Energy System Assessment in Metastatic Breast Cancer: A Cross-Sectional Study

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Abstract

Background: Metastasis breast cancer commonly report physical and psychosocial side effects, which requires a supervised exercise prescription with an individualized assessment. This cross-sectional study examined the feasibility of energy system-based assessment, also generating descriptive values for assessment performance in this population.

Methods: This cross-sectional study recruited 70 women diagnosed with metastatic breast cancer. After baseline assessment, participants attempted up to three energy system assessments: submaximal aerobic (multi-stage treadmill); anaerobic alactic (30-second sit-to-stand [30-STS]); and anaerobic lactic (adapted burpees). Heart rate and rating of perceived exertion (RPE) were recorded. Secondary outcomes included body composition, CRF and upper- and lower-limb functionality.

Results: 64 and 70 of the participants performed the submaximal aerobic test and the 30-STS, respectively, and 5 completed the adapted burpees task. Heart rate 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)].

Conclusions: Using a combination of heart rate 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.

Trial registration: ClinicalTrials.gov ID NCT03879096

Background

Breast cancer rates related to both diagnosis and survival remain high worldwide, in part due to advanced and early medical care access [1]. However, while primary breast cancer 5-year survival rates are estimated at 91%, this significantly drops in relation to metastatic breast cancer, estimated at 27% [2]. This re-diagnosis is typically accompanied by various physical and psychosocial side effects, such as fatigue, pain and depression [3–5]. However, even in metastatic patients, there is a call for and suggested benefit of physical activity [6–10].

While research on the benefits of exercise in breast cancer survivors is extensive and has led to development of general prescription guidelines [11, 12], less is known about optimal prescription for those with metastatic breast cancer. Further, metastatic breast cancer presents even greater challenges in relation to being able to use generic exercise guidelines, due to factors such as variation in physical recurrence location and treatment options. As such, a significant gap exists in ability to provide more personalized exercise prescription in metastatic breast cancer. While initial research suggests basic exercise appears safe and feasible in those with advanced and metastatic cancer [9, 10, 13–15], findings highlight a strong need for individualization and further research. Given the variable impact of metastatic disease and unique challenges faced by this group of cancer patients, exercise prescription variables warrant further investigation to better support feasibility and efficacy. While general guidelines exist around overall physical activity duration and frequency, including exercise [11, 12], there is no research on assessing and prescribing intensity. This serves as an important prescription variable as it can promote self-management and monitoring due to being measured through means such as heart rate (HR), perceived exertion (RPE) and number of repetitions [16].

Central to exercise intensity is the existence of three interrelated systems in the body responsible for providing energy: anaerobic alactic, anaerobic lactic and aerobic. While adenosine triphosphate (ATP) is required across all systems in production of muscular contraction, how ATP is utilized by each system primarily depends on form of exercise. Maximal or near-maximal, short-duration activity relies on energy produced via the anaerobic alactic path, or phosphagen system [17]. Sub-maximal high-intensity activity ranging from about 30 to 120 seconds primarily relies on energy provided via the anaerobic lactic pathway, fueling activity via breakdown of glucose through glycolysis [18]. Finally, longer, low-to-moderate-intensity activity primarily uses aerobic pathways for glycolysis and fat metabolism to produce energy and allow sustained activity for a longer time period than the other systems [17, 18].

As highlighted in previous research [19], limited information of exercise intensity guidelines is often compounded by physical assessments in those with breast cancer focusing on cardiovascular/aerobic pathway exercise intensities. While both submaximal and maximal exercise testing may be used, these do not provide information on anaerobic energy system capacity and therefore limited intensity guidance [20]. As such, more repeatable, transferable tests are required to provide exercise capacity assessment across all three energy systems. While this has been examined in breast cancer survivors [19], there is a need to expand this research to women with metastatic breast cancer. Given the three energy systems play an imperative role in performance of daily activities, enabling individuals to undertake both short, high-intensity activity as well as lower-intensity, sustained activity, it is understandable these various systems should be addressed in assessment. Not only would this enable better understanding and monitoring of treatment side effects and rehabilitation effectiveness, but also support improved ability to individualize exercise prescription. Therefore, this study presents an oncological evaluation of energy system assessments in metastatic breast cancer patients, guiding development of descriptive values for this population.

Methods

Study design

This cross-sectional study evaluated each of the three primary energy systems, guided by previous research in non-metastatic breast cancer survivors [19] and adapted to consider additional factors and challenges associated with metastatic breast cancer such as metastasis location and enhanced neuropathy issues. Assessments were completed at University Clinical Hospital, Málaga, Spain.

Participants

Potential study participants were recruited between February 2018 and April 2019 by medical oncologists from the University Clinical Hospital Virgen de la Victoria (Málaga, Spain). To be eligible, participants needed to be 18 and over, with a diagnosis of metastatic breast cancer not amenable to curative treatment. Individuals were excluded if they had suffered a recent cardiovascular event (within the past year), defined as: stable or unstable angina; acute pulmonary oedema; cardiac rhythm disorders; or syncope of an unknown cause. Ethical clearance from the University Clinical Hospital and informed consent from all participants were obtained for the study, following the Helsinki declaration.

Procedure

Once deemed eligible, women underwent an initial consultation to collect demographic information and assess current symptoms and limitations via a musculoskeletal assessment. They then completed symptom-limited energy system testing, which comprised of up to three different tasks to evaluate aerobic, anaerobic alactic and anaerobic lactic systems, following these safety considerations:

- Submaximal multi-stage treadmill test (aerobic assessment): Participants were eligible for this test if they were able to treadmill walk without external technical aid and had sufficient balance not affected by factors such as brain metastasis or chemotherapy induced peripheral neuropathy.
- 30-second sit-to-stand test (30-STS) (anaerobic alactic assessment): Participants were eligible if they were able to raise from a chair without assistance of arms and had no lack of function related to the required movement.
- Two minutes of adapted burpees (anaerobic lactic assessment): Participants were eligible if they were able to perform ≥15 repetitions in the 30-STS with an RPE ≤ Additionally, women who had presented any kind of symptoms or lower-limb issues during the 30-STS were deemed ineligible to undertake this assessment.

While overall assessment protocols followed those outlined by Cuesta-Vargas et al [19], adaptations were made to assessment progression based on the additional potential symptoms associated with metastatic breast cancer. For example, due to factors such as location of metastases and impacted structures (e.g. brain, bones), women may experience significant limitations in walking ability but be capable of rising and sitting in a chair. As such, women who were unable to either undertake or fully complete the initial treadmill assessment were still given the opportunity to undertake the following anaerobic assessments, with eligibility and progression based on the aforementioned considerations.

Outcomes

General medical and oncology-specific variables were collected from participants prior to testing. These included information on other comorbidities and cardiovascular risk factors, as well as information on previous and current oncology treatments, type of metastatic disease and location of metastases.

The primary outcome of this study was performance in up to three different assessments targeting each of the energy systems highlighted above. Briefly, these were a submaximal multi-stage treadmill test (aerobic system); a 30-second sit-to-stand (30-STS; anaerobic alactic system); and 2 minutes of adapted burpees (anaerobic lactic system).

Both objective and subjective data were collected during these assessments to provide physiological and perceived capacity. A summary is provided below on this outcome, with further details provided in a recent publication by Cuesta-Vargas and colleagues [19]. For all energy system assessments, resting heart rate (HR) was determined and then monitored during each task with a pulsometer Polar M400 with a Thoracic band H7 HR (POLAR Spain) [21] for both safety and participant response monitoring. Following the protocol outlined by Cuesta-Vargas et al [19], 85% estimated maximum HR was used (220-age) as a cut-off during the first two energy system assessments to ensure tests remained submaximal [22]. During the final system assessment (adapted burpees), to enable collection of reference values, participant HR was monitored but only used as a test cessation factor when accompanied by other contraindications (e.g. participant requests to stop, pain). Rating of Perceived Exertion (RPE), based on the modified Borg Scale [23], was also recorded during all energy system assessments to provide perceived capacity and a more comprehensive assessment of overall functioning [23, 24].

Secondary outcomes for this study included body mass index, cancer-related fatigue (CRF) and upper- and lower-limb functionality, using the same scales as Cuesta-Vargas et al [19]. These included the Spanish version of the Piper Fatigue Scale-Revised (PFS-R) for cancer-related fatigue (CRF) [25] and the Spanish versions of the Upper- and Lower-Limb Functional Index (ULFI and LLFI) questionnaires to assess functionality [26, 27].

Statistical analysis

Descriptive analyses were applied to calculate the percentage, means, standard deviations, minimum and maximum of anthropometric variables. Distribution and normality were determined by one-sample Kolmogorov-Smirnov tests (significance <0.05).

Results

Participant characteristics

Participants were classified as ‘overweight’ based on BMI (26.8 [5.2] kg/m^2) (Table 1). The majority of participants had undergone a mastectomy (70%) or breast-conserving surgery (20%) and were hormone-receptor positive (80%). Additionally, 50% reported non-visceral metastatic disease, and 83% had multiple (more than 3) metastases. Additional descriptive and clinical variables are presented in Table 1.

Table 1
Participant descriptive, medical and oncological variables

	Mean (SD)	Min-Max
Age (years)	51.55 (8.55)	34–71
BMI (kg/m2)	26.83 (5.22)	18.49–36.72
Estimated Max HR	168.73 (8.45)	149–186
		n (%)
Affected breast side	Right	26 (37.15%)
	Left	37 (52.85%)
	Bilateral	7 (10.3%)
	Lymphedema	20 (28.57%)
Comorbidities/CV risk factors	Arterial hypertension	7 (10%
	Diabetes	2 (2.85%)
	Hyperlipemia	3 (4.28%)
	Smoker	2 (2.85%)
	Ex-smoker	2 (2.85%)
Hystologic subtype	HHRR positive - HER2 neg	49 (70%)
	HHRR positive- HER2 pos	7 (10%)
	Triple-negative	7 (10%)
	HHRR neg - HER2 positive	7 (10%)
Surgery	Mastectomy	49 (70%)
	Breast-conserving	14 (20%)
	None	7 (10%)
Systemic treatment	Chemotherapy	21 (30%)
	ET	19 (27%)
	CT + monoclonal ab	5 (7%)
	Monoclonal ab	7 (10%)
	ET +/- CDK inhib	18 (26%)

BMI: body mass index; HR: heart rate; HHRR: Hormone Receptors; ET: Endocrine Therapy; CT: chemotherapy; CDK: Cyclin-dependent kinases CNS: central nervous system

	Mean (SD)	Min-Max
Metastatic disease site	Visceral (liver, lung or CNS)	14 (20%)
	Non-visceral	35 (50%)
	Visceral and Non-visceral	21 (30%)
BMI: body mass index; HR: heart rate; HHRR: Hormone Receptors; ET: Endocrine Therapy; CT: chemotherapy; CDK: Cyclin-dependent kinases CNS: central nervous system		

In relation to energy system assessment, 64 of 70 participants were eligible to undertake the submaximal multi-stage treadmill test. The reasons for test exclusion for the 6 remaining women were: lack of balance (3, various causes); lack of balance and severe muscle weakness (1); and unable to walk on treadmill unassisted (2). Regarding the anaerobic alactic 30-STS test, all participants met criteria to perform this task. Based on 30-STS testing, only 5 participants were eligible to perform the anaerobic lactic test, adapted burpees (see Fig. 1).

Table 2 presents results for the aerobic energy system assessment, the submaximal multi-stage treadmill test. While all participants completed stage 1 (1.4 km/h), only 9 reached final speed of 6.5 km/h. During the anaerobic alactic task (30 s STS), women performed a mean of 17.3 (6.4) repetitions at 71.8% of their maximum predicted HR (Table 3). Table 4 presents results from the anaerobic lactic task, modified burpees, which was completed by 5 participants performing a mean 75.4 (19.9) repetitions at 94% predicted maximum HR.

Table 2
Submaximal aerobic test performance outcomes.

Treadmill speed	n	HR (mean[SD])	RPE (mean[SD])	% Max HR [mean(SD)]
1.4 km/h	64	97.29 (11.92)	2.23 (1.72)	57.64 (7.34)
2.9 km/h	60	105.78 (14.50)	3.58 (1.75)	62.64 (8.86)
4.3 km/h	56	112.71 (14.22)	4.83 (1.71)	66.79 (9.07)
5 km/h	49	118.62 (13.26)	5.83 (1.64)	70.15 (9.09)
5.5 km/h	33	122.78 (12.90)	6.32 (1.73)	72.26 (8.47)
6 km/h	18	131.97 (15.93)	7.98 (1.83)	77.68 (10.03)
6.5 km/h	9	136.38 (14.74)	7.43 (1.93)	79.48 (7.67)
HR: heart rate; SD: standard deviation; RPE: rating of perceived exertion				

Table 3
Anaerobic alactic test performance outcomes.

30-STS (n = 70)	Mean (SD)	Min-Max
Repetitions	17.28 (6.35)	1–34
HR	121.31 (14.53)	88–152
RPE (0–10)	6.02 (1.41)	1–9
% Max HR	71.81 (8.55)	53.66–86.96
30-STS: 30-second sit-to-stand; SD: standard deviation; HR: heart rate; RPE: rating of perceived exertion		

Table 4
Anaerobic lactic test performance outcomes.

Adapted Burpees (n = 5)	Mean (SD)	Min-Max
Repetitions	75.40 (19.85)	53–101
HR	164.66 (4.04)	160–167
RPE	9.6 (0.57)	9–10
% Max HR	94 (3.31)	88.89–97.08
SD: standard deviation; HR: heart rate; RPE: rating of perceived exertion		

Secondary outcomes are presented in Table 5, with participants self-reporting moderate average fatigue (4.5 out of 10), and both upper- and lower-limb functionality as less than 75% (70.8% and 68.4%, respectively).

Table 5
Self-reported cancer-related fatigue and upper- and lower-limb functionality

Measure	Mean (SD)	Min-Max
CRF (PFS-R, scores 0–10)	4.48 (2.50)	0–10
ULFI (%)	70.77 (20.28)	20–100
LLFI (%)	68.43 (26.39)	16–100
SD: standard deviation; CRF: cancer-related fatigue; PFS-R: Piper Fatigue Scale-Revised; ULFI: Upper-Limb Functional Index; LLFI: Lower-Limb Functional Index		

Discussion

While recent research has evaluated the three energy systems in breast cancer survivors [19], this study has expanded that research into women with metastatic breast cancer. Additionally, it is the first to use a separate assessment to target each energy system, allowing development of initial reference values related to performance in each test. Findings of this research provide further support of the need to individualize exercise programs beyond general guidelines [28]. Research by Yee et al [29] reported aerobic fitness in women with metastatic breast cancer as 21% lower than healthy controls and impacting functioning, but no data were found assessing anaerobic fitness. Given the symptom burden of fatigue and reduced physical functioning reported by metastatic patients [30–32], and the positive associations between physical activity participation and fatigue reduction as well as improved physical functioning, research is needed that further dissects the link of both aerobic and anaerobic fitness to such symptoms. Central to enabling this is a more comprehensive baseline assessment [11, 33], with this research providing support for scope to include energy system assessments for a more complete cardiorespiratory fitness measurement. Particularly, including both objective and subjective measures as part of these assessments, such as HR and RPE alongside fatigue and functionality self-report outcomes, can provide health professionals working with oncology patients a more patient-centered approach to assessment and prescription.

While maximal VO_2 tests are gold standard for cardiorespiratory capacity determination [34], they require extensive equipment, may be uncomfortable for the participant and have limited use in women with metastatic breast cancer [9]. However, studies in non-metastatic breast cancer survivors provide support for the use of submaximal, HR-based tests in this population, with an example study finding a 90% VO_2 corresponds with 89.1% age-predicted maximum HR [22]. The findings from this current study, alongside previous research, suggest HR can be used as a marker of more individualized intensity [16, 19, 35, 36]. Additionally, quantifying intensity via an objective (HR) and subjective (RPE) measurement may provide a more balanced and clinically feasible approach to prescribing exercise, as done in the present study and supported by findings that higher HR was accompanied by increased RPE.

Worth noting is that anaerobic alactic task performance resulted in a lower average maximum HR (119.5 [15.3] bpm) and RPE (5.8 [1.4]) than those measured during the higher-intensity anaerobic lactic test (164.7 [4.0] bpm; 9.6 [0.6]). Such findings, however, may have resulted from only 5, compared to 70, women completing the adapted burpees versus 30-STS, and these 5 completed it after the submaximal aerobic test and 30-STS. However, a higher HR and RPE was expected with adapted burpees compared to 30-STS due to longer time and combined upper- and lower-limb movement. Average % maximum HR also reflected this, with participants in the adapted burpees actually exceeding 85% maximum HR (94.0% [3.3]), although not accompanied by other symptoms warranting test cessation. Despite these expectations though, there exists potential influences of testing order and fatigue, as all tests were performed the same day. As such, future research could conduct each task on three separate days. Additionally, as women completing the modified burpees test exceeded the 85% maximum HR but were not symptom-limited, this further supports the necessity to further research on suitable exercise intensities in this population, particularly from an individualized basis. For consistency in clinical translation, health professionals conducting these energy system assessments could still ensure 85% maximum HR is used as a cut-off to maintain consistency with other submaximal testing.

A key translation from this research is the benefit of using measurements that patients can use to self-monitor exercise performance and intensity. As findings support an objective measure (HR) correlating with a subjective measure (RPE), health professionals can provide education on using RPE to both gage exercise intensity and monitor progression. Additionally, the anaerobic tasks provide a baseline repetitions number, which can be used to guide more personalized exercise prescription and give patients progression towards self-management. For example, women could monitor the number of repetitions they are able to perform before reaching a certain RPE on various days and develop an exercise routine for 'high' versus 'low' days. This would also allow patients to better self-monitor their overall functioning ability and potential worsening of health that may warrant medical follow-up.

As done in the present study, a more physically comprehensive patient assessment can allow better establishment of activity tolerance and baseline by progression determined by individual response. For example, lack of walking balance or inability to walk unaided on a treadmill during the aerobic test stopped a few participants from being able to undertake this task, but they were still able to complete at least one of the anaerobic tasks. As such, these patients may require a cycling-based aerobic assessment to determine whether to prioritize aerobic or anaerobic fitness. Additionally, while the energy system demands for the aerobic assessment are less than those for the anaerobic assessments, this research found the perceived physical demand was reversed for some women. That is, patients reported that the unilateral loading required with walking posed a greater challenge than the anaerobic task or tasks they undertook. As such, health practitioners should take into account such individual factors and design assessments accordingly, attempting to get a baseline for each of the energy systems where possible for program integration.

Additionally, this research also supported potential benefit of integrating subjective and objective assessments for a more patient-centered approach. Research developing an assessment method for cancer-related fatigue using an integrated subjective (PFS-R) and objective (30-STS) measure highlights the scope of exercise testing in better monitoring patient symptoms and allowing personalization [37]. All 70 participants undertook the 30-STS test (Fig. 1), supported by a relatively high functionality reported (lower-limb: 68.4% [26.4] and upper-limb 70.8% [20.3]). However, only five of these individuals met criteria to progress to the modified burpees, which potentially is reflected by a moderate level of CRF (4.5 [2.5] out of 10) [38]. Future research should aim to look at 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.

As the main limitations, care must be taken in interpreting these results, as all participants were female metastatic breast cancer patients with moderate functioning but also moderate fatigue. Regardless, findings support incorporating objective assessment of the three key energy systems with such self-report measures, as only five individuals were able to undertake all three assessments. Additionally, on average participants were classified as 'overweight' based on BMI (26.8 [5.2] kg/m^2), with recent research suggesting a task-dependent increase in fatigability with increased BMI [39]. Future research should aim to incorporate lower-functioning participants, further investigate the relationship between body composition and functional ability and examine reliability and validity of these tests in metastatic breast cancer. Additionally, although women reported a moderate level of lower-limb functionality, six were unable to undertake the treadmill test due to physical limitations and multiple others reported it posed a significant biomechanical challenge compared to the anaerobic task(s) that used bilateral leg functioning. As such, future research should examine a cycling-based or other seated aerobic task and participant progression ability as such. There also remains a need to undertake longer-term training at various intensities, purposely targeting each system, to observe more chronic effects on both objective and subjective measures. Important to note is no adverse events were associated with completion of this testing, with testing progression carefully based on symptom-free participation and return to baseline HR during and following the previous task. For both health professionals and patients, these findings support integration of both objective and subjective measurements of effort to improve exercise prescription and monitoring, as well as providing a more personalized assessment and prescription that considers all three energy systems as tolerated.

List Of Abbreviations

ATP: Adenosine Triphosphate

BMI: Body Mass Index

CDK: Cyclin-Dependent Kinases

CNS: Central Nervous System

CRF: Cancer-Related Fatigue

CT: chemotherapy

EORTC QLQ-C30: *The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30*

EORTC QLQ-BR23: *The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life questionnaire*

ET: Endocrine Therapy

HHRR: Hormone Receptors

HR: Heart Rate

LLFI: Lower-Limb Functional Index

PFS-R: Piper Fatigue Scale-Revised

QoL: Quality of life

RPE: Rating of Perceived Eexertion

SD: standard deviation

ULFI: Upper-Limb Functional Index

30-STS: The 30-second Sit-To-Stand Test

Declarations

Ethics approval and consent to participate

Ethical approval for the study was granted by the Ethics Committee of The University Clinical's Hospital. The study complied with the principles laid out in the Declaration of Helsinki. All participants in this study signed an informed consent form prior to inclusion, and their participation was voluntary.

Consent for publication

Not applicable.

Availability of data and materials

Data are available upon reasonable request.

Competing interests

No potential conflicts of interest were disclosed.

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Authors' contributions

EA-C, BP-H and AIC-V conceived this study. EA-C, BP-H and AIC-V developed the protocol. AIC-V, CR-J and JB analyzed and interpreted the data. JB, CR-J, BP-H, MT-F, EA-C, ED-B and AIC-V drafted the manuscript and revised it critically for important intellectual content. All authors gave final approval of the version to be published.

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Figures

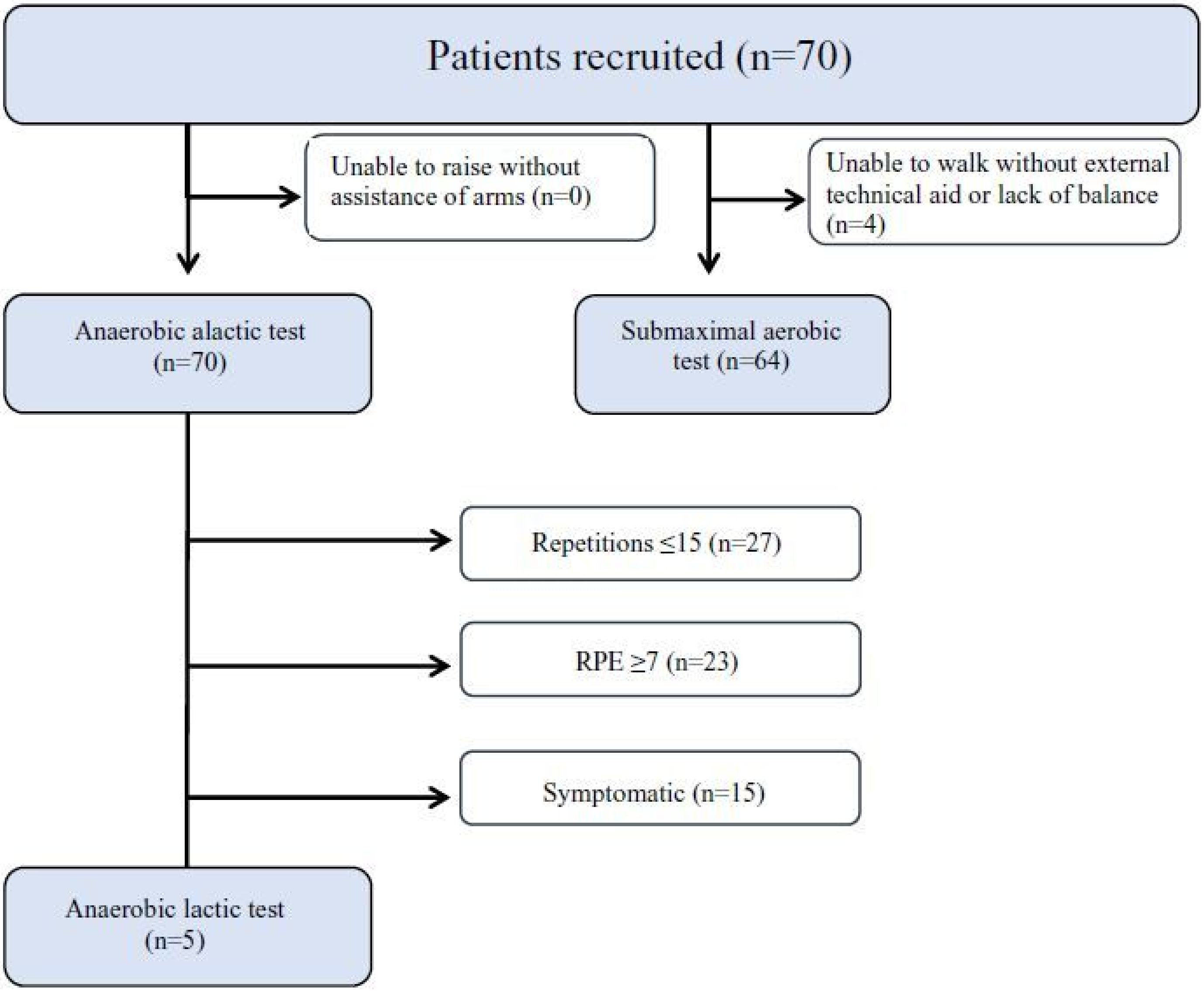

Figure 1

Flowchart of patients who meet criteria for each test.