Local Tissue Water in At-Risk and Contralateral Forearms of Women with and without Breast Cancer Treatment-Related Lymphedema

*Harvey N. Mayrovitz, PhD, College of Medical Sciences, Health Professions Division, Nova Southeastern University, 3200 S. University Drive, Davie Fl 33328

Daniel N. Weingrad, MD, FACS, Cancer HealthCare Associates, 1400 N.W. 12th Avenue, Suite 104, Miami, FL 33136

Suzanne Davey, OTR/L, CLT-LANA, Healing Hands of Lymphatics, 110 N. Federal Hwy., Suite 201, Hallandale Beach, FL 33009

*Corresponding Author:

Harvey N. Mayrovitz, PhD

College of Medical Sciences

Nova Southeastern University

3200 S. University Drive

Ft. Lauderdale, Florida 33328

Phone: 954-262-1313

Fax: 954-262-1802

Email: mayrovit@nova.edu

ABSTRACT

Background: Quantitative measurements to help detect incipient or latent lymphedema in patients at risk for breast cancer treatment-related lymphedema (BCRL) are potentially useful supplements to clinical assessments. Suitable measurements for routine use include arm volumes, arm bioimpedance and local tissue water (LTW) determined from the tissue dielectric constant (TDC). Because BCRL initially develops in skin and subcutis, measures that include whole arms may not be optimally sensitive for detecting the earliest changes. Thus there is also a need for a local measurement in which tissues most likely to demonstrate early lymphedematous changes can be more selectively assessed. The TDC method satisfies this criteria. Our goal was to use this method to compare arm-to-arm differences in LTW within and among women grouped as healthy normal (HN), diagnosed with breast cancer (BC) but prior to surgery and established unilateral lymphedema (LE).

Methods and Results: LTW was determined on both anterior forearms to a measurement depth of 2.5 mm in 30 women of each group. TDC arm ratios were determined as dominant/non-dominant for HN and BC, at-risk/contralateral for BC and lymphedematous/contralateral for LE. Results showed that TDC values for all arms except lymphedematous arms were very similar and insignificantly different with values among arms (mean±SD) ranging from 24.9±3.8 to 25.7±3.8. Arm ratios did not differ between HC and BC whereas dominant/non-dominant arm ratios for HN and BC separately and combined (1.006±0.085) were significantly less than the lymphedematous/contralateral ratio of the LE group
(1.583±0.292).

Conclusions: The findings indicate that LTW of at-risk arms is not affected by breast cancer and that lymphedema does not significantly affect LTW of contralateral arms as measured with the TDC method. Further, based on the standard deviation of measured arm ratios, an at-risk/contralateral TDC ratio of 1.26 is suggested as a possible threshold for detecting pre-clinical or latent lymphedema.

Abbreviated Abstract

The tissue dielectric constant (TDC) method was used to compare arm-to-arm differences in local tissue water (LTW) within and among three groups of 30 women; healthy normal (HN), recently diagnosed with breast cancer (BC) and unilateral lymphedema (LE). TDC values and arm ratios were insignificantly different within and between HN and BC with a dominant/non-dominant ratio of 1.006±0.085 compared to 1.583±0.292 for LE. Results indicate that LTW of at-risk arms is unaffected by breast cancer and that lymphedema doesn't affect contralateral arm LTW. Results suggest that an at-risk/contralateral TDC ratio of 1.26 as a possible threshold for detecting pre-clinical lymphedema.

INTRODUCTION

Quantitative measurements of arm parameters to aid in the detection of incipient or latent lymphedema in patients at risk for breast cancer treatment related lymphedema (BCRL) are potentially useful supplements to standard clinical assessments. Suitable measurements for routine use include arm volumes[1-4], arm bioimpedance[5,6] and local tissue water determined by measuring the tissue dielectric constant[7-10] at various sites and tissue depths[11-13]. Because BCRL initially develops in skin and subcutis[14] within the epifascial compartment, measures that include the whole arm may not be optimally sensitive for detecting the earliest changes. Bioimpedance methods that use either multifrequency[15,16] or single frequency[17,18] signals to measure changes in whole arm electrical impedance can detect changes in water content and have provided important insights[17-21] However, because the entire arm is included in impedance measurements there is also a need for a more local measurement approach in which the tissue compartment that is most likely to demonstrate early lymphedematous changes can be more selectively assessed. Initial results of such an approach has recently been reported[22] whereby local tissue water (LTW) to a depth of up to 5 mm below the skin surface was determined based on measurements of the tissue dielectric constant (TDC).

In patients that have unilateral arm involvement, whichever measurement method is used, a preferred approach is to compare the at-risk arm to the apparently unaffected arm with respect to differentials or ratios. When such paired arm comparisons are initially made prior to a patient’s surgery then subsequent changes in assessment parameter values can take into account baseline differentials that may be present. However, often such pre-surgery measurements are not made thereby making such comparisons made at later dates, following surgery and/radiation treatment, potentially less reliable for judging at-risk arm changes. A contributing factor to such uncertainty is the rather limited knowledge of the extent to which cancer presence or lymphedema development may alter aspects of the contralateral, apparently unaffected arm. Although bioimpedance measurements made pre-surgically in patients diagnosed with breast cancer[23], in healthy controls[24] and in patients with BCRL[17] provide important insights with respect to the impedance parameter, corresponding data with respect to local tissue water is not available. Thus, our goal was to determine the extent to which LTW in the non-at-risk arm was affected by either breast cancer presence or lymphedema of the at-risk arm and to further characterize TDC variability among subjects. For this purpose LTW was determined using the TDC method in both forearms of 90 women, 30 healthy controls, 30 recently diagnosed with breast cancer but prior to surgery or treatment and 30 with established unilateral BCRL.

METHODS

Subjects

A total of 90 women, 30 healthy normal controls (HC) , 30 recently diagnosed with breast cancer but prior to surgery (BC) and 30 with unilateral BCRL (LE) were evaluated after signing a University Institutional Review Board approved informed consent. Entry requirements for the BC group were that they had recently (within one month) been diagnosed with breast cancer and were awaiting surgery. These patients were referred by their surgeon for a pre-surgery evaluation. Entry requirements for the LE group were that they had unilateral lymphedema and had been physician referred for lymphedema therapy. Entry requirements for the HC group were that they had not had any previous surgery or serious trauma to either arm and were in self-reported good health. Pertinent features of the three groups are summarized in table 1.

TDC Measurement Device

The device used in this study to measure the tissue dielectric constant was the MoistureMeter-D (Delfin Technologies Ltd, Kuopio Finland www.delfintech.com). It consists of a cylindrical probe connected to a control unit that displays the tissue dielectric constant when the probe is placed in contact with the skin. The physics and principle of operation has been well described[7-9,25,26]. In brief, a 300 MHz signal is generated within the control unit and is transmitted to the tissue via the probe that is contact with the skin. The probe itself acts as an open-ended coaxial transmission line[7,25]. The portion of the incident electromagnetic wave that is reflected depends on the dielectric constant of the tissue, which itself depends on the amount of free and bound water in the tissue volume through which the wave passes. Reflected wave information is processed within a control unit and the relative dielectric constant is displayed. For reference, pure water has a value of about 78.5 and the display scale range is 1 to 80. The effective measurement depth depends on the probe dimensions, with larger spacing between inner and outer conductors corresponding to greater penetration depths. Previous work[22], in which various probes were used to assess TDC values to measurement depths of 0.5, 1.5, 2.5 and 5.0 mm showed a sharp decrease in TDC values between 1.5 and 2.5 mm but little difference between values obtained at 2.5 and 5.0 mm measurement depths. Thus in this study only the 2.5 mm probe was used that has an outside diameter of 23 mm and inner-to-outer conductor spacing of 5 mm.

TDC Measurement Procedure

TDC measurements were started after a subject was lying supine for 10 minutes on a padded examination table with arms at her side with hands positioned palm up to expose the anterior surface of both forearms. A standardized measurement site, along the forearm midline located 6 cm distal to the antecubital fossia was marked with a dot to serve as a reference center point for probe placement. A single measurement was obtained by placing the probe in contact with the skin of one arm and held in position using gentle pressure. After about 10 seconds an audible signal indicated completion of the measurement. The probe was then used to make a measurement on the other arm to complete a measurement pair. This process was continued to obtain triplicate measurement pairs. Alternating between arm sides was used as a way to help obtain paired values as close in time as possible. Fore each arm the three measurements were averaged and used to characterize the arm site average TDC value.

Segmental and Arm Volumes

After the TDC measurements, circumferences of the arm at the reference center point and at 2 cm proximal and 2 cm distal were measured using a calibrated Gulick-type spring-loaded tape-measure with a tension gauge to help insure uniform measurements. From these measures, the segmental volume of the 4 cm length encompassing the TDC measurement site was calculated using a truncated-cone model. In this method segmental volumes V_S are determined by the formula $V_S = L/12\pi\ (C_1^2+C_1C_2+C_2^2)$ in which C_1 and C_2 are the measured circumferences at either end of a given segment of length L, in the present case equal to 2 cm. The 4 cm segment volume was then determined as the sum of the two 2 cm segments. The percentage difference in segmental volumes between arms was calculated as $100(V_A - V_C/)V_C$ in which V_A is the segmental volume for the at-risk arm in the BC group or the affected arm in the LE group or the dominant arm in the control group. V_C is the segmental volume of the corresponding other arm. In addition to segmental volumes associated within the TDC measurement region, total arm volumes were also determined using circumference measurements starting at the wrist with measurements repeated at 4 cm intervals extending up the arm toward the axilla. Arm volumes were calculated using the measured circumference values in the truncated-cone model with calculations done using automated software (Limb Volumes Professional 5.0, Clinical Software Innovations www.clinsoft.org). Arm total volume is determined as the sum of all 4 cm segment volumes. This method of estimating limb volume has been extensively tested and validated[3,27-29]. For additional comparison purposes, arms were designated as either dominant or non-dominant depending on the self-reported handedness of the subject.

Data Reduction and Analysis

Mean values ± SD and parameter ratios between paired arms for each parameter (TDC, segmental volume and whole arm volume) were determined. For the BC and LE groups initial comparisons were based on the at-risk and contralateral arms with the ratio of at-risk/contralateral arms used. For the HN group comparisons were based on the dominant and non-dominant arms with the dominant/non-dominant ratio used.. Overall differences among the three groups was initially tested for using a general linear model (GLM) for repeated measures with arm as the within factor. Differences between arm sides was subsequently tested for using paired t-tests. Differences in ratios among groups was tested for using a one way analysis of variance. In all cases a p-value <0.05 was taken as significant. Tests for correlations among parameters was done using Pearson coefficients. All statistical analyses were done using SPSS (SPSS Inc., 233 S. Wacker Drive, 11th floor, Chicago, IL 60606-6307 www.spss.com version 12.0)

RESULTS

Segmental and Arm Volumes

Arm and segmental volumes did not significantly differ between arm sides for either the NH or BC groups nor did volumes or arm ratios differ between these groups as summarized in **table 2**. Contrastingly, and as should be expected, arm and segmental volumes of the LE group differed between sides, with the lymphedematous arm volumes being significantly greater. However, volumes of the non-affected contralateral arm LE group did not significantly differ from arm volumes of either the NH or BC groups. Based on whole arm volume measurements the percentage edema of the lymphedematous arm was 26.4±28.2 % whereas based on segmental volumes it was 44.1±29.2 %. Corresponding paired arm ratios (lymphedematous/contralateral) were 1.276±0.247 and 1.428±0.261 respectively. The smaller percentage edema and ratio obtained when whole arm volumes are used is because whole arm measurements include more non-edematous parts of the arm in the determination than does the segmental volume.

TDC and Local Tissue Water

As shown in **table 2**, TDC values did not significantly differ between arm sides for either the NH or BC groups nor did absolute TDC values or paired arm ratios differ between these groups. Contrastingly, TDC values of lymphedematous arms of the LE group were significantly greater than contralateral arms and significantly greater than both arms of the NH and BC groups. Because the results indicated essentially no difference between the TDC values of the HN and BG groups an overall comparison was made between dominant and non-dominant arms of the combined group (N=60). Results of this analysis showed that TDC values for the dominant and non-dominant arms to be 25.36 ± 3.80 vs. 25.33 ± 4.07 respectively with an overall dominant/non-dominant TDC ratio of 1.006±0.085. To explore the possible impact of BMI or age on this ratio, TDC values were compared based on HN and BC group subjects who had a BMI below (N=30) vs. above (N=30) the combined median BMI (27.27 Kg/m^2) and also based on subjects in these groups who were younger (N=30) or older (N=30) than the combined median age (54.0 years). Results indicate no significant differences between subjects in the lesser BMI group compared to subjects in the greater BMI group (1.021 ± 0.085 vs.0.989 ± 0.0832) or between younger and older subjects (1.0155 ± 0.0719 vs. 0.997).

Correlation Among Parameter Ratios

As might have been anticipated there was a strong positive correlation between total arm and segment volume ratios (p<0.001, r=0.901). In addition, a significant positive correlation was found between arm TDC ratios vs. arm volume ratios (p<0.001, r=0.690) and segmental volume ratios (p<0.001, r=0.770). **Figure 1** illustrates the relationship between TDC ratios (TDCr) vs. segmental volume ratios (Vr) for the BC and LE groups, that were nearly matched with respect to both age and BMI (table 1). The regression line for these data (N=60) is given by TDCr = 0.956Vr + 0.142, p<0.001, r=0.752.

DISCUSSION

Measuring local tissue water based on the tissue dielectric constant[11-13,22] represents a new, potentially adjunctive approach toward better characterizing lymphedema and potentially an earlier detection of latent or incipient lymphedema. The TDC method differs from limb volume[1-4,29] and bioimpedance methods[5,6,21,24] in that with a 2.5 mm measurement depth as used in the present study, it only interrogates skin and subcutaneous tissue compartments in which some of the earliest changes are likely to occur[14,30]. Because it is a local measurement it can be used at virtually any anatomical site that may be at-risk for lymphedema development. Although the principles and biophysical basis of this measurement method have been well described[7-10,25,26] it has not been widely used as a lymphedema assessment or investigative tool probably in part due to an insufficient characterization of patterns of differentials among patients. Although differences in tissue water between frankly lymphedematous and contralateral non-affected limbs are known to be present[22,31], similar information as to differentials between limbs of healthy normal persons and persons with breast cancer but without lymphedema have not been well defined. Such information has relevance with respect to the potential utility and interpretation of TDC assessments. Thus, the principal goals of the present study were to determine the extent to which LTW, as judged by TDC measurement, differed between arms of healthy normal (HN) women, women with breast cancer (BC) prior to their breast cancer surgery and women with frank unilateral arm lymphedema (LE) and to better define the variability of the TDC measurement to aid in the process of developing suitable reference ranges and possible thresholds that might indicate latent lymphedema.

A principle result of the paired arm comparisons demonstrates that only in the LE group are differentials in TDC values between arms significant. When expressed as the TDC ratio of at-risk (lymphedematous) to contralateral arm, this ratio (mean ±SD) for the 30 evaluated women with lymphedema was 1.583±0.292. Contrastingly TDC arm ratios for women in the HN and BC groups were close to unity being 1.017±.077 and 0.994±0.093 respectively. Not only were TDC arm ratios similar in these two groups but the TDC mean values for all arms among groups differed by less than 1.0 TDC unit (table 2). Further, TDC values of contralateral arms of women in the LE group were insignificantly different from TDC values of either the HN or BC groups with mean values differing from them by less than 1.0 TDC units. Based on these findings it is reasonable to conclude that breast cancer in the BC group did not significantly affect TDC, and thereby LTW, in either arm and lymphedema in the LE group did not significantly affect it in the contralateral arm of these women.

Because the at-risk arm may be the dominant or the non-dominant arm (table 1) it is useful to also characterize the dominant/non-dominant TDC ratio with as large a data set as available. Since analysis indicated no difference between HN (dominant/non-dominant) and BC (at-risk/contralateral) group volumes or TDC ratios, these groups could be reliably combined (N=60) to determine a combined dominant/non-dominant TDC ratio. Results showed an overall TDC ratio of 1.006±0.085 which was insignificantly affected by BMI or age. This ratio may be compared to whole arm ratios obtained for a group of 60 control subjects using bioimpedance[24] where a dominant to non-dominant ratio of 0.964 ± 0.034 was obtained and for a control group of 32 subjects in which the dominant to non-dominant ratio was determined to be 1.024[17]. It should be noted that with impedance measurements higher values of arm water yield lower impedance values so a ratio of less than one indicates a slightly higher water in dominant arms.

Impedance values have been used in an effort to help detect sub-clinical or latent lymphedema following breast cancer treatment based on standard deviations of arm ratios measured in control subjects[19]. An approach adopted was to define a threshold at which the arm impedance ratio exceeded a pre-surgical value by three standard deviations of that obtained on the group of 60 control subjects[24]. Thus an at-risk to contralateral arm ratio greater than 0.102 of the pre-surgical value was used to define lymphedema presence[6,24]. Applying the same conservative criteria to the present TDC data based on the 60 dominant to non-dominant TDC ratios indicates a threshold 3SD value of 0.225. It should be noted that it has been reported[17] that the bioimpedance threshold ratio may need to take into account the handiness of the patient who is at-risk because of the dominant to non-dominant bias of the control group data. However, a similar adjustment is apparently not needed with the TDC ratio as the dominant/non-dominant ratio differs insignificantly from unity. Thus based on the present findings a TDC ratio between at-risk and contralateral arms that exceeds 1.26 may indicate the presence of preclinical latent lymphedema. It should be emphasized that this TDC threshold has not as yet been prospectively substantiated and is the target of current research efforts.

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Author Disclosure Statement

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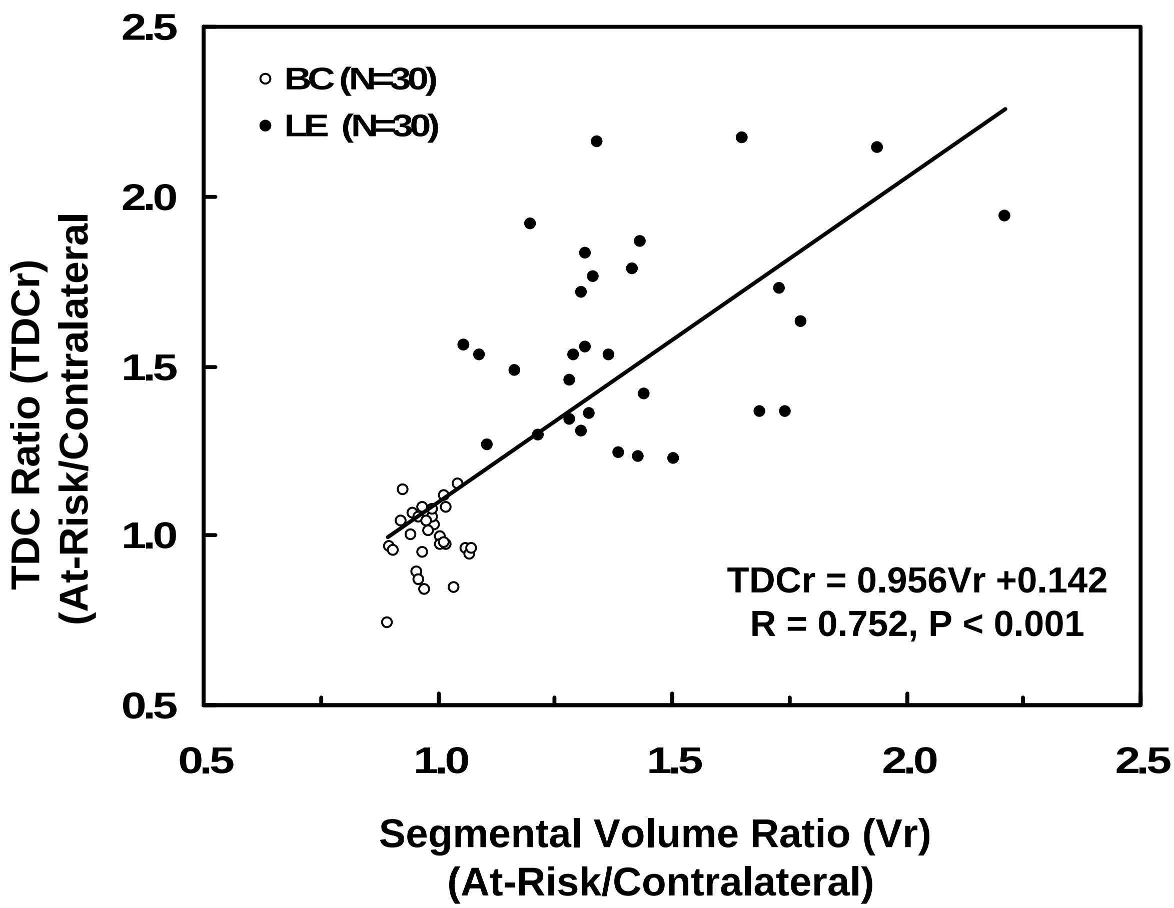
Figure 1. Relationship between arm TDC ratios and segmental volume ratios. Open circles are for the breast cancer group (BC) and filled circles are for the lymphedematous group (LE). The solid line is the linear regression with the equation and parameters given in the figure inset.



	Group HN - Controls	Group BC - Breast Cancer	Group LE - .Lymphedema
Number of Subjects (N)	30	30	30
Age (years)	45.3 ± 14.9* [25-71]	62.4 ± 12.1 [42-82]	68.0 ± 11.8 [42-91]
BMI (Kg/m^2)	26.4 ± 5.7 [17-38]	28.6 ± 6.8 [18-45]	28.6 ± 4.4 [19-34]
BMI < 25 Kg/m^2 - Normal	14/30 (46.7%)	8/30 (26.7%)	8/30 (26.7%)
BMI 25-29.9 Kg/m^2 - Overweight	9/30 (30%)	12/30 40%)	7/30 (23.3%)
BMI >= 30 Kg/m^2 - Obese	7/30 (23.3%)	10/30 (33.3%)	15/30 (50.0%)
Right Arm Dominant	28/30 (93.3%)	28/30 (93.3%)	27/30 (90.0%)
Dominant Arm is At-Risk Arm		11/30 (36.6%)	16/30 (53.3%)
Lymphedema Duration (years)			7.7 ± 5.6 (2.5-14)

Table 1. Summary of pertinent features of the study groups. Values are mean ± SD where applicable with [ ] indicating range; BMI is body mass index. * HN age significantly less than for either BC or LE p<0.001. At-Risk arm in BC group corresponds to the breast side diagnosed with cancer, At-Risk arm in the LE group corresponds to the lymphedematous arm.

	Group HN - Controls	Group BC - Breast Cancer	Group LE - .Lymphedema
Number of Subjects (N)	30	30	30
Whole Arm Volumes (ml)			
Dominant or At-Risk	2418±549	2318±766	3293±972*
Non-Dominant or Contralateral	2387±548	2326±768	2577±526†
Ratio of Arms	1.014±.046	0.995±.054	1.276±0.247*
Segmental Volumes (ml)			
Dominant or At-Risk	194.7±42.8	191.4±38.5	282.9±79.3*
Non-Dominant or Contralateral	191.4±46.0	193.9±39.0	196.9±45.9‡
Ratio of Arms	1.021±.043	0.983±.048	1.428±0.261*
TDC Values			
Dominant or At-Risk	25.2±3.9	25.4±3.4	39.6±7.4*
Non-Dominant or Contralateral	24.9±3.8	25.7±3.8	25.1±2.7‡
Ratio of Arms	1.017±.077	0.994±0.093	1.590±0.286*

Table 2. Summary of Volume and TDC Results. Values are mean ± SD. For the HN group dominant vs. non-dominant arms are used. For the BC and LE groups the at-risk and contralateral arms are used. At-risk arm in the BC group corresponds to breast side diagnosed with cancer and in LE group corresponds to the affected lymphedematous arm. Ratios are dominant/non-dominant for HN and at-risk/contralateral for BC and LE. * LE significantly greater than either HN or BC (p<0.001); † p<0.01 compared to affected arm, ‡p<0.001 compared to affected arm. Differences between arm sides were statistically insignificant for the HN group (p=0.48) and for the BC group (p=0.72). Except for the LE affected arm neither volume or TDC values differed among groups.