Influence of Heart Rate on Mortality in a French Population : Role of Age, Gender, and Blood Pressure

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Influence of Heart Rate on Mortality in a French Population
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Abstract—The aim of the present study was to assess the effects of high heart rate on mortality in different subgroups in a French population according to age, gender, and blood pressure levels. We studied 19 386 subjects (12 123 men, 7263 women), aged 40 to 69 years, who had a routine health examination at the Centre d'Investigations Préventives et Cliniques (IPC) between 1974 and 1977. Heart rate (HR) measured by ECG was classified into 4 groups: HR1, <60; HR2, 60 to 80; HR3, 81 to 100; and HR4, >100 bpm. Mortality data were recorded for the period of 1974 through 1994. In both sexes, HR was a significant predictor of noncardiovascular mortality. In men, the relative risk (95% confidence interval) for cardiovascular death after adjustment for age and other risk factors in the HR2, HR3, and HR4 groups was 1.35 (1.01 to 1.80), 1.44 (1.04 to 2.00), and 2.18 (1.37 to 3.47), respectively, when compared with HR1. In women, HR did not influence cardiovascular mortality. The association of HR with cardiovascular mortality in men was (1) related to a strong association with coronary but not cerebrovascular mortality, (2) independent of age and hypertension, and (3) influenced by the level of pulse pressure; in patients with high pulse pressure (>65 mm Hg), accelerated HR was not associated with increased cardiovascular mortality. In conclusion, in a large French population, accelerated resting HR represents an independent predictor of noncardiovascular mortality in both genders, and of cardiovascular mortality in men, independent of age and the presence of hypertension. Further investigations are needed to explain the complex interactions between HR, pulse pressure, and cardiovascular complications. **(*Hypertension*. 1999;33:44-52.)**

Key Words: mortality ■ heart rate ■ pulse pressure ■ coronary artery disease ■ cerebrovascular disorders

Several epidemiological studies have reported that high heart rate (HR) is a predictor of both cardiovascular and noncardiovascular mortality.[1–4] However, several questions have been raised concerning the association between high HR and cardiovascular disease (CVD) in normotensive and hypertensive populations.[5] First, the role of accelerated HR on CVD mortality has not been demonstrated in women, and this is generally attributed to the low number of cardiovascular events in this population.[1,6,7] Second, it is not yet known whether HR is a significant marker of CVD risk regardless of age. Finally, whereas some studies have shown that HR, independently of other more classic risk factors, is a significant predictor of CVD, recent reports showed complex interactions between HR on one hand and high blood pressure (BP) or dyslipidemia[5,6] on the other. More specifically, a report from the Framingham study[7] showed that the predictive role of HR on cardiovascular morbidity was observed primarily in hypertensive men, suggesting that in this particular population HR and BP might act synergistically in the development of cardiovascular complications. The underlying mechanisms that link BP and HR to CVD mortality are difficult to establish. Experimental studies indicate that fatigue and fracture of elastic fibers within the arterial wall are related to both steady and cyclic strains.[8] In vivo, the former is primarily dependent on the mean BP, whereas the latter is related to the amplitude of pulse pressure (PP) and also to the number of strain cycles (HR). In monkeys, plaque formation in carotid atherosclerosis correlates positively with HR, whereas lowering the HR delayed aortoiliac atherosclerosis.[9,10] In clinical studies, it has been reported that high arterial stiffness, the major determinant of pulsatile pressure, is strongly associated with high HR, even after adjustment for age and BP.[11] Thus, when examining the relationship between BP and HR, it is relevant to determine whether PP and HR have cumulative effects on CVD mortality.

In a large general French population with relatively low cardiovascular risk, we investigated the effects of high HR as an independent predictor of long-term CVD and non-CVD mortality in different subgroups according to age, gender, and the presence or absence of hypertension. In addition, we assessed the cumulative contribution of HR and PP to mortality, taking into account the possible interaction between these 2 factors.

Methods

Subjects

The French public healthcare system (Securité Sociale-CNAM) provides all working and retired persons and their families with a free health examination every 5 years. The Centre d'Investigations Préventives et Cliniques (IPC) is one of the largest medical centers

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of this kind in France, having performed approximately 15 000 examinations per year since 1970 for persons living in the Paris area. In this study, we present data that describe a population comprising 12 123 men and 7263 women, aged 40 to 69 years, who had a free health checkup at the IPC Center during the period of May 1974 through May 1977. All subjects meeting this age criterion were included. Of the men, 84% were white-collar workers and 8.5% were retired; for the women, these figures were 62% and 11%, respectively. All other socioprofessional categories were underrepresented in our cohort. (Blue-collar workers represented only 2% of our entire population.) On the basis of national statistics on mortality, our cohort presented a 20% lower mortality rate than the general French population. This can be explained by the fact that persons coming for the health checkup are apparently healthy and motivated to be followed up. Interestingly, compared with the national data, the distribution of the different causes of mortality in our cohort was identical to that in the general population.

HR was measured by ECG after the subject had rested for 5 to 7 minutes in the supine position and was recorded in 1 of the following classifications: HR1$<$60, 60$\leq$HR2$\leq$80, 80$<$HR3$\leq$100, and HR4$>$100 bpm.

A nurse measured supine BP in the right arm using a manual sphygmomanometer. After a 10-minute rest period, BP was measured 3 times and the mean of the last 2 measurements was calculated. The first and the fifth Korotkoff phases were used to define systolic and diastolic pressures. Smoking status and physical activity were assessed with a self-administered questionnaire composed of dichotomic (yes or no) questions regarding tobacco use (current consumption of $>$10 cigarettes/d) and physical activity ($\geq$2 h/wk). Plasma cholesterol was measured with a Technicon SMA-12.

The follow-up study period ended in December 1994 (mean follow-up was 18.2 years). Deceased subjects were identified from the mortality records of the Institut National de Statistiques et d'Etudes Economiques (INSEE). A patient from our cohort was classified as deceased when the same first name, last name, gender, and date of birth as the patient was listed in the INSEE mortality records during the period of the follow-up. Only subjects meeting all 4 of these criteria were classified as deceased. Individuals who matched for gender, last name, and only 1 of the 2 other criteria were excluded from the study. All other subjects were classified as alive at the end of the follow-up period. Following this procedure, 2646 subjects (2036 men and 610 women) from our cohort were classified as having died during the follow-up period. Causes of mortality were taken from the death certificates. These data were provided by the INSERM Department of Mortality (Unit SC 8). Causes of death were codified according to the *International Classification of Disease* (8th revision until 1978, 9th revision thereafter). To validate this procedure we took a sample of 250 subjects and compared our data with those found at the city halls. An error was found in 2 cases ($<$1%).

All subjects gave their written informed consent for their data to be used for epidemiological studies. Permission to obtain mortality data was given by the Comité National de l'Informatique et des Libertés (CNIL).

Data Analysis

Because gender distribution was not representative in our population, men and women were studied separately. For the purpose of the analysis, subgroups were compared according to age (40 to 54 versus 55 to 69 years) and presence of or lack of hypertension (systolic BP $>$140 mm Hg, diastolic BP $>$90 mm Hg, or antihypertensive treatment).

To compare the HR groups, the following statistical tests were used. (1) Mean values of morphometric parameters, BP, and total cholesterol were compared using a 1-way ANOVA. A χ^2 trend test was used for tobacco consumption, physical activity status, antihypertensive medication, and history of diabetes and myocardial

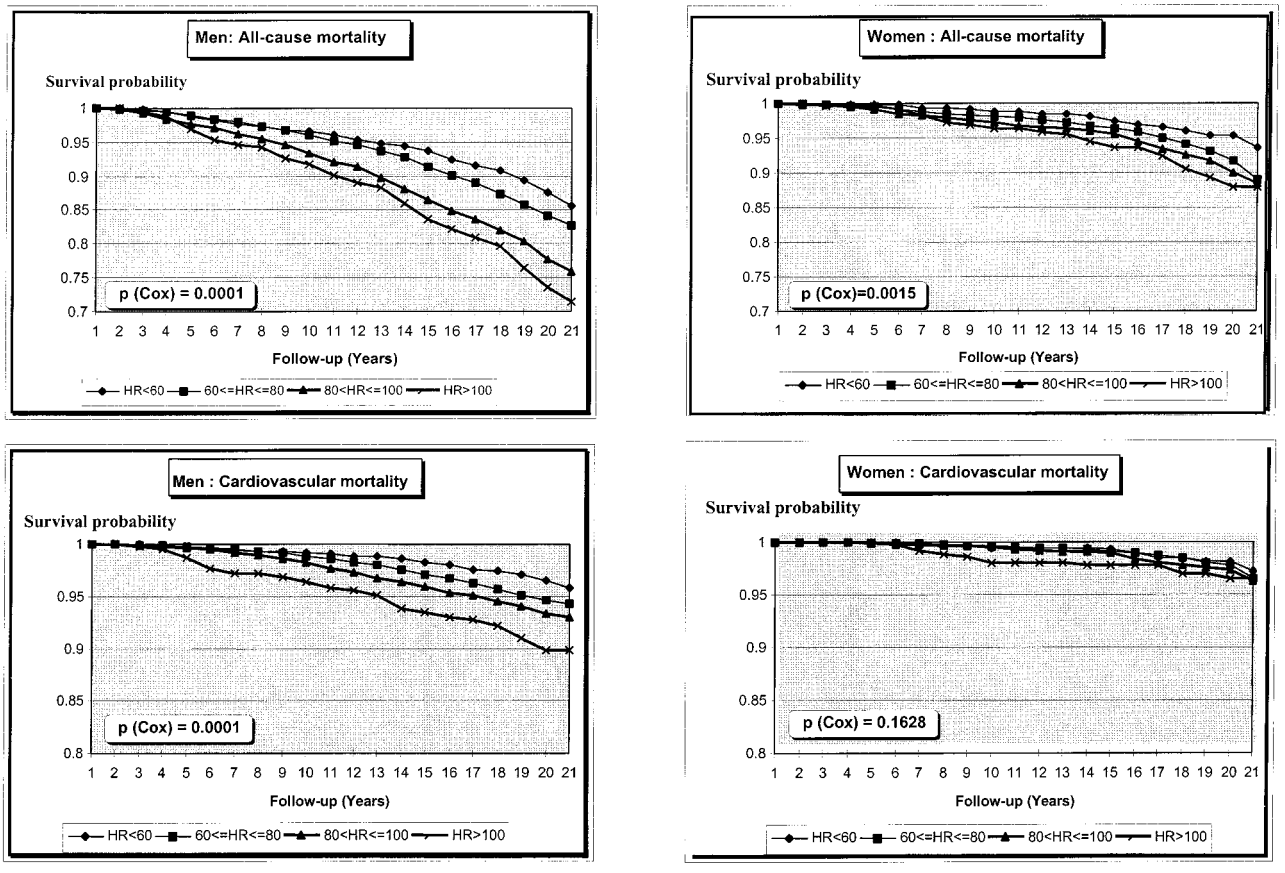


Figure 1. Survival probability curves for all-cause and cardiovascular mortality in men and women according to HR class. *P* values were obtained after adjustment for age and other risk factors.

TABLE 1. Mean±SD of Principal Parameters According to HR in Men and Women

	Men					Women				
	HR<60	60≤HR≤80	80<HR≤100	HR>100	*P*	HR<60	60≤HR≤80	80<HR≤100	HR>100	*P*
No.	1517	8030	2192	384		544	4857	1503	359	
Age, y	51.0±7.9	51.2±7.9	51.1±7.8	50.9±7.8	0.67	52.5±7.5	52.1±8.2	52.1±8.9	52.1±9.0	0.69
Weight, kg	75.3±9.3	75.1±10.1	75.0±10.9	73.5±11.2	0.017	59.5±8.7	59.9±9.3	60.0±10.2	60.2±10.5	0.62
Height, cm	173±6	172±6	172±6	171±6	0.0001	160±6	159±6	159±6	158±6	0.001
BMI, kg/m^2	25.1±2.8	25.3±3.0	25.5±3.2	25.2±3.5	0.01	23.4±3.3	23.7±3.4	23.9±3.8	24.3±4.2	0.001
SBP, mm Hg	135±18	140±19	147±19	155±23	0.0001	128±18	134±18	140±21	148±22	0.0001
DBP, mm Hg	83.9±11.9	87.3±12.6	90.4±13.3	94.4±15.0	0.0001	79.0±10.9	82.5±11.3	85.6±12.8	89.6±13.3	0.0001
MBP, mm Hg	101±13	105±14	109±15	114±17	0.0001	95±12	100±13	104±15	109±15	0.0001
PP, mm Hg	51.1±11.0	53.0±11.2	56.3±11.8	60.0±14.1	0.0001	49.5±11.3	51.5±11.4	54.6±12.6	58.6±14.6	0.0001
Cholesterol, mg/mL	216±34	219±35	223±37	225±36	0.0001	218±35	219±37	222±38	227±39	0.001
Physical activity, %	37.7	26.5	19.6	16.9	0.001	23.0	16.4	14.0	12.0	0.001
Smokers, %	30.9	35.5	43.3	47.7	0.001	18.8	14.3	12.7	10.6	0.001
Anti-HT treatment, %	4.4	5.1	6.4	7.8	0.001	5.5	7.8	8.7	8.1	0.05
Diabetes history, %	9.4	8.8	10.0	9.1	0.55	4.6	6.0	7.3	5.9	0.45
MI history, %	1.1	0.8	0.6	0.3	0.38	0	0.2	0.3	0.8	0.08

SBP indicates systolic BP; DBP, diastolic BP; MBP, mean BP; Anti-HT, antihypertensive; and MI, myocardial infarction.

infarction. (2) Death rates for the different causes of mortality were compared using a χ^2 trend test. *P* values refer to the difference between all groups of HR. (3) Survival probability for the different causes of mortality in the 4 HR groups were compared using a Cox regression analysis. Curves presented in Figure 1 were not adjusted for other risk factors. The *P* values presented in Figure 1 were adjusted for age, systolic BP, diastolic BP, cholesterol, body mass index (BMI), tobacco consumption, physical activity, antihypertensive treatment, and history of myocardial infarction. (4) In the different analyses, the risk ratio compares the risk of the second, third, and fourth classes to the first class (<60 bpm), which is considered as the reference class (risk ratio=1). (6) Risk ratios and 95% confidence intervals for the different causes of mortality were calculated for both genders, and in younger and older subjects, using a Cox proportional hazard regression analysis controlling for age alone or age and other risk factors (systolic BP, diastolic BP, cholesterol, BMI, tobacco consumption, physical activity, antihypertensive treatment, and history of myocardial infarction).

The interaction between HR and PP (used in different models as either continuous, quantitative, or 4-class qualitative parameters using the quartile approach) was also tested. We tested 3 models: (1) PP, age, mean BP, and other risk factors (cholesterol, tobacco consumption, physical activity, antihypertensive treatment, history of myocardial infarction, and BMI); (2) model 1 plus HR; and (3) model 2 plus PP and HR interaction, using a likelihood-ratio test.

The qualitative separation for PP was accomplished by defining the following quartiles: PP1≤45; 45<PP2≤50; 50<PP3<65; and PP4≥65 mm Hg. This classification by increments of 5 mm Hg is the closest to the quartile distribution in the entire population.

The level of statistical significance was 5%. All statistical analyses were performed using SAS software.

Results

Table 1 summarizes the clinical characteristics of the population according to the level of HR. Higher HR is associated with higher BP, plasma cholesterol, BMI, and tobacco consumption and with lower body height and physical activity in men. Age was not related to the level of HR. Similar findings were observed in women except for tobacco consumption, which surprisingly tended to decrease with increasing HR.

Table 2 shows the mortality rates in men and women according to the HR class. In men, frequencies of all-cause, noncardiovascular, cardiovascular, and coronary heart disease (CHD) mortality were significantly increased in the higher HR groups ($P<0.001$), whereas cerebrovascular mortality was found to be unrelated to the HR level. In women, the effect of HR was observed for all-cause and non-CVD mortality, and a trend was also observed for stroke mortality ($P=0.054$).

Figure 1 shows the survival probability curve according to HR classes for all-cause and CVD mortality in both genders.

TABLE 2. All-Cause, Non-CVD, CVD, CHD, and Cerebrovascular (Stroke) Mortality Rates According to HR

	Men					Women				
HR Group	All-Cause (*P*=0.001)	Non-CVD (*P*=0.001)	CVD (*P*=0.001)	CHD (*P*=0.001)	Stroke (*P*=0.50)	All-Cause (*P*=0.001)	Non-CVD (*P*=0.003)	CVD (*P*=0.53)	CHD (*P*=0.89)	Stroke (*P*=0.054)
HR<60	186 (12.3)	133 (8.8)	53 (3.5)	31 (2.0)	11 (0.7)	27 (5.0)	16 (2.9)	11 (2.0)	4 (0.7)	3 (0.6)
60≤HR≤80	1259 (15.7)	833 (10.4)	426 (5.3)	223 (2.8)	86 (1.1)	396 (8.2)	282 (5.8)	114 (2.4)	46 (1.0)	36 (0.7)
80<HR≤100	488 (22.3)	342 (15.6)	146 (6.7)	95 (4.3)	23 (1.1)	146 (9.7)	103 (6.9)	43 (2.9)	13 (0.9)	17 (1.1)
HR>100	103 (26.8)	64 (16.7)	39 (10.2)	21 (5.5)	5 (1.3)	41 (11.4)	29 (8.1)	12 (3.3)	3 (0.8)	7 (2.0)
Total	2036 (16.8)	1372 (11.3)	664 (5.5)	370 (3.1)	125 (1.0)	610 (8.4)	430 (5.9)	180 (2.5)	66 (0.9)	63 (0.9)

Values represent absolute number of deaths (%).

In men, high HR was associated with all-cause, CVD, and CHD mortality ($P<0.001$) (not shown). In women, this association was observed only for all-cause mortality.

Table 3 indicates the risk ratios and confidence intervals in both sexes for the different causes of mortality according to HR values. In men, after adjustment for age (upper section), HR was a significant predictor of non-CVD and CVD mortality. For non-CVD mortality, the risk significantly increased for HR>80 bpm compared with the reference group (HR<60 bpm). For CVD mortality, the risk was already significantly increased in the group 60≤HR≤80 and progressively increased in the higher HR groups. The association between HR and CVD mortality was due to an increase in CHD mortality but not to an increase in stroke mortality. After controlling for other risk factors (lower section), there was an overall decrease in the risk ratios, but they remained significant. For women, HR was associated with all-cause and non-CVD mortality but not with CVD mortality.

Table 4 presents the risk ratios for the different causes of mortality in younger and older men, adjusted for age alone (upper section) and for age and other risk factors (lower section). In both age groups, the same associations were observed between HR and the different causes of mortality. Nevertheless, a trend for higher risk ratios for non-CVD mortality was observed in younger men. In women, the risk of all-cause and non-CVD mortality related to HR did not differ according to age (not shown).

Figure 2 shows the mortality rates in normotensive and hypertensive subjects according to HR level. As expected, in both genders, the presence of hypertension was associated with an increased risk in the different causes of mortality. HR was significantly associated with all-cause, CVD, and non-CVD mortality (not shown), both in normotensive and hypertensive subjects. High HR was associated with a higher CHD mortality only in hypertensive men ($P<0.01$); in normotensives the same trend was observed but was not statistically significant ($P=0.12$). However, no significant interaction between HR and presence of hypertension on CHD mortality was observed. The level of HR did not predict stroke mortality regardless of BP level (not shown). In women, a significant association between HR and all-cause mortality was observed in normotensives. HR was not associated with CVD mortality in women. In fact, in hypertensives, there even seems to be an inverse trend for CVD and CHD mortality, although the associations are not significant. This is probably due to the low number of cardiovascular deaths in women.

We also studied the combination effect of PP and HR on the different causes of mortality by comparing the 3 models: PP (model 1); PP and HR (model 2); PP, HR, and the interaction PP×HR (model 3) (see Methods). In both genders, PP and HR were independent predictors of all-cause and non-CVD mortality, with no significant interaction, indicating that the effect of HR on non-CVD mortality was not influenced by the level of PP. For CVD and especially CHD mortality, PP and HR were again significant predictors in men (model 1 versus model 2: $\chi^2=12.7$ for CVD mortality and 9.2 for CHD mortality; $P<0.001$ for both), but a negative interaction between the two was observed (interaction term following the likelihood-ratio test model 2 versus model 3 was significant for CVD: $\chi^2=17.9$, $P<0.0001$, and $\chi^2=9.1$ for CHD, $P<0.001$). Figure 3 shows CVD and CHD death rates according to HR and PP classes. In the first 3 groups of PP, an elevated level of HR was associated with a higher mortality rate for both CVD and CHD. In the last group of PP (≥65 mm Hg), however, no significant association between HR and CVD or CHD was observed. For an increment from one class to the next of HR, the mean risk (95% confidence interval) for CVD, after adjustment for age and other risk factors, was as follows: PP1, 1.55 (1.10 to 2.10); PP2, 1.35 (1.06 to 1.73); PP3, 1.38 (1.13 to 1.67), and PP4, 0.92 (0.75 to 1.13). In women, no such interaction was observed, and the effect of HR was not significant for CVD and CHD mortality regardless of PP level (not shown).

Discussion

Our study clearly shows that in a large, relatively low-risk population (volunteers for a free medical examination), HR measurements may help in evaluating individual cardiovascular risk in men. These results should be interpreted with caution and taking into account a number of limitations: (1) single measurements of HR and other clinical parameters that reduce the precision of our estimation; (2) nonassessment of possible confounding factors not tested in our cohort, such as alcohol use and other indicators of general health; and (3) low mortality rate in women responsible for low statistical power in our population. However, as we mentioned in the Methods section, our population is representative of a general French population in terms of the distribution of mortality causes, and the type of health data is similar to data used by physicians for the evaluation of their patients' CVD risk. Our results demonstrate that in men, high HR is a predictor of global and CVD mortality, independent of other known CVD risk factors such as age, systolic and diastolic BP, total cholesterol, BMI, history of myocardial infarction, antihypertensive treatment, smoking, and physical activity. The increase in CVD mortality with high HR was due to an increase in coronary but not cerebrovascular mortality. We previously reported similar findings for PP[12]: in men, a wide PP was an independent and significant predictor of coronary but not cerebrovascular mortality. In fact, in both our previous[12] and present studies, mean BP but not PP was the significant predictor of cerebrovascular mortality. The data of these 2 studies show that pulsatile stress characterized by its amplitude (PP) and its frequency (HR) is a determinant for CHD mortality, whereas the steady stress corresponding to the mean BP is a significant determinant for both cerebrovascular and coronary mortality.

As previously described by others (see review),[5] we found that increased HR was not only associated with excessive CVD mortality but also with non-CVD causes of death. The explanations for this association remain unclear. It has been suggested that increased HR is a nonspecific variable of health and mortality rates. Interestingly, as for HR, BP levels are also a strong predictor for both CVD and non-CVD mortality.

TABLE 3. Risk (95% Confidence Interval) Related to HR for Different Causes of Mortality, According to Gender

	Men				
HR Group	All-Cause	Non-CVD	CVD	CHD	Stroke
Adjusted for age only					
60≤HR≤80*	1.27 (1.09–1.48)	1.16 (0.96–1.39)	1.50 (1.13–2.00)	1.34 (0.92–1.95)	1.43 (0.76–2.68)
80<HR≤100*	1.93 (1.63–2.29)	1.82 (1.49–2.25)	1.93 (1.41–2.64)	2.13 (1.42–3.19)	1.40 (0.68–2.88)
HR>100*	2.53 (1.99–3.22)	2.00 (1.49–2.70)	3.08 (2.04–4.70)	2.76 (1.59–4.80)	1.72 (0.60–4.96)
P‡	0.0001	0.0001	0.0001	0.0001	0.32
Adjusted for age and other risk factors†					
60≤HR≤80*	1.18 (1.00–1.37)	1.09 (0.91–1.32)	1.35 (1.01–1.80)	1.20 (0.82–1.75)	1.29 (0.68–2.42)
80<HR≤100*	1.54 (1.29–1.84)	1.54 (1.25–1.90)	1.44 (1.04–2.00)	1.49 (0.97–2.28)	1.18 (0.55–2.49)
HR>100*	1.97 (1.50–2.58)	1.71 (1.23–2.38)	2.18 (1.37–3.47)	1.90 (1.02–3.94)	1.23 (0.40–3.77)
P‡	0.0001	0.0001	0.0002	0.002	0.78

*Relative risk vs HR<60 bpm considered as the reference group (RR=1).

†Systolic and diastolic BP, BMI, history of myocardial infarction, antihypertensive treatment, total cholesterol, physical activity, and tobacco consumption.

‡*P* values for linear trend for HR categories.

Role of HR on CVD Mortality in Subgroups of Subjects According to Gender, Age, and Presence of Hypertension

In the present study we investigated whether the effect of HR on CVD mortality rates was different according to gender, age, and the presence of hypertension. We found that the association between HR and CVD mortality was present in men but not in women, thus confirming previously reported data.[5,6] Theoretically, differences between men and women could be due partly to the relatively small number of CVD deaths in the female population. However, as shown in Figure 3, the presence of hypertension was a strong predictor for CVD and CHD mortality in women. Thus, the observed gender differences do not seem to be the exclusive consequence of low death rates in women but might also reflect differences in the specific role of each risk factor in the cardiovascular system.

As shown in Table 1, mean age was similar in the different HR groups. The lack of association between age and HR has already been reported by others.[1–5] In the present study, we also showed that age did not influence the role of HR in CVD mortality. Thus, HR seems to be a significant predictor of CVD mortality in both younger and older subjects.

Finally, we did not observe significant interactions between the presence or absence of hypertension and high HR as predictors of CVD mortality. It is possible that the difference concerning the association of HR and CHD mortality reflects a tendency toward a more pronounced effect of HR in hypertensive subjects, but the interaction term was not significant.

TABLE 4. Risk (95% Confidence Interval) Related to HR for Different Causes of Mortality in Men, According to Age

	Age <55 y				
HR Group	All-Cause	Non-CVD	CVD	CHD	Stroke
Adjusted for age only					
60≤HR≤80*	1.39 (1.09–1.80)	1.38 (1.02–1.86)	1.41 (0.88–2.25)	1.52 (0.81–2.84)	1.15 (0.40–3.31)
80<HR≤100*	2.44 (1.87–3.20)	2.52 (1.83–3.45)	2.08 (1.25–3.45)	2.78 (1.43–5.38)	1.69 (0.53–5.39)
HR>100*	2.75 (1.90–3.98)	2.42 (1.55–3.78)	3.23 (1.69–6.16)	3.13 (1.30–7.55)	0.91 (0.10–8.18)
Adjusted for age and other risk factors†					
60≤HR≤80*	1.24 (0.96–1.60)	1.26 (0.93–1.71)	1.17 (0.73–1.88)	1.24 (0.66–2.34)	0.99 (0.34–2.87)
80<HR≤100*	1.78 (1.34–2.36)	1.89 (1.35–2.63)	1.43 (0.83–2.45)	1.92 (0.95–3.86)	1.22 (0.36–4.14)
HR>100*	2.02 (1.30–3.13)	1.71 (1.01–2.90)	2.95 (1.34–6.50)	2.66 (0.90–7.83)	0.48 (0.04–6.42)

*Relative risk vs HR<60 bpm considered as the reference group (RR=1).

†Systolic and diastolic BP, BMI, history of myocardial infarction, antihypertensive treatment, total cholesterol, physical activity, and tobacco consumption.

TABLE 3. Continued

Women				
All-Cause	Non-CVD	CVD	CHD	Stroke
1.67 (1.13–2.47)	2.02 (1.22–3.34)	1.09 (0.59–2.02)	1.24 (0.45–3.44)	1.20 (0.37–3.91)
1.86 (1.23–2.80)	2.24 (1.32–3.80)	1.19 (0.60–2.30)	0.89 (0.29–2.76)	1.75 (0.51–6.02)
2.28 (1.40–3.71)	2.71 (1.47–5.00)	1.46 (0.64–3.33)	0.89 (0.19–4.04)	2.99 (0.76–11.7)
0.002	0.003	0.48	0.90	0.07
1.55 (1.05–2.30)	1.96 (1.18–3.26)	0.93 (0.50–1.73)	1.09 (0.39–3.04)	1.03 (0.31–3.34)
1.60 (1.04–2.44)	1.98 (1.15–3.40)	0.99 (0.49–1.99)	0.79 (0.24–2.64)	1.54 (0.43–5.47)
1.90 (1.09–3.31)	2.49 (1.24–5.00)	1.06 (0.42–2.68)	0.65 (0.11–3.81)	3.23 (0.72–13.4)
0.03	0.001	0.79	0.82	0.16

Interactions of the Two Components of the Cyclic Strain: PP and HR

To better understand the role of the 2 components of pulsatile stress on the different causes of mortality, we evaluated the combined effects of PP and HR. In the present investigation, elevated levels of PP were observed in subjects with higher HR (Table 1). Similar results were reported in other epidemiological studies in which correlations between HR and BP were generally stronger with systolic than with diastolic BP,[13–15] showing higher PP levels in subjects with increased HR. In the present study, associations between HR and PP remained significant even after adjustment for age, body weight, height, smoking, and other possible confounders. However, a recent report from the SAVE trial found no relationship between HR and PP in postinfarction patients with impaired left ventricular function.[16] These differences may be related to underlying pathologies and/or to the use of medication in the population of the SAVE study.

We observed that the association of high HR and high PP has cumulative effects on all-cause and non-CVD mortality, ie, no interaction was observed between the 2 parameters. On the contrary, a negative synergistic effect was observed in men for CVD and CHD mortality, indicating that the CVD risk for the combined presence of high HR and PP was lower than expected. It has been shown previously that high PP, which mainly reflects arteriosclerotic alterations of the aorta and other large arteries, was an independent risk marker for cardiovascular morbidity and mortality.[12,17,18] It is therefore possible that a common mechanism enhances both PP and HR and that this mechanism is the main cause of cardiovascular complications. Interestingly, a similar negative interaction between HR and cholesterol was recently reported by Mensink et al.[6] Some authors (see Reference 5) suggest that sympathetic overactivity could be the common factor acting on cholesterol, HR, and PP.

Another explanation for the negative synergistic effect of HR and PP on CVD mortality is that in subjects with high HR, PP levels at the site of the brachial artery do not reflect central aortic PP. Actually, the relation between central and peripheral PP is determined by transfer function, which is frequency dependent.[19] This transfer function has a peak modulus of ≈3, at a frequency of 4 Hz. This implies that PP amplification between aorta and brachial artery increases

TABLE 4. Continued

Age ≥55 y				
All-Cause	Non-CVD	CVD	CHD	Stroke
1.20 (0.99–1.46)	1.03 (1.09–1.29)	1.56 (1.09–2.24)	1.24 (0.78–1.98)	1.59 (0.73–3.48)
1.62 (1.30–2.01)	1.40 (1.08–1.82)	1.84 (1.24–2.75)	1.76 (1.05–2.96)	1.15 (0.46–2.88)
2.36 (1.71–3.26)	1.72 (1.15–2.57)	3.01 (1.75–5.16)	2.61 (1.28–5.34)	2.01 (0.58–6.96)
1.13 (0.93–1.38)	0.99 (0.79–1.25)	1.44 (1.00–2.08)	1.16 (0.72–1.86)	1.49 (0.68–3.26)
1.40 (1.11–1.76)	1.31 (1.00–1.73)	1.43 (0.94–2.17)	1.27 (0.74–2.18)	1.00 (0.38–2.62)
2.02 (1.43–2.87)	1.63 (1.05–2.52)	2.25 (1.26–4.01)	2.08 (0.94–4.58)	1.33 (0.35–5.04)

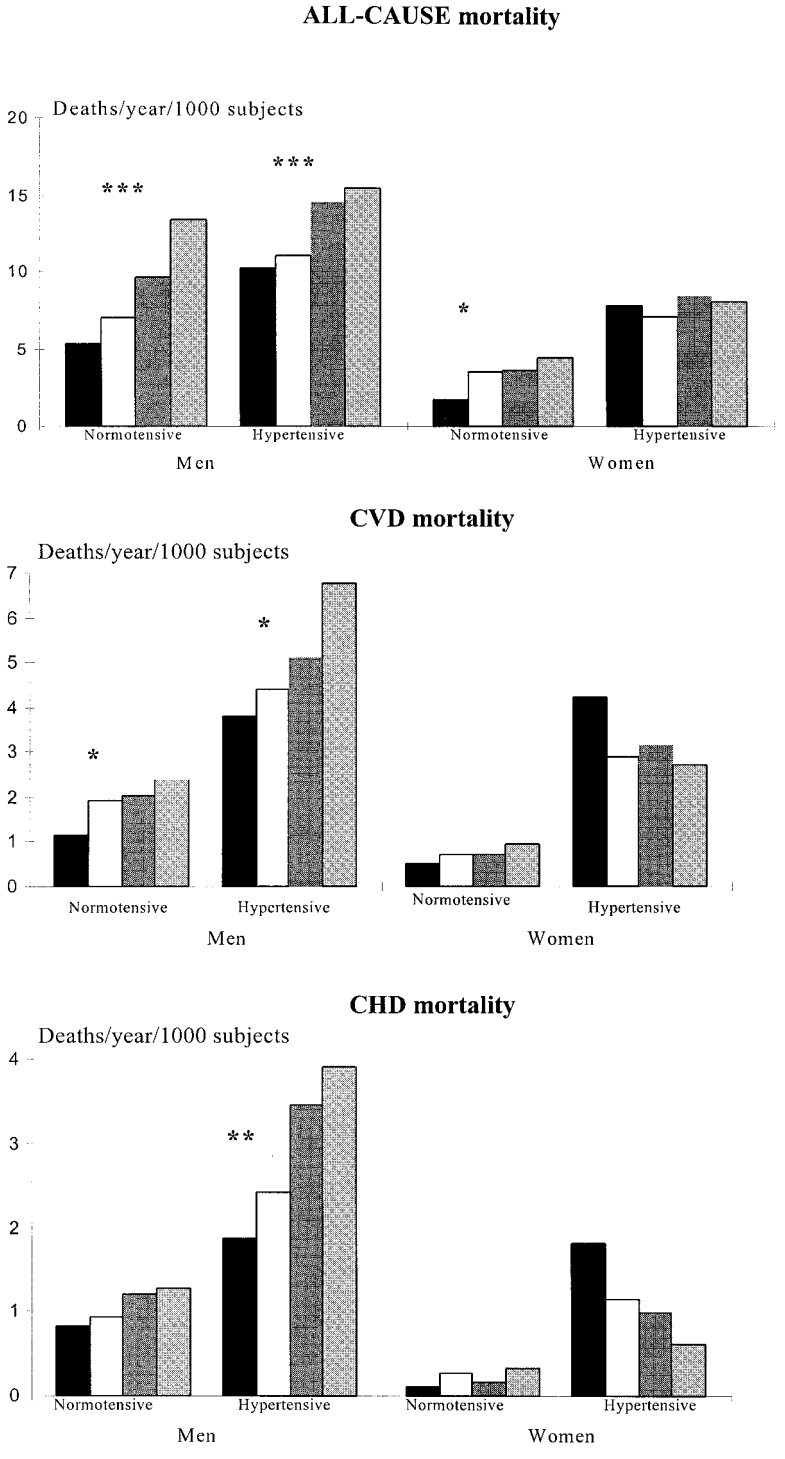
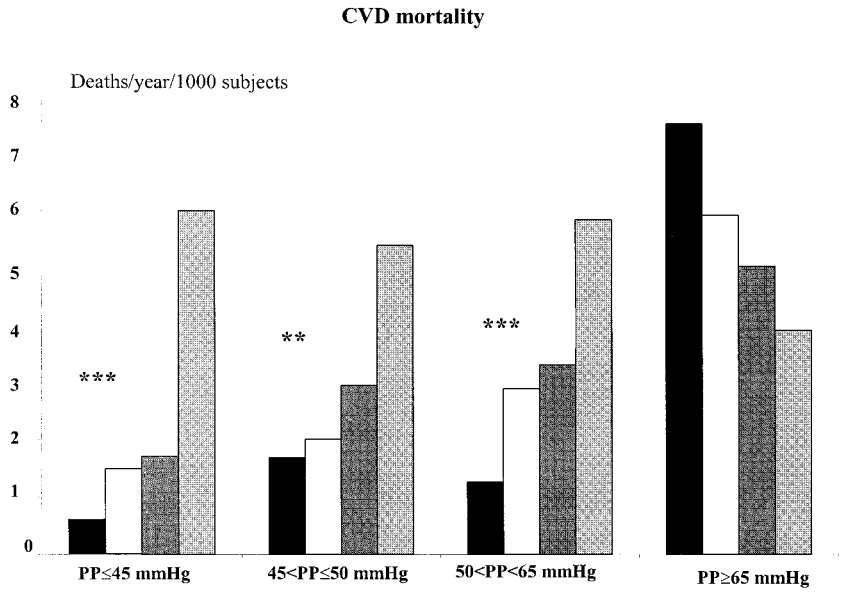


Figure 2. Mortality rates (deaths per year per 1000 subjects) in normotensive and hypertensive subjects according to HR class during the 18-year follow-up period. Effect of HR on mortality rates in each group was tested using a χ^2 trend test: $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. Black bars indicate HR<60; white bars, 60≤HR≤80; dark gray bars, 80<HR≤100; and light gray bars, HR>100 bpm.

with HR.[20] It has been calculated that an increase in HR of 10 bpm increases PP amplification by 10% (Alberto Avolio, personal communication, 1998). Thus, tachycardic subjects with high brachial PP may be at lower risk than expected since their aortic PP (which is a major determinant of cardiac afterload) is overestimated because of the amplification phenomenon.

Finally, we can also suggest that since PP and HR are the 2 components of cyclic stress, at lower levels (categories 1 to 3) the increase in HR is the stronger determinant of total cyclic stress, while at higher PP (>65 mm Hg), the effect is primarily driven by the marked increase in arterial stiffness.

The results of the present study suggest that accelerated HR represents an independent predictor of all-cause mortality for both genders and of CVD mortality in men, independent of age and the presence of hypertension. The combination of high HR and high PP increases the risk of all-cause and non-CVD mortality. Further investigations are needed to explain the complex interactions between HR, PP, and cardiovascular complications.



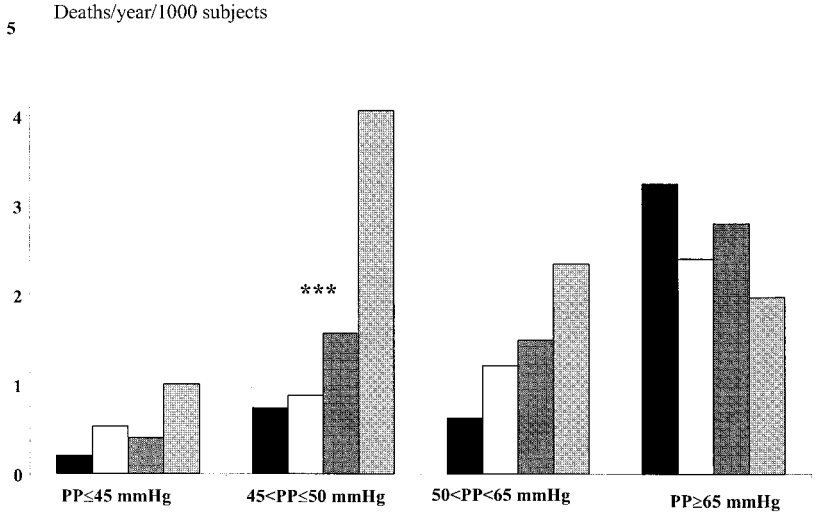


Figure 3. CVD and CHD mortality rates in men (deaths per year per 1000 subjects) according to the HR in the 4 PP groups. *P* values for a crude χ^2 trend test: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. Black bars indicate HR<60; white bars, 60≤HR≤80; dark gray bars, 80<HR≤100; and light gray bars, HR>100 bpm.

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