THE EFFECT OF UPPER BODY EXERCISE ON SECONDARY LYMPHEDEMA FOLLOWING BREAST CANCER TREATMENT

by

ANDREA LEIGH KALDA

B.Sc., The University of Victoria, 1995

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

(Faculty of Education; School of Human Kinetics)

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

April 1999

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of HUMAN KINETICS

The University of British Columbia
Vancouver, Canada

Date APRIL 29, 1999

DE-6 (2/88)

Abstract

The effect of upper-body aerobic exercise on lymphedema secondary to breast cancer treatment was examined in 14 subjects. Subjects were assigned to either an Exercise group (n=7) or a Control group (n=7). Before subject recruitment, groups were created by selecting a subject number and a group out of two separate containers. As subjects were recruited, they were sequentially assigned a number, and thereby a group. One subject was allowed to enroll as a control subject instead of in the assigned exercise group for geographical reasons.

All subjects were assessed over an eight week period, during which the exercise subjects followed an upper body exercise program including but not limited to a Monark Rehab Trainer arm ergometer. Control subjects maintained their lifestyle as before the study. Lymphedema was assessed by arm circumference measurements as well as arm volume measurements by water displacement. The Medical Outcomes Trust Short-Form 36 Survey was used to measure quality of life before and after the intervention. Significance was set at $\alpha \leq .01$.

No changes were found in arm circumference or arm volume as a result of the exercise program. Three of the quality of life domains showed trends towards increases in the exercise group, although findings were not statistically significant: physical functioning ($p=.050$), general health ($p=.048$), and vitality ($p= .023$). Mental health increased, although not significantly, for all subjects ($p=.019$). Arm volume measured by water

displacement was correlated with calculated arm volume ($r=.973$, $p<.001$), although the exercise and control group means were significantly different ($t=-24.19$, $p<.001$).

Arm volume does not appear to increase in women with lymphedema following breast cancer due to participation in an upper-body aerobic exercise program, and they may experience an increase in quality of life. This suggests that further studies should be done in this area to determine the optimum training program.

Table of Contents

List of Tables

List of Figures

Acknowledgments

Dr. Don McKenzie: A huge thank you for letting me "flail around for a little while", but always stepping in with the right words when I needed them. Having the opportunity to work with someone I respect so much has been an experience I will never forget and one for which I will always be thankful.

Dr. K. Coutts & Dr. S. Harris: Thank you for taking the time to be a part of this project, and for helping to make this study as strong as possible.

All of the women who participated in this study: Without you this wouldn't have been possible! I can't thank you enough for volunteering your time and energy to this project. I have never met more inspiring people. You were the spirit behind the science, and I wish you all the best in the future.

My parents, Denise and Riho Kalda: Just like the kitchen wall that Graham built, you're the place I run to when there's an earthquake. Thank you for supporting me in so many different ways. They say you can't choose your parents, but I'm sure I chose you and I couldn't have picked better parents. I love you!

My sister, Robyn Kalda: Who else would I call to calm me down when I'm panicking? You're the best at it, but then you've been practicing for about 25 years... Thank you!

Richard Wooles: A constant presence, even when you're far away. "How can I be alone? Love keeps me company."

My lab-mates and friends: Thank you Sherri Neisen, Lisa Wiley, and Dana Sinclair for paving the way, Bill Sheel for being the voice of reason, Andrea Dalton for putting up with my mess all over the living room when I was writing, and Dale Tiessen, Kevin McKim, and Mike Bodner for the great venting sessions.

Introduction

Lymphedema secondary to breast cancer treatment is a chronic high-protein fluid accumulation in the upper extremity. It is characterized by swelling that is pitting in the early stages and then progresses to a hard, non-pitting state due to collagen deposition in the upper extremity. The exact cause of onset remains unclear, although axillary dissection, radiotherapy to the breast, radiotherapy to the axilla, pathological nodal status, obesity, and tumor stage appear to be predisposing factors (Kissin, Rovere, Easton, & Westbury, 1986). Estimates of the incidence of lymphedema are varied, but in the United Kingdom a large scale prevalance study found that 28% of women who were treated for breast cancer and were still surviving had lymphedema (Mortimer, Bates, Brassington, Stanton, Strachan, & Levick, 1996). This is similar to other recent studies, with reported incidence of 25.5% (Tobin, Lacey, Meyer, & Mortimer, 1993) and 24% (Maunsell, Brisson, & Deschenes, 1993). Many treatment options are available, but so far none offer a permanent reduction or elimination of arm swelling.

In the rehabilitation of breast cancer survivors, it is generally accepted that multimodal physical therapy mobilizes lymphatic fluid (Mirolo,Bunce, Chapman, Olsen, Eliadis, Hennessy, Ward, & Jones, 1995). However, upper-body aerobic exercise is rarely mentioned, and seems to be considered contraindicated in the clinical lore, especially for women who have developed lymphedema following breast cancer treatment. This recommendation can not be substantiated in the literature.

There are several reasons to think that upper-body aerobic exercise may help reduce lymphedema (McKenzie, 1998). Propulsion of lymph may be increased by both the extrinsic and

intrinsic muscle pumps. Because extrinsic muscle pumping may be involved in lymph propulsion (Witte & Witte, 1987), increasing the activity of the muscles may help to restore lymph flow. The intrinsic smooth muscle of the lymphatic vessels themselves is stimulated by nitric oxide (NO), which is released locally in response to endurance exercise (Levine & Balady, 1993). The increase in blood flow due to the gradual reintroduction of exercise will supply more oxygen to the whole limb, but particularly to the smooth muscle layers and adventitia of the lymphatic vessels which have high oxygen requirements (Ohhashi, 1993).

The effect of upper-body aerobic exercise on patients with lymphedema has not been investigated systematically. Therefore, this study examined the changes in arm circumference, arm volume, and quality of life in women with secondary lymphedema due to breast cancer treatment throughout an 8 week upper-body aerobic exercise program. Two methods of arm volume determination were used: water displacement, and calculation of volume from arm circumference measurements (calculated arm volume).

Hypotheses

The null hypotheses are:

(1) There will be no difference in arm volume measured by water displacement over time between subjects in the experimental and control groups.

(2) There will be no difference in calculated arm volume over time between subjects in the experimental and control groups.

(3) There will be no difference between volume measurements done by water displacement and calculated from arm circumference for the study sample as a whole.

(4) There will be no relationship between total work completed and change in percent difference in calculated arm volume for the study sample as a whole.

(5) There will be no difference in quality of life over time between subjects in the experimental and control groups.

Methodology

Subjects

Fourteen subjects were recruited from physiotherapists, massage therapists, doctors, posted notices, newspaper advertisements, and an advertisement in a breast cancer newsletter. They were assigned to either the treatment group (n=7) or the control group (n=7). Prior to subject recruitment, the numbers 1 to 20, representing the expected sample size, were placed in one container, and 10 letter "E"'s and 10 letter "C"'s were placed in a separate container. A number was drawn, and then a letter, and subjects were thereby assigned to groups. All subjects except one were assigned using this method. In the one exception, an exercise subject was allowed to join the control group instead for geographical reasons.

Prior to testing, subjects completed the Informed Consent form (Appendix 2), the Par-Q Readiness to Exercise form, and were given a complete verbal explanation of the study. Both the study and the Informed Consent form were approved by the Clinical Screening Committee for Research and Other Studies Involving Human Subjects of the University of British Columbia.

Subjects were eligible for the study if they had undergone breast cancer treatment for stage I or II breast cancer which had been completed more than six months before enrolling in the study, and had subsequently developed unilateral lymphedema that was greater than 2cm and less than 8cm on at least one point (Cluzan, Alliot, Ghabboun, & Pascot, 1996). It was also required that they be free from active disease. They were excluded if they had third stage lymphedema, which is characterized by overproduction of connective tissue and hardening of the

skin (Farncombe, Daniels, & Cross, 1994). Other exclusion criteria were diagnosis of any other major diseases, or if they were taking any drugs such as diuretics that may affect upper extremity swelling. If a woman had been undergoing treatment for lymphedema for more than one month, she was eligible for the study as long as she continued with the treatment. However, treatments started during the study would exclude her from finishing the study. Subjects recorded information regarding stage of breast cancer, date and type of treatment received for breast cancer, and past or current treatment for lymphedema. Characteristics of treatment for breast cancer and lymphedema are presented in Tables 1 and 2.

Table 1. Characteristics of Treatment for Breast Cancer

	Exercise Group	Control Group	Total
Number with Stage I breast cancer	4	2	6
Number with Stage II breast cancer	3	5	8
Number who received surgery	7	7	14
Chemotherapy	5	6	11
Radiotherapy	4	7	11
Mean time since treatment ± SD (years)	8.62 ± 12.34	5.36 ± 4.66	6.52 ± 9.12

Table 2. Characteristics of Treatment for Lymphedema

	Exercise Group	Control Group	Total
Mean time since onset of lymphedema (years)			
Affected limb = Dominant limb	2	6	8
Manual lymphatic drainage (past)	2	2	4
Manual lymphatic drainage (during study)	0	0	0
Sequential pneumatic pump (past)	3	4	7
Sequential pneumatic pump (during study)	2	4	6

Eighteen women responded to the requests for subjects. Of these women, 12 were not eligible, and 6 were eligible but chose not to enrol in the study. Fifteen subjects were recruited and tested. Of the 15 subjects tested, 14 met the criteria for the study. One was excluded because the difference between the normal arm and the affected arm was less than 2cm on all measurement points at time 1. All 14 remaining subjects completed the study.

Two subjects had other medical conditions that caused them pain during the eight-week testing period and therefore may have affected their self-report of quality of life. One exercise subject experienced a flare-up of pre-existing carpal tunnel syndrome during the exercise program, and one control subject had arthritis of the knee.

Tests

All subjects were tested every two weeks for eight weeks, beginning with the baseline measurement, giving a total of five measurements. Height and weight were measured to 0.1 cm and 0.1 kg respectively.

For the arm circumference measurements, subjects lay prone, arms relaxed by their sides and elbows straight. Both arms were measured at each test date. Circumference was measured every three centimeters beginning at the ulnar styloid process and continuing 45cm proximally, as well as at the metacarpals and mid-hand. The measuring tape was placed around the extremity so that there was no slack but also so there was no indentation in the tissue.

Upper extremity volume was measured by water displacement. Two volume measurements were taken for each upper extremity; the first to the ulnar styloid process only (hand), the second to 45cm proximal to the ulnar styloid process (hand, forearm, and arm). The arm was kept straight and was immersed slowly into the water, sliding the fingers straight down the inside wall of the volumeter. Water was collected from the instant the arm was first immersed until after the pen mark for the measurement point was just below the surface and water was dripping less than once per second. Water was displaced into a graduated cylinder, and the volume was read to the nearest 5 milliliters.

Both intervention and control subjects completed daily log books, recording any activity that they felt may have affected the swelling of their arm. Exercise subjects also recorded their exercise program, including number of repetitions of each exercise and the weight used.

The Medical Outcomes Trust 36-Item Short-Form Health Survey (SF-36 U.S. Acute Version 1.0) general quality of life questionnaire was administered at the first and last measurement dates. This scale has been validated and reliably detects quality of life deficits in general medical patients (Ware, Snow, Kosinski, & Gandek, 1993). This eleven-question form measures eight domains: Physical functioning, role of physical functioning, bodily pain, general health, vitality, social functioning, role of emotional functioning, and mental health. It was

scored according to the SF-36 Health Survey Manual and Interpretation Guide (Ware et al., 1993).

Exercise Program

Experimental subjects completed an eight-week exercise program. The use of a professionally fitted elastic compression sleeve was encouraged for all exercise sessions, and all exercise subjects followed this recommendation. A light resistance training program including flexibility exercises (McKenzie & Jespersen, 1998) was started immediately after the baseline test and was continued three times per week for the duration of the experimental period. The purpose of this resistance and flexibility training was to help prevent injury. One stretch for each major body part was prescribed. Resistance training included specific exercises, beginning with a very light weight and progressing as tolerated by the subject. Strength exercises prescribed were the seated row, bench press, latissimus pulldown, one arm bent over rowing, tricep extension, and bicep curl. Two sets of 10 repetitions for each exercise were done for the first week, three sets of 10 done thereafter. Exercises were done slowly in a controlled manner to prevent injury. The training sessions were composed of a five to seven minute light aerobic warm-up such as walking or biking, five to seven minutes of stretching, strength training, and a cool-down stretch.

After two weeks an upper body aerobic component, using a Monark Rehab Trainer arm ergometer, was added. Subjects exercised under the supervision of the primary investigator, following a progressive program as outlined in Table 1. This program was used as a guide, but was adjusted according to subjects' self-report of fatigue or pain in their affected arm. Work in kilojoules was calculated for each session for every subject, and this was used to calculate

cumulative work done over the course of the program. Heart rate was monitored during the arm ergometry sessions using a polar heart rate monitor.

Control subjects were given no specific exercise instruction until after they completed the study, at which time they had the option of being taught the exercise program. It was explained to the control subjects that if they commenced any activity or treatment that may affect their lymphedema, it may affect the results of the study and so unfortunately they would not be eligible to continue with the testing. However, they would still be able to continue with the exercise program if they were an exercise subject, or to learn the exercise program if they were a control subject and were interested in being taught.

Table 3. Progression of Upper Body Aerobic Exercise Program

Day	Resistance (Watts)	Duration of exercise (minutes)	Length of breaks (seconds)
1	8.3	5 x 1 minute	30
2	8.3	10 x 1 minute	30
3	8.3	15 x 1 minute	30
4	8.3	20 x 1 minute	30
5	8.3	20 x 1 minute	15
6	8.3	20 continuously	0
7	8.3	20 continuously	0
8	8.3	20 continuously	0
9	16.6	20 continuously	0
10 to end	up to 25	20 continuously	0

Procedural Definitions

Calculation of Body Mass Indices

Body mass indices were calculated from the height (cm) and weight (kg) data.

$$BMI = weight / height^2$$

Calculation of arm circumference difference

Arm circumference (arm circ) difference was calculated for each test according to the following formula:

arm circ difference = Σcircumferences (affected arm) - Σcircumferences (unaffected arm)

Absolute scores were then converted to ratios, expressed as percentages, by dividing the value for the unaffected limb by that of the affected limb, at each time period, as in the following equation:

$$\% \text{ difference in arm circumference} = \frac{\text{circumference of affected limb at Time X}}{\text{circumference of unaffected limb at Time X}} \times 100$$

Calculation of arm volume from circumference measurements

The volume of each arm was calculated from the arm circumference measurements. The following formula for volume of a simple cylindrical object was used, where circumference = the mean of the two bounding circumferences, and height = 30 millimeters (the length of each segment between circumference measurements):

$$\text{Volume} = \pi \left(\text{circumference} / 2\pi \right)^2 h$$

The sum of all of the segments from the ulnar styloid process to 45cm proximal for each arm equals the total volume of the arm, excluding the hand (Farncombe et al., 1994).

Absolute scores were then converted to ratios, expressed as percentages, by dividing the value for the unaffected limb by that of the affected limb, at each time period, as is shown in the following equation:

$$\% \text{ difference in arm volume} = \frac{\text{volume of affected limb at Time X}}{\text{volume of unaffected limb at Time X}} \times 100$$

Calculation of Work

Total work per session was calculated from the time in seconds that subjects were exercising on the arm ergometer, multiplied by the Watts that they were pushing as read from the meter on the ergometer.

Total work (joules) per session = Power (Watts = joules/sec) x time (secs)

Calculation of Transformed SF-36 scores

Raw scores for each of the eight categories were converted to a percentage of the highest possible score using the following formula:

$$\text{Transformed Scale} = 100 \times \frac{\text{Actual raw score - lowest possible raw score}}{\text{Possible raw score range}}$$

Statistical Analyses

The study design was a 2 (group) by 5 (time) factorial Analysis of Variance with repeated measures across time. Student's t-tests were done for descriptive data and to ensure homogeneity of groups at time 1. Significance was set at $P<0.01$ for all comparisons to compensate for the number of tests being done on a small sample.

One of the subjects missed a testing session (time 3). In order to maintain sample size, regressions were used to predict values for arm circumference, measured arm volume, and

calculated arm volume from the other 13 subjects values at times1, 2, 4, and 5 (R^2 values between 0.879 and 0.999).

General linear model repeated measures ANOVAs were done using SPSS. Percent difference in arm circumference, percent difference in measured arm volume, and percent difference in calculated arm volume were tested separately. Pearson product-moment coefficients of correlation were calculated to determine the relationships between measurement techniques, and paired-samples t-tests were used to determine if the means were significantly different. The eight SF-36 domains were also tested using separate repeated measures ANOVAs. The difference between domain scores at time 1 and time 2 was then calculated for those domains that showed a significant difference in the ANOVA, and these difference scores were then correlated with the difference in both measured and calculated volumes (time 2 - time 1). Pearson product-moment correlation coefficients were determined for the four domains with p-values less than or equal to .05 from the repeated measures ANOVAs in order to assess the viability of these results.

Work done by each exercise subject was calculated for each 2 week inter testing period, and a Pearson product-moment coefficient of correlation was calculated to determine if a relationship existed between work and percent difference in measured arm volume.

Subjects in the Control Group were 3, 4, 5, 6, 7, 13, and 15.

Results

Baseline Measures

Group characteristics at time 1 are shown in Table 4. Subject characteristics are shown in Appendix 2, Table A1. There were no significant differences found between groups at time 1 with respect to age (t=.06, p=.473), weight (t=.86, p=.102),height (t=.37, p=.721), BMI (t=.61, p=.517), average circumference difference (t=-1.08, p=.303), percent circumference difference (t=-1.42, p=.182), or percent water displacement volume difference (t=-.73, p=.482). It is interesting to note that 9 of the 14 subjects qualify as overweight or obese according to their BMI.

Table 4. Group characteristics at baseline, where average circumference difference (Avg. Circ. Diff.) is the average of all circumference measurements of the affected arm, percent circumference difference (% Circ. Diff.) is the ratio between the affected and normal arm, and percent water displacement volume difference (% W.D. Vol. Diff.) is the ratio of the affected arm to the normal arm.

Group	Age (years)	Weight (kg)	Height (cm)	BMI (kg/cm^2)	Avg. Circ. Diff. (cm)	% Circ. Diff.	% W.D Vol. Diff.
Exercise Group* Mean ± SD	56.4 ± 10.4	77.8 ± 20.6	162.9 ± 4.8	29.1 ± 6.6	2.5 ± 1.3	109.6 ± 5.9	123.5 ± 15.6
Control Group† Mean ± SD	56.9 ± 8.2	67.3 ± 9.1	162.2 ± 1.9	25.6 ± 3.3	3.2 ± 1.2	113.3 ± 4.3	128.9 ± 12.2
Total Mean ± SD	56.6 ± 9.0	72.6 ± 16.2	162.5 ± 3.6	27.3 ± 5.3	2.8 ± 1.2	111.5 ± 5.0	126.2 ± 13.6

* Subjects in the Exercise Group were 1, 2, 8, 10, 11, 12, and 14.

† Subjects in the Control Group were 3, 4, 5, 6, 7, 13, and 15.

Water Displacement Arm Volume

The independent samples t-test showed no significant difference in percent difference of water displacement arm volume between group means at time 1 (t=-.74, p=.478, equal variances not assumed due to Levene's test for equality of variances F=4.75, p=.050). Although there were no significant differences in percent difference of measured arm volume found by the ANOVA, there was a linear trend which shows that the groups may have changed differently over time (F=3.77, p=.076). Results are shown in Figure 3 and Table A2.

Calculated Arm Volume

Homogeneity of groups on percent difference of calculated arm volume was confirmed by an independent samples t-test (t=-1.40, p=0.186). No significant differences due to the intervention were found over time, either within subjects or between groups (Figure 4).

Comparison of Volume Measurement Techniques

Pearson product-moment coefficients of correlation were calculated to determine if the two methods of measuring volume were correlated, and paired-samples t-tests were used to determine if the means were significantly different. The highest correlation was found between measured arm volume of the affected arm, excluding the hand, and calculated arm volume of the affected arm (N=140, r=.97, p<.001), although the t-test showed that the means of the two techniques, shown in Table 2, were significantly different (t = -24.19, p < .001). There was also a correlation between measured arm volume of the affected arm, including the hand, and

calculated arm volume of the affected arm (N=140, r=.97, p<.001), but again the means were found to be significantly different (t=5.76, p<.001). Percent difference of arm volume calculated from the two measurement techniques were also correlated (N=70, r = .94, p < .001), although the means were significantly different (t = 3.63, p = .001).

Work Done

Heart rate response varied between subjects. The heart rate of subject 1 remained within 60 to 80% of the maximum predicted by age during all training sessions, whereas subject 11 did not reach her target heart rate zone during any of the sessions. The remainder of the exercise subjects began to reach their target heart rate zones between sessions 8 and 12, when they completed more than 100 kJ of work per session (work completed in exercise session 8=110 kJ, work completed in exercise session 16=152 kJ) .

Figure 1. Sum of work completed by the exercise group per exercise session

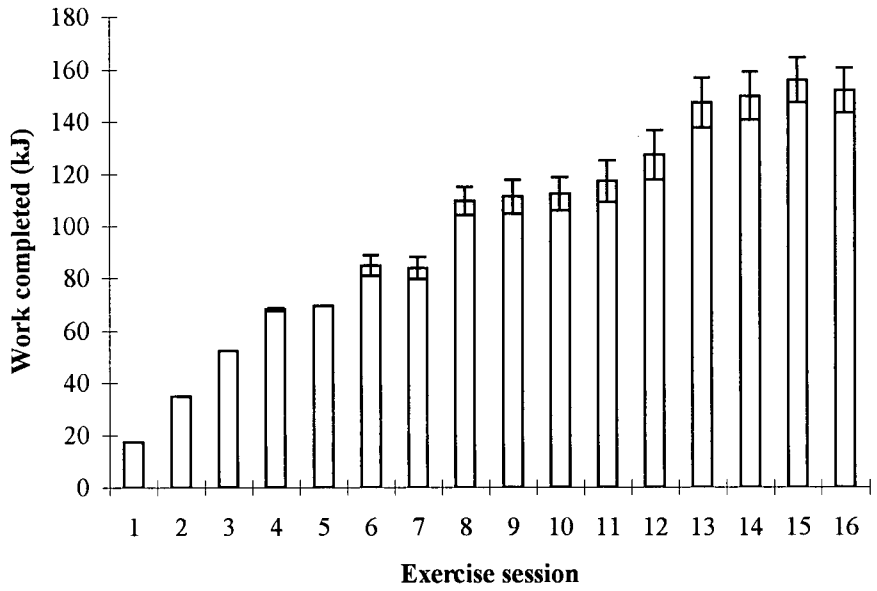
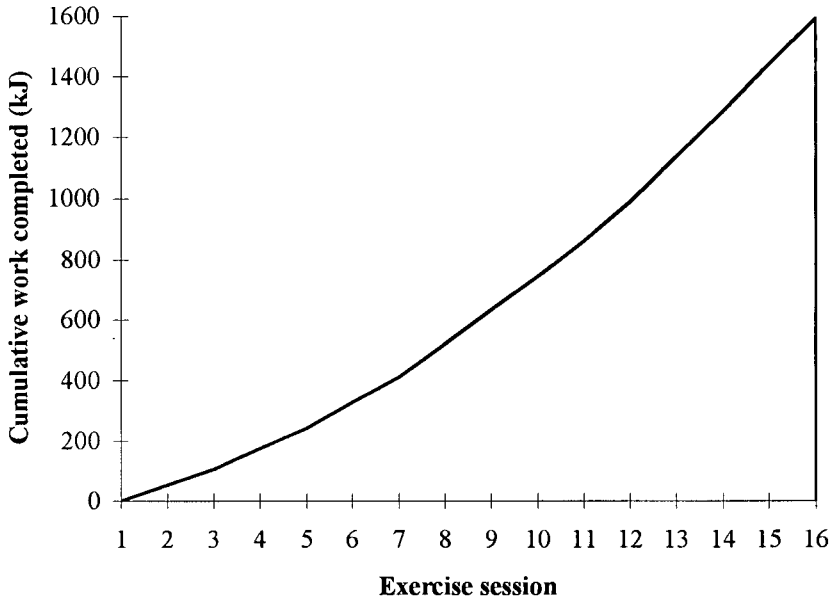


Figure 2. Cumulative work completed by the exercise group



Quality of Life

P-values less than or equal to .05 were found for four of the SF-36 domains, and although these findings are not statistically significant, they may indicate trends. Physical functioning (F=4.73, p= .050) (Figure 5), general health (F=4.85, p=.048) (Figure 6), and vitality (F=6.78, p=.023) (Figure 7) increased in the exercise group and decreased in the control group, although the changes were not significantly different between groups across time. Mental health increased over time in all subjects (F=7.34, p=.019) (Figure 8), although again this was not statistically significant. There was a trend suggesting that as percent difference of calculated volume decreased, the general health domain increased (r=-.53, p=.052). There was a decrease, although not statistically apparent, in the bodily pain scores of both groups (Figure 9). The changes over time of the other three domains (role physical, social functioning, and role emotional) were not statistically significant. The results for these domains are shown in Figures 10, 11, and 12.

The Pearson product-moment correlation coefficients for the pre and post scores of the four SF-36 domains with p-values less than or equal to .05 from the repeated measures ANOVAs are presented in Table 5.

Table 5. Intertemporal correlations of four SF-36 domains

Domain	Pearson r
Physical functioning	.43
General health	.88*
Vitality	.72*
Mental health	.75*

* Significant at the 0.01 level (2-tailed)

Figure 3. Response of arm volume measured by water displacement

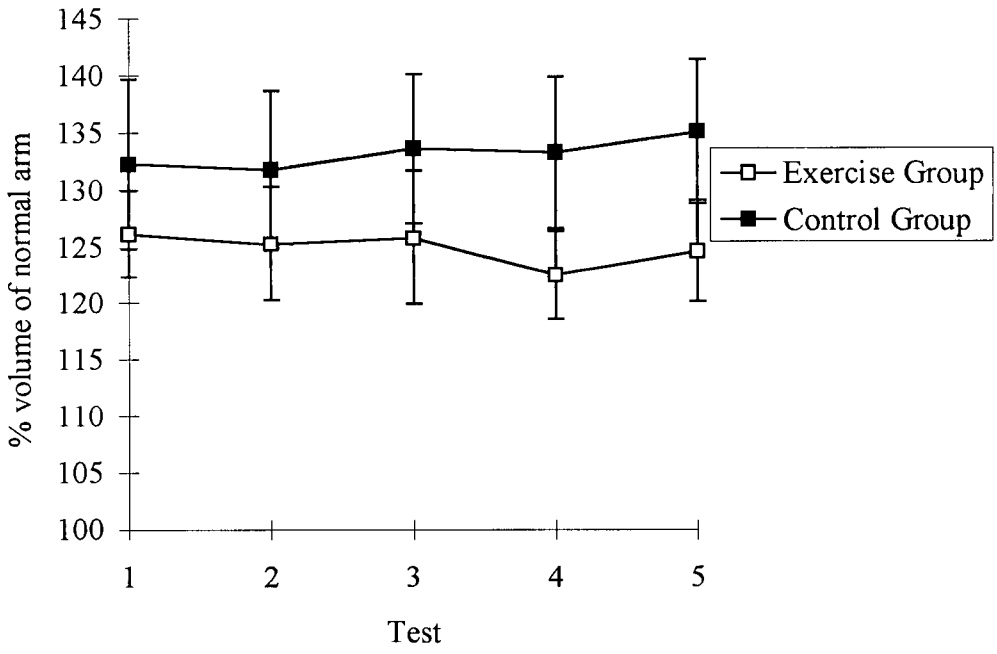


Figure 4. Response of arm volume calculated from arm circumference

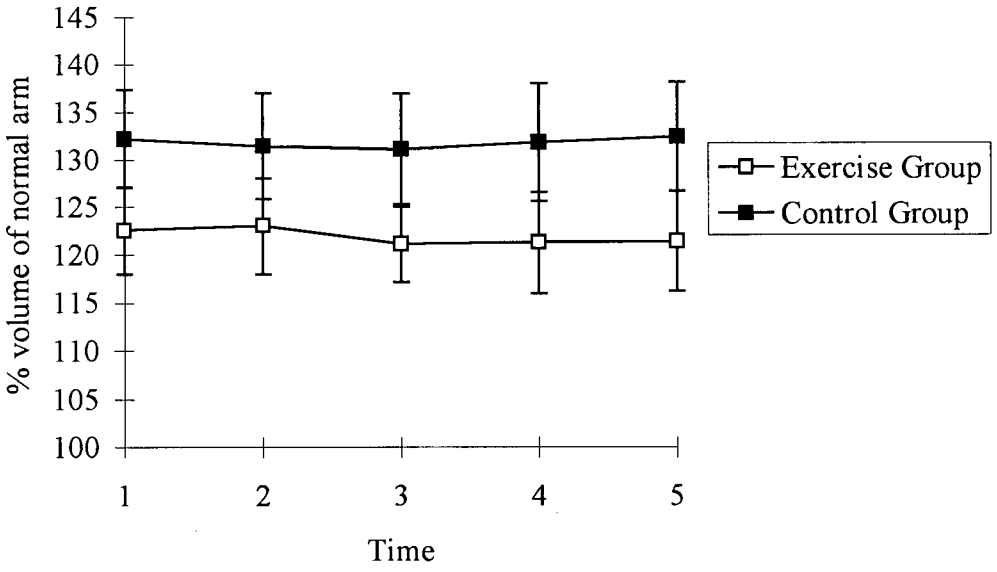


Figure 5. Changes in physical functioning

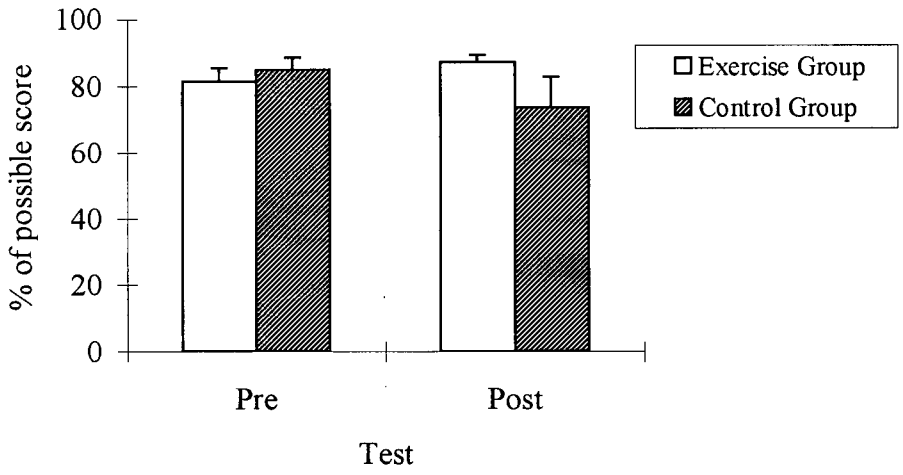


Figure 6 Changes in general health

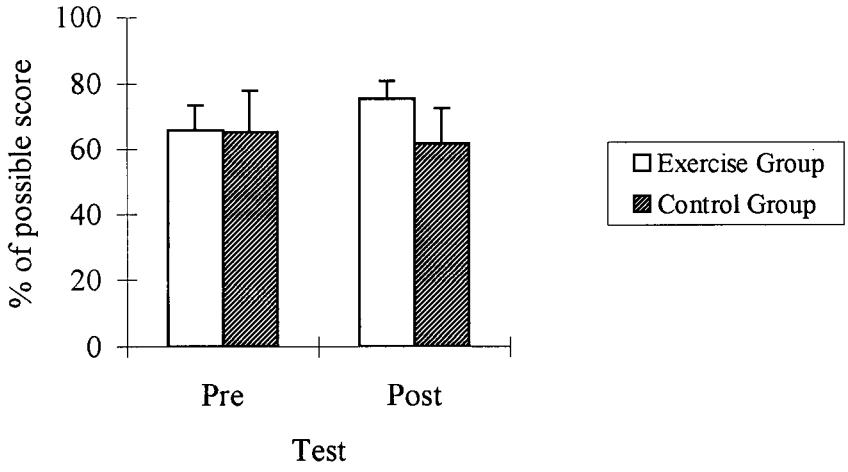


Figure 7. Changes in vitality

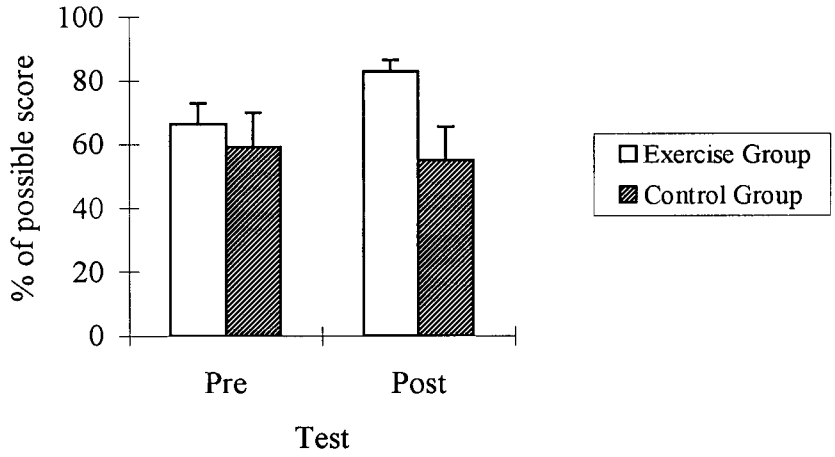


Figure 8. Changes in mental health

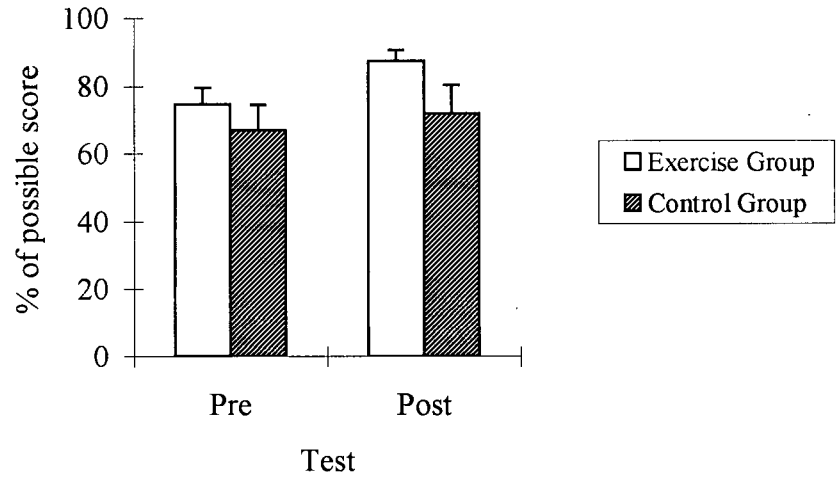


Figure 9 Changes in bodily pain

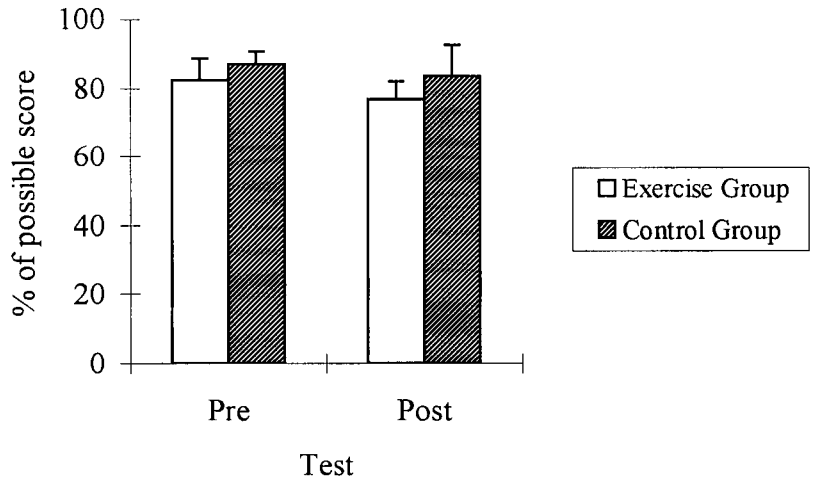


Figure 10 Changes in the role of physical functioning

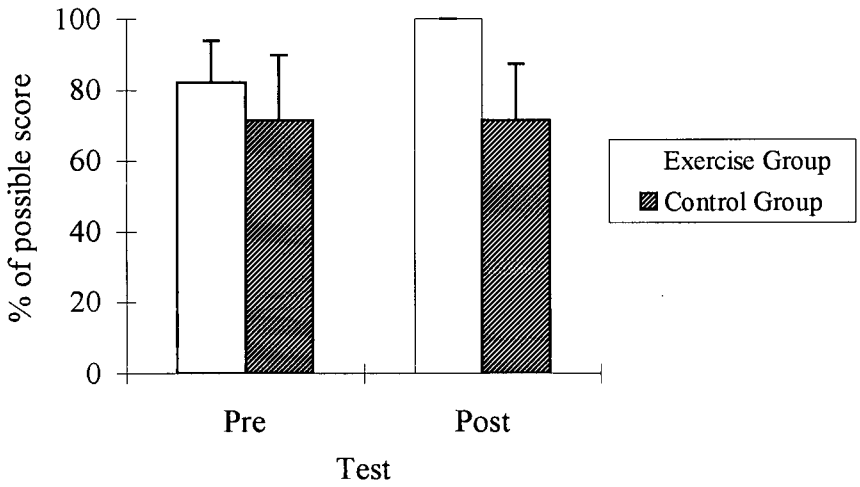


Figure 11. Changes in social functioning

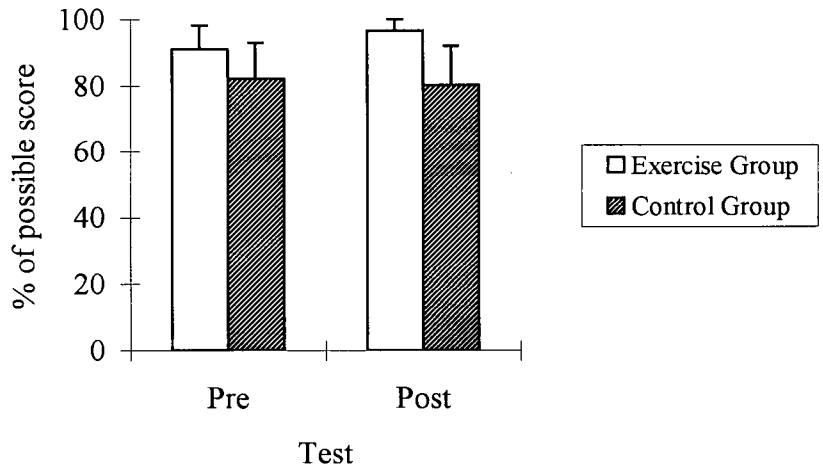
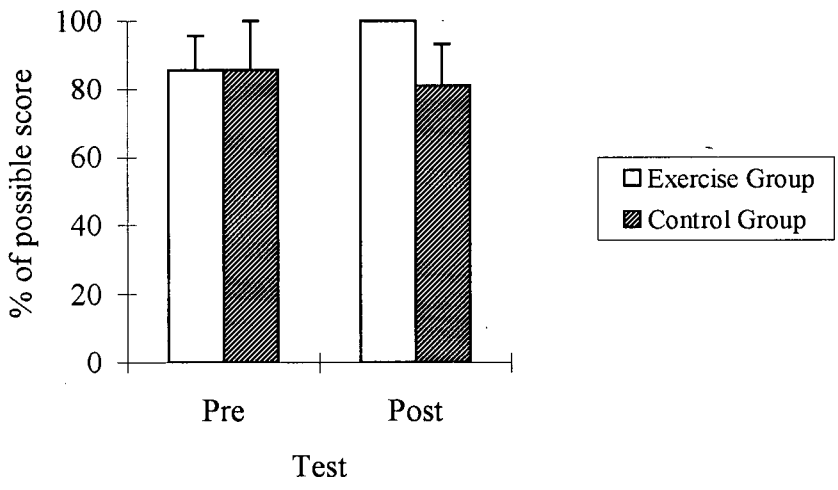


Figure 12. Changes in the role of emotional functioning



Discussion

Women with lymphedema following breast cancer therapy are cautioned to avoid strenuous physical activity, particularly involving the upper extremity (Brennan, 1992). There is no research supporting or disproving this recommendation. There are several physiological theories supporting the use of a gradual, progressive upper-body aerobic exercise program in the rehabilitation of lymphedema. Lymph is propelled by both passive and active forces, and so activating both of these types of forces should aid the body in clearing edema from the affected arm. Passive forces are already promoted as treatment for lymphedema: manual lymphatic drainage massage therapy, sequential pneumatic compression pumping, elastic compression sleeves, and limb elevation. These treatments mimic the passive forces of the body, such as skeletal muscle pumping, respiratory movement, and arterial pulsation. Upper body aerobic exercise stimulates skeletal muscle pumping, instead of mimicking it externally. This type of exercise should also stimulate the active propelling force, the contraction of the lymph vessels themselves, regulated by the sympathetic nervous system. Regaining control over these internal contractions by resetting the sympathetic nerve tone to these vessels through upper body aerobic exercise may be a possible long-term treatment for lymphedema. The present study examined the effect of an eight-week exercise program on arm swelling and quality of life in women with secondary lymphedema due to breast cancer.

The results from this study demonstrate that a progressive, controlled upper-body aerobic exercise program does not significantly affect the volume of the upper extremity in women with lymphedema following breast cancer treatment. This is an important finding, since the data do show a trend towards increases in self-reported physical functioning, general health, and vitality,

with participation in an upper-body aerobic exercise program. Mental health scores increased for both groups, although not significantly, suggesting that this change may be a result of being a participant in a study. This study suggests that restricting progressive upper-body aerobic exercise in women with secondary lymphedema due to breast cancer treatment may be unnecessary.

Quality of life

The trend towards increases in physical functioning scores in the exercise group supports the theory that upper-body aerobic exercise is beneficial for women with secondary lymphedema following breast cancer treatment. Exercise subjects expressed feeling more confident using their affected arm for activities of daily living, and some mentioned lifting objects or carrying groceries with that arm without thinking twice. This may be the cause of the trends towards increased general health and vitality scores, since the exercise subjects were reminded less often of their disease and therefore felt healthier overall. The decrease in physical functioning scores in the control group perhaps represents the normal progress of the disease, with the arm gradually becoming more congested over time. It appears that upper-body aerobic exercise may result in an improvement in physical functioning.

The bodily pain domain scores decreased slightly in both groups, although this was not statistically significant. This may be attributable to other medical problems such as arthritis of the knee or carpal tunnel syndrome. Exercise subjects were instructed to inform the primary investigator if they felt any pain in their affected arm while performing the upper-body aerobic exercise, and only one subject experienced any pain. This was due to carpal tunnel syndrome,

and the handle grip was modified after which the pain gradually subsided. Therefore, there is no reason to conclude that the exercise program caused the subjects pain such that it would have decreased their scores for this domain.

The SF-36 has been studied extensively to determine it's reliability and validity. Estimates of score reliability have determined that it exceeds acceptable standards for group comparisons ($r = 0.50$ or higher), with estimates for 7 of the domains at $r > 0.80$, with the median estimate for the Social Functioning domain equaling 0.76 (Ware et al., 1993). A study has been done (Brazier, Harper, Jones, O'Cathain, Thomas, Usherwood, & Westlake, 1992) that tested the internal consistency of the SF-36 in 1,582 general practice patients in the United Kingdom, and found $r > 0.90$ for all domains except Bodily Pain and Social Functioning. McHorney, Ware, Lu, & Sherbourne (1994) also estimated reliability using internal consistency methods. They looked at 24 subgroups of patients, with different sociodemographic characteristics, diagnoses, and disease severities. Across all patient groups, the scales for all domains passed tests for item-internal consistency (97% passed) and item-discriminant validity (92% passed). Reliability coefficients ranged from 0.65 to 0.94 across scales. These findings support the use of the SF-36 for group comparisons, in diverse populations with varying levels of health.

To detect 2 to 20 point differences in changes over time between two experimental groups with a repeated measures design, the sample size needed varies between domains (Ware et al., 1993). For the three domains found to change differently between groups in this study, the sample sizes needed per group are 15 (physical functioning), 11 (general health), and 12 (vitality) in order to detect a 20 point difference, assuming a correlation of 0.60. This suggests that the sample size is not large enough to detect real differences in any of these domains. The present

study's sample size would not have been able to detect changes in role-physical (30), social functioning (14), role-emotional (28), mental health (9), and bodily pain (15), and so we can not confidently say that the intervention had no effect on these domains. A possible explanation for the low p-values found in this study are the high correlations between pre and post scores for the general health, vitality, and mental health scores. These correlations are greater than 0.60, which was assumed in the calculation used to derive the sample sizes necessary to detect 2 to 20 point differences in scores over time.

Arm Volume

No changes in arm volume were found due to the exercise intervention. This may have been because of a lack of sensitivity of the measures used, too small a sample, or possibly because the exercise program itself was not long or intense enough to produce large enough changes to be statistically significant. Most of the exercise subjects only reached heart rates in their training zone (60 - 80% of their maximum heart rate based on their age) half way or farther through the arm ergometry program, leaving only approximately three weeks of aerobic training. One subject didn't reach her target heart rate zone at all. This suggests that perhaps a longer training program, working up to a higher intensity, may be more effective. A larger sample may also have enabled us to show the changes that we expected.

Changes in arm composition were controlled for by using the subjects' normal arms as controls for their affected arms, assuming that changes would be occurring in both arms equally. This method has been used previously (Bunce, Mirolo, Hennessy, Ward, & Jones, 1994; Mirolo et al., 1995). However, it is impossible with these measurement techniques to know what tissue

changes were taking place in the arms, for instance, what changes were due to muscle hypertrophy, fat loss, or fluid decrease. Even if arm circumference did not change, we do not know if the amount of arm swelling did not go down since muscle hypertrophy may have negated any decrease. In future research, it is recommended that techniques such as Magnetic Resonance Imaging be used to measure changes in all tissues within the limb.

Previously published methods for measuring arm circumference have been found to be inaccurate for diagnosis of lymphedema due to the variability of tissue constriction applied (Kissin et al., 1986). However, they reported that only two measurements of each arm were taken, and the purpose of the study was to determine cut-off points for diagnosis of lymphedema, not repeated measurements for determining the effect of an intervention. Therefore, the methods used for this study were modified from those used by Farncombe et al, which are "more precise and allow for more accurate and detailed comparisons with the other arm and with the same arm over time" (Farncombe et al., 1994). They measured circumference at the 3rd finger, thumb, mid-hand, wrist, and every 2cm proximal from the wrist to the axilla, and then applied an adapted formula for the volume of a cylinder to determine arm volume (excluding the hand). Bunce et al. (1994) also used a similar method, taking measurements at 100mm intervals from the ulnar styloid process to 400mm proximal.

The slight increase in the arm volume means (both measured by water displacement and calculated from circumference) of the exercise group at time 5 may be due to changes in the proportion of tissues within the arm. As muscle is more dense than both adipose tissue and lymph fluid (Duck, 1990), the overall density of the limb may have increased due to muscle hypertrophy or loss of adipose tissue or lymph. Therefore, the volume may have increased because of increased density while the circumference stayed constant. The increase may

alternately be attributed to uncontrollable factors that were reported by subjects. One subject installed a cabinet the week before her last test, and another carried a load of bricks two days before her final test. Another exercise subject experienced swelling that was measurable at time 3, possibly brought on by carrying heavy objects for a garage sale. The handle of the arm ergometer was modified to maintain her wrist in a neutral position and increase the circumference of the grip, and the swelling decreased at both time 4 and 5. Two exercise subjects and two control subjects flew on commercial aircraft during the study, which they reported in their log books increased their swelling despite wearing compression sleeves during the flights.

Anecdotally, subjects felt that the exercise program improved the health of their affected arm in ways that were not measurable with our techniques. They reported softening of hardened areas, reduced pain and swelling when using their arm for activities of daily living, and reappearance of hand tendons. Many subjects continued the exercise program independently after they completed the study.

Limitations

Sample size was a major limitation in this study. The time commitment and realistic rigors of a longitudinal study were discussed with subjects, a strategy used previously (Ganz, Schag, Lee, Polinsky, & Tan, 1992) that appeared to contribute to an extremely low attrition rate in their study. Because of the time commitment needed from the subjects for the present study, six eligible women chose not to enroll, although there was no attrition among subjects who did enroll. However, with the small effect size seen in this study, future studies should try to recruit a larger sample.

Measurement techniques were also a limitation in this study, in that they could only demonstrate size changes and not changes within the arm. To determine the actual effect of an upper-body aerobic exercise program on secondary lymphedema due to breast cancer, it is necessary to develop a technique for monitoring tissue changes. Arm circumference and volume are able to demonstrate that arm swelling is not increased by upper-body aerobic exercise, but the change in lymph fluid in the arm is impossible to quantify.

Obesity and arm dominance have been shown to confound circumference and volume measurements of the arms (Bunce et al., 1994). They can mask the severity of the lymphedema by either enlarging the normal arm relative to the affected arm, or enlarging both arms and thereby lowering the proportion of the affected arm to the normal arm. This can be problematic for diagnosing lymphedema, and may have affected our results by lowering the percentage ratios of arm circumference and arm volume. However, as the primary question of this study involved change in arm swelling due to an intervention and not categorization of lymphedema due to severity, this was most likely not a major limitation.

Summary

Lymphedema can be viewed as primarily a quality of life issue for the women whom it affects. Difficulties functioning at work or at home, altered body image, low self-esteem, problems with dress, and a loss of interest in social activities have all been shown to result from living with lymphedema (Woods, Tobin, & Mortimer, 1995). Many of the difficulties performing activities of daily living, such as lifting or carrying, cleaning, and reaching up or down, may be due to a lack of strength and flexibility in the affected arm, as well as a lack of confidence. This

eight-week upper-body aerobic exercise program does not affect arm swelling significantly, however the trend toward improvement in quality of life is an important reason to suggest it as therapy for secondary lymphedema due to breast cancer treatment.

References

Brazier, J. E., Harper, R., Jones, N. M. B., O'Cathain, A., Thomas, K. J., Usherwood, T., & Westlake, L. (1992). Validating the SF-36 Health Survey Questionnaire: New outcome measure for primary care. *Brit Med J, 305*(6846), 160-164.

Brennan, M. J. (1992). Lymphedema Following the Surgical Treatment of Breast Cancer: A Review of Pathophysiology and Treatment. *J Pain Sympt Manag, 7*(2), 110-116.

Brennan, M. J., DePompolo, R. W., & Garden, F. H. (1996). Focused Review: Postmastectomy Lymphedema. *Arch Phys Med Rehabil, 77*, S-74 - S-80.

Brennan, M. J., & Weitz, J. (1991). Lymphedema thirty years after radical mastectomy. *Am J Phys Med Rehabil, 70*(6).

Bunce, I. H., Mirolo, B. R., Hennessy, J. M., Ward, L. C., & Jones, L. C. (1994). Post-Mastectomy lymphoedema treatment and measurement. *Med J Aus, 161*, 125-128.

Campisi, C. (1991). A Rational Approach to the Management of Lymphedema. *Lymphology, 24*, 48-53.

Canada, N. C. I. (1996). *Canadian Cancer Statistics*. Toronto, Canada.

Cluzan, R. V., Alliot, F., Ghabboun, S., & Pascot, M. (1996). Treatment of Secondary Lymphedema of the Upper Limb with Cyclo 3 Fort. *Lymphology, 29*, 29-35.

Duck, F. A. (1990). *Physical properties of tissue*. San Diego: Academic Press Limited.

Eisenhoffer, J., Kagal, A., Klein, T., & Johnston, M. G. (1995a). Importance of Valves and Lymphangion Contractions in Determining Pressure Gradients in Isolated Lymphatics Exposed to Elevations in Outflow Pressure. *Microvasc Res, 49*, 97-110.

Eisenhoffer, J., Yuan, Z.-Y., & Johnston, M. G. (1995b). Evidence that the L-Arginine Pathway Plays a Role in the Regulation of Pumping Activity in Bovine Mesenteric Lymphatic Vessels. *Microvasc Res, 50*, 249-259.

Farncombe, M., Daniels, G., & Cross, L. (1994). Lymphedema: The Seemingly Forgotten Complication. *J Pain Sympt Manag, 9*(4), 269-276.

Ganz, P. A., Schag, A. C., Lee, J., Polinsky, M. L., & Tan, S.-J. (1992). Breast Conservation Versus Mastectomy: Is There a Difference in Psychological Adjustment or Quality of Life in the Year After Surgery? *Cancer, 69*(7), 1729-1738.

Hicks, J. E. (1990). Exercise for cancer patients. In J. V. Basmajian & S. L. Wolf (Eds.), *Therapeutic Exercise* (5 ed., pp. 351-369). Baltimore: Williams & Wilkins.

Kent, H. (1996). Breast-cancer survivors begin to challenge exercise taboos. *Can Med Assoc J, 155*(7), 969-971.

Kissin, M. W., Rovere, G. Q. d., Easton, D., & Westbury, G. (1986). Risk of Lymphoedema following the treatment of breast cancer. *Brit J Surg, 73*(July), 580-584.

Levine, G. N., & Balady, G. J. (Eds.). (1993). *The Benefits and Risks of Exercise Training: The Exercise Prescription*. (Vol. 39). Massachusetts: Mosby-Year Books, Inc.

Maunsell, E., Brisson, J., & Deschenes, L. (1993). Arm Problems and Psychological Distress After Surgery for Breast Cancer. *Can J Surg, 36*(4), 315 - 320.

McHorney, C. A., Ware, J. E., Lu, J. F. R., & Sherbourne, C. D. (1994). The MOS 36-Item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care, 32*(1), 40-66.

McKenzie, D. C. (1998). Abreast in a Boat -- a race against breast cancer. *Can Med Assoc J, 159*(4), 376-8.

McKenzie, D. C., & Jespersen, D. K. (1998). Abreast in a Boat - team manual . Vancouver: Allan McGavin Sports Medicine Centre.

Miller, L. T. (1994). Lymphedema: Unlocking the Doors to Successful Treatment. *Innov Onc Nurs, 10*(3), 53, 58-62.

Mirolo, B. R., Bunce, I. H., Chapman, M., Olsen, T., Eliadis, P., Hennessy, J. M., Ward, L. C., & Jones, L. C. (1995). Psychosocial benefits of postmastectomy lymphedema therapy. *Cancer Nurs, 18*(3), 197-205.

Mortimer, P. (1986). Lymphostatic Disorders. In C. Regnard (Ed.) (Vol. 293, pp. 347-348). Brit Med J.

Mortimer, P. S., Bates, D. O., Brassington, H. D., Stanton, A. W. B., Strachan, D. P., & Levick, J. R. (1996). The prevalence of arm oedema following treatment for breast cancer. *Quart J Med, 89*, 377-380.

Ohhashi, T. (1987). Comparison of Viscoelastic Properties of Walls and Functional Characteristics of Valves in Lymphatic and Venous Vessels. *Lymphology, 20*, 219-223.

Ohhashi, T. (1993). Mechanisms for Regulating Tone in Lymphatic Vessels. *Biochem Pharm, 45*(10), 1941-1946.

Pedersen, B. K., & Bruunsgaard, H. (1995). How Physical Exercise Influences the Establishment of Infections. *Sports Med, 19*(6), 393-400.

Piller, N. B. (1976). Conservative Treatment of Acute and Chronic Lymphoedema with Benzo-pyrones. *Lymphology, 9*, 132-137.

Pippard, C., & Roddie, I. C. (1987). Comparison of Fluid Transport Systems in Lymphatics and Veins. *Lymphology, 20*, 224-229.

Price, J., & Purtell, J. R. (1997). Prevention and treatment of lymphedema after breast cancer. *Amer Journal Nurs, 97*(9), 34-37.

Pyne, D. B. (1994). Exercise, Training, and the Immune System. *Sports Med, Train, Rehab, 5*, 47-64.

Sacchi, G., Weber, E., Agliano, M., & Comparini, L. (1994). Subendothelial Nerve Fibers in Bovine Mesenteric Lymphatics: An Ultrastructural and Immunohistochemical Study. *Lymphology, 27*, 90-96.

Svensson, W. E. (1995). Response to Letter to the Editor. *Eur J Cancer, 31A*(9), 1545.

Tobin, M. B., Lacey, H. J., Meyer, L., & Mortimer, P. S. (1993). The Psychological Morbidity of Breast Cancer-Related Arm Swelling. *Cancer, 72*(11), 3248-3252.

Tsyb, A. F., Bardychev, M. S., & Guseva, L. I. (1981). Secondary Limb Edemas Following Irradiation. *Lymphology, 14*, 127-132.

Ware, J. E., Snow, K. K., Kosinski, M. K., & Gandek, B. (1993). *SF-36 Health Survey Manual and Interpretation Guide*. Boston, Massachusetts: Nimrod Press.

Whitman, M., & McDaniel, R. W. (93). Preventing Lymphedema: An Unwelcome Sequel to Breast Cancer. *Nursing, Dec*, 36-39.

Witte, C. L., & Witte, M. H. (1987). Contrasting Patterns of Lymphatic and Blood Circulatory Disorders. *Lymphology, 20*, 171-178.

Woods, M., Tobin, M., & Mortimer, P. (1995). The psychosocial morbidity of breast cancer with lymphoedema. *Cancer Nurs, 18*(6), 467-471.

Zelikovski, A., Haddad, M., & Reiss, R. (1986). Non-Operative Therapy Combined with Limited Surgery in the Management of Peripheral Lymphedema. *Lymphology, 19*, 106-108.

Appendix 1

All women who undergo treatment for breast cancer have a chance of developing post-mastectomy lymphedema any time from immediately following treatment to 30 years later (Brennan & Weitz, 1991). There is currently no effective, permanent treatment, and it compromises the quality of the life the woman fought so hard to keep. Upper body aerobic exercise is currently not a modality used in physiotherapy for lymphedema or breast cancer, and is considered "wise to recommend the avoidance of prolonged and strenuous work with the extremity" (Brennan, 1992). However, there are theories based in physiology that support a gradual, progressive, upper body aerobic exercise program as a method of reducing post-mastectomy lymphedema.

Normal Lymphatic Physiology

The lymphatic system plays an important role by regulating the physiological environment of the body. It returns proteins, cells, macromolecules, and fluid to the general circulation, and also removes metabolic byproducts, dying and mutant cells, microbes, and inorganic matter from the interstitial fluid (Mortimer, 1986). The lymphatic vessels of the arm are present at both deep and superficial levels, which are connected by the lymph nodes at the elbow. Both systems empty into the axillary lymph nodes. Lymph is propelled by active and passive forces, and is normally dependent upon the rate of lymph production in organs and tissues (Ohhashi, 1993). The passive forces propel lymph through compression and suction of lymph vessels, and include

skeletal muscle pumping, respiratory movement, and arterial pulsation. It has also been suggested that peristalsis, piston-like action of intestinal villi, and transmitted arterial pulsation aid in the propulsion of lymph (Witte & Witte, 1987). The active driving force is the contraction of the lymph vessels themselves, which use smooth muscle to pump lymph much the same way as the heart pumps blood.

The role of the skeletal muscle pump in moving lymph is controversial. It has been assumed for many years that the contraction and relaxation of skeletal muscles throughout the body squeezed the lymph vessels and propelled the lymph, the same way blood is propelled in the veins. However, in a study using anaesthetized sheep, it was shown that gravitational changes occur in venous pressure but not in lymphatic pressure (Pippard & Roddie, 1987), suggesting an incompleteness of the fluid column in limb lymphatics. This would make extrinsic pumping less effective at low intralymphatic pressures, although extremely effective at high intralymphatic pressures. High lymphatic pressures can also be created by active exercise, which was shown by inducing shivering in anaesthetized dogs. This type of exercise was shown to produce a lymph flow equal to that produced by massage.

Although extrinsic muscle pumping may play a role in the movement of lymph, most of the propulsive force comes from an intrinsic smooth muscle pump (Pippard & Roddie, 1987; Ohhashi, 1987). The smooth muscle layer of the lymphatic vessels contracts independently of skeletal muscle use, and through sequential contraction pushes lymph along the vessel. Spontaneous contractions are regulated by the magnitude of stretch, as well as the rate and acceleration of deformation (Ohhashi, 1987). This response may be regulated by nitric oxide (NO), along with other neurohumoral and local influences (Levine & Balady, 1993). It has been suggested that basal production of NO facilitates the spontaneous lymphatic pumping induced by

distention of the lymph vessels (Eisenhoffer, Yuan, & Johnston, 1995b). This suggestion is supported by correlation of lymphatic wall tension with frequency of contractions, suggesting a myogenic origin of contraction (Ohhashi, 1993). The smooth muscle layer has also been shown in bovine mesenteric lymphatics to be innervated by nonmyelinated nerve fibers, which were demonstrated to be immunoreactive to substance P (SP) and calcitonin gene related peptide (CGRP) (Sacchi, Weber, Agliano, & Comparini, 1994). This led to the hypothesis that these fibers are mechanoreceptors. Since SP, potentiated by CGRP, is a vasoconstrictor in lymphatics and increases their rate of contraction, it has been suggested that the mechanism of contraction of bovine mesenteric lymphatics may be neurogenic, as well as myogenic (Sacchi et al., 1994).

Physiology of Lymphedema

Damage to the lymphatic system can cause edema, chronic inflammation, fibrosis, and an abnormal collection of excessive tissue proteins (Brennan, 1992); collectively, this condition is called lymphedema. Lymphedema may occur in women who have been treated for breast cancer, and is referred to as secondary (post-mastectomy) lymphedema. It is distinct from primary lymphedema, which is due to congenital absence of, or abnormalities in, the lymphatic system (Brennan, 1992). Secondary lymphedema is a result of axillary dissection, a surgical procedure that removes lymph nodes, and is exacerbated by radiotherapy (Farncombe et al., 1994; Kissin et al., 1986; Tsyb, Bardychev, & Guseva, 1981; Whitman & McDaniel, 93).

Lymphedema after breast cancer treatment manifests as swelling of the ipsilateral arm. This is due to compression of lymph vessels due to damage of surrounding tissues (Svensson, 1995). The lymphatics can not effectively drain fluid from the arm, leading to heightened

susceptibility to infection and diffuse interstitial fibrosis (Witte & Witte, 1987). The high-protein edema in secondary lymphedema is dense, but may be reduced if the arm is elevated (Farncombe et al., 1994). The skin has normal colour, the venous pattern is expressed, and there is no trophic disorder (Tsyb et al., 1981). Patients experience many symptoms, including aching joints, "bursting" or "shooting" pains, pins and needles, warmth, a feeling of tightness or heaviness, reduced mobility, and/or impaired limb function (Mortimer, 1986). Tobin et al. (1993) found that 46% of patients with arm swelling reported some functional impairment, poorer adjustment to their illness, and considerable difficulty in the areas of domestic environment and relationships within the family.

The reported incidence of lymphedema varies greatly in the literature, where figures of 5.5 to 80% have been quoted (Brennan, 1992). This is partly due to the changing techniques used to treat breast cancer. The use of breast conserving surgery and modified radical mastectomy instead of Halsted's radical mastectomy, along with a reduction in prevalence of total axillary dissection have reduced reported incidence. However, the use of axillary radiotherapy appears to increase a woman's risk of developing lymphedema (Kissin et al., 1986; Mortimer et al., 1996).

In the United Kingdom a large scale prevalance study found that 28% of women who were treated for breast cancer and were still surviving had lymphedema (Mortimer et al., 1996). This is similar to other recent studies, with reported incidence of 25.5% (Tobin et al., 1993) and 24% (Maunsell et al., 1993). The Canadian Cancer Statistics (Canada, 1996) report that there were 18600 new cases of female breast cancer in 1996. Therefore, with a conservative estimate of 20% incidence of lymphedema, there would be 3720 new cases of post-mastectomy lymphedema in Canada in 1996 alone.

Current Treatment of Lymphedema

To date, there is no cure for lymphedema. Current treatments aim at reducing the swelling and preventing infection of the affected arm. Education is a vital part of the management of this condition, as it can prevent further exacerbations due to infections. Simply elevating the limb above the level of the heart may reduce swelling (Farncombe et al., 1994), although there is no experimental proof of this (Brennan, DePompolo, & Garden, 1996). Skin surface massage has been recommended as a method of restoring local lymph movement (Brennan et al., 1996). Skin hygiene helps to prevent infection of the affected arm, thereby helping to keep the swelling under control (Whitman & McDaniel, 93). External compression, including sequential pneumatic compression pumps, lymphatic massage, and compression sleeves are fairly effective methods of reducing swelling or preventing it from increasing (Brennan, 1992; Farncombe et al., 1994). Drug therapy, including diuretics, antibiotics, steroids, and experimental treatment drugs, have varying efficacy and some serious side-effects (Mortimer, 1986). Exercise, such as gentle stretching and strengthening, are recommended to recover or maintain joint range of motion and functionality of the affected arm (Miller, 1994; Mortimer, 1986; Whitman & McDaniel, 93). Surgery is a final option, reserved for severe cases of lymphedema that do not respond to conservative treatment. (Brennan, 1992; Farncombe et al., 1994)

Exercise and Lymphedema

Gradual stretching and light strengthening exercises have been recommended to all women who are treated for breast cancer (Whitman & McDaniel, 93). These exercises help to prevent adhesions and joint contracture, increase range of motion, help prevent edema and infection, restore self-esteem and well-being, restore the person to their previous vocational activity, and increase or recover cardiovascular fitness. However, exercise is only briefly mentioned, if at all, in most literature concerned with lymphedema treatments (Brennan, 1992; Bunce et al., 1994; Campisi, 1991; Farncombe et al., 1994; Kissin et al., 1986; Maunsell et al., 1993; Miller, 1994; Piller, 1976; Tsyb et al., 1981; Zelikovski, Haddad, & Reiss, 1986). It has been suggested that the "usual daily activities" may be sufficient exercise if the edema is mild or moderate, although formal exercises were recommended for those with more severe swelling (Farncombe et al., 1994). The type of "formal exercise" was not discussed in this paper. In a case study, "active assisted arm exercises" were initiated, and some sensation and function was noted to slowly return to the arm (Farncombe et al., 1994). Resistance exercise is occasionally recommended, but weight is to be limited to fifteen pounds for resistance training (Whitman & McDaniel, 1993). Dance programs have been recommended (Hicks, 1990) as a method of maintaining range of motion and strength in post-mastectomy patients, although no specific program is described for women with lymphedema.

An exception to this are Price and Purtell's ('97) exercise recommendations for preventing and treating lymphedema. They outlined a clear program of flexibility exercises and gentle strengthening. They stressed that weight used for strengthening exercises should not

exceed 3 to 5 pounds, and resistive weight on exercise machines should not be set higher than 25 to 30 pounds No mention was made of aerobic exercise.

There is only one mention (Kent, 1996) in the literature of the usefulness of endurance exercise with respect to lymphedema, although this type of exercise is known to increase sympathetic tone (Levine & Balady, 1993). This is due to neurohumoral and local influences on peripheral vascular tone, causing major shifts in regional blood flow. Levine & Balady (1993) showed that long-term training causes an increase in fatty acid and glucose metabolism, as well as increased capillary density. This facilitates nutrient exchange, decreases the distance that oxygen has to travel, and increases red blood cell transit time in muscle beds.

If the lymphatic vessels become damaged by the pressure of the excess fluid present with lymphedema, there is the possibility that the valves of the vessels could fail. This hypothesis was tested by Eisenhoffer et al (1995a), using bovine mesenteric vessels. The failure of the vessels caused by lymphedema was found to be due not to valve failure but to the progressive inability of lymphangions to empty. This suggests that if lymphatic pumping could be restarted, the valves would still be functional.

A major contributing factor in the continued swelling of the lymphedematous arm over time is the susceptibility to infection. Each time the arm becomes infected, an immune response is stimulated that causes increased arm swelling. Therefore, it is important to examine the effect of exercise on the establishment of infections. It has been found (Pedersen & Bruunsgaard, 1995; Pyne, 1994) that regular moderate aerobic exercise will temporarily enhance various components of the immune system. The distribution and trafficking of peripheral mononuclear cells is altered, and Natural Killer (NK) cells, cytokines, B cells, and T cells are also recruited to the blood. This increases the total lymphocyte count in the blood. NK cells have been shown to

be the first line of defense against acute and chronic viral infections as well as tumour spread. Cytokines are necessary for the growth, differentiation, and functional activation of all cells of the immune system. The source of the cells responsible for increased synthesis of cytokines may be macrophages, endothelial cells, and fibroblasts in the muscle used in exercise. Stress hormones, such as catecholamines, Growth Hormone (GH), beta-endorphins, corticotrophin (ACTH), alpha-cortisol, and epinephrine, also stimulate synthesis of cytokines. Since there is no shortage of macrophages in the lymphedematous arm, but a shortage of *activated* macrophages, an increase in circulating cytokines may help to remove some of the protein accumulation. An increase in circulating NK cells, B cells, and T cells may improve the natural defense system that has been compromised by the lymphedema. A restoration of this defense system may help people with lymphedema to break the cycle of infection and increased swelling.

In summary, there is lack of research on upper body aerobic exercise done by women with secondary lymphedema following breast cancer treatment. Specific training protocols should be researched to determine the effect of this type of exercise on upper extremity swelling.

Appendix 2

Table A1. Baseline individual subject characteristics, where average circumference difference (Avg. Circ. Diff.) is the average of all circumference measurements of the affected arm, percent circumference difference (% Circ. Diff.) is the ratio between the affected and normal arm, and percent water displacement volume difference (% W.D. Vol. Diff.) is the ratio of the affected arm to the normal arm.

Subject No.	Age (years)	Weight (kg)	Height (cm)	BMI (kg/cm^2)	Avg. Circ. Diff. (cm)	% Circ. Diff.	% W.D. Vol. Diff.
1	62	101.5	162.2	38.6	2.5	108.8	127.5
2	77	54.0	157.7	21.7	4.3	118.9	140.3
3	56	64.7	162.0	24.7	2.5	110.4	107.4
4	43	53.5	159.5	21.0	2.9	113.7	124.7
5	64	77.7	164.5	28.7	2.4	109.8	123.6
6	53	68.1	163.4	25.5	1.3	105.6	109.3
7	69	75.2	159.8	29.4	4.8	118.0	148.9
8	50	104.2	168.6	36.7	3.5	111.9	120.2
10	50	55.3	156.5	22.6	1.3	105.7	115.5
11	47	65.0	161.3	25.0	1.3	105.2	114.4
12	57	82.5	165.6	30.1	3.0	110.6	129.3
13	57	58.1	163.0	21.9	4.2	118.7	145.5
14	52	82.4	168.4	29.1	1.5	106.2	117.4
15	56	73.8	163.0	27.8	4.2	116.9	143.1

Arm Circumference

The exercise and control groups had homogeneous means for percent difference of arm circumference at time 1 (t=-.407, p=.185). No significant differences in percent difference of arm circumference were found by the repeated measures ANOVA within subjects or between groups. Results are shown in Figure A1 and Table A1.

Table A2. Mean responses of arm circumference to intervention

Mean Circumference (affected limb)[*] ± SD (%)	Time 1	Time 2	Time 3	Time 4	Time 5
Exercise Group	109.63 ± 4.82	109.75 ± 4.98	109.08 ± 4.33	109.17 ± 5.49	109.08 ± 5.51
Control Group	113.29 ± 4.91	112.98 ± 5.51	112.93 ± 5.59	113.23 ± 5.82	113.52 ± 5.55

[*] Calculated as a percentage of the circumference of the unaffected limb, measured at the same time

Figure A1. Response of arm circumference

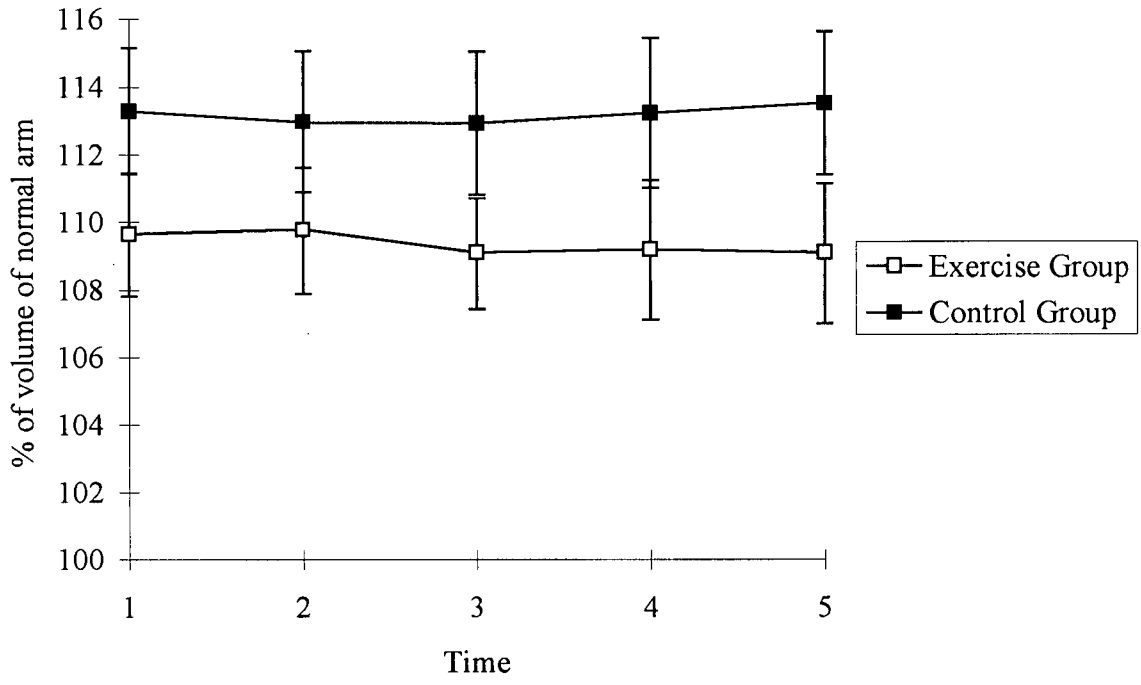


Table A3. Mean responses of arm volume to intervention

Mean Volume (affected limb) ± SD (%)	Time 1	Time 2	Time 3	Time 4	Time 5
Measured volume*					
Exercise Group	126.13 ± 10.06	125.28 ± 13.29	125.77 ± 15.58	122.48 ± 10.40	124.60 ± 11.88
Control Group	132.24 ± 19.42	131.76 ± 18.67	133.59 ± 16.72	133.26 ± 16.58	135.10 ± 15.36
Calculated volume♈					
Exercise Group	122.58 ± 12.010	123.07 ± 13.30	121.14 ± 10.46	121.31 ± 14.02	121.46 ± 13.87
Control Group	132.20 ± 13.57	131.44 ± 14.76	131.12 ± 15.37	131.83 ± 16.40	132.40 ± 15.18

* Calculated as a percentage of the measured volume of the unaffected limb, measured at the same time.

♈ Calculated as a percentage of the calculated volume of the unaffected limb, measured at the same time.

Table A4. Mean quality of life responses to intervention

	Exercise Group		Control Group	
Domain	Pre	Post	Pre	Post
Physical Functioning	81.43 ± 10.69	87.14 ± 5.67	85.00 ± 9.57	73.57 ± 24.45
Role Physical	82.14 ± 31.34	100.00 ± .00	71.43 ± 48.80	71.43 ± 41.90
Bodily Pain	82.29 ± 16.63	76.88 ± 13.61	86.86 ± 9.99	83.43 ± 24.05
General Health	65.71 ± 20.46	75.29 ± 14.40	65.14 ± 33.73	61.43 ± 28.91
Vitality	66.43 ± 17.01	82.86 ± 9.51	59.29 ± 28.64	55.00 ± 27.99
Social Functioning	91.07 ± 18.70	96.43 ± 9.45	82.14 ± 28.74	80.36 ± 30.47
Role Emotional	85.71 ± 26.23	100.00 ± .00	85.71 ± 37.80	80.94 ± 32.55
Mental Health	74.86 ± 13.01	87.43 ± 8.46	66.86 ± 20.23	72.00 ± 22.15

Table A5. Arm circumference data (% of unaffected arm)

Subject	Time 1	Time 2	Time 3	Time 4	Time 5
1	108.8	108.7	108.3	106.1	109.1
2	118.9	120.1	117.1	120.2	120.1
3	110.4	108.9	107.7	106.7	107.9
4	113.7	110.0	109.9	110.0	110.8
5	109.8	109.9	111.2	112.1	113.7
6	105.6	106.8	106.2	107.8	106.4
7	118.0	118.4	120.4	119.6	118.9
8	111.9	109.9	110.1	110.0	108.5
10	105.7	105.1	104.1	103.2	103.8
11	105.2	106.4	106.9	107.4	106.3
12	110.6	110.8	111.5	110.9	111.3
13	118.7	121.5	119.6	121.9	121.4
14	106.2	107.3	105.6	106.4	104.5
15	116.9	115.5	155.9	114.7	115.4

Subject 9 was excluded from the study because the difference between the affected arm and the normal arm was <2cm on all points.
Arm circumference expressed as percentage ratios of affected arm to unaffected arm.

Table A6. Water displacement arm volume data (% of unaffected arm)

Subject	Time 1	Time 2	Time 3	Time 4	Time 5
1	127.5	119.2	122.6	109.7	120.8
2	140.3	150.0	155.5	140.8	146.4
3	107.4	109.4	115.9	112.8	118.3
4	124.7	127.0	122.0	129.3	125.7
5	123.6	124.9	127.3	123.9	131.7
6	109.3	113.0	111.8	114.3	113.2
7	148.9	150.8	147.3	150.6	148.0
8	120.2	117.3	117.6	120.7	117.1
10	117.5	112.7	112.6	110.8	115.4
11	114.4	119.7	117.8	120.6	118.4
12	129.3	124.5	122.5	120.0	129.9
13	145.5	146.1	147.2	144.5	149.3
14	117.4	113.1	116.3	117.8	111.7
15	143.1	132.0	133.5	131.9	134.7

Subject 9 was excluded from the study because the difference between the affected arm and the normal arm was <2cm on all points.
Arm volume expressed as percentage ratios of affected arm to unaffected arm.

Table A7. Calculated arm volume data (% of unaffected arm)

Subject	Time 1	Time 2	Time 3	Time 4	Time 5
1	121.0	119.1	119.3	113.1	121.0
2	146.4	151.3	141.3	150.2	150.1
3	121.6	118.1	114.9	112.5	116.1
4	134.7	125.3	125.6	124.4	128.1
5	124.3	124.6	127.8	129.2	131.1
6	111.2	114.2	111.8	115.8	112.8
7	145.9	146.4	150.6	150.6	148.4
8	126.3	122.3	122.3	121.2	119.0
10	112.2	110.8	108.9	106.1	108.1
11	111.4	114.6	115.8	117.1	114.3
12	124.7	125.0	125.9	124.3	125.4
13	147.1	153.3	148.6	155.5	153.3
14	115.9	118.3	114.5	117.2	112.3
15	140.6	138.3	138.5	134.9	136.9

Subject 9 was excluded from the study because the difference between the affected arm and the normal arm was <2cm on all points.
Arm volume expressed as percentage ratios of affected arm to unaffected arm.

Table A8. Independent t-tests for subject characteristics

Variable	t	DF	Sig. (2-tailed)	Mean Difference	Std. Error Difference
Age	.06	12	.95	.30	4.72
Weight	.86	12	.41	7.37	8.61
Height	.37	7.76	.72	.73	1.97
BMI	.61	12	.55	1.91	3.13
Avg. Circ. Diff.	-1.08	12	.30	-.70	0.65
% Circ. Diff.	-1.42	12	.18	-3.69	2.60
% W.D. Vol. Diff.	-.73	9.28	.48	-5.41	7.39

Table A9. RMANOVA, Arm circumference (5) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	259.259	1	259.259	1.950	.188
ERROR	1595.746	12	132.979		
WITHIN SUBJECTS					
SOURCE					
LEVELS	1.707	4	.427	.289	.884
LEVELS X GROUPS	2.797	4	.699	.474	.755
ERROR	70.812	48	1.475		

Table A10. RMANOVA, Water displacement arm volume (5) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	1217.608	1	1217.608	1.133	.308
ERROR	12899.842	12	1074.987		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	38.282	4	9.570	.564	.690
LEVELS X GROUPS	67.489	4	16.872	.994	.420
ERROR	815.073	48	16.981		

Table A11. RMANOVA, Calculated arm volume (5) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	1710.282	1	1710.282	1.814	.203
ERROR	11313.731	12	943.061		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	14.832	4	3.708	.418	.795
LEVELS X GROUPS	13.569	4	3.392	.382	.820
ERROR	426.232	48	8.880		

Table A12. RMANOVA, Physical functioning (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	175.000	1	175.000	.566	.466
ERROR	3710.714	12	309.226		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	57.143	1	57.143	.526	.482
LEVELS X GROUPS	514.286	1	514.286	4.734	.050
ERROR	1303.571	12	108.631		

Table A13. RMANOVA, Role Physical (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	2700.893	1	2700.893	1.194	.296
ERROR	27142.857	12	2261.905		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	558.036	1	558.036	1.875	.196
LEVELS X GROUPS	558.036	1	558.036	1.875	.196
ERROR	3571.429	12	297.619		

Table A14. RMANOVA, Bodily Pain (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	217.286	1	217.286	.496	.495
ERROR	5257.143	12	438.095		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	137.286	1	137.286	1.042	.328
LEVELS X GROUPS	7.000	1	7.000	.053	.822
ERROR	1581.714	12	131.810		

Table A15. RMANOVA, General Health (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	364.321	1	364.321	.295	.597
ERROR	14832.857	12	1236.071		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	60.036	1	60.036	.942	.351
LEVELS X GROUPS	308.893	1	308.893	4.848	.048
ERROR	764.571	12	63.714		

Table A16. RMANOVA, Vitality (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	2143.750	1	2143.750	2.433	.145
ERROR	10571.429	12	880.952		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	258.036	1	258.036	2.331	.153
LEVELS X GROUPS	750.893	1	750.893	6.782	.023
ERROR	1328.571	12	110.714		

Table A17. RMANOVA, Social Functioning (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	1093.750	1	1093.750	1.120	.311
ERROR	11718.750	12	976.562		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	22.321	1	22.321	.185	.675
LEVELS X GROUPS	89.286	1	89.286	.738	.407
ERROR	1450.893	12	120.908		

Table A18. RMANOVA, Role Emotional (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	635.556	1	635.556	.534	.479
ERROR	14292.383	12	1191.032		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	158.413	1	158.413	.399	.539
LEVELS X GROUPS	635.556	1	635.556	1.601	.230
ERROR	4763.811	12	396.984		

Table A19. RMANOVA, Mental Health (2) by group (2)

UNIVARIATE REPEATED MEASURES ANALYSIS					
BETWEEN SUBJECTS					
SOURCE	SS	DF	MS	F	P
GROUP	960.571	1	960.571	1.939	.189
ERROR	5945.143	12	495.429		
WITHIN SUBJECTS					
SOURCE	SS	DF	MS	F	P
LEVELS	549.143	1	549.143	7.336	.019
LEVELS X GROUPS	96.571	1	96.571	1.290	.278
ERROR	898.286	12	74.857		

Table A20. Pearson product-moment correlation coefficients, total work for each two week period paired with difference in arm circumference for that same two week period.

	N	R	Sig
work & circ diff at time 3	7	-.095	.839
work & circ diff at time 4	7	.437	.327
work & circ diff at time 5	7	.114	.807