

Long-term risk of stroke and myocardial infarction in middle-aged men with a hypertensive response to exercise: a 44-year follow-up study

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Introduction: Data on the prognostic value of hypertensive response to exercise in cardiovascular disease are limited. The aim was to determine whether SBP reactions during exercise have any prognostic value in relation to the long-term risk of stroke and myocardial infarction (MI).

Patients and methods: A representative cohort of men from Gothenburg, Sweden, born in 1913, who performed a maximum exercise test at age 54 years, ($n = 604$), was followed-up for a maximum of 44 years with regard to stroke and MI.

Results: Among the 604 men, the mean resting and maximum SBP was 141.5 (SD 18.8) and 212.1 (SD 24.6) mmHg, respectively. For maximum SBP, the risk of stroke increased by 34% (hazard ratio 1.34, 95% confidence interval 1.11–1.61) per 1-SD increase, while no risk increase was observed for MI. The highest risk of stroke among blood pressure groups was observed among men with a resting SBP of at least 140 mmHg and a maximum SBP of at least 210 mmHg with an hazard ratio of 2.09 (95% confidence interval 1.29–3.40), compared with men with a resting SBP of less than 140 mmHg and a maximum SBP of less than 210 mmHg, independent of smoking, blood glucose, cholesterol and BMI.

Conclusion: Among middle-aged men with high resting and maximum blood pressure during maximum exercise workload, an increased risk of stroke was observed but not for MI. Further studies with larger sample sizes are needed to investigate the underlying mechanisms of the increased risk of stroke among individuals with hypertensive response to exercise.

Keywords: blood pressure, cardiovascular disease, epidemiology, exercise test, myocardial infarction, stroke

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HRE, hypertensive reaction to exercise; MI, myocardial infarction

INTRODUCTION

Globally, stroke and myocardial infarction (MI) are two of the most common causes of death and disability among adults [1]. Previous studies have

shown a strong correlation between high blood pressure (BP) and an increased risk of stroke and MI [2,3]. The exercise stress test, as an addition to myocardial scintigraphy and coronary angiography, has been used for a long time in clinical practice to evaluate the risk of cardiovascular disease (CVD), especially in terms of coronary events among high-risk patients. During exercise stress tests, symptoms, electrocardiography and a variety of physiological responses to physical activity are assessed, including repeated measurements of BP. BP levels increase physiologically during exercise. For some individuals, SBP may increase beyond 210 mmHg, known as hypertensive response to exercise (HRE) [4]. It is well known that resting BP is strongly correlated to the risk of CVD, while knowledge relating to the prognostic value of HRE for CVD, such as stroke and MI, is limited [5–8]. In addition, many but not all patients with hypertension also have an HRE, but there is no common consensus on the predictive value of this response for CVD or other health-related causes in clinical practice, as the results from previous studies diverge [6,9–11]. The aim of the current study was more specifically to identify the role of SBP reactions during maximum workload using an exercise stress test on the long-term risk of stroke and MI.

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PATIENTS AND METHODS

Study population

A detailed description of the study population has previously been reported [12,13]. In brief, all men born in 1913 on dates evenly divisible by three and living in Gothenburg, Sweden, in 1962 were invited to participate in a medical examination. Of the 973 invited, 855 men (88%) accepted and were examined in 1963. A re-examination of the men, in which 803 men participated, was performed in 1967. The re-examination included a submaximum exercise test, followed by a maximum exercise test, as described, in which 792 men were eligible [14].

Medical examination and exercise test

Before the exercise test, a medical and physical examination was performed and a medical history was taken. At the time of the study in 1967, a maximum workload test was considered to be a risk for persons with CVD. Therefore, specific conditions were set up to decide whether or not a maximum workload could be applied after a submaximum load. In summary, participants with an established heart disease were subjected only to submaximal testing. Moreover, those with chest pain significant ECG changes, arrhythmias and SBP of more than 300 mmHg or severe airway obstruction during submaximal testing were excluded from performing a maximal exercise test. Participants treated for hypertension were also excluded from maximum exercise testing [14].

The exercise test was performed with workloads, using the principles of Åstrand and Rodahl, which were the standards at the time of the study [15,16]. One or several maximum workloads above the lowest load were used. Each individual was assumed to perform a total working time of 4–6 min at maximum level. The test was only interrupted due to severe fatigue or dyspnoea or pain in muscles, joints or the chest and electrocardiography changes during exercise. Maximum oxygen uptake ($\text{VO}_{2\text{max}}$) was estimated, as previously described, using the determined submaximum and maximum heart rates (HRs) and an internally validated formula based on a subsample of the present material, where maximum oxygen uptake was determined during ergospirometry [12,17].

Definitions of blood pressure groups and other risk factors

Resting BP was recorded in the right arm, with the participant in a sitting position after a 5-min rest, with a mercury sphygmomanometer cuff size of 12 × 23 cm. Normal resting SBP was defined as a BP of less than 140 mmHg. During the exercise test, BP was measured during the fifth minute for each workload at the submaximum workloads and at the maximum load after 2 min of exercise. The HR from electrocardiography was measured initially every minute and then every 30 s to establish the maximum HR. During exercise, the patient reported the rated perceived exertion according to the well established Borg scale [18]. Using the scale steps from 6 (no exertion) to 20 (maximum exertion), it was recorded repeatedly to establish the peak value of maximum exertion. In the current study, an SBP of 210 mmHg or

higher during the exercise test was regarded as an HRE, as defined by the American Heart Association [4]. Participants were divided into BP groups depending on SBP at rest and maximum levels during the exercise test.

- (1) Group 1: Low rest and low response BP group, defined as less than 140 mmHg SBP at rest and as less than 210 mmHg maximum SBP during the exercise test.
- (2) Group 2: Low rest and high response BP group, defined as less than 140 mmHg SBP at rest and as at least 210 mmHg maximum SBP during the exercise test.
- (3) Group 3: High rest and low response BP group, defined as at least 140 mmHg SBP at rest and as less than 210 mmHg maximum SBP during the exercise test.
- (4) Group 4: High rest and high response BP group, defined as at least 140 mmHg SBP at rest and as at least 210 mmHg maximum SBP during the exercise test.

Body weight was measured with a lever balance to the nearest tenth of a kilogram, while height was measured to the nearest centimetre. BMI was measured as weight (kg)/height (m)². Waist circumference (centimetres) was measured with a soft tape over the umbilicus. After an overnight fast, blood samples for serum cholesterol (measured as mg/100 ml but converted to mmol/l) and blood glucose (measured as mg/100 ml but converted to mmol/l) were drawn from an antecubital vein, with light stasis, and analysed according to standard laboratory procedures. Smoking habits were measured by a questionnaire. Smoking was defined as ongoing smoking or smoking cessation less than 1 month previously.

Follow-up and clinical endpoints

All the participants were followed from baseline after the exercise test in 1967 until the first event of a stroke, MI or until the end of this study, on 31 December 2011 (44-year follow-up). Data on hospital admissions were obtained from follow-up data in the study and from the National Hospital Discharge Register, covering all hospital admissions in the country. Mortality data were obtained from the National Cause of Death Register, covering all deaths domestically or abroad among Swedish residents, whether or not they were citizens. Mortality and hospital discharge diagnoses were classified according to the International Classification of Diseases (ICD) codes ICD 8 until 1986; ICD 9 until 1996 and ICD 10 from 1997 onwards. For stroke, we requested medical records from the hospital where the patient was diagnosed for a stroke according to the National Hospital Discharge Register. These records were then scrutinised and reviewed by specialists in neurology and internal medicine to verify the stroke diagnosis. In 14 strokes, we never received the requested medical records. In these cases, the stroke diagnoses according to the National Hospital Discharge Register were accepted, ICD 8, 9 430–438 and ICD 10 I60–I64, I69 and G45. For MI, the following discharge diagnosis was used, ICD 8, 9 430 and ICD 10 I21. The positive predictive value for discharge diagnosis in the

Swedish National Hospital Discharge registers differs for diagnoses, but it is generally high, 85–95% [19,20].

Statistical analysis

For continuous variables, baseline characteristics are shown as the means and SDs, while, for categorical variables, they are shown as numbers (*n*) and percentages (%). For group comparisons an analysis of variance (continuous variables) and chi-squared (categorical variables) test was used, a *P* value of less than 0.05 was considered statistically significant. The incidence rate per 1000 person-years was estimated as the total number of events divided by the total follow-up time for stroke and MI separately. A Cox proportional hazard regression model was used to estimate the risk of stroke and MI separately, yielding hazard ratios with 95% confidence intervals (CIs) and a *c*-index for each model. For continuous variables, resting SBP levels at rest and maximum SBP, the risk of stroke and MI were estimated after standardization (*z*-score), showing the risk per 1-SD increase. Spearman's rank correlation was used to test the correlation between resting and maximum SBP. For BP groups, participants with a resting SBP of less than 140 mmHg and maximum SBP of less than 210 mmHg were used as a reference group. All final models were adjusted for smoking, blood glucose, serum cholesterol and BMI. An assessment of proportionality was performed using Schoenfeld residuals and all final models met proportionality. When comparing the predictive value of resting and maximum SBP (standardized), both predictors were simultaneously entered in a forced-entry Cox model adjusted for covariates with interaction effects and a *P* value of less than 0.05 was considered significant. Cubic splines (four knots) were used to estimate resting and maximum SBP for stroke and MI separately per mmHg increase; an SBP of 120 mmHg was used as a reference level for resting and 210 mmHg for maximum SBP. Cumulative risks were estimated after

adjusting for competing risk of all-cause mortality using a cumulative incidence function according to the Fine–Gray method and are reported as the cumulative probability. All statistical analyses were implemented with R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) [21].

Ethics

Informed consent was given by all participants and followed the Declaration of Helsinki in 1964. Research ethics approval was obtained on several occasions, first from the Research Ethics Committees in Gothenburg and Uppsala, Sweden, and later from the Regional Ethics Review Board, Uppsala, Sweden, No 2011/304.

RESULTS

Of the 792 men who were eligible for the exercise test, 136 did not complete the maximum exercise test [12]. Of these, 39 had incomplete data on maximum SBP, nine men were taking prescribed antihypertensive drugs or medications affecting HR and four men had incomplete mortality dates. These men were excluded from the analysis. As a result, the final study population consisted of 604 men.

Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. Of the 604 men, the overall mean value for normal resting and maximum SBP was 141.5 (SD 18.8) and 212.1 (SD ± 24.6) mmHg, respectively. The maximum HR for those performing a maximum exercise test was 172.2 bpm (SD ± 12.1), with an increasing rate for each incremental BP group. Smoking was prevalent in each BP group. A total of 237 men (21.5%) had a resting SBP of at least 140 mmHg and a maximum SBP of at least 210 mmHg. From the first to the last SBP group, DBP,

TABLE 1. Baseline characteristics of the study population and by blood pressure groups in men aged 54 years

	All, N = 604	Group 1, N = 144	Group 2, N = 109	Group 3, N = 114	Group 4, N = 237	<i>P</i>
SBP at rest (mmHg)	141.5 ± 18.8	123.0 ± 8.7	125.6 ± 7.7	148.7 ± 10.0	156.6 ± 14.4	<0.001
Max SBP (mmHg)	212.1 ± 24.6	187.6 ± 13.1	223.7 ± 12.2	191.0 ± 11.6	231.9 ± 16.5	<0.001
DBP (mmHg)	89.3 ± 11.1	81.9 ± 10.1	84.6 ± 8.8	92.4 ± 8.9	94.4 ± 10.2	<0.001
Heart rate at rest (bpm)	66.2 ± 11.4	64.7 ± 11.6	63.9 ± 10.1	67.7 ± 11.2	67.5 ± 11.7	<0.05
Heart rate at max workload (bpm), SD	172.2 ± 12.1	170.1 ± 12.0	171.6 ± 12.5	172.1 ± 11.9	173.9 ± 12.0	<0.05
VO _{2max} (l/min)	2.3 ± 0.3	2.2 ± 0.3	2.3 ± 0.2	2.2 ± 0.2	2.3 ± 0.3	<0.05
S-cholesterol (mmol/l)	6.3 ± 1.0	6.2 ± 1.1	6.2 ± 1.0	6.4 ± 1.0	6.4 ± 1.0	NS
Waist circumference (cm)	86.8 ± 9.3	84.1 ± 8.5	87.2 ± 9.4	85.8 ± 9.0	88.8 ± 9.4	<0.001
BMI (kg/m ²), SD	25.0 ± 3.1	24.0 ± 2.8	25.2 ± 3.1	24.7 ± 3.1	25.7 ± 3.1	<0.001
Blood glucose (mmol/l)	3.7 ± 1.1	3.7 ± 0.8	3.7 ± 1.2	3.7 ± 0.7	3.8 ± 1.5	NS
Rated perceived exertion	17.7 ± 1.5	17.8 ± 1.5	17.8 ± 1.7	17.8 ± 1.5	17.6 ± 1.5	NS
Smoking, <i>n</i> (%)	319 (52.8%)	72 (50.0%)	61 (56.0%)	66 (57.9%)	120 (50.6%)	NS
Number of events						
Stroke, <i>n</i> (%)	137 (22.7%)	24 (16.7%)	24 (22.0%)	24 (21.1%)	65 (27.4%)	NS
Myocardial infarction, <i>n</i> (%)	183 (30.3%)	39 (27.1%)	37 (33.9%)	30 (26.3%)	77 (32.5%)	NS
Stroke and myocardial infarction, <i>n</i> (%)	47 (7.8%)	9 (6.2%)	10 (9.2%)	3 (2.6%)	25 (10.5%)	NS
Death, <i>n</i> (%)	588 (97.4%)	140 (97.2%)	107 (98.2%)	110 (96.5%)	231 (97.5%)	NS
Age at death (years)	80.1 ± 9.8	81.6 ± 9.4	81.3 ± 9.6	79.2 ± 9.5	79.1 ± 10.2	<0.05
Follow-up time (years)	26.1 ± 9.8	27.6 ± 9.4	27.3 ± 9.6	25.2 ± 9.5	25.1 ± 10.2	<0.05

Results on continuous variables are expressed as mean ± SD. Group 1: Low rest/low response blood pressure group, defined by less than 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 2: Low rest/high response blood pressure group, defined by less than 140 mmHg resting SBP and at least 210 mmHg maximum SBP. Group 3: High rest/low response blood pressure group, defined by at least 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 4: High rest/high response blood pressure group, defined by at least 140 mmHg resting SBP and at least 210 mmHg maximum SBP.

TABLE 2. Proportional hazards regression of risk of stroke, myocardial infarction and all-cause mortality by SD for SBP at rest and maximum SBP during an exercise test

	Model 1			Model 2			Model 3			P for interaction
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI	
Stroke										
Resting SBP	1.24	1.05	1.46	1.25	1.06	1.49	1.18	0.98	1.43	0.42
Maximum SBP	1.30	1.10	1.55	1.34	1.11	1.61	1.28	1.05	1.56	
Myocardial infarction										
Resting SBP	1.15	0.99	1.33	1.15	0.98	1.34	1.08	0.91	1.28	0.52
Maximum SBP	1.21	1.04	1.41	1.19	1.01	1.40	1.14	0.96	1.37	
All-cause mortality										
Resting SBP	1.12	1.03	1.21	1.11	1.02	1.21	1.09	1.00	1.20	0.08
Maximum SBP	1.07	0.98	1.16	1.05	0.96	1.15	1.01	0.92	1.12	

Model 1 = unadjusted, Model 2 = adjusted for smoking, BMI, cholesterol and blood glucose, Model 3 = resting and maximum SBP forced entry Cox model adjusted for smoking, diabetes, BMI, cholesterol and blood glucose with *P* value for interaction. CI, confidence interval; HR, hazard ratio.

cholesterol, blood sugar glucose, waist circumference and BMI increased, while VO_{2max} remained similar. The mean follow-up time was longest among the men with a resting and maximum SBP of less than 140 mmHg and less than 210 mmHg.

Risk of stroke, myocardial infarction and death according to resting and maximum SBP

During follow-up, 137 men (22.7%) suffered a stroke, 183 men (30.3%) had an MI and 47 (7.8%) suffered both a stroke and MI. A total of 588 men (97.4%) died during the follow-up (Table 1). First, the risk of resting SBP vs. maximum SBP was explored. Table 2 shows the risk of resting and maximum SBP per 1-SD increase for stroke, MI and all-cause mortality separately. The risk of stroke increased by 25% for resting SBP (hazard ratio 1.25, 95% CI 1.06–1.49) and 34% for maximum SBP (hazard ratio 1.34, 95% CI 1.11–1.61) respectively per 1-SD increase, after adjusting for smoking, blood glucose, cholesterol and BMI. However, in the forced Cox regression models, only maximum SBP remained significant for the risk of stroke (hazard ratio 1.28, 95% CI 1.05–1.56). The risk of MI per 1-SD increase was NS for SBP at rest (hazard ratio 1.15, 95% CI 0.98–1.34), but it was significant for maximum SBP (hazard ratio 1.19, 95% CI 1.01–1.40) (Table 2). In the forced Cox regression model, none of the SBP measurements was associated with an increased risk of MI (resting SBP: hazard ratio 1.08, 95% CI 0.91–1.28 CI, maximum SBP: hazard ratio 1.14, 95% CI 0.96–1.37). For all-cause mortality, the risk per 1-SD increase was statistically significant for SBP at rest (hazard ratio 1.11, 95% CI 1.02–1.21) but not for maximum SBP (hazard ratio 1.05, 95% CI 0.96–1.15). Only resting SBP remained significant in the forced Cox regression model (resting SBP: hazard ratio 1.09, 95% CI 1.00–1.20).

To explore the threshold effects of risk and commonly used cut-offs, cubic spline models were explored. Figure 1 shows the cubic splines of resting and maximum SBP per mmHg increase. The risk of stroke among men increased incrementally per mmHg after 135 mmHg for resting SBP. For maximum SBP, the risk started to increase after 230 mmHg. However, for MI, no significant difference in risk was observed for resting or maximum SBP respectively (Fig. 1).

Risk of stroke, myocardial infarction and death according to blood pressure groups

The correlation between resting and maximum SBP was modest ($r=0.4$, $P<0.01$). By combining resting and maximum SBP cut-offs, four categorical BP groups were created. Table 3 shows the incidence rates of stroke, MI and all-cause mortality by BP groups, while Fig. 2 shows the probability of an event adjusted for competing risk of death. The incidence rate of stroke increased for each level of BP groups, from 6.20 (95% CI 3.98–9.23) in the first group to 11.60 (8.95–14.78) per 1000 person-years in the last group. The incidence of MI between BP groups was less pronounced, 9.84 (95% CI 7.00–13.45) to 11.59 (95% CI 9.97–13.39) per 1000 person-years. Similar trend for BP groups was observed for all-cause mortality but with an overall higher incidence rate (37.29 per 1000 person-years, 95% CI 34.34–40.43) than both stroke and MI.

The risk of stroke was similar among the different BP groups during the first years, but it started to differ after 10 years (Fig. 2). At the end of the study (44 years of follow-up), the risk of stroke was 16% in the first group, 22% in the second group, 21% in the third group and 27% in the last group. For MI, the risk between BP groups started to differ after 10 years of follow-up. The corresponding risk of MI before the end of the study was 27, 34, 26 and 32%, respectively.

Table 4 shows the risk of stroke, MI and all-cause mortality by BP groups. In overall terms, the highest risk of stroke was observed among men with a resting SBP of at least 140 mmHg and a maximum SBP of at least 210 mmHg, with an hazard ratio of 2.08 (95% CI 1.30–3.32). The risk remained after adjusting for smoking, blood glucose, cholesterol and BMI (hazard ratio 2.09, 95% CI 1.29–3.40). The analysis did not suggest any risk for BP levels on MI or all-cause mortality. A sensitivity analysis with adjustment for VO_{2max} in addition to other comorbidities was performed with similar results; HRE remained predictive for stroke during a maximum exercise load, but not for MI or all-cause mortality (data not shown).

DISCUSSION

The main finding in the current study showed that HRE increased the risk of stroke but not of MI or all-cause

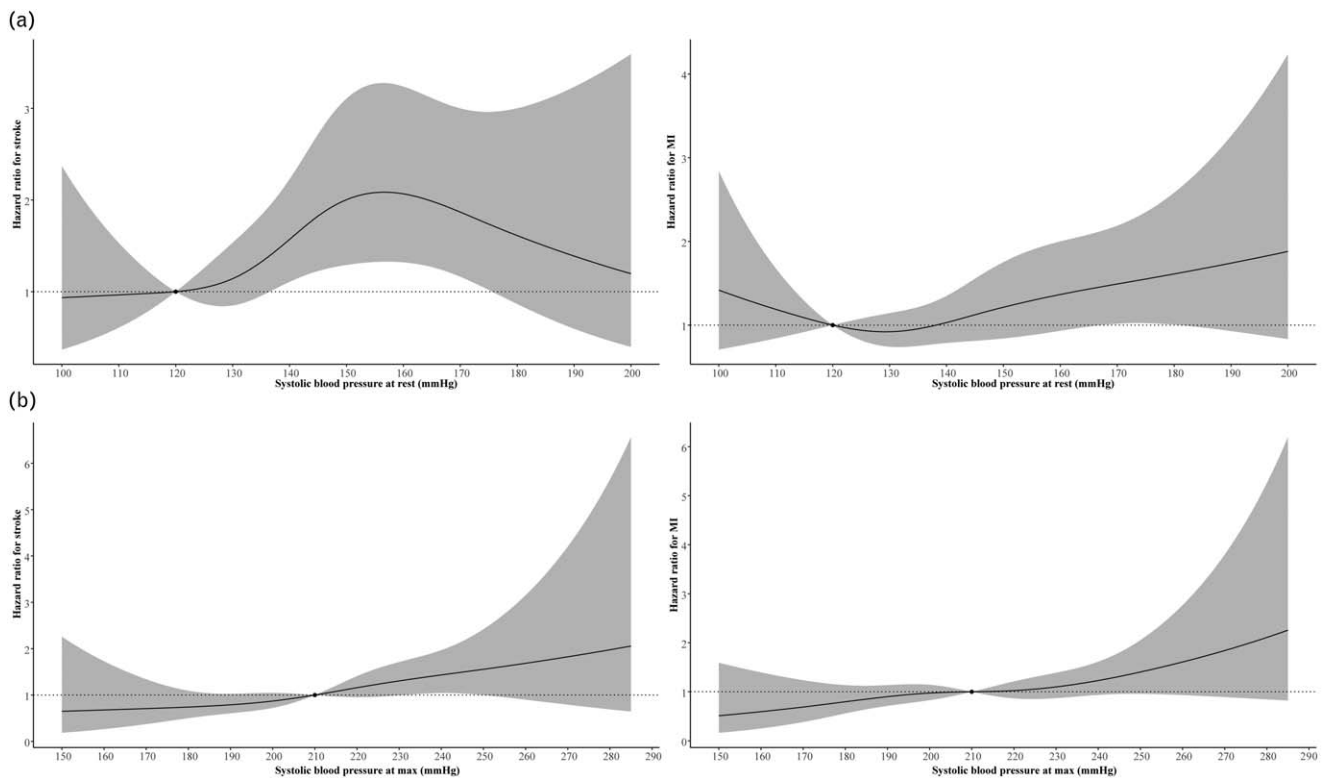


FIGURE 1 Cubic spline models for continuous variables of resting and maximum SBP and the risk of stroke. Panel (a) shows the risk of stroke and myocardial infarction per unit increase in SBP at rest, while panel (b) shows SBP at max (mmHg).

mortality. This was independent of BP at rest or other CVD risk factors among men and was consistent in both the linear and the category model during a 44-year follow-up.

In the current study, we observed that the risk of stroke was two times higher among men with an HRE and a high resting SBP (resting SBP of ≥ 140 and maximum SBP of

≥ 210 mmHg) when compared with a normotensive group and a normal response to exercise (SBP of < 140 mmHg and maximum SBP of < 210 mmHg). This categorical analysis is further supported by cubic spline analysis, which showed that, for resting SBP, the excess risk of stroke was observed after 135 mmHg, close to the well established cut-off of

TABLE 3. Events, person-years at risk and incidence rates with 95% confidence intervals of stroke, myocardial infarction and all-cause mortality by SBP groups

	Events, n (%)	Person-years	Incidence rate per 1000 person-years	Lower 95% CI	Upper 95% CI
Stroke					
Group 1	24 (17.5%)	3868	6.20	3.98	9.23
Group 2	24 (17.5%)	2856	8.40	5.38	12.50
Group 3	24 (17.5%)	2779	8.64	5.53	12.85
Group 4	65 (47.4%)	5605	11.60	8.95	14.78
All	137	15 108	9.07	7.61	10.72
Myocardial infarction					
Group 1	39 (21.3%)	3963	9.84	7.00	13.45
Group 2	37 (20.2%)	3031	12.21	8.60	16.83
Group 3	30 (16.4%)	2878	10.42	7.03	14.88
Group 4	77 (42.1%)	5923	13.00	10.26	16.25
All	183	15 795	11.59	9.97	13.39
All cause-mortality					
Group 1	140 (23.8%)	3970	35.27	29.67	41.62
Group 2	107 (18.2%)	2973	35.99	29.50	43.50
Group 3	110 (18.7%)	2870	38.32	31.50	46.19
Group 4	231 (39.3%)	5956	38.78	33.94	44.12
All	588	15 769	37.29	34.34	40.43

Group 1: Low rest/low response blood pressure group, defined by less than 140mmHg resting SBP and less than 210mmHg maximum SBP. Group 2: Low rest/high response blood pressure group, defined by less than 140mmHg resting SBP and at least 210mmHg maximum SBP. Group 3: High rest/low response blood pressure group, defined by at least 140mmHg resting SBP and less than 210mmHg maximum SBP. Group 4: High rest/high response blood pressure group, defined by at least 140mmHg resting SBP and at least 210mmHg maximum SBP. CI, confidence interval.

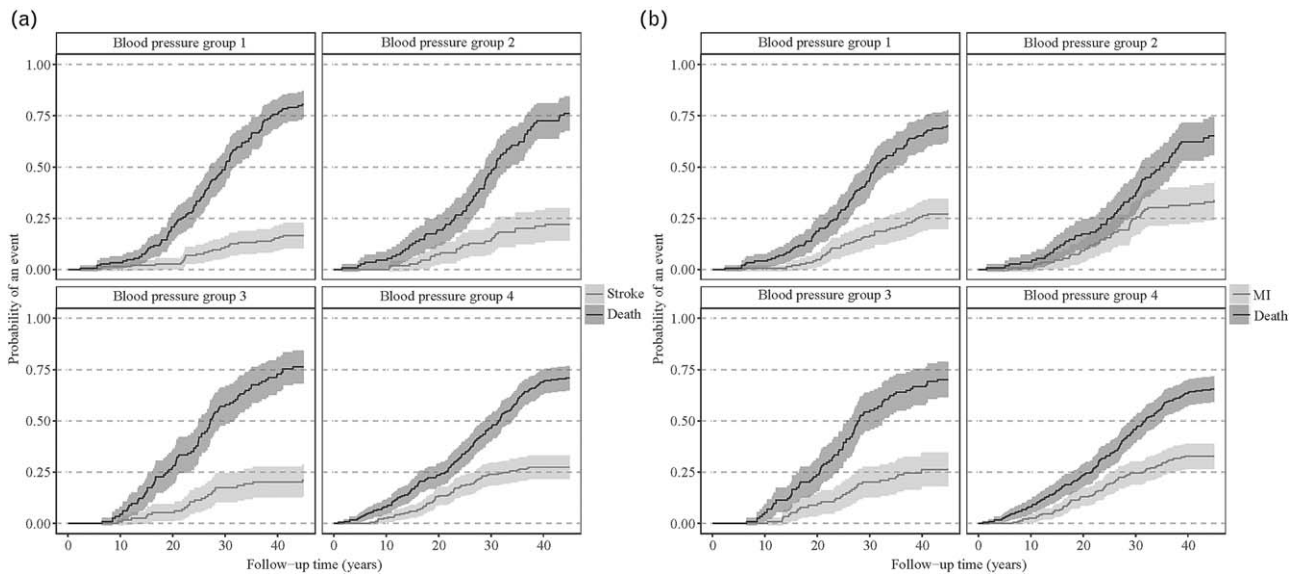


FIGURE 2 Cumulative probability of stroke and myocardial infarction by blood pressure groups adjusted for competing risk of death. Panel (a) shows the risk of stroke and panel (b) the risk of myocardial infarction.

140 mmHg, and, for maximum SBP, an excess risk of stroke was found after 230 mmHg (Fig. 1). Exercise SBP or HRE has been shown to increase mortality, but with conflicting results regarding the correlation to CVD risk [6,22–24]. Our findings suggest that the elevation of SBP during exercise is associated with an increased risk of stroke, independent of CVD risk factors, but not of MI. Our results are in line with those of a previous study from eastern Finland that showed an increased stroke risk for those with HRE during (and post) exercise [25].

There is no consensus on the definition of HRE. Some authors suggest cut-offs to define HRE, while others are more descriptive [24,25]. Some studies suggest an SBP of at least 210 mmHg in men and more than 190 mmHg in women, while others define HRE at at least 215 or at least

230 mmHg [23,26,27]. High BP or hypertension is the main risk factor for stroke (population attributable risk of 49%) and less pronounced for MI (population attributable risk 18%) [2,3]. The BP reaction during maximum working capacity in the current study further emphasises the risk of stroke in contrast to the risk of MI. These differences in the risk of MI and stroke separately by HRE could be related to the fact that stroke and MI share similar risk factors, but the impact of CVD risk factors differs [2,3,28]. The underlying mechanism is unknown. One possible explanation for the HRE could be a combination of an increased risk of endothelial dysfunction, left ventricular hypertrophy and arterial stiffness in the blood vessels [29–31]. Another factor might be that HRE might cause, or be a result of, a lower aerobic physical working capacity (i.e. VO_{2max}),

TABLE 4. Proportional hazards regression of risk of stroke, myocardial infarction and all-cause mortality by four different blood pressure groups

	Model 1			Model 2		
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
Stroke						
Group 1	Ref.			Ref.		
Group 2	1.38	0.78	2.43	1.45	0.81	2.57
Group 3	1.54	0.87	2.71	1.56	0.88	2.76
Group 4	2.08	1.30	3.32	2.09	1.29	3.40
Myocardial infarction						
Group 1	Ref.			Ref.		
Group 2	1.23	0.78	1.93	1.17	0.74	1.85
Group 3	1.19	0.74	1.91	1.13	0.70	1.82
Group 4	1.44	0.98	2.12	1.29	0.87	1.92
All cause-mortality						
Group 1	Ref.			Ref.		
Group 2	1.04	0.81	1.33	1.04	0.80	1.34
Group 3	1.23	0.96	1.58	1.19	0.93	1.53
Group 4	1.21	0.98	1.49	1.11	0.90	1.38

Model 1 = unadjusted, Model 2 = adjusted for smoking, BMI, cholesterol and blood glucose. Group 1: Low rest/low response blood pressure group, defined by less than 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 2: Low rest/high response blood pressure group, defined by less than 140 mmHg resting SBP and at least 210 mmHg maximum SBP. Group 3: High rest/low response blood pressure group, defined by at least 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 4: High rest/high response blood pressure group, defined by at least 140 mmHg resting SBP and at least 210 mmHg maximum SBP. CI, confidence interval, HR, hazard ratio, Ref., reference group.

which was a strong negative and independent predictor of total mortality in these men [12,32]. Consequently, physical maximum working capacity was a strong, independent, positive factor associated with reaching both 90 and 100 years in the study of men born in 1913, in Gothenburg, Sweden [33,34].

The use of an exercise test for coronary risk prediction is decreasing in favour of other methods, such as coronary angiography, scintigraphy and coronary computed tomography [35]. The results of the current study suggest that an exercise test may contain important information beyond the maximum aerobic capacity. The data suggest that the high BP response to exercise provides additional prognostic information beyond the well established relationship between SBP at rest and the risk of stroke.

The limitations of this study are the sample size and the fact that only men from one single city were studied. However, they were all of the same age, 54 years at start, and, consequently, no age adjustment was needed. The study was design in 1962. At that time the knowledge on the impact of cardiovascular risk factors was scarce, and no power calculation was performed. The lack of association found between hypertensive response to exercise and MI might simply be due to a type-2 error. Furthermore, changes in risk factors and the standard of care in the treatment of them over time were inevitable. The strengths are the prospective design, including a random sample from the general population, and the unique follow-up time of 44 years. On the contrary, only a single resting BP was available. The homogenous cohort from the same geographical area might further limit the generalization of the results. The aim was, however, to investigate whether a BP measurement during an exercise test in midlife was able to predict the risk of stroke and MI over time (*P* for interaction NS).

In conclusion, a hypertensive response to a maximum exercise test in men at age 54 predicted stroke, but not MI, during a 44-year follow-up. The results provide additional prognostic information beyond the well established relationship between SBP at rest and the risk of stroke. The clinical implications are twofold; first, a maximum exercise test is of importance in cardiovascular risk prediction. Second, for better risk intervention not only resting but also BP after exercise should be managed, for example by individual advice linked to the degree of physical exercise.

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Conflicts of interest

P.L. is an employee of AstraZeneca R&D.

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