

Predicting maximal oxygen uptake from the 6 min walk test in patients with heart failure

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Abstract

Aims A cardiopulmonary exercise (CPX) test is considered the gold standard in evaluating maximal oxygen uptake. This study aimed to evaluate the predictive validity of equations provided by Burr *et al.*, Ross *et al.*, Adedoyin *et al.*, and Cahalin *et al.* in predicting peak VO_2 from 6 min walk test (6MWT) distance in patients with heart failure (HF).

Methods and Results New York Heart Association Class I–III HF patients performed a maximal effort CPX test and two 6MWTs. Correlations between CPX $\text{VO}_{2\text{ peak}}$ and the predicted $\text{VO}_{2\text{ peak}}$, coefficient of determination (R^2), and mean absolute percentage error (MAPE) scores were calculated. *P*-values were set at 0.05. A total of 106 participants aged 62.5 ± 11.5 years completed the tests. The mean $\text{VO}_{2\text{ peak}}$ from CPX testing was 16.4 ± 3.9 mL/kg/min, and the mean 6MWT distance was 419.2 ± 93.0 m. The predicted mean $\text{VO}_{2\text{ peak}}$ (mL/kg/min) by Burr *et al.*, Ross *et al.*, Adedoyin *et al.*, and Cahalin *et al.* was 22.8 ± 8.8 , 14.6 ± 2.1 , 8.30 ± 1.4 , and 16.6 ± 2.8 . A significant correlation was observed between the CPX test $\text{VO}_{2\text{ peak}}$ and predicted values. The mean difference (0.1 mL/kg/min), R^2 (0.97), and MAPE (0.14) values suggest that the Cahalin *et al.* equation provided the best predictive validity.

Conclusions The equation provided by Cahalin *et al.* is simple and has a strong predictive validity, and researchers may use the equation to predict mean $\text{VO}_{2\text{ peak}}$ in patients with HF. Based on our observation, equations to predict individual maximal oxygen uptake should be used cautiously.

Keywords Heart failure; Cardiopulmonary testing; 6 min walk test; Prediction; Peak VO_2

Received: 8 August 2020; Revised: 9 November 2020; Accepted: 23 November 2020

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Introduction

Maximal oxygen uptake ($\text{VO}_{2\text{ max}}$) is considered the gold standard for measuring aerobic exercise capacity.¹ Clinically, peak oxygen consumption ($\text{VO}_{2\text{ peak}}$) is often used as a surrogate for $\text{VO}_{2\text{ max}}$ for patient populations. $\text{VO}_{2\text{ peak}}$ is determined by cardiopulmonary exercise (CPX) testing, typically performed on a treadmill or bicycle ergometer, with incremental increases in exercise workloads to maximal effort, generally limited by symptoms or fatigue. Results from CPX testing are used to assess exercise tolerance, develop exercise prescriptions, evaluate treatment efficacy, and investigate exercise-induced adaptations of the oxygen transport and

utilization system.¹ Maximal effort CPX testing is generally well tolerated by patients with cardiovascular diseases.² In patients with heart failure (HF), the landmark HF-ACTION study and other meta-analyses reported no adverse effects of CPX testing in HF with both preserved and reduced ejection fraction.^{3–5} However, with greater than minimal risk involved,⁶ it is recommended that maximal effort CPX testing in patients with clinically stable HF be performed in a laboratory setting supervised by trained medical personnel.⁷ Because the test is expensive and the required infrastructure and qualified personnel may not be readily available, alternate forms of testing to measure functional capacity are often used. For patients with HF, the sub-maximal 6 min walk

test (6MWT), with established reliability and validity, is commonly recommended as an alternate choice.^{8,9}

The 6MWT is cost-effective, easy to administer, and well tolerated.¹⁰ It is used as an outcome measure to determine activity of daily living¹¹ and quality of life outcomes^{12–14} and in clinical practice to evaluate treatment response and exercise capacity, predict frailty, and evaluate mortality and 30 day re-hospitalization rate in patients with HF.^{15–17} With 6MWT distance correlating with VO_2 values,¹⁸ its ability to accurately predict physiologic change in VO_2 peak in patients with HF can have practical utility.

Over the years, various equations to predict a VO_2 max or VO_2 peak from a 6MWT have been proposed. In this study, we evaluated each of the four prediction equations developed by Burr *et al.*,¹⁹ Ross *et al.*,²⁰ Adedoyin *et al.*,²¹ and Cahalin *et al.*²² and assessed their ability to accurately predict VO_2 peak from the 6MWT in patients with HF. The equations, as described in the Methods section, are different from each other in how they were formulated, the population they were tested on, and the number of variables required to predict VO_2 peak. These equations were specifically selected for their simplicity and ease of use whereby the estimation of VO_2 peak is calculated from easily assessable information such as age, sex, weight, resting heart rate (HR), and 6MWT distance. Cahalin *et al.*²² provided several prediction equations from their study of patients with HF. We excluded the equations that required values of forced vital capacity, forced expiratory volume, cardiac index, rate pressure product, pulmonary artery pressure, or left ventricular ejection fraction for computing peak VO_2 , as these values may not be readily available or would require additional testing. Additionally, treatment guidelines for the management of HF, including the use of beta-blockers and other drugs that impact cardiac function, have undergone modifications in the past 15 years.^{23–30} Consequently, because each of the study equations were developed before more recent treatment modifications came into effect, there is need to re-evaluate their ability to accurately predict peak VO_2 in stable patients with HF. Therefore, the purpose of the study was to evaluate and compare the predictive validity of equations provided by Burr *et al.*,¹⁹ Ross *et al.*,²⁰ Adedoyin *et al.*,²¹ and Cahalin *et al.*²² in predicting peak VO_2 from 6MWT distance in patients with stable HF.

Methods

This secondary analysis utilizes baseline measures of peak VO_2 from CPX testing and 6MWT data from the National Institutes of Health-funded longitudinal study titled Heart failure Exercise And Resistance Training (HEART) Camp (R01-HL112979). The two-site HEART Camp study was a facility-based randomized controlled intervention designed to improve adherence to the recommended 150 min/week

of aerobic exercise in patients with HF. The investigation conforms with the principles outlined in the *Declaration of Helsinki* and was approved by the Institutional Review Board at the University of Nebraska Medical Center (Chairperson: Dr. Bruce Gordon; IRB# 608-11-FB, approved 14 December 2011). Participants signed informed consent before participation. The primary study protocol and its results have been published.^{31,32} For this study, we use data from the Lincoln (NE) site.

Subjects

A total of 119 participants diagnosed with HF with New York Heart Association (NYHA) scale I–III were recruited for the study. Of these, 12 participants dropped out after enrolment or did not complete the second 6MWT, leaving a sample size of 106. Power analysis was performed using G* power.³³ The post-hoc *t*-test for correlational statistic (VO_2 and 6MWT) using a sample size of 106, α of 0.05, and a moderate effect size of 0.30 gave a power of 0.90. Participants were recruited from the Bryan Heart Clinic in Lincoln, Nebraska. Inclusion criteria for participation were (i) diagnosis of HF (Stage C chronic HF confirmed by echocardiography and clinical evaluation); (ii) 19 years of age or older; (iii) able to speak and read English; (iv) telephone access in-home; and (v) stable pharmacologic therapy per guidelines for past 30 days. Exclusion criteria included (i) clinical evidence of decompensated HF; (ii) unstable angina pectoris; (iii) myocardial infarction, coronary artery bypass surgery, or biventricular pacemaker <6 weeks prior; (iv) orthopaedic or neuromuscular disorders preventing participation in aerobic exercise and strength/resistance training; (v) participation in three times per week aerobic exercise during the past 8 weeks; (vi) cardiopulmonary stress test results that precluded safe exercise training; (vii) plans to move >50 miles from the exercise site within the next year; (viii) peak oxygen consumption >21 mL/kg/min in women and >24 mL/kg/min in men; and (ix) planned or current pregnancy. Additionally, per recommendations by Ross *et al.*,²⁰ 6MWT distances > 600 m were not considered for analysis. Their prediction equation underestimated VO_2 peak in participants walking >600 m in the 6MWT. In our sample, one person walked a distance of 605 m. We excluded this value in the analysis.

Experimental procedure

The study was divided into two parts: (i) conducting a CPX test to evaluate VO_2 peak and (ii) participants completing two 6MWTs to record distance covered in 6 min. These measurements were done during baseline testing for the HEART Camp study. Data were collected between 2013 and 2015.

The values from the 6MWT were used to predict the maximal oxygen uptake using the equations in *Table 1*.

- i CPX test: On Day 1 of the study, participants performed a maximal effort CPX using a 10-stage ramp protocol to determine VO_2 peak. The test was conducted by an exercise specialist and supervised by a nurse practitioner/physician assistant/physician. The treadmill speed was started at 1 mile/h with 0% incline. Both the speed (max 3.3 miles/h) and incline (max 15%) were increased every 2 min until voluntary exhaustion or if HR, respiration, and/or physical appearance indicated peak effort.²⁹ For patients who were not limited by symptoms, the respiratory exchange ratio was also assessed to determine maximal effort during the test. Rating of perceived exertion (RPE) was recorded at each stage of the test. Heart rhythm was monitored throughout the test.
- ii 6MWT: Two 6MWTs were performed by each participant. The first test was performed on the day of the CPX test. Participants were given at least 3 h of rest after the CPX test before performing the 6MWT. Two baseline tests were performed in a 30 m long hallway as per the instructions provided by the American Thoracic Society.¹⁰ The second 6MWT was performed 7–10 days after the first 6MWT as per the protocol of the HEART Camp study.³¹ Participants vocalized their RPE using the Borg (6–20) scale at the end of the test.^{34,35} For the purpose of consistency, the best score of the two walks was used for analysis, as it is a better representation of the participant's functional capacity than the mean score of the two testing results of the 6MWT.
- iii Description of the prediction equations:

Data analysis

Participants with atrial fibrillation were considered for analysis if their HRs were controlled for the past year with stable dosing of beta-blockers. Pearson's correlations between the VO_2 peak achieved at maximal effort on the CPX test and the

calculated VO_2 peak from three prediction equations were analysed to test for predictive validity. The mean differences and error estimates were calculated for the VO_2 peak from the CPX testing and the predicted VO_2 peak from the equations. If no mean difference was found between the two values, the predictive validity of the equations to predict peak VO_2 of patients belonging to different NYHA functional classes were tested. Bland–Altman plots were created to compare the standardized VO_2 measures. To evaluate the accuracy of the predictive equations against the observed values from CPX testing, coefficient of determination (R^2) to explain the amount of variance in the VO_2 peak from CPX testing and mean absolute percentage error (MAPE) were calculated. A lower MAPE score indicates better predictive accuracy. IBM-SPSS 25 and R 3.6.2 were used to analyse the data. The P -values were set at 0.05.

Data availability

The primary study associated is available at <https://clinicaltrials.gov/> (study identifier NCT01658670).

Results

With 12 participants dropping out of the study before completing the second 6MWT, and one participant walking >600 m during the 6MWT, we were left with a final sample size of 106 participants. No significant difference was observed in the baseline characteristics of the participants who dropped out and the sample included for analysis. The test–retest reliability of the two 6MWT test was 0.94. The mean age of the participants in the study was 62.4 ± 11.4 years. Of the 106 participants, 65 were men and 41 women. The clinical characteristics included ejection fraction ($40.4 \pm 10.6\%$), months to HF diagnosis (61.1 ± 64.9), ischaemic cardiomyopathy (33%), and HF with reduced ejection fraction (87.7%). The sample consisted of four NYHA Functional Class I, 72 NYHA Functional Class II, and 30 NYHA Functional Class III patients. Descriptive

Table 1 Description of the prediction equations

Author	Equation	Population/data source
Burr <i>et al.</i> (2011) ¹⁹	$VO_{2\max} = 70.161 + 0.023 * 6MWT (m) - 0.276 * \text{weight (kg)} - 6.79 * \text{sex (M = 0; F = 1)} - 0.193 * \text{resting HR (b.p.m.)} - 0.191 * \text{age (years)}$	Tested on healthy middle-aged individuals
Ross <i>et al.</i> (2010) ²⁰	$VO_{2\text{peak}} = 4.948 + 0.023 * \text{mean 6MWT distance (m)}$	Data from the literature involving studies on HF and chronic obstructive pulmonary disease patients
Adedoyin <i>et al.</i> (2010) ²¹	$VO_2 = 0.0105 \times \text{distance (m)} + 0.0238 \text{ age (years)} + 0.03085 \text{ weight (kg)} + 5.598$	NYHA Class II–III HF patients
Cahalin <i>et al.</i> (1996) ²¹	$VO_{2\text{peak}} = 0.03 * \text{distance (m)} + 3.98$	Advanced symptomatic HF patients

CPX, cardiopulmonary exercise; F, female; HR, heart rate; M, male; NYHA, New York Heart Association; VO_2 , oxygen uptake.

statistics including age, height, weight, HR, and 6MWT distance are described in *Table 2*.

The results (mean \pm standard deviation; range) of $VO_{2\text{ peak}}$ from CPX testing and estimated $VO_{2\text{ peak}}$ (mL/kg/min) from the four prediction equations are CPX (16.5 ± 3.9 ; 7.0–26); Burr *et al.*¹⁹ (22.8 ± 8.8 ; –10 to 41); Ross *et al.*²⁰ (14.6 ± 2.1 ; 8.2–18.8); Adedoyin *et al.*²¹ (8.03 ± 1.4 ; 3.6–11.6); and Cahalin *et al.*²² (16.6 ± 2.8 ; 8.2–22.1). Mean difference between $VO_{2\text{ peak}}$ from CPX testing and predicted $VO_{2\text{ peak}}$ was as follows: Burr *et al.*¹⁹ = 6.3, Ross *et al.*²⁰ = –1.9, Adedoyin *et al.*²¹ and Cahalin *et al.*²² = 0.10. The Burr *et al.*¹⁹ ($r = 0.48$, $P < 0.0001$; $R^2 = 0.90$) and Adedoyin *et al.*²¹ ($r = 0.61$; $P < 0.0001$; $R^2 = 0.96$) equations showed a moderate correlation, while the Ross *et al.*²⁰ ($r = 0.75$, $P < 0.0001$; $R^2 = 0.98$) and Cahalin *et al.*²² ($r = 0.75$, $P < 0.0001$; $R^2 = 0.98$) equations strongly correlated with the mean $VO_{2\text{ peak}}$ values from CPX testing. MAPE scores for Burr *et al.*¹⁹, Ross *et al.*²⁰, Adedoyin *et al.*²¹ and Cahalin *et al.*²² were 0.56, 0.15, 0.48, and 0.14, respectively. *Figure 1* reflects the ordered CPX $VO_{2\text{ peak}}$ values vs. predicted individual $VO_{2\text{ peak}}$ values from the four equations. *Figures 2 and 3* show the association between CPX $VO_{2\text{ peak}}$ values and predicted $VO_{2\text{ peak}}$ from the three equations using Bland–Altman and scatter plots.

We did not find a significant difference ($P = 0.58$) between CPX $VO_{2\text{ peak}}$ and calculated predicted $VO_{2\text{ peak}}$ with the

Cahalin *et al.*²² equation, while significant mean differences ($P < 0.001$) were observed using the other equations. Therefore, the Cahalin *et al.*²² equation was further analysed to predict VO_2 by NYHA functional class. The predicted values were compared with the CPX values (*Table 3*). For this analysis, the four NYHA Class I participants were included with the NYHA Class II participants. Mean difference, standard error, and significant correlation (r) categorized by NYHA classes included Class I and II combined (–0.22, 0.27; $r = 0.63$) and Class III (–0.86; 0.3; $r = 0.67$). No significant differences were observed within the NYHA classes.

Discussion

The results from our study show that while the four equations were able to explain $\geq 90\%$ of the variance present in the peak VO_2 values from CPX testing, there was a difference in their predictive ability as measured by MAPE. Mean differences show that the predicted $VO_{2\text{ peak}}$ using the four equations either grossly overestimated (Burr *et al.*¹⁹), grossly underestimated (Adedoyin *et al.*²¹), slightly underestimated (Ross *et al.*²⁰), or closely predicted (Cahalin *et al.*²²) the peak VO_2 as observed from CPX testing. The Bland–Altman (*Figure 2*) and scatter plots in (*Figure 3*) show that the individual scores

Table 2 Mean, SD, and range for age, height, weight, resting heart rate, and 6 min walk test distance of participants ($n = 106$)

	Age (years)	Height (cm)	Weight (kg)	Resting HR (b.p.m.)	6MWT (m)
Mean	62.4	172.4	102.95	72.68	419.2
SD	11.4	10.1	25.68	12.67	93.0
Range	25–84	150–172.4	56.4–206.4	41–109	141–600

Figure 1 Ordered cardiopulmonary exercise (CPX) $VO_{2\text{ peak}}$ values (y-axis) vs. predicted individual $VO_{2\text{ peak}}$ values from the three equations (x-axis).

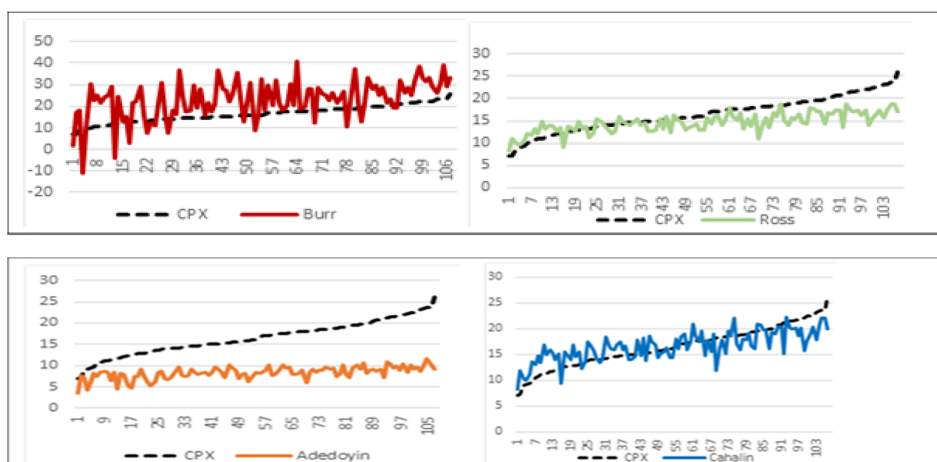


Figure 2 Bland–Altman plot for standardized VO₂ values [Burr *et al.*¹⁹ vs. cardiopulmonary exercise (CPX); Ross *et al.*²⁰ vs. CPX; Cahalin *et al.*²¹ vs. CPX].

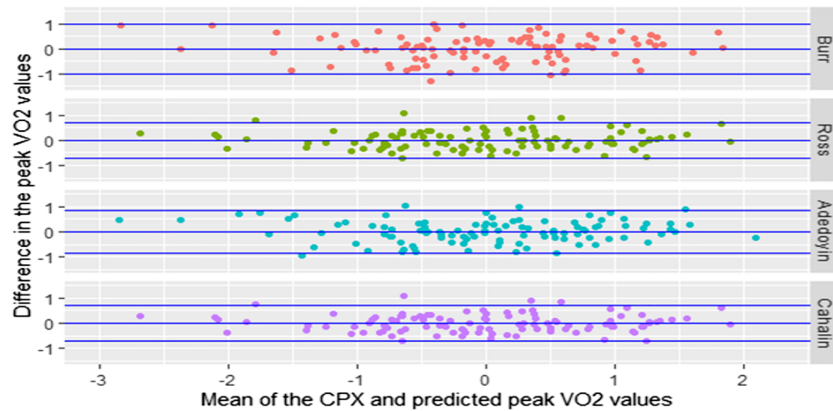


Figure 3 Scatter plot showing the association between VO_{2 peak} values from cardiopulmonary exercise (CPX) testing and VO_{2 peak} from the prediction equations.

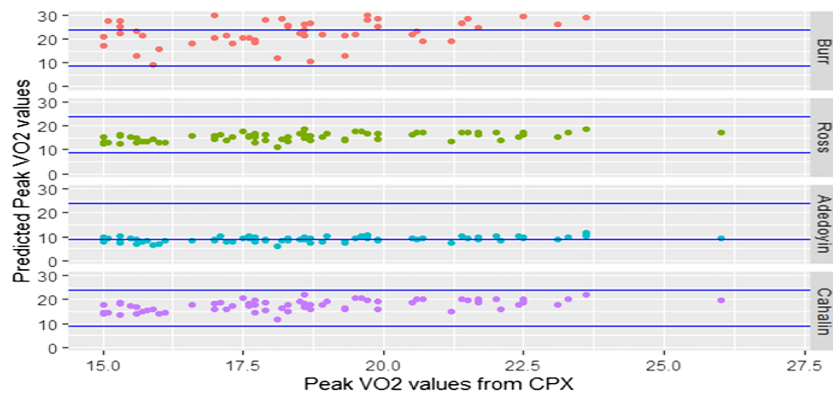


Table 3 Peak VO₂ (mean, median, standard deviation, mean difference, and standard error in mL/kg/min) and correlational values from cardiopulmonary exercise and predicted by New York Heart Association functional class using Cahalin *et al.*²¹ equation

NYHA	Method	Mean	Median	SD	Mean difference (standard error)	Correlation (<i>r</i>)
Class I and II (<i>n</i> = 76)	CPX	17.5	17.7	3.5	0.22 (0.27)	0.63*
	Cahalin equation	17.3	17.4	2.5		
Class III (<i>n</i> = 30)	CPX	13.8	14.4	3.5	−0.86 (0.3)	0.67*
	Cahalin equation	14.48	14.63	2.7		

*A significant correlation between actual CPX testing VO_{2 peak} and predicted VO_{2 peak} values at *P* = 0.05.

predicted by each of the equations are spread out, which resulted in a moderate-to-strong correlation between the CPX and predicted peak VO₂ values. The equations with a larger mean difference between predicted and observed values showed a moderate correlation, while the equations with small differences in mean values showed a stronger correlation. When categorized by NYHA functional classes, the predicted values using the Cahalin *et al.*²² equation showed a significant positive correlation with a small mean difference

of ≤1. Ross *et al.*²⁰ have stated that generalized equations may be useful for accurately estimating mean peak VO₂ values from mean 6 MWT distance scores, but they may not be accurate in making predictions for individual patients. From the spread seen in the scatter plots in our study, the opinion expressed by Ross *et al.*²⁰ is justified and can also be extended to the other prediction equations as well. Overall, when comparing the four equations using the predicted mean peak VO₂ and the MAPE scores, we found that the predictive ability of

Cahalin *et al.*²² (0.1 mL/kg/min; MAPE = 0.14) equation was superior to that of the Burr *et al.*¹⁹ (6.8 mL/kg/min; MAPE = 0.54), Ross *et al.*²⁰ (1.9 mL/kg/min; MAPE = 0.16), and Adedoyin *et al.*²¹ (−8.47 mL/kg/min; MAPE = 0.48) equations.

It is reported that the use of sub-maximal exercise tests to predict $\text{VO}_2 \text{ max}$ may underestimate the actual $\text{VO}_2 \text{ max}$.^{36–38} The 6MWT is generally considered a sub-maximal exercise test where participants do not reach their maximal exercise capacity and are also allowed to rest, if needed, during testing.¹⁰ As such, it can be assumed that predictions of $\text{VO}_2 \text{ peak}$ values using the 6MWT distance will slightly underestimate the peak VO_2 values from CPX testing for a participant. This phenomenon was observed with the equation provided by Ross *et al.*²⁰ While the Burr *et al.*¹⁹ equation grossly overestimated the mean VO_2 values from CPX testing, the results of the Adedoyin *et al.*²¹ equation, which grossly underestimated the observed mean peak VO_2 , were surprising. With the equation formulated by testing a sample of stable NYHA Class II and III HF patients, we expected the Adedoyin *et al.*²¹ equation to be the most accurate in predicting peak VO_2 in our study. The gross inaccuracy may be explained by the difference in the samples between the two studies. Whereas our sample consisted of participants who were mostly Caucasian, the Adedoyin *et al.*²¹ study, done in Nigeria, although not described by the authors, most likely consisted mostly of Black population. Another important factor may be a difference in the medication management of HF. The use of beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and diuretics is part of the standard clinical therapy that our participants were provided as part of their usual care. Such therapy has been shown to improve functional capacity in patients with HF.^{24,29} This information along with observed $\text{VO}_2 \text{ peak}$ from CPX testing is not reported in the Adedoyin *et al.*²¹ study. Our study also excluded participants with peak oxygen consumption >21 mL/kg/min in women and >24 mL/kg/min in men, which may contribute to the differences in peak VO_2 values from CPX testing. The differences found in the mean peak VO_2 values using the predicted equations may be explained by the participant demographics used to formulate these equations and the fact that the treatment of HF has undergone significant changes in the past 20 years.

The population that Ross *et al.*²⁰ used to formulate their prediction equation included a diverse group of clinical patients that included HF patients. The equation proposed by Cahalin *et al.*²² was based on the testing of advanced, symptomatic HF patients, while our sample was composed of stable HF patients. Burr *et al.*¹⁹ developed their prediction equation based on their results from testing of healthy adults with ages ranging between 28 and 60 years. This may explain the gross overestimation in mean $\text{VO}_2 \text{ peak}$ values for our clinical population when using the Burr *et al.*¹⁹ equation. The sample sizes in the four studies were different as well. Burr *et al.*¹⁹ had a sample size of 44; Ross *et al.*²⁰ mostly used

raw data from previously published research and had a sample size of 1083 that included 673 HF patients; Adedoyin *et al.*²¹ had a sample of 65 (30 men and 35 women); and Cahalin *et al.*²² had a sample size of 45. Our sample was similar to that of the Burr *et al.*,¹⁹ Ross *et al.*,²⁰ and Cahalin *et al.*²² studies where the majority of participants were Caucasian. The sample size and demographic are crucial components in developing prediction equations to accurately represent the population and to avoid errors.

Considering that HF patients, depending on the extent of their disease, can be severely compromised in their ability to exercise, it may be argued that predicted peak VO_2 values should be as accurate as possible or for safety purposes and it may be better to underestimate peak VO_2 by a small margin than risk grossly overestimating it. While it may be argued that HF patients have safely performed high-intensity exercise and the risk associated with overestimation of $\text{VO}_2 \text{ peak}$ may be exaggerated, such programmes have been conducted in supervised settings, mostly with NYHA Class I–III HF patients and may not be appropriate for non-supervised performance in the community setting.^{39–42} Also, the HF-ACTION study found moderate-intensity exercise to be safe for patients with HF, and the current HF exercise guidelines from various organizations reflect the same.^{8,23,43,44} As such, the equation provided by Burr *et al.*,¹⁹ developed from testing conducted on healthy adults, may not be appropriate for predicting peak VO_2 for patients with HF to prescribe exercise. It may also be argued that the RPE from 6MWT may in itself be adequate for developing exercise prescriptions for this population, as monitoring improvement in functional capacity pre-exercise to post-exercise training by use of a 6MWT is a common outcome measure. Although this may be true, the validity of these prediction equations needs to be established for accurate estimation of $\text{VO}_2 \text{ peak}$, as they may also be used for research purposes. The strength of the study is that it takes into account four different equations developed by testing of diverse populations. Variations seen in our study in the predictive ability of the four equations should not be taken as a testament to their value or utility. Our sample consisted of stable HF patients who were mostly Caucasian, and our findings suggest the use of population-specific VO_2 prediction equations. We agree with Ross *et al.*²⁰ in utilizing caution in using these predictions to estimate individual peak VO_2 . We found the Cahalin *et al.*²² equation to be the most accurate in predicting mean peak VO_2 scores in patients with HF. The simplicity of the equation also justifies its use for practical purposes.

Conclusions

The use of a population-specific prediction equation to predict mean $\text{VO}_2 \text{ peak}$ from mean 6MWT distance in

patients with HF may be a viable alternative to a CPX VO_2 peak exercise test when constraints of cost and available personnel cannot be overcome. However, with the possibility of grossly underestimating or overestimating exercise capacity, caution is advised when using these equations to predict peak VO_2 at an individual level. Based on our finding, for research purposes, where the mean peak VO_2 needs to be estimated, the Cahalin *et al.*²² equation may be used when the study sample is similar to that of Cahalin *et al.*²² and our study. Future studies should investigate the development of prediction equations that are more accurate in predicting peak VO_2 at the individual level.

Conflict of Interest

None declared.

Funding

The primary HEART Camp study was supported by NHLBI of the National Institutes of Health (award number R01HL112979). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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