Published in final edited form as:

J Cardiopulm Rehabil Prev. 2020 November ; 40(6): 434–437. doi:10.1097/HCR.0000000000000502.

Peak Oxygen Uptake Recovery Delay After Maximal Exercise in Patients With Heart Failure

Dinesh Kadariya, MD,

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond

Justin M. Canada, PhD,

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond

Marco Giuseppe Del Buono, MD,

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond

Jessie van Wezenbeek, MS,

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond

Inna Tchoukina, MD,

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond

Ross Arena, PhD,

Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago

Benjamin Van Tassell, PharmD,

Department of Pharmacotherapy and Outcome Sciences, Virginia Commonwealth University, Richmond

Antonio Abbate, MD, PhD

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond

Abstract

Purpose: Peak oxygen uptake recovery delay ($\dot{V}O_{2\text{peakRD}}$), measured as the time until post-exercise oxygen uptake ($\dot{V}O_2$) decreases below $\dot{V}O_{2\text{peak}}$ following maximal cardiopulmonary exercise testing (CPX), has been recognized as an abnormal response, associated with reduced cardiac output reserve during exercise in patients with heart failure (HF). In the current study we examined the association of $\dot{V}O_{2\text{peakRD}}$ during routine CPX testing of patients with symptomatic HF across a wide range of left ventricular ejection fraction (LVEF) values with clinical biomarkers.

Methods: In this retrospective study, 80 clinically stable symptomatic HF patients across a wide range of LVEF at our institution were evaluated that put forth a minimally acceptable effort during

Correspondence: Antonio Abbate, MD, PhD, VCU Pauley Heart Center, 1200 E. Broad St, Box 980204, Richmond, VA 23298 (antonio.abbate@vcuhealth.org).

The first two authors equally contributed to the realization of this manuscript.

The authors declare no conflicts of interest.

CPX testing (respiratory exchange ratio = 1.00). The $\dot{V}O_{2\text{peakRD}}$ was measured in 10-sec intervals following maximal CPX testing. Markers of elevated cardiac filling pressures (N-terminal pro-brain natriuretic peptide [NTproBNP] and echocardi-Doppler E/e') and other key CPX parameters were explored for their association with $\dot{V}O_{2\text{peakRD}}$.

Results: The mean $\dot{V}O_{2\text{peakRD}}$ and $\dot{V}O_{2\text{peak}}$ were 10 (interquartile range 10, 40) sec and 13.9 (11.6, 16.4) mL·kg⁻¹ · min⁻¹, respectively. $\dot{V}O_{2\text{peakRD}}$ demonstrated a positive linear trend with serum NTproBNP levels and E/e' (T_{JT} = 1239.500, z = 2.634, P < .01; T_{JT} = 1081.000, z = 2.046, P = .04, respectively).

Conclusion: Prolonged $\dot{V}O_{2\text{peakRD}}$ following exercise is associated with markers of greater disease severity in patients with HF.

Keywords

cardiopulmonary exercise test; heart failure; oxygen uptake recovery delay

Heart failure (HF) is associated with diminished exercise and functional capacity, poor quality of life, and increased morbidity and mortality.¹ Cardiopulmonary exercise testing (CPX) is the gold standard approach to objectively quantify exercise capacity and cardiorespiratory fitness. Peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) obtained during CPX is one of the most well-established markers of disease severity and prognosis in the HF population.² In addition to $\dot{V}O_{2\text{peak}}$, other variables measured during CPX provide valuable insight into the pathophysiology of exercise limitations, disease severity, and prognosis; several of these measures are now recommended as part of the routine HF assessment using CPX.³ Following termination of exercise, prolonged heart rate recovery and $\dot{V}O_2$ recovery have been associated with worse outcomes among patients with HF.⁴⁻⁹ Peak oxygen uptake recovery delay ($\dot{V}O_{2\text{peakRD}}$), defined as the time from the end of exercise until $\dot{V}O_2$ persistently decreases to below $\dot{V}O_{2\text{peak}}$ values, has been proposed as an indirect measure of impaired cardiac reserve during exercise in patients with HF.¹⁰ The purpose of this study was to determine the association of $\dot{V}O_{2\text{peakRD}}$ in routine CPX testing of patients with symptomatic HF across a wide range of left ventricular ejection fraction (LVEF) values with clinical biomarkers.

METHODS

Patients were considered for the study if they had been diagnosed with HF, clinically stable, and underwent CPX within our institution from January 2014 to January 2017. We retrospectively analyzed data collected from 80 patients with symptomatic HF (New York Heart Association functional class II-III) who underwent CPX at Virginia Commonwealth University (VCU), including patients with HF with reduced LVEF (<50%) and preserved LVEF (≥ 50%). The European Society of Cardiology 2007 diagnostic criterion based on intracardiac filling pressures, brain natriuretic peptide levels, and/or Doppler echocardiography was used for the diagnosis of heart failure with preserved ejection fraction (HFpEF). Heart failure with reduced ejection fraction (HFrEF) was defined as a diagnosis

based on symptoms/signs, biomarkers, or noninvasive/invasive measures of elevated cardiac filling pressures, and a reduced LVEF (<50%) The VCU Institutional Review Board approved the analysis and all patients provided written informed consent prior to testing. Medical history and clinical events were abstracted from the medical record. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Cardiopulmonary exercise testing was performed by a single clinical exercise physiologist according to American Heart Association recommendations.¹¹ A conservative ramping treadmill protocol was utilized with incremental changes of approximately 0.3 metabolic equivalents every 30 sec. Ventilatory gas analysis was performed pre-, during, and post-exercise to measure $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) using a TrueOne 2400 (Parvo Medics) metabolic measurement system. The metabolic cart was calibrated for volume and gas concentration before every test. Oxygen consumption was expressed in relative values ($mL \cdot kg^{-1} \cdot min^{-1}$) and recorded using 10-sec averages during exercise and the post-exercise recovery phase. Peak $\dot{V}O_2$ was defined as the highest 10-sec average value during the final 30 sec of exercise. Following peak exercise, measurement of ventilatory gas analysis was continued for 2 min into the recovery period, which consisted of walking 1.0 mph/0% grade for 1 min followed by a seated rest for an additional minute. The $\dot{V}O_{2peakRD}$ was defined as the cumulative time in 10-sec intervals from the end of exercise until the time wherein $\dot{V}O_2$ values persistently decreased below the $\dot{V}O_2$ attained at peak exercise. Percent predicted normal values for $\dot{V}O_{2peak}$ were reported using the reference values proposed by Wasserman.¹² Ten-second averaged $\dot{V}_E$ and $\dot{V}CO_2$ data throughout the entire exercise period were input into an Excel spreadsheet (Microsoft) and used to calculate the $\dot{V}_E / \dot{V}CO_2$ slope via least squares linear regression. The peak respiratory exchange ratio (RER) was used to determine subject effort with a peak value ≥ 1.00 considered the minimal acceptable effort threshold.¹¹ We evaluated 80 patients, 52 with HFrEF and 28 with HFpEF, who had impaired cardiorespiratory fitness demonstrated at CPX. Patients who interrupted the CPX for reasons other than dyspnea or volitional fatigue (ie, ischemia, arrhythmias, low RER) during the CPX were excluded.

All patients underwent resting transthoracic Doppler echocardiography and measurement of N-terminal pro-brain natriuretic peptide (NTproBNP) on the same day prior to CPX. Echocardiographic parameters of systolic and diastolic function were measured according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging and included (1) left ventricular end-diastolic and end-systolic volumes; (2) LVEF; (3) early trans-mitral diastolic flow velocity (E); and (4) early diastolic mitral annulus excursion velocity (e') by tissue Doppler averaged between the lateral and septal annuli. The E/e' ratio was calculated to estimate left ventricular filling pressure.¹³

Descriptive statistics are reported as n (%) for categorical variables, and continuous variables were expressed as median and interquartile range for variables showing deviation from Gaussian distribution (assessed with the Kolmogorov-Smirnov test) and mean $\pm$ SD for variables with Gaussian distribution. We used the Mann-Whitney *U* test to compare variables with non-Gaussian distribution and the *t* test for independent samples to compare

variables with a normal distribution. Logarithmic transformation was performed for analysis of NTproBNP. The $\dot{V}O_{2\text{peakRD}}$ was assessed as an ordinal level parameter in 10-sec intervals, rather than as a continuous variable. The Jonckheere-Terpstra nonparametric test was used to assess for linear trend between $\dot{V}O_{2\text{peakRD}}$ and markers of cardiac filling pressures and key CPX variables. SPSS Statistics version 24.0 (IBM) was used for all analyses. A P value $< .05$ was considered statistically significant.

RESULTS

The mean age was 56 ± 11 yr, 48 (60%) were male, and 56 (70%) were African American. Of the 80 patients, 52 (65%) had been diagnosed with HFrEF and 28 (35%) with HFpEF. All patients were on guideline-directed medical therapy for HF. Detailed patient demographic and clinical characteristics are reported in the Table.

The median $\dot{V}O_{2\text{peakRD}}$ for the entire cohort was 10 (10, 40) sec and the median $\dot{V}O_{2\text{peak}}$ was 13.9 (11.6, 16.4) $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. There was no statistically significant difference in $\dot{V}O_{2\text{peakRD}}$ between male and female participants (10 [10, 40] vs 10 [10, 20] sec, $P = .30$) as well as between Caucasian and African Americans (10 [10, 40] vs 10 [10, 40] sec, $P = .90$). We found a significant positive linear trend between $\dot{V}O_{2\text{peakRD}}$ prolongation and higher NTproBNP levels and Doppler echo E/e' values, reflecting elevated cardiac filling pressures ($T_{JT} = 1239.500$, $z = 2.634$, $P < .01$; $T_{JT} = 1081.000$, $z = 2.046$, $P = .04$, respectively) (Figure). Additionally, the $\dot{V}O_{2\text{peakRD}}$ median duration demonstrated an inverse linear trend relative to exercise time ($T_{JT} = 753.000$, $z = -2.317$, $P = .021$). There was no statistically significant linear trend between $\dot{V}O_{2\text{peakRD}}$ and the $\dot{V}_E / \dot{V}CO_2$ slope or $\dot{V}O_{2\text{peak}}$ ($T_{JT} = 1166.500$, $z = -1.545$, $P = .122$; $T_{JT} = 822.500$, $z = -1.667$, $P = .095$).

The $\dot{V}O_{2\text{peakRD}}$ was significantly longer in HFrEF compared with the HFpEF cohort (15 [10, 50] vs 10 [10, 18] sec respectively, $P = .006$) without any statistically significant differences in $\dot{V}O_{2\text{peak}}$ between HFrEF and HFpEF (14.1 [11.2, 16.3] vs. 13.8 [11.8, 17.7] $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ respectively, $P = .43$).

DISCUSSION

In this study, we explored post-exercise $\dot{V}O_2$ kinetics using noninvasive CPX in a group of patients with symptomatic HF across a wide range of LVEF to determine associations with markers of cardiac filling pressures (NTproBNP and E/e'). The inverse relation of post-exercise $\dot{V}O_2$ recovery delay with exercise time confirms the findings of prior studies. The direct association with markers of elevated cardiac filling pressures and myocardial strain is novel and expands the findings of these prior studies that describe prolonged $\dot{V}O_2$ recovery kinetics in HF patients using various parameters.⁴⁻¹⁰

The slow recovery of $\dot{V}O_2$ following exercise in HF patients has been suggested to be a compensatory mechanism to repay the oxygen deficit resulting from the insufficient augmentation of cardiac output (CO) during exercise relative to the peripheral metabolic

demand.¹⁴ This is supported by others who have shown the temporal characteristics of $\dot{V}O_{2\text{peakRD}}$ were not influenced by pulmonary or peripheral factors in HF patients.¹⁰ The positive association of $\dot{V}O_{2\text{peakRD}}$ with markers of elevated left ventricular filling pressures (ie, E/e') and myocardial strain (NTproBNP) in our study suggests that impaired myocardial compliance and/or relaxation adversely affecting CO augmentation may be contributing to the $\dot{V}O_{2\text{peakRD}}$ in HF patients.

While some pathophysiology overlaps between HFrEF and HFpEF in the limiting steps of the oxygen pathway during exercise, differences exist between the 2 groups. In HFpEF, due to the pathophysiology of exercise limitation and the corollary of associated comorbidities, both reduced CO and a $\dot{V}O_2$ difference may significantly contribute to exercise intolerance, and therefore, the shorter $\dot{V}O_{2\text{RD}}$ showed in HFpEF may reflect a smaller contribution of impairment in CO reserve limiting the exercise response. In addition, our HFpEF population mainly consisted of patients with morbid obesity, which may itself have contributed to reduced cardiorespiratory fitness.¹⁵

The assessment of $\dot{V}O_{2\text{peakRD}}$ is limited by the sampling interval. In the current study we had gas analysis outputs every 10 sec, and this may have limited the ability to detect differences between groups or correlations between $\dot{V}O_{2\text{peakRD}}$ and other parameters, as seen in other studies.¹⁰

When compared with prior studies, the current report includes a wider range of LVEF and $\dot{V}O_{2\text{peak}}$ values, thus, expanding the external validity of the analysis.

Our study has certain limitations as with any observational study, thus the association found in this study does not prove causality. This was a single-center, observational, retrospective study with a limited sample size. Notwithstanding the limitations of the current study, we believe that $\dot{V}O_{2\text{peakRD}}$ is a simple, noninvasive, readily available metric obtained with routine CPX, which can be incorporated as an additional informative CPX-derived variable in patients with symptomatic HF. Furthermore, the role of exercise testing in cardiac rehabilitation is constantly expanding.¹⁶ The knowledge of post-exercise recovery kinetics including $\dot{V}O_{2\text{peakRD}}$ may further help in guiding more effective exercise programs in HF patients. In conclusion, this study demonstrates that prolonged $\dot{V}O_{2\text{peakRD}}$ following exercise is associated with markers of greater disease severity in patients with HF across a wide range of LVEF.

ACKNOWLEDGMENTS

This project was supported by National Heart, Lung, and Blood Institute of the USA National Institute of Health grants to Dr Abbate and Dr Van Tassell (R34HL117026 and R34HL136816) and by a Clinical and Translational Science Award of the USA National Institute of Health to Virginia Commonwealth University (UL1TR002649, PI: F.G. Moeller).

Salvatore Carbone, PhD, Cory R. Trankle, MD, Hayley Billingsley, RD, and Roshanak Markley, MD (VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia); George Wohlford, PharmD (VCU Pauley Heart Center and Department of Pharmacotherapy and Outcome Sciences, Virginia Commonwealth University, Richmond, Virginia); and Leo Buckley, PharmD (School of Pharmacy, Brigham and Women's Hospital, Boston, Massachusetts), contributed to the data collection for the study.

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Figure.

Relationship of peak oxygen uptake recovery delay with N-terminal pro-brain natriuretic peptide (NTproBNP) and E/e'. (A) Peak oxygen uptake recovery delay increases as the tissue Doppler early transmitral diastolic flow velocity (E) to early diastolic mitral annulus excursion velocity (e') ratio (E/e') increases. (B) Peak oxygen uptake recovery delay increases as the log-transformed NTproBNP increases. Dot and bar represent median and interquartile range.

Demographic and Clinical Characteristics^a

Variables	Entire Cohort (n = 80)	HFpEF (n = 52)	HFpEF (n = 28)
Age, yr	56 ± 11	56 ± 12	54 ± 9
Male	48 (60)	38 (73)	10 (36)
African American	56 (70)	42 (81)	14 (50)
Body mass index, kg/m ²	37.2 ± 9.5	34.1 ± 8.8	43.0 ± 7.9
Coronary artery disease	21 (27)	18 (35)	3 (11)
Arterial hypertension	76 (95)	48 (92)	28 (100)
Diabetes mellitus type 2	52 (66)	29 (56)	23 (82)
New York Heart Association Functional Class			
II	26 (32)	17 (33)	9 (32)
III	54 (68)	35 (67)	19 (68)
LVEF, %	42 ± 15	33 ± 9	59 ± 6
E/e'	15.0 (10.1, 20.0)	17.0 (12.0, 24.0)	10.8 (9.0, 14.3)
NTproBNP, pg/mL	601 (170, 2056)	1334 (580, 2679)	127 (47, 247)
$\dot{V}O_{2peak}$, mL · kg ⁻¹ · min ⁻¹	13.9 (11.6, 16.4)	14.1 (11.2, 16.3)	13.8 (11.8, 17.7)
Percent-predicted peak $\dot{V}O_2$	48 (41, 54)	46 (39, 52)	51 (42, 65)
Peak respiratory exchange ratio	1.11 ± 0.09	1.11 ± 0.10	1.10 ± 0.07
$\dot{V}_E / \dot{V}CO_2$ slope	33.7 ± 7.0	35.3 ± 7.4	30.6 ± 4.9
Exercise time, min	7.4 ± 2.7	6.9 ± 2.6	8.1 ± 2.7
$\dot{V}O_{2peakRD}$, sec	10 (10, 40)	15 (10, 50)	10 (10, 18)
Angiotensin blocker	58 (73)	43 (83)	15 (54)
β-Adrenergic receptors blockers	71 (89)	48 (92)	23 (82)
Aldosterone blockers	42 (52)	27 (52)	15 (54)
Hydralazine/isosorbide	36 (33)	28 (54)	8 (29)
Loop diuretics	78 (98)	52 (100)	26 (93)
Cardiac resynchronization therapy	4 (5)	4 (8)	0
Implantable cardioverter defibrillator	21 (26)	21 (40)	0

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Abbreviations: E/e', ratio of early transmitral diastolic flow velocity (E) and early diastolic mitral annulus excursion velocity (e'); HFpEF, heart failure with preserved ejection fraction; HF-HF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro-brain natriuretic peptide; $\dot{V}_E / \dot{V}CO_2$, ratio of minute ventilation to carbon dioxide production; $\dot{V}O_{2peak}$, peak oxygen uptake; $\dot{V}O_{2peak}RD$, peak oxygen consumption recovery delay.

^aData reported as mean $\pm$ SD or median (interquartile range) for variables following a Gaussian distribution or not, respectively, or n (%).