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Prognostic Significance of Peak Exercise Capacity in Patients With Coronary Artery Disease

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Objectives. The aim of this study was to investigate the prognostic significance of peak oxygen uptake in patients with coronary artery disease who had an exercise test that could be sustained to exhaustion without limiting symptoms.

Background. Many studies have reported an inverse association between the level of exercise reached during a stress test and mortality or cardiovascular morbidity. These studies have used submaximal or symptom-limited exercise testing in patients with a recent myocardial infarction.

Methods. Peak oxygen uptake was measured in male patients ≥4 weeks after myocardial infarction (312 patients) or coronary artery surgery (215 patients) by use of a graded uninterrupted exercise test performed to exhaustion. Apart from peak oxygen uptake, several risk factors for cardiovascular disease, patient and exercise characteristics and drug treatment were considered in the Cox proportional hazards model.

Results. During the total follow-up period of 3,213 patient-years, 53 patients died. Of these 53 patients, 33 died of cardiovascular causes. All-cause and cardiovascular mortality decreased with increasing peak oxygen uptake, even after adjustment for significant covariates. The relative hazard rates of 0.43 and 0.29 indicate that a hypothetic increase in peak oxygen uptake by 1 liter/min could be associated with decreases in all-cause and cardiovascular mortality of 57% and 71%, respectively.

Conclusions. Exercise capacity is an independent predictor for subsequent all-cause and cardiovascular mortality in patients able to perform an exercise test until exhaustion.

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Exercise testing soon after myocardial infarction provides prognostic information. Angina during exercise (1–5), exercise-induced ST segment shifts (1–7) or ventricular arrhythmias (3,4,6,8,9), exertional hypotension (2–5,7,9–13) and amount of exercise performed (1–8,10–13), expressed as exercise duration, metabolic units (METs) or achieved work load, are all related to subsequent cardiovascular mortality or morbidity. Patients with a low exercise capacity have the highest incidence of cardiac events. However, most studies used submaximal exercise testing or included patients who were not allowed or were not able to perform a maximal exercise test for medical reasons. In this study we investigated whether exercise capacity is an independent prognostic factor for all-cause and cardiovascular mortality in patients with cardiovascular disease referred to an outpatient rehabilitation program for physical training for ≥3 months.

Methods

Subjects. The study group comprised all male patients, referred to an outpatient cardiac rehabilitation program during the period August 1978 to March 1988 who had a history of myocardial infarction or had undergone coronary bypass surgery.

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Before entering the program, they performed a graded maximal exercise test, a mean ± SD of 12.9 ± 2.7 weeks after the event. In 17 patients, however, it was decided before the test to perform a submaximal exercise test because of early testing after myocardial infarction or because of a history of severe ventricular arrhythmia. In another 40 patients the exercise test was interrupted because of rhythm disturbances (13 patients), ST segment depression >5 mm (4 patients), angina (17 patients), anxiety (1 patient) or claudication (5 patients) without symptoms of breathlessness or fatigue. Thus, 527 patients performed the exercise test until exhaustion: 312 patients after acute myocardial infarction and 215 after coronary bypass surgery, as classified by the last event. In the acute myocardial infarction group, coronary bypass surgery had been performed in 15 patients before their infarction and in 96 patients after a previous infarction.

Exercise protocol. In an air-conditioned laboratory with a room temperature of 18 to 22°C, the patients underwent a graded, uninterrupted exercise test on a cycle ergometer until exhaustion. The initial work load of 20 W (W = 6.12 kilopond-meters/min) was increased by 30 W every 4 min; from 1985 on, work load was increased every 3 min.

Ventilation (body temperature, pressure, saturated) was continuously measured by a pneumotachograph using an open-circuit method. Oxygen uptake standard temperature and pressure, dry (STPD) and carbon dioxide output (STPD) were calculated from the measurements of oxygen and carbon dioxide in the ambient and expired air by a paramagnetic and infrared analyzer, respectively. The respiratory

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Table 1. Clinical Characteristics of the Study Patients

	Total (n = 527)	AMI Group (n = 312)	CBS Group (n = 215)
Age (yr)	53.0 ± 7.8	52.2 ± 7.9	54.3 ± 7.6*
Height (cm)	171 ± 6	172 ± 6	172 ± 6
Weight (kg)	73.4 ± 8.6	73.3 ± 8.7	73.6 ± 8.4
Body mass index (kg/m^2)	24.9 ± 2.4	24.8 ± 2.4	24.9 ± 2.4
Rest blood pressure (mm Hg)			
Systolic	132 ± 19	130 ± 18	134 ± 20*
Diastolic	85 ± 11	85 ± 11	86 ± 12
Total cholesterol (mg/dl)	235 ± 47 (n = 491)	230 ± 46 (n = 292)	242 ± 49* (n = 199)
Smoking habits			
Previous smokers	399	237	162
Present	41	29	12
History of diabetes	17	14	3
History of hypertension	109	66	43
Family history of IHD	112	62	50
Medical therapy			
Beta-blockers	351	201	150
Vasodilating drugs	135	117	18†
Digitalis	138	46	92†
Diuretic drugs	23	15	8
Antiarrhythmic drugs	48	41	7†

*$p < 0.01$. †$p < 0.001$ when comparing the two groups. Values presented are mean value ± SD or number.
AMI = acute myocardial infarction; CBS = coronary bypass surgery; IHD = ischemic heart disease.

gas exchange ratio (carbon dioxide output/oxygen uptake) and ventilatory equivalent for oxygen (ventilation/oxygen uptake) were calculated. Heart rate (beats/min) was determined from the electrocardiogram. Blood pressure was measured with a standard mercury sphygmomanometer.

Follow-up. The follow-up period of the present study ended on December 31, 1990. The vital status of the patients was determined through contacts with authorities, the responsible physicians and family members and from data in hospital files. Information was collected for all but three patients, who moved abroad. Information about date, place, circumstances, cause of death and, if available, autopsy results were collected. Deaths were coded according to the *International Classification of Diseases, ninth revision* (14).

Statistical analysis. Data are reported as mean value ± SD. Comparisons between groups were performed by the unpaired Student *t* test and chi-square contingency analysis. The Cox proportional hazards regression model (15) was used for survival analysis. Three categories of fatal events were analyzed: 1) all-cause mortality, 2) cardiovascular mortality, and 3) noncardiovascular mortality. Relative hazard rates with 95% confidence limits are reported for single and multiple regression analysis. Variables included in the analysis were peak oxygen uptake; age; patient group (acute myocardial infarction group = 1, coronary bypass surgery group = 2); systolic and diastolic rest blood pressure, measured with the patient at rest sitting on the bicycle; occurrence of significant ST segment depression (≥1.5-mm horizontal or downsloping ST segment depression) or major ventricular arrhythmia (defined as ventricular ectopic beats at a rate of ≥10/min or couplets or triplets) during the exercise test; patient reports of dyspnea or chest pain during daily activities in the weeks before exercise testing; the risk indicators of total plasma cholesterol, body mass index (kg/m^2), previous and present smoking habits, history of diabetes (insulin-dependent and noninsulin-dependent combined), history of hypertension, family history of ischemic heart disease, defined as the occurrence of ischemic heart disease in at least one parent, brother or sister <65 years old; various drugs at the moment of exercise testing, such as beta-adrenoceptor blocking, diuretic and vasodilating agents (nitrates, molsidomine, calcium antagonists), and antiarrhythmic drugs and digitalis. Dichotomous variables were coded 0 when the condition was absent and 1 when it was present.

Results

Clinical characteristics of the patients. The characteristics of the 527 patients at the time of entry into the study are shown in Table 1. Ages ranged from 24 to 74 years, and patients who underwent coronary bypass surgery were older by 2.1 years than those with a previous myocardial infarction. Systolic blood pressure, measured at rest sitting, and total plasma cholesterol were also slightly higher in the bypass surgery group. Only 3% of the patients had diabetic disease, 21% had a history of hypertension and 21% had a positive family history of ischemic heart disease. In the

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Table 2. Data at the End of Exercise*

	Total	AMI Group	CBS Group
$\dot{V}O_2$ (ml/min)	1,704 ± 464	1,737 ± 463	1,657 ± 462
$\dot{V}O_2$/kg (ml/min per kg)	22.3 ± 6.0	23.8 ± 5.9	22.7 ± 6.1
$\dot{V}CO_2$ (ml/min)	1,811 ± 516	1,839 ± 511	1,770 ± 522
$\dot{V}E$ (liters/min)	57.8 ± 17.3	57.9 ± 16.8	57.9 ± 17.8
RER	1.06 ± 0.09	1.06 ± 0.09	1.06 ± 0.09
$\dot{V}EO_2$	34.2 ± 6.2	33.7 ± 6.3	34.9 ± 6.0
Heart rate (beats/min)	129 ± 23	130 ± 22	128 ± 24

Values presented are mean value ± SD. *No significant differences were observed between study groups. RER = respiratory gas exchange ratio; $\dot{V}E$ = pulmonary ventilation; $\dot{V}CO_2$ = carbon dioxide uptake; $\dot{V}EO_2$ = ventilatory equivalent for oxygen; $\dot{V}O_2$ = oxygen uptake; other abbreviations as in Table 1.

myocardial infarction and coronary bypass surgery groups, respectively, 76% and 75% were previous smokers, and 9% and 6% continued smoking after the event. Approximately two thirds of the patients in both groups were treated with beta-blockers. Fewer patients in the bypass surgery group were treated with vasodilating and antiarrhythmic drugs, and more patients received digitalis. Thirty-six patients in the myocardial infarction group and 35 patients in the bypass surgery group complained of dyspnea, and 82 and 46 patients, respectively, reported chest pain in daily life at the time of the evaluation.

All patients performed the exercise test until exhaustion, not limited by angina pectoris. Data at the end of exercise are presented in Table 2. Peak oxygen uptake averaged 1,704 ± 464 ml/min, or 6.65 ± 1.8 METs, and peak heart rate was 129 ± 23 beats/min. During exercise testing, 73 patients had significant ST segment depression (38 patients in the acute myocardial infarction group, 35 patients in the coronary bypass surgery group), and 91 patients had major ventricular arrhythmia. No significant differences in heart rate and respiratory variables were observed between the two groups.

Mortality. Vital status at the end of follow-up was known in 524 patients. The total follow-up period was 3,213 patient-years, and the average follow-up duration was 6.1 years (range 0.07 to 11.9). Fifty-three patients (10.1%) died (Table 3) an average of 4.3 years (range 0.07 to 10.5) after the exercise test. The mean age at the time of death was 61.0 years (range 40.7 to 75.4). The cause of death was cardiovascular in 33 patients and noncardiovascular in 20. The incidence of death and the time interval between the test and death were not statistically different between patients in the acute myocardial infarction and coronary bypass surgery groups.

Table 4 shows the clinical characteristics of the nonsurvivors and survivors. The relative hazard rate of each variable for all-cause mortality was calculated by the single Cox proportional hazards regression model.

In Table 5 the relative hazard rates for peak oxygen uptake are presented 1) unadjusted; 2) adjusted for age; 3) adjusted for age and other significant covariates, such as present smoking habits, significant exercise-induced ST segment depression, history of hypertension and history of diabetes; 4) significant drug treatment, such as beta-blockers and diuretic agents; and 5) the variable group of patients. The relative hazard rate for peak oxygen uptake, after adjustment for all significant variates, of 0.43 for all-cause mortality and of 0.29 for cardiovascular mortality indicates that an increase of 1 liter/min in peak oxygen uptake is associated with a decrease in, respectively, all-cause and cardiovascular mortality of 57% and 71%. Separate subanalyses for patients in the acute myocardial infarction and coronary bypass surgery groups indicate in general similar trends for both groups, but significance was not always reached. When the METs level (1 MET = 3.5 ml of oxygen/

Table 3. Cause of Death

	ICD-9 Codes	Total (n = 524)	AMI Group (n = 311)	CBS Group (n = 213)
All cardiovascular	(390–459)	33 (6.3%)	23 (7.4%)	10 (4.7%)
Sudden death	(798.1)	17	9	8
AMI	(410)	3	2	1
Cardiac dysrhythmia	(427)	4	4	—
Acute heart failure	(428)	6	5	1
Cerebrovascular	(430–438)	3	3	—
All noncardiovascular		20 (3.8%)	13 (4.2%)	7 (3.3%)
Neoplastic	(140–239)	17	11	6
Suicide, accident	(E953–E881)	2	2	—
Senility	(797)	1	—	1
Total		53 (10.1%)	36 (11.6%)	17 (8.0%)

ICD-9 = *International Classification of Diseases, ninth Revision* (Ref. 14); other abbreviations as in Table 1.

Table 4. Risk Indicators in Survivors and Nonsurvivors and Their Relative Hazard Rates

	Nonsurvivors	Survivors*	RHR
Age (yr)	56.7 ± 6.4	52.6 ± 7.9†	1.08†
Body mass index (kg/m²)	24.8 ± 2.7	24.9 ± 2.4	1.02
Blood pressure at rest (mm Hg)			
Systolic	136 ± 20	131 ± 19	1.01
Diastolic	88 ± 14	85 ± 11‡	1.02
Significant ST segment depression	12 (23%)	61 (13%)‡	1.71
Frequent ventricular arrhythmias	12 (23%)	79 (17%)	1.59
Patient reports of			
Dyspnea	10 (19%)	61 (13%)	1.41
Chest pain	12 (23%)	116 (24%)	0.86
Total cholesterol (mg/dl)	226 ± 33	236 ± 49	1.0
Previous smoking habits	41 (77%)	359 (76%)	1.18
Present smoking habits	9 (17%)	32 (7%)§	2.37‡
History of diabetes	6 (11%)	11 (2%)‡	4.18†
History of hypertension	17 (32%)	92 (19%)‡	1.77‖
Family history of IHD	7 (13%)	105 (22%)	0.48
Treatment			
Beta-blockers	23 (43%)	328 (69%)†	0.46§
Vasodilating agents	13 (25%)	122 (26%)	1.00
Digitalis	20 (38%)	119 (25%)‡	1.64
Diuretic drugs	7 (13%)	16 (3%)†	3.67§
Antiarrhythmic drugs	5 (9%)	43 (9%)	0.78

*Comparison made by chi-square analysis or unpaired Student *t* test. †$p < 0.001$. ‡$p < 0.05$. §$p < 0.01$. ‖$p < 0.054$. Values presented are mean value ± SD or number (%). IHD = ischemic heart disease; RHR = relative hazard rate for all-cause mortality, calculated by the single Cox regression model.

Table 5. Relative Hazard Rates and 95% Confidence Limits for Peak Oxygen Uptake*

	Total	AMI Group	CBS Group
All-Cause Mortality			
Unadjusted	0.28† (0.14–0.55)	0.29‡ (0.13–0.64)	0.23§ (0.06–0.85)
Adjusted for			
Age	0.38‡ (0.18–0.79)	0.40§ (0.17–0.94)	0.24‖ (0.06–1.02)
Age, covariates¶	0.40‡ (0.19–0.82)	0.43§ (0.18–1.00)	0.24‖ (0.06–1.01)
Age, covariates, drugs**	0.43§ (0.21–0.89)	0.48# (0.20–1.14)	0.24# (0.05–1.10)
Age, covariates, drugs, group of pts	0.43§ (0.21–0.89)	—	—
Cardiovascular Mortality			
Unadjusted	0.18† (0.07–0.44)	0.22‡ (0.08–0.60)	0.09‡ (0.01–0.55)
Adjusted for			
Age	0.22† (0.08–0.56)	0.28§ (0.10–0.82)	0.07‡ (0.01–0.54)
Age, covariates*	0.24‡ (0.10–0.59)	0.31§ (0.11–0.89)	0.09‡ (0.01–0.39)
Age, covariates, drugs¶	0.29‡ (0.12–0.73)	0.40# (0.14–1.17)	0.06§ (0.01–0.60)
Age, covariates, drugs, group of pts	0.29‡ (0.12–0.73)	—	—

*Relative hazard rates are calculated from single and multiple Cox regression models (confidence limits are in parentheses). †$p < 0.001$. ‡$p < 0.01$. §$p < 0.05$. ‖$p = 0.05$. ¶Significant covariates included present smoking habits, significant ST segment depression, history of hypertension and history of diabetes. #Not significant. **Significant drug therapy was beta-blockers and diuretic agents. pts = patients; other abbreviations as in Table 1.

min per kg) was used as an expression of exercise capacity, similar results were obtained.

All-cause and cardiovascular deaths/1,000 patient-years are presented for quintiles of peak oxygen uptake (ml/min per kg) in Table 6. In Figure 1 all-cause and cardiovascular mortality are plotted for peak oxygen uptake. These relations were standardized to patients aged 50 years, to nonsmokers and to patients without significant ST segment depression and without a history of diabetes or hypertension.

When analyzing relation with noncardiovascular deaths in all patients, noncardiovascular mortality was related to age (relative hazard rate = 1.10, $p = 0.005$) but not to peak oxygen uptake (relative hazard rate = 0.93, $p = 0.89$).

Discussion

It has been shown (1–13) that the results from exercise testing are related to subsequent cardiovascular mortality or morbidity, or both. A low exercise duration of METs level was associated with a higher incidence of mortality or recurrence of nonfatal myocardial infarction. In many studies, patients were tested soon after myocardial infarction, performing only submaximal exercise tests until a given work load or heart rate. Most studies also included patients who could not complete the exercise test because of chest pain, extensive ST segment depression, ventricular arrhythmia or exertional hypotension. It is possible that a higher mortality or higher incidence of cardiovascular events will occur in patients with symptoms, which suggests left ventricular dysfunction or ischemia at exercise. Froelicher et al. (16) even conclude from a meta-analysis that patients excluded from exercise testing for medical reasons have the

Table 6. All-Cause and Cardiovascular Deaths in Quintiles of Peak Oxygen Uptake

Quintiles of Peak Oxygen Uptake (ml/min per kg)*	All-Cause Deaths†		Cardiovascular Deaths†	
	No.	No./1,000 Pt-yr	No.	No./1,000 Pt-yr
15.5 (7.95–18.5)	18	27.2	15	22.7
20.1 (18.6–21.5)	17	24.9	9	13.2
22.8 (21.5–24.2)	12	18.1	6	9.1
25.8 (24.2–27.9)	6	9.9	3	4.9
32.3 (27.9–47.0)	0	0	0	0
Total (n = 524)				
23.3 (7.95–47.0)	53	16.6	33	10.3

*Values presented are mean values (range). †Data are unadjusted and represent total number and crude rates. pt = patient.

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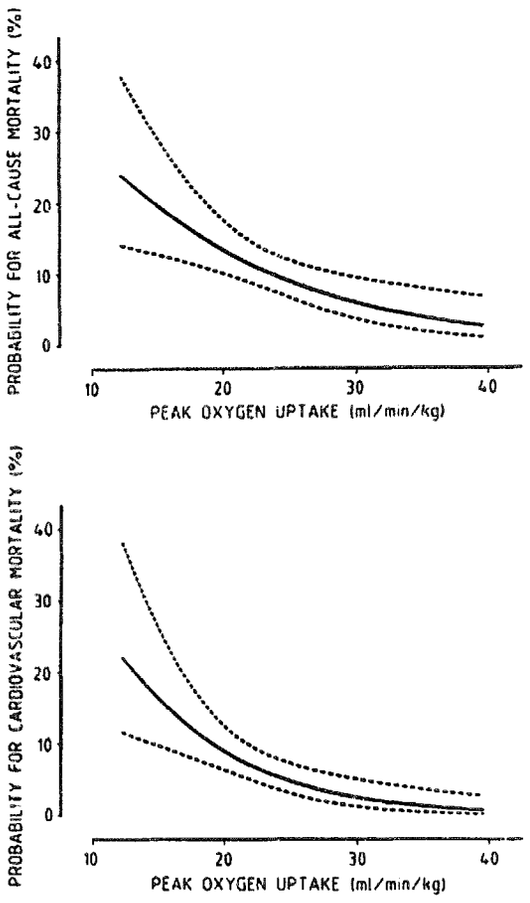

Figure 1. Relation between peak oxygen uptake (ml/min per kg) and, respectively, all-cause (top) and cardiovascular (bottom) mortality with 95% confidence limits. The relations were standardized to nonsmokers, aged 50 years, without significant ST segment depression and without history of diabetes or hypertension.

highest mortality and that submaximal or predischarge testing has greater predictive power than has postdischarge or maximal testing. Whether exercise capacity is still predictive for mortality in patients able to perform an exercise test until exhaustion remains uncertain.

Exercise capacity. The aim of the present study was to investigate the relation of exercise capacity, as assessed by an exercise test performed until exhaustion to subsequent all-cause and cardiovascular mortality in patients referred to a cardiac rehabilitation program after myocardial infarction or coronary bypass surgery. In the present analysis, all patients stopped exercising because of dyspnea or fatigue. The respiratory data, the gas exchange ratio (on average 1.06) and the respiratory equivalent for oxygen (on average 34.2) indicate a maximal to near-maximal effort.

Risk indicators. Apart from peak oxygen uptake, several other possible risk indicators for cardiovascular disease were considered for stepwise Cox regression analysis. They included age; body mass index; rest blood pressure; significant exercise-induced ST segment depression and ventricular arrhythmia; patient reports of dyspnea or chest pain in daily life; plasma cholesterol; past and present smoking habits; history of hypertension; family history of ischemic heart disease; and history of diabetes. Data on stress, habitual physical activity, left ventricular hypertrophy and alcohol consumption, were not available. Intake of certain cardiovascular drugs was also introduced into the multiple regression analysis because drug treatment may influence exercise capacity (17,18) and mortality (19–22). However, treatment with a given drug was based on clinical judgment and could be altered over time. Therefore, the relative hazard rates were reported with and without inclusion of drug treatment.

Prognostic value. A total of 53 patients died during follow-up, 33 of whom died of cardiovascular causes. The all-cause mortality rate was 16.5/1,000 patient-years. A consistent finding in all analyses is the independent relation between peak oxygen uptake and subsequent mortality: the lower the exercise capacity, the higher the risk for all-cause or cardiovascular death (Table 6, Fig. 1). This finding is in agreement with data from other studies using a symptom-limited (2,8,10,11) or maximal (13,23) exercise protocol. The "maximal" exercise test in the study of Nielsen et al. (13), however, was interrupted for symptoms in 41% of the 54 patients studied, and other significant covariates were not considered in the analysis. The present findings thus extend the frequently reported relation in postinfarction patients between submaximal or symptom-limited exercise and subsequent mortality. Whether reduced maximal exercise capacity in patients after acute myocardial infarction and the subsequent increase in mortality both reflect left ventricular dysfunction has still to be elucidated. When analyzed separately in the patients with coronary bypass surgery, significant negative relations between maximal exercise capacity and all-cause and cardiovascular mortality could also be demonstrated. Dubach et al. (23) also found a significant predictive value of METs level for combined cardiac events, such as cardiac mortality, nonfatal infarction, repeat surgery or percutaneous transluminal coronary angioplasty in patients after surgery.

In the present study, some generally accepted risk indicators were not predictive of mortality: total cholesterol, body mass index, family history of ischemic heart disease, rest systolic or diastolic blood pressure, patient reports of dyspnea or chest pain in daily life (at the time of the exercise test) and occurrence of major ventricular arrhythmia during exercise. The patients were referred to the cardiac rehabilitation program and thus reflect a selected population. Furthermore, they were referred while receiving medical therapy that could not be interrupted. Therefore, some variables could not be studied under standardized conditions, and treatment may have influenced certain variables, particularly serum cholesterol and blood pressure.

Conclusions. Exercise capacity, determined by a graded exercise test until exhaustion, is an independent predictor for all-cause and cardiovascular mortality in patients referred to a rehabilitation program after myocardial infarction

or coronary bypass surgery. Whether this correlation, based on a retrospective analysis, indicates a causal relation cannot be established on the basis of the present data.

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