

Relation of Heart Rate at Rest and Long-Term (>20 Years) Death Rate in Initially Healthy Middle-Aged Men

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The prognostic implications of heart rate (HR) change over years have never been assessed. It was hypothesized that an increase in HR in apparently healthy persons observed over years could be associated with an increase in mortality risk and conversely. A total of 5,139 asymptomatic working men (aged 42 to 53 years) free of clinically detectable cardiovascular disease were recruited from 1967 to 1972 and had their HRs measured at rest in standardized conditions every year for 5 consecutive years. HR change was defined as the difference between HR at examination 5 and HR at inclusion, and subjects were divided into tertiles according to decrease >4 beats/min, unchanged (from -4 to +3 beats/min), and increase >3 beats/min. After >20 years of mortality surveillance, 1,219 deaths were observed. After adjustments were made for confounding factors, including baseline HR at rest, and compared with subjects with unchanged HRs, subjects with decreased HRs during the 5 years had a 14% decreased mortality risk (RR 0.86, 95% confidence interval 0.74 to 1.00, $p = 0.05$), whereas subjects with increased HRs during the 5 years had a 19% increased mortality risk (RR 1.19, and 95% confidence interval 1.04 to 1.37, $p < 0.012$). In conclusion, change in HR at rest over 5 years was an independent predictor of mortality in middle-aged men. © 2009 Published by Elsevier Inc. (Am J Cardiol 2009;103:279–283)

Heart rate (HR) is under the control of the autonomic nervous system and is regulated according to different mechanisms, such as physical activity, ventilation, anxiety, myocardial contractility and capacitance, and vascular bed resistance.^{1–4} To the best of our knowledge, the prognostic value of change in HR at rest over years has never been assessed.^{5–13} If a decrease in HR observed in healthy subjects over years was associated with a decrease in mortality and, conversely, an increase in HR was associated with an increase in mortality, it would be an additional step toward the potential association between HR and mortality. Moreover, it could help identify high-risk subjects easily.

The aim of this study was to assess whether change in HR at rest observed during 5 years was associated with change in later mortality risk.

Methods

Recruitment, design, and procedures of the Paris Prospective Study 1 have been described elsewhere.^{14,15} Briefly, the consecutive examination of 7,746 native Frenchmen employed by the Paris Civil Service and aged 42 to 53 years was carried out from 1967 to 1972. Oral informed consent was given by each subject, and the research protocol was

approved by the appropriate institutional board (Commission Nationale Informatique et Liberté). This sample consisted of 93.4% of the total number of employees in early 1967 who were born in 1917 to 1928. Subjects had electrocardiograms and physical examinations conducted by a physician, provided blood samples for laboratory tests, and answered questionnaires administered by trained interviewers. HR at rest was determined by measurement of the radial pulse during a 1-minute recording after a 5-minute rest in a supine position. Diabetes mellitus was defined as past or present reported diabetes, regardless of whether treated.

Subjects with known or suspected cardiovascular disease of any grade or cause or with any of the conditions of systolic blood pressure at rest >180 mm Hg or abnormality in 12-lead standard electrocardiogram at rest (Minnesota code) were excluded from the study. Ventricular function was not assessed. Subjects were invited to return every year for 4 additional examinations that were performed in the same baseline standardized conditions. Only subjects who completed examination 5 were considered for the present analysis. Therefore, numbers of subjects were different compared with those from previous publications that considered all subjects without prevalent cardiovascular condition at inclusion.^{12,14–16}

Until retirement, the administrative department in charge of the study population provided a list of subjects who died annually. All available data relevant to the causes of death were collected from specific inquiries, such as medical records from hospital departments or general practitioners. Data were then reviewed by an independent medical committee. After retirement, causes of death were obtained from death certificates. The end of follow-up was January 1, 1994. Vital status could not be determined for 355 subjects (4.6%).

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Table 1

Baseline characteristics of men by tertiles of heart rate (HR) at inclusion in the Paris Prospective Study 1

Variable*	HR Tertiles (beats/min)			p Value [†]
	<64 (n = 1,703)	64–70 (n = 1,581)	>70 (n = 1,855)	
Age (yrs)	47.6 ± 2.0	47.5 ± 2.0	47.6 ± 1.9	0.89
Body mass index (kg/m ²)	25.7 ± 2.9	26.1 ± 3.1	26.0 ± 3.4	0.0005
Tobacco consumption (g/d)	10.5 ± 9.7	10.7 ± 10.2	12.0 ± 10.6	0.0001
Current sport activity*	18% (303)	14% (220)	13% (242)	0.0001
Diabetes mellitus*	0.6% (10)	1.2% (19)	2.1% (38)	0.0001
Systolic blood pressure (mm Hg)	134 ± 18	138 ± 19	146 ± 22	0.0001
Diastolic blood pressure (mm Hg)	77 ± 12	78 ± 12	83 ± 14	0.0001
Total cholesterol (mg/dl)	218 ± 42	222 ± 40	227 ± 44	0.0001

Data expressed as mean ± SD for continuous variables and percent (number) of positive answers for categorical variables. Tobacco consumption refers to mean consumption in grams per day during the last 5 years.

* Categorical variables.

[†] Analysis of variance and chi-square trend tests for continuous and categorical variables, respectively.

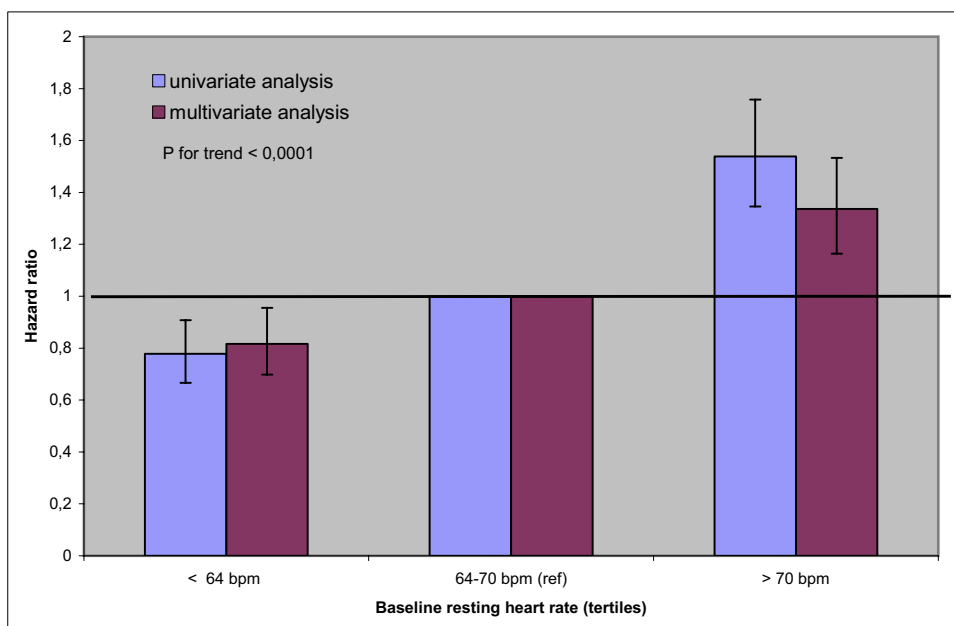


Figure 1. Hazard ratios and 95% CIs in univariate analysis and after adjustments for age, tobacco consumption, current sport activity, diabetes, body mass index, systolic blood pressure, and cholesterol. The second tertile is the reference (ref) group. bpm = beats per minute.

Baseline characteristics of the 355 subjects lost to follow-up and those who did not complete examination 5 were not substantially different from the remaining 5,139 men studied in the present analysis. Baseline HR at rest was divided into tertiles. Because a large number of subjects had a round value of HR at rest, the number of subjects by tertiles was lightly unbalanced. HR change was defined as the difference between HR at rest at examination 5 and HR at rest at examination 1 and was also divided into tertiles. Baseline characteristics of subjects were compared across tertiles of HR at rest and tertiles of changes in HR at rest using univariate analysis of variance or Cochran-Armitage trend test for continuous and categorical characteristics, respectively. For the latter comparisons, adjustment was made for baseline HR at rest to take into account regression toward the mean.

Survival analyses were performed using the Cox proportional hazard model to test the potential association between total mortality and HR at rest and HR evolution, first separately and then simultaneously. For the HR at rest survival study, relative risks of mortality in tertiles 1 and 3 (vs tertile 2) were estimated without and with adjustment for “usual” risk factors (i.e., age, body mass index, tobacco consumption, current sport activity, diabetes status, systolic blood pressure, and total cholesterol). For the HR evolution survival study, adjustments were made for baseline HR at rest in addition to the set of usual risk factors (as listed). Kaplan Meier survival curves were built on categories combining tertiles of HR at rest and tertiles of change in HR (9 categories), and survival was compared using log-rank test. All analyses were performed using Statistical Analysis System, version 9.1 (SAS Institute, Cary, North Carolina), and p values were 2 sided.

Table 2
Main characteristics of men according to heart rate (HR) change after 5 years of follow-up in the Paris Prospective Study 1

Variable*	HR Change (beats/min)			p Value†
	Decreased (>4) (n = 1,515)	Unchanged (−4 to +3) (n = 1,741)	Increased (>3) (n = 1,883)	
Age (yrs)	47.3 ± 1.9	47.6 ± 2.0	47.7 ± 2.0	0.0001
Body mass index (kg/m ²)	25.8 ± 2.9	25.9 ± 3.0	26.1 ± 3.3	0.05
Tobacco consumption (g/d)	10.3 ± 9.6	10.8 ± 10.3	12.1 ± 10.5	0.0001
Current sport activity*	15.4% (193)	14.3% (209)	13.9% (216)	0.001
Diabetes mellitus*	1.6% (20)	1.4% (20)	0.9% (14)	0.89
Systolic blood pressure (mm Hg)	136 ± 19	139 ± 20	143 ± 21	0.0001
Diastolic blood pressure (mm Hg)	77 ± 12	79 ± 13	82 ± 14	0.0001
Total cholesterol (mg/dl)	220 ± 41	223 ± 40	224 ± 42	0.03

Data expressed as least-squares mean ± SE for continuous variables and percent (number) of positive answers for categorical variables. Tobacco consumption refers to mean consumption in grams per day during the last 5 years.

* Categorical variables.

† Analysis of variance and chi-square trend tests for continuous and categorical variables after adjustment for HR at rest, respectively.

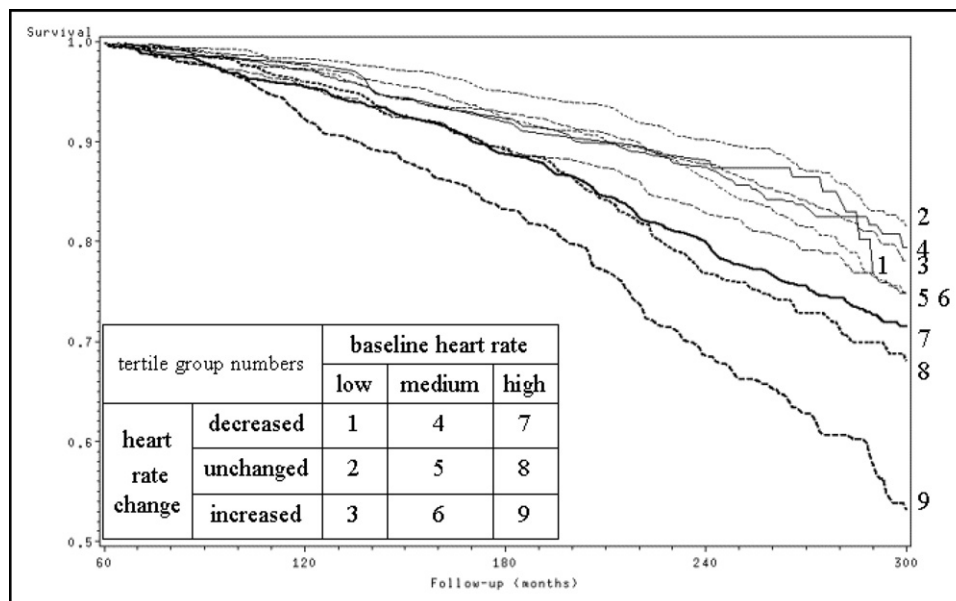


Figure 2. Survival curves of follow-up in the Paris Prospective Study 1 over 20 years are Kaplan-Meier estimates for the 3 × 3 tertile groups of baseline HR and HR change after 5 years of follow-up.

Results

In the 5,139 men during the 23 years of follow-up, there were 1,219 deaths (23.7%) from all causes. Characteristics of subjects are listed in Table 1 according to baseline HR at rest. HR at rest was positively associated with levels of all risk factors and negatively associated with current sport activity, whereas no relation was found with age.

As shown in Figure 1, mortality risk increased progressively with level of HR at rest in univariate analysis and after adjustment for age, tobacco consumption, current sport activity, diabetes status, body mass index, systolic blood pressure, and serum cholesterol.

Baseline characteristics of subjects are listed in Table 2 according to HR change after 5 years after adjustment for baseline HR at rest. The average HR for the entire population of 5,139 subjects was unchanged after the 5-year follow-up (mean of the difference -0.24 ± 10.1 beats/min;

$p = 0.86$). Baseline age, body mass index, tobacco consumption, systolic and diastolic blood pressure, and cholesterol were lower in subjects with decreased HR after the 5 years (decrease >4 beats/min), intermediate in subjects with unchanged HR (from -4 and $+3$ beats/min), and higher in subjects with increased HR (increase $>+3$ beats/min). The opposite relation was observed for current sport activity.

After adjustments were made for confounding factors and baseline HR at rest and compared with subjects with unchanged HR, subjects with decreased HR during the 5 years had a 14% decreased mortality risk (RR 0.86, 95% confidence interval [CI] 0.74 to 1.00, $p = 0.05$), whereas subjects with increased HR during the 5 years had a 19% increased mortality risk (RR 1.19, 95% CI 1.04 to 1.37, $p < 0.012$). This was observed for both cardiovascular and noncardiovascular mortality (data not shown).

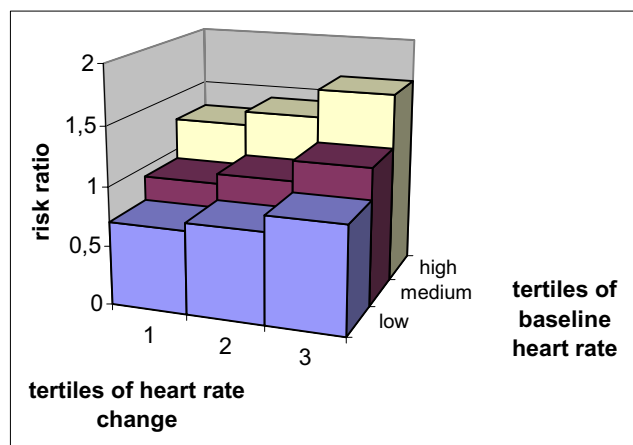


Figure 3. RRs of global mortality according to HR at rest at inclusion and HR change after 5 years after adjustment for the usual risk factors. The central group (i.e., tertile 2 for both variables) is the reference. Tertiles of baseline HR are defined as low (<64 beats/min), medium (64 to 70 beats/min), and high HR (>70 beats/min). Tertiles of HR change are tertile 1, decrease >4 beats/min; tertile 2, -4 to +3 beats/min; and tertile 3, increase >3 beats/min.

Kaplan-Meier survival curves according to tertiles of HR at rest and tertiles of HR change combined together showed that mortality rates were different among the 9 groups ($p < 0.01$; Figure 2). Subjects with both high HR at rest at baseline and an increase during the 5 years showed the worst survival rate (group 9).

Figure 3 shows multivariate RRs for mortality associated with both baseline HR at rest and HR change over 5 years using subjects with medium HR at rest at baseline and unchanged HR after 5 years as the reference group. RRs increased with level of baseline HR at rest and its increase after 5 years. Subjects with a low baseline HR at rest and decreased HR during the 5 years had the lowest mortality risk (RR 0.71, 95% CI 0.56 to 0.89, $p = 0.003$), whereas subjects with a high HR at rest at baseline and increased HR during the 5 years had a higher mortality risk (RR 1.64, 95% CI 1.34 to 2.00, $p < 0.0001$). To take into account possible changes observed during this 5-year period in levels of confounding risk factors, we performed additional adjustments for changes during the 5 years in blood pressure, tobacco consumption, body mass index, and cholesterol level. Similar results were observed (data not shown).

Discussion

The present findings, collected in a large cohort of apparently healthy subjects, indicated that HR at rest and its change over 5 years were both predictors of mortality independently from the standard cardiovascular risk factors. The high variability in HRs between subjects and within subjects over time decreased the statistical power. Therefore, it was likely that the observed association between mortality and these markers was underestimated. Whether this association was causal is an issue that has to be addressed.

The association between high HR at rest and mortality was consistent with data already published in epidemiologic studies with different designs and populations.⁵⁻¹³ A high

HR at rest could reflect underlying abnormalities. It can be a marker of autonomic imbalance, a term used to describe abnormalities in the balance between vagal and adrenergic tone, and autonomic imbalance, whether caused by vagal withdrawal, adrenergic overdrive, or both, was associated with higher mortality risk.^{17,18} Moreover, high HR at rest could reflect poor functional capacity and, indirectly, low socioeconomic status. These conditions together were associated with increased mortality in cardiovascular patients.¹⁹ This association was probably also observed in asymptomatic subjects with greater exposure to tobacco and less possibilities for safe outdoor exercise, 2 factors usually associated with level of HR at rest.

That a high level of HR at rest was associated not only with cardiovascular mortality, but also with noncardiovascular mortality, was not specific to our study and indicated that this association was not restricted to cardiovascular mechanisms only. A high HR at rest could also be a marker of increased risk of developing hypertension, as recently suggested in a Japanese cohort.²⁰

We found that change in HR over a 5-year period conferred additional information beyond HR at rest and the usual risk factors. Associations might be caused by changes during the 5 years in other risk factors. However, this possibility was minimized because results were unchanged after adjustment for these changes, including blood pressure. The regression toward the mean, as in subjects with a high level of a biologic variable were more likely to have a lower level at a second examination, might also have been involved. To account for this phenomenon, we adjusted for baseline HR at rest. The potential effect of β -blocking agents deserved some comment. These medications might be responsible for the decrease in HR observed over 5 years and subsequently for the risk reduction in mortality observed in subjects with a decreasing HR after 5 years. However, use of such treatment in the present study was likely to be small, and as a result, the net effect on mortality risk reduction should be marginal for the following reasons. At the time of the study in the late 1960s, these medications were seldom used. In addition, cut-off values for prescribing blood pressure-lowering agents, such as β -blocking agents, were much higher at the time of the study than currently. Last, subjects with decreased HR already had lower blood pressures than others and were consequently less likely to receive antihypertensive treatment. One question is whether there was a threshold level for the HR higher or lower than that at which the risk changed abruptly. Our results did not support this issue for either HR at rest or its 5-year change. When we used cut-off values other than tertiles for determination of HR change (arbitrary 5 or 10 beats/min), similar results were observed.

Increased HR could be a causal risk factor for mortality. Increased HR increases mechanical stress on the arterial wall and heart, and it was suggested that HR could be involved in the development of coronary atherosclerosis in primates²¹⁻²³ and humans.²⁴ There was also the very intriguing hypothesis about the possible universal relation between biologic scaling and mortality that linked HR and life span in mammals.²⁵⁻²⁷

Our present results were based on observational (although prospective) data, and to go through causality, the

next step should be an interventional trial aimed at investigating whether an induced HR decrease is associated with a decrease in mortality risk.

The present study had some limitations that should be emphasized. Although change in risk factor level of major confounders was controlled for, change in risk factor level after year 5 of examination was not available or controlled for.

The present association between increased HR and mortality might reflect the presence of underlying cardiac failure at inclusion. Echocardiography was not available and/or routinely performed at the time of the study in the late 1960s. However, the young age and the nature of the population (healthy policemen) suggested that the prevalence of heart failure, if any, was very low and thus had a marginal effect on our results. Our population consisted of asymptomatic men considered healthy employed by the Paris Civil Service by the end of the 1960s. Socioeconomic status, prevalence of smoking, extent of alcohol use, and other factors might differ from those of the general population. Therefore, the extent to which the present findings could be generalized in a more unselected and/or recent population cohort was unclear. Particularly, we did not know whether our results could apply in women, although the association between increased HR and increased mortality also was observed.¹³

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