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

Xavier Jouven, M.D., Ph.D., Jean-Philippe Empana, M.D., Peter J. Schwartz, M.D., Michel Desnos, M.D., Dominique Courbon, M.S.C., and Pierre Ducimetière, Ph.D.

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.
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 causes7 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 (V5 and V6) 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 1-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* 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.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (N=5503)†</th>
<th>Sudden Death from Myocardial Infarction (N=81)</th>
<th>Nonsudden Death from Myocardial Infarction (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Relative Risk (95% CI)‡</td>
<td>Baseline Level</td>
<td>Baseline Level</td>
</tr>
<tr>
<td>Age — yr</td>
<td>47.6±1.9</td>
<td>48±1.8</td>
<td>1.23 (0.98–1.54)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>25.7±3.1</td>
<td>26.7±3.3</td>
<td>1.34 (1.09–1.66)</td>
</tr>
<tr>
<td>Tobacco use — g/day§</td>
<td>11.4 (10.5)</td>
<td>15.5 (10.0)</td>
<td>1.41 (1.18–1.70)</td>
</tr>
<tr>
<td>Resting heart rate — beats/min</td>
<td>68.1±9.5</td>
<td>71.4±9.8</td>
<td>1.39 (1.15–1.68)</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>137.8±17.4</td>
<td>142.7±22.0</td>
<td>1.31 (1.08–1.60)</td>
</tr>
<tr>
<td>Total cholesterol — mg/dl ¶</td>
<td>221±41.6</td>
<td>246.8±43</td>
<td>1.67 (1.40–2.00)</td>
</tr>
<tr>
<td>Triglycerides — mg/dl ¶</td>
<td>132±106.5</td>
<td>152.2±99.2</td>
<td>1.26 (1.04–1.53)</td>
</tr>
<tr>
<td>Duration of exercise test — min</td>
<td>7.3±2.5</td>
<td>6.0±2.3</td>
<td>0.59 (0.47–0.73)</td>
</tr>
<tr>
<td>Diabetes — no./total no. (%)</td>
<td>268/5255 (51.1)</td>
<td>7/78 (6.4)</td>
<td>2.39 (0.87–6.53)</td>
</tr>
<tr>
<td>Current physical activity — no./ total no. (%)</td>
<td>823/5446 (15.1)</td>
<td>11/80 (13.8)</td>
<td>0.87 (0.46–1.65)</td>
</tr>
<tr>
<td>Parental history — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>366/5442 (6.7)</td>
<td>5/79 (6.3)</td>
<td>0.92 (0.37–2.28)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>570/5443 (10.5)</td>
<td>15/79 (19.0)</td>
<td>2.02 (1.15–3.53)</td>
</tr>
</tbody>
</table>

* 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.
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±1.0 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. Data are missing for five subjects who died of any cause, including one who died suddenly from myocardial infarction.
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native state, these data support responses to exercise are under the control of the
strong predictor of sudden death. Since heart-rate
profile during exercise and recovery is a
of apparently healthy persons, indicate that the
berate with a lower increase in heart rate but not with
value as compared with the highest quintile and 3.98
adjustment for confounding factors (95 per-
jacent confidence interval, 1.39 to 10.61). When these
maller, when stepwise multiple regression analysis and after adjustment for confounding
 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), nonfatal 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, choles-
terol level, presence or absence of a parental history of sudden death or myo-
infarction, and exercise duration. 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
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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 bal-
ance may precede manifestations of cardiovascular
disease and may contribute to the early identifica-
tion of persons at high risk for sudden death.
In most cases of sudden death in adults, coro-
nary lesions are present, together with traditional
risk factors for atherosclerosis. In addition, it has
been suggested that reflex sympathetic activation
elicited by acute myocardial ischemia 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 car-
diac causes and the absence of such an association
with nonfatal 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 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
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died of any cause, including one who died suddenly from myocardial infarction.
... inability to increase heart rate properly during exercise, a phenomenon called chronotropic incompetence. 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. 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 and clinical 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...
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. 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.

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