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Reliability of Maximal Cardiopulmonary Exercise Testing in Men with Prostate Cancer

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Abstract

Purpose—In order to accurately assess exercise interventions and to evaluate acute and chronic cardiovascular effects in patients with early-stage cancer, consistently reliable functional outcome measures must be obtained. An incremental cardiopulmonary exercise test (CPET) with gas exchange measurement, to assess peak oxygen consumption (peak VO_2), provides the gold standard outcome of cardiorespiratory fitness.

Methods—In the context of a randomized controlled trial, 40 prostate cancer patients (mean age 59 ± 7 years) following radical prostatectomy performed two maximal CPETs within 5.6 ± 5.5 days of each other. Incremental treadmill tests were performed in the morning under identical laboratory conditions. Reliability and within subject variability from test 1 to test 2 for peak and submaximal variables were assessed by correlation coefficients, intraclass correlations (ICC), Bland-Altman plots, coefficient of variation (CV), and paired t-tests.

Results—There was high reliability between CPETs for peak VO_2 ($r=0.92$, $p<0.001$, $\text{ICC}=0.900$); ventilatory threshold (VT; $r=0.88$, $p<0.001$, $\text{ICC}=0.927$); minute ventilation-carbon dioxide production relationship (VE/VCO_2 ; $r=0.86$, $p<0.001$, $\text{ICC}=0.850$); and peak heart rate (HR; $r=0.95$, $p<0.001$, $\text{ICC}=0.944$). However, high within-subject variability was observed for all CPET parameters (mean coefficient of variation: 4.7%). Compared to test 1, significantly higher mean values were observed for peak VO_2 (27.0 ± 5.6 vs. $28.1 \pm 5.3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $p<0.05$), VT (1.91 ± 0.5 vs. $1.97 \pm 0.4 \text{ L} \cdot \text{min}^{-1}$, $p<0.05$) and VE/VCO_2 (31.3 ± 5.8 vs. 32.8 ± 3.4 , $p<0.05$) in test 2.

Conclusion—These findings indicate the presence of significant, and potentially clinically important, variability in CPET procedures in men with clinically-localized prostate cancer, and have important implications for the application and utility of CPETs to evaluate the efficacy of interventions to improve aerobic capacity in the oncology setting.

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Keywords

test reproducibility; prostate cancer; oncology; cardiovascular fitness

INTRODUCTION

Paragraph 1

Prostate cancer (PC) is the most common non-skin cancer diagnosis in North American men.(1) Radical prostatectomy (RP), a primary treatment for early stage localized PC, is associated with 10 year survival rates of ~90%.(1, 24) However, RP side effects include urinary incontinence, erectile dysfunction, pain, and reduced physical functioning.(6) Collectively, these side effects negatively affect health-related quality of life for up to 12 months following surgery.(9) Despite significant advances in pharmacotherapy, continuing development of new interventions to improve health-related quality of life remains a high priority for this patient population.(22) We, and others, have proposed that aerobic based exercise training may improve cardiorespiratory fitness and cardiovascular risk profiles in patients with PC.(18, 23) However, in order to accurately assess exercise interventions and evaluate acute and chronic cardiovascular late-effects in patients with early-stage disease, consistently reliable functional outcome measures must be obtained.

Paragraph 2

Over the past half-decade, non-invasive cardiopulmonary exercise testing (CPET) has emerged as a research and clinical tool of immense value given its ability to accurately evaluate aerobic capacity (peak VO_2 ; which, in turn, can be used for risk stratification or evaluation of intervention efficacy), to assess the principal determinants of exercise intolerance, and to develop individualized aerobic training prescriptions.(14, 16, 17) Importantly, the within-patient variability of CPET variables in PC has not been ascertained. Consequently, establishing repeatability of CPET in PC is critical, not only to ensure accurate assessment of changes in cardiorespiratory fitness across interventions, but also to precisely characterize acute and chronic cardiovascular effects for risk stratification. Accordingly, as a prespecified sub study of a randomized trial investigating the efficacy of aerobic training in men with clinically-localized prostate cancer following radical prostatectomy (RP), we evaluated the reproducibility of peak VO_2 and other important CPET parameters to assess the need for repeat testing.

METHODS

Patient Cohort, Setting, and Procedures

Paragraph 3—This is a secondary analysis of baseline data obtained in the context of a randomized trial investigating the efficacy of aerobic training in men with clinically-localized prostate cancer following radical prostatectomy (RP). Full details of the study methods have been reported previously.(18) In brief, major eligibility criteria were: (1) 4 months from RP to study enrollment, (2) no absolute contraindications to a maximal CPET, (3) willingness to travel to Duke University Medical Center (DUMC), (4) primary attending

urologist approval, and (5) peak VO_2 ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) below that of age-matched sedentary normative values.(18) All study procedures were reviewed and approved by the DUMC institutional review boards. All subjects signed a written consent prior to the initiation of any study-related procedures. Following initial eligibility determination, all patients performed a maximal CPET as part of study screening procedures (visit 1). If no CPET-related adverse events were detected, all patients returned to perform a repeat CPET (visit 2).

Maximal Cardiopulmonary Exercise Testing Procedures

Paragraph 4—All CPETs were performed using an incremental treadmill test (modified Balke protocol) on a motorized treadmill with 12-lead ECG monitoring (Mac® 5000, GE Healthcare). Participants were provided with detailed, standardized, verbal instructions prior to each test and were told to avoid exercise, caffeine, and alcohol for 24h, and consume medications as normal. All testing was performed between 8am and 10am. Complete calibration of gas concentrations using primary standard gases and flow using a 3L syringe were performed before each test. All tests were performed by the same two certified exercise physiologists. To avoid bias, testers intentionally did not view the results of test 1 immediately before conducting test 2. Prior to beginning the test subjects were familiarized with the mouthpiece and walking on the treadmill for approximately 10 minutes, followed by 10 minutes of rest. After stable resting metabolic values were achieved (including blood pressure and heart rate), subjects began walking at pace selected in the warm-up as a comfortable but brisk pace (~2.5–4.0 mph) at 0% grade for 2 minutes. During the test, participants were encouraged to walk for as long as possible resulting in a peak, symptom-limited exhaustive effort. Grade was increased every 2 minutes until ventilatory threshold (VT) (determined independently in each test), and then every minute thereafter until exhaustion or a symptom-limitation.(15) Ratings of perceived exertion were evaluated at the end of each workload using the modified Borg Scale. Whether patients gave a maximal effort was determined based on a combination of symptoms (dyspnea on exertion and/or fatigue as primary endpoints) and physiological measures (defined as a plateau in oxygen consumption during the final stage, maximal heart rate > 85% of age-adjusted predicted maximal heart rate, and respiratory exchange ratio (RER)> 1.10).(10) Metabolic gas exchange was measured continuously during exercise and averaged over 30-second intervals (ParvoMedicsTrueOne® 2400, Sandy, UT). Peak VO_2 was defined as the highest VO_2 value for a given 30-second interval within the last 60 seconds of exercise. The VO_2 at VT was independently determined by a blinded reader using standard methods.(3, 26) The minute ventilation-carbon dioxide production relationship (VE/VCO_2 slope) was determined by measuring the slope across the entire duration of the test.(2)

Statistical Analyses

Paragraph 5—Means are expressed using either $\pm$ standard deviation or with 10th and 90th percentiles. Within-subject variability from test 1 to test 2 was evaluated by within-subject absolute change (i.e., either increase or decrease from test 1 to test 2) and tested using paired samples t-tests. Bland-Altman plots were constructed, defined as the difference in values from test 2 and test 1 plotted versus the average of the values from tests 1 and 2 with standard deviation of the difference (average difference $\pm$ 1.96 standard deviation of the difference).(7) Reliability of the CPET outcome measures was assessed by Pearson

correlations and intraclass correlations (ICC). One-sided 95% confidence intervals of Pearson correlations were made using Fisher's z transformation. For each variable, the coefficient of variation (CV) was defined as the (within-subject standard deviation/within-subject mean) $\times$ 100%. Significance for all tests was set at $p < 0.05$.

RESULTS

Participant Characteristics

Paragraph 6—Details regarding response rates and profiles of the participants have been reported previously.⁽¹⁸⁾ In brief, a total of 50 patients were randomized in the parent trial and 40 (80%) successfully completed two baseline CPETs (3) (Table 1). Participant recruitment took place between November 2009 and July 2012. The two baseline CPETs were separated by 5.6 ± 5.5 days. No serious or life-threatening adverse events (SAEs) were observed during any CPET procedures. During baseline CPETs, ischemic ECG changes (> 2.0 mm ST depression) were observed in 3 patients.

Test – Retest Reliability

Paragraph 7—Pearson's correlations and ICC for peak and submaximal variables are summarized in Table 2. There was a significant correlation between the two tests with correlation coefficients of 0.94 (absolute peak VO_2 , heart rate), 0.96 (VT), and 0.67 (RER). ICCs ranged from 0.927 (absolute peak VO_2 , RER, exercise time), 0.790 (VT), and 0.938 (heart rate).

Within Subject Test – Retest Variability

Paragraph 8—Test-retest variability (CV) for peak and submaximal parameters ranged from 2.2% (HR), 4.2 % (indexed and absolute peak VO_2), and up to 7.6% (exercise duration). Exercise duration (11.3 ± 2.2 vs. 11.5 ± 2.2 min), peak VO_2 (2.39 ± 0.5 vs. 2.49 ± 0.5 L/min; 27.0 ± 5.6 vs. 28.1 ± 5.3 mL $\cdot$ kg $^{-1}$ min $^{-1}$ $p < 0.01$), peak heart rate (161 ± 17 vs. 163 ± 16 bpm), VT (1.91 ± 0.4 vs. 1.97 ± 0.4 L/min) and VE/ VCO_2 (32.1 ± 5.8 vs. 32.8 ± 3.4) increased from test 1 to test 2 (Table 3). The percentage of subjects who increased on test 2 was greater than those who decreased for peak VO_2 (72%), exercise time (75%), heart rate (68%), VE/ VCO_2 (83%) and VT (65%). As shown in Figures 1 a and b there was high variability between tests for peak variables (95% CI of 25.2 to 29.8 mL $\cdot$ kg $^{-1}$ min $^{-1}$; 2.2 to 2.66 L/min (peak VO_2) 155 to 167 bpm (HR)); and submaximal variables Figures 2 a and b (95% CI of 31.0 to 33.8 (VE/ VCO_2); 1.72 to 2.09 L/min (VT)). Variability was similar for subjects with lower versus higher peak VO_2 (Figures 1 and 2).

DISCUSSION

Paragraph 9

The principal finding of this ancillary analysis was that despite good test-retest CPET reliability there was significant within-subject variability in peak and submaximal variables (CV ranging from 2% to 8%) in men with localized PC. Accordingly, we contend our data suggests the need to perform two CPETs at baseline to obtain valid, baseline peak VO_2 and other CPET results in men following RP for clinically-localized PC. Such variability has

critical implications for the acquisition of accurate baseline VO_2 data which, in turn, could impact prognosis and risk stratification, and the magnitude of intervention efficacy to change VO_2 in cancer patients.

Paragraph 10

A number of studies have closely examined the variability of measurements obtained during CPET in other clinical populations with conflicting results. In the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) trial, the mean peak VO_2 was not different in test 1 and 2 (15.2 ± 5.0 vs. $15.2 \pm 5.0 \text{ mL}\cdot\text{kg}^{-1}\text{min}^{-1}$; $p=0.78$).⁽⁵⁾ However, there was a large within-subject variability (6.6%) for peak VO_2 which the authors attributed to variations in subject factors specific to heart failure patients such as daily hemodynamic and volume status fluctuations. A more recent investigation involving heart failure patients with preserved ejection fraction reported no difference in peak VO_2 between tests 1 and 2 (14.4 vs. $14.3 \text{ mL}\cdot\text{kg}^{-1}\text{min}^{-1}$), with authors concluding that the incremental gain in information should be balanced by the increase in participant burden and cost.⁽²⁵⁾ In contrast, current CPET guidelines in clinical populations with cardiovascular and respiratory disease recommend at least two CPETs are conducted in all clinical and research settings; these recommendations were formulated on the basis of prior work demonstrating that peak VO_2 significantly varies over serial tests.^(3, 12) For example, Elborn et al. (8) performed three consecutive treadmill-based CPETs separated by two weeks in 30 subjects with heart failure. The mean peak VO_2 improved significantly from the first to the second test (14.1 vs. $14.9 \text{ mL}\cdot\text{kg}^{-1}\text{min}^{-1}$, $p<0.005$) with no difference between test 2 and 3, while the average within subject CV was 6%. These findings are consistent with those observed here in which peak VO_2 increased significantly from 27.0 to $28.1 \text{ mL}\cdot\text{kg}^{-1}\text{min}^{-1}$; and the within subject CV was 4.2%. Additionally, the percentage of subjects who increased on test 2 (72%) was greater than those who decreased (28%). Submaximal responses such as VT and VE/VCO_2 slope have been used with greater frequency to classify exercise intolerance and to risk stratify in clinical populations.^(5, 25) In contrast to previous investigations with heart failure patients reporting nearly identical mean values on test 1 and 2 for submaximal indices, ^(5, 25) here, we found that 83% (33/40) and 65% (26/40) of subjects increased VE/VCO_2 slope and VT respectively on test 2. Taken together, these findings are indicative of variability in men with localized PC. We did not conduct a third CPET; however, based on previous literature an additional test is unlikely to provide clinically relevant changes.^(8, 13, 21)

Paragraph 11

The variability in both maximal and submaximal CPET parameters observed in the present study is potentially clinically meaningful. For example, there is growing evidence supporting the utility of VO_2 for both prognostic ^(14, 20) and risk stratification ^(4, 27) purposes in numerous oncology clinical scenarios. These findings underscore the significance of accurate CPET-derived peak and submaximal measures, particularly given the increasing number of cancer diagnoses combined with the large and rapidly growing number of cancer survivors who could benefit from a global measure of the integrative capacity of the pulmonary, cardiovascular, and skeletal muscle systems to deliver and utilize O_2 . Furthermore, in the parent trial, we found that mean peak VO_2 increased from 28.1

$\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at baseline (as recorded in the second CPET) to $30.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at week 24; an increase of 9% among patients randomized to supervised aerobic training. There were no differences in peak VO_2 between baseline (as recorded in the second CPET) and 6 months in the usual care group. It could be speculated that had we not conducted two CPETs at baseline, the increase in peak VO_2 may have been inflated to 12% (27.0 vs. $30.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) in the exercise group, and increased in the usual care group ($27.9 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ vs. $29.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Interestingly, in a meta-analysis of 6 randomized controlled trials assessing the efficacy of exercise training on direct measurement of peak VO_2 in cancer patients, the mean increase in peak VO_2 was $2.91 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, or approximately 12% compared to controls.(19) It is important to note that all of these trials conducted only one CPET at baseline. On the basis of the present findings, it is possible that testing variability may have contributed to the observed improvements. Although some testing variability could potentially be controlled for by comparing changes in exercise groups to controls groups, our findings raise important questions regarding CPET methodology before, during, or following intervention and for cardiovascular risk assessment in the oncology setting. For example, given that the peak VO_2 decreased in 28% of subjects on test 2 in the present investigation, future studies should examine whether the highest data point, the mean of two points, or the second data point should be used for final baseline assessments.

Paragraph 12

In order to accurately assess test-retest reliability it is important to adhere to stringent CPET methodology. To this end we adhered to the following procedures: standardized participant instructions, testing at the same time of day, screening for intercurrent acute illness or injury or change in condition, calibration and validation of the gas exchange unit before each test, and strong encouragement to reach volitional exhaustion or symptom limitation. However, there were several factors and testing methodology limitations that may contribute to increased variability in the measurement of peak and submaximal CPET parameters. First, to facilitate the achievement of peak aerobic capacity in a timely and standardised way, several maximum incremental, ramp protocols are available. These protocols are classified according to the application of work rate: constant increments (i.e., application of same workload increments for all patients); or individualised increments (i.e., variable workload increments based on patient characteristics). We used individualised protocols, as recommended by the American Thoracic Society.(3) Individualised protocols enable the selection of workload increments that are appropriate for a patient. Such flexibility is particularly useful for CPET of patients with cancer many of whom have been treated with cytotoxic combination therapy and present with concomitant comorbid disease.(16) Second, there is considerable day to day biological variation in humans that is well documented in healthy subjects.(11) In patients with a chronic condition on a variety of medications, the biological variance could be even greater. Indeed, although all subjects in the present investigation achieved maximal effort as outlined by the American Thoracic Society,(3) it is possible there was inherent variability in the effort deconditioned subjects were willing to exert from day to day.(21) To this end, there were variations in HR between tests, suggesting inconsistency of effort. Third, there is also considerable technical variation in when VO_2 max occurs depending on how many breaths occur during the sampling period

(30s for the present investigation). It is possible a small change could be associated with when the gas sampling occurs in comparison to breathing pattern. Finally, this was prespecified sub study of a randomized trial with a modest sample size.

Paragraph 13

In summary, findings of the present study demonstrating an increase in maximal as well as submaximal CPET-derived measures in the second test among men with clinically-localized prostate cancer suggest that two baseline CPETs are required, when feasible, in all studies examining the efficacy of interventions on peak VO_2 in the oncology setting. Importantly, analyses of similar studies in both children and adult cancer patients that include evaluation of CPET before, during, and following therapy are now required to establish standardized methodology and interpretation of results, to formulate reference values, and to increase the clinical utility of CPET. Such efforts will lead to the development of standardized CPET guidelines / recommendations for patients with cancer.

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Figure 1.
Bland-Altman plot for peak variables: A) peak VO₂, B) peak heart rate (HR).

Figure 2. Bland-Altman plot for submaximal variables: A) minute ventilation-carbon dioxide production relationship (VE/VCO_2), B) ventilatory threshold (VT).

Table 1

Participant characteristics (n=40)

Variable	Overall (n=40)
Age – yr	60 (7)
Weight – kg	87.6 (12.8)
Body Mass Index – kg·m ⁻²	28.0 (3.3)
Race – no. (%)	
White	27 (68)
Black	11 (28)
Asian	2 (5)
Current smoker – no. (%)	1 (3)
Comorbid conditions – no. (%)	
Hypertension	24 (60)
Hyperlipidemia	22 (55)
Diabetes mellitus	6 (15)
CAD	3 (8)
Pulmonary disease	12 (30)
None of these comorbid conditions	7 (18)
Tumor characteristics	
PSA	6.2 (4.2)
PSA category – no. (%)	
<4	7 (18)
4 – 10.0	30 (75)
10.1 – 19.9	2 (5)
20.0 – 49.9	1 (3)
Gleason sum – no. (%)	
<7	18 (45)
7	22 (55)
Type of surgery – no. (%)	
Robotic	15 (38)
Radical	25 (63)
Days post-surgery to randomization	74 (38)

Values are expressed as n (%) or mean ± SD.

Table 2

Reliability of cardiopulmonary exercise testing

	Test 1	Test 2	R	1-sided 95% CI	ICC	P-Value
Exercise time (min)	11.3 ± 2.2	11.5 ± 2.2	0.750	0.541	0.927	<0.001
Indexed peak oxygen uptake (ml/kg/min)	27.0 ± 5.6	28.1 ± 5.3	0.919	0.861	0.900	<0.001
Absolute peak oxygen uptake (L/min)	2.39 ± 0.5	2.49 ± 0.5	0.943	0.856	0.927	<0.001
Heart rate (beats/min)	161 ± 17	163 ± 16	0.949	0.945	0.938	<0.001
Ventilation per carbon dioxide slope	31.3 ± 5.8	32.8 ± 3.4	0.864	0.851	0.864	<0.001
Oxygen uptake at ventilatory threshold (L/min)	1.91 ± 0.4	1.97 ± 0.4	0.957	0.790	0.873	<0.001
Respiratory exchange ratio	1.18 ± 0.08	1.19 ± 0.07	0.670	0.440	0.927	<0.001

p-value corresponds to the R value.

Table 3

Test-retest variability of CPET variables

	Test 1	Test 2	P-Value	Absolute Change (2 - 1)	% 2 > 1	% 1 > 2	CV (%)
Exercise Time (min)	11.3 (9.0, 15.0)	11.5 (9, 14.5)	0.35	0.23	75	25	7.6
Indexed oxygen uptake (ml/kg/min)	27.0 (20.9, 33.7)	28.1 (22.3, 34.9)	0.003	1.1	72	28	4.2
Absolute oxygen uptake (L/min)	2.39 (1.86, 2.97)	2.49 (1.92, 3.03)	0.001	0.10	72	28	4.2
Heart rate (beats/min)	161 (146, 187)	163 (146, 184)	0.14	2	68	32	2.2
Ventilatory threshold (L/min)	1.91 (1.37, 2.29)	1.97 (1.43, 2.45)	0.01	0.07	65	35	7.5
Ventilation per carbon dioxide slope	32.1 (29.1, 37.1)	32.8 (29.0, 37.3)	0.02	0.65	83	17	2.9
Respiratory exchange ratio	1.18 (1.11, 1.31)	1.19 (1.11, 1.32)	0.14	0.01	65	35	3.1

Values expressed as mean (10th percentile, 90th percentile) unless noted otherwise. P-Value corresponds to a paired t-test of the null hypothesis that the mean of test 2 minus the mean of test 1 = 0.