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Peak Oxygen Intake and Cardiac Mortality in Women Referred for Cardiac Rehabilitation

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OBJECTIVES This study investigated the prognostic importance of measured peak oxygen intake ($\dot{V}O_{2peak}$) in women with known coronary heart disease referred for outpatient cardiac rehabilitation.

BACKGROUND Exercise capacity is a powerful predictor of prognosis in men with known or suspected coronary disease. Similar findings are described in women, but fewer studies have utilized measured $\dot{V}O_{2peak}$, the most accurate measure of exercise capacity.

METHODS A single-center design took data from 2,380 women, age 59.7 ± 9.5 years (1,052 myocardial infarctions, 620 coronary bypass procedures, and 708 with proven ischemic heart disease), who underwent cardiorespiratory exercise testing. They were followed for an average of 6.1 ± 5 years (median 4.5 years, range 0.4 to 25 years) until cardiac and all-cause death.

RESULTS We recorded 95 cardiac deaths and 209 all-cause deaths. Measured $\dot{V}O_{2peak}$ was an independent predictor of risk, values ≥13 ml/kg/min (3.7 multiples of resting metabolic rate) conferring a 50% reduction in cardiac mortality (hazard ratio [HR] 0.5, p = 0.001). Considered as a continuous variable, a 1 ml/kg/min advantage in initial $\dot{V}O_{2peak}$ was associated with a 10% lower cardiac mortality. Adverse predictors were diabetes (HR 2.73, p = 0.0005) and antiarrhythmic therapy (HR 3.93, p = 0.0001).

CONCLUSIONS As in men, measured $\dot{V}O_{2peak}$ is a strong independent predictor of cardiac mortality in women referred for cardiac rehabilitation. (J Am Coll Cardiol 2003;42:2139–43) © 2003 by the American College of Cardiology Foundation

The long-term prognosis of men with known or suspected coronary artery disease is strongly related to exercise capacity (1–3). The same relationship has been described in healthy women (4) and in women with ischemic heart disease (IHD) (5–8). However, most reports have expressed exercise capacity as a treadmill time or MET value (multiples of the resting metabolic rate) rather than measured peak oxygen intake ($\dot{V}O_{2peak}$), the most accurate measure of exercise capacity (9). We therefore examined the prognostic value of measured $\dot{V}O_{2peak}$ in a substantial sample of women with proven coronary heart disease (CHD).

METHODS

Study population. A total of 2,380 women (1,052 myocardial infarctions [MIs], 620 coronary artery bypass graft procedures [CABGs], and 708 documented cases of IHD, including 161 statistically similar patients who underwent a percutaneous coronary intervention) were referred for exercise testing 13.9 ± 4.1 weeks after the event, procedure, or, in the case of IHD, diagnosis. Referrals grouped in five-year intervals were as follows: 1973 to 1977, n = 72; 1978 to 1982, n = 235; 1983 to 1987, n = 394; 1988 to 1992, n = 549; 1993 to 1998, n = 1,130.

Follow-up. Health status was obtained from a questionnaire mailed at approximately 12- to 18-month intervals. Death certificates were examined for decedents resident in Ontario; for 15 decedents no longer resident in Ontario, cause of death was determined from information obtained from a physician, spouse, or other family members.

Cardiorespiratory testing. All patients underwent maximal cardiorespiratory exercise testing on the cycle ergometer, using the identical protocol we have previously employed in men (3). Measurements included continuous electrocardiographic monitoring, resting and exercise blood pressure, the rating of perceived exertion on the original Borg scale, and analysis of respiratory gases for $\dot{V}O_{2peak}$ and ventilatory threshold.

Statistical methods. Data were analyzed using univariate and multivariate Cox proportional hazard models. Survival time was defined as the day of the exercise test to cardiac death, all-cause death, or last contact. The $\dot{V}O_{2peak}$ was treated both as a continuous variable and then as a binary variable, with the optimal cutoff point determined by recursive partitioning (10,11). Hazard ratios (HRs) were calculated for individual risk factors, agreement between measured and predicted $\dot{V}O_{2peak}$ assessed using kappa statistic, and paired comparison made using McNemar's chi-square test. Kaplan-Meier survival curves were also generated. SAS Software version 8.2 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

RESULTS

Clinical and physiologic characteristics. The mean age at the time of testing was 59.7 ± 9.5 years. We were unable to

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CHD = coronary heart disease
CI = confidence interval
HR = hazard ratio
IHD = ischemic heart disease
METs = multiples of resting metabolic rate
MI = myocardial infarction
$\dot{V}O_{2peak}$ = peak oxygen intake

contact 103 patients (4.3% of sample). Patients tended towards obesity (27% had a body mass index ≥30; mean 34.4 ± 4.0 kg/m^2), and approximately one-half were taking a platelet inhibitor (most commonly aspirin) or a beta-blocker (Table 1).

The average $\dot{V}O_{2peak}$ values were typical of those we and others have reported on postcoronary women in their late 50s (12,13). Complex ventricular arrhythmias, significant ST-segment depression (≥0.2 mV), and exertional angina occurred in 9.1%, 7.7%, and 10.4% of patients, respectively.

The average follow-up time was 6.1 ± 5 years (median 4.5 years, range 0.4 to 25 years). During follow-up, 95 cardiac deaths (59 MI, 23 CABG, 13 IHD) and 209 all-cause deaths (4% and 8.8%, respectively, of the sample) were recorded. The average time from the exercise test to cardiac death was 7.3 ± 4.6 years (median 6.8 years) and to all-cause death 8.3 ± 3.2 years (median 7.7 years).

Table 1. Demographic and Clinical Characteristics of All Subjects According to Diagnosis

Variable	MI	CABG	IHD	All Subjects
Diagnosis (%)	1,052 (44.2)	620 (26.1)	708 (29.7)	2,380
Demographic				
Age at CRXT, yrs*	58.5 ± 9.8	61.3 ± 8.9	59.9 ± 9.2	59.7 ± 9.5
Body mass, kg	68.4 ± 13.7	68.3 ± 12.3	73.3 ± 15.8	69.8 ± 14.2
Body mass index, kg/m^2	26.7 ± 5.1	27.2 ± 4.6	28.7 ± 5.8	27.4 ± 5.3
Clinical				
Total cholesterol ≥240 mg/dl; 6.2 mmol/l; n (%)	250 (23.8)	164 (26.5)	178 (25.1)	592 (24.9)
History of hypertension (%)	31.6	29.4	30.2	30.6
Smoking, current (%)	16.5	5.1	13.1	12.5
History of smoking (%)	66.0	57.9	56.6	61.1
Diabetes (%)	8.7	15.8	9.4	10.8
Medication (%)				
Platelet inhibitor	59.0	81.6	62.4	65.9
Beta-blocker	60.0	45.6	48.4	52.9
Nitrate	21.6	5.0	15.1	41.7
Calcium antagonist	29.2	18.2	55.6	34.2
Statin	5.5	7.1	6.7	19.3
Angiotensin-converting enzyme-inhibitor	6.8	3.6	3.8	14.2
Digoxin	7.5	14.2	3.4	8.0
Antiarrhythmic	5.1	2.7	1.4	3.4
Cardiorespiratory measurements				
Resting values				
Heart rate, beats/min	68.6 ± 13.3	75.7 ± 14.4	70.3 ± 14.0	71.0 ± 14.1
Blood pressure, mm Hg				
Systolic	134.7 ± 21.3	143.6 ± 21.6	140.5 ± 21.3	138.7 ± 21.7
Diastolic	81.7 ± 11.9	84.5 ± 11.9	82.5 ± 11.9	82.6 ± 12.0
Peak Values				
Heart rate, beats/min				
Beta-blocked	111.2 ± 19.4	110.5 ± 19.3	108.4 ± 17.6	110.3 ± 19.0
Non–beta-blocked	132.3 ± 18.2	135.0 ± 18.3	134.0 ± 19.8	133.7 ± 18.8
Power output, W	79.3 ± 26.5	73.7 ± 23.2	88.0 ± 27.9	80.4 ± 26.6
Blood pressure, mm Hg				
Systolic	176.4 ± 25.1	188.2 ± 24.5	185.0 ± 26.8	182.1 ± 25.9
Diastolic	91.1 ± 12.7	93.4 ± 13.2	90.2 ± 12.8	91.4 ± 12.9
$\dot{V}O_{2peak}$, ml/kg/min	15.4 ± 4.0	14.0 ± 3.3	15.6 ± 4.0	15.1 ± 3.9
Ventilatory threshold, ml/kg/min	11.1 ± 2.3	10.7 ± 2.1	11.4 ± 2.3	11.1 ± 2.2
Respiratory exchange ratio, U	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
BORG rating of perceived exertion, U	18.7 ± 1.7	18.8 ± 1.6	18.8 ± 1.6	18.8 ± 1.6
ST-segment depression ≥0.2 mV (%)	7.4	6.0	9.6	7.7
Exertional angina (%)	8.8	7.4	15.2	10.4
Ectopy at CRXT, Lown grade 3, 4, 5 (%)	9.5	12.3	5.6	9.1
Exertional hypotension (%)†	6.8	5.0	6.8	6.3

Values are mean ± SD for continuous variables and n (%) for categorical variables. *CRXT indicates cardiorespiratory exercise test. †Exertional hypotension was defined as a drop in systolic blood pressure below resting value or a failure to rise more than 10 mm Hg with two successive increases in power output (33.4 W).

CABG = coronary artery bypass graft; MI = myocardial infarction; IHD = ischemic heart disease; $\dot{V}O_{2peak}$ = peak oxygen intake.

Table 2. Univariate and Multivariate Cox Proportional Hazards Model for Cardiac Death at Entry to Study

Variable	Hazard Ratio	Confidence Interval	p Value
Univariate			
$\dot{V}O_{2peak}$, <13 ml/kg/min, referent	1.0	—	—
$\dot{V}O_{2peak}$, ≥13 ml/kg/min	0.5	0.34–0.76	0.001
Antiarrhythmic therapy	3.4	1.87–6.3	0.0001
History of hypertension	1.7	1.09–2.5	0.017
Diabetes	3.0	1.72–5.13	0.0001
Angiotensin-converting enzyme inhibitors	2.2	1.1–4.4	0.025
Digoxin	2.1	1.25–3.57	0.005
Multivariate			
$\dot{V}O_{2peak}$, <13 ml/kg/min, referent	1.0	—	—
$\dot{V}O_{2peak}$, ≥13 ml/kg/min	0.5	0.38–0.80	0.001
Diabetes	2.7	1.55–4.82	0.0005
Antiarrhythmic therapy	3.9	2.3–7.21	0.0001

$\dot{V}O_{2peak}$ = peak oxygen intake.

The Kaplan-Meier curves for MI, CABG, and IHD patients showed that the survival profiles for cardiac and all-cause death were similar for the three diagnostic categories (log rank test, $p > 0.05$) and, therefore, the data for all three diagnoses were pooled.

Predictors of mortality. Univariate and multivariate analyses of predictors of cardiac death are shown in Table 2. Variables not achieving statistical significance on univariate analysis were age, obesity (BMI ≥30 kg/m^2), ST segment depression ≥0.2 mV or anginal symptoms on test, exertional ectopy (Lown 3, 4, or 5), current smoking or history of smoking, hypercholesterolemia (total cholesterol ≥240 mg/dl, 6.2 mmol/l), exertional hypotension, and ventilatory threshold, as well as taking aspirin, a beta-blocker, a calcium antagonist, a nitrate, a statin, or an anticoagulant. Three of the six variables achieving statistical significance after univariate analysis remained on multivariate analysis. Taking a $\dot{V}O_{2peak}$ of <13 ml/kg/min (~ 4 METs) as the referent, values at or above this level conferred a 50% reduction in cardiac death. When $\dot{V}O_{2peak}$ was treated as a continuous variable, for each 1.0 ml/kg/min advantage in $\dot{V}O_{2peak}$ subjects gained a 10% lower cardiac mortality (HR 0.90, 95% confidence interval [CI] 0.85 to 0.96, $p = 0.001$) within the range of the observed sample. Therapy with antiarrhythmic drugs and a history of diabetes were significant adverse predictors of cardiac death.

Age did not emerge as a significant predictor of cardiac death in the univariate analysis, and, therefore, we conclude that the protective effect of a high $\dot{V}O_{2peak}$ as well as the adverse effects of antiarrhythmic therapy and of diabetes are not influenced by age.

In terms of all-cause death, $\dot{V}O_{2peak}$ values ≥13.0 ml/kg/min conferred a 29% reduction in mortality, but because almost one-half of the deaths were cardiac in origin, it seemed likely that the association was heavily influenced by this fact (Table 3).

We also considered the prognostic value of $\dot{V}O_{2peak}$ predicted from the peak power output on the cycle ergometer (14). As we found in men (3), the predicted $\dot{V}O_{2peak}$ tended to overestimate aerobic power, with the result that in 21% of the total sample there was a discrepancy between predicted and measured $\dot{V}O_{2peak}$. This differential discordance between the predicted and the measured $\dot{V}O_{2peak}$ values was statistically significant (McNemar's test p value <0.0001). In fact, at this cutoff, the agreement between the predicted and measured values was moderate at best (kappa coefficient = 0.47, 95% CI 0.43 to 0.51).

Kaplan-Meier curves. The Kaplan-Meier survival curves for cardiac and all-cause deaths are shown in Figure 1. When data were grouped by initial $\dot{V}O_{2peak}$, there was a marked protective effect with regard to cardiac death (Fig. 2) and for all-cause death (Fig. 3) for those at or above $\dot{V}O_{2peak}$ 13 ml/kg/min. Cardiac survival prospects were substantially worsened by a history of diabetes (15-year survival: 64.4% vs. 88.2%, $p < 0.0001$) and by antiarrhythmic therapy (15-year survival: 71.4% vs. 87.6%, $p < 0.0001$).

Table 3. Multivariate Proportional Hazards Model for All-Cause Death

Variable	Hazard Ratio	Confidence Interval	p Value
$\dot{V}O_{2peak}$, <13 ml/kg/min, referent	1.00	—	—
$\dot{V}O_{2peak}$, ≥13 ml/kg/min	0.71	0.53–0.95	0.0204
History of hypertension	1.52	1.14–2.04	0.0042
Diabetes	1.99	1.29–3.07	0.0019
Antiarrhythmic therapy	2.13	1.30–3.51	0.0027
Digoxin	1.47	1.00–2.16	0.0493

$\dot{V}O_{2peak}$ = peak oxygen intake.

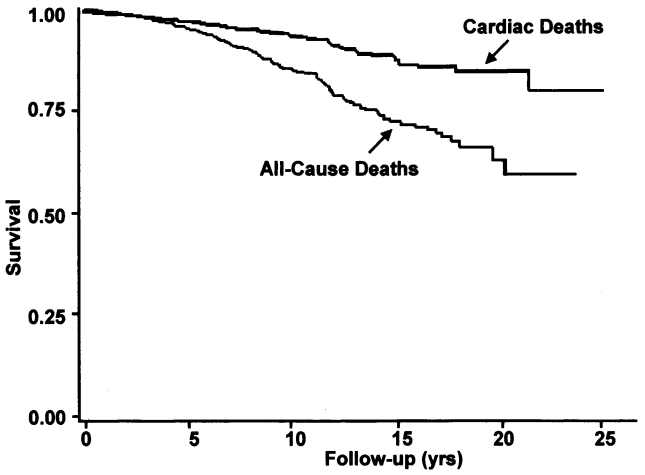

Figure 1. Kaplan-Meier survival curves for cardiac and all-cause deaths.

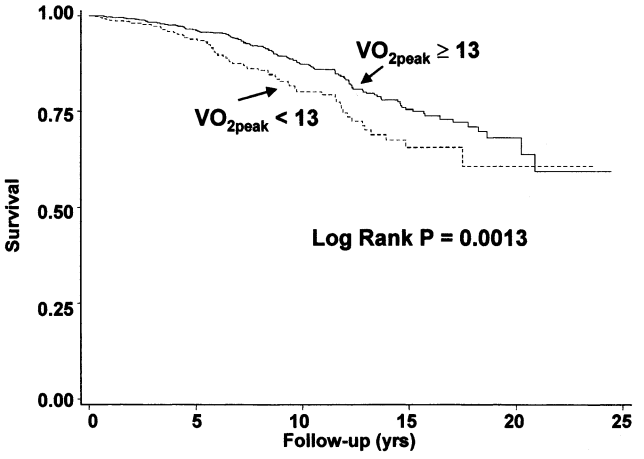

Figure 3. Kaplan-Meier survival curves for all-cause deaths by peak oxygen intake ($\dot{V}O_{2peak}$) categorized at, or above, or below 13 ml/kg/min.

DISCUSSION

Our data demonstrate that, as in men, the prognosis of women with coronary artery disease is strongly linked to their exercise capacity, and this observation is in keeping with prior work (5,6,8). Using techniques identical to those we had previously used in men (3), we found that the magnitude of the advantage of well-conserved aerobic function is relatively independent of gender. Thus, the $\dot{V}O_{2peak}$ cutoff point above which there is a marked benefit in prognosis (13 ml/kg/min in women versus 15 ml/kg/min in men), as well as the 1 ml/kg/min advantage in $\dot{V}O_{2peak}$ when treated as a continuous variable (10% lowering of cardiac mortality in women versus 9% in men), is similar to that we had previously noted in men (3).

Other significant multivariate predictors in our analysis were diabetes and antiarrhythmic therapy (for cardiac deaths), and a history of hypertension, diabetes, or antiarrhythmic or digoxin therapy (for all-cause deaths). The increase in risk associated with the taking of an antiarrhythmic drug is likely due to the fact that 40% of these patients were taking proarrhythmic agents (quinidine, disopyramide, procainamide), which were commonly prescribed in the early years of the follow-up period.

Exercise-induced ST-segment depression is less sensitive in women than in men (15,16), and, therefore, it is not surprising that in our data this variable was not a significant predictor of death.

Study limitations. Our conclusions are based on relatively young women (<70 years) with stable CHD who were referred for cardiac rehabilitation, and may not apply across the spectrum. No patients were in overt heart failure, and severe comorbidities such as peripheral vascular disease, chronic pulmonary disease, and disabling arthritis were rare. Also, our sample contained few subjects from ethnic minority groups, being predominantly white and from the middle classes. Finally, secular trends in behavior and environmental factors, inevitable in a long follow-up, as well as shifts in clinical practice, may have influenced the shape of the mortality curves.

Conclusions. From a clinical viewpoint, in men as in women with proven coronary artery disease, measured $\dot{V}O_{2peak}$ is a strong independent guide to prognosis, is not influenced by age, and is more valid than a predicted $\dot{V}O_{2peak}$.

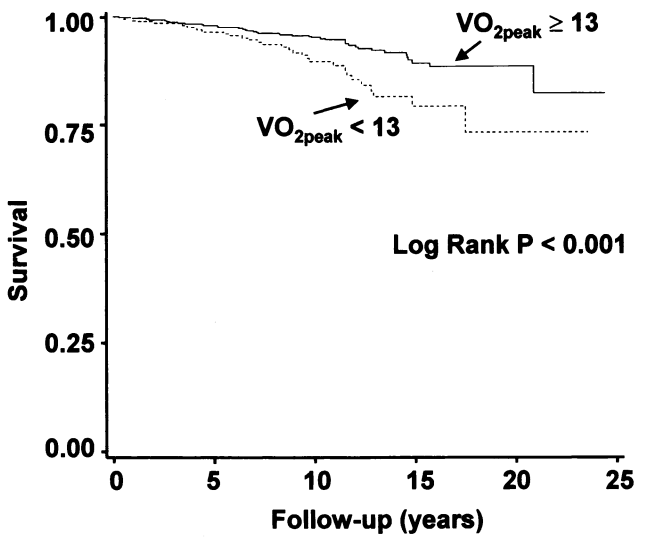

Figure 2. Kaplan-Meier survival curves for cardiac deaths by peak oxygen intake ($\dot{V}O_{2peak}$) categorized at, or above, or below 13 ml/kg/min.

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