The New England Journal of Medicine

VOLUME 343 SEPTEMBER 21, 2000 NUMBER 12

LONG-TERM OUTCOME IN ASYMPTOMATIC MEN WITH EXERCISE-INDUCED PREMATURE VENTRICULAR DEPOLARIZATIONS

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ABSTRACT

Background Exercise testing is widely used in the diagnosis of coronary artery disease, but the long-term outcome for asymptomatic persons with exercise-induced premature ventricular depolarizations remains unclear. We used data from the Paris Prospective Study I to assess the long-term outcome of such persons.

Methods A total of 6101 asymptomatic French men (42 to 53 years of age) who were free of clinically detectable cardiovascular disease underwent a standardized graded exercise test between 1967 and 1972. Subjects were prospectively classified as having or not having frequent premature ventricular depolarizations (a run of two or more consecutive premature ventricular depolarizations or premature ventricular depolarizations constituting more than 10 percent of all ventricular depolarizations during any of the 30-second electrocardiographic recordings).

Results During exercise, 138 subjects had frequent premature ventricular depolarizations. After 23 years of follow-up, these subjects had a higher risk of death from cardiovascular causes than the men without frequent premature ventricular depolarizations during exercise (relative risk, 2.67; 95 percent confidence interval, 1.76 to 4.07). In a multivariate model, with adjustment for standard coronary risk factors and the presence or absence of premature ventricular depolarizations before exercise and during recovery from exercise, both exercise-induced ischemia and the occurrence of frequent premature ventricular depolarizations during exercise remained independently associated with an increased risk of death from cardiovascular causes, with similar relative risks (2.63 [95 percent confidence interval, 1.93 to 3.59] and 2.53 [95 percent confidence interval, 1.65 to 3.88], respectively).

Conclusions The occurrence of frequent premature ventricular depolarizations during exercise in asymptomatic middle-aged men is associated with a long-term increase in the risk of death from cardiovascular causes. (N Engl J Med 2000;343:826-33.)

EXERCISE testing is widely used to detect coronary heart disease and to assess the short- and long-term prognosis in patients with the disease. Numerous studies have shown that an ischemic ST-segment response to exercise is a powerful predictor of major coronary events, including death, in apparently healthy persons.[1-7]

Whether the occurrence of premature ventricular depolarizations during exercise is useful in the diagnosis of coronary heart disease and in the assessment of prognosis remains controversial. Although an association between the occurrence of premature ventricular depolarizations during exercise and coronary heart disease has been described in patients at high risk for coronary heart disease, it is uncertain whether there is such an association in asymptomatic men.[8-13] The short- and long-term prognosis of persons with exercise-induced premature ventricular depolarizations is also uncertain.[1,14-19]

The occurrence of premature ventricular depolarizations during exercise in asymptomatic subjects raises the question of whether such depolarizations may be a normal response to exercise.[20] If so, long-term mortality should not be affected. We used data from 23 years of follow-up in the Paris Prospective Study I to answer this question.

METHODS

Subjects

Details of the study have been described elsewhere.[21] Briefly, after their oral informed consent was obtained, 7746 Frenchmen who were employed by the Paris Civil Service and who were between 42 and 53 years of age were examined from 1967 through 1972. This sample represented 93.4 percent of all the men em-

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ployed by the Paris Civil Service in early 1967 who had been born in France between 1917 and 1928. The subjects underwent electrocardiography and physical examinations, provided blood samples for laboratory tests, and supplied information on questionnaires administered by trained interviewers. The means of three measurements of diastolic and systolic blood pressure were used for analysis. The subjects were classified as diabetic if they reported having ever had diabetes, whether or not it was treated.

Subjects could be excluded for technical or medical reasons. Subjects underwent exercise testing unless they had known or suspected cardiovascular disease of any grade or cause, a systolic blood pressure above 180 mm Hg at rest, or any abnormality on 12-lead standard electrocardiography at rest according to the Minnesota code (definite Q waves, atrioventricular block or conduction defects, ST-segment abnormalities, supraventricular tachycardia, or polymorphic premature ventricular depolarizations). No attempt was made to assess ventricular function. Complete data were available for 6456 of 6565 men who completed the exercise test.

Exercise-Test Protocol

The bicycle exercise test was conducted according to a standard protocol.[22] It 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 maximal duration of 10 minutes. Cardiac rhythm was continuously monitored, and 30-second recordings were made from a bipolar lead (V_5 and V_5R) while the subject was at rest and every 2 minutes during a maximum of 10 minutes of exercise, at maximal effort, and every 1 minute during the 10-minute recovery time, or whenever the monitoring physician observed an arrhythmia. Testing was terminated if the subject had fatigue, dyspnea, leg discomfort, any chest pain, systolic blood pressure above 250 mm Hg, a heart rate of 180 beats per minute or more, ventricular tachycardia, or electrocardiographic changes indicative of ischemia. An ischemic response was defined as a J-point depression of at least 1 mm, with a flat or downsloping ST segment, during exercise or recovery. At the time of each electrocardiographic recording, the frequency of premature ventricular depolarizations was assessed as the maximal number of premature ventricular depolarizations divided by the total number of ventricular depolarizations during any of the 30-second recordings. Subjects with a run of two or more consecutive premature ventricular depolarizations or with premature ventricular depolarizations constituting more than 10 percent of all ventricular depolarizations on any of the electrocardiograms recorded with the subject at rest, during exercise, or during recovery were classified as having had frequent premature ventricular depolarizations during that period. Subjects classified as having infrequent premature ventricular depolarizations were those with premature ventricular depolarizations constituting 10 percent or less of all ventricular depolarizations. These criteria were defined in the study protocol and coded by the physician who conducted the examination.

Follow-up

The administrative department in charge of the study population provided an annual list of all subjects not yet retired who had died during the year. All available data relevant to the cause of death were obtained from hospital records or from the subjects' general practitioners, as identified by their relatives. The data were then reviewed by an independent medical committee. For subjects who died after retirement, the cause of death was obtained from death certificates. The cause of death was coded according to the eighth revision of the *International Classification of Diseases.*[23] Sudden death was defined as a natural death occurring within one hour after the onset of acute symptoms. Death was coded as due to myocardial infarction only if the death was found to be definitely related to myocardial infarction.

The follow-up period ended on January 1, 1994. Vital status could not be determined for 355 (5.5 percent) of the 6456 subjects for whom complete exercise-test data were available. Their characteristics at base line and during exercise were not significantly different from those of the remaining 6101 men whom we studied.

Statistical Analysis

Analysis of variance and chi-square analysis were used for comparisons between groups. Because of the skewed distribution of triglyceride values, log-transformed values were used in the analysis of this factor. Analysis of variance and logistic regression were used to identify factors associated with an exercise test that was positive for ischemia and factors associated with the occurrence of frequent premature ventricular depolarizations, after mutual adjustment. The relative risks of death were adjusted for confounding factors and estimated by the Cox proportional-hazards model. SAS software (SAS Institute, Cary, N.C.) was used for analysis.

RESULTS

There were no serious complications of exercise testing (such as death, myocardial infarction, or ventricular fibrillation). The test was positive for ischemia in 271 of 6101 subjects (4.4 percent). Frequent premature ventricular depolarizations occurred in 48 subjects (0.8 percent) before exercise, in 138 (2.3 percent) during exercise, and in 174 (2.9 percent) during recovery. The mean (±SD) heart rate at the end of exercise was 167±16 beats per minute (96±9 percent of the predicted maximal heart rate). During the 23 years of follow-up, 1635 subjects (26.8 percent) died, including 435 from cardiovascular causes (7.1 percent).

Rates of Death among Subjects with Premature Ventricular Depolarizations

Forty-eight of the 6101 subjects (0.8 percent) had frequent premature ventricular depolarizations before exercise, 121 (2.0 percent) had infrequent premature ventricular depolarizations, and 5932 (97.2 percent) had none (Table 1). There were no significant differences among these three groups in the rates of death from all causes, death from noncardiovascular causes, or death from cardiovascular causes (which included sudden death, fatal myocardial infarction, and death from other cardiovascular causes).

During exercise, 138 subjects (2.3 percent) had frequent premature ventricular depolarizations, 520 (8.5 percent) had infrequent premature ventricular depolarizations, and 5443 (89.2 percent) had none. The rates of death from all causes and death from cardiovascular causes were significantly ($P<0.001$) higher in subjects with frequent premature ventricular depolarizations than in the other two groups (death from all causes: 41.3 percent, vs. 27.9 percent in the group with infrequent premature ventricular depolarizations and 26.3 percent in the group with none; death from cardiovascular causes: 16.7 percent, vs. 7.3 percent and 6.8 percent). The rate of death from noncardiovascular causes did not differ significantly among the three groups. There were no significant differences in the rates of death from all causes, death from noncardiovascular causes, or death from cardiovascular causes between subjects with infrequent premature ventricular depolarizations and those without such depolarizations.

During recovery from exercise, 174 subjects (2.9

TABLE 1. DEATH RATES ACCORDING TO THE FREQUENCY OF PREMATURE VENTRICULAR DEPOLARIZATIONS OCCURRING BEFORE, DURING, OR AFTER EXERCISE.*

CATEGORY	BEFORE EXERCISE				DURING EXERCISE				AFTER EXERCISE			
	0 (N=5932)	≤10% (N=121)	>10% (N=48)	P VALUE	0 (N=5443)	≤10% (N=520)	>10% (N=138)	P VALUE	0 (N=5479)	≤10% (N=448)	>10% (N=174)	P VALUE
	percent				percent				percent			
Death from all causes	26.8	28.1	25.0	0.91	26.3	27.9	41.3	<0.001	26.5	27.7	35.0	0.05
Death from noncardiovascular causes	19.7	16.5	18.8	0.67	19.5	20.6	24.6	0.28	19.4	20.6	27.0	0.04
Death from cardiovascular causes	7.1	11.6	6.2	0.16	6.8	7.3	16.7	<0.001	7.1	7.1	8.0	0.89
Fatal myocardial infarction	2.4	3.3	0	0.45	2.3	2.3	5.1	0.11	2.4	2.2	1.1	0.53
Sudden death	1.4	2.5	0	0.43	1.3	1.7	2.9	0.25	1.4	2.0	1.7	0.49
Other	3.3	5.8	6.2	0.16	3.2	3.3	8.7	0.002	3.3	2.9	5.2	0.35

*The frequency of premature ventricular depolarizations was defined as the maximal number of premature ventricular depolarizations divided by the total number of ventricular depolarizations recorded on any of the 30-second electrocardiograms. The subjects with more than 10 percent premature ventricular depolarizations include subjects with runs of consecutive premature ventricular depolarizations. P values are by global chi-square test, with 2 df.

percent) had frequent premature ventricular depolarizations, 448 (7.3 percent) had infrequent premature ventricular depolarizations, and 5479 (89.8 percent) had none. The rates of death from all causes and from noncardiovascular causes were significantly higher among subjects with frequent premature ventricular depolarizations during recovery than in the other two groups. The rates of death from cardiovascular causes were similar in the three groups.

Occurrence of Premature Ventricular Depolarizations during Exercise

There were no significant differences in cardiovascular risk factors between the subjects with infrequent premature ventricular depolarizations and those without premature ventricular depolarizations during exercise. The 271 subjects (4.4 percent) with a positive exercise test were equally distributed among the three groups. The exercise test was stopped because of chest pain in 8 subjects (0.1 percent), none of whom had premature ventricular depolarizations; the test was stopped because of runs of two or more premature ventricular depolarizations in 16 subjects (0.3 percent).

Premature Ventricular Depolarizations before, during, and after Exercise

Among the 48 subjects with frequent premature ventricular depolarizations before exercise, 3 (6 percent) continued to have frequent premature ventricular depolarizations during exercise and 15 (31 percent) had a recurrence of frequent premature ventricular depolarizations during recovery from exercise. Among the 138 subjects who had frequent premature ventricular depolarizations during exercise, 3 (2.2 percent) also had frequent premature ventricular depolarizations before exercise, 125 (90.6 percent) had no premature ventricular depolarizations before exercise, 21 (15.2 percent) continued to have frequent premature ventricular depolarizations during recovery, and 96 (69.6 percent) had none during recovery.

Occurrence of Ischemia or Frequent Premature Ventricular Depolarizations during Exercise

Because of their similar characteristics and mortality rates, the groups with infrequent and with no premature ventricular depolarizations during exercise were combined and compared with the group with frequent premature ventricular depolarizations during exercise. Older age and higher levels of total cholesterol and triglycerides were significantly associated with a positive exercise test, but not with frequent premature ventricular depolarizations during exercise (Table 2). The body-mass index (the weight in kilograms divided by the square of the height in meters) was significantly lower and tobacco consumption was significantly higher among subjects with frequent premature ventricular depolarizations, but neither was associated with a positive exercise test. The maximal heart rate and the percentage of the predicted maximal heart rate achieved during exercise were significantly higher in subjects with evidence of ischemia on the exercise test. The duration of the exercise test was significantly shorter among subjects with a positive exercise test and among those with frequent premature ventricular depolarizations. Diabetic status, extent of physical activity, heart rate at rest, systolic blood pressure at rest, and maximal systolic blood pressure were not significantly associated with either the exercise-test result or with the presence or absence of frequent premature ventricular depolarizations.

Death Rates and Relative Risks of Death from Cardiovascular Causes

Subjects with evidence of ischemia on exercise testing or with frequent premature ventricular depolar-

TABLE 2. CHARACTERISTICS OF SUBJECTS ACCORDING TO THE PRESENCE OR ABSENCE OF ISCHEMIA AND FREQUENT PREMATURE VENTRICULAR DEPOLARIZATIONS (PVDS) DURING EXERCISE.*

CHARACTERISTIC	ISCHEMIA ABSENT, FREQUENT PVDS ABSENT (N=5700)	ISCHEMIA PRESENT, FREQUENT PVDS ABSENT (N=263)	ISCHEMIA ABSENT, FREQUENT PVDS PRESENT (N=130)	ISCHEMIA PRESENT, FREQUENT PVDS PRESENT (N=8)	P VALUE†	
					FREQUENT PVDS	ISCHEMIA
Age — yr	47.6±1.9	48.0±1.8	47.6±1.9	47.3±1.0	0.85	<0.001
Tobacco consumption — g/day‡	11.6±10.5	11.2±10.6	14.5±10.7	19.6±15	<0.001	<0.74
Diabetes — no. (%)	81 (1.4)	5 (1.9)	2 (1.5)	1 (12.5)	0.40	0.99
Body-mass index§	25.7±3.1	26.0±2.9	25.1±3.2	25.3±2.8	0.03	0.27
Physical activity — hr/week¶	1.5±1.1	1.6±1.2	1.6±1.3	1.5±1.5	0.36	0.84
Systolic blood pressure at rest — mm Hg	135±16	136±14	137±14	133±16	0.14	0.35
Heart rate at rest — beats/min	68±10	68±9	68±9	66±8	0.62	0.33
Total cholesterol — mg/dl‖	221±42	230±44	220±40	231±60	0.71	<0.001
Triglycerides — mg/dl**	133±106	150±133	128±80	113±43	0.62	0.008
Maximal heart rate — beats/min	167±14	169±14	169±15	170±10	0.12	0.05
Percentage of predicted maximal heart rate††	97.0±8.1	98.3±8.0	97.9±8.3	98.5±5.9	0.12	0.01
Maximal systolic blood pressure — mm Hg	207±34	208±34	211±33	219±45	0.22	0.61
Duration of exercise test — min	7.2±2.6	6.3±2.4	6.7±2.5	5.5±2.1	0.03	<0.001

*Plus–minus values are means ±SD.

†The association between characteristics of the subjects and the presence of ischemia or frequent PVDs was tested by analysis of variance or logistic regression, after mutual adjustment.

‡Tobacco consumption is the average daily consumption during the five years preceding the screening.

§The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶Level of physical activity is the average number of hours per week spent in physical activity during the five years preceding the screening.

‖To convert values for total cholesterol to millimoles per liter, multiply by 0.02586.

**To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

††The percentage of the predicted maximal heart rate was calculated as follows: maximal heart rate ÷ (220 – age in years).

izations during exercise had significantly higher rates of death from all causes and from cardiovascular causes, but not from noncardiovascular causes (Table 3). Those with a positive exercise test had significantly higher rates of death from myocardial infarction and of sudden death, but not of deaths due to other cardiovascular causes. Those with frequent premature ventricular depolarizations during exercise had significantly higher rates of death due to myocardial infarction and other causes of cardiovascular death, but not of sudden death. There was no significant interaction between the exercise-test result and the presence or absence of frequent premature ventricular depolarizations during exercise.

As Figure 1 shows, the proportion that did not die from cardiovascular causes did not differ markedly between subjects with an exercise test that was positive for ischemia and those with frequent premature ventricular depolarizations during exercise.

A multivariate analysis was performed with adjustment for age, body-mass index, heart rate at rest, systolic blood pressure, tobacco use, level of physical activity, diabetic status, total cholesterol level, the occurrence of premature ventricular depolarizations before exercise, and the occurrence of premature ventricular depolarizations during recovery. The results showed that a positive exercise test and the occurrence of frequent premature ventricular depolarizations during exercise were independently associated with a higher mortality rate from cardiovascular causes, with similar relative risks (Table 3). The relative risks were 2.63 (95 percent confidence interval, 1.93 to 3.59) for ischemia and 2.53 (95 percent confidence interval, 1.65 to 3.88) for frequent premature ventricular depolarizations.

Runs of Premature Ventricular Depolarizations

Runs of two or more consecutive premature ventricular depolarizations were induced in 16 subjects during exercise and in 6 other subjects during recovery, and they all resolved spontaneously. The characteristics of these subjects did not differ significant-

TABLE 3. RATES AND RELATIVE RISKS OF DEATH FROM CARDIOVASCULAR CAUSES ASSOCIATED WITH THE PRESENCE OR ABSENCE OF ISCHEMIA OR FREQUENT PREMATURE VENTRICULAR DEPOLARIZATIONS (PVDS) DURING EXERCISE.

VARIABLE	ISCHEMIA ABSENT, FREQUENT PVDS ABSENT (N=5700)	ISCHEMIA PRESENT, FREQUENT PVDS ABSENT (N=263)	ISCHEMIA ABSENT, FREQUENT PVDS PRESENT (N=130)	ISCHEMIA PRESENT, FREQUENT PVDS PRESENT (N=8)	P VALUE*	
					FREQUENT PVDS	ISCHEMIA
			percent			
Death from all causes	26.2	33.1	40.7	50.0	<0.001	0.011
Death from noncardiovascular causes	19.8	16.4	24.6	25.0	0.12	0.18
Death from cardiovascular causes	6.4	16.7	16.1	25.0	<0.001	<0.001
Fatal myocardial infarction	2.1	7.2	4.6	12.5	0.04	<0.001
Sudden death	1.2	4.6	2.3	12.5	0.15	<0.001
Other	3.1	4.9	9.2	0	<0.001	0.16
	ISCHEMIA: PRESENT VS. ABSENT		FREQUENT PVDS: PRESENT VS. ABSENT			
	relative risk (95% confidence interval)					
Relative risk of death from cardiovascular causes						
Univariate analysis	2.76 (2.03–3.75)		2.67 (1.76–4.07)		<0.001	<0.001
Multivariate analysis	2.63 (1.93–3.59)		2.53 (1.65–3.88)		<0.001	<0.001

*Logistic regression was used to test the association between death rates and the presence of ischemia or frequent PVDs, after mutual adjustment. In the multivariate model, relative risks of death and 95 percent confidence intervals were estimated by the Cox proportional-hazards method and adjusted for age, body-mass index, heart rate at rest, systolic blood pressure, tobacco use, level of physical activity, presence or absence of diabetes, total cholesterol level, and presence or absence of PVDs before exercise and during recovery from exercise.

ly from those of subjects who had frequent premature ventricular depolarizations without complex runs. When data from the subjects with complex runs were excluded from the preceding analysis, the results did not change significantly: the occurrence of frequent premature ventricular depolarizations during exercise remained independently associated with higher mortality from cardiovascular causes, with a relative risk of 2.17 and a 95 percent confidence interval of 1.34 to 3.50.

DISCUSSION

The occurrence of premature ventricular depolarizations during exercise may be related to exercise-induced myocardial ischemia.[15-19] However, subjects with an exercise test that was positive for ischemia and subjects with frequent premature ventricular depolarizations during exercise do not share the same pattern of risk factors. It is striking that among the 271 subjects with a positive exercise test, only 3 percent had frequent premature ventricular depolarizations during exercise. Conversely, among the 138 subjects with frequent premature ventricular depolarizations during exercise, only 6 percent had an exercise test that was positive for ischemia.

The occurrence of premature ventricular depolarizations during exercise may be mediated by the increase in plasma catecholamines related to exercise,[24] and both epinephrine and norepinephrine levels have been shown to continue to increase during the first three minutes after exercise.[25] Only 21 of 138 subjects (15.2 percent) had frequent premature ventricular depolarizations both during and after exercise. The outcome for this group was not different from that of subjects who had frequent premature ventricular depolarizations only during exercise, but the numbers were too small for any firm conclusions to be drawn.

The higher rate of death from noncardiovascular causes among subjects who had frequent premature ventricular depolarizations during the period of recovery from exercise than in those without such depolarizations remains difficult to explain. It is likely that different mechanisms cause premature ventricular depolarizations before, during, and after exercise. It appears that the occurrence of frequent premature ventricular depolarizations during exercise identifies only subjects at higher risk of death from cardiovascular causes.

According to our clinical findings, hypertensive cardiomyopathy is unlikely to be the cause of premature ventricular depolarizations, although other types of subclinical nonischemic cardiomyopathy could be involved. Hypertrophic cardiomyopathy is usually a familial disorder with a variable clinical course[26] that frequently includes premature ventricular depolariza-

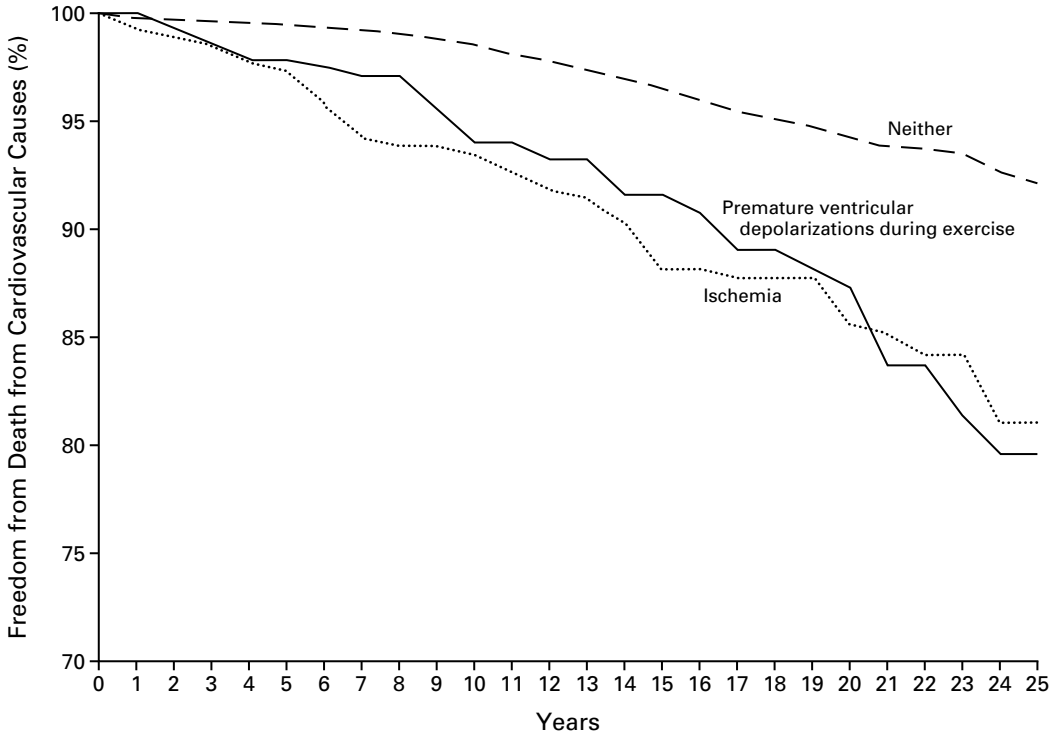

Figure 1. Percentage without Death from Cardiovascular Causes among Subjects with an Exercise Test That Was Positive for Ischemia, Subjects with Frequent Premature Ventricular Depolarizations during Exercise, and Subjects with Neither a Positive Exercise Test nor Frequent Premature Ventricular Depolarizations.

The data were analyzed by Cox proportional-hazards methods. Cox estimates were adjusted for age, tobacco use, diabetic status, body-mass index, level of physical activity, systolic blood pressure, the heart rate at rest, total cholesterol level, the presence or absence of premature ventricular depolarizations before exercise, and the presence or absence of premature ventricular depolarizations during recovery from exercise. Data were censored if subjects died of other causes.

tions.[27,28] Left ventricular hypertrophy may be absent or mild, and the disease may be asymptomatic and clinically undetectable at an early stage. Arrhythmogenic right ventricular dysplasia is characterized by the replacement of right ventricular myocardium by fibrous tissue and fat,[29] a change that is usually responsible for frequent premature ventricular depolarizations associated with left bundle-branch block.[30] Early diagnosis can be quite difficult, since there may be only minor signs of disease on the electrocardiogram. Premature ventricular depolarizations may also be due to dilated cardiomyopathy,[31] which may not be detectable at early stages, or to mitral-valve prolapse. The latter condition is associated with an increased frequency of premature ventricular depolarizations[32] and usually has few adverse effects.[33]

The occurrence of frequent premature ventricular depolarizations during exercise is associated with an increase in the rate of death from cardiovascular causes, which is related to an increase in various cardiovascular causes of death. A greater increase in the rate of sudden death was expected in this group, but the number of patients was too small to allow precise conclusions.

The higher mortality rate from cardiovascular causes that is associated with frequent premature ventricular depolarizations during exercise in asymptomatic men has consequences for clinical practice. Such subjects should certainly be evaluated and treated for cardiovascular risk factors, and it should be strongly recommended that they quit smoking. Regular clinical follow-up is advisable.

The presence or absence of premature ventricular depolarizations before exercise was determined from the analysis of one conventional electrocardiogram recorded at entry into the study and one 30-second electrocardiogram recorded before the beginning of exercise. The occurrence of premature ventricular depolarizations in an individual patient is highly variable.[34] Therefore, two electrocardiograms taken at rest are clearly insufficient for us to conclude that a subject has no premature ventricular depolarizations.

It is likely that some subjects were wrongly classified as having infrequent premature ventricular depolarizations or none, but such misclassification would have had only a small effect on our results.

Evidence of ischemia on the exercise electrocardiogram and a run of consecutive premature ventricular depolarizations were both reasons for termination of the test. We cannot exclude the possibility that frequent premature ventricular depolarizations might have occurred in some subjects who had ischemia if the test had been prolonged and, conversely, that the exercise test might have been positive for ischemia in subjects who had premature ventricular depolarizations during exercise.

The study population consisted of healthy men without symptoms of cardiovascular disease who were employed by the Paris Civil Service; these men may have differed from the general population in socioeconomic status, use of alcohol and tobacco, or other characteristics. Therefore, caution must be used in extending the results to the general population. The study included only men, but there is no reason to expect that different conclusions would have been reached if the study had included women.

In order to achieve the maximal predicted heart rate in asymptomatic subjects as rapidly as possible, an unusual protocol of exercise tests was used. The rapidity with which the workload was advanced may have influenced the results, and it is possible that the conclusions may not be applicable to subjects who undergo testing according to the standard Bruce protocol, which is now routinely used.

The occurrence of frequent premature ventricular depolarizations during exercise in asymptomatic middle-aged men is associated with increased long-term mortality from cardiovascular causes. The relative risk is similar to that associated with an exercise test that is positive for ischemia, even after adjustment for confounding variables. For this population, additional examinations and regular medical follow-up should be encouraged, and patients should be urged to modify risk factors and particularly to quit smoking. Further studies are required to identify the causes and mechanisms of the association between frequent premature ventricular depolarizations during exercise and death from cardiovascular causes.

We are indebted to Beverley Balkau and Professor Claude Guérot for their support.

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