Electrocardiographic changes during exercise in asymptomatic men: 3-year follow-up

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Summary: Electrocardiographic (ECG) changes during maximal bicycle exercise and risk factors for coronary heart disease (CHD) were studied in 510 male civic employees who were followed for 3 years. Clinical CHD developed in 15 (24.6%) of the 61 men with an ischemic exercise ECG on the initial examination and in 11 (2.4%) of the 449 subjects with a normal initial exercise ECG. A normal maximal exercise ECG is no guarantee that severe CHD does not exist and that a subject will not soon sustain major myocardial damage; and an ischemic exercise ECG does not necessarily indicate underlying CHD. In the former group angina was the most frequent clinical CHD episode; in the latter group, infarction. Among those with an abnormal initial exercise ECG, CHD was most likely to develop in association with a poor exercise capacity. Subjects with subsequent clinical CHD and those with abnormal ECGs after 3 years tended to have a higher frequency of risk factors; subjects whose abnormal ECGs reverted to normal after 3 years tended to have a lower frequency of risk factors.

Résumé: *Modifications du tracé électrocardiographique durant l'effort chez des hommes asymptomatiques: catamnèse de 3 ans*

Chez 510 employés civils de sexe masculin nous avons étudié les modifications de l'électrocardiographe (ECG) pendant un exercice maximal de bicyclette et les facteurs de risque de cardiopathie coronarienne (CC). Les évaluations ont été faites en deux occasions, séparées par un intervalle de 3 ans. Une CC clinique est apparue chez 15 (24.6%) des 61 hommes dont l'ECG d'effort était ischémique lors du premier examen et chez 11 (2.4%) des 449 sujets dont l'ECG d'effort initial était normal. Un ECG d'effort maximal normal ne constitue pas une garantie de l'absence d'une CC sévère, ni qu'un sujet ne souffrira pas bientôt d'un épisode coronarien majeur. Un ECG d'effort ischémique ne signe pas obligatoirement une CC sous-jacente. Chez le premier groupe l'épisode de CC le plus fréquent était l'angine; chez le dernier groupe, un infarctus. Parmi les sujets dont l'ECG d'effort initial était anormal, ceux qui couraient le plus de risque de souffrir d'une CC étaient ceux qui ne possédaient qu'une médiocre capacité d'effort physique. Les sujets qui ont présenté une CC clinique subséquente et ceux dont l'ECG est devenu anormal après 3 ans tendaient à présenter une plus forte fréquence de facteurs de risque. Quant à ceux dont l'ECG s'était normalisé après 3 ans, ils tendaient à présenter une fréquence plus faible de facteurs de risque.

Electrocardiographic (ECG) changes consistent with ischemia occur during exercise in up to 20% of asymptomatic men aged 40 to 65 years. In subjects with these changes there is a much greater chance that clinical coronary heart disease (CHD) will develop.[1-3] By means of follow-up histories and, where possible, repeat maximal exercise tests, we have studied a population of 510 men initially investigated 3 years before,[4] in order to answer the following questions:

- What is the comparative frequency of subsequent coronary events in those with normal and abnormal maximal exercise ECGs?
- Does a normal maximal exercise ECG indicate that a coronary event is unlikely in the next few years?
- What is the relationship of exercise intensity at the time of appearance of ischemic ECG changes to the development of CHD?
- Is there a difference in the presentation of CHD between subjects with normal and abnormal exercise ECGs?
- Do exercise ECGs provide information beyond that obtained from the study of accepted risk factors in predicting coronary events?
- Does volunteering for an exercise test and risk factor study lead to any major alterations in health habits?

Subjects

The initial series comprised 510 male civic employees aged 40 to 65 years. These subjects included aldermen and executives but were mostly workers for the police, fire, hydroelectric, waterworks, garbage disposal and street engineering departments. They were contacted through the City of Winnipeg personnel office and appointments were made by mail and phone for follow-up history and examina-

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tion. Those who did not wish to return for examination were interviewed by phone, with the emphasis being on a history of chest pain,[3] using questions devised by the London (England) School of Hygiene and Tropical Medicine.[5]

Methods

The methods used were similar to those described in the previous report.[4] The exercise test was performed on a calibrated electric bicycle ergometer with two consecutive 6-minute submaximal workloads. The loads were about the same as used previously by the subjects, although minor adjustments were made when necessary to have the first workload produce a heart rate of 65% of the age-predicted maximum and the second workload a heart rate of 85% of the predicted maximum. For the majority of subjects, after the 12 minutes of exercise the workload was increased by 300 kpm*/min each minute until the subject could no longer maintain the cycling speed. Exercise was terminated if any chest pain developed, if there were three or more consecutive ventricular ectopic beats or multifocal ectopic beats, if there were any symptoms of distress other than leg fatigue, or if there was an ischemic-type ST segment depression of more than 2 mm. In half of the subjects restudied, lead CM_5 was monitored as before; in the other half the bipolar lead was from the forehead to the C position of the Frank lead system, which gave patterns essentially the same as those of lead CM_5. ECGs were recorded during exercise and for 5 minutes of recovery, and during recovery the subjects were supine to eliminate any postural ECG changes.

For each subject a follow-up medical history was taken, a resting ECG recorded, vital capacity, skin-fold thickness and serum cholesterol concentration were measured and urinalysis was performed.

*kpm = kilopond (also known as kilogram-force) metre.

Table I—Participation of subjects in 3-year follow-up

Participation	Classification of initial exercise ECG: Abnormal (no. of subjects)	Normal (no. of subjects)
Participated in retesting	50	398
Did not participate in retesting		
Not interested	7	39
Died of CHD	2	2
Died of other causes	0	2
Had left province	0	4
Had health problems other than CHD	0	3
Had CHD; doctor advised against retesting	2	1
Total	61	449

Table II—Data of subjects with normal initial exercise ECGs and subsequent clinical CHD

Subject	Age at initial test (yr)	Results of initial testing: Test severity	Max. heart rate (beats/min)	Max. workload (kpm/min)
		Angina		
1	54	Submaximal	157	600
2	53	Submaximal	165	750
		Myocardial infarct, survived		
3	50	Maximal	173	900
4	43	Maximal	195	1100
5	49	Maximal	182	1000
6	50	Maximal	162	1200
7	61	Submaximal	131	600
8	48	Maximal	158	1050
9	52	Maximal	165	1200
		Myocardial infarct, died		
10	47	Maximal	183	1400
11	56	Submaximal	170	700

Results

Details of participation in the follow-up are summarized in Table I. Of the 510 men initially studied, 88% made themselves available for retesting approximately 3 years after their initial test, 3% were unavailable because of death, moves out of the province or illness, and 9% did not wish to take part in any further tests.

Data of the 11 subjects in whom CHD developed within 3 years of a normal exercise ECG are presented in Table II. Angina developed in two men and myocardial infarction in nine. The two deaths occurred within 12 hours of the onset of chest pain. Autopsy was done only in subject 10, who had an occlusion of the left anterior descending coronary artery caused by a subintimal hemorrhage, the remainder of this vessel and the other coronary vessels being widely patent; before the fatal event the coronary circulation in this man would not have been severely impaired. Seven of the 11 subjects had performed maximal exercise tests and had attained maximal heart rates; a review of their exercise ECGs failed to reveal any abnormalities. Three subjects had performed 12-minute submaximal tests only, not doing the third (maximal) test because of fatigue. However, age-predicted maximal heart rates had been reached by two of these subjects, suggesting that they also had worked to near maximal levels. Subject 7, aged 61 years, stopped work after 6 minutes at 600 kpm/min because of leg fatigue; his heart rate was 131 beats/min (81% of age-predicted maximum).

The data of the 15 subjects with abnormal initial exercise ECGs in whom symptoms of CHD developed are set forth in Table III. Angina developed in 11 of the 15 (73%). In contrast, angina was the CHD abnormality in only 2 of the 11 subjects (18%) with initially normal exercise ECGs and subsequent clinical CHD. There were two myocardial infarctions, one fatal, and two sudden deaths. Subject 26 died suddenly while jogging. He had been retested 2 months before his death and had been warned to see his family doctor before taking any exercise. (A letter was

Table III—Data of subjects with abnormal initial exercise ECGs and subsequent clinical CHD

Subject	Age at initial test (yr)	Results of initial testing: Test severity	Heart rate at time of ischemia (beats/min)	Workload at time of ischemia (kpm/min)
		Angina		
12	52	Submaximal	150	700
13	64	Submaximal	125	450
14	63	Maximal	153	750
15	54	Submaximal	130	750*
16	56	Submaximal	142	450
17	58	Submaximal	150	450
18	58	Submaximal	140	620
19	55	Submaximal	156	750
20	48	Submaximal	153	600
21	61	Submaximal	125	850
22	46	Maximal	185	1350
		Myocardial infarct survived		
23	53	Submaximal	145	800
		Myocardial infarct deceased		
24	53	Maximal	160	1650
		Sudden death		
25	54	Submaximal	150	600
26	48	Submaximal	165	750

*Carried on with test and worked at 1250 kpm for 3 minutes after appearance of ischemic ST change.

sent to his doctor at that time and the doctor was unsuccessful in arranging an appointment with him.) The other sudden death occurred while the subject was relaxing at his summer cottage. Infarctions constituted only 13% of the episodes (2 out of 15) in this group, compared to 82% (9 out of 11) in the normal initial ECG group. Twelve of the subjects in this "abnormal" group stopped exercising after the second submaximal workload, five because of fatigue and seven (by the test supervisor) because of an ischemic ECG change. The ischemic ECG change occurred with the submaximal load in these 12 subjects and in 1 of the 3 subjects who performed maximal exercise. In the other two subjects the ischemic change occurred only with maximal exercise; subject 24 was able to work at 1650 kpm/min for 3 minutes, yet had a fatal infarction 18 months later. Subject 22 was able to work at 1350 kpm/min for 3 minutes in 1970 with no chest pain; in 1973 fast walking produced angina.

The classification of ECGs at initial and follow-up testing is summarized in Table IV. In the "abnormal" group 50 subjects were retested; in 7 (14%) the ECG pattern was now normal. There was no major change in the health habits or coronary risk factors in any of these subjects. In the "normal" group 398 were retested; 379 (95%) continued to have a normal exercise ECG. Nineteen subjects (5%) had a change in their exercise ECG pattern from normal to abnormal; in three subjects this was associated with the development of clinical CHD but the others remained asymptomatic.

The frequency of each of a number of arbitrary CHD risk factors at the time of initial testing in seven categories of subjects is shown in Table V. Those men who initially had a normal exercise ECG were divided into three groups: those in whom clinical CHD developed, those in whom clinical CHD did not develop, and those without clinical CHD whose exercise ECG was abnormal at follow-up. Among the subjects with subsequent clinical CHD there were more smokers and more with hypertension. There were more overweight and unfit subjects in the group with abnormal exercise ECGs only at follow-up.

Subjects who had an abnormal initial exercise ECG were compared for risk factors in two ways. Of the 50 who were retested, 7 then had a normal exercise ECG pattern. These subjects tended to have a lower frequency of hypertension, smoking, positive family history, high serum cholesterol value and low fitness than those whose exercise ECG remained abnormal. Of the 61 subjects with abnormal initial exercise ECGs, clinical CHD developed in 15. These subjects tended to have a lower handgrip strength and to be less active than those in whom clinical CHD did not develop. The sample was too small to permit multivariate analyses and these data have not been subjected to statistical analysis.

Table IV—Comparison of ECG classification at initial and follow-up testing

	Classification of initial ECG	
Status at 3-year follow-up	Abnormal (n = 61)	Normal (n = 449)
Unchanged	43	379
Changed category	7	19
(Not tested)	(9)	(47)
(Deceased)	(2)	(4)

Discussion

The 88% availability of the subjects for repeat testing was encouraging, for maximal testing using a bicycle ergometer requires considerable effort and motivation. In addition, the subjects did not belong to any closely knit group such as the YMCA, a health club or a businessmen's group or coronary club. The men were asked to volunteer and did not come to us for any health screening, and the fact that 10% of the men did not wish to participate in any further testing was not surprising.

Master has repeatedly stated that a negative double Master's test virtually rules out the presence of coronary artery disease.[6] Our results indicate that a negative maximal exercise test is no assurance that major myocardial damage will not occur in a few years. One of the fatalities was due to a subintimal hemorrhage and there was minimal coronary atherosclerosis; a negative exercise test is to be expected in this situation. The pathogenesis of some of the nonfatal episodes of clinical CHD in the normal group may have been similar. Reported series correlating results of coronary angiography and exercise tests indicate that negative tests may occur in up to 75% of symptomatic patients with narrowing of only one major coronary artery, and in up to 50% of subjects with previous infarctions.[7] It seems clear that a negative exercise test is no guarantee that severe coronary artery disease is not present.

Table V—Frequency of risk factors and follow-up course

	% of subjects with risk factors on initial testing						
	Normal initial exercise ECG			Abnormal initial exercise ECG			
				At follow-up			
Risk factor	No CHD (n = 414)	CHD (n = 11)	Abnormal ECG at follow-up (n = 19)	Unchanged (n = 43)	Improved (n = 7)	CHD (n = 15)	No CHD (n = 46)
% fat > 32.5% *	22	9	26	29	29	33	39
Weight > 1.3 × ideal†	44	36	58	47	43	40	52
Blood pressure (mm Hg)							
Resting							
Systolic >145	9	19	5	39	0	47	28
Diastolic > 90	6	19	5	31	0	47	17
Exercise >220	3	0	5	9	14	8	9
Positive family history‡	27	27	5	39	14	67	44
Smoking > 10 cigarettes/d	39	70	42	25	9	20	44
Minor t-wave changes on resting ECG	5	10	5	39	14	33	39
Handgrip strength < 52.8 kg	22	20	42	14	29	40	9
Cholesterol, upper quartile	55	50	68	66	29	77	62
$\dot{V}O_2$ max. (ml/kg · min) < 27.5	39	36	63	77	29	62	61
Inactive§	19	19	21	25	14	33	16

*% of body weight from skinfold thicknesses.
†Ideal based on medium frame and height from actuarial study.
‡Parent or sibling with clinical CHD before age 60 years.
§Clerical or desk job; no recreational physical activity.

The importance of myocardial vulnerability in clinical CHD and in sudden death remains an enigma. It is not known whether exercise tests measure this vulnerability factor, and proof of the existence of this factor in the human is difficult to obtain. Anderson[8] recently reviewed evidence that supported the importance of myocardial factors.

Of the asymptomatic subjects with an abnormal initial exercise ECG, clinical CHD developed in 25%, but of the subjects with a normal initial exercise ECG, clinical CHD developed in 2.5% (risk ratio, 10). This value is similar to that found by Bruce and McDonough.[3]

Angina was the presenting abnormality of clinical CHD in 73% of those with an abnormal initial exercise ECG, compared to 18% of those with a normal initial exercise ECG. Most of those in whom angina subsequently developed did not perform the maximal part of the initial test. Five stopped because of leg fatigue; the test supervisor was ready to stop the test because of the ECG change and did not encourage them to continue. These subjects did not admit to any chest pain at the time of the test, but clinical experience suggests that many patients with angina often must experience major episodes of pain before they recognize early anginal symptoms, and many anginal patients seem to get an "inner feeling" that they should not do any more work. The other seven subjects were stopped by the supervisor during the exercise test because of pathologic ST-segment depression exceeding 0.2 mV before chest pain developed; five had angina during the repeat exercise test.

Of the subjects with ischemic changes in their initial exercise ECG, 75% have remained active and free of symptoms. To say categorically that in all of these subjects occult but definite coronary artery disease is the cause of this exercise ECG change is an oversimplification. This is of more than theoretic importance, for it has been recommended that some employee groups, such as pilots, should undergo yearly exercise ECGs, with abnormalities being an indication for grounding. For a cautious interpretation of the significance of ST changes on exercise, the reader is referred to the 7-year study of van Buchem *et al.*[9] These authors found that an exercise test identified only 42% of those with subsequent CHD, and they emphasized that in many cases "ischemic" ST depression does not imply the presence of coronary insufficiency; clinical CHD developed most frequently in the older subjects with higher serum cholesterol values who had abnormal exercise ECGs. Recently Froelicher *et al*[10] studied coronary arteriograms in 87 aircrew members, all of whom were asymptomatic but had abnormal ECGs; 61% of men with exercise ECG changes only had normal coronary angiograms.

Although the small number of subjects did not permit complex statistical analyses, it appeared that subjects with abnormal initial exercise ECGs in whom specific coronary disorders subsequently developed generally had a higher frequency of various risk factors including hypertension, positive family history, low handgrip strength and fitness, and inactivity. An improvement in the exercise ECG was more likely in the absence of these risk factors. The group of subjects with a normal initial exercise ECG in whom CHD developed included more smokers and more subjects with hypertension than the group of subjects in whom CHD did not develop. The predictive value of the maximal exercise ECG beyond that offered by conventional risk factors must await a larger series suitable for multivariate analysis.

Because of the high incidence of subsequent clinical CHD among men with an abnormal exercise ECG, such men are well advised to take every measure possible to reduce the influence of any of the known risk factors associated with clinical CHD. The American Heart Association booklet entitled "Reduce Your Risk Factors" was distributed to all 510 subjects during the 1st year of the study. The risk factors of all subjects, those with and those without exercise ECG changes, were emphasized in a personal report mailed to each individual. Each man with an abnormal exercise ECG had a personal interview to discuss this finding. To avoid creating anxiety and iatrogenic disease, the interviewer stressed that the exact meaning of the ST change was not known, and that false-positive test results were frequent. However, any subject with risk factors was urged to take remedial action. A report was sent to all family doctors, and any subject with ECG changes, hypertension or other problems was advised to consult his doctor. With few exceptions (a few patients had hypertension brought under control with medication) these subjects have made little change in their health habits. All subjects available for retesting were asked, "Have you changed your smoking, eating, exercise or any other health habit since the initial test?" The answer to this question was negative in all but a few subjects. On the other hand, as soon as clinical symptoms developed, all of the subjects were quite keen to go on a strict medical regimen, with an attempt at weight loss, more regular exercise and cessation of smoking.

According to 1961 statistics[8] five coronary fatalities might have been expected in the population we studied; five were observed. It is not known whether our contact with these men has had any effect on the natural history of CHD in this population.

Conclusion

Further education of the public and physicians on the importance of risk factors is essential, but knowledge of the risks is not sufficient, and popular public movements to reduce cigarette use, to correct dietary errors and to increase physical activity must be devised. Mild or moderate hypertension, which may only require for control mild salt restriction, a few changes in living habits, and a small amount of medication each day, is likely the easiest of all of the important risk factors to eliminate, yet much hypertension is unrecognized or untreated. Recognition of preclinical CHD is of no value if the process cannot be halted by a reasonable change in living habits; intervention trials with a multivariate approach are urgently needed.

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