] and this has also been demonstrated in hypertension, acute myocardial infarction and heart failure or left ventricular dysfunction.

Heart rate in coronary heart disease

A high resting heart rate in patients with known coronary artery disease is associated with an increase in cardiovascular mortality e.g. in the CASS-study of 24 913 patients with stable coronary artery disease followed up for a mean of 14.7 years.[3] Both all-cause and cardiovascular mortality were directly related to resting heart rate at study entry. This predictive capacity was independent of all cardiovascular risk factors, left ventricular ejection fraction and number of diseased coronary vessels.

Similarly, a high resting heart rate in patients presenting with a ST-segment elevation myocardial infarction (STEMI) increases the mortality.

It is possible that a high resting heart rate can increase shear stress and increase atherosclerostic plaque vulnerability and so cause plaque rupture.[4]

CRUSADE is a large observational study designed to promote evidence-based treatment of acute coronary syndrome. In 139 194 patients with a non-ST-segment elevated acute coronary syndrome (NONSTEMI), a clear J-shaped correlation was found between resting heart and all-cause mortality.[5] The lowest mortality rate were in patients with resting heart rates between 50 and 70 beats per minute, but mortality doubled when heart rate was below 50 beats/minutes.

Mortality was the lowest with a heart rate 50–60 beats/minute without beta-blockers, but doubled when heart rate reduction was achieved with beta-blockers in this group. If heart rate was < 100 beats/minute, reduction of heart rate with beta-blockers reduced mortality. Natural tachycardia (>100 beats/minute) was associated with an increase in mortality.

Heart rate in prediction scores

Resting heart rate is included in risk assessment for patients after acute coronary syndromes e.g. the Global Registry of Acute Coronary events (GRACE) risk prediction score. Heart rate, however, is not included in some widely used risk scores for cardiovascular disease.

The problem

Lowering heart rate could reduce mortality and so could lower cardiovascular events, but this has not been specifically investigated, because drugs that lower heart rate such as beta-blockers and non-dehydropyridine calcium channel blockers have also other cardiovascular actions that confound the results.

Effects on mortality reduction of beta-blockers among patients with acute myocardial infarction or heart failure have been amply demonstrated.

This reduction in mortality could at least in part be associated with the drug-mediated heart rate reduction, but beta-blockers have numerous other actions, some beneficial, some undesirable. Although the association of heart rate

and cardiovascular outcome is suggestive, it does not, by itself, prove causality.

Is there an optimal heart rate

Although heart rate varies widely, there is a pattern of distribution in different populations with segregated heart rate values of between 75 beats/minute and 85 beats/minute. From epidemiological data, it seems desirable to maintain heart rate in the normal rather then the high range. There seems to be a continuous increase in risk with increasing heart rate, at least for values above 60 beats/minute with no evidence of a threshold.

Role of a specific heart-rate lowering drug: Ivabradine

Ivabradine is a specific inhibitor of the *If* current in the sinoatrial node and is a pure heart-rate lowering agent in patients with sinus rhythm. Clinical investigation into heart-rate reduction is now possible with ivabradine. The antianginal and anti-ischaemic efficacy of ivabradine in patients was demonstrated in controlled clinical trials previously. In everyday practice, in the REDUCTION study, four months treatment of ivabradine in angina patients was associated with a reduction in heart rate, a reduction in angina pectoris attacks, a reduction in consumption of short-acting nitrates and was well tolerated.[6] Heart rate reduction by ivabradine in the ASSOCIATE study produced similar results.[7] This specific heart rate lowering drug has demonstrated the clinical benefit of specific heart rate lowering in the symptomatology of coronary artery disease patients. Ivabradine has a beneficial effect on ischaemia-related symptoms.[7]

In the BEAUTIFUL trial, the use of ivabradine in patients with coronary artery disease and a reduced left ventricular ejection fraction, when the heart rate was above 70/minute, reduced the secondary end points of admission to hospital with fatal and non-fatal myocardial infarctions and coronary revascularisations.[8]

Conclusion

The first well-established concept is that in the community, an increased resting heart rate is predictive of mortality and cardiovascular events and this association has no demonstrable threshold. Naturally occurring lower heart rates in the population at large are associated with improved general health (physical activity, not smoking, normal weight, healthy eating habits).

The next concept is that an increased heart rate is predictive of mortalility in cardiovascular diseases such as hypertension, heart failure and angina pectoris. A partial explanation of mortality reduction with beta-blockers for instance, relates to heart rate lowering. In patients with stable coronary artery disease, the relationship between elevated heart rate and long-term cardiovascular outcome is linear. Also, the specific heart-rate lowering drug, ivabradine, when used in stable coronary artery disease with angina, reduces ischaemic pain and reduces myocardial infarctions and revascularisations.

The next concept is the role of heart rate in acute coronary syndromes. With acute coronary events, heart rate on admission has a j-curve distribution in association with mortality. Heart rates at the extremes (< 50 beats/minute and > 100 beats/minute) are associated with poor in-hospital outcome in acute coronary events. Drug-lowering therapy achieving a heart rate of < 70 beats/minute but > 50 beats/minute will reduce patient mortality. All indications are that we should maybe start to pay more attention to resting heart rate in cardiovascular medicine as heart rate is indeed an independent risk factor.

Reference

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