Cardiopulmonary Exercise Testing Characterizes Silent Cardiovascular Abnormalities in Asymptomatic Pediatric Cancer Survivors

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Research Article

Keywords: Cardiotoxicity, cancer treatment, cardiopulmonary exercise testing (CPET), exercise performance, peak oxygen consumption (pVO2), submaximal exercise

Posted Date: March 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1460124/v1

Abstract

Background

Late-onset cardiovascular complications are of serious concerns for even asymptomatic pediatric cancer survivors (PCS). We investigated whether cardiopulmonary exercise testing (CPET) can delineate the underlying pathophysiology of preclinical cardiovascular abnormalities in PCS.

Methods

We examined CPET data via cycle ergometer in asymptomatic PCS with normal echocardiogram and age-matched controls. Peak and submaximal parameters were analyzed.

Results

Fifty-three PCS and 60 controls were studied. Peak oxygen consumption (VO2), peak work rate (WR), and ventilatory anaerobic threshold (VAT) were significantly lower in PCS than controls (1.86 ± 0.53 vs. 2.23 ± 0.61 L/min, 125 ± 45 vs. 154 ± 46 watt, and 1.20 ± 0.35 vs. 1.42 ± 0.43 L/min, respectively; all $p < 0.01$), whereas peak heart rate (HR) and ventilatory efficiency (a slope of minute ventilation over CO2 production or DVE/DVCO2) were comparable. Peak respiratory quotient (RQ) was significantly higher in PCS ($p = 0.0006$). Stroke volume (SV) reserve was decreased in PCS, indicated by simultaneous higher dependency on HR (higher ΔHR/ΔWR) and lower peak oxygen pulse (OP) at the peak exercise. Twelve PCS with high peak RQ (≥ 1.3) revealed lower pVO2 and VAT than the rest of PCS despite higher ventilatory efficiency (lower DVE/DVCO2), suggesting fundamental deficiency in oxygen utilization in some PCS.

Conclusions

Poor exercise performance in PCS is mainly attributed to limited stroke volume reserve, but the underlying pathophysiology is multi-factorial. Combined assessment of peak and submaximal CPET parameters provided critical information in delineating underlying exercise physiology of PCS. (244 words)

Introduction

Recent remarkable progress in cancer treatment has enabled nearly 80% of pediatric cancer patients to survive into adulthood cancer free [1]. At the same time, long-term cardiovascular complications have become concerns for pediatric cancer survivors (PCS) [2, 3]. The pathobiology of progression of cardiovascular complications in PCS has been extensively studied, and multiple pathological mechanisms have been proposed. However, the clinical manifestations of long-term cardiovascular complications remain poorly understood [4]. Routine echocardiographic surveillance is recommended by

multiple clinical guidelines to screen at-risk patients [5], but its reliability in detecting subtle preclinical cardiovascular impairment is limited.

Cardiopulmonary exercise testing (CPET) is a useful, noninvasive method to assess cardiopulmonary fitness level in children and adolescents with heart disease. Unlike echocardiogram and magnetic resonance imaging (MRI), which primarily assess cardiac function at the resting condition, CPET mainly measures the functional reserve of all organs involved in exercise performance, including heart, lung, blood, vasculature, and skeletal muscles, in which cardiac output accounts for approximately 70% of total exercise performance. Several studies have shown that PCS have a reduced exercise performance compared with age-matched normal controls [6–9], but the underlying pathophysiology of reduced exercise performance remains elusive.

In this study, we investigated overall exercise performance by combinational assessment of submaximal CPET parameters that represent a dynamic trend during intermediate phase of exercise and conventional peak CPET parameters. We hypothesized that the underlying mechanisms of poor exercise performance in PCS can be delineated by this new combinational approach with submaximal and peak CPET parameters.

Patients And Methods

A retrospective chart review of CPET data from the database of the Exercise Laboratory, Nemours Cardiac Center, Nemours Children's Hospital Delaware, Wilmington, DE, was conducted from 2017 to 2020. The study was approved by the Institutional Review Board of the hospital.

Patients

We retrospectively studied asymptomatic PCS followed at the Cancer Survivorship Program at Nemours Children's Hospital, Delaware, who were referred for CPET to assess physical fitness levels. The inclusion criteria consisted of the following: 1) age ≥ 10 years, 2) off cancer treatment ≥ one year, 3) intact musculoskeletal system and neurological function, 4) body mass index (BMI) < 30 kg/m^2, and 5) left ventricular shortening fraction (LVSF) ≥ 28% or left ventricular ejection fraction (LVEF) ≥ 55% by echocardiogram. Age, sex, height, weight, and BMI of the patients were collected at the time of CPET. For PCS, primary diagnosis, age at diagnosis, cumulated dosage of anthracycline (mg/m^2), and history of radiation therapy were recorded. Sex-, age-, and weight-matched control patients were recruited from the database of the Exercise Laboratory at the Nemours Cardiac Center.

Cardiopulmonary Exercise Testing (CPET)

The study was performed on bike ergometer (VIA Sprint 150 P, Yorba Linda, CA) following RAMP protocol with 10- to 25-watt (W)/min increments up to peak exercise (approximately 0.3 W/kg/min). Heart rate and oxygen saturation (SaO2) were continuously monitored by standard 12-lead electrocardiogram (ECG) and pulse oximeter, respectively. Blood pressure was measured every 2 to 3 minutes during exercise and

recovery phases. Oxygen consumption (VO2), carbon dioxide production (VCO2), and minute ventilation (VE) were measured continuously during all exercise testing using a calibrated metabolic measurement system (Vmax Sensor Medics, Palm Springs, CA). The exercise protocol was continued until the patient stopped because of symptomatic limitations. Achievement of peak exercise level was confirmed by either peak HR of more than 90% of estimated maximum HR for age (220 – age) or respiratory quotient (RQ) of 1.1 or higher.

Peak and submaximal exercise parameters were obtained in combination with continuous monitoring of vital signs and ECG recording. Peak values of HR (pHR), VO2 (pVO2), VCO2 (pVCO2), oxygen pulse (pOP), work rate (pWR), minute ventilation (pVE), and peak RQ (pRQ) were measured. Submaximal CPET parameters consist of ventilator anaerobic threshold (VAT) and submaximal slope parameters, including ΔVO2/ΔWR (efficiency of exercise metabolism), ΔHR/ΔWR (heart rate dependency), ΔVO2/ΔHR (stroke volume), oxygen uptake efficiency slope (OUES; a slope in a relationship between logarithm of VE and VO2) [10]. and ΔVE/ΔVCO2 (ventilatory efficiency). Submaximal CPET slopes represent a physiological trend of how exercise parameters change in response to the intermediate phase of programmed incremental exercise up to the anaerobic threshold (AT) (**Suppl. Figure 1**). All CPET parameters were presented as an absolute value. Peak VO2, VAT, ΔVO2/ΔHR, and ΔHR/ΔWR were also presented as relative values indexed by a body weight (*indicates that the values were indexed by body weight).

Statistics

Distribution of patients' demographics as well as peak and submaximal parameters were compared between PCS and control groups. Mean and standard deviation (SD) for continuous variables and count and percentage for categorical variables are reported. Two-sample t-test and Chi-square test were used to compare the mean and proportion, respectively, between two groups. Analysis of covariance (ANCOVA) was used to compare the regression lines between two groups. Model/test assumptions were checked before data analysis. All tests were two-tailed at the level of significance of 0.05. The statistical software R (version 3.5.2: R Core Team) was used for data analysis.

Results

Clinical Profile of PCS

Fifty-three PCS (26 male and 27 female) with various malignancies were studied (Table 1). The ages at diagnosis of malignant diseases and CPET were 6.4 ± 4.5 years and 14.5 ± 2.8 years, respectively. Total cumulated anthracycline dosage was 235 ± 102 [60 to 450] mg/m^2. Sixteen patients received radiation therapy: 7 chest/mediastinum, 3 flank/lumbar region, 2 total body irradiation, and 4 others. Echocardiogram revealed LVSF 33.9 ± 3.1%, LVEF 61.7 ± 5.8%, and left ventricular myocardial index (LVMI) 28.9 ± 6.9 (normal < 39). Sixty age-, sex-, and weight-matched control patients were selected.

Table 1
Pediatric Cancer Survivors

Diagnosis	N	Radiation
Leukemias		
ALL	17	4
AML	4	
Lymphomas		
Hodgkin's lymphoma	5	1
Non-Hodgkin's lymphoma	2	
Burkitt lymphoma	2	
B-cell lymphoma	1	
Solid tumors		
Wilms tumor	6	5
Neuroblastoma	4	2
Ewing's sarcoma	4	1
Hepatoblastoma	2	
Osteosarcoma	2	
Miscellaneous	4	
	53	14

ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia.

Assessment of Exercise Performance by CPET

Table 2 summarizes the demographic profile and results of CPET. Although weight and BMI were comparable between PCS and control groups, the height of PCS was significantly lower than controls. Peak HR was comparable between the two groups. Peak exercise parameters, pVO2, pOP, and pWR, were significantly lower in PCS than in controls. Peak RQ was significantly higher in PCS than in controls, but pVE was comparable. Pediatric cancer survivors showed significantly lower VAT, OUES, and ΔVO2/ΔHR than controls. However, the difference was not statistically significant when VAT and ΔVO2/ΔHR were indexed by weight. Heart rate dependency (ΔHR/ΔWR) was significantly higher in PCS than in controls in

both absolute and weight-indexed values. Exercise efficiency (ΔVO2/ΔWR) and ventilatory efficiency (ΔVE/ΔVCO2) were comparable between the two.

Table 2
Cardiopulmonary Exercise Testing

	PCS (n = 53)	Controls (n = 60)	*p* value
Age (years)	14.5 ± 2.8	14.7 ± 1.9	0.76
Sex (M : F)	M 26 : F 27	M 31 : F 29	0.93
Weight (kg)	55.5 ± 14.0	58.0 ± 13.4	0.27
Height (cm)	161 ± 14	166 ± 10	**0.033**
BMI (kg/m2)	21.3 ± 3.5	21.1 ± 3.4	0.71
Peak parameters			
HR (beat/min)	187 ± 10	186 ± 10	0.86
VO2 (L/min)	1.86 ± 0.53	2.23 ± 0.61	**0.002**
VO2* (ml/kg/min)	34.3 ± 8.5	38.8 ± 7.6	**0.005**
VCO2 (L/min)	2.29 ± 0.75	2.60 ± 0.69	**0.037**
OP (ml/beat)	10.0 ± 2.9	12.1 ± 3.4	**0.009**
WR (watts)	125 ± 45	154 ± 46	**0.0024**
VE (L/min)	70.8 ± 22.3	77.3 ± 22.9	0.18
RQ	1.23 ± 0.12	1.17 ± 0.08	**0.0006**
Submaximal parameters			
VAT (L/min)	1.20 ± 0.35	1.42 ± 0.43	**0.008**
VAT*(ml/kg/min)	22.3 ± 6.2	24.4 ± 6.9	0.084
OUES (Log_{10}[ml/min]/min)	1941 ± 525	2317 ± 598	**0.0007**
DVO2/DHR (ml/beat)	15.4 ± 5.2	17.8 ± 5.4	**0.016**
DVO2*/DHR (ml/beat/kg)	0.29 ± 0.09	0.32 ± 0.08	0.071
DHR/DWR	0.73 ± 0.29	0.61 ± 0.18	**0.004**
DHR/DWR*	38.8 ± 11.0	33.8 ± 8.8	**0.004**
DVO2/DWR	10.7 ± 2.6	10.5 ± 1.6	0.46
DVE/DVCO2	23.6 ± 2.6	24.2 ± 2.7	0.18

PCS: pediatric cancer survivors, BMI: body mass index, HR: heart rate, VO2: oxygen consumption, VCO2: carbon dioxide production, OP: oxygen pulse, WR: work rate, VE: minute ventilation, RQ: respiratory quotient, VAT: ventilatory anaerobic threshold, OUES: oxygen uptake efficiency slope

Body Mass and CPET Parameters

Relationships between the weight and exercise parameters in absolute CPET values were examined (Fig. 1). In controls, a strong positive relationship was demonstrated between weight and CPET parameters including pVO2 (r = 0.73), pWR (r = 0.74), and OUES (r = 0.59), suggesting exercise performance is proportional to body weight. In PCS, not only were the positive relationships weaker (r = 0.39 ~ 0.58), but each slope was more gradual than in controls, indicating that PCS group consisted of more diverse body composition and that the body weight in PCS did not contribute to the increase in CPET parameters as effectively as in controls. However, these differences did not reach the statistical significance.

Chronotropic Function and Stroke Volume Reserve

As shown in Table 1, ΔHR/ΔWR was significantly higher, and pOP and pVO2 were significantly lower in PCS than controls. With simultaneous presentation of ΔHR/ΔWR and pOP as well as ΔHR/ΔWR and pVO2, a combination of lower pOP or pVO2 and higher ΔHR/ΔWR was more prominent in PCS, suggesting that the increased HR dependency is more noticeable in PCS probably due to limited stroke volume reserve. The slopes of a correlation line of ΔHR/ΔWR-pOP and ΔHR/ΔWR-pVO2 were statistically significant between PCS and controls (Fig. 2).

Submaximal Exercise Parameters to Predict Peak Exercise Performance

An excellent correlation was demonstrated between submaximal parameters (VAT, OUES, and ΔVO2/ΔHR) and pVO2 with no significant difference between PCS and control groups, suggesting these submaximal parameters can reliably predict peak pVO2 equally in both groups (Fig. 3). However, the distribution is markedly different between PCS and controls on the almost identical correlation lines; PCS revealed lower values in both x- and y- axes, as also shown in Table 2. The data suggest that there is no difference in exercise persistence in a partially anaerobic condition up to peak exercise between PCS and controls but that overall exercise performance was significantly lower in PCS.

Ventilation and Peak Exercise Performance

Ventilatory efficiency in O2 uptake and CO2 elimination at the peak exercise were examined by the correlations of pVE-pVO2 and pVE-pVCO2, respectively, which demonstrated excellent positive linear correlations in both PCS and controls (Fig. 4). There was no statistically significant difference in the correlation lines between PCS and controls (p = 0.62 and 0.52 for pVE-pVO2 and pVE-pVCO2, respectively), suggesting no significant differences in ventilatory efficiency for O2 uptake or CO2 elimination.

Higher Peak RQ in PCS

Peak RQ (= pVCO2/pVO2) was significantly higher in PCS than in controls. Although both pVCO2 and pVO2 were significantly lower in PCS than in controls, higher pRQ in PCS may indicate disproportionally low pVO2 as an essential feature of PCS rather than excessive exercise effort or hyperventilation. When VAT* was plotted with pRQ, there was a negative correlation in both groups (Fig. 5A). Compared with controls, PCS had an extreme group with higher RQ and lower VAT*. Lower VAT* indicates earlier initiation of anaerobic metabolism. When PCS were divided into higher pRQ (≥ 1.3; n = 12) and lower pRQ (< 1.3; n = 41) subgroups (Fig. 5B), the higher pRQ group showed significantly lower pVO2*, VAT, and VAT* with higher ventilatory efficiency (lower ΔVE/ΔVCO2) than the lower pRQ group (Fig. 5C), suggesting that the higher RQ group in PCS is characterized by lower aerobic capacity and lower overall exercise performance with enhanced ventilator efficiency.

ΔVO2/ΔWR and Possible Cardiovascular Risk in PCS

A correlation between pWR and pVO2 was excellent in both PCS and controls, and the two correlation lines were almost identical (Fig. 6A). Although ΔVO2/ΔWR was comparable between PCS and controls (Table 1), PCS consisted of two outlier groups, including *a*) higher ΔVO2/ΔWR and relatively lower pVO2* (n = 4) and *b*) markedly lower ΔVO2/ΔWR and significantly low pVO2* (n = 4) compared with the rest (n = 45), as shown in Fig. 6B. The rest group of PCS nearly overlaps with controls. The presence of these two extreme groups indicates a diversity of PCS. Group *a* was characterized by comparable or slightly lower exercise performance than the rest but with significantly higher DHR/DWR* (HR dependency) and higher DVO2/DWR than the rest. On the other hand, group *b* showed significantly poorer overall exercise capacity and lower DVO2/DWR than the rest, suggesting intrinsically limited VO2 increase in response to exercise. These data suggest substantial heterogeneity regarding underlying pathology in exercise performance in PCS as a preclinical cardiovascular abnormality (Fig. 6C).

Discussion

Our current study demonstrated that asymptomatic PCS presented with significantly diminished exercise performance than controls despite normal global LV systolic function at rest and that the causes of their poor exercise performance are likely multifactorial. The simultaneous presentation of DHR/DWR and pOP indicated that PCS in general had higher dependency on HR increase than increase of OP at the peak exercise, suggesting primary limitation in stroke volume reserve. Peak RQ (= pVCO2/pVO2) was significantly higher in PCS than in controls, and a group of PCS with higher pRQ (≧1.3) revealed significantly lower pVO2* than PCS with lower pRQ (< 1.3), suggesting a limitation in aerobic capacity in some PCS. There were two small outlier groups of abnormal exercise performance in PCS with different underlying mechanisms. These findings represent the significant heterogeneity of abnormal cardiovascular presentation in PCS.

Decreased Exercise Performance in Asymptomatic PCS

Anthracycline-induced cardiotoxicity is a major cause of late cardiovascular complications in PCS that occur decades after the initial treatment [11]. Late-onset cardiotoxicity is insidious and nonspecific yet

progressive and irreversible [12]. Thus, early recognition of cardiotoxicity is essential to protect patients from developing symptomatic cardiomyopathy or advanced heart failure. Reliability of echocardiogram in predicting late cardiovascular complications is limited as normal myocardial status in younger ages may not be completely free from late cardiotoxicity [13] [14]. Indeed, treatment-mediated direct myocardial impairment may not be the only cause of long-term cardiovascular complications in PCS.

In this study, we demonstrated that peak exercise performance values including pVO2, pOP, and pWR were significantly lower in PCS than controls, in agreement with the previous published studies [6-9,15-18]. Two recent studies demonstrated no significant difference in parameters obtained by stress echocardiogram between PCS and age-matched controls at peak exercise [19,20], suggesting that markers of ventricular myocardial performance may not always be a sensitive marker of preclinical cardiovascular abnormality and that other peripheral factors, skeletal muscle alteration and/or vascular dysfunction, may also be contributing to a reduced exercise performance. Ness et al. studied 1041 adult survivors of childhood cancer and demonstrated high incidence of exercise intolerance (63.8%) due to a combination of cardiac, pulmonary, autonomic nervous system-mediated, and peripheral muscular impairment [21]. A similar trend has been presented in adult breast cancer survivors with preserved LVEF, in which impaired peripheral vascular function and skeletal muscle dysfunction were attributed to decreased pVO2 in addition to impaired cardiac function [22]. Worsening of exercise efficiency (high DVO2/DWR) may represent vascular dysfunction commonly seen in elderly people because of loss of vascular elasticity (vascular senescence) [23]. Premature aging either by DNA damage or telomerase shortening in the cardiovascular system is suggested as a cause of increased incidence of cardiovascular events in PCS [24].

Possible Mechanisms of Preclinical Cardiotoxicity Characterized by CPET

From our current study, we propose certain underlying mechanisms responsible for the poor exercise performance in PCS. First, reduced pOP in PCS was noted in combination with preferential increase in HR in PCS (**Figure 2**). A limited stroke volume reserve with higher dependency on HR increase was previously reported in a small group of asymptomatic PCS [25]. With an exercise MRI study, Foulkes et al. demonstrated that reduced peak exercise performance in PCS was associated with decreased stroke volume reserve and cardiac index [26]. A combination of low pVO2 and high pRQ was noted to have significantly higher mortality in adult patients with chronic heart failure [27], suggesting that an impaired VO2 increase is a fundamental abnormality in PCS. In contrast, relatively lower pRQ was noted during an intense exercise in well trained athletes than that in sedentary controls [28]. Collectively, a reduced peak oxygen delivery/consumption is a central pathophysiology in PCS regardless of identifiable global ventricular dysfunction, underscoring the critical importance of CPET in risk-stratifying asymptomatic PCS.

Second, there may be a difference in the composition of metabolically active skeletal muscle mass between PCS and controls, as shown in **Figure 1**, although we were not able to demonstrate statistical significance. Sarcopenia and skeletal muscle dysfunction are known complications after cancer

treatment [29,30]. A difference in capillary density and mitochondria concentration within the myocytes can also affect oxygen utilization at a tissue level [31]. Repetitive skeletal muscle contraction is also known to augment venous return and thus cardiac output (muscle pump). It is plausible that PCS are more prone to inactive lifestyle responsible for physical deconditioning [32]. Altered peripheral oxygen utilization may contribute to poor exercise performance despite normal ventricular systolic function in some PCS.

Lastly, there were small subgroups of outliers of high DVO2/DWR and low DVO2/DWR (group *a* and *b* in **Figure 6B**, respectively). High DVO2/DWR implies a high oxygen cost to perform external work, commonly seen in obesity, use of additional muscles, or recruitment of less efficient muscle fibers [33]. These people showed comparable exercise performance with the rest but had decreased peak WR and significantly increased HR dependency similar to group *b*. A combination of low DVO2/DWR and low pVO2 indicates decreased cardiac output frequently seen in patients with chronic heart failure [34] and should be regarded as a high-risk group. Although obese subjects were not included in this study, it is plausible that some PCS with decreased skeletal muscle mass and presumably increased body fat present with elevated DVO2/DWR.

Application of Simultaneous Assessment by Two CPET Parameters

We have characterized a new method of assessing CPET data by combining peak and submaximal parameters (including weight) simultaneously to compare the trends of two groups (“Two-dimensional CPET Analysis”). These submaximal parameters are useful and informative but have been underutilized in conventional pediatric CPET analysis.

A simultaneous assessment of DHR/DWR and pOP (= a surrogate of stroke volume at peak exercise) or pVO2 showed not only a good inverse relationship between the two parameters but also demonstrated a clear difference between PCS and controls (**Figure 2**). Submaximal parameters, VAT, OUES, and DVO2/DHR, were plotted with pVO2 in both groups, which showed an excellent positive correlation with almost identical correlation lines, suggesting that these submaximal parameters are reliable markers to predict peak exercise performance in both groups (**Figure 3**). Two-dimensional analyses by DVO2/DWR and pVO2* further identified two distinctive outliers in PCS: one with probably inefficient peripheral energy production (group *a*) and the other with limited ventricular myocardial reserve with lower aerobic capacity (group *b*) (**Figure 6**). The two-dimensional CPET correlation analysis is easy to perform even retrospectively from any existing standard exercise worksheet and provides substantial additional information to interpret baseline exercise physiology without extra investment [35].

Limitations

There are several limitations in our study that need to be addressed. This is a retrospective study with a relatively small sample size in a single center. The PCS group represents a heterogeneous population regarding primary diagnosis, cumulated dosage of anthracycline, years at diagnosis, years after remission, body habitus, and the level of baseline physical activities. Notably, physical conditioning was

not specifically addressed in either group. Skeletal muscle mass was not directly measured, which could affect the interpretation of CPET results. There may be a selection bias as PCS included in this study were those who were willing undergo CPET for functional assessment of their exercise performance. We also excluded the obese PCS from the study primarily to optimize the CPET interpretation as obesity may be an important pathological feature in PCS. Despite these limitations, our current study clearly underscores the primary involvement of the reduced stroke volume with heterogenous abnormalities other than direct myocardial impairment in otherwise asymptomatic PCS.

Conclusions

Early recognition and management of preclinical cardiac dysfunction is critical in optimizing survival and improving quality of life of PCS [3, 36, 37]. Our study indicates that multiple factors are involved in decreased exercise performance in PCS. Long-term cardiovascular complications for PCS not only pertain to direct myocardial dysfunction and heart failure but also include increased incidence of coronary artery disease, stroke, and variable vascular diseases [38]. In this regard, CPET is an important surveillance tool in risk-stratifying future cardiovascular complications in PCS. Regular exercise is proven to be beneficial in attenuating progression of anthracycline-induced cardiotoxicity in both human and animal studies [39, 40]. The decrease in exercise performance without myocardial dysfunction may still imply increased future cardiovascular risk. Whether these CPET abnormalities during pediatric ages predict serious cardiovascular complications in an adulthood decades after the completion of cancer treatment is to be investigated. .

Declarations

Acknowledgement

We thank the Nemours Summer Student Research Program offered by Nemours Children’s Hospital Delaware, Wilmington, DE (for A. G.). Authors thank Ms. Theresa Michel for editing the manuscript text.

Author Contribution

Takeshi Tsuda primarily conceptualized and designed the study and organized the research team. Material preparation, data collection, and analysis of cardiopulmonary exercise testing (CPET) were performed by Takeshi Tsuda, Daphney Kernizan, Austin Glass, and Gina D'Aloisio. Jobayer Hossain is a biostatistician who carefully analyzed the entire data and provided critical suggestions regarding statistics. Joanne Quillen is in charge of Oncology Survivorship Program who provided the patients' medical information regarding diagnosis and treatment of primary disease and their current clinical status. The first draft of the manuscript was written by Takeshi Tsuda, and all authors commented on the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

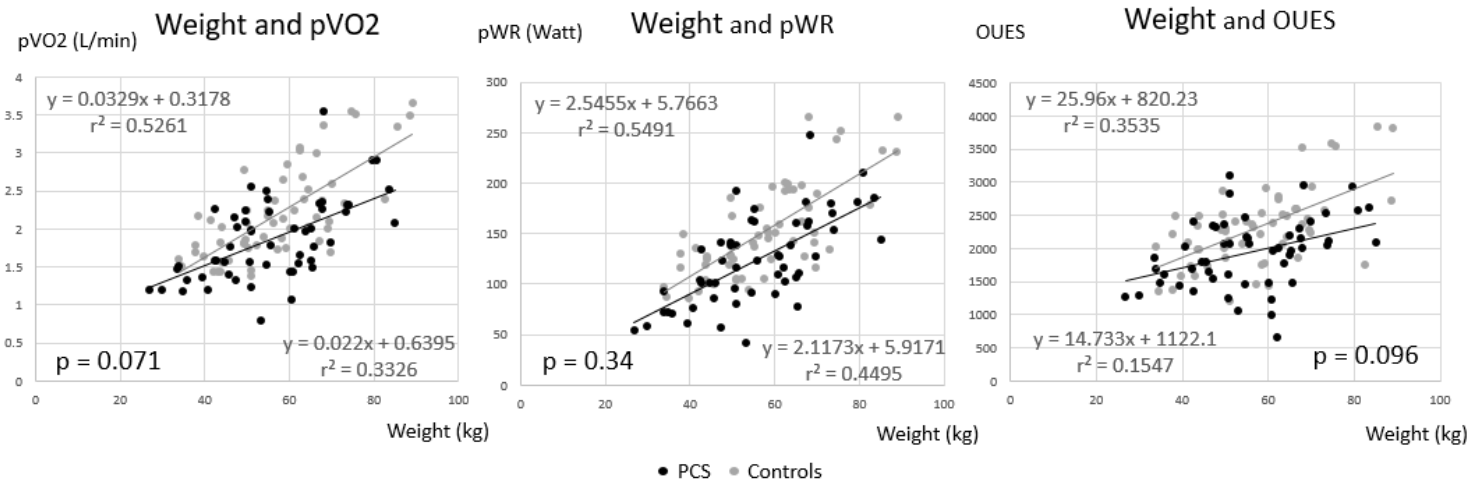


Figure 1

Body mass effects.

Correlations between weight (kg) and exercise parameters, including peak oxygen consumption (pVO2) (L/min), peak work rate (pWR) (watt), and oxygen uptake efficiency slope (OUES) (ml/Log_{10}[L/min]) in pediatric cancer survivors (PCS) and controls. Closed black circle and closed gray circle indicate PCS and controls, respectively.

Figure 2 Heart Rate Response and Stroke Volume Reserve

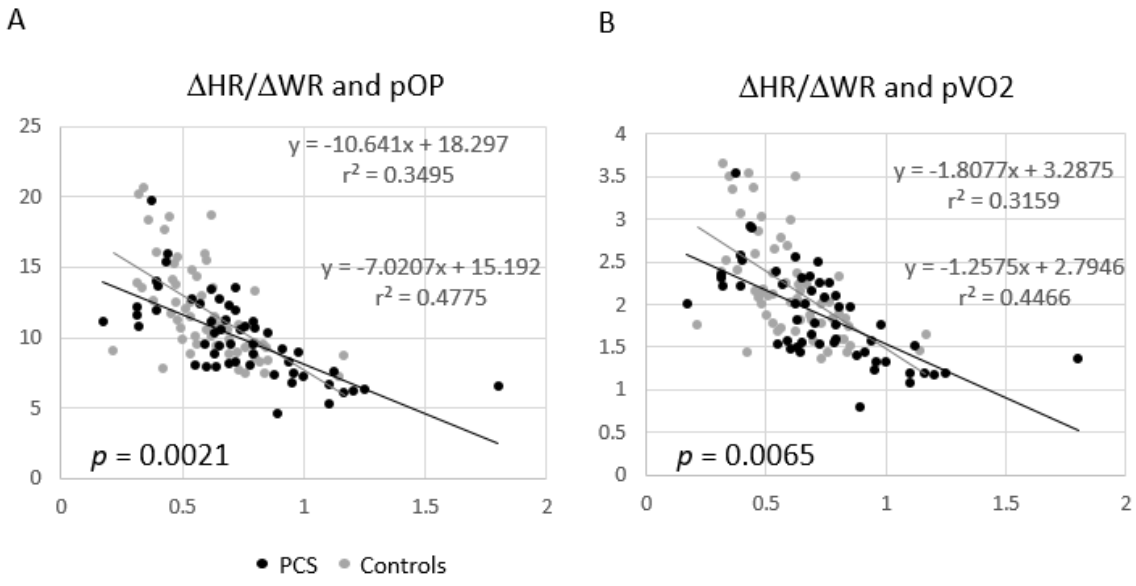


Figure 2

Stroke volume reserve and heart rate dependency.

DHR/DWR and pOP (**A**) and DHR/DWR and pVO2 (**B**) were simultaneously plotted to assess the overall trend as to how subjects responded to exercise. Controls tended to show higher pOP and pVO2 with lower DHR/DWR compared with PCS, suggesting that PCS may have limited stroke volume increase compared with controls. HR: heart rate, WR: work rate.

Figure 3

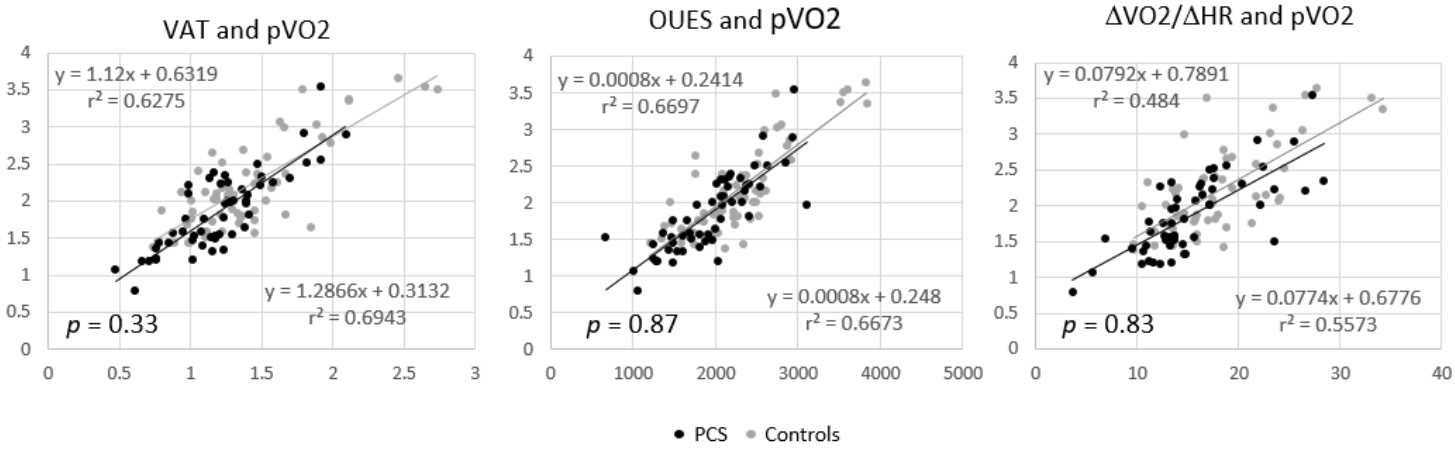


Figure 3

Submaximal and peak CPET values.

The correlations between submaximal exercise parameters including ventilatory anaerobic threshold (VAT), oxygen uptake efficiency slope (OUES) and a slope of oxygen consumption (VO2)/heart rate (HR) (DVO2/DHR), and pVO2. Note excellent correlations between submaximal parameters and pVO2 in both pediatric cancer survivors (PCS) and controls. The correlation lines are almost identical in both groups, suggesting submaximal parameters predict peak exercise performance equally in both groups.

Figure 4

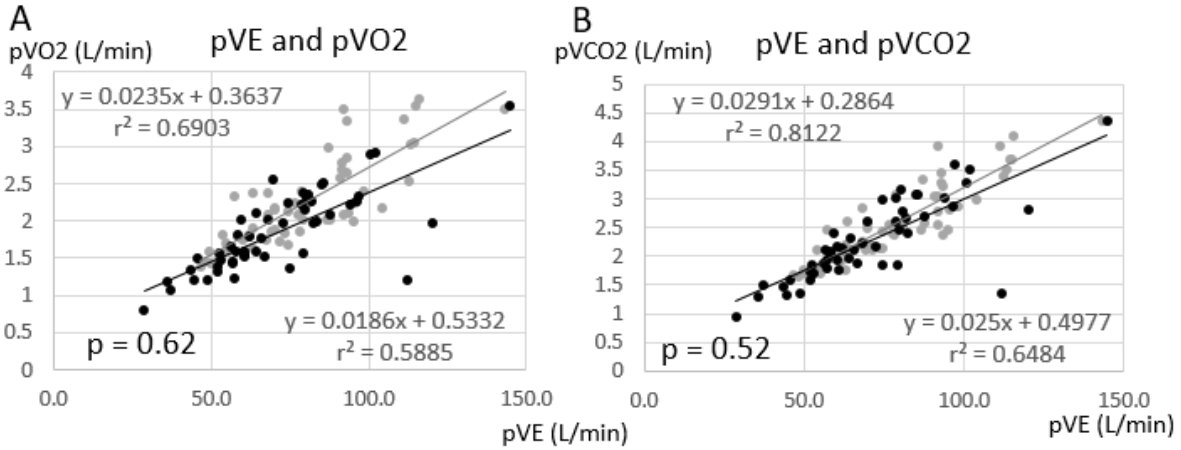


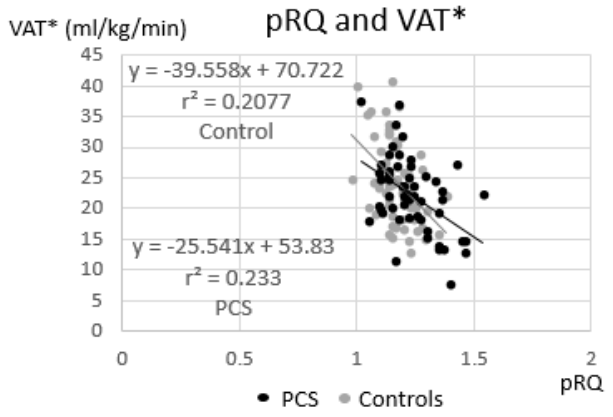
Figure 4

Ventilatory effort and peak gas exchange

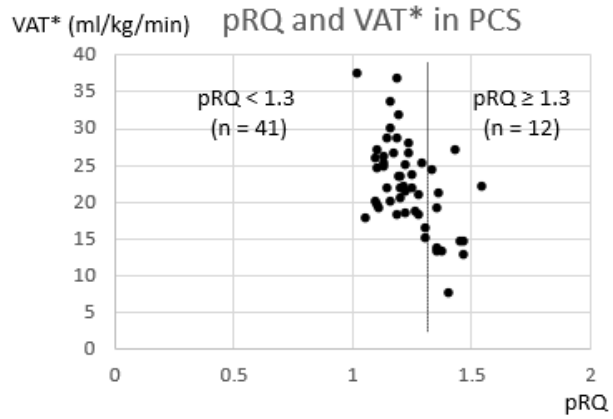
Peak minute ventilation (pVE) was plotted with peak oxygen consumption (pVO2) (**A**) and peak carbon dioxide production (pVCO2) (**B**). There was no significant difference between PCS and controls.

Figure 5

A



B



C

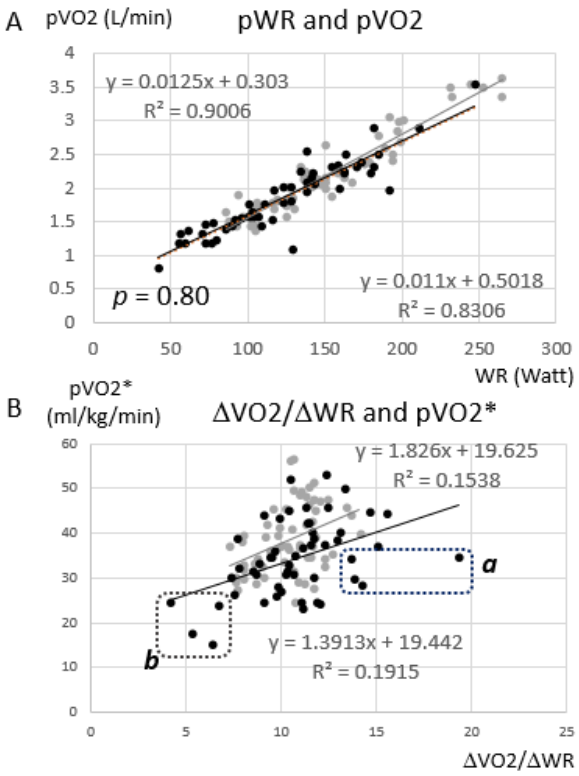
	pRQ < 1.3	pRQ ≥ 1.3	*p* value
Number	41	12	
pRQ	1.18 ± 0.07	1.40 ± 0.06	
Anthracycline dosage (mg)	219 ± 97	244 ± 102	0.46
Age at diagnosis	8.2 ± 5.6	5.9 ± 4.1	0.12
Age at CPET	**13.9 ± 2.6**	**16.3 ± 2.6**	**0.007**
Male (%)	46	50	0.95
Radiation (%)	27	25	0.65
pVO2 (L/min)	1.89 ± 0.56	1.77 ± 0.49	0.52
pVO2* (ml/kg/min)	**35.8 ± 8.4**	**29.6 ± 7.6**	**0.026**
VAT (L/min)	**1.25 ± 0.33**	**0.99 ± 0.31**	**0.02**
VAT* (ml/kg/min)	**23.9 ± 5.6**	**17.1 ± 5.7**	**0.0006**
pVE	69.7 ± 22.3	73.9 ± 23.5	0.59
ΔVE/ΔVCO2	**24.1 ± 2.3**	**22.1 ± 2.4**	**0.01**

Figure 5

Relationship between pRQ and VAT*.

A: Peak respiratory quotient (pRQ) was plotted with ventilatory anaerobic threshold (VAT*) (ml/kg/min) in PCS and controls, where pRQ and VAT* revealed inverse correlations. **B:** Subgrouped PCS into low pRQ (< 1.3) and high pRQ (≧ 1.3). **C**: High pRQ group (≧ 1.3) presented with significantly lower pVO2*, VAT, and VAT* than low pRQ groups. Closed black circle and closed gray circle indicate PCS and controls, respectively.

Figure 6



C

	Group *a* (n = 4)	Group *b* (n = 4)	The Rest (n = 45)
Age at CPET (years)	13.5 ± 1.9	**16.5 ± 1.7†**	14.5 ± 2.9
Wt (kg)	50.0 ± 11.7	59.2 ± 4.2	56.2 ± 14.9
Ht (cm)	**157 ± 11.7†**	164 ± 4	161 ± 15
ATX dosage (mg/m2)	260 ± 49	204 ± 115	234 ± 106
Rest HR	80 ± 4	94 ± 19	83 ± 15
Peak HR	188 ± 18	190 ± 14	187 ± 10
pVO2* (ml/kg/min)	30.8 ± 6.2	**20.8 ± 5.2† #**	35.6 ± 7.9
pWR* (Watt/kg)	1.8 ± 0.4	**1.6 ± 0.6†**	2.3 ± 0.5
pVE (L/min)	74.1 ± 20.0	**44.8 ± 14.1† #**	73.2 ± 21.9
pRQ	1.38 ± 0.10	1.26 ± 0.13	1.22 ± 0.11
VAT* (mi/kg/min)	17.8 ± 3.6	**13.8 ± 6.1†**	23.3 ± 5.8
OUES*	40.5 ± 7.6	**22.2 ± 6.8† #**	36.6 ± 10.0
ΔVO2/ΔWR	**15.2 ± 2.8†**	**6.4 ± 0.9† #**	10.9 ± 2.3
ΔVE/ΔVCO2	23.7 ± 2.6	24.6 ± 2.8	23.4 ± 2.5
ΔHR/ΔWR*	**51.2 ± 15.4†**	49.0 ± 12.3	36.2 ± 10.0

● PCS
● Controls

Figure 6

Exercise efficiency (DVO2/DWR) and CPET parameters.

A: Correlation between peak work rate (pWR) and peak oxygen consumption (pVO2) showed strong positive linear regression in both PCS and controls. **B**: DVO2/DWR was plotted with peak VO2* (ml/kg/min) in both PCS and controls. **C**: The comparison of three subgroups of PCS. See text for details. †: $p < 0.05$ compared with the rest, #: $p < 0.05$ compared with group *a*.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplFig12102022.pptx