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Rapidly upsloping ST-segment on exercise ECG: a marker of reduced coronary heart disease mortality risk

Christian Hodnesdal^{1,*}, Erik Prestgaard^{1,*}, Gunnar Erikssen²,
Knut Gjesdal^{1,3}, Sverre E Kjeldsen^{1,3}, Knut Liestol¹,
Per Torger Skretteberg³, Jan Erikssen¹ and Johan Bodegard³

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Abstract

Background: The prognostic value of an isolated J-point depression, or rapidly upsloping ST-segment, on an exercise ECG has long been assumed to be a benign variant. However, little or no data supporting this assumption may be found in the literature. Our task was to examine if a rapidly upsloping ST-segment on an exercise ECG is associated with changes in risk of dying from CHD in 2014 healthy middle-aged men followed for 35 years.

Methods: A group of healthy middle-aged men ($n = 2014$) participated in a cardiovascular survey. They underwent an examination programme including a symptom-limited ECG bicycle exercise test. Exercise induced ST-segments were categorised in three groups: normal ST-segment ($n = 1383$), rapidly upsloping ($n = 401$), and ST-depression ($n = 230$). Survival analyses were adjusted for smoking status, total cholesterol, systolic blood pressure, maximal heart rate, and physical fitness. The mean follow-up time was 35 years.

Results: The rapidly upsloping group had a 30% decreased risk of CHD death (hazard ratio, HR, 0.70, 95% CI 0.51–0.95) compared to the normal ST-segment group. The risk of CVD-death was numerically lower in the rapidly upsloping group (HR 0.82, 95% CI 0.65–1.04) compared to the normal ST-segment group. The ST-depression group had a 1.45-fold (HR 1.45, 95% CI 1.09–1.90) increased risk of CHD death compared to the normal ST-segment group.

Conclusions: The rapidly upsloping ST-segment was a common finding (20%) on exercise ECG among healthy middle-aged men and was associated with a 30% reduced risk of dying from CHD compared to individuals with normal ST-segment. A rapidly upsloping ST-segment on exercise ECG may represent the true healthy state.

Keywords

Autonomic nervous system, CHD mortality, exercise ECG, rapidly upsloping ST-segment

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Introduction

Exercise testing generates several changes in the electrocardiogram (ECG), both in non-ST and ST-parameters, valuable when assessing the future cardiovascular risk.^{1,2} ST-changes during exercise have not only a diagnostic, but also a prognostic value even among presumed healthy individuals.^{1,3} The depth of the ST-depression is an established important prognostic marker of future coronary heart disease (CHD) and cardiovascular disease (CVD).^{4–6} The slope of the ST-change during exercise test may be categorised as upsloping, horizontal, or downsloping.⁷ From a depressed J-point, an upsloping ST-segment may either be rapidly or slowly upsloping. While a rapidly

upsloping ST-segment might be a normal finding,^{1,8} and possibly associated with a well-balanced control of the autonomic nervous system, the slowly upsloping segment may potentially represent ischaemia.^{9,10}

¹University of Oslo, Oslo, Norway

²Oslo University Hospital, Rikshospitalet, Norway

³Oslo University Hospital, Ullevaal, Norway

*These authors contributed equally to this work.

Corresponding author:

Johan Bodegard, Department of Cardiology, Oslo University Hospital, Ullevål, PB 4956 Nydalen, 0424 Oslo, Norway
Email: johan.bodegard@gmail.com

Figure 1. Description of the three groups according to ST-segment during a symptom-limited exercise ECG.

(1) Normal ST-segment: ST-depressions <0.100 mV at 0.08 s were classified as normal ($n = 1383$). (2) Rapidly upsloping ST-segment: this group consists of men with isolated junction depression >0.050 mV and having no ST-depression at 0.08 s ($n = 401$). (3) The ST-depression group consists of men with any ST-depression ≥ 0.100 mV at 0.08 s ($n = 230$).

A recent study finds that a rapidly upsloping ST-segment on a standard 12-lead resting ECG is a benign phenomenon.¹¹ However, to our knowledge, the prognostic value of a J-point depression with a rapidly upsloping ST-segment during exercise is unknown and has not been studied in a large group of presumably healthy individuals. We explored if a rapidly upsloping ST-segment on an exercise ECG, compared to a normal ST-segment, is associated with changes in risk of dying from CHD in 2014 healthy middle-aged men followed for 35 years.

Methods

All apparently healthy men aged 40–59 years, working in five governmental agencies in Oslo, Norway, were invited to participate in a cardiovascular survey examination.^{12–14} The main aim was to assess the age-specific prevalence of suspect, latent CHD. Of 2341 eligible men, 2014 (86%) agreed to participate in the survey. The baseline examination started in August 1972 and ended in March 1975.^{12–14} Eligibility was decided after scrutinizing the company health records of all subjects. The following diseases or conditions caused primary exclusion: known or suspected CHD or other heart diseases including atrial fibrillation, drug treated hypertension, diabetes mellitus, malignancy diagnosed during the last 5 years, miscellaneous other serious diseases (e.g. chronic hepatic, renal, or pulmonary diseases), and any chronic drug regimen. Those who were unable to complete a symptom-limited bicycle exercise test for various reasons were also excluded. Eight men

initially expected to be eligible were excluded after the baseline examination because they reported one of the above-mentioned conditions, not registered in the company files. Detailed information of their conditions was not obtained. Subjects who reported acute febrile illnesses in their pre-survey period had to wait at least 14 days to be examined, and none were lost for this reason. Further details about the selection and inclusion criteria have been reported elsewhere.^{12–14}

All men met for the examination in the morning. They had been requested to fast for at least 12 h and to abstain from smoking for at least 8 h. On arrival, the men had filled in an extensive health questionnaire dealing with various health issues, e.g. the WHO-angina questionnaire,¹⁵ British Medical Research Council respiratory questionnaire,¹⁶ and comprehensive questions on working conditions. Detailed description of the examination procedures can be found in earlier publications.^{12,17}

The examination programme included an ECG-monitored bicycle exercise test, using an electrically braked Elema bicycle. The initial load was 600 km/min/min (100 W), increased by 300 km/min/min (50 W) every 6 min. All tests were continued until exhaustion if not terminated prematurely for safety reasons or lack of will to continue.¹⁸ The starting load was chosen from findings in a pre-survey pilot study conducted in 80 males of similar age, all of whom easily completed a starting load of 600 km/min/min (100 W). At the baseline exercise test, only 15 (0.7%) men were unable to reach 150 W, supporting that start load level and the step-wise load increase were appropriate for

this study population. The present exercise protocol was chosen for the following reason: by using 6 min intervals, a haemodynamically steady state should be reached on each load up to the final one, considering that a steady state is normally reached after 3–4 min on an unchanged load. In comparison to an exercise protocol with, for example, increase by 10 W/min, an increase of 50 W in 6 min is less steep. The ECG recorder was an Ink Jet Mingograph 80 (Siemens).

Physical fitness was defined as working capacity divided by bodyweight, with working capacity defined as the cumulated work performed at test termination as reported earlier.¹⁷

Systolic blood pressure was measured with a mercury sphygmomanometer at 1, 3, and 5 min on each load and immediately prior to exercise termination.¹⁴ ECGs were recorded at 2, 4, and 6 min on all loads while sitting on the bicycle and immediately prior to exercise termination.¹⁸ A paper speed of 50 mm/s was used, and 1 vertical mm equals 0.1 mV. Chest-head leads (CH1–CH6) were used during the test.¹⁹ At exercise termination a continuous 30-s recording was taken while the subjects remained sitting on the bicycle, pedalling slowly at zero resistance. Thereafter, conventional supine post-exercise 12-lead ECGs were recorded at 1, 2, 3, and 5 min.⁵

The ECG was read by measuring the ST-segment deviation from the PQ (PR) line to the nearest 0.25 mm at 0.08 s from the J-point, using a magnifying glass with an inbuilt ruler. The average ST change, present in at least three consecutive beats of good technical quality, was recorded.⁵ The registration of ECG findings was carried out manually and twice by a trained cardiologist (JE).

We grouped the ST-findings in three categories according to the following criteria (Figure 1). Men with ST-depressions <0.100 mV (<1.00 mm) at 0.08 s after the J-point were classified as having normal ST-segments (except for men who satisfied the criteria for rapidly upsloping ST-segments). Rapidly upsloping ST-segments were classified according to the Minnesota Code 4.6 and 4.7 consisting of men with isolated junction depression >0.050 mV (>0.50 mm) and having no ST-depression at 0.08 s. The men who had an ST-segment depression >0.100 mV (>1.00 mm) extending 0.08 s after the J-point were classified as having significant ST-depressions regardless of slope.¹⁹ If minor ST-depressions were present in the resting ECGs, these values were subtracted from any observed ST-deviations noted during the exercise test before coding took place.⁵ ST-segment deviations observed in relation to new arrhythmias or intraventricular or bundle branch blocks during exercise have not been included.

Data on the participants' psychosocial stress level at work were obtained from a self-assessment

Figure 2. Flow chart.

questionnaire, with four response alternatives: always ($n = 1263$), frequently ($n = 252$), occasionally ($n = 197$), or never ($n = 302$). Always and frequently were defined as high-level stress ($n = 1515$) and occasionally and never were defined as low-level stress ($n = 499$).

Morbidity and mortality data

Morbidity data was consecutively obtained from three clinical surveys in 1980–82 (survey 2), 1989–90 (survey 3), and 1995–96 (survey 4) and one postal questionnaire survey in 1987 (Figure 2). The clinical examination and health questionnaires at the baseline survey were similarly repeated at all consecutive surveys (surveys 2–4). Additionally, two nationwide searches of all patient records in all Norwegian hospitals were performed in 1995–99 (survey 5) and 2005–08 (survey 6) (Figure 2). Patient admissions were identified by linking the study database with the patient journal system, using a unique personal identification number (Norwegian social security number). The complete patient hospital journal was retrieved for each patient with an admission, and was manually inspected on site. Morbidity and mortality data were obtained from all available sections in the journals, e.g. outpatient notes, general practitioners' letters, autopsy reports, ECG readings, surgery notes, and admission and discharge letters.

Mortality data was also obtained from the nationwide Norwegian cause of Death register (Statistics Norway) by using the same linkage method described above. The present morbidity and mortality data are completed up to 31 December 2008, and none were lost to follow up. Data collection was performed after having permissions from the Norwegian Data Inspectorate, the Norwegian Board of Health, and all Norwegian hospitals. Permission to store and analyse data in the study has been given from the Norwegian Data Inspectorate until the year 2042. The primary endpoint, CHD mortality, includes sudden unexpected death, ventricular fibrillation, and myocardial infarction.

Statistical methods

Differences in baseline data between groups were tested by Student's *t*-test or Pearson's chi-squares test according to data type. The risk of CHD mortality was estimated by Kaplan–Meier plots and tested with log rank test. All *p*-values are two-tailed and are considered significant if *p* < 0.05. Cox proportional-hazard modelling was used when calculating hazard ratios (HRs). The Cox-model included covariates earlier identified as important predictors: smoking status, total cholesterol, systolic blood pressure, maximal heart rate, and physical fitness.^{17,20} Diagnostic plots of logS(t) versus log(t) indicated that the proportional hazard assumption was acceptable. The linearity assumptions were tested by evaluating regression results with the variables split into categories. All models were computed using JMP 9 (SAS Institute).²¹

Results

Normal ST-segment was detected during or after the exercise ECG testing in 1383 men. A sizable group with rapidly upsloping ST-segments (*n* = 401; 19.9%) included fewer smokers, had a shorter PQ interval, higher prevalence of left ventricular hypertrophy, higher maximal heart rate, and a faster heart rate recovery compared to men with normal ST-segment. The mean age in these two groups was identical (Table 1).

Men with ST-depression ≥ 1.00 mm (*n* = 230) were older, had higher blood pressures, elevated fasting blood glucose, a shorter PQ (PR) interval, a higher prevalence of left ventricular hypertrophy, lower maximal heart rate, higher systolic blood pressure at 100 W reduced physical fitness, and lower maximal load on exercise compared to men with normal ST-segment.

CHD mortality risk was lower in the group with rapidly upsloping ST-segment group and higher in the group with ST-depression compared to the group with normal ST-segment (Figure 3). The crude mortality rates from CHD, CVD, and all causes were lower in

Table 1. Baseline data in three groups according to ST-segment during exercise ECG test among 2014 apparently healthy men

	Normal ST-segment (<i>n</i> = 1383)	Rapidly upsloping (<i>n</i> = 401)	ST-depression ≥ 1.00 mm (<i>n</i> = 230)
Age (years)	49.5 $\pm$ 5.5	49.5 $\pm$ 5.3	52.4 $\pm$ 5.0***
Smoking	631 (45.6)	156 (38.9)*	95 (41.3)
BMI (kg/m ²)	24.6 $\pm$ 2.8	24.4 $\pm$ 2.6	24.7 $\pm$ 2.6
Systolic BP (mmHg)	129.8 $\pm$ 17.3	128.0 $\pm$ 17.7	135.9 $\pm$ 20.0***
Diastolic BP (mmHg)	87.1 $\pm$ 10.2	86.4 $\pm$ 10.6	88.3 $\pm$ 11.2*
Cholesterol (mmol/l)	6.6 $\pm$ 1.2	6.7 $\pm$ 1.3	6.7 $\pm$ 1.2
Triglycerides (mmol/l)	1.3 $\pm$ 0.7	1.3 $\pm$ 0.7	1.3 $\pm$ 0.7
Fasting blood glucose (mol/l)	4.4 $\pm$ 0.5	4.5 $\pm$ 0.5	4.5 $\pm$ 0.7**
ESR (mm/h)	7.2 $\pm$ 6.7	7.3 $\pm$ 6.1	8.7 $\pm$ 7.4**
Potassium (mmol/l)	4.3 $\pm$ 0.3	4.2 $\pm$ 0.3*	4.3 $\pm$ 0.4
PQ (PR) interval (ms)	17.3 $\pm$ 2.5	16.7 $\pm$ 2.3***	16.9 $\pm$ 2.5*
LVH-ECG	56 (4.0)	23 (5.7)*	27 (11.7)***
Resting heart rate (beats/min)	61.4 $\pm$ 9.7	61.4 $\pm$ 9.4	61.3 $\pm$ 10.1
Maximal heart rate (beats/min)	162.7 $\pm$ 13.7	164.4 $\pm$ 12.0*	160.7 $\pm$ 14.8*
Systolic BP at 100 W (mmHg)	180.5 $\pm$ 24.2	181.1 $\pm$ 22.8	188.3 $\pm$ 26.1***
Physical fitness (kJ/kg)	2.0 $\pm$ 0.8	2.0 $\pm$ 0.8	1.7 $\pm$ 0.7***
Maximal load on exercise (W)	178.3 $\pm$ 34.5	177.6 $\pm$ 33.1	170.3 $\pm$ 29.6***
Heart rate recovery (beats/min) ^a	34.6 $\pm$ 11.6	36.7 $\pm$ 10.8**	35.9 $\pm$ 13.5

Values are mean $\pm$ SD or *n* (%). ^aHeart rate decrease 1 min after exercise termination. Significant differences from the group with no ST-changes: **p* < 0.05, ***p* < 0.01, ****p* < 0.001. BMI, body mass index; BP, blood pressure; ESR, erythrocyte sedimentation rate; LVH-ECG, left ventricular hypertrophy registered in resting ECG by Minnesota Code 3.1 and 3.3.

the group with rapidly upsloping ST-segment, and higher in the ST-depression group, compared to the group with normal ST-segment (Table 2). No significant difference in the risk of non-fatal CHD was observed between the group with rapidly upsloping ST-segment and the group with normal ST-segment though the group with ST-depression had a numerically higher incidence.

Figure 3. Kaplan–Meier curves for the groups according to ST-segment during a symptom-limited exercise ECG.

Table 2. Crude mortality and CHD morbidity during 35 years of follow up in three groups according to ST-segment during exercise ECG test among 2014 apparently healthy men

	Normal ST-segment (<i>n</i> = 1383)	Rapidly upsloping (<i>n</i> = 401)	ST-depression ≥ 1.00 mm (<i>n</i> = 230)
Death from CHD	230 (16.6)	49 (12.2)	67 (29.1)
Non-fatal CHD	429 (31.0)	122 (30.4)	104 (45.2)
Death from CVD	350 (25.3)	88 (21.9)	90 (39.1)
All-cause death	797 (57.6)	222 (55.4)	159 (69.1)

Values are *n* (%). CHD, coronary heart disease; non-fatal CHD, angina pectoris and myocardial infarction; CVD, cardiovascular disease.

The 401 men with a rapidly upsloping ST-segment had a 30% decreased risk of dying from CHD after adjustment for all covariates, but a similar risk of non-fatal CHD compared to the normal ST-segment group (Table 3). The ST-depression group had a 1.45-fold and 1.65-fold higher adjusted risk of CHD death and non-fatal CHD, respectively, compared to the normal ST-segment group. No significant differences in risks were observed for CVD or all-cause death in either group. The additional adjustment for left ventricular hypertrophy, PQ (PR) interval, and heart rate recovery did not alter the risk estimations of CHD death (HR 0.70; 95% CI 0.51–0.95), when comparing the rapidly upsloping group with the normal ST-segment group.

In the rapidly upsloping group, a significantly lower proportion of men reported high-level stress compared

to the normal ST-segment group and the ST-depression group: 69.8% (*n* = 280); 76.1% (*n* = 1053), and 79.1% (*n* = 182) respectively.

Discussion

We have shown that rapidly upsloping ST-segments during exercise are a common finding (20%) in healthy middle-aged males and that they predict significantly reduced CHD mortality; the risk was reduced by 30% when adjusting for age, smoking status, total cholesterol, systolic blood pressure, maximal heart rate, and physical fitness. We confirm previous knowledge that ST-depressions carry a 1.45-fold increased adjusted risk of death from CHD compared to normal ST-segments.

The ST-segment is defined by its onset at the J-point (i.e. J-junction or QRS-end) and changes are measured by the distance from the isoelectric ECG baseline. In subendocardial ischaemia, the ECG baseline is elevated, resulting in ST-segment depression. At rest, the J-point is below, on, or above the isoelectric ECG baseline. During exercise the J-point is typically depressed in lateral leads, reaching maximal depression at peak exercise, and then gradually returns toward pre-exercise values in recovery.⁷ The J-point is influenced by a transient outward potassium current (I_{to} in phase 1 of the action potential), and the magnitude of this current is modified by the sympathetic and parasympathetic nerve activity.²² Athletes have a vagal dominance that increases I_{to} and, hence, frequently an elevated J-point and an early repolarization pattern is seen in their resting ECG.^{8,11} Tikkanen et al.¹¹ recently demonstrated that early repolarization at rest (J-point elevation)

Table 3. Cox model analyses showing the risk of various endpoint events with different ST-segments compared to the group with normal ST-segment among 2014 men

	Normal ST-segment (n = 1383)	Rapidly upsloping (n = 401)	ST-depression ≥ 1.00 mm (n = 230)
Death from CHD			
Age-adjusted HR	1.00	0.69 (0.50–0.94)	1.47 (1.11–1.93)
Multiple-adjusted HR ^a	1.00	0.70 (0.51–0.95)	1.45 (1.09–1.90)
Non-fatal CHD			
Age-adjusted HR	1.00	0.98 (0.80–1.19)	1.61 (1.29–2.00)
Multiple-adjusted HR ^a	1.00	0.98 (0.79–1.19)	1.65 (1.32–2.05)
Death from CVD			
Age-adjusted HR	1.00	0.82 (0.64–1.03)	1.26 (0.99–1.59)
Multiple-adjusted HR ^a	1.00	0.82 (0.65–1.04)	1.24 (0.97–1.56)
All-cause death			
Age-adjusted HR	1.00	0.90 (0.77–1.04)	0.98 (0.82–1.16)
Multiple-adjusted HR ^a	1.00	0.92 (0.79–1.07)	0.99 (0.83–1.21)

Values are HR (95% CI). ^aFurther adjusted for smoking status, total cholesterol, systolic blood pressure, maximal heart rate, and physical fitness. CHD, coronary heart disease; CVD, cardiovascular disease.

followed by a rapidly ascending ST-segment (>0.1 mV at 0.1 s) is not associated with sudden arrhythmic death in a general population followed for 30 ± 11 years. The present study assesses the ST-segment after the J-point at maximal exercise, independently of potential early repolarization at rest, and uses a different definition of rapidly upsloping ST-segment. In a Finnish general population, the prevalence of early repolarization was 5.5%, and rapidly upsloping ST-segments, as defined by that study, was 1.5%. On exercise, J-point depressions followed by a rapidly upsloping ST-segment were a much more common phenomenon and were associated with a significantly lowered risk of CHD death compared to a normal ST-segment.

In the presence of sympathetic dominance during exercise, I_{to} is weaker and J-point depression may appear.²² Thus, the J-point and the ST-segment are influenced by different mechanisms: autonomic tone and ischaemia, respectively.¹¹ Well-trained men, who have vagal dominance at rest, might be more sensitive to catecholamines during exercise, thus explaining their more prevalent J-point depression, and they present a rapidly ascending ST-segment since there is no ischaemia.

The group of men with a rapidly upsloping ST-segment had a lower work-related psychosocial stress level and contained fewer smokers. These men might have a vagal dominance at rest and a larger sympathetic reserve at exercise compared to men without this phenomenon. Psychosocial stress is in general associated with higher sympathetic nerve activity, as supported by increased plasma levels of catecholamines in young

men who were subjected to a mental arithmetic stress test.²³ Perceived stress has also been shown to be a risk factor for unfavourable changes in health behaviour and cardiac risk profile, e.g. physical activity and smoking habits.²⁴ A large number of physical features of the work environment have recently been reported to have a significant effect on the physiological stress response, e.g. heart rate variability and the morning rise in cortisol levels.²⁵ Inhaled cigarette smoke releases nicotine to the blood stream and induces a rise of plasma catecholamine levels, increasing sympathetic nerve activity.²⁶ The large number of reported stress factors, both mental and physical, suggests that the identification of stress levels is a complex task, and that a general self-reported stress assessment could be sufficient. The faster heart rate recovery in the group with rapidly upsloping ST-segment suggests their prompt restoration of vagal tone and fast return to autonomic equilibrium, and supports the notion of higher vagal dominance at rest in this group.²⁷

A rapidly upsloping ST-segment during exercise has never been considered a sign of coronary artery disease. On the contrary, the phenomenon is frequently observed in healthy athletes.⁸ Assumedly, the rapidly upsloping ST-segment is more frequent among individuals with higher physical fitness and exercise-induced myocardial hypertrophy. We found a significantly higher prevalence of myocardial hypertrophy in the group with rapidly upsloping ST-segments, but unchanged resting heart rate, no increased physical fitness and an even shorter PQ (PR) interval. However, we still observed a reduced risk of CHD death, even

when adjusting for exercise data such as maximal heart rate and physical fitness.

CHD is mainly represented by myocardial infarctions. The group with rapidly upsloping ST-segments had a similar risk of non-fatal CHD, but decreased risk of fatal CHD, when compared to the group with normal ST-segment. Fatal arrhythmias contribute significantly to deaths from CHD, both during infarction and ischaemia, and our results fit well with the hypothesis that serious arrhythmic events occur less frequently in the group with rapidly upsloping ST-segments. Such arrhythmias are related to activity of the sympathetic nervous system, as illustrated by the efficacy of beta-blocking agents for the prevention of ventricular fibrillation. Thus, men in the rapidly upsloping group may have benefited from an arrhythmia-protective equilibrium of their autonomic nervous system.

Other factors may also influence the level of the J-point. The PR segment shortens and often slopes downward during exercise. The downward slope has been attributed to atrial repolarization (the T_a wave) and can cause false-positive ST-depression in the inferior leads.⁷ Baseline PQ (PR) interval in the present study differed between those with a rapidly upsloping ST-segment and the others, and perhaps an ST-pseudodepression caused by T_a contributed. Further, ST-segment depression is the most common manifestation of exercise-induced myocardial ischaemia. The ST-segment depression represents electrical gradients caused by myocardial ischaemic segments, the extent of the ischaemic zone, previous areas of myocardial necrosis, and location of the recording electrodes.⁷ With an increasing (ischaemic) ST-vector, the ST-segment will be depressed (slowly ascending, horizontal, or downsloping). Our findings confirm the increased risk of CHD morbidity and mortality in this group, thus strengthening the external validity of our study.^{28–34}

Strengths and limitations

The present study is prospective in design, all data sets are virtually complete, and the findings refer to an apparently healthy population of middle-aged men followed for up to 35 years. The cohort was homogenous and methods are meticulously described and applied. All men were followed by using a unique identification number, and none were lost to follow up. We have no work-up bias and all event data are based on cause-specific death records and complete hospital records. Since the study has not interfered with patient care, bias is minimized. Stress level data were obtained from non-validated questionnaires, but the questions were simple and might have a scientific value in this study, assessing the significance of a new survival

factor. Our study included only healthy, middle-aged and full time working Norwegian men. The results of the present study should therefore neither be generalized to men of different ethnicity, age or those with concomitant diseases. Another major limitation is that this study only includes men, and ECG changes during exercise have been much less studied in women.

Conclusion

The prevalence of rapidly upsloping ST-segment on exercise ECG test of 2014 healthy middle-aged men was high (20%) and associated with a reduced risk of CHD death compared to men with normal ST-segments. Men with a rapidly upsloping ST-segment had several findings suggesting a lower activity of their sympathetic nervous system (less smokers, lower work related stress levels, and faster heart rate recovery after exercise) compared to men with a normal ST-segment, but data are not fully consistent and other explanations should also be considered.

Rapidly upsloping ST-segments on exercise ECG seem to be a new, firm marker of reduced long-term risk of death from coronary heart disease, and should perhaps be considered as the 'true healthy state'.

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