Acute response to resistance exercise and later development of arm lymphedema in breast cancer survivors: An exploratory follow-up of a randomized cross-over trial

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Acute response to resistance exercise and later development of arm lymphedema in breast cancer survivors: An exploratory follow-up of a randomized cross-over trial☆

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ABSTRACT

Background: In breast cancer survivors at risk for lymphedema, variation in lymphatic function and arm volume has been observed related to a bout of exercise, with potential for prediction of breast cancer-related arm lymphedema (BCRaL). This novel, exploratory study examined the acute lymphatic response to resistance exercise and later development of BCRaL in women at high risk for BCRaL.

Methods: One year after participation in a cross-over trial evaluating the acute lymphatic response to upper-extremity resistance exercise (low-and heavy-load), participants were assessed for BCRaL (n = 16). The response to exercise was assessed before and after (post, 24- and 72-hrs) each exercise bout as extracellular fluid (L-Dex; bioimpedance spectroscopy (BIS)), interarm volume % difference (IVD; Dual-energy x-ray absorptiometry (DXA)) and symptoms (Numeric rating scale, 0–10 (NRS)). BCRaL at follow-up was defined as presence of one objective indicator (L-Dex >10, change ≥+6.5, IVD >5%) plus one objective or subjective indicator (interarm symptom ≥1 or visual inspection). Descriptive statistics were used to compare the acute response between participants with and without BCRaL at follow-up.

Results: No trends indicating a similar acute response to exercise was observed in participants who later developed BCRaL (n = 5). There were no observable differences in acute lymphatic response between participants that developed BCRaL and those who did not, both at an individual and group level.

Conclusions: Findings from this exploratory study showed no evidence to suggest that the acute response to resistance exercise can predict BCRaL development.

Key points

- In breast cancer survivors at risk for lymphedema, variation in the acute lymphatic response to exercise has been observed. This has led to speculation that the acute response to an exercise bout could predict subsequent development of lymphedema.
- This one-year follow-up of a randomized cross-over trial is the first study to explore acute response to resistance exercise and later development of lymphedema.
- No observable trends emerged to indicate that the acute lymphatic response to resistance exercise can predict later development of lymphedema.

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1. Introduction

Breast cancer is the most frequent form of cancer with 2.26 million new cases in 2020, corresponding to 11.7% of all cancers [1]. With an increasing incidence and increased survival [2], more people live with the consequences of treatment, including breast cancer-related arm lymphedema (BCRaL). BCRaL is pathological swelling of the affected arm, negatively impacting multiple aspects of daily living including quality of life, mental health and work [3,4]. Initially, BCRaL is characterized by excess protein-rich extracellular fluid, which is potentially reversible in its early stages [5]. However, as the condition progresses to more advanced stages, BCRaL becomes incurable [5].

BCRaL affects one in five breast cancer survivors [6]. Approximately 80% of cases occur within the first two years after cancer treatment (surgery, chemotherapy, radiotherapy) as a result of damage to-, or disruption of, the axillary lymphatics caused by treatment or the cancer itself [3,6]. However, the exact pathophysiology of BCRaL is not clearly understood [3,7]. Nevertheless, well-documented risk factors for developing BCRaL have been identified including axillary lymph node dissection (ALD), radiotherapy of regional lymph nodes and receipt of chemotherapy, as well as modifiable risk factors including body mass index (BMI) $\geq$25 at cancer diagnosis and being insufficiently active or sedentary [6]. Indeed, evidence suggests that exercise has the potential to prevent BCRaL [8]. Although the strength of evidence underpinning known risk factors has improved, it is not yet possible to predict who will develop BCRaL. Yet, better prediction could facilitate early identification as evidence suggests that early detection with intervention likely reduces the risk of developing chronic BCRaL [9].

In healthy individuals, the acute response to exercise causes an increase in arterial blood pressure and cardiac output resulting in greater capillary filtration, and a shift of fluids from plasma to intracellular and interstitial spaces [10,11]. This ultimately leads to increased volume of lymphatic fluid. Concurrently, lymph transport is increased, with at least 2-3-fold increases in lymph clearance observed during exercise that return to pre-exercise levels upon exercise cessation [11–13]. As such, interstitial fluid accumulation usually does not persist beyond the exercise bout.

However, in breast cancer survivors at risk for lymphedema, considerable variation in the acute response to exercise has been observed in lymphatic function [14] and arm swelling [15] with some participants returning to pre-exercise levels (or less) post-exercise, while a delayed response (levels remained elevated) was observed for others. This variation brings into question whether the acute lymphatic response to an exercise bout (e.g. extracellular fluid remains elevated) could predict subsequent development of lymphedema. The aim of this study was to explore the acute lymphatic response to resistance exercise between those who subsequently developed BCRaL and those who did not.

2. Materials and methods

This study is an exploratory follow-up of a sample of breast cancer survivors who had participated in a randomized cross-over trial (ISRCTN97332727) [16,17]. One year follow up of this sample provides the opportunity to compare the lymphatic response to exercise bouts in those who subsequently went on to develop BCRaL compared with those who did not. Adherence to the Consolidating Standards of Reporting Clinical Trials (CONSORT) guidelines extension to randomized crossover trials can be found in Supplementary file 1.

2.1. Response to resistance exercise

The original trial was designed to compare the acute lymphatic response to low- and heavy-load resistance exercise of the upper extremities in participants at high risk for BCRaL [16,17]. Participants were women who had undergone unilateral axillary lymph node dissection, were receiving taxane-based chemotherapy at the time of study participation and had no objective evidence of BCRaL (as determined by bioimpedance spectroscopy (BIS) and visual inspection (swelling, visibility of anatomical structures, pitting edema and axillary cording). Potential participants were excluded if they had a clinical diagnosis of BCRaL, previous breast cancer diagnosis, conditions that limited participation in upper extremity resistance exercise, or participation in regular (>1/week) heavy-load upper extremity resistance exercise within the previous month. Detailed information regarding recruitment, randomization and the intervention can be found elsewhere [16,17]. Briefly, 17 participants provided full data in the cross-over study between March 2015 and December 2016. Participants were randomized to the order of a low- (two sets of 15–20 RM) or heavy-load (three sets of 5–8 RM) resistance exercise session first, with a one-week washout period between each session. Extracellular fluid, arm volume and BCRaL symptoms were assessed using BIS, dual energy x-ray absorptiometry (DXA), and numeric rating scale 0–10 (NRS), respectively, before and after (post (within 30 min), 24- and 72-hrs) the resistance exercise sessions. Participants did not use compression garments during exercise sessions.

2.2. One-year follow-up BCRaL assessment

One year after participation in the cross-over study, participants who had provided full data (n = 17) were invited to partake in a follow-up assessment. Here, extracellular fluid, arm volume and symptoms were evaluated at the Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet. Further, a visual inspection of both arms followed by a structured interview was carried out by the last author. In total, the follow-up session lasted approximately 1.5 h. Medical records were searched for treatment-related characteristics (radiotherapy, targeted treatment, endocrine treatment). As no golden standard for measuring lymphedema exists, nor criterion for defining BCRaL, it has been proposed that using a combination of assessment methods (e.g. symptom assessment, physical examination, objective measures) could improve accurate diagnosis [18,19]. As such, participants in this study were defined as having BCRaL if they presented with one objective indicator of BCRaL (L-Dex >10, $\Delta \geq$+6.5 or IVD >5%) plus one other objective or subjective indicator (interarm symptom $\geq$1 or visual inspection).

2.2.1. Extracellular fluid

Extracellular fluid of the arms was measured by BIS (SFB7, Impedimed, Brisbane, Australia). BIS measurement of each arm was performed lying supine with arms and legs abducted from the body and palms down. Electrode placement has been described previously [16,17]. The difference in impedance between ipsilateral and contralateral arm was calculated, taking arm dominance into account and side of surgery, and converted to an L-Dex score. L-Dex >10 at follow-up or $\Delta \geq$+6.5 (from baseline (first pre-measurement) to follow-up) was considered indicative of BCRaL [20,21].

2.2.2. Interarm volume % difference

Arm volume was measured by DXA (Lunar Prodigy Advanced Scanner, GE Healthcare, Madison, WI). Both arms were scanned separately and positioned as previously described [16,17]. Subsequent analysis of scanned images was performed by a clinical expert using small animal software (ENCORE version 14.10) as described by Gjorup et al. [22]. The volume of fat, fat-free mass and bone mineral content were calculated based on known densities for bone mineral content (1.85 g/ml), fat (0.9 mg/l) and fat-free mass (1.1 mg/l)) [20]. Interarm volume % difference

Table 1
Participant characteristics (n = 16).

Sociodemographic	All (n = 16)	BCRaL (n = 5)[+]	No BCRaL (n = 11)
	n (%)/Median [range]	n (%)/Median [range]	n (%)/Median [range]
Age (yrs)	47 [30; 61]	41 [30; 54]	47 [40; 61]
BMI baseline (kg/m^2)*	24 [19; 37]	25 [21; 31]	23 [19; 37]
BMI follow-up (kg/m^2)	26 [20; 33]	26 [20; 30]	26 [20; 33]
Children 0–6 yrs living at home	4 (25)	2 (40)	2 (18)
Education level			
- Currently a student	1 (6)	1 (20)	0 (0)
- Tertiary (<3 yrs)	2 (13)	1 (20)	1 (9)
- Tertiary (3–4 yrs)	6 (38)	1 (20)	5 (45)
- Tertiary (≥5 yrs)	7 (44)	2 (40)	5 (45)
Physically demanding work			
- Not demanding	9 (56)	3 (60)	6 (55)
- Moderately demanding	7 (44)	2 (40)	5 (45)
Physical activity level (hrs/wk)[#]			
- Walk and/or bikeride <3	4 (25)	3 (60)	1 (9)
- Regular physical activity ≥3	11 (69)	2 (40)	9 (82)
- Hard physical training >4	1 (6)	0 (0)	1 (9)
Breast cancer treatment			
Axillary lymph nodes removed	21 [10; 38]	27 [21; 38]	16 [10; 30]
Metastatic lymph nodes removed	2 [1; 25]	3 [2; 6]	2 [1; 25]
Time from surgery to follow-up (mo)	17 [16; 18]	17 [17; 18]	17 [16; 18]
Surgery on dominant side	8 (50)	3 (60)	5 (45)
Breast surgery			
- Lumpectomy	6 (38)	2 (40)	4 (36)
- Mastectomy	10 (63)	3 (60)	7 (64)
No. postoperative seroma drainage	5 [0; 8]	5 [3; 8]	5 [0; 8]
Chemotherapy			
- CE + docetaxel	9 (56)	3 (60)	6 (55)
- CE + paclitaxel	7 (44)	2 (40)	5 (45)
Regional lymph node radiotherapy			
- 40Gyx15F	4 (25)	1 (20)	3 (27)
- 50Gyx25F	11 (69)	4 (80)	7 (64)
- Andet	1 (6)	0 (0)	1 (9)
Trastuzumab	3 (19)	0 (0)	3 (27)
Endocrine treatment			
- Letrozol	8 (50)	3 (60)	5 (45)
- Tamoxifen	7 (44)	2 (40)	5 (45)

Abbreviations: *BMI* body mass index, *ALD* axillary lymph node dissection, *CE* cyclophosphamide & epirubicin, *BCRaL* breast cancer-related arm lymphedema, *IVD* interarm volume % difference.
[+]Defined as L-Dex >10, Δ ≥+6, 5 or IVD >5% plus one other objective or subjective finding (symptom or visual inspection), *Baseline = first pre-exercise assessment, [#]Within the previous three months of follow-up [27].

(IVD) was calculated using the formula: $\frac{(ipsilateral\ arm - contralateral\ arm)}{contralateral\ arm} \times 100$. IVD >5% was considered indicative of BCRaL [3].

2.2.3. BCRaL symptoms

Immediately following BIS and DXA, participants were asked to rate current BCRaL symptoms (heaviness, swelling, pain and tightness) of both arms using a numerical rating scale (NRS), (0 (no discomfort) – 10 (worst imaginable discomfort)) [23]. The difference in scores between arms was calculated. An interarm difference ≥1 was considered indicative of BCRaL [24].

2.2.4. Visual inspection

Visual inspection of both arms was performed to evaluate visible swelling, obscuration of anatomical structures and pitting edema. A positive finding on the ipsilateral arm compared to the contralateral arm was considered indicative of BCRaL [25].

2.2.5. Structured interview

A structured interview elucidated often cited risk-reduction behaviors related to the development of BCRaL, as these behaviors could potentially influence development of BCRaL in the interim between the cross-over trial and follow-up [26]. This included use of prophylactic compression garment, performance of self-drainage massage or remedial exercises with the intent to prevent BCRaL, whether compression was worn during air travel, and whether extreme temperatures (e.g. sauna) and blood pressure or draws on the surgical side had been avoided. Sociodemographic variables were also collected including age of children living at home, educational background, work status and characteristic (physically demanding) and physical activity levels within the last three months [27]. Finally, BCRaL specific questions (if, when and by whom they were diagnosed with BCRaL) were posed.

2.3. Blinding

The structured interview and visual inspection at follow-up were performed blinded to results of objective measures. Medical laboratory technicians who performed the measurements and the clinical expert that carried out the analysis of all DXA scans were blinded to the order of resistance exercise allocation and BCRaL status.

2.4. Data analysis

The results of the original cross-over trial found no difference in the acute response to resistance exercise between low or heavy loads [16]. As such, low-and heavy-load interventions were considered jointly as a single exercise group in the follow-up study.

Due to the limited sample size, no inferential statistical analysis was performed. Instead, descriptive analyses were carried out with observation of potential trends or patterns. Sample characteristics (socio-demographics, treatment, risk factors, risk prevention behavior and BCRaL status at baseline (first pre-measurement) and one-year follow-up) were analyzed descriptively. Categorical variables were presented as number

Table 2
Acute changes in extracellular fluid (L-Dex) and arm volume (IVD) after a bout of low-and heavy-load resistance exercise and development of BCRaL at one year follow-up.

	Participant	2	6	7	11	12	14	15	16	5	13	4	8	1	10	3	9
		ACUTE RESPONSE TO RESISTANCE EXERCISE															
Low-load (L-Dex)																	
	Pre-post	–	–	+*	–	–	+	+	+	+	+	=	–	–	+*	+*	+
	Pre-24 h			–			–	–	+	–	–				+*	–	–
	Pre-72 h								–						+*		
Heavy-load (L-Dex)																	
	Pre-post	–	–	+	+	–	+	+	+	+	+*	=	–	+	–	+	–
	Pre-24 h			–	–		+	–	–	–	=			–		+	
	Pre-72 h						+*									–	
Low-load (IVD)																	
	Pre-post	+	+	=	–	+	–	+	+	+	+	–	=	+	+	+	–
	Pre-24 h	+	–			+		+	+	+	+			–	–	+	
	Pre-72 h	–				+		+	+	+	+					+	
Heavy-Load (IVD)																	
	Pre-post	–	=	+*	–	+	=	–	–	+	+*	+	–	–	–	–	+
	Pre-24 h			+		=				+	+	+					+
	Pre-72 h			+*						–	+	–					+
		INDICATORS OF BCRaL AT ONE-YEAR FOLLOW-UP															
Indicators of BCRaL (Yes/No)																	
Objective measures	L-Dex >10	Y	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N
	Δ L-Dex ≥6.5	Y	N	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N
	IVD >5%	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
Self-reported symptoms	Heaviness**	Y	N	N	Y	N	Y	Y	Y	N	N	N	N	N	N	N	N
	Swelling**	Y	N	N	N	Y	Y	Y	Y	N	N	N	Y	N	Y	N	N
	Pain**	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N
	Tightness**	N	N	N	N	Y	Y	N	Y	Y	N	N	N	N	N	N	N
Visual inspection	Visible swelling	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N
	Obscur. Anatomy	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	N
	Pitting edema	Y	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N
Sum of BCRaL indicators																	
	Objective measure	3	1	2	2	2	0	0	0	0	0	0	0	0	0	0	0
	Symptoms	2	0	0	1	3	3	2	3	1	1	0	1	0	1	0	0
	Visual inspection	3	1	0	0	1	2	1	0	0	0	1	0	1	0	0	0
	Total	**8**	**2**	**2**	**3**	**6**	5	**3**	**3**	1	**1**	**1**	**1**	**1**	**1**	0	0

Abbreviations: BCRaL, breast cancer-related arm lymphedema; IVD, interarm volume % difference.
+ indicates increase, - indicates decrease, = indicates pre-exercise level.
*Exceeding pre-determined clinically relevant thresholds (L-Dex >3, IVD >3%) (16).
**ipsilateral interarm difference ≥1 (numeric rate scale 0–10).
Grey columns = BCRaL cases at follow-up as per study criteria.
Bold = participants self-reporting a clinical diagnosis of BCRaL within the one-year follow-up period.

(%), while continuous variables were presented as median [range] as data were not normally distributed. The analysis was carried out for the entire study population and with stratification according to BCRaL status.

Spaghetti plots examined the acute response to low- and heavy-load resistance exercise on an individual level with comparison between those with and without BCRaL at follow-up. Further, a descriptive analysis (presented as median [range]) was performed for each of the measurement time points, and for the change between two consecutive time points with stratification according to BCRaL status at follow-up, with overlap of ranges between groups assessed. All analyzes were performed in Statistical Analysis Software (SAS) version 9.4.

3. Results

Sixteen of seventeen participants (94%) agreed to partake in the follow-up (median 17 months post-surgery) (Table 1).

3.1. BCRaL cases

Five participants were identified as having BCRaL as per the study criterion (Table 2).

One participant (participant 2) was defined as having BCRaL based on all objective measures and had eight indicators of BCRaL. The four other participants had two to six indicators of BCRaL, with one participant (participant 7) only having objective measures. On a group level, observed median L-Dex (both criterion) and IVD levels were higher among participants defined with BCRaL versus those who were not, while symptom severity appeared similar between groups (Table 3).

3.2. Risk factors

Participants with BCRaL had more lymph nodes removed (median 27 vs. 16) and relatively more participants with BCRaL were overweight (3/5 vs. 5/11), with a median BMI of 25 vs. 23 at baseline (Tables 1 and 3, Supplementary file 2). Further, relatively fewer participants with BCRaL had performed remedial arm exercises (3/5 vs.10/11) and reported physical activity levels ≥ 3 h per week at follow-up (2/5 vs. 10/11). All other characteristics were similar between those that developed BCRaL and those who did not (Table 1 and Supplementary file 2).

3.3. The acute response to resistance exercise and BCRaL development

3.3.1. L-Dex and IVD

Overall, the acute exercise response appeared similar between participants that developed BCRaL and those that did not, on an individual (Fig. 1 and Table 2) and group level (Table 4). Most participants (n = 11 and 13, (L-Dex and IVD, respectively) had elevated levels of extracellular fluid and arm volume post exercise vs. pre-exercise (Table 2). At 24 and 72 h, L-Dex and IVD levels continued to be increased in four and ten, and two and nine, participants, respectively. No pattern emerged between the acute response (e.g. extracellular fluid and volume remained elevated)) and development of BCRaL.

Table 3
BCRaL status and related variables at follow-up.

Objective BCRaL measurement	All (n = 16)	BCRaL (n = 5)+	No BCRaL (n = 11)
	n (%)/Median [range]	n (%)/Median [range]	n (%)/Median [range]
L-Dex	0.9 [-4,7; 42.0]	11.5 [-0.3; 42.0]	0.7 [-4.7; 7.2]
ΔL-Dex from baseline	−0.3 [-5.4; 40.4]	7.7 [-2.6; 40.4]	−0.9 [-5.4; 6.2]
IVD	1.6 [-7.8; 23.6]	7.7 [0.9; 23.6]	−0.1 [-7.8; 5.0]
Visual inspection			
Swelling	4 (25)	3 (60)	1 (9)
Obscuration anatomical structure	4 (25)	1 (20)	3 (27)
Pitting edema	2 (12,5)	1 (20)	1 (9)
Self-reported			
Symptom severity*			
- Heaviness	0 [0; 4]	0 [0; 4]	0 [0; 1]
- Swelling	0 [0; 5]	0 [0; 5]	0 [0; 2]
- Pain	0 [0; 1]	0 [0; 1]	0 [0; 1]
- Tightness	0 [0; 3]	0 [0; 3]	0 [0; 2]
Clinical BCRaL diagnosis	12 (75)	5 (100)	7 (64)
Months from surgery to BCRaL diagnosis			
- 6 - 8	3 (25)	1 (20)	2 (29)
- 9 - 11	5 (42)	2 (40)	3 (43)
- ≥12	4 (33)	2 (40)	2 (29)
Participation in preventative behaviors			
Prophylactic compression garment **	4 (25)	1 (20)	3 (27)
Remedial exercises	13 (81)	3 (60)	10 (91)
Air travel			
- No air travel	3 (19)	0 (0)	3 (27)
- No compression garment	9 (56)	3 (60)	6 (55)
- With compression garment**	4 (25)	2 (40)	2 (18)
Avoidance blood pressure**			
- Yes	6 (38)	2 (40)	4 (36)
- Don't know***	10 (63)	3 (60)	7 (64)
Avoidance Blood draws**			
- Yes	10 (63)	3 (60)	7 (64)
- No	2 (13)	1 (20)	1 (9)
- Don't know***	4 (25)	1 (20)	3 (27)
Avoidance extreme temperatures			
- Yes	10 (63)	3 (60)	7 (64)
- Sauna	5 (31)	2 (40)	3 (27)
- Sauna + winter bathing	1 (6)	0 (0)	1 (9)

Abbreviation: *BCRaL* breast cancer-related arm lymphedema, *IVD* interarm volume % difference, *ALD axillary lymph node dissection*, +Defined as L-Dex >10, Δ ≥+6,5 or IVD >5% plus one other objective or subjective finding.
* Numeric rating scale 0–10 (interarm difference), **Ipsilateral arm, ***Not consistent or not aware.

Four and two participants had *a priori* clinically relevant post-exercise fluctuations >3 L-Dex units and IVD >3%, respectively [16]. One of these, (participant 7) had developed BCRaL at follow-up.

3.3.2. Symptoms

Few symptoms were reported. (Supplementary file 3) Symptom response appeared similar between participants that developed BCRaL and those who did not, both at the individual and group level (Supplementary file 3 and 4). One participant (participant 15) had post-exercise symptoms (heaviness and swelling) fluctuating >1 in severity (considered *a priori* clinically relevant [16]). This participant did not have BCRaL at follow-up.

3.3.3. Indicators of BCRaL

Three participants (participants 14, 15, 16) had three or more indicators of BCRaL but were not defined as a BCRaL case as no objective measures were found (Table 2). Additionally, twelve participants self-reported that they had been diagnosed with BCRaL during the follow-up period. No trends in acute response were observed to indicate later development of BCRaL in analyses including these participants as BCRaL cases. (Supplementary files 5 and 6, Table 2).

4. Discussion

To the authors knowledge, this exploratory study is the first to examine the acute response of extracellular fluid, arm volume and symptoms to exercise and subsequent development of BCRaL. One year after participation in the cross-over trial, five participants were defined as having BCRaL. No trends emerged to suggest a relationship between the acute lymphatic response to resistance exercise and the development of BCRaL.

4.1. Timeframe

An increase in lymph fluid volume and transport is expected during exercise as observed by increased lymphatic clearance rates in non-cancer populations and survivors of breast cancer [10,12–14,28,29]. While limited research has explored how quickly clearance rates return to pre-exercise levels, studies have observed lymphatic clearance rates returning to pre-exercise levels within 15 min in the legs of healthy men after both resistance and aerobic exercise [12,13]. In women previously treated for breast cancer (n = 23), McNeely et al. observed mean arm volume estimates (assessed by circumference measurement) that returned to pre-exercise levels within 30 min after cessation of arm-cranking [15]. In the present study, most participants had increased levels of extracellular fluid or volume at the post-intervention assessment which was taken within 30 min of exercise cessation. Future research should seek to assess lymphatic function closer to exercise bouts and at regular intervals during the first hour post exercise to better understand how quickly lymphatic fluid returns to pre-exercise levels in breast cancer survivors at risk for BCRaL.

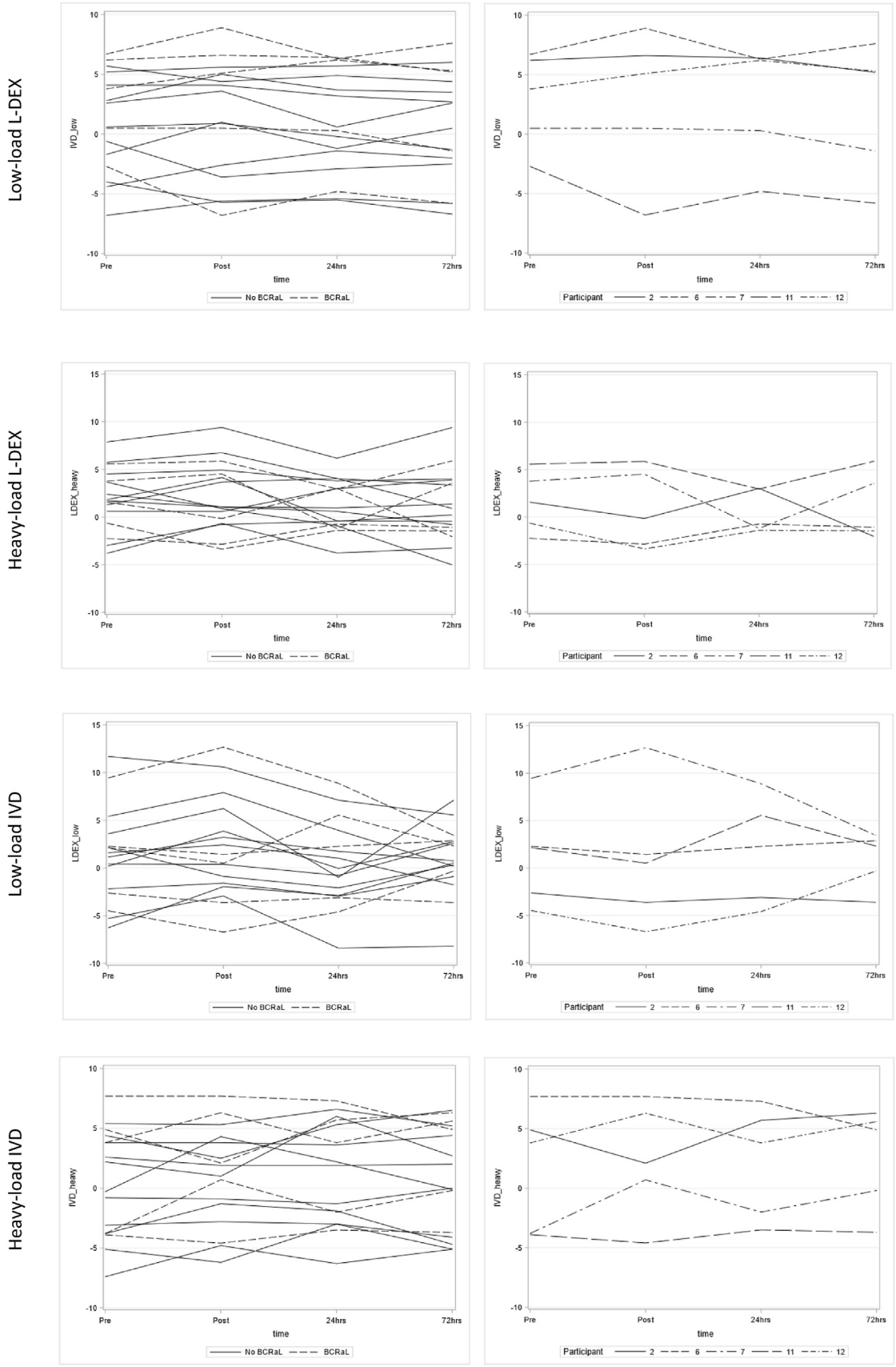

Fig. 1. *Individual extracellular fluid (L-Dex) and interarm volume % difference (IVD) response to low- and heavy-load resistance exercise. Left-side shows response for all participants (n = 16), while right-side shows response in participants defined with breast cancer-related arm lymphedema at follow-up (n = 5).* Abbreviation: *BCRaL* breast cancer-related arm lymphedema, *IVD* inter-arm volume % difference.

Table 4
Extracellular fluid (L-Dex) and interarm volume % difference (IVD) after a bout of low- and heavy-load resistance exercise in participants with (n = 5) and without (n = 11) BCRaL at follow-up.

L-Dex	Pre Median [range]	Post Median [range]	24 h Median (range)	72 h Median [range]
Low-load				
BCRaL	2,1 [-4,5; 9,5]	0,5 [-6,7; 12,7]	2,3 [-4,6; 8,9]	2,3 [-3,6; 3,4]
No BCRaL	1,2 [-6,3; 11,7]	2,4 [-2,9; 10,6]	−0,8 [-8,4; 7,1]	0,5 [-8,2; 7,1]
Heavy-load				
BCRaL	1,6 [-2,2; 5,6]	−0,2 [-3,4; 5,9]	−0,7 [-1,4; 3,0]	−1,1 [-2,1; 5,9]
No BCRaL	1,8 [-3,8; 7,9]	1,1 [-0,8; 9,4]	1,0 [-3,8; 6,2]	0,9 [-5,0; 9,4]
IVD				
Low-load				
BCRaL	3,8 [-2,7; 6,7]	5,1 [-6,8; 8,9]	6,2 [-4,8; 6,4]	5,2 [-5,8; 7,6]
No BCRaL	0,6 [-6,8; 5,7]	1,0 [-5,7; 5,6]	−0,2 [-5,5; 5,7]	0,5 [-6,7; 6,0]
Heavy-load				
BCRaL	3,8 [-3,9; 7,7]	2,1 [-4,6; 7,7]	3,8 [-3,5; 7,3)	4,9 [-3,7; 6,3]
No BCRaL	−0,3 [-7,4; 5,4]	1,0 [-6,2; 5,3]	1,9 [-6,3; 6,6]	0,0 [-5,1; 6,5]

L-Dex	Δ Pre–post Median [range]	Δ Post–24 h Median [range]	Δ 24–72 h Median [range]
Low-load			
BCRaL	−1,0 [-2,2; 3,2]	0,8 [-3,8; 5,0]	−0,5 [-5,5; 4,3]
No BCRaL	2,1 [-3,0; 4,3]	−1,5 [-7,2;-0,9]	2,1 [-3,8; 8,1]
Heavy-load			
BCRaL	−0,6 [-2,7; 0,7]	1,96 [-5,7; 3,2]	−0,06 [-5,1; 4,8]
No BCRaL	1,0 [-2,8; 3,1]	−1,1 [-4,5; 2,4]	0,2 [-4,1; 3,2]
IVD			
Low-load			
BCRaL	0,4 [-4,1; 2,2]	−0,2 [-2,6; 2,0]	−1,0 [-1,7; 1,3]
No BCRaL	0,4 [-3,0; 2,7]	0,1 [-3,0; 1,2]	−0,4 [-1,2; 2,0]
Heavy-load			
BCRaL	0,0 [-2,8; 4,5]	−0,4 [-2,7; 3,6]	0,6 [-2,4; 1,8]
No BCRaL	−0,1 [-1,9; 4,6]	−0,2 [-2,1; 3,2]	−1,1 [-3,3; 1,3]

Abbreviations: *IVD* interarm volume % difference, *BCRaL* breast cancer-related arm lymphedema.

4.2. Variable response and BCRaL prediction

In the aforementioned study by McNeely and colleagues [15], post-exercise changes in arm volume were observed in both directions on an individual level, compared to pre-exercise. Similarly, in a three-group study by Lane et al. (n = 30), a variable response of radiopharmaceuticals (measured by lymphoscintigraphy) reaching the axilla and forearm after 60 min of moderate-intensity arm cranking was observed in breast cancer survivors at risk for BCRaL (n = 10) [14]. Some participants responded similarly to healthy controls. However, others showed an acute response that resembled participants with BCRaL, leading the authors to speculate that these participants may develop BCRaL. In the present study, individual variability was also observed. However, no trends were observed between those who later developed BCRaL and those who did not. As such, our findings do not support the hypothesis that breast cancer survivors that later develop BCRaL have an altered acute lymphatic response to resistance exercise. Notably this was an exploratory study and was not originally designed to assess this relationship.

4.3. Measure of lymphatic response

Surrogate measures of lymphatic response were used in the present study. Direct measures of lymphatic function may provide a better understanding of the acute lymphatic response to resistance exercise. Indocyanine green (ICG) lymphography is a newer technology [30] that provides direct imaging of lymphatic function. This technology uses a non-radioactive solution that travels via the lymphatics enabling high-resolution, real-time imaging of lymphatic function. Utilization of ICG would likely be more sensitive to subtle acute changes in lymphatic function, when compared with changes detected by BIS and DXA and should therefore be considered for use in future research.

4.4. BCRaL incidence

As expected, some participants did develop BCRaL within one year of the cross-over study. Specifically, 5/16 (31%) met our study criteria for BCRaL. While this incidence is higher than the generally accepted incidence rate of approximately 20%, participants in this study were at higher risk (all had received ALD, regional lymph node radiotherapy and taxane-based chemotherapy) than the wider breast cancer population. This is of relevance as the cumulative treatment burden alone can influence incidence rates as exemplified by a Danish population-based study (n = 3253), finding BCRaL prevalence ranging from 13% (SLNB and breast surgery alone) to 65% in women who had been treated with mastectomy, ALD, radiotherapy, and chemotherapy [31].

4.5. BCRaL cases vs. self-reported clinical diagnosis

Twelve participants (75%) reported that they had been diagnosed with BCRaL during the follow-up period. This disparity between BCRaL cases at follow-up and self-reported diagnosis can, at least in part, be explained by several factors. First, it is well established that choice of diagnostic method, and criterion applied, influences incidence or prevalence estimates [7]. This is well illustrated in a study by Hayes et al. that found an over 2-fold difference in baseline BCRaL prevalence depending on the measurement method applied (22% (arm circumference) vs. 52% (self-reported swelling)) [32]. Second, participants diagnosed with BCRaL likely had received or were receiving treatment. Therefore, objective measures at follow-up could be missed, as well-treated BCRaL may regress the condition, preventing objective detection. However, as treatment for BCRaL was not recorded, this cannot be confirmed. Finally, the higher incidence of a clinical diagnosis may be due to transient swelling [33,34]. Indeed, in a population-based study monitoring women

diagnosed with breast cancer during the first 18 months after diagnosis (n = 278), 58% of the participants identified with BCRaL (n = 62) displayed transitory swelling lasting <3 months [34]. As such, transient cases could mistakenly have been reported as chronic BCRaL in the present study, inflating self-reported clinical diagnosis estimates.

4.6. Risk factors

Consistent with strong evidence supporting the increased risk of BCRaL related to the extent of axillary surgery [3,6] and BMI ≥25 [3,6,35], participants identified with BCRaL had more lymph nodes removed and a higher median BMI than participants that did not develop BCRaL. This adds confidence to the credibility of the identified BCRaL cases. Also, participants that developed BCRaL self-reported less physical activity compared to participants without. While we cannot know if physical activity levels reported at follow-up are representative of physical activity prior to developing BCRaL. This finding is noteworthy considering that a recent systematic review and meta-analysis (n = 522), found that the risk of BCRaL decreased with exercise participation in breast cancer survivors with ≥5 lymph nodes removed (RR: 0.49 (CI95% 0.28–0.85)) [8], supporting the role of exercise as a strategy to prevent BCRaL.

4.7. Strengths and limitations

This study has several limitations. First, this was a small, exploratory study and findings can therefore only be considered observational. Second, the median follow-up time since surgery was 17 months. Considering that 80% of cases are detected within the first two years, more participants could potentially develop BCRaL. Further, though participants were instructed not to partake in strenuous activities in the days following the training sessions, the lack of control in this time-period could potentially account for some variations seen at 24 and 72 h. Finally, inherent to studies investigating lymphedema, the lack of gold standard measures and uniform definition of what constitutes lymphedema brings uncertainty to the incidence of BCRaL at follow-up. Indeed, results of this study indicate limited overlap of the various measurement methods, highlighting the need for research in BCRaL measurement and criterion applied. Nonetheless, two validated and reliable objective measurement methods were used, enabling the detection of BCRaL in both early and late stages, alongside symptoms and visual inspection. Importantly, additional analyses including participants with three or more indicators of BCRaL (but no objective measures), and in participants with a self-reported clinical diagnosis yielded similar findings.

4.8. Prospective surveillance

The results do not suggest that the acute lymphatic response to exercise can aid in better prediction of BCRaL, of potential for early identification. Currently, prospective surveillance with intervention is considered the most optimal strategy to prevent BCRaL. This is supported by a recent systematic review and meta-analysis (12 studies; n = 1527) finding that the pooled rate of chronic BCRaL was 6% in breast cancer survivors with ALD who had participated in prospective surveillance vs. generally accepted incidence rates (approximately 20%) [9]. Going forward, until the pathophysiology of this condition is better understood (allowing for targeted intervention) and considering the chronicity of the condition once established, early intervention strategies should be considered to prevent BCRaL, especially for the subgroup of patients at highest risk.

5. Conclusion

Similar trends in the acute lymphatic response to resistance exercise were observed between participants who subsequently developed BCRaL and those who did not at one year. Findings from this exploratory study do not support that the acute lymphatic response to resistance exercise can predict later development of BCRaL.

Data statement

Data can be made available upon reasonable request to the corresponding author.

Ethics

The study was approved by the Danish Data Protection Agency (30-1430) and the Danish Capital Regional Ethics Committee (H-3-2014-147). The study was performed in accordance with the Helsinki Declaration and written informed consent was obtained from participants before inclusion to the study.

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Declaration of competing interest

All authors declare no competing interests exist, financial or otherwise.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsampl.2024.100057.

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