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Upper extremity lymphatic function at rest and during exercise in breast cancer survivors with and without lymphedema compared with healthy controls

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Lane KN, Dolan LB, Worsley D, McKenzie DC. Upper extremity lymphatic function at rest and during exercise in breast cancer survivors with and without lymphedema compared with healthy controls. *J Appl Physiol* 103: 917–925, 2007. First published June 21, 2007; doi:10.1152/japplphysiol.00077.2007.—Lymphoscintigraphy was used to measure lymphatic function at rest and during exercise in breast cancer survivors with lymphedema (BCRL, $n = 10$), breast cancer survivors (BC, $n = 10$), and controls (Cont, $n = 10$). After injection of ^{99m}Tc-antimony colloid to the hands, subjects rested or performed 12 repeated sets of arm cranking for 2.5 min at 0.6 W/kg followed by 2.5 min of rest. One-minute spot views were taken with a gamma-radiation camera immediately postinjection and every 10 min over 60 min to calculate clearance rate. As well, an upper body scan was taken at 65 min postinjection to measure radiopharmaceutical uptake in the axilla (Ax) and forearm (Fore). All groups displayed similar increases in clearance rate with exercise ($P = 0.000$). Ax significantly increased with exercise in Cont only [Cont: (mean ± SD) 4.9 ± 2.6 vs. 7.9 ± 4.2%, $P = 0.000$; BCRL: 1.4 ± 1.2 vs. 1.7 ± 2.1%, $P = 0.531$; BC: 3.9 ± 3.4 vs. 5.2 ± 3.2%, $P = 0.130$], whereas Fore, indicating dermal backflow, significantly increased in BCRL only (BCRL: 2.4 ± 0.87 vs. 4.4 ± 2.0%, $P = 0.004$; BC: 1.1 ± 0.25 vs. 1.1 ± 0.31%, $P = 0.784$; Cont: 0.93 ± 0.26 vs. 1.0 ± 0.20%, $P = 0.296$). The results indicate that, in women with BCRL, exercise causes radiopharmaceuticals to clear from the hand at the same rate as BC and Cont, but, instead of reaching the axilla, a greater amount of activity gets trapped in the dermis of the forearm. BC, meanwhile, have similar lymphatic function as Cont; however, there is a highly variable response that may suggest that some BC subjects may be at risk for developing lymphedema.

lymphoscintigraphy

APPROXIMATELY 28% OF WOMEN treated for breast cancer are at risk for developing breast cancer-related lymphedema (BCRL) (18, 35), yet it remains a poorly understood complication of this disease. Treatment variables commonly associated with increased risk (mastectomy, extent of axillary surgery, axillary radiotherapy, radiotherapy to the breast, nodal disease status) do not, on their own, accurately distinguish the at-risk population (45). Furthermore, little is known about how to manage BCRL. Although compression sleeves (6, 11), pneumatic pumping (13, 22, 23, 43), manual lymphatic drainage (2, 50, 53, 54), and low-level laser therapy (8, 44) are often recommended to contain swelling, research investigating their efficacy has had equivocal results. Exercise was originally thought to exacerbate BCRL; however, recent studies (1, 9, 17, 21, 28, 52) have shown no significant change in arm volume with resistance training or upper body aerobic exercise.

Research investigating the efficacy of potential therapeutic interventions to manage and/or prevent BCRL is often limited by the use of anthropometric measurements, such as arm volume and arm circumference, to reflect a change in lymphedema status. While anthropometric measurements are simple and noninvasive, they do not provide information on changes in the physiology of the lymphatic system. Lymphoscintigraphy has added another dimension to the evaluation of lymphatic function. This technique was developed to assess lymphatic status in patients with a variety of conditions that cause lymphatic obstruction (24, 56). Typically, lymphoscintigraphy applied to BCRL involves administering a radiopharmaceutical to the finger web space or forearm and imaging the upper extremity using a gamma-camera at various time points postinjection. The radiopharmaceutical is generally a technetium-labeled macromolecule or colloid that is of sufficient size (i.e., between 4 and 100 nm) to enter the lymphatic capillaries and not blood capillaries (24, 51, 56).

Lymphoscintigraphy is increasingly being used in the investigation of the pathology of BCRL (30, 36–42, 46–49) and in the examination of various therapeutic interventions prescribed to manage BCRL (12, 15, 19, 29, 50). While these studies provide some new insight into the pathophysiology of BCRL and potentially useful therapeutic interventions, they are limited in the application of the lymphoscintigraphy protocol. Specifically, studies using lymphoscintigraphy to examine lymphatic function in women treated for breast cancer have been essentially performed at rest. Intermittent forearm exercise, such as clenching the fists or squeezing a rubber ball between imaging scans, has been used in several studies to stimulate lymph flow (36–38, 40, 46, 50, 55). However, we have previously shown depot clearance rates (CR) in healthy women to be similar between rest and handgrip exercise (25). There are several advantages to measuring lymphatic function in breast cancer survivors, with and without BCRL, during moderate-intensity exercise. First, a standardized exercise protocol can help to decrease variability in the data, especially when the intensity and duration of the activity are quantified. For example, we have demonstrated a lower coefficient of variation for depot CR during moderate-intensity arm cranking exercise vs. low-intensity exercise (26). Second, evaluating the lymphatic system in a "stressed" situation can help to diagnose

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pathologies that may be latent at rest, similar to the way exercise is used by a cardiologist or respirologist. Therefore, the purpose of this exploratory study was to evaluate upper extremity lymphatic function at rest and during intermittent, moderate-intensity, upper body exercise in breast cancer survivors with BCRL (BCRL group), breast cancer survivors (BC group), and age-matched controls (Cont group).

METHODS AND MATERIALS

Subjects. Three subject groups (breast cancer survivors with lymphedema, BCRL, $n = 10$; breast cancer survivors with no lymphedema, BC, $n = 10$; healthy age-matched women, Cont, $n = 10$) were included in the prospective, cross-sectional analysis. Both BC and BCRL included women diagnosed in the past 25 yr with stage I-III breast cancer with treatment, including axillary lymph node dissection and radiation. Those with BCRL had clinically significant lymphedema defined as a difference of >2.0 cm at either of the following measuring points: 10 cm distal to the lateral epicondyles, or 15 cm proximal to the lateral epicondyles. BC subjects were matched to BCRL by number of axillary lymph nodes excised. Cont included healthy women with no history of breast cancer that were matched by age and body mass index (BMI) to BC and BCRL. Descriptive data are provided in Table 1, while details of breast cancer treatment are provided in Table 2.

Before testing, informed consent was obtained from each subject, and the study was approved by the Clinical Screening Committee for Research and Other Studies Involving Human Subjects at the University of British Columbia.

Experimental design. A prospective, exploratory, between-groups design was used to compare differences in lymphatic function in the three subject groups. The independent variables were the intermittent exercise protocol and rest, whereas the dependent variable was lymphatic function. The primary outcome measure of lymphatic function was depot CR, whereas secondary outcome measures included uptake of the radiopharmaceuticals at the axilla (Ax) and forearm (Fore) at 65 min postinjection relative to the initial dose.

Imaging. Lymphoscintigraphy was used to quantify lymphatic function and was performed at Vancouver General Hospital, Department of Nuclear Medicine. Subjects were asked to arrive hydrated and rested. They were also asked to avoid caffeine in the 6 h before the start of the study. The same technician prepared and administered subcutaneous injections of the radiopharmaceutical ^{99m}Tc-antimony colloid to all of the subjects on each testing day.

Four injections with a total activity of 18 MBq, each dose in 0.05 ml, were introduced into the first and fourth web spaces of each hand before the start of the exercise protocol. Subjects placed both hands prone on a gamma-camera equipped with a low-energy, ultra-high-resolution collimator (Sopha Medical Vision). Only the forearms and the hands were in the field of view of the camera, and a single camera head was used. One-minute static acquisitions with a 20% energy window centered on a 140-kV peak were taken within 1 min of the injection and again every 10 min postinjection thereafter, over a total period of 60 min, to allow for the calculation of CR. At 65-min postinjection, an upper body scan was taken to allow for calculation of Ax and Fore. Subjects were in the supine position for the upper body scan, and the camera head moved from the axilla to fingertips. The images were stored on a hard drive as a 256 × 256 Word frame format for later analysis.

The images were processed using Siemens Icon software (version 8.5, Siemens Medical Systems). The region of interest (ROI), or the selection of pixels for analysis, was drawn around each of the injection sites to give the number of activity counts, and each ROI was corrected for physical decay of ^{99m}Tc. All ROIs for CR and Ax were normalized to an area of 1,500 pixels, whereas all ROIs for Fore were normalized to an area of 3,000 pixels.

CR was calculated from images of the depot sites. The two counts from each hand were included in the same ROI, and the corrected count at each time point was divided by the corrected count measured immediately after injection and was plotted against time. CR from the injection site was linear and, therefore, expressed as a slope (% administered activity/min). R^2 values for the time-activity relationship during exercise for the three subject groups, BCRL, BC, and Cont, were 0.92, 0.94, and 0.92 for the contralateral arm, respectively, and 0.94, 0.95, and 0.95 for the ipsilateral arm, respectively.

ROIs were drawn around the axilla and forearms from the images generated from the upper body scan taken at 65 min postinjection. These were expressed relative to the initial amount of radioactivity at the injection site to determine Ax and Fore.

Rest and exercise conditions. On separate days, subjects did either the intermittent exercise protocol (12 repeated sets of arm cranking for 2.5 min at 0.6 W/kg followed by 2.5 min of rest) or seated rest. The exercise began immediately after the first imaging scan and continued to 60 min postinjection and was performed on a calibrated Lode arm ergometer (Angio single set model). Figure 1 shows a photo of a subject performing the arm cranking protocol. As subjects were not strapped into a seat, they were asked to minimize trunk and lower body involvement while arm cranking. Heart rate (HR) was recorded every 10 min throughout using a Polar T31 HR monitor (Polar Electro, Lake Success, NY). Not all subjects were able to complete the prescribed power output for exercise (five BCRL subjects, one BC subject, and one Cont subject). For these subjects, power output was decreased by 10–15 W so they could complete the 60-min intermittent exercise challenge.

Statistical analyses. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS, Chicago, IL), and significance was set at $P = 0.05$. Descriptive statistics (mean ± SD) were calculated for subject characteristics. Differences in age, BMI, axillary lymph node dissected, exercise power output, exercise HR, and forearm and upper arm circumferences (affected arm relative to unaffected arm) were compared using one-way ANOVA. For Cont subjects, the right or left arm was

Table 1. *Sample characteristics for women treated for breast cancer with breast cancer-related lymphedema, women treated for breast cancer, and control subjects*

	BCRL	BC	Cont
Age, yr	61.6 (11.0)	59.3 (6.4)	60.3 (6.9)
BMI, kg/m^2	30.4 (5.8)	25.0 (3.1)	27.3 (5.5)
Exercise power output, W	39.9 (10.3)	40.6 (5.7)	39.2 (5.5)
Exercise heart rate, beats/min	129.8 (16.0)	136.5 (15.5)	132.5 (17.8)
Axillary lymph nodes dissected, no.	16.2 (6.5)	16.5 (9.0)	
Arm circumference, % (affected arm relative to unaffected arm)			
Forearm	116.0 (10.8)*	101.9 (2.5)	100.1 (2.9)
Upper arm	110.7 (12.7)*	99.8 (1.8)	100.2 (2.1)

Values are means (SD). BCRL, breast cancer-related lymphedema; BC, breast cancer; Cont, control; BMI, body mass index. *Significantly different from BC and Cont ($P < 0.05$).

Table 2. *Details of patients treated for breast cancer*

Subject No.	BCRL or BC	Age, yr	BMI, kg/m^2	Affected Arm	Year of Diagnosis	Type of Surgery	Nodes Excised, no.	Nodes Positive, no.	RT to Axilla	CT	BCRL Duration, yr	Increase in Volume, %	
												Forearm	Upper Arm
1	BCRL	50	28.2	Left	1996	M	19	0	Y	Y	10	125	100
2	BCRL	52	37.5	Right	2000	M	20	1	Y	Y	5	108	107
3	BCRL	46	33.0	Left	2005	M	16	2	Y	Y	1	115	100
4	BCRL	59	40.6	Left	2004	M	14	1	N	Y	2	102	109
5	BCRL	65	25.0	Left	2003	M	7	0	Y	Y	3	117	103
6	BCRL	74	28.8	Left	2000	L	20	3	Y	Y	6	133	116
7	BCRL	74	29.7	Right	1984	L	4	0	Y	N	18	127	142
8	BCRL	77	29.2	Right	1993	M	16	7	Y	Y	12	123	119
9	BCRL	64	20.4	Right	2001	L	25	2	Y	Y	1	111	102
10	BCRL	55	31.9	Right	2004	M	21	4	Y	Y	1	102	109
11	BC	59	23.3	Right	2000	M	13	0	N	Y		100	101
12	BC	59	31.8	Left	1995	M	13	0	N	N		104	99
13	BC	59	24.9	Right	2000	M	40	2	N	Y		103	102
14	BC	66	22.4	Right	1998	L	14	3	Y	N		105	98
15	BC	58	28.2	Right	1999	M	6	0	N	N		100	100
16	BC	58	25.9	Left	1996	L	13	2	Y	Y		99	100
17	BC	60	23.2	Left	2003	L	19	3	Y	Y		98	96
18	BC	72	21.3	Left	1995	M	16	0	Y	N		103	101
19	BC	54	24.0	Right	2004	M	19	2	Y	Y		102	99
20	BC	48	25.0	Right	2005	M	12	2	Y	Y		105	103

L, lumpectomy; M, mastectomy; Y, yes; N, no; RT, radiation therapy; CT, chemotherapy. Increase in volume is relative to circumference on contralateral side.

randomly designated as the affected arm using a random numbers generator.

3 × 2 (Between-within) ANOVAs were used to determine differences in lymphatic function between groups at rest and during exercise. The affected and unaffected arms were analyzed separately. This was done to determine whether lymphatic function in the unaffected, or contralateral, arm in women treated for breast cancer is normal (i.e., similar to control data). Post hoc analysis for any main effects was performed using Tukey's test of honest significant differences.

RESULTS

Subject characteristics. Characteristics of the study participants are summarized in Table 1. Age, BMI, number of axillary lymph nodes excised, exercise power output, and exercise HR were similar between groups. Subjects with BCRL had a significantly greater forearm circumference (P = 0.000) and upper arm circumference (P = 0.010) compared with both BC and Cont. Details of breast cancer treatment are provided in Table 2.

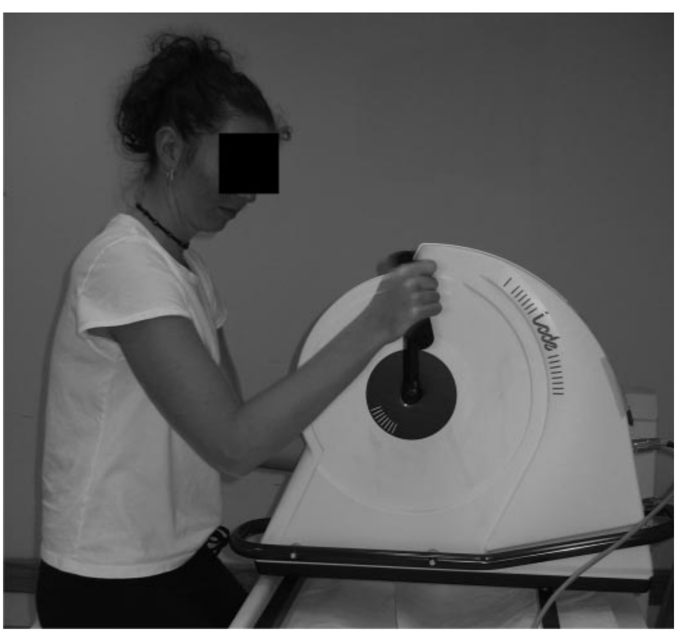

Fig. 1. Photo of subject performing arm cranking protocol.

Lymphatic function in the unaffected arm. Lymphatic function (CR, Ax, and Fore) in the unaffected arm in women treated for breast cancer (BC and BCRL) was not significantly different than results obtained for the Cont group at rest and during exercise (Table 3). All groups displayed a significant increase in CR with exercise ($P < 0.05$). However, Ax increased with exercise in Cont only (P = 0.008). A trend was seen for an increase in Ax with exercise in both BCRL and BC, but these did not reach significance (P = 0.249 and P = 0.108, respectively). Fore, indicating dermal backflow, did not change from rest to exercise in any group.

Lymphatic function in the affected arm. Figure 2*A* shows no significant difference in CR of the affected or treated arm between groups. Additionally, all groups demonstrated similar increases from rest to exercise (BCRL: −0.09 ± 0.04 vs. −0.17 ± 0.06%/min, P = 0.002; BC: −0.09 ± 0.06

Table 3. *Lymphatic function in the unaffected arm during rest and exercise in women treated for breast cancer with breast cancer related lymphedema, women treated for breast cancer, and controls*

	BCRL	BC	Cont
CR rest	−0.12 (0.06)	−0.11 (0.05)	−0.10 (0.06)
CR exercise	−0.18 (0.07)*	−0.20 (0.06)*	−0.19 (0.07)*
Ax rest	6.4 (3.1)	6.0 (4.6)	5.7 (3.4)
Ax exercise	7.4 (3.0)	8.5 (3.0)	8.6 (3.6)*
Fore rest	1.0 (0.3)	1.1 (0.2)	1.2 (0.4)
Fore exercise	1.0 (0.2)	1.2 (0.3)	1.2 (0.3)

Values are means (SD). CR, clearance rate; Ax, radiopharmaceutical uptake at the axilla 65 min postinjection relative to the initial dose; Fore, radiopharmaceutical uptake at the forearm 65 min postinjection relative to the initial dose. *Significantly different ($P \leq 0.05$) value compared with rest condition.

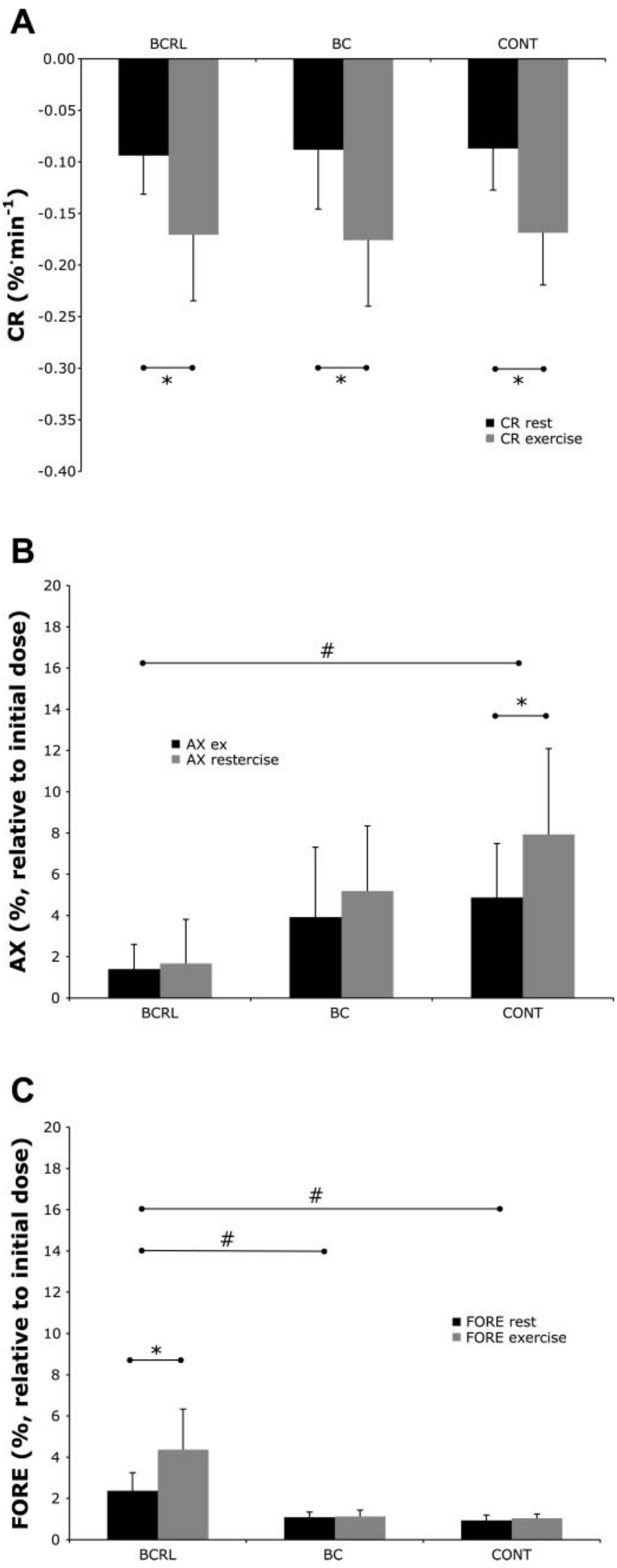

Fig. 2. Lymphatic function as represented by depot clearance rate (CR; *A*), uptake in the axillary lymph nodes at 65 min postinjection (Ax; *B*), and uptake in the forearm region at 65 min postinjection (Fore; *C*) at rest and during exercise in the ipsilateral (affected) arm of women treated for breast cancer with lymphedema (BCRL), women treated for breast cancer with no lymphedema (BC), and age-matched controls (Cont). Resting data are indicated by solid bars, and exercise data by shaded bars. *Significant difference between resting and exercise values ($P < 0.05$). #Significant difference between groups ($P < 0.05$).

vs. −0.18 ± 0.06%/min, P = 0.001; Cont: −0.09 ± 0.04 vs. −0.17 ± 0.05%/min, P = 0.000).

Radiopharmaceutical uptake at the axilla 65 min postinjection relative to the initial dose (Ax) for the affected arm is shown in Fig. 2*B*. Ax significantly increased with exercise in Cont only (Cont: 4.9 ± 2.6 vs. 7.9 ± 4.2%, P = 0.000; BCRL: 1.4 ± 1.2 vs. 1.7 ± 2.1%, P = 0.531; BC: 3.9 ± 3.4 vs. 5.2 ± 3.2%, P = 0.130). BCRL had significantly lower Ax compared with Cont during both rest (P = 0.019) and exercise (P = 0.001), while no difference was found between BC and Cont.

Figure 2*C* shows uptake in the forearm 65 min postinjection relative to the initial dose (Fore) significantly increased with exercise in BCRL only (BCRL: 2.4 ± 0.87 vs. 4.4 ± 2.0%, P = 0.004; BC: 1.1 ± 0.25 vs. 1.1 ± 0.31%, P = 0.784; Cont: 0.93 ± 0.26 vs. 1.0 ± 0.20%, P = 0.296). BCRL, at rest, also had significantly greater Fore than both BC (P = 0.002) and Cont (P = 0.000). Similarly, during exercise, BCRL had significantly greater Fore than both BC (P = 0.000) and Cont (P = 0.000). There was no difference between BC and Cont for either condition.

Lymphatic function in the affected arm vs. unaffected arm. Paired t-tests were run on affected and unaffected data from breast cancer subjects (BCRL and BC) to determine differences in lymphatic function between arms. Both BCRL and BC had significantly lower Ax on the affected side at rest (P = 0.014 and P = 0.019, respectively) and during exercise (P = 0.003 and P = 0.000, respectively). Only BCRL had significantly greater Fore on the affected side at rest (P = 0.010) and during exercise (P = 0.006).

DISCUSSION

This is the first study to measure lymphatic function during intermittent, moderate exercise in women treated for breast cancer with and without lymphedema and age-matched, healthy controls. The principal findings of this prospective, exploratory study are the following: *1*) all variables used to measure lymphatic function in the unaffected arm were similar between groups; *2*) lymphatic function in the affected arm was similar between Cont subjects and BC, while BCRL subjects had a significantly lower axillary uptake (Ax) and a significantly greater forearm activity (Fore); and *3*) the addition of exercise significantly increased CR in the affected arm of all groups, Ax in both arms of Cont only, and Fore in the affected arm of BCRL only. Fore, indicating dermal backflow, is not expected to increase with exercise.

Radiopharmaceutical CR from the injection depot. The rate that radiopharmaceuticals clear from the injection depot (i.e., CR) is a typical outcome variable used to describe lymph transport in women treated for breast cancer. Considering that breast cancer survivors (BCRL and BC) had an average of 16 lymph nodes dissected, we hypothesized that CR would be impaired in these subjects at rest and during exercise. However, CR in all groups approximately doubled with exercise. This response to exercise is comparable to data we have collected in healthy, college-aged women (K. N. Lane, unpublished comparison of data from Refs. 25 and 26). Thus the excision of axillary lymph nodes does not appear to affect subcutaneous CR from the hand.

Making direct comparisons between the findings in the present study and other research is difficult due to differences in lymphoscintigraphy protocols (i.e., particulate administered, location of injection, type, intensity, and duration of exercise, such as fist clenching or ball squeezing performed intermittently between imaging scans, etc.). Moreover, no study has investigated lymphatic function during moderate-intensity exercise in women treated for breast cancer. Although several investigations had subjects with BCRL perform intermittent forearm exercise, such as clenching the fists or squeezing a rubber ball between imaging scans to stimulate lymph flow (36–38, 40, 46, 50, 55), we have previously shown depot CR in healthy women to be similar, whether rest or handgrip exercise was performed (25).

Despite differences in methodology between the present study and those published in the literature, present research has indicated that resting CR in women with BCRL may depend on whether radiopharmaceuticals are administered to swollen or spared tissue of the affected arm. For example, administering radiopharmaceuticals subcutaneously (30, 38–40, 46, 48) or subfascially (47) to swollen tissue during resting conditions has demonstrated slower lymph drainage compared with a similar injection site on the unaffected arm. Yet when injections are administered to the spared region of the swollen arm during resting conditions, CR is similar (38, 40) or even faster (46). Although hand volume was not measured in the present study, 3 of 10 subjects with BCRL had noticeably slower CR during exercise in the affected arm compared with the unaffected arm, while another three had noticeably faster CR in the affected arm during exercise. There is the possibility that the BCRL subjects with a slower CR were also the ones with swollen hands, while subjects who displayed a similar or faster CR had spared hands. The remaining four subjects had comparable CR between arms. Future research investigating the effects of exercise on lymphatic function should ensure that hand volume, as well as arm volume, is measured and considered as a confounding variable.

It is expected that CR will increase from rest to exercise in those with normal lymphatic transport. Arm cranking exercise involves the forearm flexors and extensors, biceps brachii, triceps brachii, and the muscles of the upper back and shoulders at different phases of the circular motion. During exercise, capillary hydrostatic pressure and capillary surface area both increase, thereby leading to an increase in capillary filtration and thus interstitial fluid pressure (31). In healthy individuals, interstitial edema accumulation usually does not persist beyond the exercise bout due to an increase in lymph formation and lymph transport. This is because normal physiological responses to exercise, such as an increase in cardiac output, sympathetic nervous system activity, skeletal muscular contractions, and respiration, are also mechanisms that assist with lymph formation and propulsion (3, 59). Thus a concomitant increase in lymph flow with increased exertion would be expected and has been shown in animal (10, 27) and human (34) research by cannulating a lymphatic vessel.

Radiopharmaceutical uptake in the axillary lymph nodes. In the absence of taking blood samples, the percentage of radiopharmaceuticals in the axillary lymph nodes relative to the initial dose at a set time point postinjection (i.e., Ax) may be a potential indicator of the efficiency of the lymphatic drainage system (7, 24, 32, 51). There are some limitations, however, to considering Ax as an outcome measure. For example, lymph node retention of tracer is only a "snapshot" of the amount of tracer present in the axillary lymph nodes at any one time. Despite colloids having good regional lymph node retention (24, 58), these particles will migrate through the lymph nodes and eventually enter the systemic circulation. It is unknown how long the radiopharmaceuticals are retained in the lymph nodes and what factors speed or slow tracer exit from a lymph node. Another limitation of Ax is that breast cancer treatment often involves lymph node excision and/or radiation therapy, thereby reducing the number of functional nodes on the affected side. Consequently, analyzing the axillary lymph nodes may result in an artificially lower percentage on the affected side simply due to fewer functional lymph nodes. To control for this potential confounding variable, we matched BC and BCRL subjects based on the number of axillary lymph nodes dissected.

As expected, our results demonstrated significantly lower Ax values in the affected arm of BCRL compared with Cont at rest and during exercise. However, despite BCRL and BC subjects having similar number of axillary lymph nodes dissected, BC subjects had a noticeably higher Ax compared with BCRL subjects during exercise (5.2 ± 3.2 vs. 1.7 ± 2.1%, $P = 0.065$). In fact, BC subjects had Ax values at rest and during exercise that were more comparable to Cont than BCRL. Age-matched Cont subjects had a significant 3.0% increase in Ax from rest to exercise, whereas BCRL had a 0.3% increase on the affected side ($P = 0.531$) and BC had a 1.3% increase ($P = 0.130$). The significant increase in Ax in Cont subjects indicates the capacity of the axillary lymph nodes to store greater amounts of radiopharmaceuticals and facilitated transport through lymphatic vessels. It is unknown if lymph nodes have a maximum capacity for radiopharmaceutical storage. Even though there are limitations to using Ax as an outcome variable as previously mentioned, BC subjects as a group had a 1.3% increase in Ax from rest to exercise. While this was nonsignificant ($P = 0.130$) and one-half the increase seen by Cont subjects, only a change of 0.3% was seen in BCRL subjects, who also had 16 lymph nodes dissected. Thus, even with similar numbers of lymph nodes dissected, BC patients have a variable response to an exercise stimulus in terms of axillary lymph node uptake of radiopharmaceuticals. While some BC subjects showed an increase in Ax with exercise that was similar to that of Cont subjects, others had a response that was more typical of BCRL. It is unknown from the present study if the inability of lymph nodes at the axilla to increase storage of radiopharmaceuticals during exercise may indicate a latent pathology. It is possible that the BC subjects who present in a similar manner as Cont subjects in terms of Ax values have regeneration of lymphatic pathways after lymph node removal, allowing lymph to return to the venous system. Jila and colleagues (20) demonstrated the regeneration of lymphatic pathways in sheep after obstructing lymph flow downstream from the popliteal lymph node. Further research is needed to evaluate the suitability of comparing rest and exercise Ax in a larger cohort of breast cancer survivors to identify latent pathologies.

Radiopharmaceutical uptake in the forearm. Fore was investigated to determine the presence of dermal backflow in the arms of women treated for breast cancer. Stanton et al. (46) describe dermal backflow as a rerouting of lymph toward skin that is represented by diffuse activity in the ipsilateral arm with intense amounts of activity at the periphery of the image. Only the forearm was included in the ROI for this measure due to a large number of subjects displaying localized foci of activity in the upper arm (likely epitrochlear lymph nodes). As hypothesized, women with BCRL had significantly greater Fore compared with both BC and Cont during rest and exercise. Other studies administering subcutaneous injections of radiopharmaceuticals to the hand of women with BCRL have also observed dermal backflow, regardless of whether or not the hand of the affected arm was swollen or spared (46, 48). However, dermal backflow was not seen with subfascial injections to the forearm (47). Considering that dermal backflow has been observed in both swollen and spared hands, Stanton and colleagues hypothesize that the access point for radiopharmaceuticals to dermal lymphatic routes is likely near the hand or the wrist.

As expected, Fore did not change from rest to exercise in BC and Cont; however, there was a significant increase in Fore in BCRL subjects. Taken with the CR and Ax data, this would indicate the following. In women with BCRL, radiopharmaceuticals are able to clear from the hand at the same rate as other subject groups, but, instead of reaching the axilla, the activity pools in the dermis, as evidenced by the significantly lower Ax and significantly higher Fore. BC subjects, on the other hand, responded to the exercise stimulus in a manner more similar to Cont subjects. While there was reduced accumulation of radiopharmaceuticals reaching the axilla, the amount of activity in the forearm region stayed at levels consistent with Cont values, and the amount of forearm activity did not change from rest to exercise. However, several BC subjects had a response to exercise that was more typical of what was seen in BCRL patients. There is the possibility that BCs who present in a similar manner as BCRL to an exercise task may be at risk for developing lymphedema, but this speculation requires further research.

Unaffected arm lymphatic function. Stanton et al. (48) compared CR in the unaffected arm of BCRL subjects with a swollen hand to those with a spared hand (swollen forearm). While a significantly faster CR was observed in the unaffected arm of the swollen hand group (unaffected arm of swollen hand group = −0.157%/min vs. unaffected arm of spared hand group = −0.095%/min), CR in the affected arm was similar between groups. This suggested that the unaffected arm might not, in fact, be normal, and preoperative differences in lymphatic function may exist.

Since hand volume was not measured in the present study, we compared lymphatic function in the unaffected arms of subjects with BCRL, BCs, and age-matched Cont. The results of this study indicate no significant differences in lymphatic function (as assessed by CR, Ax, and Fore) of the unaffected arm at rest or during exercise. However, the response of the unaffected arm to the exercise stimulus differed between groups. For example, a significant increase in lymphatic function was observed in Cont for each variable (except Fore, which was not expected to change with exercise). But BCRL and BC subjects did not show a significant rise in Ax with

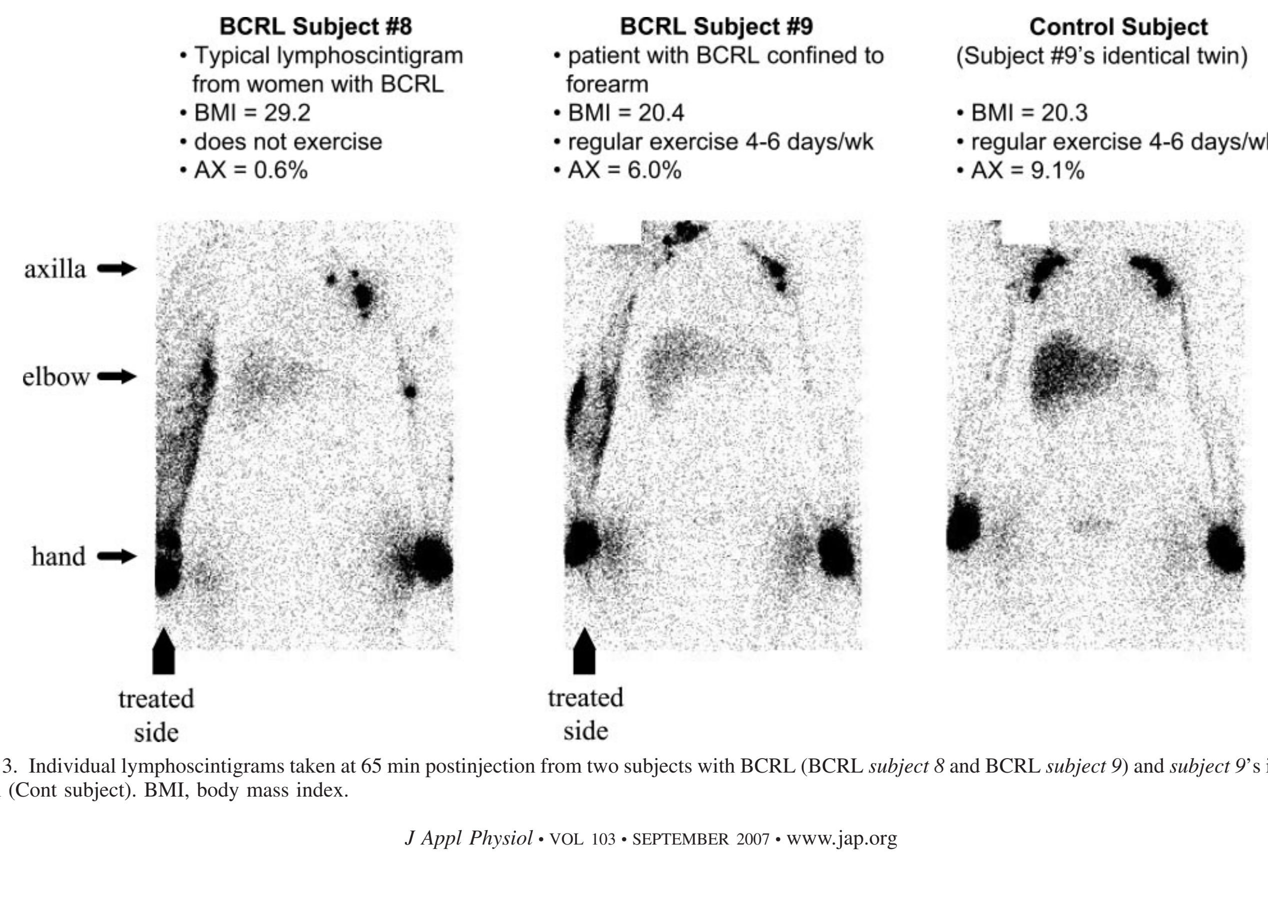

Fig. 3. Individual lymphoscintigrams taken at 65 min postinjection from two subjects with BCRL (BCRL *subject 8* and BCRL *subject 9*) and *subject 9*'s identical twin (Cont subject). BMI, body mass index.

exercise, although a trend toward an increase was observed for both groups (BCRL: 6.4 vs. 7.4%; BC: 6.0 vs. 8.5%). The variability in resting BC data likely reduced the power to detect a significant difference in Ax between resting and exercising conditions. It must also be considered that systemic changes in lymphatic function occurred due to breast cancer treatment and that contralateral arm lymphatic function was not normal in these subjects.

Clinical implications. Another important finding of this study is that not all subjects treated for breast cancer have similar lymphatic function during exercise. To give one example, mean (± SD) Ax in the affected arm of BCRL subjects during exercise was 1.7 ± 2.1%; however, one subject with BCRL (BCRL *subject 9*, Fig. 3) had an Ax value of 6.0% on the affected side, despite having the most lymph nodes excised in the BCRL group (25 vs. BCRL average of 16.2). *Subject 9*, compared with others in the BCRL group, was also unique in other aspects: she had the lowest BMI (20.4 vs. 30.4 kg/m^2), was only one of two BCRL subjects who reported performing moderate-intensity exercise more than 4 days/wk, and had a region of swelling confined to the distal portion of the forearm. Interestingly, *subject 9*'s lymph nodes on the affected side appear to be closer to the neck than the axilla. This is likely not a genetic abnormality, as her identical twin sister (Cont subject, Fig. 3) was also investigated and has symmetrical lymph nodes in the axillary region.

Although aerobic fitness was not assessed in this study, there is the possibility that the regular exercise performed by *subject 9* resulted in adaptations to the lymphatic system, such as lymphangiogenesis, around the damaged axillary lymphatics. Yoon et al. (57) found VEGF-C therapy reversed swelling through lymphangiogenesis in an animal model of lymphedema. As habitual exercise in a healthy population is known to induce angiogenesis through upregulation of other isoforms of VEGF (16), then it is reasonable to expect concurrent lymphangiogenesis through upregulation of VEGF-C. Moreover, Goldman et al. (14) showed that a reduction in interstitial flow caused a decrease in lymphangiogenesis in the mouse tail, even with exogenously administered VEGF-C. Thus normal interstitial flow appears to be an important factor for lymphangiogenesis. Considering exercise increases clearance of radiopharmaceuticals from the hand depot in BCRL, as shown by our CR findings, then regular exercise may be necessary to invoke lymphangiogenesis. Lymphangiogenesis could help to reduce the stress put on the lymphatic vasculature damaged by axillary lymph node dissection and radiation to the axilla. Perhaps the regular exercise performed by *subject 9* resulted in the creation of new lymphatic vessels draining into lymph nodes found near the neck on the affected side. This speculation requires further research.

Experimental conditions. Several limitations must be taken into consideration when examining the findings from this study. Efforts were made to control extraneous variables that may influence lymphatic function. All subjects arrived at the testing location at the same time of day and were asked to drink normal amounts of water in the 3 days prior. They were also asked to avoid caffeine and exercise during the day of measurement. However, other factors may also have an influence on lymphatic function, such as medications, hypertension, and location of arm swelling in women with BCRL. A brief medical history was taken from each subject, but neither blood pressure nor hand swelling was recorded.

Although changes in muscle tone and pressure were assumed to be similar between groups, there is the possibility that the arm swelling in lymphedema may further increase pressure within and around the muscles of the arm. If the swelling is primarily in the upper arm region, then this may hinder radiopharmaceutical clearance from the swollen region of the arm during exercise and lead to pooling of activity in the hand or forearm. Furthermore, there is evidence that hemodynamic factors, such as venous pressure, arterial inflow, microvascular density, and sympathetic control of the vasculature, may be abnormal in BCRL (33). It is possible that these hemodynamic differences may also account for the different distribution of lymph in those with BCRL, as shown by the significantly higher Fore and significantly lower Ax.

Conclusions. Our results demonstrate that BCRLs have similar clearance of ^{99m}Tc-antimony colloid from the hand depot during exercise, but reduced accumulation of radiopharmaceuticals reaching axillary lymph nodes on the affected side that was not overcome with exercise. BCs had lymphatic function more similar to Cont subjects but did not show a significant increase in axillary uptake of radiopharmaceuticals with exercise. Furthermore, BCRLs present with significantly greater activity in the forearm region, suggesting dermal backflow, that worsens with exercise. Considering the individual variation in lymphatic function from rest to exercise in BCs, it is possible that the inability of the lymphatic system to respond to an exercise stimulus by increasing Ax without a concomitant increase in Fore may indicate a greater risk of development of breast cancer-related lymphedema. This hypothesis requires further research.

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GRANTS

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