

Excessive heart rate increase during mild mental stress in preparation for exercise predicts sudden death in the general population

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Aims

The aim of this study involves the early identification, among apparently healthy individuals, of those at high risk for sudden cardiac death. We tested the hypothesis that individuals who respond to mild mental stress in preparation for exercise test with the largest heart rate increases might be at highest risk.

Methods and results

Data from 7746 civil servants participating in the Paris Prospective Study I, followed-up for 23 years, allowed to compare heart rate changes between rest and mild mental stress (preparation prior to an exercise test) between subjects who suffered sudden cardiac death ($n = 81$), non-sudden ($n = 129$) coronary death, or death from any cause ($n = 1306$). The mean heart rate increase during mild mental stress was 8.9 ± 10.8 b.p.m. Risk of sudden cardiac death increased progressively with heart rate increase during mental stress and the relative risk of the third vs. the first tertile was 2.09 (95% confidence interval, 1.13–3.86) after adjustment for confounders. This relationship was not observed for non-sudden coronary death.

Conclusion

An important heart rate increase produced by a mild mental stress predicts long-term risk for sudden cardiac death. Heart rate changes before an exercise test may provide a simple tool for risk stratification.

Keywords

Sudden death • Heart rate • Risk factors • Epidemiology • Population study

Introduction

Sudden death remains to be a major public health problem and accounts for 200 000–400 000 deaths every year in the USA.^{1,2} Most often, sudden death is caused by fast ventricular tachycardia or ventricular fibrillation complicating an ischaemic cardiac event in adults. Successful resuscitation is still below 5%. The early identification, within the general and apparently healthy population, of the subjects at high risk of sudden death during acute myocardial ischaemia remains a major challenge for contemporary cardiology.^{3,4}

We have previously tested the association between sudden death risk and heart rate increase during physical stress and have

shown that an insufficient increase in heart rate during strenuous exercise is predictive of sudden death in a healthy population.⁵

Compared with heart rate recorded at rest, heart rate increases usually by a few beats per min just before the exercise test, while the subjects are preparing themselves mentally for exercise. We considered this as a 'mild mental stress' in preparation for exercise. Whereas numerous studies^{6–8} have focused on the well-documented relationship between a major stress (e.g. earthquakes, strenuous exercise) and sudden death, the potential role of a mild mental stress has not been investigated in the general population. The potential destabilizing effects of mild mental stress on ventricular arrhythmias has been only described in very high-risk patients

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with implanted cardioverter-defibrillators.^{9,10} The physiological response to stress is an increase in heart rate, mostly mediated by the activation of the sympathetic nervous system. Heart rate changes reflect the balance between vagal and sympathetic activity at the sinus node level, often referred to as 'autonomic balance'. There is strong experimental^{11,12} and clinical^{13,14} evidence that alterations in the autonomic balance, best quantified by a reduction in baroreflex sensitivity, are strong predictors of sudden death during acute myocardial ischaemia or after a myocardial infarction.

Moreover, we were intrigued by the potential implications of the fact that whereas the large heart rate increases occurring during exercise depend essentially on blood-borne catecholamines (norepinephrine and epinephrine), the more modest heart rate increases observed during mild mental stress depend on simultaneous vagal withdrawal and release of norepinephrine by the nerve endings. Whether or not the subjects who increase heart rate more than others during mild mental stress are the same who increase it more during physical exercise is unknown.

On this basis we tested our hypothesis that the prognostic information derived by heart rate changes during mild mental stress could differ from that provided by strenuous exercise and might further help in identifying subjects at higher, or lower, risk for sudden cardiac death. Our underlying assumption was that the faster the vagal withdrawal in response to a mental stress, the greater will be—during any ischaemic episode—the deleterious effect of sympathetic activation unopposed by vagal activity. For this objective, we used the healthy population and the long follow-up period (>20 years) of the Paris Prospective Study I.^{4,5}

Methods

Details of the Paris Prospective Study I concerning recruitment, design, and procedures have been described elsewhere.^{4,5} Briefly, 7746 native Frenchmen, aged 42–53 years and employed by the Paris Civil Service, were consecutively examined between 1967 and 1972. This sample consisted of 93.4% of the total number of employees in early 1967 who were born between 1917 and 1928. The subjects had electrocardiograms and physical examinations conducted by a physician, provided blood samples for laboratory tests, and answered questionnaires administered by trained interviewers. Resting heart rate was determined by the measurement of the radial pulse during a 1-min recording, after a 5-min rest in supine position.

An exercise test was then performed. Subjects with known or suspected cardiovascular disease of any grade or aetiology or with any of the following conditions were excluded from the study and did not undergo the exercise stress test: resting systolic blood pressure >180 mmHg, resting 12-lead standard electrocardiogram abnormality (Minnesota code: definite Q waves, atrioventricular block or conduction defects, ST-segment abnormalities, supraventricular tachycardia, polymorphic premature ventricular depolarizations). The exercise stress test was completed by 6565 men, but complete data were available for only 6456.

Exercise test protocol

The standardized protocol of the bicycle exercise test consisted of three successive workloads: 2 min at 82 W, 6 min at 164 W, and the last 2 min at 191 W for a maximal 10-min test duration. Cardiac rhythm was continuously monitored, and a bipolar lead (V5 and V5R) was recorded at rest and for 30 s every 2-min during exercise,

at maximal effort and every 1-min during the 10-min recovery time. Heart rate was measured at rest just before exercise, every 2 min during exercise, at peak exercise, and every minute during recovery.

We considered that whenever a subject was seated on the bicycle just before exercise, he was under mild mental stress because of the preparation to begin exercise. Accordingly, we used the heart rate measured just before exercise to define 'mild mental stress' heart rate.

Subjects ($n = 271$) with an ischaemic response to exercise and subjects ($n = 117$) with an impaired chronotropic response (who did not achieve 80% of the predicted maximum heart rate, defined as 220 b.p.m. minus age) were excluded from analysis.

Follow-up

Until retirement, the administrative department in-charge of the study population provided a list of deceased subjects every year. All available data relevant to the causes of death were collected. The data were then reviewed by an independent medical committee. After retirement, causes of death were obtained from death certificates. Sudden cardiac death was defined as a natural death, occurring within 1 h after the onset of acute symptoms. All but two sudden cardiac deaths occurred before age 65 years, consequently, only two cases were obtained from death certificates. Non-sudden coronary death was coded only if the death was found to be directly related to myocardial infarction. The end of the follow-up period was 1 January 1994. The vital status could not be determined for 355 subjects (4.6%). Their characteristics at baseline and during exercise were not significantly different from the remaining 5713 men.

Statistical analysis

Heart rate change during mild mental stress was estimated by calculating the difference between heart rate at rest and heart rate measured just before exercise test protocol (mental stress heart rate). The heart rate change during exercise was calculated as the difference between heart rate at rest and heart rate measured at the end of the bicycle exercise test. These two variables were considered in tertiles in order to assess simultaneously their effect in the same model. Tertile groups were lightly unbalanced because of the over-representation of round measures of heart rate. The baseline characteristics of subjects were compared according to the tertiles of heart rate change during mental stress using analysis of variance (quantitative variables) or logistic regression analysis (qualitative variables), and the existence of a trend was tested.

The relative risks (RR) of death and their 95% confidence intervals (CI) associated with heart rate change during mental stress and during exercise were first estimated separately and then in the same Cox proportional hazard models. Three different outcomes were considered: sudden cardiac death, non-sudden coronary death, and death from any cause. In each model, adjustment was made for the same traditional risk factors measured at baseline and including age, body mass index (BMI), tobacco consumption, systolic blood pressure, current sport activity, diabetes, and total cholesterol. The first tertile of each heart rate feature (during mental stress and during exercise) was taken as the reference category, and we computed the RR of the second and the third against the first tertile.

The proportionality assumptions of the Cox models were assessed graphically (log–log survival). All statistical tests were two-sided. All analyses were performed with SAS 9.1 (Statistical Analysis System, Cary, NC, USA) and P -values were two-sided.

Table 1 Baseline characteristics according to the tertiles of heart rate change during mild mental stress

Variables	Heart rate change (b.p.m.)			P-value (test for trend) ^a
	<4 (n = 1797)	4–12 (n = 2120)	>12 (n = 1796)	
Heart rate at rest (b.p.m.)	70.0 (9.7)	67.1 (9.3)	67.5 (9.6)	<0.0001
Tobacco (g/day)	11.4 (10.2)	12.1 (10.6)	11.1 (10.6)	0.43
Age (years)	47.8 (1.9)	47.6 (1.9)	47.4 (2.0)	<0.0001
BMI (kg/m ²)	25.5 (3.0)	25.8 (3.1)	25.8 (3.1)	0.0004
SBP (mmHg)	14.3 (2.1)	14.2 (2.0)	14.4 (2.1)	0.21
Total cholesterol (mg/dL)	219.4 (40.5)	222.3 (43.4)	223.8 (42.0)	0.002
Diabetes status	0.95 (17)	1.5 (31)	1.1 (20)	0.65
Current physical activity	15.9 (281)	14.0 (293)	15.3 (273)	0.65

Data are mean (SD) and % (n) for quantitative and qualitative variables, respectively. BMI, body mass index; SBP, systolic blood pressure.

^aP-values for ANOVA and logistics regression model for quantitative and qualitative variables, respectively.

Results

Among the 5713 subjects, the mean heart rate increase during mild mental stress was 8.9 ± 10.8 b.p.m. and the cut-off values of the tertiles of heart rate increase during mild mental stress were <4 b.p.m., between 4 and 12 b.p.m., and above 12 b.p.m. The baseline characteristics of subjects according to the tertile of heart rate change during mental stress are compared in Table 1. Resting heart rate was higher in the first tertile. There were no other meaningful differences between the three groups even though statistical significance was reached for age, BMI, and total cholesterol levels.

During the mean follow-up period of 23 years, they were 1516 deaths including 81 sudden cardiac deaths and 129 non-sudden coronary deaths. As shown in Figure 1A, the risk of sudden cardiac death increased progressively with an increase in heart rate during mental stress (P for trend = 0.02) and the RR of the third vs. the first tertile was 2.09 (95% CI, 1.13–3.86) after adjustment for confounders. Conversely, no such relationship was observed for non-sudden coronary death. A moderate but statistically significant relative increased risk of death from any cause was found for the third tertile only.

During exercise, the mean heart rate increase was 100.7 ± 14.5 b.p.m. When subjects were divided into tertiles according to their heart rate increase during exercise, the cut-offs were below 96 b.p.m. for the first tertile, between 96 and 108 b.p.m. for the second, and above 108 b.p.m. for the third tertile.

As shown in Figure 1B, a large heart rate increase during exercise was associated with a significantly lower risk for sudden cardiac death and the RR of the third vs. the first tertile was 0.47 (95% CI, 0.24–0.90) after adjustment for the confounders. Similar results were observed for death from any cause with an RR of 0.64 (95% CI, 0.56–0.73). Conversely, no clear relationship was observed for non-sudden coronary death.

Figure 2 displays the respective values of heart rate increase during mental stress and exercise. The correlation between the two heart rate measures was 0.18, meaning that one can explain only 3.2% of the variability of the other. The number of subjects within the nine combinations (quadrants) of each heart rate

measure ranged from 440 to 753, illustrating again the modest correlation between the two variables. Interestingly, this figure also indicates that no sudden cardiac deaths occurred among the subjects who increased their heart rate the least during mild mental stress and the most during exercise (upper left quadrant). Conversely, the highest proportion of sudden cardiac deaths was found among the subjects who increased their heart rate the most during mild mental stress and the least during exercise (lower right quadrant).

This is further illustrated in Figure 3 where the combined RRs of sudden cardiac death associated with the tertiles of heart rate increase during mental stress and exercise are represented, taking subjects from the first tertile of each heart rate change as reference. After adjustments for the confounders, subjects with an elevated heart rate increase during mild mental stress and a modest increase during exercise had the highest RR (2.33; 95% CI, 1.26–4.32). On the other hand, subjects with a small heart rate increase during stress and a large heart rate increase during exercise had the lowest RR (0.42; 95% CI, 0.22–0.80). Additional adjustment for resting heart rate recorded at inclusion provided similar results.

Similar but less striking results were observed for death from any cause. Subjects who had a large heart rate increase during mild mental stress and a small one during exercise had an RR of 1.29 (95% CI, 1.13–1.47), whereas those with a low heart rate increase during mental stress and a high heart rate increase during exercise had a decreased risk of death from any cause with an RR of 0.62 (95% CI, 0.54–0.71).

None of these relationships was observed for non-sudden coronary deaths (Table 2).

Discussion

The present results obtained in a large cohort of apparently healthy men, show that the heart rate increase during a mild mental stress in preparation for exercise is a strong predictor of sudden death. Specifically, individuals with the largest heart rate increase during mild mental stress and the smallest increase in

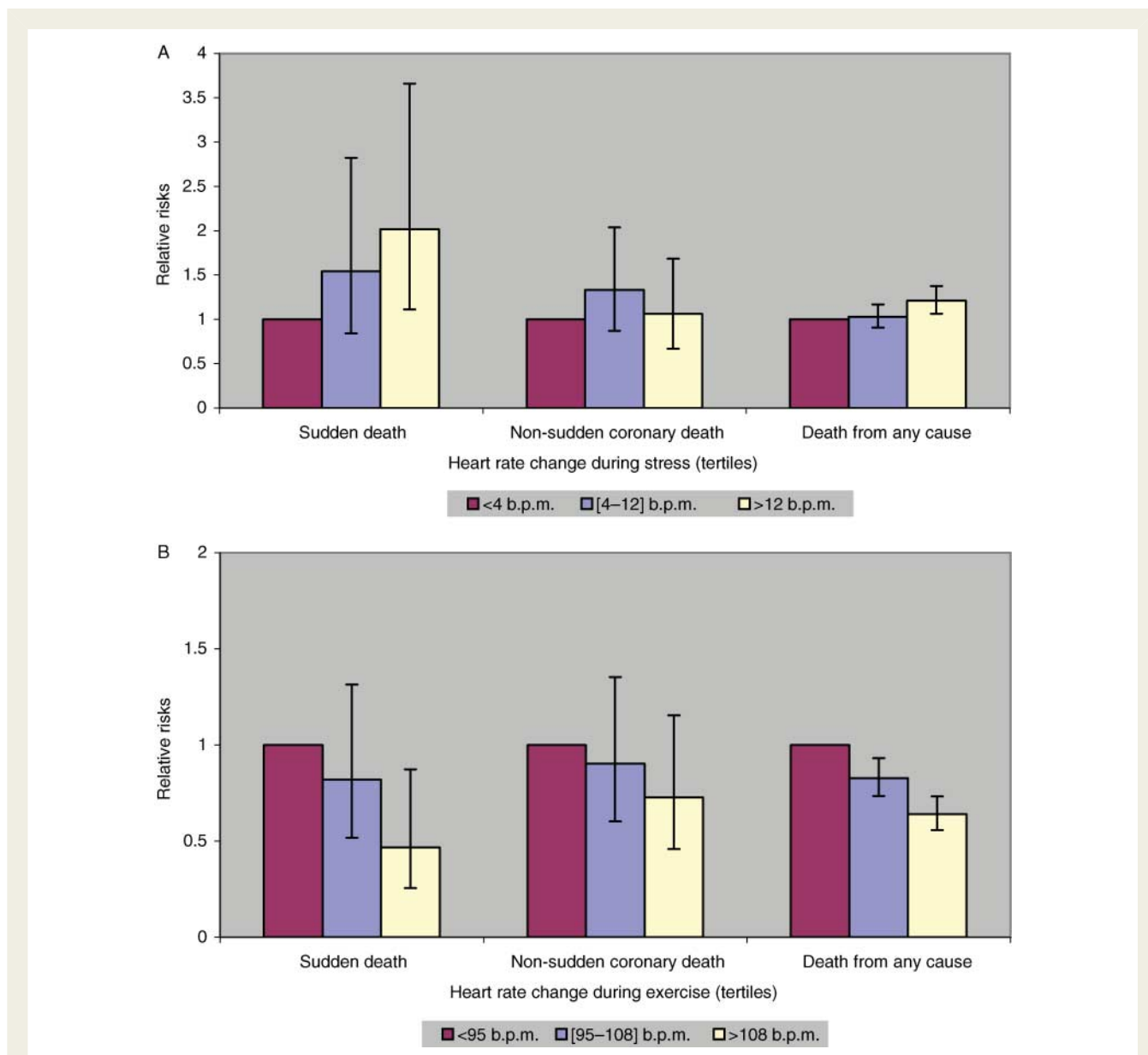


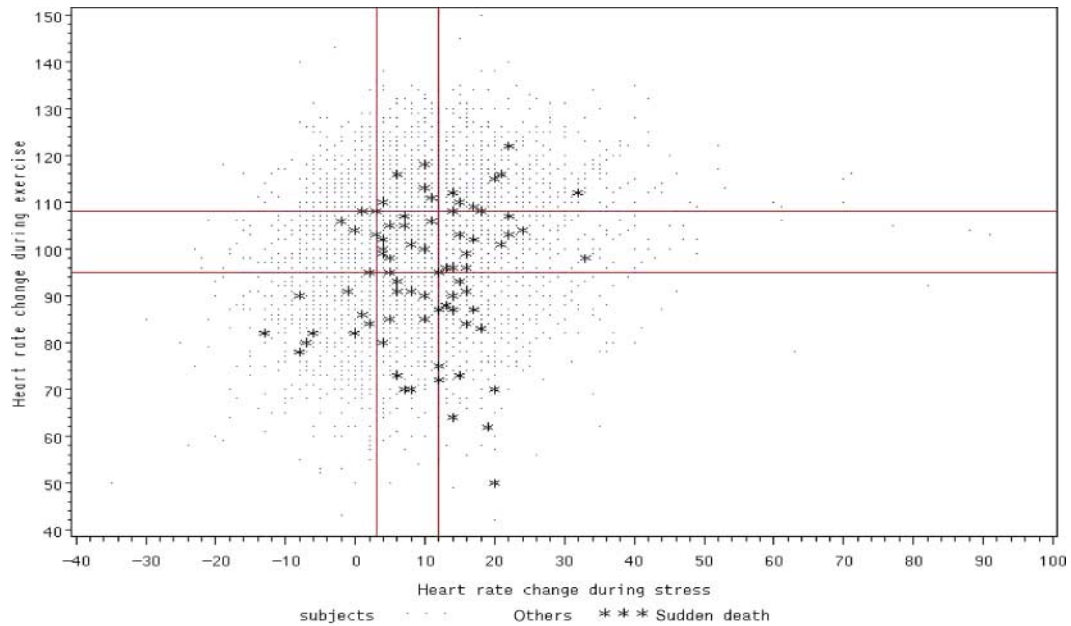
Figure 1 Multivariate-adjusted relative risks of sudden cardiac death, non-sudden coronary death, and death from any cause associated with heart rate change during mild mental stress (A) and heart rate change during exercise (B). The Paris Prospective Study I.

heart rate during an exercise test are at higher risk. As these parameters are easy to obtain, non-invasive and inexpensive, the present results carry very practical clinical implications.

240 These findings may also have conceptual implications. They expand the existing knowledge on the tight relationship between the autonomic nervous system and sudden cardiac death by providing novel and largely unexpected data, which suggest a high specificity of neural responses to different types of stress with a differential impact on arrhythmic risk. Furthermore, because of the special characteristics of the population under study⁴ and based on extremely recent insights in the neural control of heart rate,¹⁵ they raise the intriguing possibility of a genetic predisposition to the autonomic responses associated with higher or lower risk for sudden cardiac death.

Stress, heart rate, and cardiac mortality 250

The two types of stress examined here represent two different stimulations. The exercise stress test involved a significant effort and peak exercise represents a moment in which the release of both epinephrine and norepinephrine is maximal. Under these circumstances it is the blood-borne epinephrine to have the dominant effect and, because of its simultaneous effect on all cardiac cells, this may reduce electrical heterogeneity and increase electrical stability. In contrast, mild mental stress does not activate the adrenal glands and does not generate a widespread increase in epinephrine but elicits only a localized release of norepinephrine from the neural terminals, which increases regional heterogeneity and increases electrical instability. The individuals who, when faced



		Heart rate change during exercise (b.p.m.)		
		>108	[95; 108]	< 95
Heart rate change during stress (b.p.m.)	<4	0 (0/440)	0.83 (5/609)	1.33 (10/753)
	[4; 12]	0.73 (5/687)	1.36 (10/733)	2.28 (16/702)
	>12	1.14 (8/704)	2.12 (13/614)	2.97 (14/471)

Data are % (n/N)

Figure 2 Values of heart rate change during exercise vs. heart rate change during mild mental stress. The Paris Prospective Study I. The vertical and horizontal lines are the limits defining the tertiles of heart rate change during stress and during exercise. The stars represent subjects who die of sudden death, the points represent all other subjects (either dead from another cause or alive at the end of the follow-up). The ratio 'number of sudden death/number of subjects' within the nine subgroups defined by the tertiles are shown in the table.

with a mild mental stress, react with a larger increase of norepinephrine—as indicated by the larger increase in heart rate—are likely to be those who during the onset of acute myocardial ischaemia will increase more norepinephrine as a counterpart of the arrhythmogenic excitatory cardio-cardiac sympathetic reflex^{16,17} and will be at greater risk of life-threatening arrhythmias and sudden death.

Similar findings have been observed in a canine model for sudden death, involving conscious dogs with a prior myocardial infarction undergoing a transient myocardial ischaemia during a submaximal exercise stress test.^{10,18} The animals that developed ventricular fibrillation during the test compared with the animals that survived without arrhythmias had the same heart rates while resting but as they stood on the motor-driven treadmill their heart rate reached markedly higher values (from 108 ± 16 to 134 ± 22 b.p.m. vs. from 110 ± 18 to 120 ± 16 b.p.m.; $P < 0.05$; Schwartz *et al.*, unpublished results). Thus, dogs as humans react by increasing heart rate in preparation for running and, as humans, those who increase heart rate more in response to this

mental stress are more likely to fibrillate during acute myocardial ischaemia.

Another mechanism potentially contributing to a rapid increase in heart rate during mental stress is vagal withdrawal. Patients likely to respond to any stress with rapid vagal withdrawal could be more likely to become at risk for life-threatening arrhythmias during episodes of acute myocardial ischaemia because the attendant reflex sympathetic activation will be unopposed by the protective vagal activity.^{19,20} During the first minutes of exercise, the main cause of heart rate increase is mainly related to vagal withdrawal, and its association with mortality is still discussed. In over 500 Italian patients with ischaemic heart disease, it has been shown that the increase in heart rate during the first minute of exercise, was significantly associated with increased mortality risk during a mean follow-up of 6 years.²¹ Contradictory results were obtained in 1959 patients from Palo Alto (CA, USA) showing that a rapid heart rate increase was associated with improved survival.²² During recovery after exercise, there is an important parasympathetic reactivation, and an attenuated heart rate recovery has

been associated with increased risk of mortality in different studies.^{23–25} However, all of these previous studies concerning the first minutes of the exercise or the recovery recorded all-cause of death or cardiovascular mortality. None of them recorded sudden cardiac death specifically.

Genetic predisposition

In this population the probability of sudden cardiac death is strongly influenced by genetic predisposition, as the RR of sudden death was 2.76, whenever the mother had died suddenly and that it increased to a staggering 9.34 whenever both parents had died suddenly.⁴ The concept that sudden cardiac death is correlated with family history of sudden death has been recently confirmed.^{26,27} So far, however, the genes potentially involved remain totally unknown.

The autonomic nervous system might act as a ‘modifier’ for the risk of ventricular fibrillation during acute myocardial ischaemia,²⁸ and those individuals genetically either more prone to release

norepinephrine or less capable of activating vagal reflexes during ischaemic episodes might be at higher risk.

A genetic predisposition towards augmented sympathetic responses—or toward reduced vagal responses—which would be of no consequence under normal conditions would become very important under conditions of acute myocardial ischaemia or infarction. However, additional adjustment for parental sudden death in our study did not change our results.

Limitations

The heart rate increase observed during preparation for exercise is probably associated with other mechanisms than mental stress only. Resting heart rate was measured in supine position during inclusion into the study, whereas the subjects were sitting on bicycle when heart rate was recorded before exercise. It is likely that postural heart rate reactivity could play a role in the heart rate increase, and although we could expect its impact to be limited to a few beats per minute, we are unable to measure its effect. However, it is difficult to envisage that postural reactivity from supine to sitting position could explain such an important increase (9 ± 11 b.p.m.) observed in the present study.

We do not know to what extent other mental stress obtained in different conditions would have had similar results. There was no use of standardized methods to measure the level of stress and further studies are needed. Therefore, the results of the present study should probably be restrained to such a condition (mental preparation before exercise), although it has been already shown that mental stress obtained by different methods may induce myocardial ischaemia.^{29–31} In a recent study, mental stress triggered by a speaking task involving the role of playing a difficult interpersonal situation has produced a 21 ± 12 b.p.m. heart rate increase and myocardial ischaemia in some subjects with coronary artery disease and negative exercise test.³¹

Since echocardiography was not available/routinely performed at the time of the study in the late-1960s, we can neither preclude the presence of an underlying cardiac failure, nor can we preclude that several subjects received beta-blocking agents at inclusion. However, the young age and the nature of the population (healthy policemen) suggests that the prevalence of heart failure if any is very low and thus have marginal effect on our results. Moreover, beta-blocking agents were seldom used by the end of the 1960s.

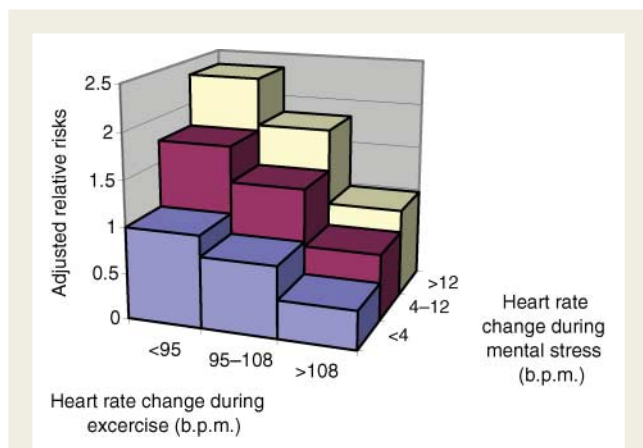


Figure 3 Multivariate-adjusted relative risks of sudden death according to tertiles of heart rate change during mild mental stress and during exercise. Relative risks of heart rate change during stress and exercise were estimated in the same Cox proportional hazard model taking the first tertile of heart rate change as the reference category. Adjustment was made on risk factors measured at baseline examination including age, body mass index, tobacco consumption, systolic blood pressure, diabetes, current physical activity, and total cholesterol.

Table 2 Multivariate-adjusted relative risks of sudden death, non-sudden death from myocardial infarction, and death from any cause associated with heart rate change during stress and during exercise

Heart rate change features	Sudden death		Non-sudden coronary death		Death from any cause	
	RR and 95% CI	P	RR and 95% CI	P	RR and 95% CI	P
During mental stress	2.33 (1.26, 4.32)	0.007	1.11 (0.70, 1.78)	0.65	1.29 (1.13, 1.47)	0.0001
During exercise	0.42 (0.22, 0.80)	0.009	0.71 (0.45, 1.13)	0.15	0.62 (0.54, 0.71)	<0.0001

Relative risks (RRs) and 95% confidence intervals were estimated in the same Cox proportional hazard model taking the first tertile of heart rate change as the reference category. For ease of presentation, only the RR of the third against the first tertile was reported. Adjustment was made for risk factors measured at baseline examination including age, body mass index, tobacco consumption, systolic blood pressure, diabetes, current physical activity, and total cholesterol.

Our population consisted of asymptomatic healthy males employed by the Paris Civil Service. Socioeconomic status, prevalence of smoking, and extent of alcohol use, as well as other factors might differ from the general population. As the study was conducted in men only, it is possible that findings in women might differ. Searching for risk factors of sudden death in middle-age men require long-term cohort studies and, as it is for long-term prospective studies, conditions existing at the beginning of the study may have changed. Therefore, the extent to which the present results could be generalized in a more unselected and/or recent population cohort is unclear.

Clinical implications

The present findings might carry significant clinical implications. Few measurements in medicine are as inexpensive and as easy to obtain in large general populations as to measure the heart rate difference between resting and being ready to perform an exercise test. If the exercise test is actually performed, additional data useful for risk-stratification will be obtained and special attention will be paid to the possibility of a mismatch (lower than normal heart rate increase at peak exercise, after exclusion of chronotropic incompetence as done in our study¹³), as described here. Individuals showing a high heart rate increase with mild mental stress would be considered for additional investigations and for tailored preventive strategies aimed in first place to reduce the probability of ischaemic heart disease.

Conclusion

This large and long prospective study has disclosed a higher risk for sudden death for those apparently healthy individuals whose heart rate responses are exaggerated under mild mental stress and below normal during peak exercise. This implies novel and simple ways for the early identification of subjects at increased future risk for sudden cardiac death.

Author's contribution

Writing: X.J., P.J.S., P.D.; **Interpretation of results:** X.J., P.D., J.P.E., P.J.S., and C.S.; **Statistical analysis:** S.E., M.T.; **Study management:** P.D., M.D., X.J.

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