Is heart rate a prognostic factor for cardiovascular disease?

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Many sophisticated techniques are employed in order to diagnose cardiovascular disease and assess long-term prognosis. It may be that the simple measurement of resting heart rate can provide useful prognostic information. Epidemiological studies show that a resting tachycardia is associated with increased risk of cardiovascular disease and sudden death. Elevated heart rate is also highly and independently predictive of 6-month and 1-year mortality following acute myocardial infarction. This article reviews some of these studies and supports the view that measurement of the heart rate at rest should be an integral and routine part of the clinical examination and that it should have a role in determining patient prognosis.

One of the most important undertakings in patients who present with symptoms of cardiovascular disease is to determine prognosis. Many clinical, angiographic, and hemodynamic variables are related to patient outcome. The complications of coronary artery disease (CAD) considered to constitute a "bad" prognosis vary, and include heart failure and myocardial infarction (MI), as well as reversible end points such as life-threatening arrhythmias, unstable angina, and need for revascularization.[1] The other patient population in whom risk assessment must be considered includes those who undergo health screening, perhaps as an occupational requirement—such as pilots—and particularly those with a family history of premature CAD, who have no manifest signs or symptoms, but who might be considered "at risk." Exercise electrocardiography remains the most reliable initial test both as a means to investigate stable chest pain (inducible ischemia) and as part of the medical workup in health screening. Findings from exercise testing, interpreted in conjunction with glucose, cholesterol, and other biochemical tests, and the presence or absence of classic risk factors such as hypertension, smoking, and obesity may be revealing. The diagnostic usefulness of exercise testing is limited, however, as sensitivity and specificity are inversely related, and affected by the population tested. Thus, false-negative responses are frequent in patients with clinically suspected CAD, and false-positive responses are frequent in asymptomatic patients.[2] That said, impaired chronotropic response to exercise,[3] or a delayed decrease in the heart rate recovery immediately after exercise, is a powerful predictor of overall mortality independent of workload, presence or absence or myocardial perfusion defects,

SELECTED ABBREVIATIONS AND ACRONYMS

(A)MI	(acute) myocardial infarction
BRHS	British Regional Heart Study
CAD	coronary heart disease
CARDIA	Coronary Artery Risk Development In young Adults
CASTEL	Cardiovascular Study in the ELderly
GISSI-2	Gruppo Italiano per lo Studio della Sopravivvenza nell'Infarto Miocardico II
IPC	Investigations Préventives et Cliniques

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and changes in heart rate during exercise in individuals who are candidates for coronary angiography.[4] How useful is resting heart rate prognostically in the healthy population and in those with a high likelihood of, or with confirmed CAD? In other words, is resting heart rate a useful clinical marker?

"NORMAL" HEART RATE

Among mammals, there is an inverse relationship between heart rate and life expectancy, that is, generally speaking, the faster the heart the shorter the life span.[5] For example, the giant (Galapagos) tortoise, with a heart rate of 6 beats per minute (bpm) can live up to 177 years, while a mouse, which ticks over at about 500 bpm, probably has a life expectancy of 1 year. Humans are said to have "stretched the boundaries of biology" to achieve a life expectancy of around 80 years. But what is a normal human heart rate? Normal sinus rhythm is generally regarded to range between 60 and 100 bpm, and is usually between 70 and 80 bpm.[6] Epidemiological studies show that a high resting heart rate is associated with an increased risk of development of hypertension, CAD, and sudden death (see reviews in references 7, 8, and 9), and that it may be sensible to redefine the threshold of tachycardia to around 85 bpm. Some of the more pertinent epidemiological studies will now be reviewed.

EPIDEMIOLOGICAL STUDIES OF HEART RATE

A number of studies have enrolled and followed healthy men and women over a course of years.

The Framingham Study

The Framingham Study,[10] which began in 1948, is probably the longest running prospective study of cardiovascular disease. Heart rates were determined at rest in all 5209 men and women entering the study. Analysis of the "heart rate effect" over 30 years in 5070 subjects, free of cardiovascular disease at entry, shows that rates tended to increase with age in both sexes, with rates in women exceeding those in men by 3 bpm. About 5% of heart rates were >95 and <60 bpm. While overall mortality increased progressively with resting heart rate (with no indication of "safe" or "hazardous" thresholds) in both young and old, the number of deaths at any heart rate was greater in men than in women. There was also a substantial excess in noncardiovascular death in the Framingham Study, and the authors commented that heart rate may be a nonspecific measure of health and mortality rates.

A further analysis from Framingham[11] looked at 2037 male and 2493 female participants who, at the time of examination, had a blood pressure level which exceeded 140/90 mm Hg. Over 36 years' follow-up, some 565 men and 367 women died from cardiovascular causes. Elevated blood pressure was positively correlated with heart rate. Adjusted for age and blood pressure, each 10-bpm increase in heart rate was associated with a 20% increase in overall mortality and a 14% increase in cardiovascular mortality in both sexes. Coronary mortality increased by 16% in men and 12% in women. Adjusting for coexisting risk factors and excluding those who died in the first 4 years of hypertension onset to eliminate those with rapid heart rates due to poor health did not substantially change the results. Increased heart rate, therefore, appears to be an independent risk factor for cardiovascular and coronary mortality in hypertension, and the effect is stronger for fatal than nonfatal events.

The British Regional Heart Study (BRHS)

This large prospective study[12] of middle-aged British men followed 7735 men aged 40 to 59 years drawn at random from age-sex registers in general practices, for a period of 8 years. It showed that, in men without preexisting 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 deaths, and sudden cardiac deaths *(Figure 1, see next page).* This association remained significant even after adjustment for age, systolic blood pressure (SBP), cholesterol, smoking, social class, heavy drinking, and physical activity, with a particularly high risk in those with heart rates >90 bpm. The increased risk in those with sinus tachycardia was five times higher than in those with heart rates <60 bpm.

Coronary Artery Risk Development In young Adults (CARDIA) study

The Coronary Artery Risk Development In young Adults (CARDIA) study examined whether baseline heart rate predicts subsequent blood pressure independently of baseline blood pressure.[13] This US longitudinal study involved 4762 black and white men and women between 18 and 30 years without any history of cardiovascular disease, in whom baseline heart rate and blood pressure measurements were performed and repeated at 2, 5, 7, and 10 years. Heart rate was shown to be an independent predictor of diastolic blood pressure (DBP) over the next 10 years in white men and women and black men, regardless of initial blood pressure and other potential confounders, with a 0.7-mm Hg increase per 10 bpm.

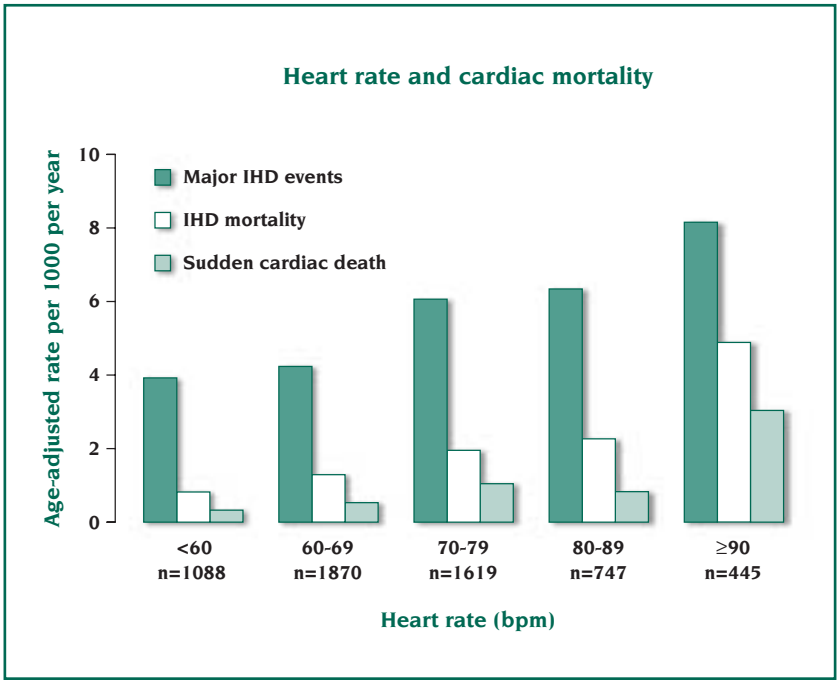

Figure 1. *Age-adjusted rates for major ischemic heart disease (IHD) events, mortality from IHD, and sudden cardiac death in men without preexisting IHD in five heart rate groups.*

Adapted from reference 12: Shaper AG, Wannamethee G, Macfarlane PW, Walker M. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. Br Heart J. *1993; 70:49-55. Copyright © 1993, BMJ Publishing Group.*

Thus, a high heart rate was considered a risk factor for development of high DBP in young adults. The authors suggest that some individuals who develop hypertension have increased sympathetic tone (manifested by higher heart rates prior to blood pressure elevation), which can lead to smooth muscle cell proliferation, with subsequent reduced compliance of the peripheral vasculature and, consequently, raised DBP.

Centre d'Investigations Préventives et Cliniques (IPC) Study

A larger study[14] conducted at the Centre d'Investigations Préventives et Cliniques (IPC) in Paris assessed the effects of high heart rate on mortality in different subgroups in a "relatively low-risk" French population according to age, gender, and blood pressure levels. They studied 19 386 subjects (12 123 men and 7263 women) aged 40 to 69 years undergoing routine health checks. Heart rates (HR) were divided into four groups (HR1 <60 bpm; HR2 = 60-80 bpm; HR3 = 81-100 bpm; HR4 >100 bpm), and mortality was recorded over the subsequent 20 years. Heart rate was shown to be an independent predictor of all-cause mortality for both genders and for cardiovascular mortality in men, the explanation for which "remains unclear." Higher heart rate was associated with higher blood pressure and plasma cholesterol. In men, the relative risk for cardiovascular death after adjustment for age and other risk factors, in the HR2, HR3, and HR4 groups was 1.35, 1.44, and 2.18, respectively, when compared with HR1. Heart rate did not influence cardiovascular mortality in women, which may be explained by the relatively small number of cardiovascular deaths in the female population.

Spandau Health Test

The Spandau Health Test[15] involved a survey among 1827 men and 2929 women aged 40 to 80, followed for 12 years, but in total some 6410 participants had at least one primary health record and a follow-up. Participants were examined on average three times. An almost linear increase in all-cause mortality with initial heart rate was observed for men. An increase in the age-standardized all-cause and cardiovascular mortality rates *(Figure 2)* was also seen in men, but only in 60-to-80-year-old women, whereas in women with heart rates <70 bpm no cardiovascular mortality was noted. Again, low mortality rates are probably responsible for the absence of an association between heart rate and overall cardiovascular death in women. No significant association between heart rate and cancer was seen. The authors commented that the observed difference of about 3 to 5 bpm between former East Germany (which has higher mortality) and West Germany may partly explain the discrepancies in life expectancy between the two parts of Germany.

Cardiovascular Study in the ELderly (CASTEL)

The Cardiovascular Study in the ELderly (CASTEL) investigated whether a high heart rate is associated with mortality in elderly men and women.[16] The study was carried out in 763 men and 1175 women aged 65 or older, with a 12-year follow-up. It showed that an elevated heart rate is a strong predictor of cardiovascular death in elderly men. Its predictive power is greater than that of the classic risk factors. This effect was greater in men, but the association was not statistically significant in women. The authors

suggest that heart rates >80 bpm should be "considered hazardous" in elderly men.

POST–MYOCARDIAL INFARCTION PATIENTS

Hjalmarson et al[17] studied 1807 patients admitted with acute myocardial infarction (AMI) and the relationship of heart rate to in-hospital mortality, post-discharge mortality, and total mortality from day 2 to 1 year in patients with and without heart failure. Both in-hospital and post-discharge mortality increased with increasing admission heart rate, and total mortality (day 2 to 1 year) was:

- 15% for admission heart rates 50-60 bpm;
- 41% for heart rates >90 bpm;
- 48% for heart rates >100 bpm.

Severe heart failure carried a worse prognosis, and mortality was high regardless of admission heart rate. In patients with less severe heart failure, cumulative mortality for patients with admission heart rate >90 bpm was over twice as high as those with admission heart rates <90 bpm (39% vs 18%, respectively). The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio II (GISSI-2) database[18] allowed the reevaluation of the prognostic significance of different levels of heart rate in a large number of patients all treated by thrombolysis. Heart rate values were available at entry for 8915 (in-hospital phase) and at discharge for 7831 patients. There was a progressive increase in mortality with increasing heart rate in the overall population from 7.1% for heart rates <60 bpm to 14.3% for heart rates >100 bpm. Similar to the data from the entry readings, a progressive increase in 6-month mortality with increasing heart rate was seen at discharge, from 0.8% for heart rates <60 bpm to 14.3% for heart rates >100 bpm. Multivariate analysis confirmed the independent prognostic significance of heart rate.

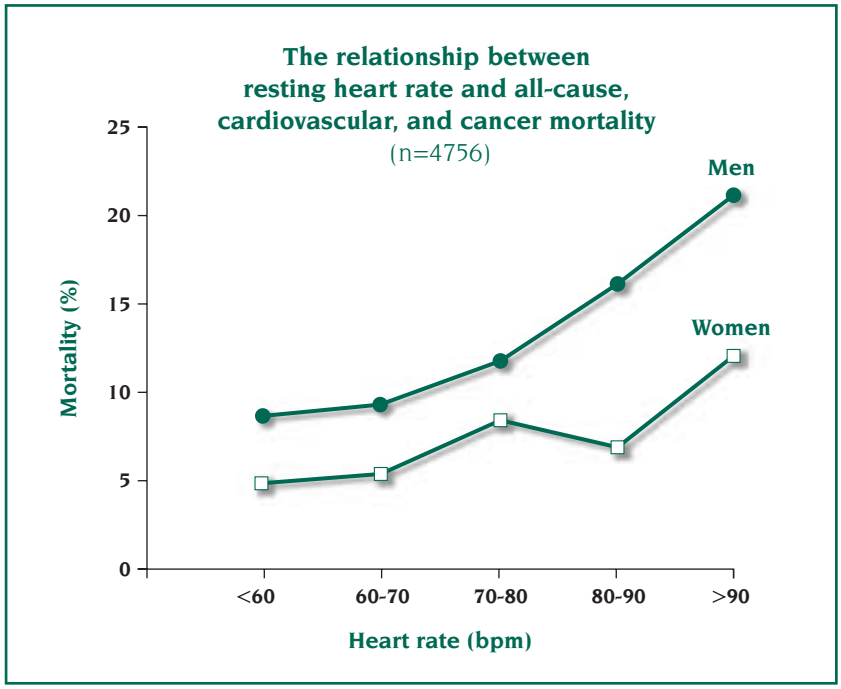

Figure 2. *All-cause mortality for 12 years against resting heart rate levels in men and women aged 40 to 80 years (n=4756).*

Adapted from reference 15: Mensink GBM, Hoffmeister H. The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. Eur Heart J. *1997;18:1404-1410. Copyright © 1997, European Society of Cardiology.*

In a smaller study[19] of 576 MI survivors who were followed for 2 years, both heart rate and heart rate variability were stronger predictors of mortality than ejection fraction. Further mechanistic insights were provided by another small study[20] of 56 men below the age of 45 years who survived AMI, which showed that high heart rate correlated positively with angiographic scores of global severity of diffuse atherosclerosis and stenoses, independently of other risk factors.

DISCUSSION

Some of the many epidemiological studies that involved baseline measurement of the heart rate taken from a standard resting 12-lead ECG, ambulatory Holter ECG, or some other technique, have been reviewed. A consistent finding in these studies is that among subjects who were apparently well on entry, the resting heart rate is a sensitive independent marker of cardiovascular disease. In some studies, the relationship is more robust for men than for women, in whom (in the population studied) the disease prevalence may be lower. In males, resting tachycardia in particular has been shown to be a strong, independent predictor of cardiovascular death, which persists into old age. High heart rates are also associated with the development of hypertension and are an ominous finding in both sexes. Heart rate is also a strong predictor of mortality in men and women after AMI, and this is compounded by congestive heart failure and other complications of infarction.

Figure 3. *Perhaps we should take a lesson from the physicians of the past on the merits of the resting pulse rate. All rights reserved.*

It seems sensible to revise the normal limits of heart rate. It is regrettable that heart rate, even though it is simple, inexpensive, and easily measured, has become somewhat clinically neglected in favor of more sophisticated noninvasive techniques. Perhaps we should look to the wise physicians of the past *(Figure 3)* who held that there is no substitute for a good medical history and physical examination and who could not resort to "hi-tech" investigations.

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