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Clinical research

Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease

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KEYWORDS
High resting heart rate;
Prognosis;
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Rehospitalizations

Aims Heart rate reduction is the cornerstone of the treatment of angina. The purpose of this study was to explore the prognostic value of heart rate in patients with stable coronary artery disease (CAD).
Methods and results We assessed the relationship between resting heart rate at baseline and cardiovascular mortality/morbidity, while adjusting for risk factors. A total of 24 913 patients with suspected or proven CAD from the Coronary Artery Surgery Study registry were studied for a median follow-up of 14.7 years. All-cause and cardiovascular mortality and cardiovascular rehospitalizations were increased with increasing heart rate ($P < 0.0001$). Patients with resting heart rate $\geq$83 bpm at baseline had a significantly higher risk for total mortality [hazard ratio (HR) = 1.32, CI 1.19–1.47, $P < 0.0001$] and cardiovascular mortality (HR = 1.31, CI 1.15–1.48, $P < 0.0001$) after adjustment for multiple clinical variables when compared with the reference group. When comparing patients with heart rates between 77–82 and $\geq$83 bpm with patients with a heart rate $\leq$62 bpm, the HR values for time to first cardiovascular rehospitalization were 1.11 and 1.14, respectively ($P < 0.001$ for both).
Conclusion Resting heart rate is a simple measurement with prognostic implications. High resting heart rate is a predictor for total and cardiovascular mortality independent of other risk factors in patients with CAD.

Introduction

The total number of heartbeats in a lifetime remains fairly constant across species and there exists an inverse relationship between resting heart rate and life expectancy.[1] Epidemiological studies have addressed the issue of the importance of heart rate in healthy humans.[2–12] The association between resting heart rate and mortality has been observed in patients with hypertension, with metabolic syndrome, and in the elderly.[13–18] However, there is little information on the prognostic value of resting heart rate in patients with stable coronary artery disease (CAD).

Although heart rate reduction is helpful in preventing angina, it is not clear whether a lower heart rate is associated with a more favourable prognosis in patients with CAD. This question is clinically important because it may support the relevance of testing the effect of lowering heart rate to reduce cardiovascular mortality and morbidity. Experimental and clinical studies have already suggested that heart rate reduction

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may improve coronary endothelial function and atherosclerosis.[19–29] The objective of the present study was to evaluate the relationship between resting heart rate and future cardiovascular events in a large population of patients with suspected or proven CAD with an extended follow-up.

Methods

The Coronary Artery Surgery Study (CASS) was a multicentre research programme consisting of a randomized trial of medical vs. surgical therapies and a large registry of patients undergoing coronary arteriography for the presence of suspected or proven CAD. From August 1975 through May 1979, a total of 18 894 men and 6065 women underwent coronary arteriography at one of the 15 participating sites (total number of patients: 24 959). From this pool of patients, those meeting specific selection criteria were randomized into medical and surgical treatment groups. This study focuses on all patients included in the registry. A detailed description of CASS has been published elsewhere.[30] The registry at each participating centre included all patients whose primary indication for coronary angiography was suspected or proven CAD. Patients studied because of suspicion of CAD who were diagnosed to have another form of heart disease were excluded from the registry. Some patients who underwent coronary angiography for evaluation of other conditions, such as valvular disease, cardiomyopathies, and congenital heart disease, were also excluded even if subsequent evidence showed that CAD was, indeed, a major clinical problem because they had not been referred for suspected or proven CAD. Exclusion criteria for the registry consisted of the following: (i) inaccessibility for follow-up; (ii) substantial language barrier; (iii) referral to a CASS site expressly for surgery with coronary angiography performed elsewhere; (iv) cardiomyopathy not due to ischaemic heart disease; (v) idiopathic hypertrophic subaortic stenosis; and (vi) significant valvular heart disease. Patients with minimal regurgitation due to mitral valve prolapse were included in the registry. Enrolment was contingent upon obtaining the patient's written informed consent and it was usually obtained before the initial index coronary angiogram. Baseline resting heart rate was obtained manually at enrolment with one radial pulse measurement during 60 s with the patient in the sitting position. The variables evaluated in CASS have been previously described in detail.[30] Variables for the current study were chosen based on previous literature, data availability, and clinical relevance (*Table 1*).

Table 1 Description of variables used in this study

Variable	Definition
Variables to be included in all models	
RHR in quintiles	Obtained manually from radial pulse during 60 s at baseline
Age	At the time of enrolment
Gender	Males/females
Use of β-blockade	At baseline
EF	Single-plane area-length method EF = (EDV − ESV)/EDV
Potential variables	
Hypertension	History of hypertension, confirmed by a physician
Diabetes mellitus	Confirmed by a physician
Cholesterol level	Expressed in milligrams per decilitres
BMI	Weight in kg divided by the square of height in metres
Smoking status	Within 3 months prior or after enrolment. Presently, formerly, or never smoked cigarettes
NDCV	According to CASS criteria
Recreational activity	At baseline. Strenuous, moderate, mild, or sedentary
Antiplatelet therapy	At baseline, mainly ASA or dipyridamole
Diuretics	At baseline, mainly furosemide or hydrochlorothiazide
Lipid-lowering drugs	At baseline
Outcomes	
Total mortality	Vital status obtained from FU forms, final survey, and NDI records
CV mortality	Cause of death if known, obtained from FU forms, final survey, and NDI records. CV death included cardiac direct, cardiac contributory, and sudden unexplained death
Rehospitalizations due to CV cause	Ever hospitalized for MI, angina, stroke, CHF, revascularization, or rhythm disturbance
MI	Ever hospitalized for MI, diagnosis based on ECG and/or enzyme analysis
Angina	Ever hospitalized for angina or chest pain for >5 days
Stroke	Ever hospitalized for stroke or transient ischaemic attack
CHF	Ever hospitalized for CHF for >5 days

ASA, aspirin; CHF, congestive heart failure; CV, cardiovascular; EDV, end-diastolic volume; ESV, end-systolic volume; FU, follow-up; NDI, national death index; RHR, resting heart rate.

Patient follow-up

The date of enrolment was that of the initial angiographic evaluation. Annual clinical follow-up was mandatory for all patients in the registry. Additional information was obtained for all patients in the registry who suffered a 'coronary event'. The CASS follow-up requirements for various situations designated as 'coronary events' included the following:

(i) If a patient experienced a myocardial infarction (MI), all relevant information, including electrocardiograms (ECGs) and the results of enzyme studies, was obtained regardless of whether the patient was hospitalized.
(ii) Detailed reports of hospitalizations for any cardiac event or stroke were collected if the period of hospitalization exceeded 5 days.
(iii) If a patient was hospitalized for coronary angiography or cardiac surgery, a specific description of the hospitalization and the procedures performed was obtained.
(iv) If a patient died, a detailed report of the circumstances of death was filled out.

Patients were followed annually through 1982 and thereafter by a final mail survey between 1988 and 1991 to which 94% responded. Vital status among non-responders at last follow-up was obtained through 1991 from the National Death Index and,

in some cases, from next of kin, such that the status of 95.8% of all CASS patients was known. Median duration of follow-up (and interquartile range) was 14.7 years (9.0–16.1 years).

Statistical methods

In order to summarize the independent variables and to better understand their relationship to heart rate, descriptive statistics are presented by heart rate quintiles. Quintiles were chosen according to the resting heart rate distribution in the general sample population: heart rate 1, ≤62; heart rate 2, 63–70; heart rate 3, 71–76; heart rate 4, 77–82; and heart rate 5, ≥83 bpm. For the purpose of data presentation, heart rate quintiles are compared using χ^2 test for categorical variables and one-way ANOVA for continuous variables. Risk factors or covariates were chosen based on their clinical relevance (covariates to be included in all models), and if they had a *P*-value ≤0.25 on univariate analyses that were performed using Cox proportional hazard (PH) models. All the clinically important variables were available and selected a priori for analysis in this large database. No chosen variable had >10% of missing values, except for left ventricular ejection fraction (EF) and total cholesterol that were considered because of their clinical importance, although not available in 20% of patients. For each potential covariate, the PH assumption was assessed graphically with log–log plots for categorical variables or Schoenfeld residual plots for continuous variables. There were no time-dependent covariates. Once the selection of the potential covariates was done for a given outcome, a multivariable Cox PH model was fitted. The linearity assumption was assessed by log transformation of each continuous variable and graphical testing against survival time (or time to event). Colinearity was verified with Pearson's correlation coefficient for variables with high clinical suspicion of colinearity. When correlation was found, one of the variables was removed, according to clinical relevance. Correlation between insulin treatment and diabetes and antihypertensive treatment and hypertension was identified and analyses were performed without these two treatments. After colinearity checks, covariates were entered in the multivariable analysis. Formal analyses were performed using heart rate as a continuous and as a categorical variables as well. In every multivariable model, approximately the same probability values were obtained with either heart rate as a continuous variable or heart rate as a categorical variable. Therefore, and solely for presentational purposes, heart rate was reported in quintiles because it is clinically more relevant. Results are expressed in hazard ratios (HR) for Cox PH model, compared with the reference group (≤62 bpm) and with 99% CI. Because of the large number of patients and variables, we used two-tailed *P*-values of ≤0.01 as significant differences. Subgroup analyses were performed with heart rate as a continuous variable. HR and 95% CI for each subgroup were calculated for every one SD increment in heart rate. All analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The baseline demographic and clinical characteristics of the 24 913 patients included in this study are presented in *Table 2*. The mean age was higher in the lower heart rate quintiles. The proportion of males was larger than females in all groups, with women having a trend towards a higher resting heart rate. There were higher proportions of dyslipidaemics, smokers, hypertensives, and diabetic patients in the higher quintiles. The number of clinically significant diseased coronary vessels (NDCV) per patient at baseline was higher in the lowest heart rate range. EF was lower in patients with a high heart rate at baseline. Patients in the higher heart rate quintiles received less treatment with β-blockers and were treated more often with diuretics. There were no significant differences between the different quintiles with regards to body mass index (BMI) and use of antiplatelets or lipid-lowering drugs.

Table 2 Baseline characteristics divided by resting heart rate quintiles ($n = 24\,913$ patients)

	≤62 (bpm)	63–70 (bpm)	71–76 (bpm)	77–82 (bpm)	≥83 (bpm)	Overall *P*-value
Age (years)	54.8 ± 8.9	53.5 ± 9.2	53.0 ± 9.2	52.8 ± 9.3	52.1 ± 9.6	<0.001
Males (%)	79.2	77.4	75.3	74.0	71.6	<0.001
Total cholesterol (mg/dL)[a]	227.1 ± 47.0	231.3 ± 50.0	230.6 ± 50.0	232.9 ± 50.6	232.5 ± 53.8	<0.001
BMI (kg/m^2)	25.8 ± 3.6	25.8 ± 3.6	25.7 ± 3.7	25.8 ± 3.8	26.0 ± 4.2	0.03
NDCV	1.6 ± 1.1	1.5 ± 1.1	1.4 ± 1.1	1.4 ± 1.1	1.4 ± 1.1	<0.001
EF (%)	60.5 ± 13.5	59.5 ± 14.6	59.3 ± 15.2	59.0 ± 16.1	58.1 ± 17.6	<0.001
Hypertension (%)	35.7	38.6	41.8	44.2	49.5	<0.001
Diabetes mellitus (%)	9.6	9.9	11.0	11.0	12.5	<0.001
Cigarette smoking						
Presently	26.7	31.6	33.5	35.1	39.2	<0.001
Formerly	49.6	44.4	41.4	40.2	36.9	
Sedentary (%)	37.5	35.7	34.1	33.2	33.4	<0.001
β-Blockers (%)	69.5	52.2	40.5	33.3	26.4	<0.001
Antiplatelets (%)	6.3	6.1	6.6	6.8	7.1	0.23
Diuretics (%)	20.1	21.5	23.2	24.5	29.1	<0.001
Lipid-lowering drugs (%)	3.6	4.4	4.8	4.2	4.3	0.06

Continuous variables are expressed in mean ± one SD. Categorical variables are presented as relative frequencies. bpm, beats per min. Differences between different heart rate quintiles at baseline were assessed using χ^2 test for categorical variables and one-way ANOVA for continuous variables.
[a]Total cholesterol was not available in 20% of patients and was not included in multivariable analyses.

Table 3 Multivariable Cox regression survival analysis for total mortality

	Total mortality	
	HR (99% CI)	Overall *P*–value
Resting heart rate (bpm)		
≤62	Reference	<0.0001
63–70	1.06 (0.97–1.17)	
71–76	1.09 (0.98–1.21)	
77–82	1.16 (1.04–1.28)	
≥83	1.32 (1.19–1.47)	
Age	1.05 (1.04–1.05)	<0.0001
Male gender	1.18 (1.08–1.28)	<0.0001
Hypertension	1.26 (1.17–1.35)	<0.0001
Diabetes mellitus	1.61 (1.48–1.75)	<0.0001
Cigarette smoking		
Presently	1.63 (1.48–1.78)	<0.0001
Formerly	1.15 (1.05–1.25)	
NDCV at baseline		
One	1.64 (1.45–1.85)	<0.0001
Two	2.18 (1.94–2.45)	
Three	2.87 (2.56–3.22)	
EF	0.97 (0.97–0.97)	<0.0001
Treatment with β–blockers	1.01 (0.95–1.08)	0.52
Recreational activity		
Strenuous	Reference	<0.0001
Moderate	1.01 (0.79–1.29)	
Mild	1.09 (0.86–1.39)	
Sedentary	1.22 (0.96–1.54)	
Antiplatelet treatment	0.98 (0.87–1.11)	0.79
Diuretic treatment	0.68 (0.64–0.74)	<0.0001
Lipid–lowering treatment	1.01 (0.87–1.18)	0.76

Table 4 Multivariable Cox regression survival analysis for cardiovascular mortality

	CV mortality	
	HR (99% CI)	Overall *P*–value
Resting heart rate (bpm)		
≤62	Reference	<0.0001
63–70	1.05 (0.94–1.18)	
71–76	1.07 (0.94–1.21)	
77–82	1.14 (1.00–1.29)	
≥83	1.31 (1.15–1.48)	
Age	1.04 (1.03–1.04)	<0.0001
Male gender	1.08 (0.97–1.21)	0.04
BMI	1.01 (1.00–1.02)	<0.01
Hypertension	1.33 (1.22–1.44)	<0.0001
Diabetes mellitus	1.53 (1.38–1.70)	<0.0001
Cigarette smoking		
Presently	1.49 (1.33–1.66)	<0.0001
Formerly	1.11 (1.00–1.23)	
NDCV at baseline		
One	2.30 (1.94–2.73)	<0.0001
Two	3.55 (3.02–4.18)	
Three	4.87 (4.15–5.71)	
EF	0.96 (0.96–0.97)	<0.0001
Treatment with β-blockers	1.06 (0.98–1.15)	0.04
Recreational activity		
Strenuous	Reference	<0.0001
Moderate	1.03 (0.77–1.38)	
Mild	1.07 (0.81–1.43)	
Sedentary	1.22 (0.92–1.62)	
Antiplatelet treatment	0.96 (0.83–1.11)	0.50
Diuretic treatment	0.63 (0.58–0.69)	<0.0001
Lipid–lowering treatment	0.96 (0.80–1.14)	0.55

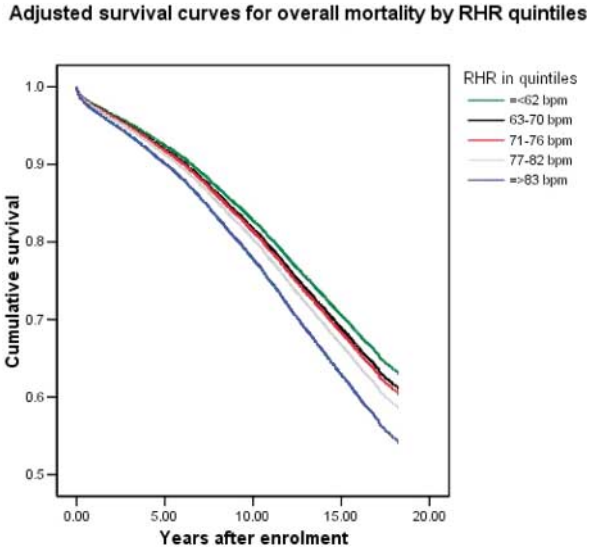

Figure 1 Adjusted for age, gender, hypertension, diabetes mellitus, cigarette smoking, clinically significant coronary vessel disease, EF, recreational activity, treatment with antiplatelets, diuretics, beta-blockers, and lipid-lowering drugs. RHR, resting heart rate.

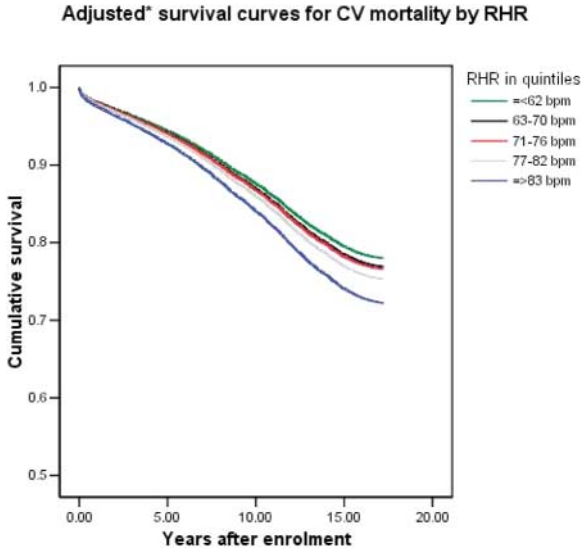

Figure 2 Asterisk indicates adjusted as *Figure 1* plus BMI. CV, cardiovascular; RHR, resting heart rate.

Multivariable analysis

Overall mortality

Table 3 displays the adjusted multivariable Cox PH model for total mortality. After adjusting for age, sex, hypertension, diabetes, cigarette smoking, NDCV, EF, type of recreational activity, and treatment with diuretics, β-blockers, antiplatelets, and lipid-lowering drugs, patients with resting heart rate between 77 and 82 bpm had a significantly higher risk for total mortality

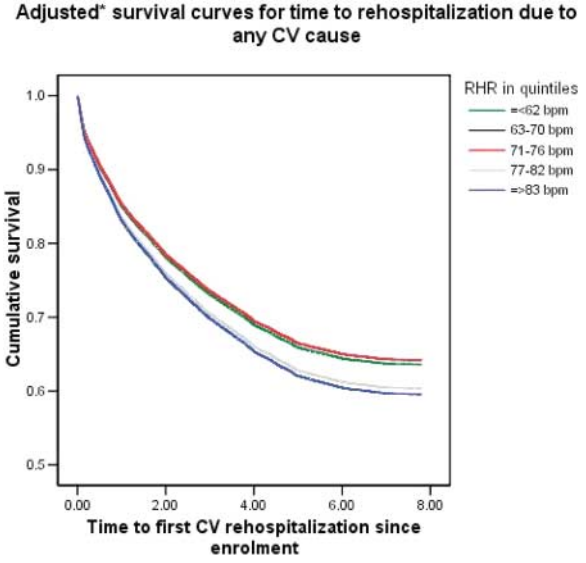

Figure 3 Asterisk indicates adjusted as *Figure 1*. The green and black lines are superimposed. CV, cardiovascular; RHR, resting heart rate.

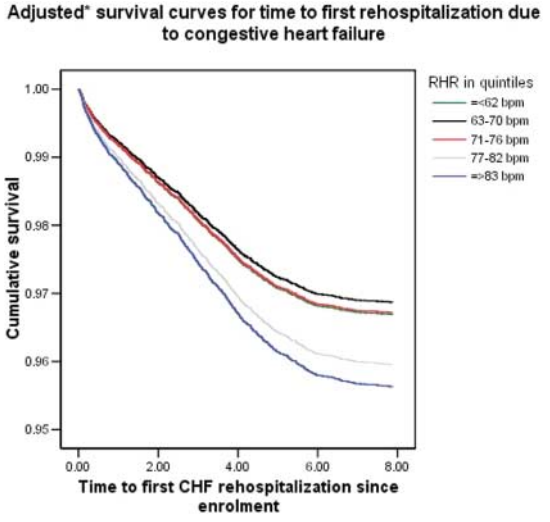

Figure 4 Asterisk indicates adjusted for age, gender, hypertension, diabetes mellitus, clinically significant coronary vessel disease, EF, recreational activity, treatment with antiplatelets, diuretics, β-blockers, and lipid-lowering drugs. CHF, congestive heart failure.

Table 5 Multivariable Cox regression analysis for time to rehospitalization due to any cardiovascular cause or acute MI

	Rehospitalization due to any CV cause		Rehospitalization due to acute MI	
	HR (99% CI)	Overall *P*-value	HR (99% CI)	Overall *P*-value
Resting heart rate (bpm)				
≤62	Reference	<0.0001	Reference	0.73
63–70	0.98 (0.88–1.08)		1.10 (0.89–1.36)	
71–76	0.97 (0.88–1.08)		1.03 (0.82–1.29)	
77–82	1.11 (1.00–1.24)		1.02 (0.81–1.29)	
≥83	1.14 (1.02–1.27)		1.07 (0.84–1.35)	
Age	1.01 (1.00–1.01)	<0.0001	1.00 (0.99–1.01)	0.36
Male gender	0.85 (0.78–0.92)	<0.0001	1.09 (0.90–1.33)	0.21
Hypertension	1.22 (1.14–1.31)	<0.0001	1.45 (1.24–1.68)	<0.0001
Diabetes mellitus	1.30 (1.19–1.43)	<0.0001	1.46 (1.20–1.77)	<0.0001
Cigarette smoking				
Presently	1.25 (1.13–1.37)	<0.0001	1.37 (1.12–1.67)	<0.0001
Formerly	1.10 (1.01–1.21)		0.95 (0.78–1.16)	
NDCV at baseline				
One	1.86 (1.67–2.07)	<0.0001	3.30 (2.50–4.36)	<0.0001
Two	1.85 (1.66–2.06)		3.86 (2.93–5.08)	
Three	1.82 (1.64–2.03)		3.91 (2.96–5.16)	
EF	0.99 (0.99–0.99)	<0.0001	0.99 (0.98–0.99)	<0.0001
Treatment with β-blockers	0.99 (0.92–1.06)	0.76	1.16 (1.00–1.34)	<0.01
Recreational activity				
Strenuous	Reference	<0.0001	—	—
Moderate	1.14 (0.88–1.46)			
Mild	1.27 (1.00–1.63)			
Sedentary	1.38 (1.08–1.77)			
Antiplatelet treatment	0.97 (0.85–1.10)	0.59	0.93 (0.71–1.21)	0.49
Diuretic treatment	0.83 (0.77–0.90)	<0.0001	0.97 (0.81–1.15)	0.66
Lipid-lowering treatment	0.91 (0.78–1.06)	0.14	—	—

Table 6 Cox regression analysis for time to rehospitalization due to angina, stroke or congestive heart failure

	Rehospitalization due to angina		Rehospitalization due to stroke		Rehospitalization due to CHF	
	HR (99% CI)	Overall *P*-value	HR (99% CI)	Overall *P*-value	HR (99% CI)	Overall *P*-value
Resting heart rate (bpm)						
≤62	Reference	0.016	Reference	0.44	Reference	<0.01
63–70	1.01 (0.90–1.13)		0.99 (0.69–1.42)		0.94 (0.71–1.24)	
71–76	0.98 (0.87–1.11)		1.17 (0.81–1.69)		0.99 (0.74–1.32)	
77–82	1.09 (0.96–1.23)		1.19 (0.82–1.73)		1.22 (0.92–1.62)	
≥ 83	1.12 (0.99–1.27)		1.20 (0.82–1.76)		1.32 (1.007–1.75)	
Age	0.99 (0.99–1.00)	0.26	1.04 (1.03–1.06)	<0.001	1.04 (1.03–1.05)	<0.001
Male gender	0.76 (0.69–0.84)	<0.001	0.91 (0.69–1.21)	0.43	0.76 (0.62–0.94)	0.001
Hypertension	1.21 (1.11–1.32)	<0.001	1.50 (1.18–1.91)	<0.001	1.41 (1.18–1.69)	<0.001
Diabetes mellitus	1.28 (1.15–1.43)	<0.001	1.78 (1.34–2.35)	<0.001	1.60 (1.30–1.97)	<0.001
Cigarette smoking						
Presently	1.29 (1.15–1.43)	<0.001	–	–	–	–
Formerly	1.14 (1.03–1.27)					
NDCV						
One	1.88 (1.67–2.12)	<0.001	1.78 (1.18–2.69)	<0.001	1.96 (1.39–2.75)	<0.001
Two	1.80 (1.60–2.04)		2.12 (1.42–3.16)		2.22 (1.60–3.09)	
Three	1.64 (1.44–1.86)		2.29 (1.54–3.39)		2.38 (1.72–3.30)	
EF	0.99 (0.99–1.00)	0.02	0.98 (0.98–0.99)	<0.001	0.95 (0.95–0.96)	<0.001
Treatment with β-Blockers	0.86 (0.79–0.93)	<0.001	1.21 (0.95–1.54)	0.04	1.21 (1.009–1.45)	<0.01
Recreational activity						
Strenuous	Reference	<0.001	Reference	<0.01	Reference	<0.001
Moderate	0.99 (0.74–1.31)		1.84 (0.56–6.03)		1.36 (0.56–3.33)	
Mild	1.14 (0.87–1.50)		1.87 (0.58–6.02)		1.72 (0.72–4.12)	
Sedentary	1.24 (0.94–1.63)		2.45 (0.76–7.90)		2.22 (0.93–5.31)	
Antiplatelet treatment	0.92 (0.80–1.07)	0.18	–	–	1.04 (0.73–1.46)	0.76
Diuretic treatment	0.85 (0.77–0.93)	<0.001	0.78 (0.60–1.01)	0.014	0.48 (0.40–0.58)	<0.001
Lipid–lowering drugs	0.88 (0.73–1.05)	0.06	–	–	0.95 (0.63–1.44)	0.79

HR = 1.16 (99% CI 1.04–1.28). This effect was even larger for patients with a resting heart rate ≥83 bpm, with a HR = 1.32 (CI 1.19–1.47; *Figure 1*). Besides a high resting heart rate, age (HR = 1.05), male gender (1.18), hypertension (1.26), diabetes (1.61), current smoking (1.63), and NDCV per patient (triple-vessel disease: HR = 2.87) were all independently associated with risk of death. Conversely, a higher EF (HR = 0.97) and diuretics (0.68) showed a protective effect.

Cardiovascular mortality

Table 4 shows the HR for cardiovascular mortality obtained after a multivariable Cox PH model adjusting for the same covariates as for overall mortality plus BMI. A high resting heart rate (≥83 bpm) was a strong predictor of cardiovascular mortality (HR = 1.31, CI 1.15–1.48). Age, hypertension, diabetes, BMI, current smoking, and NDCV remained strongly associated with cardiovascular death. EF and treatment with diuretics showed a protective effect. *Figure 2* shows the adjusted cumulative survival curves for cardiovascular mortality by quintiles of resting heart rate.

Time to rehospitalization

There was a marked difference in time to first cardiovascular rehospitalization between the two highest heart rate quintiles and the other groups (*Figure 3*). *Tables 5* and *6* display HR for independent covariates for time to rehospitalization due to cardiovascular causes. When comparing patients with heart rates between 77–82 and ≥83 bpm with patients with a heart rate of ≤62 bpm, the HR for time to first rehospitalization due to any cardiovascular event was 1.11 and 1.14, respectively (*P*-values <0.0001 for both). A high resting heart rate was also an independent predictor of time to first rehospitalization due to angina and congestive heart failure (*Figure 4*).

Subgroup analysis

The association between heart rate and total mortality held true in all analysed subgroups: men vs. women, old (>65 years) vs. young, diabetics vs. non-diabetics, hypertensives vs. normotensives, BMI >27 or <27, those with EF >50% or EF <50%, and patients treated with β-blockers vs. those without such a treatment (*Figure 5*).

Discussion

In a study of approximately 25 000 patients with suspected or proven CAD, we have found that resting heart rate is a predictor of overall and cardiovascular

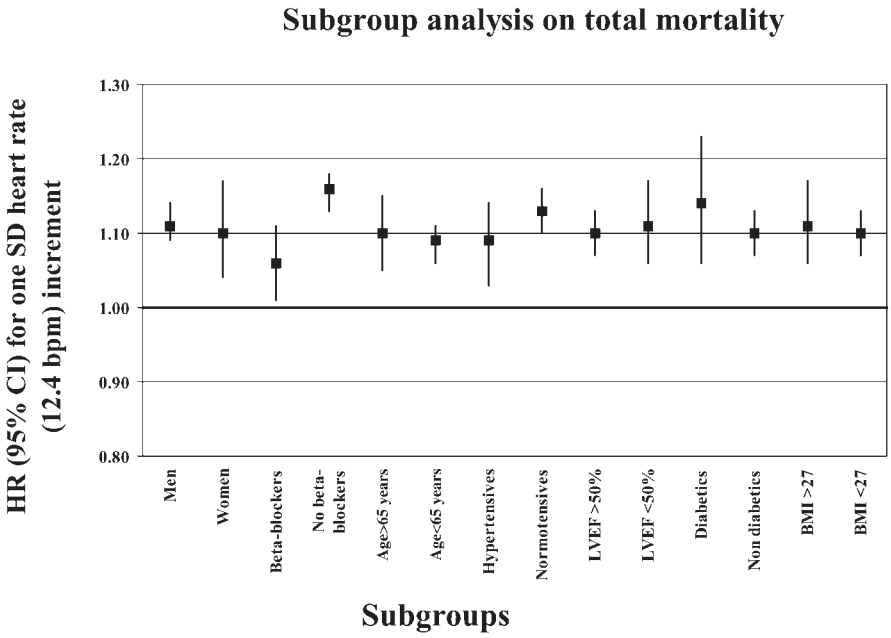

Figure 5 Subgroup analyses on total mortality per SD (12.4 bpm) of heart rate increment.

mortality, independent of other known risk factors such as hypertension, diabetes, and smoking. The size of the study also allowed us to adjust the multivariable model for two of the strongest predictors of cardiovascular mortality and morbidity: the left ventricular EF and the NDCV. Resting heart rate proved to be an independent risk factor for total and cardiovascular mortality, even after adjusting for such covariates. Resting heart rate was also a risk factor for time to rehospitalizations due to cardiovascular cause.

There is strong evidence linking an increase in resting heart rate to an increased risk of cardiovascular morbidity and mortality in the general population.[2,7,8] The relationship between reduction in heart rate and decrease in mortality has been well established with β-blockers especially after MI and in patients with heart failure.[31–34] A high heart rate leads to both greater myocardial oxygen consumption (MVO_2) and decreased myocardial perfusion, the latter by shortening the duration of diastole, which can induce or exacerbate myocardial ischaemia. Heart rate is significantly correlated with the severity and the progression of atherosclerosis on coronary angiography among men who had developed MI at a young age.[27,28] Experimental data have also demonstrated that a reduction in heart rate can delay the progression of coronary atherosclerosis in monkeys.[20,25] Beere *et al.*[20] showed that male cynomolgus monkeys subjected to sinus node ablation or those with innately low heart rates had significantly less coronary atherosclerosis than animals with higher heart rates. These observations are supported by results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS) randomized trial, which have shown that a β-blocker reduced the rate of progression of carotid intima-media thickness in asymptomatic patients.[29] More recently, a high heart rate has also been associated with an increased risk of coronary plaque disruption.[35]

All of our multivariable models were adjusted for the use of β-blockers and this allowed us to evaluate the independent value of resting heart rate. This independent relationship held true in all subgroups, including men vs. women. A high heart rate may reflect an imbalance of the autonomic nervous system and may therefore be a marker of sympathetic overactivity.[14,36–38] In our study, patients with a high resting heart rate had more cardiovascular risk factors than patients in the lowest quintiles. Some investigators have hypothesized that many of the risk factors (hypertension, diabetes, dyslipidaemia, smoking, and sedentary) are also related to sympathetic overactivity.[38–40]

Limitations of this study

This study was performed with a population of patients who were referred for cardiac catheterization, therefore our results may not be applicable to all other patients with CAD. Different times of day or circumstances under which basal resting heart rate was measured may have introduced increased variability of this parameter. Nevertheless, this limitation enhances rather than diminishes the importance of resting heart rate. The fact that the predictive power of resting heart rate remains independently of multivariable adjustment and potential methodologic issues, indicates the robustness of the association with morbidity and mortality. Total cholesterol was the only variable not included in multivariable analyses because it was not available in 20% of the 24 913 patients. Excluding patients from a multivariable model because of missing data may have introduced a selection bias.

Conclusion

Resting heart rate is a simple measurement with important prognostic implications. Previous epidemiologic studies demonstrated that high resting heart rate is a strong predictor for total and cardiovascular mortality in healthy populations. This study extends this observation to a population of patients referred for coronary angiography for suspected or proven CAD. Patients with resting heart rate $\geq$83 bpm are also prone to more rehospitalizations for cardiovascular reasons, independently of major risk factors when compared with patients with a resting heart rate $\leq$62 bpm. Resting heart rate is a predictor for total mortality and cardiovascular disease that should no longer be neglected in risk flow-charts.

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