New Equations for Predicting Maximum Oxygen Uptake in Patients With Heart Failure

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We obtained directly measured maximal oxygen uptake (VO_2 max) by open-circuit spirometry in 1,453 patients with chronic heart failure (HF) who completed a treadmill test (n = 1,453) or cycle ergometry (n = 1,838), as participants in The Fitness Registry and the Importance of Exercise National Data Base (FRIEND) dataset. We developed a new equation to predict measured VO_2 max in those using a treadmill by randomly sampling 70% of the participants from each of the following age categories: <40, 40 to 50, 50 to 70, and >70 and used the remaining 30% for validation. Multivariable linear regression analysis was applied to identify the most relevant variables and construct the best prediction model for VO_2 max. Treadmill speed and treadmill speed * grade were considered in the final model as predictors of measured VO_2 max and the following equation was generated: VO_2 max in ml O_2 kg/min = speed (m/min) * (0.17 + fractional grade * 0.32) +3.5. To assess the efficacy of the equation, we applied it to 1,612 patients in the HF-ACTION cohort. To assess the efficacy of the FRIEND cycle ergometry equation developed for healthy individuals we applied it to 1,838 HF patients in the FRIEND cohort and 306 patients in a Greek population of HF patients with directly measured VO_2 max. The FRIEND equations were superior to ACSM equations in predicting VO_2 max regardless of the cohort or exercise mode used (treadmill or cycle ergometry) to access VO_2 max. **(Am J Cardiol 2020;128:7−11)**

The availability of open-circuit spirometry for direct assessment of maximal oxygen uptake (VO_2 max), is relatively limited. Thus, regression equations were developed to estimate energy requirements from maximal treadmill speed and percent grade, or maximal cycle ergometer workload. These equations, known as the American College of Sports Medicine (ACSM) equations, were based on comparisons to direct assessments of VO_2 max at steady-state submaximal work rates obtained on relatively small numbers of healthy young subjects, and were not designed for use at peak levels of exercise.[1−4] Subsequently, they are often inaccurate for estimating VO_2 max at nonsteady state work rates. Recently, we developed alternative regression equations to estimate VO_2 max (or metabolic equivalents (METs) in apparently healthy individuals during progressive treadmill or cycle ergometer testing using the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) cohort. The FRIEND equations were based on directly measured VO_2 max using standardized exercise treadmill protocols and cycle ergometry and were significantly more accurate to the ACSM equations.[5,6] The aim of the current study was to access the efficacy of these equations in heart failure (HF) patients. We applied the FRIEND equations to 3 different HF cohorts; (1) patients with HF in the FRIEND dataset; (2) patients with HF from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial;[7] and (3) HF patients from Attikon Hospital, 2nd Department of Cardiology, University of Athens, Athens Greece. We then compared the performance of the FRIEND and ACSM equations and developed a correction factor to convert METs estimated by the ACSM equations to METs derived from the FRIEND equation.[5,6]

Methods

The equations developed to estimate VO_{2max} levels in apparently healthy individuals were based on directly measured VO_{2max} (open-circuit spirometry) assessed during a maximal exercise test using treadmill or cycle ergometry. The cohort consisted of participants in the FRIEND dataset and has been described in detail previously.[5,6,8] Briefly, the treadmill cohort included 7,854 individuals [4,763 men

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(mean ± SD age 47.2 ± 13.4 years) and 3,091 women (mean ± SD age 47.7 ± 13.4 years). The cycle ergometry cohort consisted of 5,100 subjects (3,378 men; mean ± SD age 35.9 ± 12.1 years and 1,722 women; mean ± SD age = 47.5 ± 14.0 years). All participants completed a graded exercise test to volitional fatigue. The procedures used for acquiring and managing the FRIEND registry data have also been previously reported.[9−11]

For the treadmill test, the strongest predictors of VO_2 max were treadmill speed and the interaction between treadmill speed and grade. Gender-specific formulas did not yield substantially different findings and therefore, the following equation for men and women was developed.[5]

$$VO_2max(mL/kg/min)$$

$$= Speed * (0.17 + FractionalGrade \times 0.79) + 3.5$$

Where speed is in m/min.

For cycle ergometry, work rate was the strongest predictor of VO_2 max. When gender was considered, gender-specific models provided a slightly more accurate prediction of VO_2 max for each gender.[6] Thus, the overall and gender-specific equations are:

The nongender-specific equation: VO_2 max in ml O_2/kg/min = 1.74* [Watts*6.12/body weight (kg)] + 3.5

Men: VO_2 max in ml O_2/kg/min = 1.76* [Watts*6.12/body weight (kg)] + 3.5

Women: VO_2 max in ml O_2/kg/min = 1.65* [Watts*6.12/body weight (kg)] + 3.5

The aforementioned FRIEND equations were then applied to the FRIEND dataset HF cohort using a treadmill or cycle ergometer protocol. Patients with either preserved or reduced ejection fraction were included. The treadmill cohort consisted of 1,453 patients (955 men; mean age 56.8 ± 14.6 years and 498 women; mean ± SD age 52.1 ± 15.6 years). The cycle ergometry cohort included 1,838 patients (1,013 men; mean ± SD age 63.6 ± 12.2 years and 825 women; mean ± SD age 61.5 ± 12.3 years). The procedures to assess VO_2 max were identical to those described for the apparently healthy cohort.[5,6]

When the treadmill equation developed for apparently healthy individuals was applied to the HF patients of the FRIEND dataset (n = 1,453), the prediction error was relatively high (25% compared with 5.1% error observed in apparently healthy individuals). Thus, we developed a new formula specifically for HF patients, based on the FRIEND cohort. Treadmill speed and the interaction of treadmill speed and grade were again the main determinates of VO_2 max with age and gender having only a minor impact. Sex-specific formulas did not yield substantially different findings and therefore, 1 formula for men and women was developed. The HF-specific formula for treadmill testing was:

$$VO_2max(mL/kg/min)$$

$$= Speed * (0.17 + FractionalGrade \times 0.32) + 3.5$$

Where speed is in m/min.

When the cycle ergometer equation for predicting VO_{2max} in apparently healthy individuals was applied to the HF cohort, the prediction error was relatively small (5.1%) and no adjustments in the equations were deemed necessary.

To assess the external validity of the FRIEND equations, we applied the treadmill equation developed for HF to the HF-ACTION cohort (n = 1,612; mean ± SD age 58.6 ± 12.7years), a NIH-sponsored multicenter, randomized controlled trial to evaluate medically supervised and home-based exercise training on cardiovascular outcomes in stable outpatients with HF and reduced ejection fraction.[7] We applied the cycle ergometer equation to a Greek cohort of 306 HF patients (mean ± SD age 52.4 ± 13.4 (245 men; mean ± SD age 52.2 ± 13.5 years and 61 women; mean ± SD age 52.4 ± 13.4 years) obtained from the Cardiopulmonary Exercise Laboratory, Attikon Hospital, 2nd Department of Cardiology, University of Athens, Athens Greece. Finally, we applied the ACSM equations to estimate VO_{2max} in the aforementioned cohorts and contrasted the findings with those yielded by the FRIEND equations. We also developed a correction formula that allows conversion of estimated METs using the ACSM equations to METs derived using the FRIEND equations. The formulas are:

Treadmill

FRIEND METS = ACSM-Derived METs - (1.01 × Fractional Grade-0.07) × Speed (m/min) /3.5

Cycle ergometry

FRIEND METs = ACSM-Derived METs - [(0.06 × (Watts × 6.12/kg)] + 3.5)]/3.5

To construct the best prediction model for estimation for all cohorts, we applied multivariable linear regression analysis to identify the most relevant variables associated with VO_{2max}. The models were constructed based on 70% of the participants, selected randomly, from the following age categories: <40, 40 to 50, 50 to 70 and ≥70 years. The remaining 30% of participants were used for validation. Stepwise selection was implemented. The criteria for entry of a variable to the model was set at p value ≥0.15 and removal at p value <0.15.

The contribution of the variables selected to predict VO_{2max} for both treadmill and cycle ergometry was further investigated by variable selection criteria including Akaike information criterion, corrected Akaike information criterion, the Sawa Bayesian Information Criterion, Adjusted R-square statistic, the Predicted Residual Sum of Squares Statistic and the average squared error over the validation data.

To determine whether the accuracy of predicting measured VO_{2max} differed by gender, these analyses were repeated using a sex-specific equation. All statistical tests with a p value <0.05 were considered statistically significant.

Results

Measured and estimated VO_2 max values for HF patients in the FRIEND cohort, based on the FRIEND and ACSM

Table 1
Measured and estimated oxygen uptake in heart failure patients based on the fitness registry and the importance of exercise national database (FRIEND) and the American college of sports medicine (ACSM)* equations (mean ± SD)

A. FRIEND Cohort- Heart Failure

Exercise Mode	n	Age	Measured VO_2 max (mL/kg/min)	FRIEND VO_2 max (mL/kg/min)	% Error FRIEND	ACSM VO_2 max (mL/kg/min)	% Error ACSM
Treadmill (All)	1,453	55.2 ± 15.1	21.3 ± 6.3	20.8 ± 6.0	0.04 ± 20.7	28.0 ± 11.6	29.6 ± 36.3
Men	955	56.8 ± 14.6	21.8 ± 6.3	21.1 ± 6.1	−1.0 ± 19.8	28.5 ± 11.5	29.0 ± 34.5
Women	498	52.1 ± 15.6	20.5 ± 6.2	20.4 ± 5.9	2.0 ± 22.2	27.2 ± 11.6	30.7 ± 39.4
Cycle Ergometry (All)	1,838	62.6 ± 12.3	11.9 ± 3.8	12.5 ± 4.3	5.1 ± 18.6	16.3 ± 4.5	40.0 ± 21.5
Men	1,013	63.6 ± 12.2	12.9 ± 4.0	13.9 ± 4.3	9.1 ± 17.8	17.7 ± 4.4	41.8 ± 22.2
Women	825	61.5 ± 12.4	10.8 ± 3.1	10.8 ± 3.7	0.3 ± 18.5	14.6 ± 3.8	37.8 ± 20.4

B. HF-ACTION study cohort

	n	Age	Measured VO_2 max (mL/kg/min)	FRIEND VO_2 max (mL/kg/min)	% Error FRIEND	ACSM VO_2 max (mL/kg/min)	% Error ACSM
All (Treadmill)	1,612	58.6 ± 12.7	15.3 ± 4.6	16.4 ± 2.9	14.2 ± 29.0	24.1 ± 6.0	63.7 ± 35.1
Men	1,195	59.5 ± 12.5	15.7 ± 4.7	16.5 ± 3.0	12.2 ± 28.6	24.4 ± 6.0	61.4 ± 34.2
Women	417	56.2 ± 12.9	14.2 ± 4.0	16.0 ± 2.5	20.1 ± 29.5	23.3 ± 5.6	70.2 ± 36.8

C. Greek Cohort

	n	Age	Measured VO_2 max (mL/kg/min)	FRIEND VO_2 max (mL/kg/min)	% Error FRIEND	ACSM VO_2 max (mL/kg/min)	% Error ACSM
All (Cycle Ergometry)	306	52.4 ± 13.4	19.1 ± 6.7	18.3 ± 5.8	−2.5 ± 14.3	22.3 ± 6.0	20.8 ± 18.9
Men	245	52.2 ± 13.6	19.8 ± 6.8	19.2 ± 3.0	−0.9 ± 14.0	23.2 ± 6.0	21.9 ± 19.5
Women	61	53.2 ± 12.7	16.3 ± 4.3	14.8 ± 4.0	−8.8 ± 13.5	18.7 ± 4.1	16.5 ± 16.0

* Walking and running speed equations were used when appropriate.

equations are presented in Table 1. For treadmill protocols, the prediction error of the FRIEND equation for the entire many fold lower compared with the ACSM equation and for both men and women.

Similar trends were observed for cycle ergometry, with approximately 7-fold higher accuracy for the FRIEND equation.

When the treadmill equations were applied to the HF-ACTION cohort, the prediction errors for the FRIEND equation were 3.5 to 5.0 times lower compared with the ACSM equation. Women had the highest prediction error for both equations (20.1 ± 29.5% vs 70.2 ± 36.8% for FRIEND and ACSM equations, respectively).

When the cycle ergometer equation was applied to Greek cohort, the FRIEND equation underestimated measured VO2 max by 2.5% for the entire cohort, but more so in women than men. In contrast, the ACSM equation overestimated the measured VO_2 max by nearly 21%, more so in men than women.

Discussion

We found that the newly developed FRIEND equations were consistently more accurate than the traditional ACSM equations in predicting directly measured VO_2 max for HF populations. The superiority of the FRIEND compared with the ACSM equations in predicting measured VO_2 max was evident regardless of the cohort. This was especially evident for the FRIEND treadmill equation applied to the FRIEND HF cohort (percent error 0.04 ± 20.7) and for the cycle ergometer equation applied to the Greek cohort (percent error −2.5±14.3). The performance of the ACSM equation was highly imprecise, with errors ranging from approximately 21% to 64% (Table 1).

The accuracy of estimating VO_2 max is particularly important among patients with HF, given the growing volume of data demonstrating the value of exercise capacity in stratifying risk in these patients. In addition, the inaccuracy of estimating VO_2 max from work rate is more pronounced among patients with cardiovascular disease compared with normal subjects, and there is a particularly notable overestimation of VO_2 max among patients with an impaired cardiac output response to exercise.[1,2,12] Traditional equations have generally been applied regardless of the individual undergoing testing, and to our knowledge there are no population-specific equations for patients with HF. The equations from the current study provide an improvement over traditional equations in that they are considerably more precise when applied to patients with HF.

The higher accuracy is unique and likely attributable to the significantly greater sample size provided by the FRIEND dataset and the methodology used to derive these equations. Specifically, the FRIEND treadmill equations were developed to predict directly measured VO_2 max values derived from 7,983 apparently healthy individuals and 1,453 HF patients undergoing treadmill testing. For cycle ergometry, the cohort consisted of 5,100 apparently healthy individuals and 1,838 HF patients. In contrast, the ACSM equations were based on a cohort of <200 college-aged individuals who underwent submaximal treadmill exercise testing to achieve a steady-state aerobic requirement. VO_{2max} was then extrapolated (not directly measured) based on the VO_2 levels achieved during steady-state exercise. However, steady-state oxygen uptake is rarely achieved at higher intensities during progressive exercise testing and is influenced by numerous variables, including age and chronic disease. Because most subjects in these studies were relatively young (19 to 26 years old),[1,3,4] VO_2 max is generally overestimated by the ACSM equations when used in middle-age and older populations, especially those with chronic disease. This was apparent when the ACSM equations were compared with the FRIEND dataset among patients with HF in the current study. The limited accuracy of the ACSM equations in predicting VO_2 max have been widely cited over the years, particularly in clinical populations.[1,2,13,14]

These observations have broad clinical implications. Measured VO_{2max} is considered the gold standard for cardiopulmonary function.[9,15] Because the technology to measure VO_2 directly is often not available, many clinical settings apply traditional equations, such as those from the ACSM, for estimating VO_2 max without appreciating the imprecision of doing so. Accurate estimates of VO_2 max have numerous clinical applications, including assessing the efficacy of therapeutic interventions, risk stratification, disability assessment, and exercise prescription. In fact, the higher precision provided by measured VO_2 is one of the clinical indications for the use of ventilatory gas exchange techniques.[1,15] Thus, an improvement in the estimation of VO_2 max is highly advantageous. With a measurement error that is typical of the traditional ACSM equations (historically 20% to 40%, but as high as 70% among in women with HF in the current study (Table 1), the clinical implications are obvious, and may include misclassification of risk, inappropriate judgement regarding the efficacy of therapy, and inaccurate exercise programming.

Several limitations of the FRIEND equations should also be noted. Although all tests were performed for aerobic capacity assessment, the choice of exercise protocols, equipment, and data collection procedures, while consistent with current guidelines,[1,10,13] was specific to each laboratory. In addition, we included subjects with varied risk factor profiles, including co-morbid (e.g., diabetes and obesity), and musculoskeletal conditions (e.g., back pain and osteoarthritis), which may have limited effort during maximal exercise testing in some individuals. Moreover, the magnitude of handrail holding permitted during treadmill testing, which can influence the discrepancy between directly measured and estimated aerobic requirements, was neither accounted for nor standardized from one CPX laboratory to another. We also employed a peak RER ≥ 1.0 to signify "maximal effort," which may have underestimated the true VO_{2max} in some subjects. Nevertheless, this represents a ventilatory response compatible with anaerobiosis and volitional fatigue, often observed in nonathletic populations. The percent error from the FRIEND equation when applied to the HF-ACTION cohort was also relatively large (especially in women) when compared with the insignificant error observed for the FRIEND HF cohort. One explanation for this may be that the fluid retention that typically occurs in many HF patients (especially in those with reduced ejection fraction), is a potential confounder that causes an overestimation of VO_{2max} for which the formula cannot account. This notion is supported by the substantially higher error observed in the HF-ACTION cohort in which all patients had reduced ejection fraction and the lower error in the cycle ergometry cohort in which body weight was used to calculate workload, essential in the derivation of the equation. Despite this, the FRIEND equation presents a much better alternative, as the 12.2% error for men and 20.1% error for women from the FRIEND formula was substantially less than the 61.4% error for men and 70.2% error for women yielded by the ACSM formulas. Nevertheless, we recommend that results be viewed with caution when the FRIEND equation is applied to patients with reduced ejection fraction, particularly in women.

Despite the inaccuracy of the ACSM equations in predicting VO_{2max}, the plethora of comparative data accumulated over the years using these equations and their clinical relevance should not be discarded. Nor should we discard the compelling superiority of the FRIEND equations, especially since most exercise tests are conducted for clinical reasons. The need for more accurate estimation of CRF is further highlighted by the recognition of the prognostic significance of CRF[14,16] and its role in risk stratifying patients. The current data suggest that manufacturers of exercise testing equipment and exercise laboratories consider the inclusion of the more accurate FRIEND equations for the estimation of VO_2 max during exercise testing using treadmill or cycle ergometry. Finally, the correction formulas provide a simple conversion from METs derived by the ACSM formulas to METs derived using the FRIEND formulas and yield a more precise estimation of exercise capacity.

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