Determinants of Cardiorespiratory Fitness in Patients with Heart Failure Across a Wide Range of Ejection Fractions

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Impaired cardiorespiratory fitness (CRF) in heart failure (HF) is influenced by a complex array of cardiac and extracardiac factors. The study aimed to identify clinical determinants of CRF measured as peak oxygen consumption (peak VO_2) in HF patients, and to determine a peak VO_2 prediction model using regression equations. Retrospective analysis of 200 HF patients who completed treadmill cardiopulmonary exercise testing and underwent Doppler echocardiography and/or biomarker analysis on the same day was performed. After univariate linear regression analysis, a multivariate peak VO_2 prediction model was developed using significant variables in a stepwise linear regression analysis. In subjects with repeated testing, Pearson's correlation was used to assess correlations between measured and predicted change in peak VO_2 (Δpeak VO_2) over time. Mean age was 57 years, with 55% being male. Stepwise linear regression was used to generate a weighted model for peak VO_2: 30.895 + (−0.112·age [years]) + (0.296·hemoglobin [g/dl]) + (−0.101·E/e'[unit change]) + (−0.202· body mass index [kg/m^2]) + (−0.593· N-terminal pro-brain natriuretic peptide [$\log_N$ pg/ml])) + (−1.349·CRP [log mg/L]). Predicted peak VO_2 correlated strongly with measured peak VO_2 in HF with reduced ejection fraction and HF with preserved ejection fraction patients ($r = +0.63$, $p < 0.001$; $r = +0.64$, $p < 0.001$, respectively). Predicted Δpeak VO_2 correlated with measured Δpeak VO_2 ($r = +0.23$, $p < 0.001$). In conclusion, in patients with HF across a wide range of left ventricular ejection fraction, age, systemic inflammation, oxygen carrying capacity, obesity, and elevated filling pressures are the strongest predictors of impaired CRF. The proposed CRF model allows prediction of peak VO_2 in HF patients and may be used to estimate peak VO_2 changes over time. **(Am J Cardiol 2020;125:76−81)**

Impaired cardiorespiratory fitness (CRF) is central to the heart failure (HF) syndrome, and portends a poor quality of life and an increased mortality in HF across a wide range of left ventricular ejection fraction (LVEF).[1] However, LVEF has been shown to poorly correlate with CRF in HF and additional cardiac determinants of CRF, such as cardiac output and diastolic reserve may contribute to the reduced exercise capacity.[2−4] Further, CRF may be constrained by noncardiac or systemic factors that include aging, systemic inflammation, skeletal muscle dysfunction, obesity, and pulmonary disease.[5] Cardiopulmonary exercise testing (CPX) is the gold-standard approach to assessing CRF in the HF population; however, compared with other exercise tests it is more expensive, time consuming, and requires specialized personnel. Moreover, current models in clinical practice to predict CRF are limited. Based on previous studies, we hypothesized that in HF patients, with a wide range of LVEF, severity markers of diastolic dysfunction, myocardial wall stretch, systemic inflammation, and high body mass index (BMI) are related to impaired CRF measured by peak oxygen consumption (peak VO_2). The goal of this study was therefore to define routinely clinical determinants of CRF measured as peak VO_2 in HF patients across a wide range of LVEF and determine a peak VO_2 prediction model using regression equations.

Methods

This was a retrospective review of data collected from patients with symptomatic HF (New York Heart Association class II to III) who completed one or more CPX and had one or more of the following tests done at our institution (echocardiography and/or cardiac biomarkers) on the

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

See page 80 for disclosure information.

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same day. Supplemental Table 1 shows an overview of the number of tests that were available for each analysis. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Virginia Commonwealth University Institutional Review Board. Informed consent was obtained from each patient.

All patients underwent symptom-limited CPX according to American Heart Association guidelines by a clinical exercise physiologist under the supervision of a physician with a metabolic cart connected to a treadmill using a conservative ramping protocol as described previously.[6,7] We included patients with a respiratory exchange ratio ≥1.00, as the minimally acceptable effort threshold.[6] Heart rate (HR), blood pressure, and electrocardiography were recorded continuously throughout CPX. Expired gases were collected on a breath-by-breath basis with peak VO_2 ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$) during exercise defined as the highest 10-second average value during the last 30 seconds of exercise. Minute ventilation (VE) and carbon dioxide production (VCO_2) were acquired breath-by-breath throughout exercise to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope).

Echocardiography was performed on the same day before CPX and included measurements of LV end-diastolic, end-systolic volumes, and LVEF using the modified Simpson's biplane method, early transmitral diastolic flow (E) using with pulsed-wave Doppler and e' velocity (average of lateral and septal basal regions), using pulsed-wave tissue Doppler imaging.[8] The E/e' ratio was calculated to estimate LV filling pressures.

Plasma levels of C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and hemoglobin (Hgb) were analyzed from blood samples collected on the same day before CPX.

Each test was considered as separate measurement. On average, patients had 2 (1 to 5) CPX done in a time frame of 2 to 24 weeks after baseline. Correlations between different clinical parameters and peak VO_2 obtained during CPX were evaluated for the entire cohort and within HF subgroups (HFrEF and HFpEF).[9]

Data are presented as mean ± standard deviation for normally distributed variables or as median (interquartile range) for non-Gaussian distributions. All continuous variables were normally distributed, except CRP and NT-proBNP, for which logarithmic transformation into CRP (log_{10}) and NT-proBNP (log_N) was applied. Univariate linear regression was used to assess for correlations between peak VO_2 and the following variables: gender, age, BMI, LVEF, E/e', e', NT-proBNP, CRP, and Hgb. All variables significantly associated with peak VO_2 at univariate analysis ($p < 0.05$) were included in a multivariate stepwise linear regression analysis. Using this multivariate analysis, we generated a weighted-prediction model for peak VO_2, and tested the prediction value for peak VO_2 for all visits. For patients with multiple CPX tests, we also predicted change in peak VO_2 (Δpeak VO_2) over time. Pearson correlation was used to assess for correlations between measured and model-predicted peak VO_2. Measured and predicted changes in Δpeak VO_2 followed a non-Gaussian distribution and therefore Spearman correlation was used. A receiver operating characteristic (ROC) curve analysis was performed to evaluate whether the model-predicted peak VO_2 had discriminative value for prognostic VO_2 cut points defined as <10 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ and <14 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$, respectively. SPSS Statistics 23.0 (IBM, Armonk, NY) statistical software package was used for all analyses with a p value <0.05 considered statistically significant.

Results

A total of 366 CPX from 200 different patients were evaluated. Table 1 lists a summary of general characteristics. Mean age was 57 years old and 55% were male. Echocardiography data were available in 171 patients (86%). We included 109 patients with HFrEF (64%) identified on the basis of HF signs/symptoms, and LVEF <50%. We included 62 patients with HFpEF (36%) identified on the basis of HF signs/symptoms, LVEF ≥50%, and at least one additional abnormality in cardiac filling pressures, Doppler-derived hemodynamic pressures, or natriuretic peptide values, according to the European Society of Cardiology recommendations.[9]

Age and female gender were both associated with peak VO_2 ($r = -0.172$, $p < 0.01$, $r = -0.232$, $p < 0.01$, respectively). Peak VO_2 was significantly negatively associated with CRP, NT-proBNP, BMI, and E/e' ($r = -0.350$, $p < 0.001$; $r = -0.330$, $p < 0.001$; $r = -0.286$, $p < 0.001$; $r = -0.280$, $p < 0.001$, respectively) and positively with Hgb levels and LVEF ($r = +0.431$, $p < 0.001$; $r = +0.242$, $p < 0.001$, respectively). Table 2 shows univariate predictors of peak VO_2 in HFrEF and HFpEF separately.

As shown in Table 3, age, Hgb, E/e', BMI, NT-proBNP, and CRP were independent predictors of peak VO_2 ($r = +0.386$ for the model) and were included in the prediction model: (30.895+[−0.112•age{years}] +[0.296•hemoglobin {g/dl}]+[−0.101•E/e'{unit change}]

Table 1
Clinical, laboratory, echocardiography, and CPX data of the entire cohort

Characteristics	Total population (n = 200)
Clinical characteristics	
Age (years)	57 (±10)
Men	110 (55%)
Body mass index (kg/m^2)	35.3 (±8.3)
Laboratory data	
C-reactive protein (mg/L)	3.7 [1.5-9.0]
NT-proBNP (pg/ml)	377 [106-1463]
Hemoglobin (g/dl)	13.2 (±1.7)
Echocardiography data	
Left-ventricular ejection fraction (%)	44 (±14)
E/e' ratio	15 (±8)
CPX variables	
Exercise time (minutes)	8.7 (±2.8)
Peak oxygen uptake ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$)	15.8 (±4.4)
Peak oxygen uptake (percent of predicted)	54 (±16)
VE/VCO_2 slope	32.6 (±6.6)

Data shown as mean (± standard deviation) or median and (interquartile range).

Abbreviations: CPX = cardiopulmonary exercise testing; NT-proBNP = N-terminal pro-brain natriuretic peptide, VE/VCO_2 = minute ventilation to carbon dioxide production slope.

Table 2
Univariate predictors of peak VO_2 in HFrEF and HFpEF cohorts

Correlations with peak oxygen consumption		HFrEF	HFpEF
Cardiac systolic function	LVEF	r= + 0.225, p < 0.001	r = +0.079 p = 0.472
Cardiac diastolic function	E/e'	R = −0.330 p < 0.001	r = −0.171 p = 0.188
	e'	r = −0.044 p=0.617	r = +0.328 p = 0.010
Myocardial wall stretch	NT-proBNP	r = −0.354 p < 0.001	r = −0.275 p = 0.032
Inflammation	CRP	r = −0.282 p < 0.001	r = −0.459 p < 0.001
Body composition	BMI	r = −0.237 p < 0.001	r = −0.563 p < 0.001
Other biomarkers	Hemoglobin	r = +0.440 p < 0.001	r = +0.432 p < 0.001

Abbreviations: BMI = body mass index; CRP = C-reactive protein; E/e' = ratio of early transmitral E wave velocity (E) to early averaged mitral annulus velocity (e') by tissue Doppler; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide.

+[−0.202•BMI {kg/m^2}]+[−0.593•NT-proBNP {$\log_N$ pg/ml}])+(−1.349•CRP [log mg/L]). The model-predicted peak VO_2 correlated well with measured peak VO_2 in all HF patients (r = +0.630, p <0.001, n = 166) as shown in Supplemental Figure 1. The multivariate prediction model for peak VO_2 remained valid in both HFrEF and HFpEF, as shown in Figure 1 (r = +0.638, p <0.001 for HFpEF and r = +0.625, p <0.001 for HFrEF). A sensitivity analysis was performed with one CPX per individual to avoid potential confounding related to being represented for multiple tests, which showed a similar statistical strength for peak VO_2 prediction. (r = +0.567, p <0.001, n = 74).

To assess whether the prediction model was able to predict changes in peak VO_2 over time in patients with repeated testing, we assessed correlations between measured and predicted Δpeak VO_2 between different visits. To calculate predicted Δpeak VO_2, only potentially modifiable factors from the prediction model were included, including Hgb, NT-proBNP, BMI, E/e' and CRP. As shown in Figure 2, predicted and measured Δpeak VO_2 correlated well in all HF patients (r = +0.228, n = 266, p <0.001). Supplemental Figure 2 demonstrates the ROC curve analysis for the model-predicted peak VO_2 according to the proposed formula.

Table 3
Multivariate predictors of peak oxygen consumption

Predictors of peak oxygen consumption	Unstandardized β coefficients	p Value
Constant	30.895	<0.001
Age (1 year)	−0.112	<0.001
Hemoglobin (1 g/dl)	+0.296	0.041
E/e' (1 unit)	−0.101	0.004
Body Mass Index (1 kg/m^2)	−0.202	<0.001
NT-proBNP (1 pg/ml)	−0.593	0.001
C-Reactive Protein (1 mg/L)	−1.349	0.014

Abbreviation: E/e' = ratio of early transmitral E wave velocity (E) to early averaged mitral.

Discussion

CRF is an important determinant of quality of life and a prognostic indicator in patients with HF. Our novel peak VO_2 prediction model using standard of care clinical variables may help to identify patients with impaired CRF who may need further characterization, and will allow clinicians to follow changes in estimated peak VO_2 over time. We show that in our heterogeneous HF cohort both cardiac and noncardiac factors contributed to reduced CRF.

HF is characterized by a proinflammatory state, evident from increasing inflammatory markers upon progression of the disease in HF patients, which is believe to not only impair myocardial function but affect other tissues as well thereby exacerbating the HF syndrome.[10] CRP, the preferred biomarker of systemic inflammation was inversely associated with CRF in our model aligning with the findings of previous work and this relation appears to be modifiable with exercise training and targeted anti-inflammatory strategies in HF patients.[11–13]

Additionally, we show that elevated filling pressures/ventricular wall stress (E/e', NT-proBNP levels), are predictive of impaired CRF in HF. Elevated filling pressures during exercise are the consequence of diastolic and systolic dysfunction, and cause an increase in LV wall tension leading to release of NT-proBNP.[14] Both in HFrEF and HFpEF patients, exercise intolerance has shown to correlate with elevated filling pressures and elevated NT-proBNP levels.[4,15]

Furthermore, oxygen carrying capacity of the blood, measured by Hgb levels, was shown to be predictive of CRF. Although on average, HF patients in our cohort were not anemic (Hgb > 13 g/dl), reduced Hgb concentration leads to a reduction in arterio-venous O_2 content and may contribute to reduced CRF if the O_2 carrying capacity of the blood is impaired beyond the ability of the cardiovascular and skeletal muscle systems to compensate. In HF patients with a more severely compromised CRF, a lower peak exercise arterio-venous O_2 was partially attributed to decreased Hgb levels.[16]

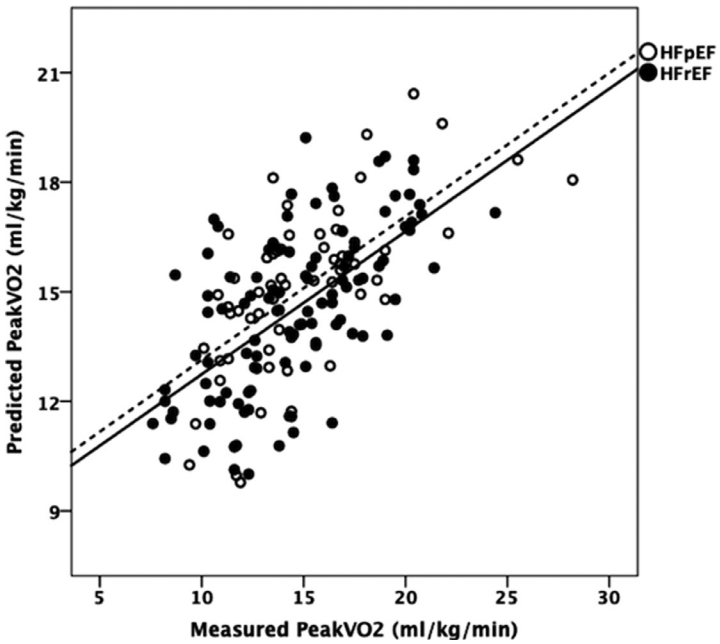

Figure 1. Scatterplot for measured and model-predicted peak VO_2 in HFrEF and HFpEF. Scatterplot showing correlations between measured peak VO_2 and model-predicted peak VO_2 according to the proposed formula in HFrEF patients ($r = +0.625$, $n = 105$, $p < 0.001$) and HFpEF patients ($r = +0.638$, $n = 59$, $p < 0.001$).

Obesity, as assessed by BMI, was also identified as strong predictor of impaired CRF. Obesity and adiposity have shown to be related to worse exercise capacity in HF[17] because it is associated with diastolic dysfunction, mechanical ventilatory limitations, and peripheral and respiratory skeletal muscle dysfunction that meaningfully contribute to the worse exercise capacity.[18] In this regard, exercise and weight loss due to caloric restriction had a synergistic effect on improving peak VO_2 even in absence of changes in systolic or diastolic cardiac function at Doppler echocardiography, suggesting a beneficial effect on adiposity, skeletal muscle mass and composition, and vascular function.[17,19]

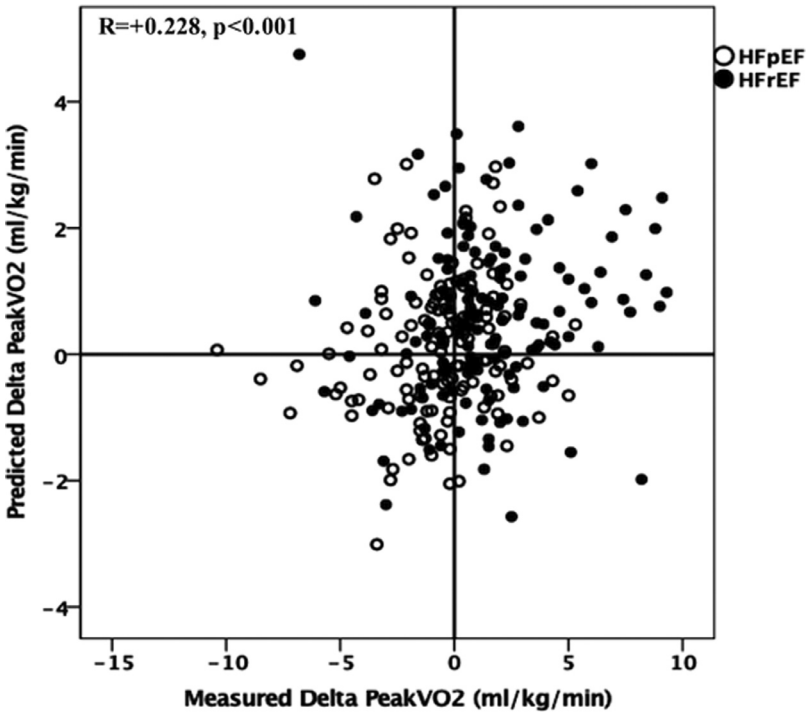

Figure 2. Scatterplot for measured and model-predicted Δpeak VO_2. Scatterplot showing correlations between measured and model-predicted change in peak VO_2 over time according to the proposed formula in all HF patients ($r = +0.228$, $p < 0.001$, $n = 266$).

However, an adjustment of peak VO_2 for fat-free mass (i.e., lean peak VO_2) it could have been a more accurate assessment of overall CRF, as adjusting peak VO_2 to total body weight (kg) may result in an underestimation of peak VO_2.[5]

Finally, we found that this novel peak VO_2 prediction model was also able to predict changes in peak VO_2 over time; the low R-squared indicates that changes in the predictor values are associated with changes in the response value in such a way that the response for one unit of change in the predictor, whereas holding other predictors in the model constant, is rather small, but large changes in the same predictor value may still have a larger cumulative effect.

Current models used in clinical practice to predict CRF are limited in terms of actionable parameters, as they mostly rely on nonmodifiable factors such as age, gender, and height. Also, most studies focus on either HFrEF or HFpEF, whereas our proposed CRF prediction model was shown to be valid in both cohorts. In previous studies of HFpEF, peak VO_2 was best predicted by age, gender, body size, Hgb, and chronotropic reserve.[20] This implies that modifiable factors such as obesity, anemia, and chronotropic incompetence may contribute to impaired CRF in HFpEF, which may provide a therapeutic window for CRF improvement.[20]

The use of the proposed formula to estimate peak VO_2 may prove useful in identifying patients with impaired CRF who may need further characterization (i.e., CPX), and may be of clinical help to follow changes in estimated peak VO_2 over time. Our findings show that there are modifiable factors associated with impaired CRF in HF, which may provide novel therapeutic opportunities to improve CRF.[5,21]

The retrospective nature of our study limited the power of our analyses, thus making a need for validation in a larger prospective cohort. Also, the sample size for HFpEF was smaller compared with HFrEF, further limiting the power of our analyses. Another limitation of our study is that every visit in the data analysis was used as separate data point, resulting in some patients being represented more than once in the analysis. Despite this limitation, our sensitivity analysis demonstrates this did not significantly affect our results. Lastly, we were not able to adequately address known peripheral determinants of CRF in HF such as the vital role of skeletal muscle, peripheral oxygen extraction, and the respiratory system. This may explain the reduced discriminative ability of our model in those with higher VO_2 values (i.e., >14 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$). Multiple studies have shown that HF patients with muscle wasting, muscle atrophy, and decreased total lean mass, have impaired CRF.[22,23]

In conclusion, by studying clinical determinants of CRF in HF patients, we found that the strongest modifiable factors for impaired CRF in HF appear to be systemic inflammation, oxygen carrying capacity, obesity, and elevated LV filling pressures. If validated by future studies, peak VO_2 scoring using the proposed model may add value as a prognostic indicator in clinical practice for HF patients.

Disclosures

None of the authors have any conflicts of interests related to this manuscript to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.09.036.

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