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Validation of 2 Submaximal Cardiorespiratory Fitness Tests in Patients With Breast Cancer Undergoing Chemotherapy

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Background: Patients with breast cancer have an impaired cardiorespiratory fitness, in part, due to the toxic effects of anticancer therapy. Physical exercise as a means of rehabilitation for patients with cancer is an emerging area of research and treatment, emphasizing the need for accurate and feasible physical capacity measurements. The purpose of this study was to evaluate the validity of peak oxygen consumption ($\dot{V}O_{2peak}$) predicted by the Ekblom-Bak test (E-B) and the Åstrand-Rhyming prediction model (A-R). **Methods:** Eight patients with breast cancer undergoing chemotherapy participated in the study. Submaximal exercise tests were performed at 2 different submaximal workloads. Estimated $\dot{V}O_{2peak}$ values were obtained by inserting the heart rate (HR) from the 2 workloads into the E-B prediction model and the HR of only the higher workload into the Åstrand nomogram. A 20-W incremental cycle test-to-peak effort was performed to obtain $\dot{V}O_{2peak}$ values. **Results:** Results from A-R overestimated $\dot{V}O_{2peak}$ by 6% (coefficient of variation = 7%), whereas results from E-B overestimated $\dot{V}O_{2peak}$ with 42% (coefficient of variation = 21%) compared with measured $\dot{V}O_{2peak}$. Pearson's correlation coefficient revealed a significant strong relationship between the estimated $\dot{V}O_{2peak}$ from A-R and the measured $\dot{V}O_{2peak}$ ($r = 0.86$; $P < .05$), whereas the relationship between the estimated $\dot{V}O_{2peak}$ from E-B and the measured $\dot{V}O_{2peak}$ resulted in a nonsignificant weak correlation ($r = 0.21$). **Conclusion:** In a situation where maximal exercise testing is not practical or undesirable from a patient safety perspective, submaximal exercise testing provides an alternative way of estimating $\dot{V}O_{2peak}$. The A-R prediction model appears to be a valid submaximal exercise test for determining cardiorespiratory fitness in this population. (*Rehab Oncol* 2016;00:1–7) **Key words:** Åstrand-Rhyming prediction model, cancer rehabilitation, Ekblom-Bak test, heart rate

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In both disease management and rehabilitation settings, the use of cardiopulmonary exercise testing is becoming increasingly important.^{1,2} Patients with breast cancer have considerable impairments in cardiorespiratory fitness (CRF) that, in part, have been linked to the toxic effects of anticancer therapy,³ which reduces peak oxygen consumption ($\dot{V}O_{2peak}$) by 6% to 10% relative to healthy individuals.⁴⁻⁶ The resulting poor CRF has direct consequences on quality of life since performance of daily activities is adversely affected.^{2,7,8} In addition, overall mortality and breast cancer–specific mortality have been linked to CRF in breast cancer survivors.³

With an increasing longevity in breast cancer survivors, long-term cardiac toxicity in combination with inactivity and weight gain contributes to an elevated risk of cardiovascular disease (CVD).⁹ Recently, the elevated risk of CVD in women with early-stage breast cancer has been recognized as a comorbid condition that poses a higher risk than breast cancer as a primary cause of death.^{2-5,10,11} Besides inducing cardiotoxicity, chemotherapy induces menopause in two-thirds of patients with breast cancer, implying a further risk for CVD.⁵ In addition to the increased risk of CVD, breast cancer survivors suffer from symptoms such as fatigue and joint pain.⁷

Physical exercise as a means of improving CRF and symptoms for patients with cancer during and after chemotherapy is an emerging area of research and clinical interest. Exercise is a safe, well-tolerated intervention for patients with curative cancer, both during and after adjuvant therapy.¹² In patients with cancer, physical exercise has recently been found to act as a cornerstone in improving general quality of life as well as specifically improving physical function such as CRF, strength, and relieving joint pain.^{2,7,9,13} Results from CRF testing have become a potent predictor of all-cause mortality in a variety of populations,^{1,4,8,14} emphasizing the need for accurate and feasible assessment of CRF and physical capacity, both during activity treatment and after treatment have been completed.

One of the most important indicators of physiological fitness is CRF/aerobic fitness.¹⁵ The “gold standard” for measuring aerobic fitness is laboratory-based incremental exercise testing procedures involving large muscle groups and analysis of expired gases, which allows for the determination of both submaximal oxygen consumption and $\dot{V}O_{2peak}$.¹⁶ To directly measure $\dot{V}O_{2peak}$, a maximal effort from the subject is required, which is associated with a certain risk in unhealthy populations. Several valid equations are available that are used to estimate $\dot{V}O_{2peak}$ on the basis of the results of submaximal testing,¹⁷ and unlike performing a $\dot{V}O_{2peak}$ test, such tests are relatively simple to perform and do not require a maximal effort or advanced equipment in a laboratory setting.^{13,17} CRF is not routinely measured at any stage of breast cancer treatment⁴; however, knowledge of a patient’s CRF can assist clinicians in accurately and correctly writing an exercise prescription. Health care professionals need access to physical fitness tests that are valid and simple to administer.¹³ One test that fulfills these requirements is the Åstrand-Rhyming test, which was the first and is the most commonly used and validated submaximal cycle ergometry test to date.¹⁸ Through the Åstrand-Rhyming prediction model (A-R), an estimation of $\dot{V}O_{2peak}$ can be made using the heart rate (HR) achieved at steady state, submaximal exercise.¹⁹ An age correction factor was later incorporated by Åstrand²⁰ to account for the decrease in maximal HR with age, leading to a higher prediction accuracy of $\dot{V}O_{2peak}$. Studies that have evaluated the validity of the Åstrand-Rhyming test are however contradictory, where both underestimation and overestimation of $\dot{V}O_{2peak}$ have been reported,

with predictive validity coefficients ranging from 0.65 to 0.80.¹⁷ The most recently developed submaximal prediction model is the Ekblom-Bak cycle test (E-B).²¹ The E-B has been shown to estimate $\dot{V}O_{2peak}$ by using heart rate difference (ΔHR) between a lower workload and an individually chosen higher workload. The reason for implementing ΔHR is to diminish sources of error such as nervousness, emotions, and intraindividual variability of $\dot{V}O_2$ at a given work rate. The E-B prediction model has been shown to predict $\dot{V}O_{2peak}$ with greater accuracy than the A-R prediction model in a healthy mixed population.²¹

Despite an increasing demand for clinically convenient and valid tests, to date, there is no submaximal exercise test for CRF assessment that has been validated in patients with breast cancer during or after chemotherapy. Therefore, the purpose of this study was to evaluate the validity of A-R and E-B for estimating $\dot{V}O_{2peak}$ in a population of patients with breast cancer during chemotherapy.

MATERIALS AND METHODS

Participants

Eight patients from the Department of Oncology Breast and Sarcoma units at Radiumhemmet and Södersjukhuset, Karolinska University Hospital in Sweden with breast cancer stage I-IIIa undergoing chemotherapy treatment (mean \pm SD body mass, height, body mass index, and age: 69.1 \pm 1.0 kg, 1.65 \pm 0.08 m, 25.7 \pm 5.5 kg/m², and 50 \pm 10 years [range, 35-64 years], respectively) were asked to participate in the study. The patients were concurrently enrolled in a randomized controlled exercise intervention trial (OptiTrain). The patients underwent 6 treatments of chemotherapy over the course of 15 weeks. The type of therapeutic drugs received is shown in Table 1. The maximal and submaximal tests described later were performed 3 weeks after the third treatment. All tests were performed at the same phase during treatment. This time point was selected to avoid side effects usually experienced during the first week after having started chemotherapy and further to reduce any acute effects on HR response from cortisone taken in combination with the anticancer drugs. Health status was determined by a physician. All subjects approached (n = 8) agreed to participate and passed the physical examination. A baseline electrocardiogram was obtained prior to start of chemotherapy treatment. A comprehensive medical history questionnaire

TABLE 1
Chemotherapy Treatment Types of the Participants

Chemotherapy Drugs	n (%)
FEC ^a	4 (50.0)
FEC + DOC ^b	1 (12.5)
DEC ^c	3 (37.5)

^aFluorouracil, epirubicin, and cyclophosphamide.

^bCombination of FEC and docetaxel.

^cDocetaxel, epirubicin, and cyclophosphamide.

was also completed by all participants. Inclusion criteria included Swedish-speaking women, 18 to 70 years old, with breast cancer stage I-IIIa. Women were excluded if they had advanced disease, cardiac pathologies, major psychiatric disorders, brain or bone metastases, or other concurrent malignant diseases. Ethical approval was obtained from the Regional Ethical Review Board in Stockholm (Dnr 2012/1347-31/1), and the subjects gave written informed consent prior to enrolment.

Test Procedure

The patients were asked to refrain from eating, drinking caffeinated drinks, or smoking during a 2-hour period prior to the tests. All tests were performed on a calibrated cycle ergometer (model 839E; Monark, Varberg, Sweden) in a laboratory environment with normal ambient conditions. After individual adjustments of seat and handlebar, the Borg 6-20 RPE (rating of perceived exertion) scale²² was introduced to the participants.

The E-B prediction model consisted of cycling at 2 submaximal workloads, 4 minutes at each load, with no rest in between at a pedal frequency of 60 rpm. The first workload (30 W) was followed by a higher individually chosen submaximal workload (90 or 120 W) to obtain an RPE of approximately 14 on the Borg scale at the end of the second workload. Mean measured HR during the last minute was recorded at each workload. The test leader did not provide any verbal encouragement and used a standardized instruction for each test. Estimated $\dot{V}O_{2peak}$ values from E-B were obtained by entering HR values from both workloads in an online spreadsheet developed by Ekblom-Bak et al.²¹ Since A-R is based on pedaling at a single submaximal load until HR has reached steady state, estimated $\dot{V}O_{2peak}$ values from A-R were obtained by applying the work rate and HR of the higher workload from E-B to the Åstrand nomogram and associated age correction factors. It was verified that the HR was within the valid range of A-R (120-170 bpm) to carry out the calculation.

Following E-B, the graded exercise test to maximal exhaustion was initiated after 10-minutes rest. The subject pedaled at an individually predetermined workload, which was increased by 20 W every minute until maximal effort was achieved. Verbal encouragement was given during the graded exercise test. Oxygen uptake was measured with a metabolic cart with a mixing chamber (OxyconPro; Jaeger GmbH, Hoechberg, Germany), calibrated prior to each test according to the manufacturer's instructions, with high-grade calibration gases (AirLiquide, Sweden). The metabolic cart was validated prior to the test by comparative in-series measurements using OxyconPro and Douglas bags analyzed separately. No significant deviation was found. Respiratory variables were averaged every 10 seconds. The highest averaged 60 seconds of recorded $\dot{V}O_2$ was taken as $\dot{V}O_{2peak}$. HR was monitored during the exercise test with a Polar Electro heart rate monitor (Kempele, Finland).

Statistical Analyses

Results are presented as mean \pm SD. All data were initially assessed for normal distribution using the Shapiro-Wilk normality test and quantile-quantile (QQ) plots. Data were normally distributed, and no outliers were found through assessment of Cook's distance. For comparison between measured and predicted oxygen uptake tests, the repeated-measures analysis of variance (RM-ANOVA) was performed. Post hoc comparisons were conducted with the Bonferroni correction for multiple comparisons. Equal variance of the differences between the sets of measurements was evaluated by Mauchly's test to assess sphericity, and the Greenhouse-Geisser ϵ correction was used to adjust the degrees of freedom when the assumption of sphericity was not satisfied. Pearson's coefficient of correlation (r) with a corresponding 95% confidence interval (CI) was used to evaluate the association between estimated and measured $\dot{V}O_{2peak}$. Coefficient of variation (CV) was used to measure the degree of variation between measured and predicted $\dot{V}O_{2peak}$. It was calculated as the ratio between the standard deviation of the difference between estimated and measured $\dot{V}O_{2peak}$ and the mean measured $\dot{V}O_{2peak}$. The Bland-Altman method²³ was used to illustrate the means and differences in oxygen uptake estimates of E-B and A-R for each subject, and a linear regression analysis was subsequently used to establish whether there was a significant systematic bias between test measurements. A standardized mean bias was calculated by dividing the mean bias by the SD of the criterion measure (measured $\dot{V}O_{2peak}$) and was interpreted according to Hopkin's modified Cohen scale²⁴ (<0.2 = trivial; 0.2-0.6 = small; 0.6-1.2 = moderate; 1.2-2.0 = large; >2 = very large). A 2-tailed $P < .05$ was considered significant. Statistical analyses were carried out using SPSS statistical software (version 22; SPSS Inc, Chicago, Illinois).

Sample Size

To determine the sample size, an online power calculation spreadsheet was used.²⁵ For the current power calculation, a correlation of 0.9 was used on the basis of previous findings.²¹ Assuming type 1 and type 2 errors of 5% and 20%, respectively, this resulted in a sample size of 7 participants. To ensure statistical power and allow for adjustment for outliers, 8 patients were included.

RESULTS

All participants ($N = 8$) completed the submaximal and maximal oxygen consumption tests without any adverse events.

Criteria for reaching $\dot{V}O_{2peak}$

According to end criteria for reaching maximal oxygen uptake,^{26,27} all participants reached their $\dot{V}O_{2peak}$. The mean Respiratory exchange ratio (RER) was 1.31 ± 0.11 (range, 1.11-1.45) measured during the last 30-second stage of the $\dot{V}O_{2peak}$ test. All participants also

TABLE 2

Physiological Variables From the Submaximal and Maximal Exercise Tests^a

HR (bpm) 30 W (n = 8)	HR (bpm) 90 W (n = 6)	Δ HR (bpm) ^b	HR (bpm) 120 W (n = 2)	Δ HR (bpm) ^c	Measured $\dot{V}O_{2peak}$ (L/min) (n = 8)	Estimated $\dot{V}O_{2peak}$ From A-R (L/min) (n = 8)	Estimated $\dot{V}O_{2peak}$ From E-B (L/min) (n = 8)
114 ± 15	146 ± 14	34 ± 7	160 ± 11	40 ± 6	1.90 ± 0.22	2.01 ± 0.24	2.69 ± 0.38

Abbreviations: A-R, Åstrand-Rhyming prediction model; E-B, Ekblom-Bak prediction model; HR, heart rate; $\dot{V}O_{2peak}$, peak oxygen consumption.

^aValues are mean ± SD.

^bDifference in HR between standard and higher workload for patients cycling at 90 W.

^cDifference in HR between standard and higher workload for patients cycling at 120 W.

exhibited an increase in ventilation while the O₂ uptake remained constant and a plateau in O₂ consumption was achieved. Maximal HR was 97% to 116% of age-predicted HR_{max} (220-age).

Validity Analyses

The mean values for measured and estimated $\dot{V}O_{2peak}$ from A-R and E-B were 1.90 ± 0.22 L/min, 2.01 ± 0.24 L/min, and 2.69 ± 0.38 L/min, respectively. Results from A-R overestimated $\dot{V}O_{2peak}$ by 0.11 L/min (6%) with a CV of 7%, whereas results from E-B overestimated $\dot{V}O_{2peak}$ by 0.79 L/min (42%) with a CV of 21% compared with the measured $\dot{V}O_{2peak}$. When the estimated $\dot{V}O_{2peak}$ was normalized to body mass (mL O₂ kg⁻¹·min⁻¹), CV was 1% higher than in the absolute term for A-R (CV = 8%). In contrast, the estimated $\dot{V}O_{2peak}$ from E-B was 3% lower (CV = 18%). RM-ANOVA showed no significant difference between the measured and estimated $\dot{V}O_{2peak}$ from A-R, *F*(2, 14) (mean difference = 0.11 L/min; 95% CI for the mean difference = -0.01 to 0.22) but revealed a significant difference between the measured and estimated $\dot{V}O_{2peak}$ from E-B, *F*(2, 28) (mean difference = 0.79 L/min; 95% CI for the mean difference = 0.46-1.12; *P* < .05).

HR levels at the low standard workload (30 W) and at the higher average workloads (90 and 120 W)

together with oxygen consumption data are presented in Table 2.

Pearson’s correlation coefficient showed a significant strong relationship between the estimated $\dot{V}O_{2peak}$ from A-R and the measured $\dot{V}O_{2peak}$ with *r* = 0.86 (95% CI = 0.40-0.97; *P* < .05), whereas the relationship between the estimated $\dot{V}O_{2peak}$ from E-B and the measured $\dot{V}O_{2peak}$ resulted in a nonsignificant weak correlation with *r* = 0.21 (95% CI = -0.58 to 0.80) (Figure 1).

The Bland-Altman plot showing the level of agreement between the measured $\dot{V}O_{2peak}$ and the predicted $\dot{V}O_{2peak}$ is presented in Figure 2. No significant systematic bias was found for A-R or E-B. The mean bias between the estimated $\dot{V}O_{2peak}$ for A-R and the measured $\dot{V}O_{2peak}$ was 0.11 L/min, and the 95% limits of agreement ranged from -0.13 to 0.36 L/min. The mean bias between the estimated $\dot{V}O_{2peak}$ for E-B and the measured $\dot{V}O_{2peak}$ was 0.79 L/min, and the 95% limits of agreement ranged from 0.01 to 1.57 L/min. The standardized mean bias for A-R was small (0.56), whereas it was very large for E-B (3.53).

DISCUSSION

The predicted $\dot{V}O_{2peak}$ obtained from A-R had a strong positive correlation with the measured $\dot{V}O_{2peak}$ and resulted in a low CV, whereas the estimated $\dot{V}O_{2peak}$ from

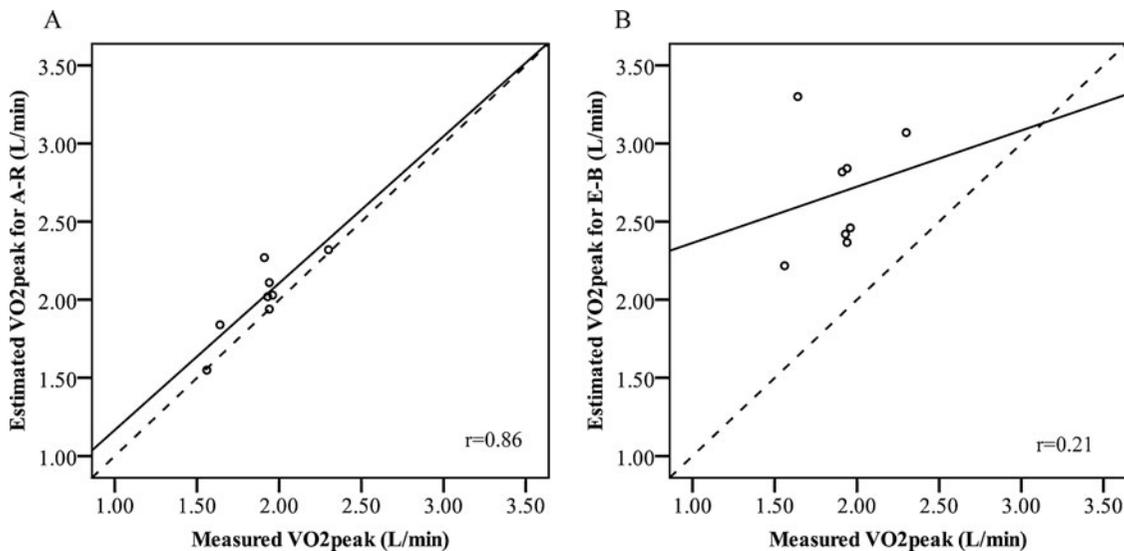


Fig. 1. Correlations between the measured versus estimated $\dot{V}O_{2peak}$ for (A) the Åstrand-Rhyming prediction model and (B) the Ekblom-Bak prediction model. The line of identity is shown as a dotted line. $\dot{V}O_{2peak}$ indicates peak oxygen consumption.

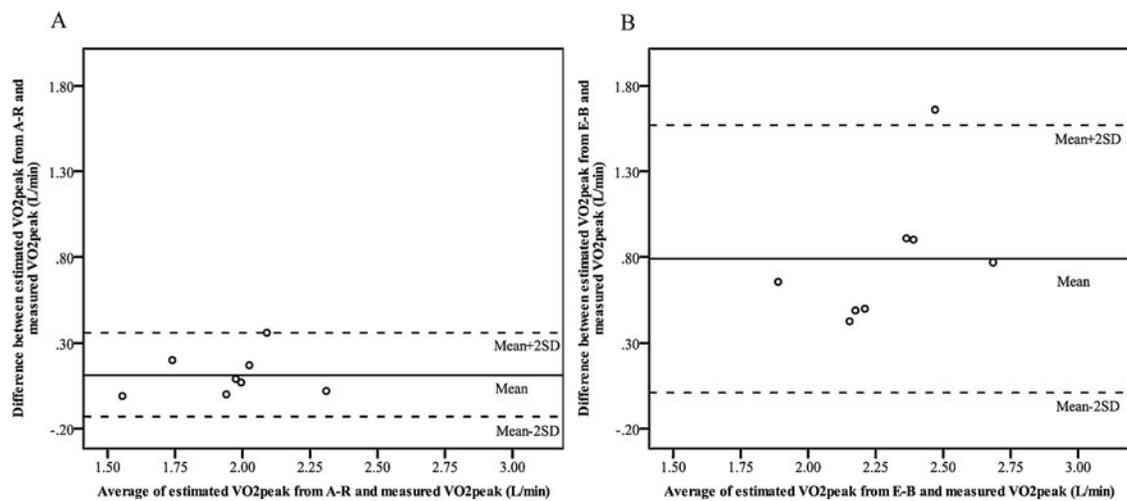


Fig. 2. Bland-Altman plot of the measured compared with predicted $\dot{V}O_{2peak}$ for (A) the Åstrand-Rhyming prediction model and (B) the Ekblom-Bak prediction model. The solid line within the graph represents the bias, and the dotted lines represent the upper and lower 95% limits of agreement. $\dot{V}O_{2peak}$ indicates peak oxygen consumption.

E-B was found to be weakly correlated with measured $\dot{V}O_{2peak}$, leading to a substantial overestimation of $\dot{V}O_{2peak}$. The main difference between the Ekblom-Bak test and the Åstrand-Rhyming test is the use of ΔHR in E-B and HR from a single higher submaximal workload used in A-R.

An overestimation of E-B was previously reported in the female population in the validation study by Ekblom-Bak et al.²¹ However, this overestimation had a CV of only 10.3%. Previous studies have also reported that A-R overestimates $\dot{V}O_{2peak}$ in females.²⁸⁻³² In the present study, the correlation coefficient of $r = 0.86$ for A-R reveals a stronger relationship with the measured $\dot{V}O_{2peak}$ than Åstrand's²⁰ own validation reports of $r = 0.78$. Since A-R incorporates the use of predicted maximal HR or the age correction factor, an over- or underestimation of $\dot{V}O_{2peak}$ is common depending on age. It has been suggested that maximal HR may be lower during chemotherapy than at the commonly used age-predicted formula $220 - \text{age}$,³³ which might explain the slight overestimation of $\dot{V}O_{2peak}$ by A-R; however, our results revealed that maximal HR was higher than age-predicted maximal HR in 7 of 8 patients, which contradicts findings by Drouin et al.³³

The E-B model has been shown to correlate very well ($r = 0.91$) with measured $\dot{V}O_{2peak}$ in a healthy population.²¹ The weak correlation found in our study suggests that HR is affected in this patient group, mainly at the low standard workload. Mean HR is substantially higher in the subjects of the current study than mean HR values from the validation study carried out by Ekblom-Bak et al.²¹ The difference in mean HR between the studies was 32 bpm at the low workload and only 12 bpm at the high workload. Chemotherapy-induced autonomic dysfunction has been discussed previously and can be a possible explanation for the variation in HR.⁴ Chemotherapy drugs that have been demonstrated to induce arrhythmias such as atrial fibrillation and/or ventricular tachycardia include anthracyclines (eg, epirubicin and doxorubicin), cyclophosphamides,^{34,35} and taxanes.³⁶ Although acute cardiotoxicity remains

poorly understood,³⁷ there is emerging evidence of an autonomic dysfunction in women with early breast cancer treated with chemotherapy, which has been explained by an increased sympathetic activity and decreased cardiac vagal tone.³⁸ On the contrary, long-term cardiotoxicity of anthracyclines has been well documented.³⁷ It is important to note that anthracyclines were received by all of the patients in this study and, in some cases, in combination with taxanes.

In a study by Evans et al,³⁹ women with breast cancer who had completed chemotherapy showed no difference in HR response at an exercise intensity of 70% of maximal HR compared with healthy women. However, resting HR has been found to be significantly higher 1 year postchemotherapy for women with breast cancer than for healthy control subjects.⁴⁰ Jones et al⁸ found an elevated resting HR in women with breast cancer during chemotherapy compared with women with breast cancer who had not yet received chemotherapy or women who had already completed oncologic treatment. Taken together, results from these studies support the notion that the large overestimation of $\dot{V}O_{2peak}$ with the Ekblom-Bak model reflects a higher HR at only the lower submaximal stage caused by altered autonomic regulation of HR. Moreover, the patient with the highest HR recording at 30 W had the largest overestimation using E-B, but not with A-R, implying an increased resting HR or an early acceleration of HR at the onset of exercise that levels off at the higher submaximal load. Elucidation of the factors underlying chemotherapy-induced tachycardia is beyond the scope of this study but warrants further research.

Women with breast cancer undergoing chemotherapy have reported specific exercise-related symptoms such as dyspnea and leg discomfort.¹⁰ Chemotherapy can induce impairments in the cardiac, pulmonary, and vascular systems, as well as reduce the skeletal muscle oxidative capacity.⁵ Identifying therapy-related decrements in CRF is therefore of great importance. Feasible and valid

exercise tests are warranted to allow health care providers to help introduce appropriate interventions in time,⁴ not only during chemotherapy but also throughout the breast cancer survivorship continuum.

We recognize that the current validation study has several limitations. The measured $\dot{V}O_{2peak}$ was performed on a cycle ergometer, whereas the E-B test was originally validated against $\dot{V}O_{2peak}$ values obtained from treadmill testing.²¹ It should be taken into account that $\dot{V}O_{2peak}$ obtained from treadmill exercise can be 5% to 10% higher.⁴¹ However, exercise to exhaustion on a treadmill is more technically advanced than exercise to exhaustion on a cycle ergometer. Moreover, $\dot{V}O_{2peak}$ testing on a treadmill needs several time-consuming familiarization sessions. Considering the included elderly patients and those with reported treatment-associated ataxia or peripheral neuropathy, cycle ergometry was favored for safety reasons. The individual treatments may have different effects on the autonomic nervous system that may affect the prediction. A strength of the study is that the patients were familiarized with the test procedures and were used to cycling on a cycle ergometer; furthermore, the same test leader carried out all the submaximal and maximal oxygen consumption tests, and all tests were carried out at the same phase during treatment and on the same equipment.

Establishing a unique prediction equation to evaluate CRF in patients with cancer is beyond the scope of the current validation study and would require a much larger study population. Further studies are warranted to determine test-retest reliability of A-R in patients with breast cancer as well as sensitivity to changes in $\dot{V}O_{2peak}$ following an intervention period.

CONCLUSION

An increasing longevity in breast cancer patients has led to a higher incidence in comorbidities and long-term treatment adverse events such as joint pain, fatigue, and CVD that can be ameliorated by participating in some form of exercise program. As the benefits of increased physical activity in this patient category are becoming better established, the ability to accurately evaluate CRF in patients with breast cancer is of increasing importance. In a situation where a maximal test is not practically feasible or unwanted from a patient safety perspective, the use of a cycle ergometer-based $\dot{V}O_{2peak}$ prediction model based on HR measurements at exercise intensities above 120 bpm at a single stage is supported by the current results. We conclude that the Åstrand-Ryhming test appears to be a valid submaximal exercise test for determining CRF in patients with breast cancer.

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