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Severely Impaired Cardiorespiratory Fitness In Patients With Recently Decompensated Systolic Heart Failure

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Abstract

Hospital admission for decompensated heart failure (HF) marks a critical inflection point in a patient's health. Despite the improvement in signs/symptoms during hospitalization, patients have a high likelihood of readmission, reflecting a lack of resolution of the underlying condition. Surprisingly no studies have characterized the cardiorespiratory fitness (CRF) of such patients. Fifty-two patients (38 [73%] male, age 57 [52–65] years, left-ventricular ejection fraction 31% [24–38]) underwent cardiopulmonary exercise testing (CPX) 4 (1–10) days after hospital discharge, when stable and without overt signs of volume overload. Transthoracic Doppler echocardiography, measurement of N-terminal pro-B-natriuretic peptide (NT-proBNP), and quality of life were also assessed. Aerobic exercise capacity was severely reduced: peak oxygen consumption (pVO_2) was 14.1 (11.2–16.3) $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Ventilatory inefficiency as indicated by the minute ventilation carbon dioxide production relationship (VE/VCO_2 slope) >30 and oxygen uptake efficiency slope (OUES) <2.0 was noted in 41 (77%) and 39 (75%) patients, respectively. Forty-five (87%) of patients had one of two high-risk features ($\text{pVO}_2 <14$

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$\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or $\text{VE}/\text{VCO}_2 >30$). Perceived functional capacity, measured by the Duke Activity Status Index (DASI) was also severely reduced, and correlated with pVO_2 . NT-proBNP levels and early transmitral velocity/early mitral annulus velocity (E/e') ratio at echocardiography showed a modest correlation with lower pVO_2 . In conclusion, patients with recently decompensated systolic HF demonstrate severe impairment in cardiorespiratory fitness severely limiting quality of life.

Keywords

systolic heart failure; cardiopulmonary exercise testing; cardiorespiratory fitness

INTRODUCTION

Peak oxygen consumption (pVO_2), measured through cardiopulmonary exercise testing (CPX), reflects cardiorespiratory fitness (CRF) in terms of maximal aerobic capacity, a well-established indicator of disease severity and of prognosis in patients with HF.^{1–3} The minute ventilation/carbon dioxide production [VE/VCO_2] slope is an independent predictor of outcomes in HF, and a measure of ventilatory efficiency.⁴ Peak VO_2 and VE/VCO_2 slope are monitored in patients with chronic HF and used for risk stratification and therapeutic strategies.⁵ Characterization of CRF parameters shortly following hospital discharge for decompensated HF has not been performed. Determining CRF in patients with recently-decompensated HF (RDHF), and its determinants, may provide new and important clinical information in this high-risk population. As such, the aim of the current investigation was to measure CRF in patients with systolic HF within 2 weeks of hospital discharge for RDHF.

METHODS

We quantified CRF via CPX in 52 patients with systolic HF at an average of 4 (range 1–10) days after hospital discharge for a decompensation episode who were being evaluated for enrollment in a clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01936909) registration NCT01936909).⁶ Briefly, for consideration in the trial, patients had to be considered stable according to the treating physician and by the exercise physiologist, without New York Heart Association Class IV symptoms (dyspnea at rest or with minimal activity) or paroxysmal nocturnal dyspnea for 72 hours, and no evidence of overt volume overload (i.e. rales, jugular vein distention, pitting edema).

A supervised CPX was administered using a metabolic cart adapted to a treadmill using a conservative ramping treadmill protocol with increases of approximately 0.3 metabolic equivalents (METs) every 30-seconds. Only subjects who were limited by shortness of breath during CPX and achieved a peak $\text{RER} \geq 1.00$ were considered for inclusion.⁵ Patients with results indicative of exercise-limiting ischemic heart disease (angina, ischemic ECG changes, and abnormal blood pressure) were excluded.

CPX was performed to quantify three primary measures: 1) pVO_2 , 2) VE/VCO_2 slope, 3) the oxygen uptake efficiency slope (OUES). The highest 10-second average value of O_2 uptake during the final 30 seconds of exercise defined pVO_2 in $\text{mLO}_2\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Percent (%) of predicted normal values for peak VO_2 were reported using the reference values proposed by

Wasserman et al.⁷ Ten second averaged VE and VCO₂ data, from the initiation of exercise to peak, were inserted into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO₂ slope via least squares linear regression. The OUES was determined using least-squares linear regression analysis (O_2 consumption= $a \log_{10}VE+b$, with VO₂ and VE expressed in L•min⁻¹) using spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA).⁸ The peak RER (VCO₂/VO₂) was used to quantify subject effort.

All subjects underwent a transthoracic Doppler echocardiogram and phlebotomy for biomarker assessment including N-terminal brain natriuretic peptide (NT-proBNP) on the same day prior to CPX. Echocardiography was performed following the American Society of Echocardiography measurement guidelines⁹: left ventricular (LV) end-diastolic and end-systolic volumes, ejection fraction, early transmitral E wave velocity, early mitral annulus e' velocities by tissue Doppler averaged between lateral and septal (e') and tricuspid annulus plane systolic excursion.⁹ The E/e' ratio was calculated to estimate LV filling pressures.¹⁰

We used two different questionnaires to quantify symptoms, functional status and quality of life (QOL); 1) the Duke Activity Status Index (DASI) which assesses general ability to complete activities¹¹; and 2) the Minnesota Living with Heart Failure (MLWHF) which addresses limitations specifically due to HF.¹²

Data are presented as either number and percentages or median and interquartile range. Correlations between continuous variables were assessed using the Spearman rank correlation test for non-parametric data. The SPSS 23.0 (IBM, Armonk, New York) statistical software package was used for all analyses with a p-value <0.05 considered statistically significant.

RESULTS

Table 1 shows the demographic and clinical characteristics of the 52 subjects. All patients had received loop diuretics during hospital admission (furosemide equivalent dose of 470 mg [range 270–820]) and were on guideline-directed HF medications at discharge, including a furosemide equivalent dose of 50 mg/day.

All patients had a peak VO₂ <100% of predicted, and all but 1 patient (98%) had a peak VO₂ 70% of predicted. Median DASI score was 26 [range 16–38] and median MLWHF score was 57 [range 44–73], indicating severe HF-related limitations in perceived functional status and QOL (Table 1). Cardiopulmonary exercise testing revealed severe reductions in CRF: median peak VO₂ was 14.1 [range 11.2–16.3] mL•kg⁻¹•min⁻¹ (% of predicted peak VO₂ was 46% [range 39–52]). Most of the patients also demonstrated ventilatory inefficiency as indicated by a VE/VCO₂ slope >30 in 41 (77%) [median 33.6 (range 30.9–40.2)] and OUES <2.0 in 39 (75%) and 1.75 in 29 (56%) [median 1.74 (range 1.24–2.04)]. Forty-five (87%) patients had at least one high-risk feature (peak VO₂<14 mL•kg⁻¹•min⁻¹ or VE/VCO₂>30) (Figure 1). The DASI score, a subjective measure of fatigue, significantly correlated with exercise time (R=+0.37, P=0.008) and peak VO₂ (R=+0.29, P=0.038)(Figure 2), whereas the MLWHF did not (all P>0.30). NT-proBNP levels and E/e' ratio at Doppler

echocardiography, but not LVEF, correlated with peak VO_2 ($R=-0.32$, $P=0.022$, and $R=-0.29$, $P=0.044$, respectively). Moreover, NT-proBNP levels and E/e' ratio correlated with both the VE/VCO_2 slope ($R=-0.50$, $P<0.001$, and $R=-0.36$, $P=0.011$, respectively) and OUES ($R=-0.53$, $P<0.001$, and $R=-0.31$, $P=0.022$, respectively). Peak VO_2 , VE/VCO_2 slope, nor OUES correlated with diuretic dose (all $R<0.30$, all $P>0.40$).

DISCUSSION

The results of this study shows that patients with systolic HF who are discharged from the hospital after an admission for acute decompensation remain highly symptomatic with respect to exercise intolerance and dyspnea. The severe reduction in pVO_2 is such that many subjects are limited in their ADLs.¹³ There is therefore an urgent need to find strategies to improve exercise capacity in this high-risk population. The concomitant presence of severe ventilatory inefficiency is equally concerning as it represents an important, and independent, mechanism of disease in this population.¹

The correlation between markers of elevated LV filling pressures (NT-proBNP plasma levels and E/e' ratio) with both impaired aerobic capacity and ventilatory efficiency suggests that, in patients with recently decompensated systolic HF, the impairment in diastolic function is very important. Whether NT-proBNP and E/e' ratio reflect a need for additional aggressive diuresis or are merely markers of worse underlying cardiac dysfunction is unknown. One possibility is that these patients simply needed more aggressive diuresis. Elevated NT-proBNP and E/e' ratio may, however, may also be only markers of more severe LV failure and not be responsive to diuresis. Of note, all patients had undergone an aggressive diuretic regimen while in-hospital, had undergone a systematic evaluation and optimization of diuretic dose prior to enrollment including multiple encounters by a multi-disciplinary team that included physicians and pharmacists trained in HF-management and specifically trained for this protocol. They were further screened with CPX, wherein those with arterial hypertension or hypotension at rest or with exercise were excluded to minimize the likelihood of including patients with hyper- or hypovolemia. Moreover, although not conclusive, the lack of any correlation between diuretic dose and CRF does not suggest a benefit of higher diuretic doses. It also appears that the impairment in peak VO_2 translates in worse quality of life in the domain of perceived physical function (DASI) and less so in symptoms of congestion (MLWHF). The role of the skeletal muscle in determining cardiorespiratory fitness (peak VO_2) in these patients was not explored in this study.¹⁴⁻¹⁵ Nevertheless, the data present herein show that the cohort of patients with recent hospital admission for HF are not only at high risk for readmission, which has been already recognized, but is also one that is severely impaired in their ADLs and thus jeopardizes their QOL after discharge.

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Figure 1. Peak aerobic capacity measured with cardiopulmonary exercise test

The graph shows moderate to severe impairment in measured (peak VO_2) and concomitant abnormalities in the ventilatory efficiency in the population.

Figure 2. Measured and perceived exercise capacity

The Duke Activity Status Index (DASI) score measured the perceived functional capacity and it has been reported to correlate with peak oxygen consumption (peak VO₂) in patients with ischemic heart disease, in whom it was developed, and in ambulatory patients with heart failure. The graph shows a significant correlation between the measured (peak VO₂) and perceived (DASI score) peak aerobic capacity in this cohort of recently decompensated heart failure patients. A correspondence between perceived and achieved peak VO₂ values and how they may correlate with the activities of daily living (ADLs) is shown.

Table 1

Demographic and Clinical Characteristics.

Variables	Overall
Age (years)	57 (52–65)
Men	38 (73%)
Black	42 (81%)
Body Mass Index (kg/m ²)	33 (28–41)
Coronary Artery Disease	18 (35%)
Arterial hypertension	48 (92%)
Diabetes mellitus	29 (56%)
C-reactive protein (mg/L)	5.65 (2.53–11.48)
N-terminal pro-Brain Natriuretic Peptide (pg/ml)	1334 (580–2679)
New York Heart Association functional class, II/III	17 (33%)/35 (67%)
Duke Activity Status Index score	26 (16–38)
Minnesota Living with Heart Failure score	57 (44–73)
Echocardiography parameters	
Left ventricular ejection fraction (%)	31 (24–38)
Early mitral inflow velocity/mitral annular early diastolic velocity ratio (E/e')	17.8 (11.9–24.5)
Cardiopulmonary Exercise Test parameters	
Exercise Time (minutes)	7.4 (4.6–9.1)
Respiratory Exchange Ratio	1.10 (1.04–1.17)
Peak Oxygen Uptake (mL•kg ⁻¹ •min ⁻¹)	14.1 (11.2–16.3)
Heart Failure Therapies	
Angiotensin blockers	43 (83%)
Beta-adrenergic receptor blockers	48 (92%)
Aldosterone blockers	27 (52%)
Hydralazine/isosorbide	28 (54%)
Loop diuretics	52 (100%)
Furosemide equivalent dose (mg)	50 (40–120)
Cardiac Resynchronization Therapy	4 (8%)
Implantable Cardioverter Defibrillator	21 (40%)