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Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphedema

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ABSTRACT

BLOOMQUIST K., P. OTURAI, M. L. STEELE, L. ADAMSEN, T. MØLLER, K. B. CHRISTENSEN, B. EJLERTSEN, and S. C. HAYES. Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphedema. *Med. Sci. Sports Exerc.*, Vol. 50, No. 2, pp. 187–195, 2018. **Purpose**: Despite a paucity of evidence, prevention guidelines typically advise avoidance of heavy lifting in an effort to protect against breast cancer–related lymphedema. This study compared acute responses in arm swelling and related symptoms after low- and heavy-load resistance exercise among women at risk for lymphedema while receiving adjuvant taxane-based chemotherapy. **Methods**: This is a randomized, crossover equivalence trial. Women receiving adjuvant taxane-based chemotherapy for breast cancer who had undergone axillary lymph node dissection (n = 21) participated in low-load (60%–65% 1-repetition maximum, two sets of 15–20 repetitions) and heavy-load (85%–90% 1-repetition maximum, three sets of 5–8 repetitions) upper-extremity resistance exercise separated by a 1-wk wash-out period. Swelling was determined by bioimpedance spectroscopy and dual-energy x-ray absorptiometry, with breast cancer–related lymphedema symptoms (heaviness, swelling, pain, tightness) reported using a numeric rating scale (0–10). Order of low- versus heavy-load was randomized. All outcomes were assessed before, immediately after, and 24 and 72 h after exercise. Generalized estimating equations were used to evaluate changes over time between groups, with equivalence between resistance exercise loads determined using the principle of confidence interval inclusion. **Results**: The acute response to resistance exercise was equivalent for all outcomes at all time points irrespective of loads lifted, with the exception of extracellular fluid at 72 h after exercise with less swelling after heavy loads (estimated mean difference, −1.00; 95% confidence interval, −3.17 to 1.17). **Conclusions**: Low- and heavy-load resistance exercise elicited similar acute responses in arm swelling and breast cancer–related lymphedema symptoms in women at risk for lymphedema receiving adjuvant taxane-based chemotherapy. These represent important preliminary findings, which can be used to inform future prospective evaluation of the long-term effects of repeated exposure to heavy-load resistance exercise. **Key Words:** ARM SWELLING, BREAST CANCER, DOSE–RESPONSE, STRENGTH TRAINING

Breast cancer–related arm lymphedema (BCRL) is a chronic condition initially characterized by regional swelling of the arm or hand due to increases in protein-rich extracellular fluid, affecting approximately 20% of breast cancer survivors as a consequence of treatment (1,2). The adverse effects of BCRL are well described in the literature, negatively affecting daily functions (3,4) and social, emotional, and psychological well-being (4,5).

More extensive surgery to the chest wall, radiotherapy, chemotherapy, and being overweight and/or physically inactive have been consistently associated with increased BCRL risk (1). However, the extent of lymph node removal is considered the strongest risk factor, with BCRL incidence four times higher after axillary lymph node dissection compared with sentinel-node biopsy (1). Despite the high-quality evidence in support of specific risk factors, the ability to predict who will develop BCRL is limited.

Historically, breast cancer survivors were advised to refrain from resistance exercise as a means of preventing BCRL (6,7). However, results from systematic reviews of clinical trials consistently indicate that resistance exercise elicits gains in muscle strength and physical components of quality of life without increased risk for BCRL (6–9).

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Nonetheless, more work needs to be undertaken to confirm safety of resistance exercise, because those considered at high risk for BCRL do not reflect the target sample of studies included in these reviews. Specifically, only one study explicitly included participants undergoing chemotherapy (10), of which 31% received adjuvant taxane-based chemotherapy. This is of importance because generalized edema with ensuing arm swelling is a known side effect to this cytostatic agent (11). In addition, just two studies (10,12) specifically included women at risk for BCRL who had undergone axillary lymph node dissection, considered the greatest risk factor.

Limitations also exist with respect to exercise prescription because resistance load has not exceeded 80% of 1-repetition maximum (RM) or 8–12 repetitions in previous studies evaluating resistance exercise and BCRL risk, because of concerns that heavier loads would trigger BCRL development (6–9,13). However, exercise science literature indicates that a dose–response relationship exists between loads lifted and gains in muscular structure and function with heavier loads shown to be more effective in eliciting strength gains compared with lighter loads (14,15).

To date, two prospective studies including women with clinically stable BCRL who had been diagnosed with breast cancer at least a year before study inclusion have evaluated the potential of heavier-load resistance exercise using 6–10 RM (16,17). These studies found that the extent of arm swelling and associated BCRL symptoms remained stable both immediately after and 24 and 72 h after one bout of resistance exercise (16), and after 12 wk of regular resistance exercise irrespective of whether low or heavy loads were lifted (17). As such, these studies provide meaningful information for women with BCRL who have completed active treatment (chemotherapy and radiotherapy). These findings cannot, however, be generalized to the at-risk population undergoing taxane-based chemotherapy.

Therefore, the purpose of this study was to undertake a phase II trial to assess the initial lymphatic response to low-load compared with heavy-load resistance exercise in breast cancer survivors at risk for BCRL development. This was undertaken by comparing acute changes in extracellular fluid, arm volume, and associated BCRL symptoms after a session of low- and heavy-load resistance exercise in women who had undergone axillary lymph node dissection and were receiving taxane-based chemotherapy during the conduct of this trial.

METHODS

Trial Design

Details of study design and methods have been previously described (18). In summary, this was a randomized, crossover, equivalence trial whereby women participated in an experimental low- and heavy-load upper-extremity resistance exercise session, with a 7-d wash-out period between sessions (Fig. 1). It was hypothesized that response would be similar between resistance exercise loads for all outcomes. The study protocol was approved by the Danish Data Protection Agency (30-1430) and the Danish Capital Regional Ethics Committee (H-3-2014-147), and written informed consent was obtained from all participants.

Participants

A convenience sample of women receiving standard adjuvant chemotherapy for stage I–III breast cancer were screened for eligibility (>18 yr of age, first diagnosis of breast cancer, unilateral breast surgery, axillary node dissection) at the Copenhagen Centre for Cancer and Health and from a wait list to the Body & Cancer program (18,19) at the University Hospitals Centre for Health Research between March 2015 and December 2016. Women with a known clinical diagnosis of lymphedema or who had conditions limiting resistance exercise of the upper extremities (e.g., fibromyalgia, frozen shoulder) or who had participated in regular upper-extremity heavy resistance exercise (>1 per week) during the last month were excluded (Fig. 1).

Those meeting eligibility were assessed for BCRL status by the first author (K.B.), after the third cycle of chemotherapy. BCRL was assessed using bioimpedance spectroscopy (BIS; SFB7; Impedimed, Brisbane, Australia [16,20,21]) and a visual inspection to detect differences in swelling between arms (Common Toxicity Criteria v3.0 [2]). Those with evidence of lymphedema according to standardized protocols for BIS (L-Dex >10) or visual inspection were then referred to a lymphedema therapist for further assessment and were excluded from participating in the study.

Exercise Sessions

All participants completed two familiarization sessions, followed by two experimental sessions (low- and heavy-load sessions) at exercise facilities located at the research center.

All resistance exercise sessions lasted approximately 30 min including a 10-min aerobic-based warm-up (rowing or cross-trainer) at low-moderate intensity. All sessions were supervised by the first author (K.B.) to ensure consistency of warm-up intensity and order of resistance exercises performed. None of the participants wore compression sleeves. During the first familiarization session, participants were introduced to four upper-extremity exercises consisting of the biceps curl performed with free weights, followed by the chest press, latissimus pull down, and triceps extension using resistance exercise machines (Technogym®, Gamettola, Italy). Hereafter, a 1RM strength test was performed in each exercise. During the second session, one set of 10–15 repetitions was performed, followed by a new 1RM strength test. Subsequent resistance exercise prescription during the experimental sessions was based on these values. After completion of the familiarization sessions, resistance exercise load order for the experimental sessions was randomly allocated (i.e., low or heavy load first) using a computer-generated random

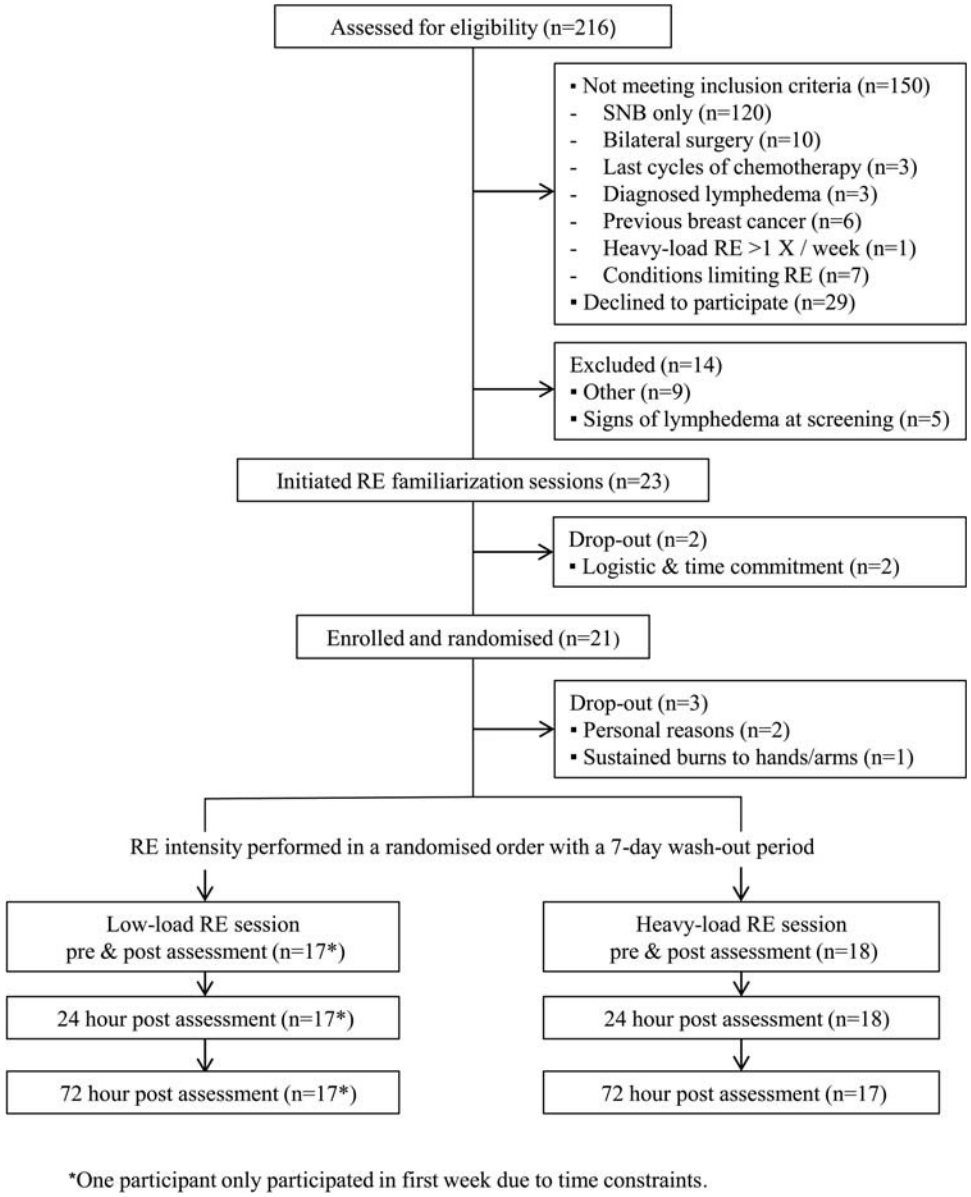

FIGURE 1—Participant flow through resistance exercise and data collection sessions. RE, resistance exercise; SNB, sentinel-node biopsy.

sequence (1/1 ratio). Women then participated in the experimental sessions, which entailed the 10-min aerobic-based warm-up, followed by the four resistance-based exercises. Resistance exercise load corresponded to 60%–65% 1RM (two sets of 15–20 repetitions) for the low-load session and 85%–90% 1RM (three sets of 5–8 repetitions) for the heavy-load session. Participants were instructed to work to muscle fatigue (until they were unable to maintain appropriate technique) within the prescribed range and with rest periods of 60–90 s between sets.

The experimental sessions were consistently performed on the same day of the week and at the same time of day, with all outcomes assessed before, immediately after (within 30 min), and 24 and 72 h after resistance exercise sessions. Blinded data collection was performed by medical technicians. Participants were instructed to maintain normal upper-body activities during the experimental period and to refrain from extraordinary activities involving the upper extremities.

Primary Outcome

Extracellular fluid. BIS was used to directly measure and compare the impedance of extracellular fluid in the upper extremities to electrical currents at a range of frequencies according to the manufacturer's software (20,21). Using the principle of equipotentials, four single-tab electrodes were placed in a tetrapolar arrangement and participants were measured in supine, with arms and legs abducted from the trunk with palms facing down. To ensure accuracy, standard protocols from the manufacturer were followed (e.g., empty bladder, no excessive exercise or caffeine consumption within 2 h). The ratio of impedance (at R0) between the at-risk

and nonaffected arm was calculated and converted into an L-Dex score taking arm dominance into account.

Secondary Outcomes

Interarm volume percent difference. Measurements of arm volume were obtained using dual-energy x-ray absorptiometry (DXA; Lunar Prodigy Advanced Scanner; GE Healthcare, Madison, WI). DXA measures tissue composition using a three-compartment model that is sensitive to changes in upper-extremity tissue composition (21,22). Using previously derived densities for fat (0.9 $g \cdot mL^{-1}$), lean mass (1.1 $g \cdot mL^{-1}$) and bone mineral content (1.85 $g \cdot mL^{-1}$), DXA measurements were converted into estimated arm volumes. Lying supine on the scan table with the arm separated from the trunk, each arm was scanned separately. If necessary, a Velcro band or the free arm was placed over the breast to ensure space between the arm and trunk. Small animal software (ENCORE version 14.10) was used to analyze the scans as described by Gjorup et al. (21,22). All scans were analyzed by a clinical expert (P.O.) in DXA scan analysis. Interarm volume percent differences (at-risk arm minus unaffected arm/unaffected arm × 100) were then calculated for each participant.

Subjective assessment of BCRL symptoms. The severity of symptoms related to BCRL was monitored using a numeric rating scale. Participants rated their perceptions of swelling, heaviness, pain, and tightness independently for each arm on a scale from 0 (no discomfort) to 10 (very severe discomfort) (16,23).

Sample Size Calculation

Sample size calculation was based on changes in L-Dex scores between baseline and 72 h after resistance exercise sessions. From the results of Cormie et al. (16), it was hypothesized that the SD in the distribution of L-Dex scores would be 1.9 units. On the basis of clinical experience, for patients with BCRL, a change score of 2.0 L-Dex units would be considered clinically relevant. However, in the at-risk population, no published normative change scores exist, nor does evidence regarding a threshold for a clinically significant acute change. A change in 2.0 L-Dex units was deemed too small in the at-risk population, on the basis of the assumption that larger fluctuations would be seen within the normal range without clinical relevance. Therefore, *a priori*, we set the clinically relevant threshold for change as being 3.0 L-Dex units. Thus, if there was no difference between intensities, then 18 participants were needed to be 90% sure that the limits of a two one-sided 95% confidence interval (CI) would exclude a difference in means of more than 3.0 L-Dex units. To allow for dropouts, 21 women were recruited.

Statistical Analyses

Descriptive statistics included counts (and percentages) for categorical values and mean ± SD for normally distributed continuous variables, unless otherwise noted. Individual responses to resistance exercise loads were first assessed descriptively, including determination of the proportion that exceeded the predetermined clinically relevant threshold. Next, generalized estimating equations (GEE) (24) were used to evaluate the effects of time (pre-, post-, 24 and 72 h post-) and load (low/heavy load), and a time–load interaction. An exchangeable correlation structure was used to model the within-subject correlation of repeated measurements over time and across intensities.

To assess equivalence, the principle of CI inclusion was used to calculate one-sided upper and lower 95% confidence limits for all outcomes (25) (reported as two-sided 90% confidence limits). If the interval between the upper and lower confidence limits was within the predetermined equivalence margin, equivalence between resistance exercise intensities was declared. For the primary outcome, the margin of equivalence was set at ±3.0 L-Dex units. On the basis of the findings by Stout et al. (26) that volume increases of >3% from preoperative measures were indicative of subclinical BCRL, an equivalence margin of ±3.0% was used for interarm volume percent differences. For all subjective measures, interarm differences were calculated and an equivalence margin was set at ±1.0 points. This threshold was based on previous findings that suggest a 2-point or 30% change to be clinically meaningful for pain (23). Per-protocol principles were applied because this is considered the most conservative approach for determining equivalence (27). Analyses were conducted in R version 3.3.1 (28) using geepack 1.2.0.1 for GEE modeling (29).

RESULTS

Participants. From the 216 women assessed for eligibility, 21 were eligible and consented to participate. Of these, 3 dropped out before initiation of the experimental exercise sessions because of time constraints and injury (Fig. 1), 1 discontinued participation after the 24-h postexercise assessment in week 1 because of logistical considerations, and 17 (81%) completed all data collections.

Characteristics of the study population are presented in Table 1. Average age of participants was 45 yr, and mean body mass index (BMI) was 25.3 $kg \cdot m^{-2}$, with 11 (53%) participants presenting with a BMI of ≥25.0 $kg \cdot m^{-2}$. On average, women had 22 axillary lymph nodes removed during axillary node dissection and 62% of the participants had received a mastectomy. As per eligibility criteria, all participants received adjuvant taxane-based chemotherapy during the experimental sessions; however, the first 10 participants received docetaxel, whereas the last 11 received paclitaxel, because standard chemotherapy changed midway through the study period.

Individual responses to resistance exercise sessions. For L-Dex and interarm volume outcomes, individual responses to resistance exercise sessions varied with no apparent group trend observed (Fig. 2A, B). For BCRL symptoms, we found that most participants were asymptomatic before

TABLE 1. Baseline characteristics of participants (n = 21).

Variables	Mean ± SD/Median (Range)
Age, yr	45.3 ± 9.2/46 (23–60)
BMI, kg·m^{-2}	25.3 ± 4.7
Cancer stage, n (%)	
II	15 (71)
III	6 (29)
Tumor size, mm	21.5 ± 12.9/18 (7–62)
Breast surgery, n (%)	
Lumpectomy	8 (38)
Mastectomy	13 (62)
Surgery on dominant side, n (%)	11 (52)
Axillary lymph nodes removed	21.7 ± 7.8
Metastatic lymph nodes[a]	5.7 ± 7/2 (1–25)
Seroma drainage	5.5 ± 3.4
Chemotherapy, n (%)	
3-wk CE × 3 → 3-wk docetaxel × 3	10 (48)
3-wk CE × 3 → 1-wk paclitaxel × 9	11 (52)
Axillary webbing at screening, n (%)	8 (38)
L-Dex at screening	−0.08 ± 2.23

[a]Micrometastase and macrometastase.
CE, cyclophosphamide and epirubicin.

exercise and remained asymptomatic throughout the subsequent data collections irrespective of loads lifted (Fig. 2C–F).

Deviations from predetermined thresholds. When data were described according to clinically relevant changes from preexercise, 16 women (89%) had experienced fluctuations in extracellular fluid beyond the predetermined threshold at one time point or more, ranging from −8.7 to 6.8 L-Dex units. Almost twice as many had fluctuations after the low-load session (n = 12 (71%)) compared with the high-load session (n = 8 (44%); Table 2). Increases above the clinical threshold were observed for seven women (41%) after the low-load session, two of which had increased pre–post measures that remained elevated above the clinically meaningful threshold at 24 and 72 h after exercise (Fig. 2A). None of these women had clinically meaningful increases in L-Dex after heavy-load resistance exercise. Four women (22%) had increases in L-Dex after the heavy-load session. Of these, two were observed immediately after the heavy load session (one of these also showed an increase in interarm volume percent difference; increases had dissipated in both cases by the 24-h post–follow-up), whereas the other two were observed at 72 h after exercise.

For interarm volume, four (24%) women experienced clinically meaningful fluctuations ranging from −4.1% to 4.6%. Three (18%) participants experienced increases after heavy-load exercise, with two seen immediately after exercise and one at 24 h after exercise (Fig. 2B). One participant (6%) experienced decreases after the low-load session immediately after exercise (Table 2). None of these observations coincided with other outcome measures (except for the previously described L-Dex pre–post measure).

For BCRL symptoms, we found that eight (44%) women responded with fluctuations ranging from −7 to 3 units. Specifically, six (33%) women reported decreases in symptoms, with reductions observed after exercise and sustained over the subsequent time points, and were equally distributed between resistance exercise load conditions (Table 2). Increases in symptoms were reported by two (11%) women. One woman reported increases in pain and tightness at 24-h post–heavy-load exercise (Fig. 2D, E), whereas the other participant experienced increases in heaviness and swelling after exercise after the heavy-load session (Fig. 2C, F), and an increase in pain 24 h after the low-load session (Fig. 2D). None of these increases were sustained at the 72-h postsession follow-up.

An overview of unadjusted means and SD for all outcomes at each time point is presented in Table 3.

L-Dex. The estimated mean difference between resistance exercise loads and associated two-sided 90% CI for L-Dex scores were contained within the predetermined equivalence margin of ±3.0 units immediately and 24 h after resistance exercise indicating equivalence between intensities (−0.97 (−2.09 to 0.16) and −0.14 (−1.63 to 1.35), respectively; Table 4). However, at 72 h after exercise, the lower CI exceeded −3.0 and equivalence between low- and heavy-load intensities could not be declared, favoring heavy-load resistance exercise.

Interarm volume percent difference. Equivalence between intensities was observed at all time points for interarm volume percent differences, as estimated mean differences and 90% CI were within the ±3.0 margin of equivalence (Table 4).

BCRL symptoms. Equivalence between resistance exercise intensities was found for all BCRL symptoms at all time points, as estimated mean differences and associated 90% CI were within the equivalence margin of ±1.0 (Table 4).

No adverse events related to exercise (i.e., sprains or strains) were reported. However, two (11%) participants were advised to seek evaluation by a lymphedema therapist at the end of the study period because L-Dex scores had exceeded 10 (Fig. 2A). One participant had a preexercise L-Dex score of 7.9 in week 1. Upon instigating the low-load session at week 2, an L-Dex score of 11.7 was observed, with subsequent measures decreasing. The other participant initiated the heavy-load session at week 1 with a preexercise L-Dex score of 3.8, and subsequent measures fluctuating less than 5.0 units. At week 2, a preexercise L-Dex score of 9.5 was observed that increased to 12.7 after exercise, with decreasing subsequent measures. Notably, this participant suffered from rapid weight gain due to generalized edema between weeks 1 and 2 that was effectively treated with diuretics. All other outcomes were within the predetermined clinical thresholds at all time points for both of these participants.

DISCUSSION

The findings of this study support the hypothesis that acute changes in extracellular fluid, arm volume, and BCRL-related symptoms were similar irrespective of whether low- or heavy-load upper-extremity resistance exercise was performed during adjuvant taxane-based chemotherapy in women with axillary lymph node dissection.

This is the first study to prospectively investigate lymphatic response to resistance exercise with heavy loads

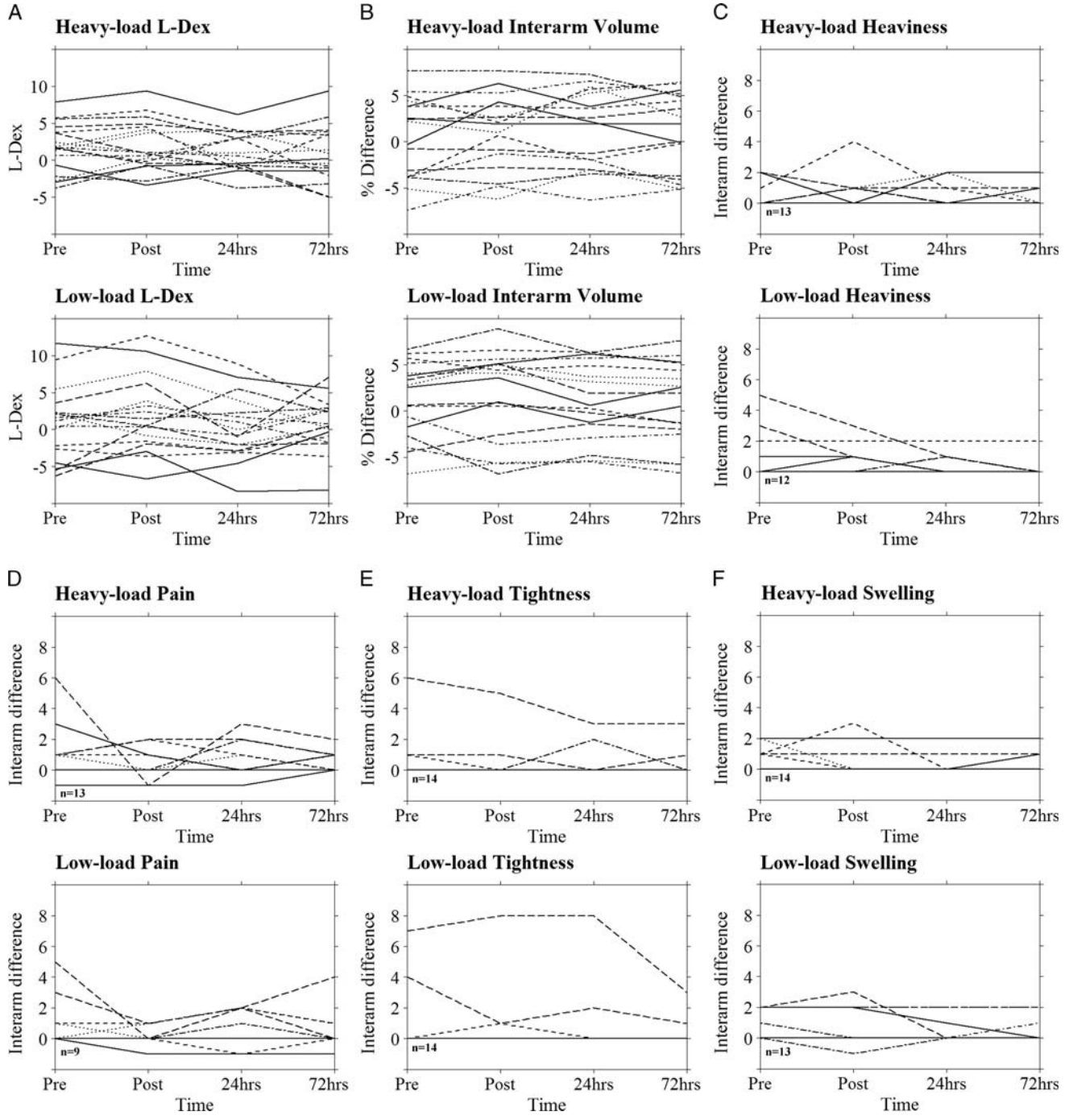

FIGURE 2—Individual response related to low- and heavy-load resistance exercise sessions for all outcomes (n = 17). A, Heavy-load L-Dex pre-, post-, and 24 h (n = 18). In subplots C–F, heavy-load breast cancer–related lymphedema symptoms preexercise and postexercise (n = 18). n refers to the number of participants with a symptom score of 0 at all time points.

(85%–90% 1RM, for 5–8 repetitions) in breast cancer survivors at risk for developing BCRL. Findings are consistent with observations from a cross-sectional study (n = 149) that showed no association between participation in a multimodal exercise intervention including heavy-load resistance exercise during taxane-based chemotherapy and BCRL development (30). Furthermore, our results are consistent with the findings of Cormie et al. (16), demonstrating that participation in a bout of resistance exercise using 6–10RM loads did not acutely exacerbate swelling or BCRL symptoms in women with stable lymphedema. As such, this lends credibility to the results of the present study.

The equivalence design was considered the most appropriate for addressing our research question and was formalized by defining equivalence margins for all outcomes. Equivalence margins ideally represent the maximum clinically acceptable difference that one is willing to accept in return for the secondary benefits of a new therapy (27),

TABLE 2. Number (%) of participants exceeding equivalence margin from preexercise to immediately postexercise and 24 and 72 h after exercise for all outcomes (n = 17).

	△ Pre–Post	△ Pre–24 h Post	△ Pre–72 h Post
L-Dex			
Heavy load	2↑ (11%)[a]	2↓ (11%)[a]	2↑ (12%), 3↓ (18%)
Low load	4↑ (24%), 1↓ (6%)	3↑ (18%), 4↓ (24%)	4↑ (24%), 4↓ (24%)
% interarm difference			
Heavy load	2↑ (12%)	1↑ (6%)	1↑ (6%)
Low load	1↓ (6%)	0	1↓ (6%)
Pain			
Heavy load	2↓ (11%)[a]	1↑ (6%), 2↓ (12%)	2↓ (12%)
Low load	2↓ (12%)	1↑ (6%), 1↓ (6%)	1↓ (6%)
Heaviness			
Heavy load	1↑ (6%), 1↓ (6%)[a]	1↓ (6%)	2↓ (12%)
Low load	2↓ (12%)	2↓ (12%)	2↓ (12%)
Tightness			
Heavy load	0[a]	1↑ (6%), 1↓ (6%)	1↓ (6%)
Low load	1↓ (6%)	1↓ (6%)	2↓ (12%)
Swelling			
Heavy load	1↑ (6%), 1↓ (6%)[a]	1↓ (6%)	1↓ (6%)
Low load	0	1↓ (24%)	2↓ (12%)

↑, higher than equivalence margin; ↓, lower than equivalence margin.
[a]n = 18.

which in this study was heavy-load resistance exercise. The value and impact of establishing equivalence depend on how well the equivalence margin can be justified in terms of relevant evidence and clinical judgment, where a narrower equivalence margin makes it more difficult to establish equivalence (27). The equivalence margin for the primary outcome was estimated as 3.0 L-Dex units. *A priori*, the threshold was chosen on the basis of change scores considered to be clinically relevant for persons with BCRL, because no known normative change scores existed for persons without BCRL. However, new normative data recently published indicate that L-Dex scores fluctuate between 9 and 11 units (31). This is in line with our results, finding that 16 (89%) participants experienced deviations from the predetermined L-Dex threshold. As such, although the equivalence margin for this outcome likely was unnecessarily narrow, this adds confidence to our findings. Furthermore, had we used broader L-Dex equivalence margins, the 90% CI

TABLE 3. Extent of swelling and breast cancer–related lymphedema symptoms for all outcomes (n = 17).

	Preexercise	Postexercise	24 h Postexercise	72 h Postexercise
L-Dex score				
Heavy load	1.7 ± 3.3[a]	1.9 ± 3.4[a]	1.0 ± 2.6[a]	0.8 ± 3.9
Low load	0.8 ± 5.0	1.9 ± 5.1	0.2 ± 4.4	0.7 ± 3.6
% interarm difference				
Heavy load	0.5 ± 4.4	1.0 ± 4.0	1.4 ± 4.2	1.1 ± 4.3
Low load	1.3 ± 4.1	1.6 ± 4.8	1.0 ± 4.2	0.8 ± 4.4
Pain				
Heavy load	0 (−1, 6)[a]	0 (−1, 2)[a]	0 (−1, 3)	0 (0, 2)
Low load	0 (0, 5)	0 (−1, 1)	0 (−1, 2)	0 (−1, 4)
Heaviness				
Heavy load	0 (0, 2)[a]	0 (0, 4)[a]	0 (0, 2)	0 (0, 2)
Low load	0 (0, 5)	0 (0, 3)	0 (0, 2)	0 (0, 2)
Tightness				
Heavy load	0 (0, 6)[a]	0 (0, 5)[a]	0 (0, 3)	0 (0, 3)
Low load	0 (0, 7)	0 (0, 8)	0 (0, 8)	0 (0, 3)
Swelling				
Heavy load	0 (0, 2)[a]	0 (0, 3)[a]	0 (0, 2)	0 (0, 2)
Low load	0 (0, 2)	0 (−1, 3)	0 (0, 2)	0 (0, 2)

L-Dex and interarm volume presented as mean ± SD. BCRL-related symptoms presented as median (range).
[a]n = 18.

TABLE 4. Equivalence between resistance exercise intensities for all outcomes (n = 17).

	Estimated Mean Difference[b]	Equivalence 90% CI
L-Dex (±3.0)[a]		
Postexercise	−0.97	−2.09 to 0.16
24 h postexercise	−0.14	−1.63 to 1.35
72 h postexercise	−1.00	**−3.17 to 1.17**
Interarm volume % difference (±3.0)[a]		
Postexercise	0.21	−0.89 to 1.31
24 h Postexercise	1.09	0.41 to 1.78
72 h Postexercise	0.96	−0.09 to 2.02
Interarm difference for pain (±1.0)[a]		
Postexercise	0	−0.43 to 0.43
24 h postexercise	−0.06	−0.58 to 0.46
72 h postexercise	−0.06	−0.61 to 0.49
Interarm difference for heaviness (±1.0)[a]		
Postexercise	0.24	−0.23 to 0.70
24 h postexercise	0.18	−0.32 to 0.67
72 h postexercise	0.24	−0.38 to 0.85
Interarm difference for tightness (±1.0)[a]		
Postexercise	−0.06	−0.45 to 0.34
24 h postexercise	−0.11	−0.50 to 0.27
72 h postexercise	0.20	−0.37 to 0.77
Interarm difference for swelling (±1.0)[a]		
Postexercise	0	−0.33 to 0.33
24 h postexercise	0	−0.33 to 0.33
72 h postexercise	0.06	−0.42 to 0.54

Boldface indicates that equivalence was not demonstrated.
[a]Equivalence margin.
[b]Estimated mean difference calculated using a GEE model with heavy load as comparator (heavy minus low).

at 72 h after exercise would have fallen within the margin of equivalence. Therefore, in light of these new normative data, it is likely that response to resistance exercise intensities was equivalent at all time points.

Equivalence was also established for all assessed BCRL symptoms at all time points, and although fluctuations beyond the predetermined thresholds were observed, it should be highlighted that the majority (82%) of these deviations indicated reductions in severity after resistance exercise with both intensities. This is relevant because symptoms can be the earliest indicator of an ensuing BCRL (32).

When interpreting the findings, several limitations should be considered. In this study, participants were excluded if they presented with evidence of BCRL according to standardized protocols for BIS (L-Dex >10) or visual inspection. It is, however, possible that these women were experiencing transient increases in extracellular fluid, either as a consequence of surgery or in response to chemotherapy (33), and/or may have been at greatest risk for developing BCRL. As such, these women may have been more likely than those included in the study to demonstrate changes in extracellular fluid, and by excluding them, it may have been easier to find equivalence between loads. Moreover, activities undertaken by participants within the 3 d after the bout of low- or high-load resistance may have influenced data collected at 24 or 72 h post–exercise session. However, participants were advised to maintain normal activities throughout the study period, and efforts were made to standardize treatment burden by placing exercise bouts and consecutive data collections between chemotherapy cycles.

Strengths of this study include that all participants had received axillary node dissection, considered the largest single risk factor for developing BCRL, lending generalizability to

breast cancer survivors at BCRL risk. Furthermore, because all exercise sessions took place during the taxane-based cycles of chemotherapy, the results extend to acute bouts of low- or high-load resistance-type activities during taxane-based treatment. Finally, validated objective measurement methods sensitive to changes in extracellular fluid were used, and all data collections and analyses were blinded to resistance load lending credibility to the results.

Findings from this study are clinically relevant for a number of reasons. First, the safety of resistance exercise in regard to BCRL risk has previously been established on the basis of exercise prescription using low- to moderate loads. For example, some resistance exercise programs started with little or no weight and slowly progressed with the smallest weight increment possible until loads lifted corresponded to weights that successfully could be lifted a minimum of 15 repetitions (12) or within a range of 10–12 repetitions (34), whereas others used loads corresponding to 60%–80% 1RM at 8–12 repetitions (10,13). As such, this work adds new information, providing initial evidence that resistance exercise prescription also can include heavier loads, specifically corresponding to 85%–90% 1RM at 5–8 repetitions.

Second, a considerable rationale exists for participating in resistance exercise during chemotherapy because it has been found to elicit increases in muscle strength (10,35,36), lean body mass (10), and self-esteem (10) as well as attenuating fatigue and quality of life (36). Moreover, it has been hypothesized that resistance exercise reduces taxane-related edema (37) through the effects of the muscle pump, and it is plausible that participation in heavy-load resistance exercise may instigate more effective lymphatic function change than low-load resistance exercise, and in doing so, potentially have a greater effect on reducing BCRL risk. As such, results from this study provide the necessary platform for future studies to explore whether additional benefits can be gained from repeated bouts of heavy-load resistance exercise during adjuvant taxane-based chemotherapy. Finally, breast cancer survivors commonly receive risk reduction advice cautioning against heavy lifting (38). This study, however, found no evidence to suggest that participation in activities of daily living that include intermittent heavy-load lifting need be avoided. Furthermore, a varied response to resistance exercise was observed for both intensities. This highlights the importance of an individualized approach to resistance exercise prescribed in accordance with signs and symptoms of BCRL, as well as an individualized approach to the risk reduction advice given to breast cancer survivors.

In conclusion, the acute lymphatic response was similar irrespective of whether low- or heavy-load resistance exercise was undertaken in women with axillary node dissection at risk for BCRL during adjuvant taxane-based chemotherapy. Future research needs to now investigate the longer-term response to regular heavy-load resistance exercise. In the interim, these findings challenge existing risk reduction advice concerning avoidance of heavy lifting and suggest that breast cancer survivors should be encouraged to participate in normal daily activities and to act accordingly if changes in sensations or BCRL symptoms are observed.

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