Temporal Patterns of Tissue Dielectric Constant (TDC) Values to Assess Local Skin-to-Fat Water Changes in Women Treated for Breast Cancer

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Background and Objectives

BACKGROUND: A woman's risk of getting breast cancer (BC) treatment-related lymphedema (BCRL) depends on surgery extent, radiation use and type, chemotherapy and obesity. Since lymphedema severity grows without treatment the need for early detection is clear. Researchers have tried to predict its occurrence with arm size and arm bioimpedance measures. Metric based criteria, tested to define BCRL presence, include inter-arm girth differences or changes > 2 cm, inter-arm volume differences > 200 ml and volumes > 10% between at-risk and contralateral arms or changes in these amounts measured on at-risk arms compared with at-risk arms pre-surgery values. A new parameter possibly useful to characterize the lymphedematous state is the tissue dielectric constant (TDC); an index of local skin tissue water (LTW). Two features of this technology render it different from whole limb measurements of volume and bioimpedance; 1) It can rapidly and non-invasively measure any body surface yielding LTW indices not restricted to arms or legs and 2) it can easily interrogate tissue volumes to different depths revealing changes in depth distributions of water from epidermis to hypodermis. Information regarding TDC in several conditions has been published but there has been no description of the pattern of sequential changes in TDC after breast cancer treatment. These patterns may reveal the natural temporal history of the post-surgical sequence and have utility as a basis for early detection.

OBJECTIVE: The goal of this research was to provide an initial pattern characterization and secondarily to compare sequential TDC patterns with those determined via arm volume and impedance measurements.

Methods

SUBJECTS: Women (N=80), newly diagnosed with BC, were initially evaluated within two weeks of their pending surgery. By study design, follow-up visits were planned for 3, 6, 12, 18 and 24 months post-surgery. Of 80 evaluated pre-surgery (month 0), decreasing numbers returned for later visits. This resulted in sub-sets in which 60 pts. were evaluated at months 0-3, 53 at months 0-3-6, 47 at months 0-3-6-12, 41 at months 0-3-6-12-18 and 35 at all months, 0-3-6-12-18-24.

PROCEDURE SEQUENCE AND ORDER: Pts. were evaluated supine on a padded examining table in a private room. Arms were marked at sites for later girth and TDC measurements (forearm, biceps, axilla and lateral thorax) on both body sides (Figure 1). Girths were measured first. Then TDC measurements started using a 2.5 mm effective depth probe at the at-risk forearm and then to biceps, axilla and thorax, each in triplicate. Immediately thereafter the same TDC sequence was started on the other body side. TDC measurements were then made to effective depths of 0.5, 1.5, 2.5 and 5.0 mm at the forearm. For each depth the 1st measurement was on the at-risk arm and then on the contralateral arm. Three pairs of these arm-to-arm TDC values constituted the measurement set for each depth. At the end of TDC measurements the bioimpedance electrodes were fitted as shown in Figure 2 and measurements made. Before any measurements, pts. completed a questionnaire aimed at determining her perceived symptoms. The questionnaire asked if any of 12 sensations had been experienced since her last visit in her arm, hand, fingers, axilla or chest. The sensations were; fullness, heaviness, tightness, numbness, tingling, tenderness, aching, pain, warmth, cold, swelling and stiffness.

Measurement Methods

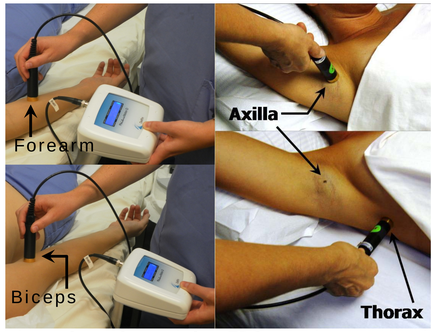


Figure 1. ***Tissue Dielectric Constant (TDC) measurements and sites***
Bilateral TDC measurements were made (MoistureMeter-D, Delfin) to an effective depth of 2.5 mm at anterior forearm (6 cm distal to the antecubital fossa), anterior biceps (8 cm proximal to antecubital fossa), at axilla and at the lateral thorax (10 cm inferior to the axilla). Each measurement takes about 10 seconds and starts when the probe is placed on the skin. In addition to the TDC measurements at the the various pictured sites TDC was also measured on anterior forearm to effective depths of 0.5, 1.5, 2.5 and 5.0 mm. TDC measurements provide an index of both free and bound water. Pure water has a value of about 78.5.

Figure 2. ***Arm Bioimpedance***
Bioimpedance values were determined using 5 electrodes; two pairs on the dorsal surface of the hand separated by 5 cm and one on the foot dorsum. After cleaning sites with alcohol, measurement electrodes were placed on the wrist at the level Of the process of the radial and ulnar bones and driving electrodes placed at least 5 cm distal on the dorsal surface of the 3rd metacarpal bone of the hands. Impedance measurements were taken with subjects supine and arms slightly abducted and palms down. Smaller impedance values reflect greater amounts of total arm extracellular water. Frequency is stated as < 30 KHz.

Arm volumes were calculated by measuring arm girths at 4 cm intervals with a spring tension tape measure and calculating volume based on a validated frustum model (www.limbvolumes.org). Girths were measured starting at the wrist with measurements continued up the arm until reaching a pre-marked level close to the level of the axilla.

Data Reduction and Analysis

The main analysis group were pts. evaluated at each planned visit at 0, 3, 6, 12, 18 and 24 months post-surgery (P-S). Sequential patterns found for this group were then compared to the sub-set groups comprised of pts. who had been seen consecutively for up to 18, 12, 6 or 3 months p-s. Since by 24 months P-S the number of the same patients seen at each visit was reduced by attrition to 35 from the initial 80 pts, additional sub-set analyses were done to determine if the significance of any observed pattern for the 0-24 month data set was consistent with or better clarified if more pts. were included at specific follow-up months. TDC values, arm volumes and bioimpedances and their inter-side differences and inter-side ratios were used in the analyses. Normality of values, tested by the Shapiro-Wilk test, indicated a non-Normal distribution ($p<0.01$) only for arm volumes. Significance of differences between sides (at-risk vs. control) was determined using paired t-tests except for arm volumes for which the Mann-Whitney test was used. Tests for statistical significance of pattern changes over time were based on a general linear model with repeated measures and significance of changes at any month compared to pre-surgery assessed via within-contrasts analysis. Tests for significance of overall arm volume pattern changes were done using the non-parametric Friedman test.

REFERENCES: Mayrovitz HN et al., Lymphology 2007;40:97-94 and 2009;42:88-98 and 2011;44:168-177; Mayrovitz HN et al., Clinical Physiology 2008;28:337-342 and 2010;30:328-332 and 2013;33:55-61; Mayrovitz HN et al., Lymphatic Res and Biology 2009;7:101-109; and 2009;7:153-158; Mayrovitz HN et al.,Skin Res & Technology 2010;16:16-22 and 2010;16:438-443 and 2013;19:47-54; Mayrovitz et al., Diabetes Tech and Therapeutics 2013;15:60-65

Main Results

Figure 3. TDC probes calibrated by exposing to varying ethanol-H_2O concentrations. TDC value is linear with %H_2O

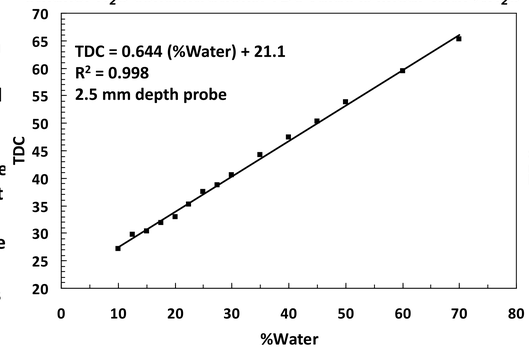
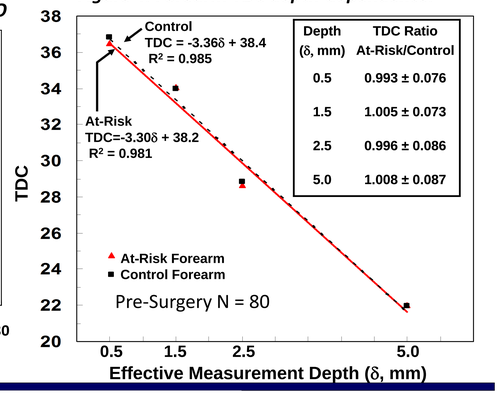


Figure 4. Forearm TDC depth-dependence:



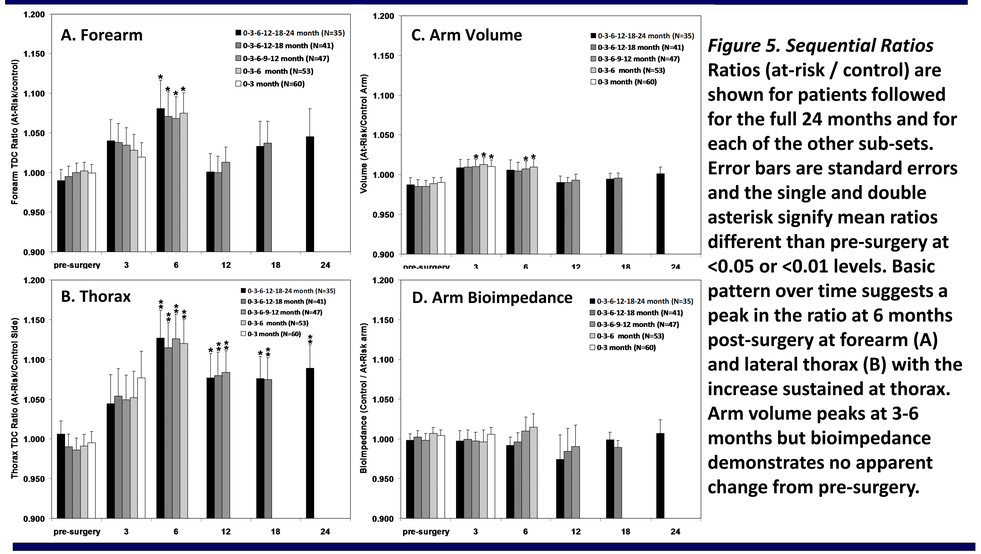


Figure 5. Sequential Ratios
Ratios (at-risk / control) are shown for patients followed for the full 24 months and for each of the other sub-sets. Error bars are standard errors and the single and double asterisk signify mean ratios different than pre-surgery at <0.05 or <0.01 levels. Basic pattern over time suggests a peak in the ratio at 6 months post-surgery at forearm (A) and lateral thorax (B) with the increase sustained at thorax. Arm volume peaks at 3-6 months but bioimpedance demonstrates no apparent change from pre-surgery.

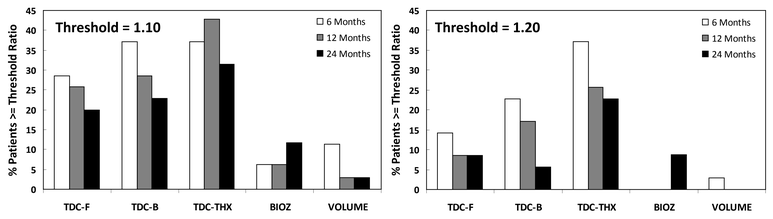


Figure 6. Percent of Pts. Experiencing Increases in A/C Ratios
Data are for threshold ratios of 1.10 and 1.20 threshold increases of 10% and 20% compared to pre-surgery ratios.

Conclusions

TDC measurements were a convenient, portable, non-invasive way for us to rapidly characterize local skin tissue water changes at multiple body sites and at various effective depths below the epidermis. Results of using TDC measurements in the present study to track changes over as long as 24 months suggest that TDC side-to-side ratios at the lateral thorax may be the most likely and sensitive parameter for potentially detecting early BCRL. However other sites may also be useful. Further work is warranted and needed to specifically associate threshold values with well documented evidence of BCRL presence.