

COMPARISON OF UPPER LIMB VOLUME MEASUREMENT TECHNIQUES AND ARM SYMPTOMS BETWEEN HEALTHY VOLUNTEERS AND INDIVIDUALS WITH KNOWN LYMPHEDEMA

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ABSTRACT

Lymphedema is a problem for breast cancer survivors. The proliferation of limb measurement techniques makes it difficult to know how best to measure an at-risk limb. Using a sample of healthy volunteers and individuals with lymphedema, this study: 1) examined the relationship between more commonly used circumferential limb measurement methods and newer measurement methods of infrared laser perometry and bioelectrical impedance; 2) compared self-reported arm symptoms in healthy volunteers and breast cancer survivors with known lymphedema; and 3) explored the relationships among self-reported arm symptoms and circumferential tape measurement, infrared laser (perometry), and single and multi-frequency bioelectrical impedance. Lymphedema index ratios were calculated to allow comparison among measurement methods. Measurement methods correlated strongly with each other. Fourteen symptoms were reported by one or more participants in the lymphedema group while participants in the healthy volunteer group reported only eight symptoms over the same time frames. Using $p < 0.001$, all measurement methods correlated with self-reported arm swelling in the past year, while only circumferential and

impedance measurements correlated with firmness. Future research needs to include serial arm measurements to explore arm volume variation in healthy and lymphedema volunteers and to further investigate possible lymphedema index ratios cut points as lymphedema diagnostic criteria.

Keywords: bioelectrical impedance, infrared scanning, perometry, breast cancer lymphedema, lymphedema measurement methods

Breast cancer is the most common non-skin malignancy in women with 211,240 new invasive cases diagnosed in 2005 (1). Although breast cancer was the second leading cause of cancer deaths in women (40,110 deaths in 2005), mortality rates have decreased approximately 2.3% per year between 1990 and 2002 (2). The current five-year survival rate is 88% across all stages of diagnosis and 80% over 10 years (2).

Lymphedema is a serious problem for a significant number of breast cancer survivors (3-7). Early identification and treatment of lymphedema before significant fluid accumulation and fibrosis occur may result in better patient outcomes (8). A recent survey of 74 breast cancer survivors with lymphedema indicates that patients are usually the first to observe the swelling, which by that time may

be substantial (Ridner, unpublished data). Both patients' and providers' lack of understanding about the need for early diagnosis may result in delayed care and less favorable patient outcomes.

The proliferation of methods of evaluating limb volume (e.g., water displacement, tape measure, infrared scanning) and extracellular fluid (bioelectrical impedance) makes it difficult for clinicians to know how best to measure an at-risk limb. This is partly related to the absence of a gold standard for measuring/detecting lymphedema (9). Historically, it has been suggested that water displacement is the preferred whole limb volume measurement technique. However, circumferential measurement methods have replaced water displacement in most clinical settings for five primary reasons. First, strong correlations have been found between circumferential measurement and water displacement (10). Second, circumferential techniques are better tolerated by patients who have difficulty bending over and placing their arms in water-filled containers. Third, there is potential for large measurement error with water displacement, particularly when patients cannot fully place their arms in the water containers or hold that position until the overflow is complete. Fourth, there is possible risk of cross-infection among patients related to inadequate equipment sterilization. Fifth, individuals with open wounds, such as psoriasis ulcers or skin infections, cannot have their affected limbs routinely measured in water.

Recent application in research studies of technology, such as infrared scanning that measures whole limb volume and single and multi-frequency bioelectrical impedance devices that have the capability to measure extracellular limb fluid (lymph), suggests that more sensitive, easy to use options than circumferential techniques may exist (9,11). Therefore, there is a need to compare alternative measurement mechanisms, such as infrared scanning and bioelectrical impedance, to the commonly used circumferential measurement.

Recent research in breast cancer treatment-related lymphedema also has brought into consideration the possibility that certain subjective, self-reported symptoms may indicate lymphedema, and findings from two studies suggest that breast cancer survivors with lymphedema may have some unique symptoms that are not present in breast cancer survivors without lymphedema (12,13). One published study reported a correlation between self-reported arm symptoms of heaviness and swelling in breast cancer survivors and a two cm circumferential change in an affected arm (12). However, comparisons of self-reported arm symptoms with multiple arm measurement techniques in both breast cancer survivors with lymphedema and healthy normal controls remain unexplored. Such comparisons would enable clinicians and researchers to distinguish between arm symptoms present in the general population and those present in breast cancer survivors with lymphedema. For example, comparisons could be used either to refine self-reported arm symptom measurement tools as potential lymphedema diagnostic aids or to rule out such subjective methods. If valid and reliable self-report measures are developed, clinicians could use these tools to assess patients for developing lymphedema prior to conducting actual physical measurements of the limb. This would be a time saving, cost effective, user-friendly assessment measure.

Thus, the objectives of this study were to: 1) examine the relationship between commonly used circumferential limb measurement methods and newer measurement methods of infrared scanning and bioelectrical impedance (measuring resistance and conductivity in the presence of protein in the tissues); 2) compare self-reported arm symptoms in healthy volunteers and breast cancer survivors with lymphedema; and 3) explore the relationships among self-reported arm symptoms and circumferential tape measurement, infrared laser (perometry), and bioelectrical impedance using single and

multi-frequency impedance devices. Specific research questions were: 1) To what extent are there significant correlations among measurement methods?; 2) To what extent do self-reported arm symptoms differ between healthy normal controls and breast cancer survivors with lymphedema?; and 3) To what extent do self-reported arm symptoms correlate with circumferential tape measurement, infrared laser perometry, and single and/or multi-frequency bioelectrical impedance?

PARTICIPANTS AND METHODS

Recruitment

All study participants were screened for eligibility by a registered nurse. Healthy volunteers (HV group) had to be age 18 or older with no self-reported history of lymphedema or breast cancer, and be capable of giving informed consent. Volunteers with a history of breast cancer treatment related lymphedema (LE group) had to be age 18 or older with a diagnosis of lymphedema in one arm only and without a self-reported history of primary lymphedema or swelling prior to breast cancer treatment. Individuals were excluded from the study if they had a medical condition that would have an impact on the measurement of limb volume by any of the methods being tested, such as, but not limited to, infection or skin lesions on limbs and allergy or sensitivity to adhesives on skin to be measured using tape measures. Because metal implants and/or pacemakers could interfere with the accuracy of impedance measurements, persons with these devices were excluded. Additionally, pregnant women were excluded because of normal patterns of fluid fluctuation unrelated to lymphedema, and not because of safety concerns for the mother or fetus.

Approval was obtained from Institutional Review Boards in two University Medical Centers: one in the mid-western and one in the southeastern United States. Of 35 individuals screened for the study, 34 were

eligible, and 31 of these completed the study. Data from 25 female participants (LE=11; HV=14) are included in this manuscript. Participants were compensated \$10 in recognition of time and effort for being involved in the study.

INSTRUMENTS

Tape Measure

A flexible, non-stretch, woven fabric tape measure was used to measure arm circumferences. To assure consistent tension over soft tissue, muscle, and bony prominences registered nurses with previous training and extensive experience in circumferential arm measurement techniques completed the measurements (9). The tape measure was calibrated in metric units (0.1 cm divisions) and manufactured by Hoechstmass of Sulzbach, Germany.

Infrared Laser Perometer

The Perometer 350S (Cuyahoga Falls, OH, Juzo) was used to map a 3-dimensional graph of the affected and non-affected extremities using numerous rectilinear light beams, and limb volume was calculated using a modification of the disc method (14). This optoelectronic method has a standard deviation of 8.9 ml (arm), less than 0.5% of limb volume with repeated measuring. Procedures for perometry documented by the European research teams of Tierney et al (14) and Stanton et al (15) and modified in our preliminary work, were followed.

Lymphometer®

A single-frequency bioelectric impedance device manufactured by Impedimed of Mansfield, Australia, was used to measure extracellular fluid volume (16,17). This instrument provides difference in fluid (ML) between the affected and non-affected limbs and gives a lymphedema index ratio (LIR)

between affected and unaffected limbs. In Australian studies, ratio means of 1.139 for affected dominant arms and 1.066 for affected non-dominant arms are possible indicators of lymphedema, and the instrument has been found to be more sensitive, valid, and reliable than circumferential arm measurements (17).

Electrical Impedance Spectrograph (EIS)

A multi-frequency Electrical Impedance Spectrograph (EIS) manufactured by UFI, Inc., Morro Bay, CA, was used to monitor fluid compartment volumes of each arm sequentially (18). The EIS scanned 40 input frequencies between 3.1 and 281 KHz and recorded the segmental resistance and reactance for each input frequency. These resistance and reactance values were then used in a resistance/capacitance network model to calculate a corresponding intracellular and extracellular resistance and fluid volume for each arm (18-20).

Lymphedema and Breast Cancer Questionnaire (LBCQ)

The LBCQ was used to assess self-reported arm symptoms. It is a two-part symptom assessment that elicits demographic and medical information such as height, weight, and type of cancer treatment (12). LBCQ reliability has been evaluated using Kuder- Richardson-20 and the test-retest methods (12).

PROCEDURES

Data were collected over 60 to 90 minutes during a one-time visit to a laboratory setting. Each participant's height and weight were obtained using a Health-O-Meter Scale, manufactured by Healthometer, Inc., Bridgeview, IL. A study nurse completed the brief medical history.

Volume measurements were conducted in order as follows:

Circumferential Measurement

Trained nurses conducted and laboratory assistants recorded circumferential measurements of each arm three times as participants sat with their arms resting horizontally, palms-down, on a bedside table placed at a level slightly below the axilla. An adhesive measurement strip (marked in cm) was placed along the limb from a point level with the axilla to the wrist to ensure consistency of measurement at four cm intervals. Arm length (in cm) from axilla to the tip of the extended longest finger also was recorded (21). Measurements were made at the hand proximal to the metacarpals, the wrist, and then every four cm from the wrist to axilla. Average measurement time for this procedure was 25 minutes.

Perometry Measurement

Participants stood with hip aligned perpendicularly to a table holding the perometer frame with arm extended. Each arm was measured in the horizontal position three times using Infra-red Perometry (Perometer 350S). Peroplus[®] software calculated limb volume and generated a three-dimensional graph of the affected and non-affected extremities. Average measurement time for this procedure was approximately five minutes, including equipment set-up.

Bioelectrical Impedance Measurement—Lymphometer[®]

Bioelectrical impedance measurements of each limb were made using the Lymphometer[®] and a multi-frequency EIS. During both impedance measurements, participants were supine with their arms extended by their side, slightly abducted from the body and palms facing down on a non-metal table, and electrode sites were prepped with an alcohol wipe prior to placement. For measurement using the Lymphometer[®], manufacturer recommended procedures were followed.

Average time to complete this procedure was approximately five minutes.

Bioelectrical Impedance Measurement—EIS

The multi-frequency EIS system outputs were recorded on a laptop computer using a Windaq 720 (Akron, OH) data acquisition system at a sampling rate of 200 Hz/channel for post-test analysis as suggested by Stewart et al (19,20). When using EIS, electrodes were placed on the back of each hand, each wrist, and on the shoulder of each arm. The hand electrodes served as the input/drive electrodes and the wrist and shoulder electrodes defined the arm segment to be monitored/measured during each impedance recording sequence. Average time to complete this procedure was six minutes.

LBCQ Measurement

Over a period of approximately 15 minutes, study staff trained in the administration of the LBCQ interviewed patients to assess arm symptoms and recorded participants' answers on the form.

ANALYSIS

Before conducting the statistical analyses, volume calculations for the actual arm measurements and limb index ratios calculations were needed.

Volume Measurements

Internal software in both the Perometer and Lymphometer® calculated volume. Formulas were used to calculate volume for the circumferential and EIS measurements (19,20,22).

Limb Index Ratios (LIRS)

Because the circumferential and perometric methods measured whole arm volume and the impedance devices measured

extracellular fluid volume, it was necessary to develop a standardized variable for comparison across methods. Thus, to directly compare measurements across techniques, all arm volume measurements were converted to LIRS of affected arm volume (actual in LE group and randomly assigned in HV group) to non-affected arm volume as follows:

Perometer. The volume calculated directly by the equipment Peroplus® software was averaged across three measurements. Volume of designated affected limb was divided by volume of designated non-affected limb.

Lymphometer. Limb ratios were directly calculated by internal equipment software (16).

Electrical Impedance Spectrograph (EIS). Volume of designated affected limb was divided by volume of designated non-affected limb.

Circumferential. The three arm measurements were averaged before computing volume and then the arm volume of the designated affected limb was divided by the volume of the designated non- affected limb.

Statistical Procedures

Data analysis was conducted using SAS® software (23). Alpha was set at .05 except when assessing the multiple correlations for objective three when a more conservative alpha level of .001 was used. Fisher's exact tests and t-test were used to compare the LE and HV groups on demographic characteristics and BMI. The research questions were analyzed as follows:

1) To what extent are there significant correlations among measurement methods? Pearson product-moment correlations were used to assess correlations among methods, and analysis of variance was used to compare mean limb ratios between the LE and HV groups.

2) To what extent do self-reported arm symptoms differ between healthy normal controls and breast cancer survivors with lymphedema? Fisher's exact tests were used to assess group differences in individual

TABLE 1
Sample Characteristics

Characteristic	HV (n=14) Frequency (%)	LE (n=11) Frequency (%)	Total (N=25) Frequency (%)	Significance
Race				p=1.00*
Caucasian	13 (93)	11 (100)	24 (96)	
African American	1 (7)	0 (0)	1 (4)	
	Mean (SD)	Mean (SD)		t-test [t(p)]
Age	46.2 (16.3)	53.6 (8.9)		[1.36(0.19)]
Education	17.5 (2.6)	16.4 (3.8)		[0.89(0.38)]
BMI	26.9 (5.5)	30.8 (7.2)		[1.51(0.14)]
*Fisher's Exact Test				

reported symptoms. Mean difference in total number of symptoms reported was determined by t-tests.

3) To what extent do self-reported arm symptoms correlate with circumferential tape measurement, infrared laser perometry, and bioelectrical impedance? Correlations among symptoms and the four measurement lymphedema index ratios were analyzed using point-biserial correlations.

RESULTS

Demographic and Medical

No significant group differences were noted in demographic variables (*Table 1*). Although not statistically significant, on average LE participants were obese with a mean Body Mass Index (BMI) of 30.8, while HV participants were overweight with a mean BMI of 26.9 (24). In the lymphedema group, 100% had surgery, 73% had radiation, and 91% had chemotherapy (*Table 2*).

Measurement Methods: Correlations and Comparisons

TABLE 2
Medical Characteristics-
Lymphedema Group

	LE (n=11) Frequency
Surgery Type	
Lumpectomy with AND*	5(46)
Modified Radical Mastectomy with AND*	2(18)
Mastectomy Unspecified AND*	2(18)
Mastectomy without AND*	1 (9)
None	1 (9)
Total Treatment	
Surgery/Radiation	1 (9)
Surgery/Chemotherapy	3(27)
Surgery/Radiation/Chemotherapy	7(64)
*Axillary Node Dissection	

Based on calculated limb ratios, a strong ($r \geq 0.7$) (25) degree of correlation among all measurement methods was noted (*Table 3*). Circumferential measurements correlated

TABLE 3
Correlations Among Instruments

	Cir	LYM	EIS
Perometer	0.877*	0.714*	0.724*
Cir		0.727*	0.708*
Lymphometer			0.987*

*p<0.001; Cir=circumferential;
LYM=lymphometer; EIS=electrical impedance spectrograph

more highly with the perometer than with the impedance measures. The two impedance measurements correlated more strongly with each other than with circumferential or perometry measures.

When HV group LIR results were compared to the LE group, ratio means were significantly different ($p<0.001$) using all measurement methods. In each case, as expected, the HV group had lower ratios than those with lymphedema (Table 4). This suggests that there is a demonstrable difference in arm size in the arms of breast cancer survivors with lymphedema and healthy normal controls.

Symptom Comparison

Using the LBCQ, a total of 14 self-reported arm related symptoms were evaluated (Table 5). All 14 symptoms were reported by one or more participants in the LE group as having occurred at some time during the past 12 months or as being present at time of study participation. Mean number of symptoms reported now was 6.58 (SD 1.88), and mean number of symptoms during the past year was 6.15 (SD 3.53). Participants in the HV group reported only eight different symptoms during the same time frame. Mean number of symptoms reported now was 1.38 (SD 1.88), and mean number of symptoms during the past year was 1.05 (SD 1.29).

TABLE 4
Mean Limb Index Ratios Across Instruments

	Perometer	Cir	LYM	EIS
HV	1.027	1.005	1.003	0.997
LE	1.131	1.177	1.171	1.204

HV=healthy volunteers; LE=subjects with lymphedema; Cir=circumferential; LYM=lymphometer; EIS=electrical impedance spectrograph. All ratios were significantly different $p<0.001$ between HV and LE groups.

Statistically significant differences ($p\leq 0.05$) between groups were noted (now and past 12 months) in 6 symptoms: arm swelling, arm swelling with pitting, firmness/tightness, heaviness, chest wall swelling, and breast swelling. Thus, there is a difference in both total number of reported symptoms and type of symptoms reported by breast cancer survivors with lymphedema when compared with healthy normal controls.

Measurement Methods and Symptom Correlation

Correlations among symptoms and the four measurement lymphedema index ratios showed few significant results (Table 6). Using a $p\leq 0.001$ level of significance, all four ratios correlated with arm swelling in the past year, but none with current swelling. Circumferential measures and both impedance measures correlated with swelling with pitting and firmness/tightness in the past year, but not with current swelling with pitting. When defining r values of >0.5 (25) as representing a strong linear relationship between two variables, additional relationships were apparent. Swelling correlated strongly with circumferential measures and both impedance measures, while firmness correlated strongly with the impedance measurements.

DISCUSSION

TABLE 5
Self-Reported Symptoms

	HV n=14	LE n=11	Fisher's Exact Test
Symptom	# YES	# YES	
Arm Tenderness			
now	6	5	1.0
past year	5	5	0.70
Arm Swelling			
now	1	10	0.001
past year	0	9	0.001
Arm Swelling/Pit			
now	0	7	0.001
past year	0	5	0.01
Arm Redness			
now	1	3	0.27
past year	1	4	0.13
Arm Blistering			
now	0	0	
past year	0	1	0.46
Arm Firm/tight			
now	1	7	0.01
past year	0	8	0.001
Arm Temperature			
now	0	3	0.07
past year	0	3	0.07
Arm Heaviness			
now	1	8	0.01
past year	1	8	0.01
Arm Numbness			
now	3	7	0.05
past year	3	6	0.12
Arm Stiffness			
now	3	3	1.0
past year	3	3	1.0
Arm Aching			
now	5	6	0.43
past year	5	5	0.70
Chest Wall Swelling			
now	0	4	0.03
past year	0	4	0.03
Breast Swelling			
now	0	4	0.03
past year	0	5	0.01
Fluid Pockets			
now	0	2	0.18
past year	0	2	0.18

TABLE 6
Correlations Between Self-Reported Symptoms and
Measurement Methods Among All Participants

Symptom	Perometer	Circumferential	Lymphometer	EIS
Tenderness				
now	-.33	-.18	-.16	-.15
past year	-.14	.06	.04	.03
Swelling				
now	.48	.52	.51	.54
past year	.62*	.76*	.65*	.62*
Swelling/Pit				
now	.43	.46	.47	.48
past year	.58	.65*	.64*	.61*
Redness				
now	.13	-.00	.47	.47
past year	.30	.32	.48	.52
Firm/tight				
now	.19	.33	.50	.51
past year	.46	.66*	.67*	.68*
Temperature				
now	-.05	-.12	.09	.13
past year	.19	.34	.29	.30
Heaviness				
now	.31	.32	.39	.41
past year	.44	.51	.34	.38
Numbness				
now	.17	.24	.30	.40
past year	.23	.32	.37	.40
Stiffness				
now	-.02	.16	-.07	-.08
past year	.01	.25	-.02	-.07
Aching				
now	-.22	-.03	.07	.00
past year	-.17	.03	.14	.06
Chest Wall Swelling				
now	.22	.32	.26	.27
past year	.19	.50	.30	.28
Breast Swelling				
now	.38	.29	.26	.30
past year	.41	.29	.44	.46
Fluid Pockets				
now	-.00	.07	.04	.07
past year	-.00	.07	.04	.07

*P ≤ 0.001; EIS=electrical impedance spectrograph

Correlations among instruments showed the two different impedance devices correlated strongly (.99) with each other. The two whole arm volume measurement methods, perometry and circumferential, also correlated strongly (.88) with each other. When electrical impedance and perometry and circumference were compared, the correlation was less strong (.72). However, it is important to note that impedance is a measure of fluid in the extracellular space, not bulk arm volume, and in this study, impedance measurement did not include the hand. Circumference and perometry are measures of the whole arm volume, including the hand. Thus, the differences in correlation would be expected and further validate the different measurement approaches.

Individuals in the LE group reported more symptoms related to arm morbidity than did the HV group. Specifically, arm swelling, arm swelling with pitting, chest wall swelling, firmness/tightness, heaviness, and breast swelling were significantly different in both the past 12 months and currently. Numbness now was significantly different between the groups with the LE group reporting this more frequently. However, both groups reported arm symptoms of tenderness, stiffness, redness, and aching now and in the past 12 months, suggesting these symptoms may not be uniquely associated with lymphedema.

When comparing subjective symptoms of lymphedema to the objective measurement techniques used, all measurement methods correlated significantly with “swelling in the past year” but not “now” when significance was held to ≤ 0.001 . Circumferential measures and the two impedance measurements correlated with the symptom of firmness/tightness, but not with the heaviness symptom as previously reported in the literature (12). These findings suggest the self-report of certain symptoms, such as swelling and tightness, may be indicative of developing lymphedema and clinicians should consider referring patients with these symptoms to lymphedema therapists for evaluation.

The incidental, but statistically non-significant, finding that breast cancer survivors with lymphedema had a BMI mean in the obese category while the mean BMI in the control group was in the overweight category is worth noting because of similar findings in previous studies (13,24). This suggests that the role of BMI in both the development of lymphedema and arm symptoms in breast cancer survivors may warrant further investigation. Alternatively, patients may exhibit higher BMI due to physical and psychosocial issues from developing or developed lymphedema.

LIMITATIONS

Study findings must be considered in light of their limitations. First, because of the relatively small number of participants, generalizability to the broader populations of both healthy individuals and those with lymphedema is limited. Specifically, it is premature to suggest that certain differences in limb ratios are indicative of lymphedema and, because dominant arm effects were not measured, it is unclear what impact that may have on the limb ratios reported. A second limitation centers around the difference in the impedance devices used. The Lymphometer[®] is a single, low frequency device, while the EIS device scanned 40 frequencies. Thus, volume measurements used to determine limb ratios were calculated differently. However, the two devices had a strong correlation across both normal and lymphedema participants. A third limitation is that participants in this study were measured at only one time during which menstrual cycle status was not ascertained, thus there is no accounting for possible normal or menstrual cycle related variations in limb ratios or in volume over time. A fourth limitation is that, although all were trained and the same nurse completed all measurements for an individual participant, different data collectors conducted circumferential measurements of participants' arms. Thus, although a rigorous

measurement protocol was established with interrater and intrarater reliability applied, variations in measurement technique may have occurred. Despite these limitations all measurement methods appear to correlate highly when ratios were used for comparison.

CONCLUSIONS

Findings from this study, coupled with stated limitations, lead to several conclusions. Each measurement method appears to be a valid technique for assessing upper limb lymphedema. Thus, both researchers and clinicians may want to consider issues such as equipment cost, time to conduct the measurements, and potential for user error when deciding which technique to use in both clinical and research settings. Further research is warranted in a larger sample to determine if the strong correlations among techniques remain constant. Serial measurements made over a period of contiguous days is indicated to explore normal volume variations in healthy and LE volunteers and to further investigate possible LIR cut points as lymphedema diagnostic criteria. Examination of dominant arm effects upon each measurement technique's ratio also is worthy of further exploration. Finally, the use and publication of calculated affected to non-affected limb index ratios in future studies of lymphedema may improve the ability of researchers to compare findings across studies using different measurement techniques.

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