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Determining the best percent-predicted equation for estimated VO_2 peak by a 1-km moderate perceptually-regulated treadmill walk to predict mortality in outpatients with cardiovascular disease

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ABSTRACT

Objectives: To determine the prognostic ability of established percent-predicted equations of peak oxygen consumption (%PRED) estimated by a moderate submaximal walking test in a large cohort of outpatients with cardiovascular disease (CVD).
Design: Population-based prospective study.
Methods: A total of 1442 male patients aged 25–85 years at baseline, underwent a moderate perceptually-regulated (11–13 on the 6–20 Borg scale) treadmill walk (1k-TWT) for peak oxygen consumption estimation (VO_2 peak). %PRED was derived from ACSM, Ades et al, Morris et al, and the Wasserman/Hansen equations, and their prognostic performance was assessed. Overall mortality was the end point. Participants were divided into quartiles of %PRED, and mortality risk was estimated using a Cox regression model.
Results: During a median 8.2 year follow-up, 167 all-cause deaths occurred. The Wasserman/Hansen equation provided the highest prognostic value. Mortality rate was lower across increasing quartiles of %PRED. Compared to the first quartile, after adjustment for confounders, the mortality risk decreased for the second, third, and fourth quartiles, with HRs of 0.75 (95% CI 0.44–1.29, p = 0.29), 0.67 (95% CI 0.38–1.18, p = 0.17), and 0.37 (95% CI 0.10–0.78, p = 0.009), respectively (p for trend <0.0001). Each 1% increase in %PRED conferred a 4% improvement in survival.
Conclusions: The percent-predicted VO_2 peak determined by Wasserman/Hansen equations applied to the 1k-TWT is inversely and significantly related to survival in cardiac outpatients. The 1k-TWT is a simple and useful tool for stratifying mortality risk in patients participating in secondary prevention programs.

1. Introduction

Peak oxygen consumption (VO_2 peak), determined during maximal incremental cardiopulmonary exercise testing (CPET) is commonly recognized to be the gold standard objective measure of cardiorespiratory fitness (CRF).[1] The determination of VO_2 peak is used for assessing disease severity, predicting prognosis for patients with various pathophysiological conditions including cardiovascular disease (CVD), and to examine the effectiveness of training programs for individuals involved in rehabilitation.[2]

The interpretation of CPET results requires knowledge of a normal response, usually considered with respect to age, gender, body weight, and exercise capacities of healthy volunteers. VO_2 peak is commonly expressed relative to body weight. However, reference values have limitations that involve sample specificity, the exercise protocol, and the presence of disease and medications. Thus, report-

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ing VO_2 peak as a percent-predicted value has been advocated, and several equations to estimate normal VO_2 peak are available.[3,4]

Few investigations have examined the prognostic value of percent-predicted VO_2 peak, over short follow-up, and reported non-univocal conclusions. In patients with severe heart failure, Aaronson and Mancini failed to demonstrate a superior prognostic impact of the percent-predicted VO_2 peak compared with absolute values,[5] while Stelken et al. reported that percent-predicted VO_2 peak was superior to the actual value for predicting mortality in patients with ischemic and dilated cardiomyopathy.[6] More recently, Arena et al. demonstrated that percent-predicted VO_2 peak provided similar or better predictive information compared to the measured value for estimating major cardiac events in a large heart failure cohort.[3]

Little is known regarding the association between submaximal approaches to exercise testing and outcomes in patients with CVD. We have demonstrated that a moderate self-paced 1-km treadmill-walking test (1k-TWT)[7] is useful for predicting survival[8,9] and hospitalization[10] in outpatients with CVD. However, few data are available regarding the application of submaximal tests and the prognostic utility of commonly used peak VO_2 prediction equations.

The aim of the current study was to assess the association between percentage of age-predicted VO_2 peak using the 1k-TWT (%PRED) and all-cause mortality in outpatients with CVD. In addition, we determined the degree to which differences in %PRED might explain variations in survival. This analysis could not only provide insight into risk stratifying patients with CVD but also facilitate discussions between physicians and their patients with regard to physical activity counseling.

2. Methods

The study population consisted of 1442 men (86.6% with coronary heart disease), aged 25–85 years at baseline, referred by their primary care physician to the exercise-based secondary prevention program at the Center for Biomedical Studies Applied to Sport at the University of Ferrara, Italy, between 1998 and 2012. The ultimate goal of the program was promotion and long-term maintenance of a physically active lifestyle in order to improve CRF and functional ability. A home program consisting of 30–60 min of moderate aerobic exercise such as brisk walking, at least 3–4 days and preferably 7 days of the week, was recommended. All patients were also encouraged to improve physical activity habits by increasing daily activities, such as walking breaks at work, gardening, or household work.

Patients included in the study were medically stable, with symptoms and therapy that have remained unchanged for at least three months before testing. Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were excluded.

Left ventricular ejection fraction derived from prior echocardiographic evaluations, and standard blood chemistry analyses previously performed were registered. Before admission to the program, participants underwent a comprehensive clinical evaluation, including medical history. Weight and height were measured and used to calculate body mass index (BMI). Blood pressure (BP) was measured, and hypertension was defined as systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or use of antihypertensive agents. The study was approved by the Ethics Committee of the University of Ferrara, no. 22–13, and all participants gave written informed consent.

VO_2 peak was estimated for each participant at the time of their baseline examination using the 1k-TWT.[6] The test was carried out as follows: the patients were instructed to select a pace that they could maintain for 10 to 20 min at a moderate perceived exercise intensity using the Borg 6–20 scale. Patients began the test walking on the level at a walking speed of 2.0 km h^{-1}, with subsequent increases of 0.3 km h^{-1} every thirty seconds up to a walking speed corresponding to a perceived exertion of 11–13 on the Borg scale. The 1k-TWT then started and the Rate of Perceived Exertion (RPE) was assessed every two minutes, adjusting walking speed to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). The equation for VO_2 peak estimation was then applied considering age, BMI, HR and time to complete the 1 k-TWT.[6] Patients unable to complete the 1k-TWT at walking speed $\geq$ 3.0 km/h were considered at very poor cardiorespiratory fitness and excluded from the analysis.

Percent-predicted VO_2 peak values were calculated according to normative values as proposed by Wasserman and Hansen,[11] Ades et al.[12] Morris et al.[13] and ACSM.[14]

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Patients were flagged by the regional Health Service Registry of the Emilia-Romagna region, who provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status. Time from initial evaluation to death was calculated in months. The prognostic significance of %PRED values derived from the above mentioned equations were assessed.

Statistical analyses were performed using MedCalc 16.2.1 software, Mariakerke, Belgium. The participants were divided into quartiles on the basis of the %PRED values by each of the equations considered. One way ANOVA was used to determine differences between quartiles in terms of age, BMI, left ventricular ejection fraction, total and HDL cholesterol, triglycerides, glycaemia and absolute estimated VO_2 peak. Differences in categorical variables were assessed using the χ^2 test for trend. Overall mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan–Meier curves. Cox proportional hazard models were employed to determine the multivariable adjusted relative risk of mortality across quartiles. Demographics and clinical characteristics significantly associated with %PRED VO_2 peak were included in the multivariable Cox regression model as potential confounders. Individuals in the lowest %PRED VO_2 peak quartile were considered the reference group in the regression model. To assess the discriminatory accuracy of percent-predicted VO_2 peak in estimating survival, receiver-operating-characteristic (ROC) curves were constructed and the corresponding areas under the curve were calculated. The level of statistical significance was set at $p < 0.05$.

3. Results

A total of 1442 patients were referred to our Center. 186 participants were unable to complete the 1k-TWT at walking speed $\geq$ 3.0 km/h, and were excluded from the analysis. The clinical characteristics of the 1256 patients included in the analysis are presented in Table 1. Average walking speed during 1k-TWT was 4.4 ± 1.1 km h^{-1}. Mean heart rate was 95 ± 14 beat min^{-1}, representing $60\% \pm 6\%$ of the age-predicted maximal heart rate (based on 220-age). VO_2 peak values predicted from 1k-TWT were 23.9 ± 4.6 ml $kg\ min^{-1}$.

During the median follow-up period of 8.2 years (interquartile range 6.1–10), there were 167 deaths from any cause with an average annual mortality of 1.3%. Patients who died compared to those who survived at the baseline examination were significantly older, had a lower left ventricular ejection fraction (LVEF), had a higher serum creatinine, a higher prevalence of Coronary Artery Bypass Graft (CABG) and Percutaneous Transluminal Coronary Angioplasty (PTCA), a higher use of diuretics, and a lower use of statins (Table 1).

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Table 1
Baseline demographics and clinical characteristics among subjects who died and subjects who survived.

Variable	Total (n = 1256)	Survived (n = 1089)	Died (n = 167)	*p*-Value
Demographics				
Age (year)	61 (10)	60 (10)	66 (8)	0.001
BMI	27.6 (3.4)	27.7 (3.4)	27.6 (3.3)	0.8
LV ejection fraction (%)	56 (11)	56 (10)	54 (11)	0.01
Risk factor				
Current smoking (%)	5.6	5.5	6.0	0.9
Hypertension (%)	56.6	56.0	63.0	0.07
Family history (%)	53.8	54.4	50.3	0.4
Fasting glucose (mg/dl)	108 (28)	107 (27)	113 (36)	0.01
Total cholesterol (mg/dl)	194 (43)	193 (43)	198 (41)	0.2
HDL cholesterol (mg/dl)	49 (14)	49 (13)	50 (15)	0.2
Triglycerides (mg/dl)	139 (80)	141 (82)	128 (58)	0.07
Serum creatinine (mg/dl)	1.11 (0.2)	1.09 (0.2)	1.21 (0.3)	<0.001
Medical history (%)				
CABG	49.6	47.3	64.8	<0.0001
Myocardial infarction	28.2	28.8	24.7	0.3
PTCA	8.8	9.6	3.7	0.02
Valvular replacement	9.0	9.5	8.0	0.1
Other	4.4	4.9	1.2	0.06
Medications (%)				
ACE inhibitor or ARB	53.3	53.5	51.5	0.7
Aspirin	74.5	73.9	78.4	0.2
β-Blocker	59.3	60.1	53.9	0.2
Calcium antagonist	12.9	13.1	11.4	0.6
Diuretic	17.8	16.4	26.9	0.001
Statin	52.9	54.3	44.3	0.02
Number of medications	3.2 (1.6)	3.2 (1.6)	3.3 (1.4)	0.4

Abbreviations: Values are presented as mean (±standard deviation) or percentage. *Abbreviations:* BMI, body mass index; LV, left ventricular; HDL, high-density lipoproteins; CABG, Coronary Artery Bypass Graft; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

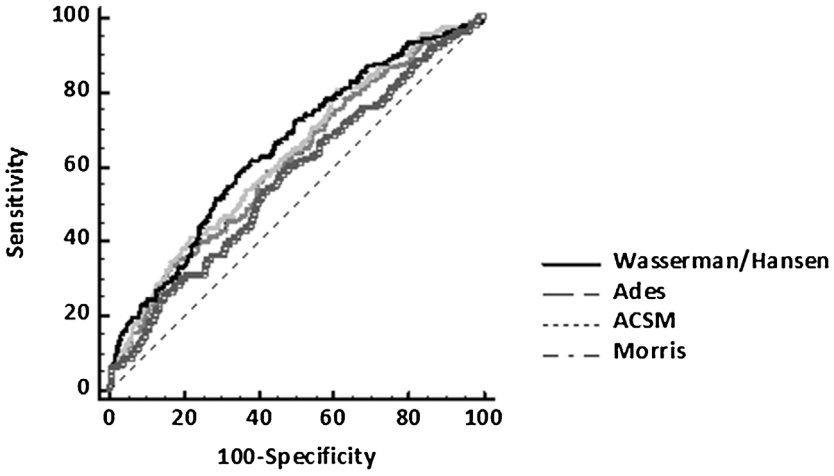

Fig. 1. Receiver operating characteristics curves for prediction of mortality over a 10 years follow-up by the four equations employed.

ROC curve analyses of the VO_2 peak prediction equations considered showed that the four prognostic classification schemes were statistically significant (Supplementary Table 1). However, the area under the ROC curve was greatest for the Wasserman/Hansen equation (0.65, 95%CI 0.63–0.68, $p < 0.0001$) with an optimal threshold ≥84% (Fig. 1). Age and estimated absolute VO_2 peak were inversely correlated, while VO_2 peak expressed as a percentage of the age-predicted value, derived from the Wasserman/Hansen equation did not differ across the age range (Supplementary Fig. 1).

Based on the Wasserman/Hansen %PRED VO_2 peak, the patients were divided into quartiles, and demographic and clinical characteristics are presented in the Supplementary Table 2. Kaplan–Meier survival analysis showed that rate of mortality decreased across increasing quartiles of %PRED (Fig. 2). Comparisons between fitness categories revealed significant differences for the following variables; age, BMI, LVEF, fasting glucose, total cholesterol, HDL cholesterol, serum triglycerides and creatinine, history of CABG, PTCA, and use of β-blockers, diuretics and number of medications, and these variables were included in the Cox regression models as covariates. Compared to the lowest %PRED VO_2 peak quartile (74% ± 6%), the adjusted relative risk mortality decreased for the second, third and fourth (103% ± 7%) quartiles, with Hazard Ratios (HR) of 0.75 (95%CI 0.44–1.29, $p = 0.29$), 0.67 (95%CI 0.38–1.18, $p = 0.17$), and 0.37 (95%CI 0.10–0.78, $p = 0.009$), respectively (p for trend <0.0001). When the %PRED value was assessed as a continuous variable in a Cox regression confounders-adjusted model, each 1% increase in %PRED was associated with a 4% lower risk of death (HR 0.96, 95%CI 0.95–0.98, $p = 0.0004$).

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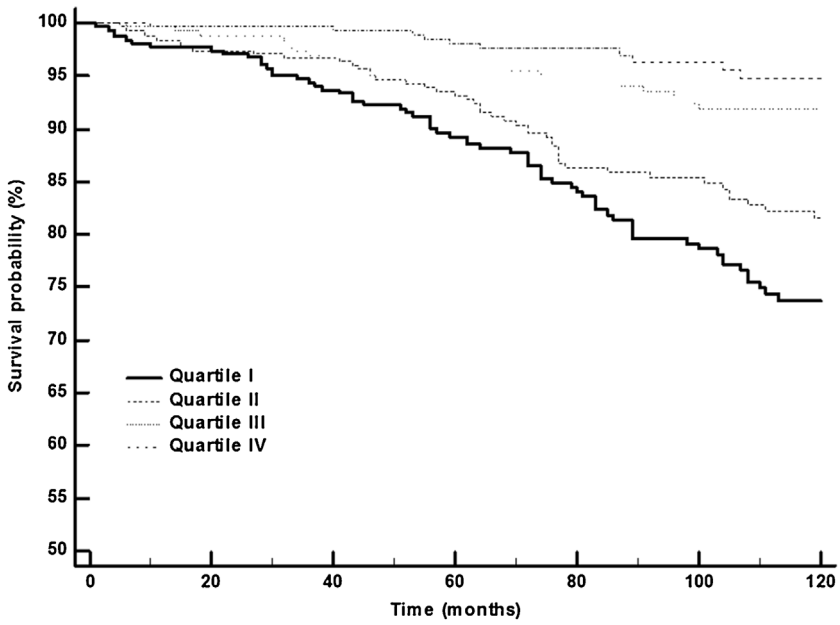

Fig. 2. Survival curves according to the percentage of age-predicted VO_2 peak using the Wasserman/Hansen equation.

4. Discussion

In the current study, we observed an inverse association between all-cause mortality and percent-predicted cardiorespiratory fitness estimated by a novel 1k-TWT in a large cohort of stable cardiac outpatients over a 10-year follow-up. Low %PRED values were associated with a high mortality rate independent of traditional cardiovascular risk factors and clinical history. Percent-predicted values obtained by the application of four common equations for VO_2 peak estimated by the 1k-TWT were different from one another. In comparing the prognostic performance between equations, the Wasserman/Hansen calculations provided the best risk estimation. The prognostic power of %PRED from the 1k-TWT is further underscored by gradients of risk illustrated by Kaplan–Meier curves (Fig. 2) and by the 63% lower mortality observed among the fittest patients relative to the least fit.

The current findings are consistent with several previous investigations.[7,15,3] Our data provide support for the superior prognostic value of the percent predicted VO_2 peak using the Wasserman/Hansen equation compared to other equations. The percent-predicted values derived from the Wasserman/Hansen approach showed the highest univariate $\chi 2$ value, and was confirmed in the multivariate regression. Our results are also consistent with Myers et al in 6213 subjects with and without CVD, over a mean of 6.2 years of follow-up.[16] The area under the receiver-operating-characteristic curves obtained were 0.67 and 0.62 for estimated VO_2 peak and percentage of age-predicted values respectively,[16] similar to the 0.65 (95% CI 0.62–0.68) value obtained in our study.

It is noteworthy the ability to measure VO_2 peak and predict mortality using the moderate and perceptually-regulated 1k-TWT. In previous studies VO_2 peak and predicted mortality were determined using maximal exercise testing.

Submaximal exercise tests, in addition to being more practical, are safer and cost-effective. Thus, they provide a reasonable option when maximal testing is not available. An advantage of the 1k-TWT is the mode of exercise. The habitual nature of walking reduces the possibility that lack of familiarity with the task reduces the predictive accuracy of the results. This characteristic may also make the 1k-TWT particularly appropriate for less fit patients or for those whom walking is their preferred form of physical activity. Another advantage is the use of perceived moderate exercise intensity. This was confirmed by the average ≈60% of the age-predicted maximal heart rate value in the present study, which falls within current recommended limits (55%–69%) for moderate intensity.[17]

In this regard, the 1k-TWT provides a learning effect (i.e. the experience of proper exercise intensity), and could be useful to facilitate transition from a supervised to a self-guided exercise program. Finally, expressing CRF as a percent-predicted value can help clinicians seeking to make judgements about "normalcy" of their patients, and has the potential to enhance a patient's understanding of their exercise capacity.

The large sample size of patients across a wide range in age and exercise capacity is one strength of the current study. The ability of the percent-predicted VO_2 peak by 1k-TWT, a simple test of function, to predict survival in patients with stable CVD is also relevant because the protocol addresses physical activity, a modifiable risk factor for secondary prevention. The Wasserman/Hansen equation can be automatically generated by manually inputting age, sex, height, weight, time, and heart rate values, in common software packages. The ease by which the various percent-predicted VO_2 peak calculations are derived by presently available software packages reduces their complexity. In addition to being a surrogate measure of fitness, the demonstration of the association between %PRED and mortality makes it applicable for assessing treatment strategies. Since every 1% increase in %PRED VO_2 peak is associated with a 4% lower risk of mortality, repeated measurement of the 1k-TWT could be used as a simple office-based tool to monitor exercise participation and to motivate patients to achieve appropriate levels of physical activity. Another advantage emerging from this study is the simplicity of the protocol and its prognostic power in outpatients with CVD with non-restrictive inclusion criteria reflecting real-world practice.

Our study has several limitations. First, patients included in the present investigation were referred with an interest in an exercise-based secondary prevention program, creating the potential for selection bias. Second, our study comprised male participants only: thus, the results may not be generalized to women. Third, participants were excluded from the test if they were unable to walk at least 3.0 km h^{-1}. The results therefore may not apply to patients with markedly low exercise capacity. Fourth, we did not consider social, behavioral or psychological factors that have been indepen-

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dently associated with reduced walking ability.[18] Finally, causal reverse effect, particularly dietary and physical activity habits, cannot be excluded.

5. Conclusion

Even though direct CRF determination remains the gold standard, variables obtained from a simple 1k-TWT provide useful prognostic insight in patients with stable CVD 25–85 years of age. Although many laboratories report percent-predicted peak VO_2 values in their report, they do not commonly consider its prognostic significance. The 1k-TWT is potentially useful as a clinical and research tool that requires only a minimal amount of time, expense and risk. Our findings suggest that equations used to determine percent-predicted peak VO_2 provide similar predictive information compared with measured values obtained from maximal testing. The percent-predicted VO_2 peak determined by Wasserman/Hansen equations applied to the 1k-TWT is inversely and significantly related to survival in cardiac outpatients. The results of the present study may have practical implications in the context of transitioning from clinically based and supervised programs to fitness facilities or self-guided exercise programs. The ability to use this test in laboratory and outdoor[19] conditions allows testing by health professionals including physiotherapists and exercise physiologists. Interestingly, several patients are able to run the test by themselves, unsupervised.

Practical implications

- In addition to absolute VO_2 peak, exercise capacity should also be expressed as a percentage of the predicted normal value and this should be a routine part of the summary report.
- The Wasserman/Hansen equation is superior to other equations in terms of prognostic power in patients with stable CVD.
- The estimated age-predicted VO_2 peak by a moderate walk is associated with a significant, dose-dependent lower all-cause mortality in cardiac outpatients.
- The 1-km walking test is a simple and clinically useful tool to follow outcomes in cardiac outpatients.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsams.2017.06.003.

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