High Heart Rate

A Risk Factor for Cardiovascular Death in Elderly Men

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Objective: To examine the association between heart rate and 12-year incidence rates of total and cardiovascular death in a cohort of elderly subjects stratified by sex.

Subjects and Methods: The study was carried out in 763 white men and 1175 women aged 65 years or older who were participating in the Cardiovascular Study in the Elderly. Subjects were divided into quintiles of heart rate; the top quintile comprised those with a heart rate of greater than 80/min and the bottom quintile, those with a heart rate of less than 64/min.

Results: In the men, the number of deaths from cardiovascular causes was significantly increased in those in the top quintile of heart rate (crude relative risk, 1.55) but decreased in those in the bottom quintile (crude relative risk, 0.65). Similar relationships were found in the women, but the associations did not reach statistical significance (all-cause, \( P = .11 \); cardiovascular, \( P = .15 \)). After adjustment for baseline age, body mass index, hypertension, diabetes mellitus, angina or previous myocardial infarction (coronary heart disease), regular medication, lipid levels, smoking, alcohol intake, forced expiratory volume in 1 second, and other confounders, the relative risk for cardiovascular death in the men was 1.38 (95% confidence interval, 0.94-2.03) for the subjects in the top quintile of heart rate and 0.82 (95% confidence interval, 0.52-1.28) for those in the bottom quintile. In the Cox analysis, predictors of time to cardiovascular death were heart rate (\( P < .001 \)), age (\( P < .001 \)), coronary heart disease (\( P < .001 \)), clinical heart failure (\( P = .001 \)), diabetes mellitus (\( P = .001 \)), hypertension (\( P = .02 \)), and triglyceride levels (\( P = .04 \)), whereas total (\( P = .20 \)) and high-density lipoprotein-cholesterol (\( P = .21 \)) levels and smoking (\( P = .74 \)) were found to be nonsignificant by the model. The heart rate–cardiovascular death association held true when subjects who died in 2 years after enrollment were excluded (\( P = .008 \)).

Conclusions: An elevated heart rate may be a strong predictor of cardiovascular death in elderly men. Conversely, a low heart rate is related to a better outcome in these subjects.

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THE RESULTS of several landmark epidemiological studies carried out in diverse population settings showed cigarette smoking, high blood pressure (BP), serum cholesterol levels, and diabetes mellitus to be strongly associated with all-cause and coronary heart disease (CHD) mortality rates. In recent years, evidence has been accumulating that a high heart rate is also an important risk factor for cardiovascular and noncardiovascular death in middle-aged persons, even though its prognostic importance has been overlooked by the scientific community and is still ignored by physicians. Clarifying whether a high heart rate is a risk factor for death remains important also in the growing population of elderly persons in industrialized countries. This is of particular interest because some risk factors for atherosclerosis, such as the total cholesterol level, smoking, and obesity, tend to lose their predictive power for morbidity and death in old age. Sex differences in the effects on mortality of a potentially modifiable risk factor such as the heart rate are also important to examine.

We undertook this study to investigate whether a high heart rate is associated with mortality in elderly men and women from the Cardiovascular Study in the Elderly (CASTEL). The secondary goal of the study is to verify, if there is an effect of the heart rate on mortality, whether this is equally distributed throughout the heart rate range or whether there is a threshold level beyond which the relationship becomes apparent.

RESULTS

Of the 2254 men and women, 226 were excluded because of missing data on relevant variables. Eighty-eight subjects with atrial fibrillation, atrial flutter, multifocal atrial tachycardia, and second-degree atrioventricular block and 2 subjects with pacemakers were also excluded, leaving 1938 subjects (763 men and 1175 wom-
SUBJECTS AND METHODS

SUBJECTS

The study cohort consisted of 2254 persons (855 men and 1399 women), aged 65 years or older, participating in the CASTEL, a prospective study conducted in the rural town of Castelfranco Veneto, northeast Italy. The selection of this cohort, methods of examination, and follow-up procedures have been described previously in detail. Briefly, the target population was noninstitutionalized subjects aged 65 years and older (N = 3088) domiciled in Castelfranco Veneto. Baseline examinations began at the end of 1983 and were essentially completed within 24 months (from December 1, 1983, through December 31, 1985). Subjects were invited by mail to participate. Those not replying to the invitation were reinvited by telephone, mail, or home visitation at a later date. Finally, 73% of the subjects agreed to participate in the study. Respondents came to the office for a medical examination and completed the survey questionnaire (lasting about 30 minutes) administered by a trained volunteer interviewer. All respondents gave informed consent after the nature of the procedures had been fully explained.

MEDICAL EXAMINATION

The medical examination included anthropometric measurements, resting blood pressure, heart rate, electrocardiography (Minnesota code10) and peak expiratory flow rate, all according to Rose et al.,11 and venipuncture for the measurement of serum glucose, total and high-density lipoprotein (HDL)-cholesterol, triglyceride, potassium, creatinine, and uric acid levels. In subjects with hypertension, all measurements were performed after antihypertensive therapy, if any, had been withdrawn for at least 2 weeks. Thus, no subject was receiving β-blocker or calcium-antagonist therapy at the baseline evaluation. The survey questionnaire included measurements of chest pain; claudication; smoking habits; alcohol consumption; family history; medications; history of major chronic conditions diagnosed by a physician, including hypertension (and its current treatment status); diabetes mellitus; CHD; stroke; heart failure; and cancer. A history of CHD was determined by the physician (E.C.) using a standardized Rose questionnaire.11 Information was verified with electrocardiography, hospital discharge data, and information from the general practitioners. Coronary heart disease was assumed to be present when a history of either myocardial infarction or angina pectoris was established. The subjects were asked to indicate their usual pattern of physical activity, which included regular walking or cycling, recreational activity, and sporting activity. On the basis of the interview, they were defined as sedentary (no physical activity) or active. The follow-up, which lasted 12 years, included the collection of all admission and discharge data at the hospital. The vital status of each participant was ascertained by annual contact with the participants or a proxy informant. Cause of death was categorized as cardiovascular or other. Cardiovascular death included death from CHD, sudden death, congestive heart failure, pulmonary embolism, and stroke. All events were verified by a review of hospital medical records. Death certificates were obtained for all decedents and coded for the underlying cause of death by a single nosologist (E.C.).

The BP and heart rate were measured in triplicate after the participants had been lying for 15 minutes. The BP was measured with the auscultatory method. Standard cuffs with an inflatable bladder 24 cm long and 12 cm wide were used for most participants. If the arm circumference exceeded 31 cm, a 35 × 15-cm bladder was used. The heart rate was measured by palpating the radial pulse for 60 seconds. For the analysis, the mean of the second and third measurements was used. To investigate whether single measurements have the same predictive value as multiple measurements, the single measurements were used in the Cox analyses.

CLINICAL CHARACTERISTICS

BY QUINTILE OF HEART RATE

To illustrate the relation between the heart rate and age, body mass index, systolic BP, diastolic BP, blood lipid levels, glucose level, and uric acid level, we have also presented the means of these factors by the quintile of heart rate (Figure 1). Age was unrelated to heart rate in both sexes. Systolic and diastolic BPs and blood lipid levels progressively increased with increasing heart rate in both sexes, whereas triglyceride levels increased only in the men. No consistent association was seen with total and HDL-cholesterol and uric acid levels (data not shown).

HEART RATE LEVELS AND MORTALITY

During the follow-up of 12 years, 408 of the 763 men died of all causes. Of these deaths, 200 were attributed to cardiovascular disease causes (23 sudden deaths); 119 deaths to cancer and 89 deaths to other noncardiovascular disease causes. Among the 1175 women, 403 died of all causes.
The forced expiratory volume in 1 second (FEV₁) was measured using a spirometer (Vitalograph Ltd, Buckingham, England) with the subject seated. Two consecutive readings were made, and the mean of these 2 readings was used. The FEV₁ values were expressed as a percentage of individual theoretical values calculated for each subject according to Cherniack and Raber. The study was approved by the CASTEL ethics committee. The procedures followed in this study were in accordance with institutional guidelines.

STATISTICAL ANALYSIS

Statistical analysis was carried out using a commercial software package (Biomedical Data Package, New System for Windows, Version 1.1, Los Angeles, Calif). Differences in mean values were tested with an unpaired Student t test. Between-quintile comparisons were performed using an analysis of variance. Proportions were compared using the χ² test. Variables significantly associated in univariate correlation analysis with heart rate were entered as independent variables in a forward-stepwise multiple regression analysis, with heart rate as the dependent variable (minimum tolerance for entry into model, .01; α to enter and α to remove, .15).

Heart rate was divided into quintiles, and then mortality rates were computed within each quintile. Because mortality was similar in the second, third, and fourth quintiles, these 3 quintiles were grouped together. The odds of death for the low and high heart rate groups relative to the intermediate heart rate group were computed based on logistic regression models. Relative odds and corresponding 2-sided 95% confidence intervals were derived from the regression coefficients in the logistic model.

The associations between heart rate and time to death from cardiovascular, noncardiovascular, and all causes were analyzed separately in the 2 sexes, first using the Kaplan-Meier life table procedure. The associations between heart rate and time to death with other variables controlled were then assessed using the Cox proportional hazards regression model. Analyses were performed using a significance level of α = .05 (2-sided). Age; body mass index (calculated as weight in kilograms divided by the square of the height in meters); total serum cholesterol, HDL-cholesterol, triglyceride, glucose, uric acid, and creatinine levels; and the FEV₁; were fitted as continuous variables. The categorical variables were grouped into classes in which smoking, having diabetes mellitus, preexisting CHD, clinical heart failure, bundle branch block on electrocardiography, history of stroke, intermittent claudication, and sedentariness were scored 1, and the lack of this status was scored 0. Heart rate and hypertension were used through indicator variables. Subjects were classified as having a low heart rate (bottom quintile), intermediate heart rate (3 middle quintiles), or a high heart rate (top quintile). On the basis of their BP level, subjects were classified as normotensive (BP < 140/90 mm Hg), borderline hypertensive (systolic BP between 160 and 140 mm Hg and/or diastolic BP between 90 and 94 mm Hg), or hypertensive (systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 95 mm Hg and/or the use of antihypertensive medication). The BP was examined also as a continuous variable. The variable alcohol use was fitted using 5 indicator variables (for the 6 alcohol groups: 0 g/wk, < 200 g/wk, 200 to < 500 g/wk, 500 to < 1000 g/wk, 1000 to < 1500 g/wk, and ≥ 1500 g/wk). Regular medication use was entered by 2 indicator variables for 3 classes: “none,” “antihypertensive drugs,” and “other medication.” All available risk factors were entered into a first model. This model was reduced by removing the variable causing the least change in significance. This procedure was continued until no further variables could be removed without producing a substantial change of the model. Subsequently, a final model was developed in which the heart rate was entered as the first variable and then was adjusted for all the other variables that were found to be significant in the previous backward-elimination model.

Data are presented as mean ± SD. All P values are 2-tailed. Statistical significance was established at P < .05.

Of these deaths, 211 were attributed to cardiovascular disease causes (33 sudden deaths); 85 deaths were attributed to cancer and 107 to other noncardiovascular disease causes. Table 3 shows the relation between the heart rate and all-cause and cardiovascular mortality by quintiles of heart rate. In the men, the all-cause mortality tended to increase with increasing heart rate, with small differences in the 3 middle quintiles. The increased risk in total mortality was largely due to a significant increase in cardiovascular mortality. Also, for cardiovascular mortality, there was little difference between the 3 middle quintiles, but risk was significantly elevated in the top quintile and significantly reduced in the bottom quintile. This trend was particularly clear for sudden death. Little difference was found between the heart-rate quintiles for cancer mortality and death from other noncardiovascular causes. Although a trend to an increase in total and cardiovascular mortality with increasing heart rate was found in the women, the between-quintile differences in mortality were smaller and nonsignificant.

The association of heart rate to mortality in the men after adjusting for each of the other characteristics examined is shown in Table 4. Because the univariate analysis had shown similar odds ratios for the 3 middle quintiles, for this analysis the middle quintiles were grouped together and taken as a reference for the bottom and top quintiles. The best association with mortality occurred for heart rate taken at the second and the third measurements. Thus, the means of these 2 values are shown in all tables and figures. Adjustment for personal characteristics (age, body mass index, smoking, alcohol intake, preexisting CHD, diabetes mellitus, regular medication, etc) and biological variables reduced the unadjusted increased risk, but a significant increase in risk still remained for both total and cardiovascular mortality. Due to the small number of events, the relation was attenuated and remained marginally significant for sudden death.

Men whose heart rate was in the bottom quintile showed a lower 12-year mortality than those in the middle quintiles, whereas men in the top quintile exhibited an increased mortality (Figure 2). A similar, though nonsignificant, trend was observed in the women (all-cause, P = .11; cardiovascular, P = .15).
In the multivariate Cox analysis, the heart rate was a significant predictor of time to all-cause death in the men. The results related to cardiovascular mortality are reported in Table 5. The predictive power of the heart rate for death from cardiovascular causes was second only to age and CHD and greater than that for diabetes mellitus. That for total- (P = .03) and hypertension (P = .05) and HDL cholesterol (P = .21) levels and smoking (P = .74) was found to be nonsignificant by the model. When the heart rate was entered into the model as the first variable and then adjusted for the other variables, its predictive power did not change. The inclusion of BP as a continuous rather than a categorical variable did not affect the predictive role of the heart rate (P = .05 for systolic BP, and P = .03 for diastolic BP).

When the men who died within 2 years after the baseline assessment were eliminated from the analysis, the heart rate still remained a significant predictor of cardiovascular mortality (P = .008). To investigate the predictive value of the single heart rate measurements, the 3 heart rates were included in separate Cox analyses. All measurements showed a significant association with either total or cardiovascular mortality. The association with cardiovascular mortality was stronger for the second (x² = 21.74) and the third measurement (x² = 23.58) than for the first 1 (x² = 18.96) (P<.001 for all).

No significant association between the heart rate and either total or cardiovascular mortality was found in the women. Also, hypertension and triglyceride level did not enter the Cox models in the women.

Although several risk factors for cardiovascular morbidity and mortality have been identified in young and middle-aged adults, their prevalence and importance are less known in the elderly. If some of these factors, such as hypertension and diabetes mellitus, have an unquestionable relationship with cardiovascular morbidity and mortality also in elderly subjects,15-17 the effects of other traditional risk factors such as total cholesterol level, smoking, or overweight seem to be much smaller in old age.4,8 Because cardiovascular disease remains the most common cause of death in persons older than 65 years, which risk factors are still “operative” in the elderly are important to identify. A high heart rate is associated with an increased risk of death from either cardiovascular or noncardiovascular causes in middle-aged persons. The effect is independent of other major risk factors, and the effect is greater in men.1,3,18 Little is known, however, about the relation between heart rate and mortality in the elderly.

Our results show that heart rate is an important risk indicator also in old persons, especially for cardiovascular mortality. Indeed, in the Cox analysis, its predictive power was greater than that of the classical risk factors.
for atherosclerosis. In middle-aged persons, the effects of major risk factors for cardiovascular diseases are stronger in men than in women.\(^1\)\(^9\) Whereas these advantages that women have vs men wane with advancing age,\(^4\)\(^,\)\(^2\)\(^0\) our study shows that the sex difference in the effects of the heart rate on mortality found by others in middle-aged persons\(^3\)\(^,\)\(^4\)\(^,\)\(^1\)\(^8\) persists into old age. This suggests that tachycardia is a marker of an abnormal pathophysiological condition more frequently present in men.

In the past years, the importance of the association between tachycardia and cardiovascular morbidity and mortality in the general population has been overlooked because of the interrelationship of the heart rate with other important risk factors such as elevated BP, smoking, and abnormal glucose and lipid levels, a finding that belied the correct interpretation of the heart rate as a risk factor.\(^2\)\(^,\)\(^1\)\(^8\),\(^2\)\(^1\) This raises the issue whether the heart rate is only a marker of underlying hemodynamic and metabolic abnormalities or whether, by itself, a low heart rate has a protective and a fast heart rate a detrimental cardiovascular effect. The relationship of the heart rate with serum glucose and triglyceride levels, how-

Table 3. All-Cause and Cardiovascular Mortality Rates and Relative Risks (RR),* by Quintile of Heart Rate†

<table>
<thead>
<tr>
<th>Quintiles of Heart Rate</th>
<th>Mean Heart Rate/min (Range)</th>
<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
<th>Mean Heart Rate/min (Range)</th>
<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
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<tr>
<td></td>
<td>No. (%) RR</td>
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<tr>
<td>First</td>
<td>59.5 ± 3.0 (50-64)</td>
<td>67 (43.8) 0.75</td>
<td>27 (17.6) 0.65</td>
<td>63.8 ± 4.4 (48-69)</td>
<td>69 (29.4) 0.83</td>
<td>34 (14.5) 0.74</td>
</tr>
<tr>
<td>Second</td>
<td>67.3 ± 2.0 (64-71)</td>
<td>76 (49.7) 0.89</td>
<td>36 (23.5) 0.96</td>
<td>71.4 ± 1.0 (69-73)</td>
<td>81 (34.5) 1.00</td>
<td>53 (22.5) 1.16</td>
</tr>
<tr>
<td>Third</td>
<td>72.4 ± 0.9 (71-74)</td>
<td>88 (57.5) 1.11</td>
<td>37 (24.2) 1.00</td>
<td>76.1 ± 1.5 (73-78)</td>
<td>82 (34.9) 1.00</td>
<td>41 (17.5) 0.90</td>
</tr>
<tr>
<td>Fourth</td>
<td>77.2 ± 1.7 (75-80)</td>
<td>88 (57.5) 1.09</td>
<td>36 (23.5) 0.94</td>
<td>80.7 ± 2.0 (78-84)</td>
<td>82 (34.9) 1.02</td>
<td>50 (21.3) 1.11</td>
</tr>
<tr>
<td>Fifth</td>
<td>89.0 ± 8.7 (81-120)</td>
<td>89 (58.9) 1.21</td>
<td>53 (34.6) 1.55</td>
<td>92.3 ± 6.8 (84-119)</td>
<td>89 (37.9) 1.13</td>
<td>46 (19.6) 1.08</td>
</tr>
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*Crude relative risks of mortality, where the reference group is the entire population.
†Mean ± SD of the last 2 measurements.

Figure 1. Age, blood pressure (BP), and serum glucose, total cholesterol, and triglyceride levels in elderly men (open bars) and women (solid bars) of the Cardiovascular Study in the Elderly, divided by quintiles of heart rate. The P value relates to the results of an analysis of variance.
ever, is complex, and we cannot rule out that in these patients, the fast heart rate may be only a marker of increased sympathetic tone. The abnormal sympathetic tone, in turn, may cause the metabolic complex of insulin resistance, hyperglycemia, and hypertriglyceridemia, as demonstrated by numerous studies.22-28

In elderly subjects, the pathogenesis of the connection between elevated heart rate and cardiovascular mortality might be also a low level of physical fitness or subclinical forms of cardiovascular disease. In these patients, a fast heart rate may reflect a loss of cardiac reserve as a result of impaired myocardial function. In the present study, that the association remained significant when the first 2 years of follow-up were eliminated indicates that the heart rate-cardiovascular mortality association was not merely an index of general poor health and a lack of vigor.

An aspect of the relationship between the heart rate and cardiovascular mortality that has not been clarified is whether the effect of heart rate on mortality is equally distributed throughout the heart rate range or whether there is a threshold level for the heart rate above or below which the risk changes abruptly. In our elderly subjects divided into quintiles of heart rate, we observed a similar risk of death from cardiovascular disease for the 3 intermediate quintiles, a lower risk for the bottom, and a higher risk for the top quintile. This type of relationship was particularly impressive for the risk of sudden death, where subjects with tachycardia had a 145% increased risk compared with the subjects with a normal heart rate. In the subjects with bradycardia, a 29% reduction in the risk of sudden death was seen. Experimental and clinical studies have convincingly demon-
correlated with total mortality. It has been proposed that increased vagal tone exerts a protective and antiarrhythmic effect. Cardiac patients with faster heart rates are, thus, conceivably at greater risk of ventricular fibrillation and sudden death. Conversely, a low heart rate may be the marker of parasympathetic activation that would exert a protective role on the electrical stability of the heart. In this respect, our results are in keeping with those from the Framingham Study, which also found a decreased rate of sudden death in men with bradycardia and an increased rate in those with tachycardia, a relationship that was not present in the women. At variance with these data, a U-shaped relationship between heart rate and sudden death was found in the men of the Chicago Heart Association Study, where low heart rates (<60/min) were also related to sudden death. The latter finding suggests that bradycardia might be symptomatic of conduction abnormalities, which in turn would predispose to sudden death. In the CASTEL, however, we excluded all subjects with bradycardia on standard electrocardiography, thereby minimizing this possibility.

According to some authors, limitations of the heart rate are that it is a highly variable clinical measurement with low reproducibility over time and that most results from the literature are related to few short-lasting measurements performed under poorly standardized conditions. To avoid this problem in the present study, the heart rate was measured 3 times from 60-second assessments. When the single measurements were entered into the Cox model separately, they all showed a close relation with mortality. This suggests that even a single measurement can be sufficient to estimate the risk of mortality related to the heart rate.

**OTHER RISK FACTORS**

In agreement with previous studies of elderly subjects, in the present analysis, total cholesterol level and overweight did not show a significant relationship with cardiovascular and total mortality. The paradoxical possibility that a high total cholesterol level is associated with longer, rather than shorter, survival in subjects in the seventh decade of life or older was even suggested by the results of the European Working Party on High blood pressure in the Elderly, in which the serum cholesterol level measured at randomization was independently and inversely correlated with total mortality. It has been proposed that the decrease in the effect of some risk factors with advancing age is due to earlier death of those subjects with higher cholesterol levels or greater body weight, leaving, as years go by, only the subjects with lower levels of these risk factors. Smoking was also rejected from the Cox model in our analysis. This finding is in agreement with previous studies that demonstrated that the relative risk attached to smoking diminishes with advancing age; and the benefit of quitting cigarette smoking on the incidence of coronary attacks could not be demonstrated in the Framingham subjects aged 65 years or older.

**CLINICAL IMPLICATIONS**

The association in men between heart rate and cardiovascular mortality shown by the present analysis suggests that tachycardia, though it may be affected by the emotional response to the conditions of measurement, should not be regarded as being innocuous, in either normotensive or hypertensive persons. This finding is in line with previous results from the Ann Arbor, Mich, and Padova, Italy, laboratories, which showed that the so-called white-coat phenomenon is associated with target-organ damage in hypertension. Thus, the data of the present study suggest that a transient heart rate elevation in response to a clinical examination may also be a marker of an adverse outcome. This raises the question whether reducing the heart rate pharmacologically might improve the prognosis in subjects with tachycardia. The long-term administration of propranolol hydrochloride was capable of retarding the development of atherosclerotic coronary artery lesions in cholesterol-fed monkeys. In humans, the beneficial effect of drugs that lower the heart rate has been demonstrated in patients who have had a myocardial infarction or in subjects with congestive heart failure. Besides β-blockers, several other antihypertensive drugs have been shown to decrease the heart rate and might, thus, have a good potential for reducing cardiovascular morbidity and mortality in hypertensive subjects with fast heart rates.

**CONCLUSIONS**

The present results confirm that risk factors derived from a middle-aged population, such as smoking, total cholesterol level, and degree of obesity, cannot be extrapolated to persons aged 65 years and older. In old subjects, attention should focus on less classical indices, and the heart rate appears to be a main risk indicator, at least in men.

According to the present results, heart rates higher than 80/min should be considered hazardous in elderly men. These data are in agreement with the results of the National Health and Nutrition Examination Survey, in which a greater risk of death from cardiovascular dis-
ease was detected in the general population for heart rates higher than 84/min.\textsuperscript{2}

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