The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 12, 2005 VOL. 352 NO. 19

Heart-Rate Profile during Exercise as a Predictor of Sudden Death

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ABSTRACT

BACKGROUND

Changes in heart rate during exercise and recovery from exercise are mediated by the balance between sympathetic and vagal activity. Since alterations in the neural control of cardiac function contribute to the risk of sudden death, we tested the hypothesis that among apparently healthy persons, sudden death is more likely to occur in the presence of abnormal heart-rate profiles during exercise and recovery.

METHODS

A total of 5713 asymptomatic working men (between the ages of 42 and 53 years), none of whom had clinically detectable cardiovascular disease, underwent standardized graded exercise testing between 1967 and 1972. We examined data on the subjects' resting heart rates, the increase in rate from the resting level to the peak exercise level, and the decrease in rate from the peak exercise level to the level one minute after the termination of exercise.

RESULTS

During a 23-year follow-up period, 81 subjects died suddenly. The risk of sudden death from myocardial infarction was increased in subjects with a resting heart rate that was more than 75 beats per minute (relative risk, 3.92; 95 percent confidence interval, 1.91 to 8.00); in subjects with an increase in heart rate during exercise that was less than 89 beats per minute (relative risk, 6.18; 95 percent confidence interval, 2.37 to 16.11); and in subjects with a decrease in heart rate of less than 25 beats per minute after the termination of exercise (relative risk, 2.20; 95 percent confidence interval, 1.02 to 4.74). After adjustment for potential confounding variables, these three factors remained strongly associated with an increased risk of sudden death, with a moderate but significantly increased risk of death from any cause but not of nonsudden death from myocardial infarction.

CONCLUSIONS

The heart-rate profile during exercise and recovery is a predictor of sudden death.

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N Engl J Med 2005;352:1951-8.

Sudden and unexpected death from cardiac causes is an important health burden in the Western world. Its effect is accentuated by the fact that sudden death is often the first manifestation of cardiovascular disease.[1,2] Thus, identification of apparently normal persons who actually are at higher-than-average risk for sudden death is a major challenge.

The past two decades have witnessed growing evidence (both experimental and clinical) of a tight relationship between abnormalities in the autonomic nervous system and death from myocardial infarction, both sudden and not sudden.[3-6] Autonomic imbalance, a term used to indicate a relative or absolute decrease in vagal activity or an increase in sympathetic activity, has been associated with an increased risk of death from cardiac causes[7] and from arrhythmic causes.[8] One common feature has been that whenever markers of tonic or reflex vagal activity are reduced, the risk of death is increased.[6] This is true for baroreflex sensitivity,[4-6] for heart-rate variability,[9] for heart-rate turbulence (immediately following a premature ventricular beat),[10] and for heart-rate recovery after an exercise stress test.[11] The last is independent of the angiographic severity of coronary artery disease,[12] suggesting that alternative mechanisms are involved. Indeed, survival during a first ischemic episode is predicted by autonomic responses,[4] suggesting a genetic predisposition.[13]

However, all these previous findings were obtained in studies of patients with known cardiac disease. We explored the possibility that abnormalities in the control of heart rate in apparently healthy men may indeed precede clinical symptoms and may allow early identification of persons at increased risk for death, particularly for sudden death from myocardial infarction.

Since exercise stress testing is an easily performed and inexpensive tool that provides a wealth of information on the state of the autonomic nervous system and on its responsiveness, we assessed the heart-rate profile during exercise as a potential predictor of sudden death in a long-term cohort study of asymptomatic middle-aged men.

METHODS

Details of the Paris Prospective Study I concerning the recruitment, design, and procedures have been described elsewhere.[14-16] Briefly, the consecutive examination of 7746 native Frenchmen employed by the Paris Civil Service (age range, 42 to 53 years) was carried out from 1967 to 1972. Oral informed consent was obtained from each participant, and the research protocol was approved by the appropriate institutional board (Commission Nationale Informatique et Liberté). This sample represented 93.4 percent of the total number of employees in early 1967 who were born between 1917 and 1928. Subjects underwent electrocardiographic 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 measurement of the radial pulse during a one-minute recording, after a five-minute rest in the supine position. Diabetes was defined as past or present reported diabetes, whether or not the condition was being treated.

Subjects with known or suspected cardiovascular disease of any grade or cause were excluded from the study and did not undergo the exercise stress test. Also excluded from the study were patients with a resting systolic blood pressure of more than 180 mm Hg or an abnormality on a resting 12-lead standard electrocardiogram (Minnesota code). Ventricular function was not assessed. A total of 6565 men completed exercise testing, but complete data were available for only 6456 (98.3 percent). Only those subjects who performed the exercise test were considered for the present analysis; therefore, numbers vary from those in previous reports that considered all subjects at enrollment.[16]

EXERCISE TEST PROTOCOL

The standardized protocol of the bicycle exercise test consisted of three successive workloads: 2 minutes at 82 W, 6 minutes at 164 W, and the last 2 minutes at 191 W, for a maximum 10-minute test duration without a cool-down period.[15] The subjects' cardiac rhythm was continuously monitored, and a bipolar lead (V_5 and V_5R) was recorded at rest and for 30 seconds every 2 minutes during exercise at maximum effort and every minute during the 10-minute recovery time or whenever the monitoring physician observed an arrhythmia. Heart rate was measured at rest, before exercise, every two minutes during exercise, at peak exercise, and every minute during recovery. The heart-rate increase was defined as the difference between the peak exercise rate and the resting rate, and heart-rate recovery was defined as the reduction in rate from the peak exercise level to the rate one minute after the cessation of

exercise. Testing was terminated because of fatigue, dyspnea, leg discomfort, chest pain, a systolic blood pressure of more than 250 mm Hg, a heart rate of more than 180 beats per minute, ventricular tachycardia, or ischemic electrocardiographic changes. An ischemic response was defined as a J-point depression of 1 mm or more, with a flat or downsloping ST-segment depression during exercise or recovery. The 271 subjects who had an ischemic response to exercise and the 117 subjects who had an impaired chronotropic response (i.e., those who did not achieve 80 percent of the predicted maximum heart rate, defined as 220 beats per minute minus age) were excluded from the analysis.

FOLLOW-UP

Until the retirement of the study subjects, the administrative department in charge of the study population provided an annual list of all the subjects who had died. All available data relevant to the causes of death were collected by means of specific inquiries (i.e., medical records from hospital departments or general practitioners). An independent medical committee then reviewed the data. After the subjects' retirement, causes of death were obtained from death certificates. The ninth revision of the *International Classification of Diseases*[17] was used for coding. Sudden death from myocardial infarction was defined as a natural death that occurred within one hour after the onset of acute symptoms. Nonsudden death from myocardial infarction was coded only if the death was found to be strictly related to myocardial infarction and had occurred more than one hour after the onset of symptoms.

The end of the follow-up period was January 1, 1994. The vital status could not be determined for 355 subjects (4.6 percent of the original 7746 subjects). Their characteristics at baseline and during exercise were not significantly different from those of the remaining 5713 men studied in the present analysis.

Table 1. Baseline Characteristics and Their Association with Selective Outcomes during Follow-up.*

Characteristic	Controls (N=5503)†	Sudden Death from Myocardial Infarction (N=81)		Nonsudden Death from Myocardial Infarction (N=129)	
		Baseline Level	Univariate Relative Risk (95% CI)‡	Baseline Level	Univariate Relative Risk (95% CI)‡
Age — yr	47.6±1.9	48±1.8	1.23 (0.98–1.54)	47.8±1.8	1.03 (0.86–1.24)
Body-mass index	25.7±3.1	26.7±3.3	1.34 (1.09–1.66)	26.1±3.1	1.15 (0.97–1.37)
Tobacco use — g/day§	11.4 (10.5)	15.5 (10.0)	1.41 (1.18–1.70)	13.7±10.9	1.29 (1.10–1.51)
Resting heart rate — beats/min	68.1±9.5	71.4±9.8	1.39 (1.15–1.68)	69.6±10.7	1.23 (1.04–1.44)
Systolic blood pressure — mm Hg	137.8±17.4	142.7±22.0	1.31 (1.08–1.60)	143.1±17.9	1.30 (1.11–1.53)
Total cholesterol — mg/dl	221.0±41.6	246.8±43	1.67 (1.40–2.00)	239.6±52.9	1.49 (1.27–1.75)
Triglycerides — mg/dl¶	132.4±106.5	152.2±99.2	1.26 (1.04–1.53)	155.8±132.4	1.31 (1.13–1.54)
Duration of exercise test — min	7.3±2.5	6.0±2.3	0.59 (0.47–0.73)	6.7±2.6	0.76 (0.63–0.90)
Diabetes — no./total no. (%)	268/5255 (5.1)	5/78 (6.4)	2.39 (0.87–6.53)	6/118 (5.1)	1.08 (0.34–3.38)
Current physical activity — no./total no. (%)‖	823/5446 (15.1)	11/80 (13.8)	0.87 (0.46–1.65)	19/129 (14.7)	0.96 (0.59–1.56)
Parental history — no./total no. (%)					
Myocardial infarction	366/5442 (6.7)	5/79 (6.3)	0.92 (0.37–2.28)	18/128 (14.1)	2.32 (1.41–3.81)
Sudden death	570/5443 (10.5)	15/79 (19.0)	2.02 (1.15–3.53)	14/128 (10.9)	1.10 (0.63–1.92)

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
† Subjects in this group either were alive or died from causes other than myocardial infarction during follow-up. This group is also the reference group for the estimation of relative risk.
‡ For continuous variables, the relative risk is for an increase of 1 SD.
§ Tobacco use is the average use (in grams per day) in the five years preceding the study.
¶ The relative risk for triglycerides is for an increase of 1 SD in the triglyceride level (0.51) after log transformation.
‖ Physical activity applies to subjects who performed more than one hour of regular activity per week. The subjects retained in the sample are those who performed the exercise test.

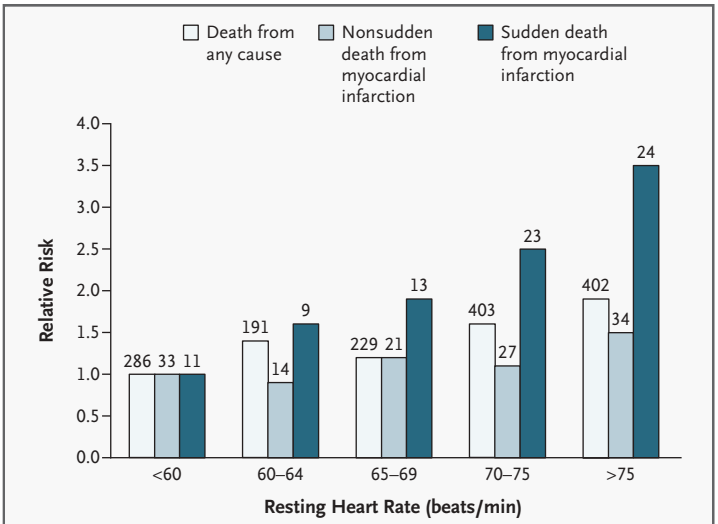

Figure 1. Relative Risks of Death from Any Cause and of Nonsudden and Sudden Death from Myocardial Infarction, According to the Quintile of Resting Heart Rate.

The reference group was subjects with a resting heart rate of less than 60 beats per minute (lowest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel–Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause ($P<0.001$), nonsudden death from cardiac causes ($P=0.02$), and sudden death from cardiac causes ($P<0.001$). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data are missing for five subjects who died of any cause, including one who died suddenly from myocardial infarction.

STATISTICAL ANALYSIS

Because of the skewed distribution of triglycerides, log-transformed values were used in the analysis. The Mantel–Haenszel chi-square test for trend was used for comparisons among quintiles of heart rate. Two-sided P values are reported. The relative risk of death was estimated with a Cox proportional-hazards model and was assessed for each quintile of heart rate. In analyses of both sudden and nonsudden death from cardiac causes, data for subjects who died from other causes were censored at their date of death. Data were analyzed with the use of SAS software (SAS Institute).

RESULTS

Among the 5713 men, and during the mean follow-up of 23 years, there were 1516 deaths (26.5 percent) from all causes, including 400 deaths from cardiac causes (7.0 percent), of which 81 were sudden deaths and 129 were nonsudden deaths from myocardial infarction. The mean (±SD) interval between the initial clinical examination and death was 11.7±5.1 years for sudden death from cardiac causes and 16.8±5.9 years for nonsudden death from cardiac causes, and the mean duration of follow-up was 21.8±4.9 years for all other participants. Baseline characteristics of the subjects are given in Table 1 according to the cause of death.

The mean maximum heart rate (expressed as the percentage of the predicted maximum heart rate) during exercise was 96±0.8 in subjects who died suddenly from cardiac causes, 97±0.6 in subjects who died from cardiac causes but not suddenly, and 98±0.1 in subjects who either died from other causes or survived (controls). The duration of exercise was 6.0±2.3 minutes in the sudden-death group, 6.7±2.6 minutes in the nonsudden-death group, and 7.3±2.5 minutes in the control group. The exercise stress test was stopped during the 164-W stage in 64 of 81 subjects who died suddenly from cardiac causes (79.0 percent), in 88 of 129 of subjects who died from cardiac causes but not suddenly (68.2 percent), and in 3247 of 5503 controls (59.0 percent). The rest of the men reached the last, 191-W stage.

After adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration, the risk of sudden death increased progressively with the resting heart rate; as compared with the risk in the lowest quintile, the risk in the highest quintile was 3.5 times as high (P for trend <0.001); the relationship was weaker, although significant, between resting heart rate and the risk of nonsudden death and death from any cause (1.5 times that in the lowest quintile [$P=0.02$] and 1.9 times that in the lowest quintile [$P<0.001$], respectively) (Fig. 1).

A statistically significant association was observed between an increase in heart rate and mortality. With a heart-rate increase of more than 113 beats per minute (highest quintile) used as the reference category, subjects with a heart-rate increase of less than 89 beats per minute (lowest quintile) had 4.0 times the risk of sudden death, 1.2 times the risk of nonsudden death, and 1.5 times the risk of death from any cause (Fig. 2).

During recovery, the patients' mean heart rate decreased progressively. Heart rates at one, two,

three, and four minutes after the cessation of exercise were all associated with death from any cause and particularly with sudden death, but not with nonsudden death from myocardial infarction. With subjects who had a heart-rate recovery (the decrease from the maximum heart rate) at one minute of more than 40 beats per minute (the highest quintile) used as the reference group, subjects with a heart-rate recovery of less than 25 beats per minute (the lowest quintile) had 2.1 times the risk of sudden death, 0.9 times the risk of nonsudden death, and 1.3 times the risk of death from any cause (Fig. 3).

The risks of death associated with these heart-rate markers are shown in Table 2. In the univariate analysis and after adjustment for confounding factors — age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration — the heart-rate profile was strongly associated with sudden death and less strongly associated with death from any cause, but it was not associated with nonsudden death from myocardial infarction (except for basal heart rate). Among these three heart-rate markers, the strongest predictor of sudden death was a lower increase in heart rate (i.e., the difference between the rate at peak maximum exercise and the rate at rest), with a relative risk of 6.18 in the univariate analysis (95 percent confidence interval, 2.37 to 16.11) for the lowest as compared with the highest quintile and 3.98 after adjustment for confounding factors (95 percent confidence interval, 1.49 to 10.61). When these three markers were simultaneously introduced in the analysis, sudden death was significantly associated with a lower increase in heart rate but not with the resting heart rate or the heart-rate recovery (because of the markers' high mutual correlations). When the analysis was restricted to subjects who stopped exercise at the 164-W level, the results were similar (data not shown).

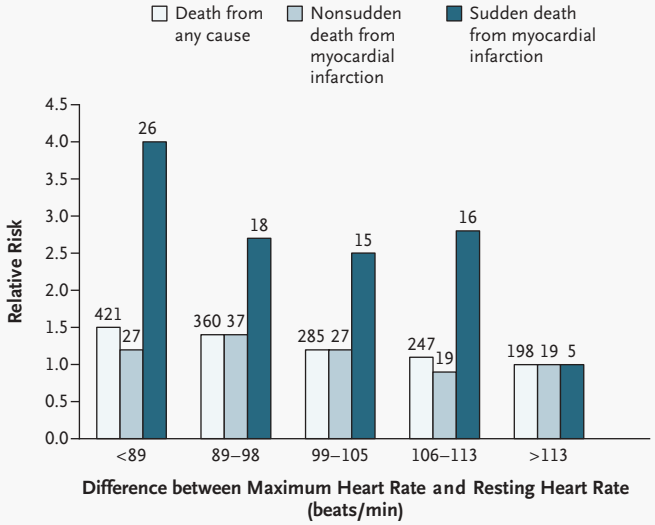

Figure 2. Adjusted Relative Risks of Death from Any Cause and from Nonsudden and Sudden Death from Myocardial Infarction, According to the Difference between the Resting and Maximum Heart Rate.

The reference group was subjects with a difference of more than 113 beats per minute between the resting and maximum heart rates (highest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel–Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause ($P<0.001$), nonsudden death from cardiac causes ($P=0.01$), and sudden death from cardiac causes ($P<0.001$). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data are missing for five subjects who died of any cause, including one who died suddenly from myocardial infarction.

DISCUSSION

Our findings, obtained in a study of a large cohort of apparently healthy persons, indicate that the heart-rate profile during exercise and recovery is a strong predictor of sudden death. Since heart-rate responses to exercise are under the control of the autonomic nervous system, these data support the concept that abnormalities in autonomic balance may precede manifestations of cardiovascular disease and may contribute to the early identification of persons at high risk for sudden death.

In most cases of sudden death in adults, coronary lesions are present[18] together with traditional risk factors for atherosclerosis. In addition, it has been suggested[19] that reflex sympathetic activation elicited by acute myocardial ischemia[20] might play a triggering role. Here, we explored the possibility that autonomic imbalance would be associated with increased risk of arrhythmia and could be unmasked by observing changes in heart rate during exercise.

The association between altered heart-rate responses during exercise and sudden death from cardiac causes and the absence of such an association with nonsudden death from myocardial infarction suggest that this risk factor is directly associated with a particular susceptibility to cardiac arrhythmia and does not reflect the development of atheroscle-

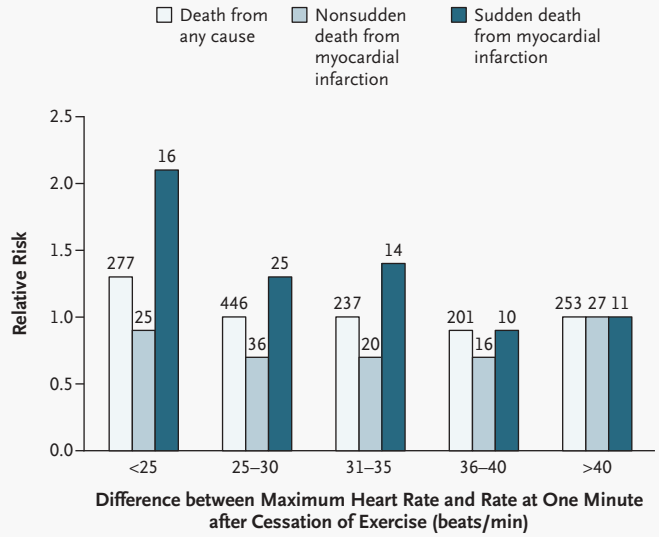

Figure 3. Adjusted Relative Risks of Death from Any Cause and from Nonsudden and Sudden Death from Myocardial Infarction, According to the Difference between Maximum Heart Rate and Heart Rate at One Minute after Cessation of Exercise.

The reference group was subjects with a difference of more than 40 beats per minute between the maximum heart rate and the heart rate at one minute after cessation of exercise (highest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel–Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause ($P<0.001$) and sudden death from cardiac causes ($P=0.03$) but was not significant for nonsudden death ($P=0.20$). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data on heart-rate recovery at one minute are missing for 102 subjects who died of any cause, including 5 who died suddenly from myocardial infarction and 5 who died, but not suddenly, from myocardial infarction.

rosis. It is consistent with the notion that autonomic imbalance predisposes persons to life-threatening arrhythmias.[4,8]

The mechanism underlying the present findings is not immediately obvious. Current knowledge, which is based on multiple associations between an increased risk of sudden death and reduced vagal activity or increased sympathetic activity,[3-6] could explain our observation that subjects who died suddenly of cardiac causes had a higher heart rate before exercise[16] and a more sluggish decrease in heart rate during the recovery period. However, one would have expected them to have a greater increase in heart rate during exercise, whereas the opposite was found.

An increased risk of death is associated with an inability to increase heart rate properly during exercise, a phenomenon called chronotropic incompetence.[21,22] This reasonable explanation, however, does not apply to our data because the subjects who did not reach 80 percent of the expected maximum heart rate were excluded from the study. Although subjects in the sudden-death group did not have chronotropic incompetence, they were nonetheless unable to increase their heart rate at peak exercise to levels that are normal for most people, a finding that indicates an impairment in the ability to increase sympathetic activity to its maximum extent.

Thus, a greater risk of sudden death was associated with an impaired ability to increase not only vagal but also sympathetic activity to appropriate levels. Such a condition could be explained by a reduced baroreflex sensitivity, with blood pressure changing in either direction. Indeed, it has previously been shown that among patients who have had myocardial infarction and have similar left ventricular ejection fractions, the inability to sustain episodes of ventricular tachycardia without circulatory collapse was predicted by depressed baroreflex sensitivity.[23-25] Thus, an impairment in baroreflex sensitivity involving both sympathetic and vagal responses favors circulatory collapse during ventricular tachycardia, a condition that precipitates ventricular fibrillation and sudden death. The clinical counterpart of this defective physiological response would be a reduced ability to increase heart rate during exercise to the maximum extent — which represents the most puzzling of the features that we found to be associated with an increased risk of sudden death.

For apparently healthy persons with a heart-rate profile that is associated with a high risk of sudden death, a possible therapeutic approach might be the correction of the autonomic imbalance. In addition to traditional management of cardiovascular risk factors, initiation of a regular exercise-training program should be recommended. Indeed, both experimental[26,27] and clinical[28] data indicate that when exercise training shifts the autonomic balance through an adequate increase in vagal activity, it can significantly improve long-term prognosis.

Assessment of the effects of an exercise-training program for high-risk persons within the general population would require an interventional trial. Our population consisted of asymptomatic, healthy men employed by the Paris Civil Service. Socioeconomic status, prevalence of smoking, extent of alcohol use, and other factors in this group

Table 2. Relative Risk of Sudden Death and Nonsudden Death from Myocardial Infarction and Death from Any Cause According to Heart-Rate Variables.*

Variable	Death from Any Cause (N=1516)		Sudden Death from Myocardial Infarction (N=81)		Nonsudden Death from Myocardial Infarction (N=129)	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Resting heart rate >75 beats/minute†						
Univariate analysis	1.31 (1.20–1.74)	<0.001	3.92 (1.91–8.00)	<0.001	1.90 (1.17–3.07)	0.009
Multivariate analysis	1.89 (1.60–2.24)	<0.001	3.46 (1.60–7.44)	0.001	1.55 (0.90–2.66)	0.11
Increase during exercise <89 beats/minute‡						
Univariate analysis	2.13 (1.79–2.52)	<0.001	6.18 (2.37–16.11)	<0.001	1.58 (0.87–2.85)	0.12
Multivariate analysis	1.51 (1.26–1.81)	<0.001	3.98 (1.49–10.61)	0.006	1.17 (0.62–2.18)	0.68
Decrease at 1 min after cessation of exercise <25 beats/minute§						
Univariate analysis	1.54 (1.30–1.84)	<0.001	2.20 (1.02–4.74)	0.04	1.36 (0.79–2.35)	0.34
Multivariate analysis	1.27 (1.06–1.53)	<0.001	2.06 (0.92–4.59)	0.08	0.93 (0.51–1.72)	0.85

* Relative risks were estimated with the Cox proportional-hazards model in univariate and multivariate analyses. The multivariate analysis was adjusted for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. CI denotes confidence interval.

† A total of 460 patients had a resting heart rate that was more than 75 beats per minute (highest quintile). The reference group was subjects with a resting heart rate of less than 60 beats per minute (lowest quintile).

‡ A total of 474 patients had an increase in heart rate during exercise that was less than 89 beats per minute (lowest quintile). The reference group was subjects with an increase in heart rate during exercise that was more than 113 beats per minute (highest quintile).

§ A total of 318 patients had a decrease in heart rate at one minute after the cessation of exercise that was less than 25 beats per minute (lowest quintile). The reference group was subjects who had a decrease in heart rate at one minute after the cessation of exercise that was more than 40 beats per minute (highest quintile).

might differ from those in the general population. The incidence of coronary heart disease has changed within recent decades and was higher in this cohort than it would be today. Moreover, the study involved only men, and the findings might be different in women.[29] Therefore, the extent to which the present findings could be generalized to a more unselected or recent population cohort is unclear. Since follow-up was focused on mortality only, the possible development of cardiovascular disease and treatment during the follow-up period were not assessed.

Because it was designed to achieve the maximum predicted heart rate in asymptomatic subjects as rapidly as possible, the exercise-test pattern was unusual. The rapidity with which workload was increased may have influenced the results, and the findings may not be directly applicable to subjects undergoing standard treadmill testing. The heart-rate values might be different with different protocols. The subjects who died suddenly had lower maximum heart rates and reached those levels more rapidly than did the other subjects. Since a heart-rate level above 180 beats per minute was a cause of cessation of the exercise test, the duration of the exercise test for these subjects was shorter. However, the same results persisted after adjustment for the duration of exercise. Moreover, when the subjects who reached the level of 191 W were excluded from the analysis, similar results were observed.

The heart-rate profile during exercise and recovery is a powerful predictor of the risk of sudden death in asymptomatic men. Impairment of the ability to increase both sympathetic and vagal activity rapidly is a possible (but hypothetical) mechanism. These findings may have clinical implications in terms of the early identification of high-risk subjects and raise the possibility of primary prevention.

Supported by INSERM, the city of Paris, and the French Ministry of Health.

We are indebted to Julien DuVignac for his help in preparing this article.

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