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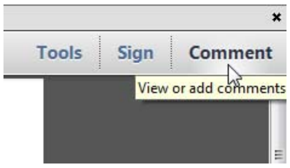

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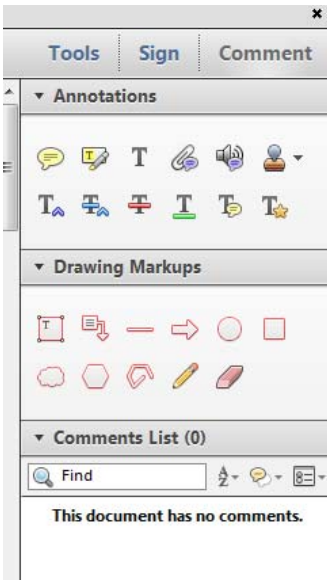

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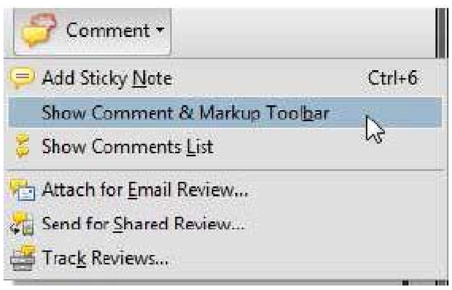

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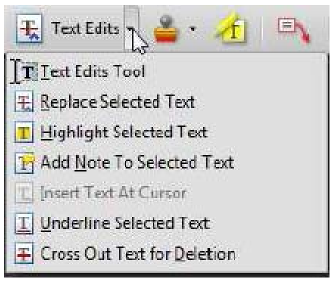

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Original Research

Energy System Assessment in Survivors of Breast Cancer

Antonio Ignacio Cuesta-Vargas, Jena Buchan, Bella Pajares, Emilio Alba, Manuel Trinidad-Fernández, Sofia Ruiz-Medina, José Manuel García-Almeida, María José Ríos-López, Cristina Roldán-Jiménez

Background Survivors of breast cancer commonly report functional limitations, including cancer-related fatigue (CRF) and decreased aerobic capacity. One key gap is addressing the 3 energy systems (aerobic, anaerobic lactic, and alactic), requiring assessment to establish a baseline exercise intensity and duration.

Objective This study examined the feasibility of energy system–based assessment, also providing descriptive values for assessment performance in this population.

Design This was a cross-sectional study.

Methods Seventy-two posttreatment survivors of breast cancer were recruited. Following a baseline musculoskeletal assessment, women attempted 3 energy system assessments: submaximal aerobic (multistage treadmill), anaerobic alactic (30-second sit-to-stand [30-STS]), and anaerobic lactic (adapted burpees). Heart rate (HR) and rating of perceived exertion (RPE) were recorded. Secondary outcomes included body composition, CRF, and upper- and lower-limb functionality.

AQ5 AQ6 **Results** Seventy of 72 participants performed the 30-STS and 30 completed the adapted burpees task. HR and RPE specific to each task were correlated, reflecting increased intensity. Women reported low-moderate levels of CRF [3% (2.1)]and moderate-high functionality levels [upper-limb: 65.8% (23.3); lower-limb: 63.7% (34.7)].

Limitations All survivors of breast cancer had relatively low levels of CRF and moderate functioning. Additionally, on average, participants were classified as "overweight" based on BMI.

Conclusion This study is the first to our knowledge to demonstrate feasibility of energy system assessment in survivors of breast cancer. Using a combination of HR and RPE, as well as baseline assessment of each energy system, clinicians may improve ability to prescribe personalized exercise and give patients greater ability to self-monitor intensity and progress.

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AQ7

Worldwide, breast cancer remains the most common cancer diagnosed in women. Although rates vary, overall survival after breast cancer has improved, particularly in countries with advanced and early medical care access.[1p0] Numerous physical and psychosocial effects of cancer diagnosis and treatment remain though. Exercise has proven effective for combating a variety of side effects, including improving quality of life, reducing fatigue, and lowering recurrence rates.[2–4] Additionally, maintaining a physically active lifestyle can also protect women against development of cancer, and, after diagnosis, being physically active is associated with a higher chance of survival.[5]

However, exercise implies a planned, structured mode of physical activity, with intensity, duration, and frequency key to define when discussing exercise effects.[6] Indeed, a limitation of current exercise therapy prescription in the oncology setting is a tendency to adopt relatively generic guidelines. There is emphasis on individualizing exercise based on personal situation, but further information and guidance on dosing of exercise is necessary to fulfill the requirements for optimal medical treatment and effectiveness of therapeutic exercise.[6,7] Particularly, parameters such as time, frequency, and type of exercise are well quantified. More difficult to consistently prescribe and quantify is intensity, another key parameter relying on monitoring variables such as heart rate (HR), perceived exertion, and number of repetitions.[8]

There are 3 interrelated energy systems involved in producing movement in the body: anaerobic alactic, anaerobic lactic, and aerobic. Although all systems require adenosine triphosphate (ATP) to produce muscular contraction, the method of using ATP differs among each metabolic pathway, with primary system use depending on the characteristics of the exercise. During maximal, short-duration exercise, the anaerobic alactic path, or phosphagen system, provides the quickest initial energy via stored ATP and creatine phosphate combining with adenosine diphosphate.[9] With longer, high-intensity exercise, around 30 seconds to 2 minutes in duration, the anaerobic lactic path dominates via breakdown of glucose through a process known as glycolysis.[10] Low- to moderate-intensity activity lasting more than 2 minutes predominantly uses aerobic pathways for glycolysis and fat metabolism to produce energy and allow sustained activity for a longer time period than the other systems.[9,10]

Alongside the recognized limitation in current literature related to lack of intensity prescription in survivors of breast cancer, assessment is typically limited to cardiovascular exercise. Submaximal VO_2 tests are commonly employed in addition to tests such as the 1-mile walk, 2-km walk, or 12-minute walk.[11] Although Cardiopulmonary Exercise Testing is an ideal clinical tool to evaluate exercise capacity, it may not be clinically feasible due to requiring metabolic cart access. As such, more repeatable, transferable tests are required to provide exercise capacity assessment across all 3 energy systems. This would allow better monitoring of treatment side effects and rehabilitation effectiveness as well as the ability to prescribe individualized exercise doses. Greater understanding of these energy systems in cancer survivors may also improve objective assessment of various side effects. For example, because cancer-related fatigue (CRF) is a common and multi-etiology symptom, exercise may be better prescribed by assessing aerobic- and anaerobic-related fatigue.[12] Therefore, this study presents an oncological evaluation of energy system assessments targeting each of the 3 systems, helping develop descriptive values for this population.

Methods

Participants

Eligible participants were recruited via medical oncologists from the University Clinical Hospital Virgen de la Victoria (Málaga, Spain) medical oncology unit. Participants were required to be 18 years or over and to have been surgically treated for their primary tumor with no evidence of recurrence at the time of recruitment. Individuals undergoing hormonal treatment, radiotherapy, or anti-Human Epidermal growth factor Receptor therapy could participate. Women were excluded if they had suffered any cardiovascular event in the year prior to inclusion, defined as stable or unstable angina; acute pulmonary edema; cardiac rhythm disorders; or syncope of an unknown cause.

Study Design

This was a cross-sectional study using 3 different assessments to evaluate each energy system. All participants signed a written informed consent form prior to inclusion. The University Clinical Hospital gave ethical clearance for the study following the Helsinki Declaration. Women completed an initial consult at the hospital to assess eligibility and collect demographic information, which included a musculoskeletal assessment to determine any movement restrictions and current symptoms. This was followed by completion of energy system testing, which was comprised of 3 different tasks to test each energy pathway (Fig. 1), listed in order of completion:

- Submaximal aerobic test: A multistage treadmill test was completed using a BH Mercury Max G6507 (BH Fitness) treadmill. Each stage of the test was 2 minutes, with speed gradually increased in the following order: 1.4, 2.9, 4.3, 5, 6, and 6.5 km/h.[13] The test was terminated when a participant's HR reached 85% of their maximum predicted HR, they requested to stop, or they experienced lack of function related to movement requiring termination of the test.[13–15] Participants then rested at least 10 minutes after this task to avoid accumulated fatigue and physiological interference between tests. During rest time, participants sat in a chair while HR was monitored until it returned to rest value.

- Anaerobic alactic test: Participants performed a 30-second Sit-To-Stand Test (30-STS), which has been shown to be superior in producing peripheral muscular fatigue compared with 5- and 30-repetition STS test variations (ie, quadriceps fatigue).[16] Participants were instructed to sit and rise from a 43-cm-high chair as rapidly as possible through the entire range of motion, repeating as many repetitions as possible in 30 seconds.[17] The task began in the standing position, with feet at hip distance apart and the upper limbs crossed over the anterior of the body to avoid lowering or pushing away from the chair with the arms. Test performance has shown a good reliability in adults (ICC = 0.85)[18] and was previously used in survivors of breast cancer.[19] Testing was terminated or not completed if women could not rise from the chair without use of arms, there was lack of function affecting the movement, and/or if the submaximal aerobic test was terminated early due to lower-limb peripheral fatigue.
- Anaerobic lactic test: Participants were instructed to perform adapted burpees (AB) for 2 minutes, developed for this study and selected for safety and movement demand purposes. This multi-joint assessment better reduces balance demands related to more traditional tests, such as the 3-minute step test, and eliminates the requirement to get on and off the ground as with traditional burpees while still placing a high-energy demand on the body through lower- and upper-body integrated movement. Each repetition involved rising from a chair, clapping hands overhead as high as possible depending on upper-limb limitations, and sitting back down. Only women who reached their 85% maximum HR without lack of function related to movement during the submaximal aerobic test and were able to complete the 30-STS test with repetitions $\geq$15 and BPE $\leq$7 (strong) were asked to perform this test. The completion of the 30-STS with a minimum of 15 repetitions and without excessive exertion would help to ensure participant capability was adequate to perform AB with reduced risk of adverse effects and as a submaximal test. An hour rest after the 30-STS was given before completing this final assessment to minimize acute fatigue impact on performance.

AQ8

Outcomes

General medical information collected included family history, comorbidities, cardiovascular risk factors, surgical interventions, and musculoskeletal system pathology. Oncology-specific data included years from diagnosis, type of surgery (breast-conserving or mastectomy), type of adjuvant treatment (radiotherapy, chemotherapy, hormone therapy, and/or monoclonal antibody), and current treatment (none, radiotherapy, monoclonal antibody, and/or hormone therapy).

The primary outcome of this study was performance in each of the 3 energy system assessments outlined above. To monitor this, objective and subjective data were collected to allow a more comprehensive assessment of physiological and perceived functional capacity. For the aerobic assessment, testing stage reached by each participant was reported. With the 2 anaerobic assessments, number of repetitions performed was recorded. HR was obtained using a pulsometer Polar M400 with a Thoracic band H7 HR (POLAR, Barcelona, Spain).[20] A resting HR was determined prior to the assessments, then monitored during each task to monitor participant response to activity and ensure expected response to exercise. Post-test HR was also recorded at the end of each assessment as well as end of each stage of the submaximal aerobic test to quantify functional capacity. As a stopping point to ensure the first 2 tests remained submaximal, 85% estimated maximum HR was used and determined based on age-predicted maximum HR (220-age formula), which has been tested in the survivors of breast cancer population.[21] Participant rating of perceived exertion (RPE) was measured using the modified Borg Scale,[22] monitored and recorded in conjunction with HR to obtain a subjective measurement of functioning. Because submaximal HR according to age is only a guide and not an absolute, both HR and RPE were monitored to provide a more comprehensive view of task effort.[15,22] For participants meeting requirements to complete the third test (AB), HR was monitored but not used as a testing cut-off to enable collection of reference values so long as no other patient factors warranted testing cessation.

Secondary outcomes for this study included body composition, CRF, and upper- and lower-limb functionality. Body mass index (BMI) was measured using a stadiometer to determine height and a Tanita TBF-300A scale (Tanita Corporation, Tokyo, Japan) to assess weight. CRF was measured using the Spanish version of the Piper Fatigue Scale-Revised (PFS-R). It contains 22 items with scores ranging from 0 to 10 and includes 4 dimensions of subjective fatigue: behavioral/severity (6 items), affective meaning (5 items), sensory (5 items), and cognitive/mood (6 items). The scale has high reliability (Cronbach $\alpha = 0.96$) in this population.[23] Upper-limb and lower-limb functionality were assessed using the Spanish versions of Upper- and Lower-Limb Functional Index questionnaires, which each consist of a 25-item scale transferable to a 100-point scale and values reported as a functionality percentage. Both scales demonstrate strong psychometric properties for reliability and validity.[24,25]

Statistical Analysis

Descriptive analyses were applied to calculate the percentage, means, SDs, and minimum and maximum of

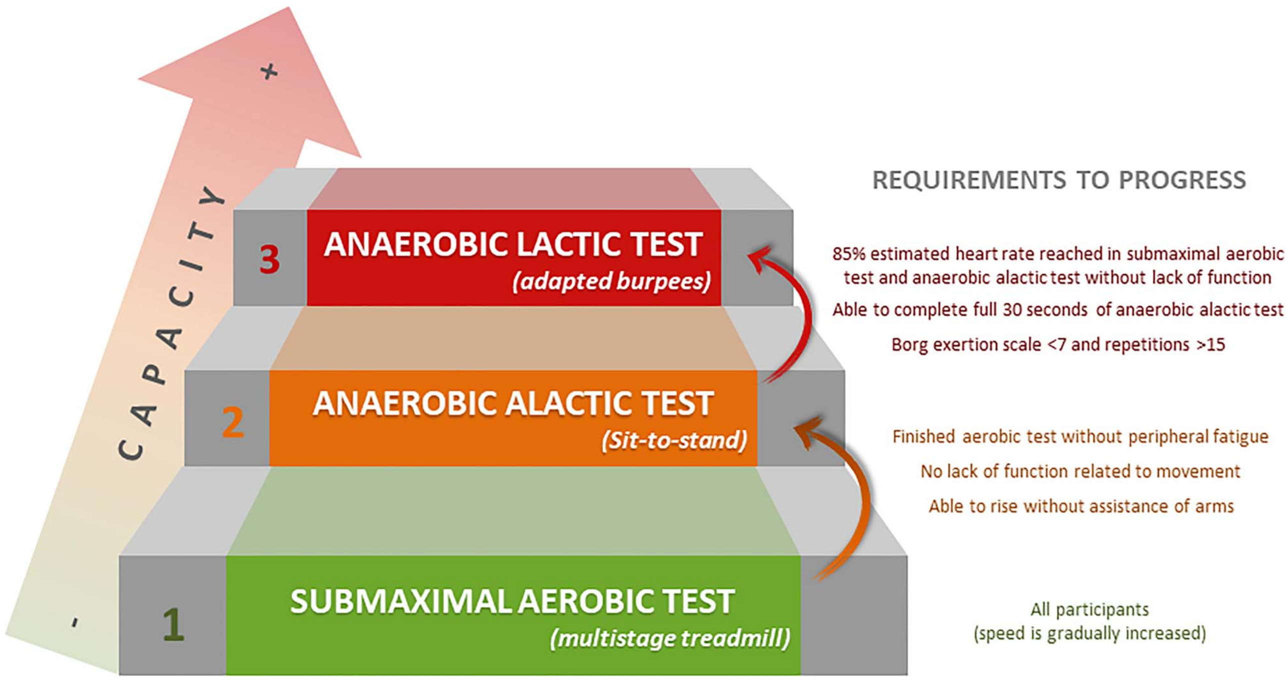

Figure 1.
Energy system assessments and associated requirements to progress.

anthropometric variables. Distribution and normality were determined by 1-sample Kolmogorov-Smirnov tests (significance <0.05).

ROLE OF THE FUNDING SOURCE

The funder played no role in the design, conduct, or reporting of this study.

Results

Participant Characteristics

All women had undergone breast-conserving surgery or mastectomy as well as chemotherapy, radiotherapy, and/or hormone therapy. The majority (60.6%) were still receiving hormone therapy. Participants were classified as overweight based on BMI (28.6 [5.6] kg/m²). Additional descriptive and clinical variables are presented in Table 1.

AQ9

Regarding assessment performance, 72 women undertook the first energy system assessment, the submaximal multistage treadmill test, and completed the first stage of the test. Seventy of these participants then met criteria to proceed to the anaerobic alactic 30-STS test. However, only 30 of these women met the aforementioned criteria to perform the anaerobic lactic test, which involved 2 minutes of AB. More details are presented in Figure 2.

Results from the submaximal multistage treadmill test demonstrated all participants were able to reach the first test speed. However, only 11 of them reached a final speed of 6.5 km/h (Tab. 2). For the 30-STS test, women performed a mean of 18.3 (5.3) repetitions at 71.2% of

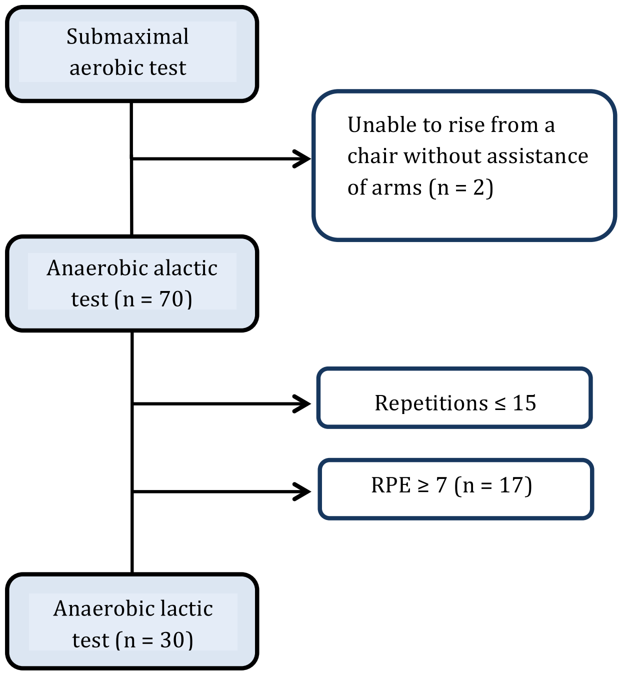

Figure 2.
Flowchart of patients who meet criteria for each test.

Table 1.
Participant Medical and Cancer-Specific Variables[a]

Variable	Mean (SD)	Min-Max	Percentage (n)
Age, y	51.4 (8.9)	32.0–69.0	
BMI, kg/m^2	28.6 (5.1)	20.3–42.0	
Years from diagnosis	2.1 (1.6)	0–7.0	
Estimated maximum HR	168.29 (8.96)	151–188	
Surgical intervention			
Breast-conserving surgery			77.8% (49)
Mastectomy			22.2% (14)
Cancer treatment			
Chemotherapy			80.6% (58)
Radiotherapy			87.5% (63)
Hormone therapy			75% (54)
Monoclonal antibody			29.2% (21)
Current treatment			
None			22.7% (15)
Radiotherapy			4.5% (3)
Monoclonal antibody			9.11% (6)
Hormone therapy			60.6% (40)

[a]BMI = body mass index; HR = heart rate.

Table 2.
Submaximal Aerobic Test Performance Outcomes[a]

Treadmill speed, km/h	n	HR, Mean (SD)	RPE, Mean (SD)	% Max HR, Mean (SD)
1.4	72	95.1 (50.1)	2.1 (1.8)	58.6 (7.7)
2.9	70	106.6 (14.0)	3.5 (1.9)	63.3 (8.98)
4.3	65	112.2 (13.4)	4.7 (1.9)	66.2 (8.1)
5	52	117.7 (12.8)	5.4 (1.4)	68.6 (6.9)
6	38	127.0 (13.4)	6.8 (1.3)	73.6 (6.5)
6.5	11	130.1 (12.5)	7.5 (1.1)	75.2 (5.4)

[a]HR = heart rate; RPE = rating of perceived exertion.

their maximum predicted HR (Tab. 3). Finally, the 30 participants who performed the 2 minutes of AB had a mean of 57.1 repetitions at an average of 84% maximum HR (Tab. 3).

In analyzing secondary outcomes self-reported by participants (Tab. 4), average fatigue was low-moderate (3.7 of 10), with both upper- and lower-limb functionality reported as less than 70% (65.8% and 63.7%, respectively).

Discussion

This study is the first to our knowledge to present an evaluation of the 3 energy systems in survivors of breast cancer using a separate assessment to target each energy system. It has also provided descriptive values related to performance in each test for this population, further highlighting the importance of individualizing exercise programs.[3] Because a baseline assessment is the first step in meeting current recommendations that survivors of breast cancer need individualized prescription,[6,7] conducting a more comprehensive fitness assessment is essential. Measuring baseline performance across each of the 3 energy systems can offer allied health professionals working in this area more individualized information about the patient's physical and perceived capacity in different efforts, particularly when combined with self-reported outcomes such as CRF and upper- and lower-limb functionality.

Table 3.
Anaerobic Alactic (30-STS) and Anaerobic Lactic Tests Performance Outcomes[a]

Test	Mean (SD)	Min-Max
30-STS (n = 70)		
Repetitions	18.3 (5.3)	3–30
HR	102.2 (44.6)	81–163
RPE	5.6 (1.6)	1–9
% Max HR	71.2 (8.7)	50.9–88.5
AB (n = 30)		
Repetitions	57.1 (12.1)	29–84
HR	152.6 (19.9)	109–183
RPE	8.7 (0.9)	7–10
% Max HR	84 (16.9)	44.3–111.04

[a]RPE = rating of perceived exertion; 30-STS = 30-second sit-to-stand.

Table 4.
Self-Reported CRF and Upper- and Lower-Limb Functionality[a]

Measure	Mean (SD)	Min-Max
CRF (PFS-R, scores 0–10)	3.7 (2.1)	0–9.1
ULFI (%)	65.8 (23.3)	0–100
LLFI (%)	63.7 (34.7)	0–100

[a]CRF = cancer-related fatigue; LLFI = Lower-Limb Functional Index; PFS-R = Piper Fatigue Scale-Revised; ULFI = Upper-Limb Functional Index.

In the exercise field, the gold standard for maximal effort is peak respiratory exchange ratio based on VO_2[26]. An alternative approach, as highlighted in previous research and supported by the findings in the study, is the use of HR as a marker of more individualized intensity.[8,27,28] Assessments that allow HR monitoring to track intensity are essential for clinicians to have access to and research around, because such tests can be performed without the extensive equipment required for VO_2 maximum tests such as the metabolic cart. In survivors of breast cancer, studies support the use of tests relying on outcomes based on age-predicted HR compared with Vo_2 consumption. An example comparison found that a 90% VO_2 corresponds with 89.1% age-predicted maximum HR in this population.[21] Further, as shown in the present study, combining an objective (HR) and subjective (RPE) measurement to quantify intensity may provide a more balanced and clinically feasible approach to prescribing exercise. For all 3 assessments, higher HR was accompanied by an increased RPE. Of note is that both average maximum HR (102.2 [44.6] bpm) and RPE (5.7 [1.6]) measured during the anaerobic alactic test were lower than those measured during the anaerobic lactic test (152.6 [19.9] bpm; 8.7 [0.9]). However, only 30 individuals met requirements to undertake the anaerobic lactic AB test, compared with 70 in the 30-STS, and this test was completed after participants had already performed the submaximal aerobic test and 30-STS. Although participants were rested and returned to baseline HR before proceeding with the next assessment, the potential influence of residual fatigue remains. Future research should determine if these outcomes differ if testing is conducting on 3 separate days. In any case, participants are expected to reach greater HR values when performing AB, because this test has a greater movement demand than the 30-STS due to longer time and combined upper- and lower-limb movement, which would suggest higher energy demands due to recruitment of more muscle groups. This was also reflected in average percent maximum HR; although the mean in both anaerobic tests supported these assessments as submaximal tests, some participants exceeded 85% maximum HR during AB. This highlights the variability between participants and further supports the need for more extensive, individualized assessment and prescription. In the clinical field, this test could be stopped in such cases to ensure the test remains on par with other submaximal tests, using 85% maximum HR as a cut-off point. AQ10

It should be noted that number of repetitions is a variable that allows individualizing exercise doses only when the assessed test is prescribed (eg, number of STS repetitions). AQ11 However, following the proposed assessments, the clinician can decide which energy system to target and use other assessment variables such as RPE or HR to guide prescription of related exercise variations (eg, 30 seconds of step-ups).

By educating patients on the subjective effort required to work at various exercise intensities, prescribing individualized exercise becomes more transferable and assists a shift towards self-management. Regarding the anaerobic tasks, establishing a baseline performance capacity (ie, number of repetitions completed) can improve ability to prescribe exercise and allows an individual to work safely within a symptom-free range and speed. Additionally, the individual can also use this as a self-monitoring tool. Future research that investigates tracking changes in each energy system assessment during exercise-based interventions would further contribute to personalized exercise, allowing monitoring of training improvements and variability among sessions. This could improve ability to design exercise schedules that incorporate patient "low" and "high" days as well as efficiency in adjusting programs around individual symptoms and subjective vs objective effort. Because survivors of breast cancer commonly experience treatment-related reductions in exercise tolerance during and following chemotherapy, radiotherapy, and other therapies,[28] modifiable and easy-to-monitor exercise dosing is imperative. Some models aiming to implement exercise as part of cancer care are individualizing exercise prescription based on treatment status, comorbidities, and location on the cancer continuum. Thus, exercise treatment is divided in phases based on such clinical variables.[29] Conversely, a baseline assessment containing variables such as those presented in this study would allow individualized exercise based on capacity. This is imperative to adequately personalize exercise, because patients can experience different, fluctuating symptoms and functional status in relation to the same clinical variables (ie, current treatment). There is moderate evidence for reliability, validity, and acceptability of submaximal exercise tests in patients with chronic pain, fibromyalgia, and chronic fatigue[30] but limited evidence in survivors of breast cancer, particularly those with issues such as CRF. Recent research developing a classification system for CRF through integration of subjective (PFS-R) and objective (30-STS) measures highlights the scope of exercise testing in better monitoring patient symptoms and allowing personalization.[17] In the present study, submaximal testing was progressive and undertaken based on the individual, allowing better establishment of baseline and exercise guidance. For example, lack of function related to movement during the aerobic test stopped an individual from proceeding in testing, and highlighted initial training should focus on building aerobic capacity. Conversely, participants able to complete the aerobic test (n = 70) and 30-STS successfully (n = 30) were then progressed to the anaerobic lactic test of AB, enabling establishment of baselines to prescribe targeted training for all 3 energy systems in their starting program. This research also highlighted that physical assessments may benefit from being accompanied by self-report questionnaires. Seventy of the 72 participants in this study were able to progress to the 30-STS test (Fig. 2), which is supported by a relatively high functionality reported (lower-limb: 63.7% [34.7] and upper-limb 65.8% [23.3]). Additionally, almost one-half of the participants undertook the AB task, potentially justified by the report of low-moderate average level of CRF (3.7 [2.1] of 10).[12] Future research should aim to investigate correlations between self-reported measures such as the PFS-R and energy system assessment results to further examine ways of providing a more comprehensive patient assessment.

Also, novel in this research was the inclusion of a test targeting anaerobic lactic energy system assessment via a 2-minute AB test. This system is a key source of energy for higher intensity, more prolonged activity, providing a transition from alactic to aerobic system use. Fatigue results from build-up of pyruvic acid in the muscles converted to lactate when no oxygen is present and requires ceasing activity to enable recovery.[10] By establishing a baseline tolerance level (eg, number of AB repetitions), exercise can be prescribed to directly target this system and improve tolerance and duration of higher intensity exercise, which is linked to key health benefits including improved strength, body composition, and aerobic endurance.[31,32] Further, current research suggests exercise impacts cancer cell glycolysis, and components such as lactate may play a role in the tumor micro-environment,[33] highlighting the need to better understand and monitor energy systems in this population.

Care must be taken in interpreting these results, because all participants were female survivors of breast cancer with relatively low levels of CRF and moderate functioning. However, the results highlight the importance of assessing various energy pathways in conjunction with such self-report measures, because less than one-half of the sample was able to complete all 3 assessments. Additionally, on average participants were classified as overweight based on BMI [28.6 (5.1) kg/m^2], with recent research suggesting a task-dependent increase in fatigability with increased BMI.[34] Future research should aim to incorporate participants with lower function, further investigate the relationship between body composition and functional ability, and examine the reliability and validity of these tests in survivors of breast cancer. In addition, although women who had suffered any cardiovascular event were excluded from participation, women from this sample had chemotherapy and/or monoclonal antibody as adjuvant treatment, exposed to trastuzumab or anthracyclines. Therefore, they may have been suffering from cardiotoxic side effects that commonly persist after the completion of cancer treatment. This should be taken into consideration because it may alter HR results. Future studies should include women with previous cardiovascular events but ensure safety with use of 12-lead ECG monitoring and other such physiological assessment. There is also a need to monitor effects of exercise training at different intensities, purposely targeting each system more directly, over time. Important to note is that no adverse events were associated with the completion of this testing, with testing progression carefully based on symptom-free completion and return to baseline HR during and following the previous task. For both clinicians and patients, the findings from this study support the use of objective and subjective measurements of effort as well as assessing and prescribing exercise across all 3 energy systems as tolerated.

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Ethics Approval

The University Clinical Hospital gave ethical clearance for the study, following the Declaration of Helsinki. All participants signed a written informed consent form prior to inclusion.

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Disclosure

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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