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ASSESSING LOCAL TISSUE EDEMA IN POSTMASTECTOMY LYMPHEDEMA

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ABSTRACT

Overall limb lymphedema can be assessed by several methods but none are suitable to determine local edema. Quantifying local edema could provide important information not previously available. Our goal was to determine the suitability of using the tissue dielectric constant (TDC) as and index of local tissue water to detect and quantify edema in postmastectomy patients with unilateral arm lymphedema. Segmental arm volume and TDC were measured in both arms of 18 women with unilateral lymphedema, and in 15 premenopausal and 15 postmenopausal controls. TDC was measured at a frequency of 300 MHz using open-ended coaxial probes with effective measuring depths of 0.5, 1.5, 2.5 and 5.0 mm. For patients and controls, absolute TDC depended on measurement depth but for any depth the TDC of lymphedematous segments was significantly greater than for non-affected contralateral arms (p<0.001). At a depth of 2.5 mm, the TDC ratio between arms for patients was 1.64±0.30 vs.1.04±0.04 for both control groups (p<0.001). No patient's TDC ratio was as low as 1.2 and no control subject's TDC ratio was as great as 1.2. Results suggest that this method is a good quantitative discriminator of the presence of lymphedema in patients with unilateral limb lymphedema.

Keywords: breast cancer, lymphedema measurement, edema measurement, lymphedema treatment, dielectric constant, tissue water, arm lymphedema

Many methods are available to assess overall limb edema via metric and volume measures (1-7), automated methods (8-11) and electrical impedance type methods (12-14). However, these are not generally suitable to determine local edema or edema in body parts other than the limbs. Quantitative assessment of local tissue edema could provide important and useful information not previously available to help initially assess and to track lymphedema progression in patients. Recently, a device, potentially useful for this purpose, became available (15). Its working principle is based on the fact that tissue electrical properties depend on water content which in turn affects the value of the tissue dielectric constant. Measurement of the tissue dielectric constant (TDC) at a suitable frequency thus provides an index of the relative tissue water. Our goal was to determine the suitability of this approach to detect edema in patients with unilateral arm lymphedema secondary to breast cancer treatment. We hypothesized that the TDC of affected arms would be significantly elevated compared to contralateral non-affected arms.

METHODS

Subjects

A total of 48 women were evaluated after signing Institutional Review Board approved informed consents. Of the 45 women, 18 had unilateral postmastectomy lymphedema, 15 were postmenopausal normal controls and 15 were premenopausal normal controls. The only entry requirement for the women with lymphedema was that the lymphedema was unilateral and was the result of a previous mastectomy done for the treatment of breast cancer. As it turned out 17 of the women also had received radiotherapy. The duration of the lymphedema and its extent were not factors that affected participation since the goal of this initial study was to determine the suitability of the method for the clear detection of localized lymphedema. The entry requirements for the control groups (both pre- and postmenopausal) were that they had not had any previous surgery or serious trauma to either arm and were in self-reported good health. Because of the possibility that sex hormones might have an effect, all premenopausal women were evaluated within 4 days of the onset their menses. The average age (± 1 standard deviation, sd) of the lymphedema group (74 ± 16 years) was greater than the postmenopausal group (60 ± 6.7 years, $p<0.05$) which was significantly greater the premenopausal group (26.2 ± 3.9 years, $p<0.001$).

Edema Measurement Device

The device used in this study is called the MoistureMeter-D, (Delfin Technologies Ltd, Finland). It consists of a 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 (16-20). 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 (19,21). 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. The reflected wave information is processed within the control unit and the relative dielectric constant is displayed. Pure water has a value of about 80 and the display scale range is 1 to 80. The effective penetration depth depends on the probe dimensions, with larger spacing between inner and outer conductors corresponding to greater penetration depths. In the present study four different dimension probes were used with effective penetration depths of 0.5, 1.5, 2.5 and 5.0 mm. The corresponding (maximum) probe diameters were 10, 20, 23 and 55 mm with conductor spacing of 1, 3, 5 and 17 mm respectively.

Edema Measurement Procedure

A subject was seated with her arms resting on a support surface at approximately 12 cm below heart level. Her hands were positioned palm up to expose the volar surface of both forearms *(Fig. 1A)*. A standardized reference measurement site, located 7 cm distal to the antecubital crease, was marked with a dot. This dot served as the reference center point for all probe placements. Measurements were begun after she had been comfortably seated for 5 minutes. For the measurements, probes were placed in contact with the skin and held in position using gentle pressure *(Fig. 1B)*. For each probe, measurements were obtained in triplicate-pairs. The first pair was done by measuring one arm and then, immediately after, measuring the other arm. This procedure was repeated twice more for each probe. The order of measurement was from smallest to largest probe with a one minute wait between changing probes. The time required to obtain a single measurement, once the probe was placed in contact with the skin, was 10-15 seconds. Preliminary work showed that repeated measurements taken at 15 second intervals for 600 seconds resulted in a coefficient of variation of only 2.8% indicating a good short term repeatability of the technique (22).

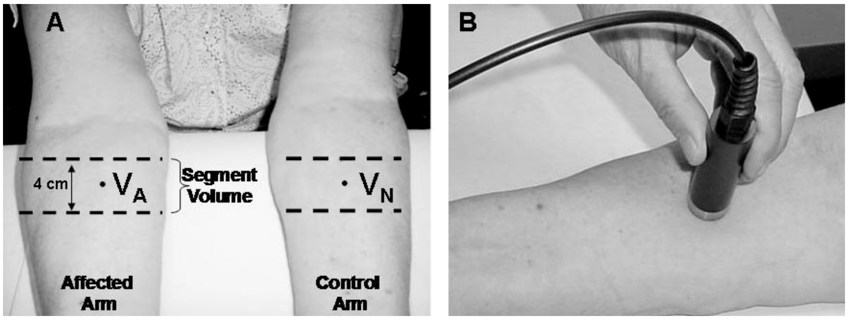

Fig. 1. Subject Positioning and Measurement. With the subject seated reference dots are put on the arm 7 cm distal to the antecubital crease. Tissue water measurements are made at these sites with each of four different size probes corresponding to depths of 0.5, 1.5, 2.5 and 5.0 mm. The 2.5 mm-depth probe is shown in B. The proximal and distal dashed lines in A illustrate the segment volume included in the analysis.

TABLE 1
Measured Values of Arm Segmental Volumes and Tissue Dielectric Constants

	Lymphedema Subjects (N=18)		Postmenopausal Subjects (N=15)		Premenopausal Subjects (N=15)	
Arm	Affected	Non-Affected	Dominant	Non-Dominant	Dominant	Non-Dominant
Segmental Volume (ml)	265±65*	187±51	178±51	175±53	178±41	176±41
Dielectric Constants						
0.5 mm depth	46.5±8.4*	30.6±4.0	30.0±6.3	29.4±5.5	28.0±3.2	28.1±3.4
1.5 mm depth	40.4±5.0*	28.1±2.7	27.8±4.5	27.7±3.5	26.8±2.2	27.3±1.9
2.5 mm depth	41.2±7.9*	25.2±2.7	26.0±4.7	25.6±3.2	25.6±2.9	26.0±2.8
5.0 mm depth	32.9±7.1*	19.9±2.3	21.4±4.8	21.1±3.5	20.9±3.5	21.3±3.1

Values are mean ± sd. * = $p< 0.001$ as compared to non-affected arm of lymphedema group.
No significant differences between arms of either the postmenopausal or premenopausal groups.

Segmental Volumes

After the edema measurements, circumferences of the arm at the reference center point and at 2 cm proximal and distal were measured using a tape measure with a tension gauge to insure uniform measurements (Gulick type tape measure). From these measures, the segmental volume of the 4 cm length encompassing the edema measurement site was calculated using the standard frustum model (3). For the postmastectomy lymphedema group, percent edema was calculated as $100(V_A - V_N)/V_N$ in which V_A and V_N are the segmental volumes of the affected and non-affected arms respectively.

Analysis

Segmental volumes and absolute TDC values for each probe were compared against the paired arm values using a paired T-test.

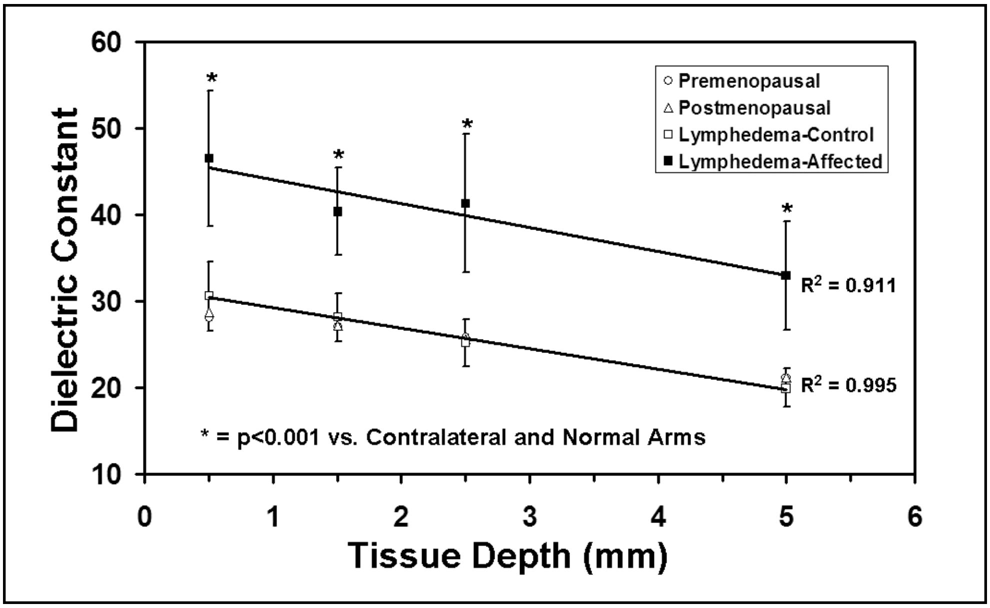

*Fig. 2. Depth Variation of Tissue Dielectric Constant. The Tissue Dielectric constant (TDC) tends to diminish with increasing measurement depth as shown by the regression lines (p<0.001). At any depth, the TDC of lymphedematous arms is significantly greater than contralateral non-affected arms and all control arms. * = p<0.001 for lymphedematous arms vs. control arms.*

The TDC values used in this analysis were the average of the triplicate measurements made on each arm. Depth dependence was analyzed using both analysis of variance and regression.

RESULTS

The main numeric results are summarized in *Table 1*. As expected, the segmental limb volume of the lymphedematous arm was greater than the contralateral non-affected arm (265±65 ml vs. 187±51 ml, p<0.001). Percentage edema calculations showed this lymphedema group had an average of 40±16% edema within the targeted segment. Based on analysis of variance, tissue dielectric constant (and hence tissue water content) depended on measurement depth (p<0.001), but for any depth, TDC values for edematous segments were significantly (p<0.001) higher than for non-affected arm segments. For edematous arms, the overall dependence of TDC values on depth was mainly due to significantly lower TDC values at 5.0 mm as compared to all other depths (p<0.001). Values obtained at all other depths did not individually significantly differ form each other (p>0.05).

For non-affected control arms the overall depth dependence was also highly significant (p<0.001). Post hoc follow-up tests showed no difference between TDC values at 0.5 and 1.5 mm depths but highly significant differences in TDC values at 2.5 and 5.0 mm with respect to each other and with respect to TDC values at 0.5 and 1.5 mm depths (p<0.001).

Absolute TDC values obtained for both control groups also depended on measurement depth, but for any depth, TDC values were very similar between arms and were all less than corresponding TDC values obtained in lymphedematous arms. Univariate analysis of variance to determine depth dependence showed an overall significant difference in TDC values (p<0.001). For the control groups, post hoc follow-up tests also showed no difference between TDC values at 0.5 and

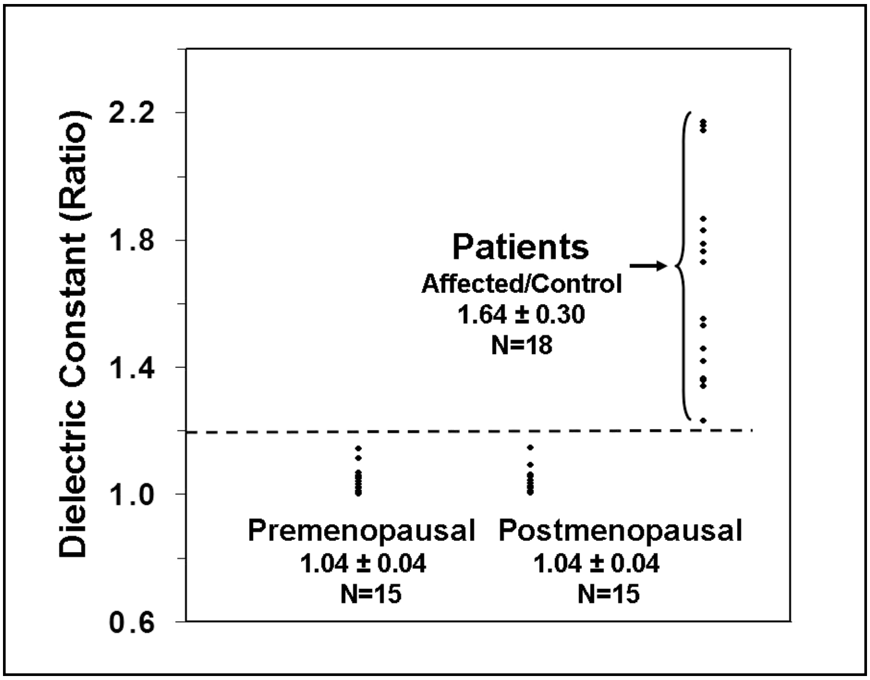

Fig. 3. Tissue Dielectric Constant Ratios. Patient ratios are determined as the TDC value of the affected arm divided by the control arm TDC value. Control group ratios are determined as the larger TDC value divided by the smaller TDC value. Patient TDC ratios all exceed the largest TDC values of both control groups. Numeric data is mean ± sd.

1.5 mm depths but highly significant differences in TDC values at 2.5 and 5.0 mm with respect to each other and with respect to TDC values at 0.5 and 1.5 mm depths ($p<0.001$).

There was no significant difference between TDC values obtained in arms of pre- and postmenopausal women. Thus, data from pre- and postmenopausal groups were combined and compared to the lymphedema group as a function of measurement depth. This result *(Fig. 2)* shows the clear and significant reduction in the measured TDC values with increasing measurement depth for all arms with a relationship characterized by parallel lines that distinguish between all normal arms and lymphedematous arms.

To further characterize this discrimination between lymphedematous and normal arms, the ratio of TDC values for paired arms for all subjects was calculated and plotted in *Fig. 3* for a measurement depth of 2.5 mm. For the calculation of the TDC ratios for pre- and postmenopausal arms shown in the figure, the larger TDC value was divided by the smaller value yielding an average value of 1.04 ± 0.04 for both groups. Corresponding values if dominant to non-dominant arm TDC ratios were used are 1.021 ± 0.068 and 1.014 ± 0.063 for premenopausal and postmenopausal groups respectively. In stark contrast to these control group ratios, the ratio of edematous arm TDC values to non-affected arm values was found to be 1.64 ± 0.30. For the patients, the corresponding ratios for depths of 0.5, 1.5 and 5.0 mm are similar, being 1.52 ± 0.21, 1.44 ± 0.14 and 1.65 ± 0.30 respectively. Further, and of considerable interest, is the fact that there was no overlap between the TDC ratios for patients and the TDC values for any control subject at any measurement depth.

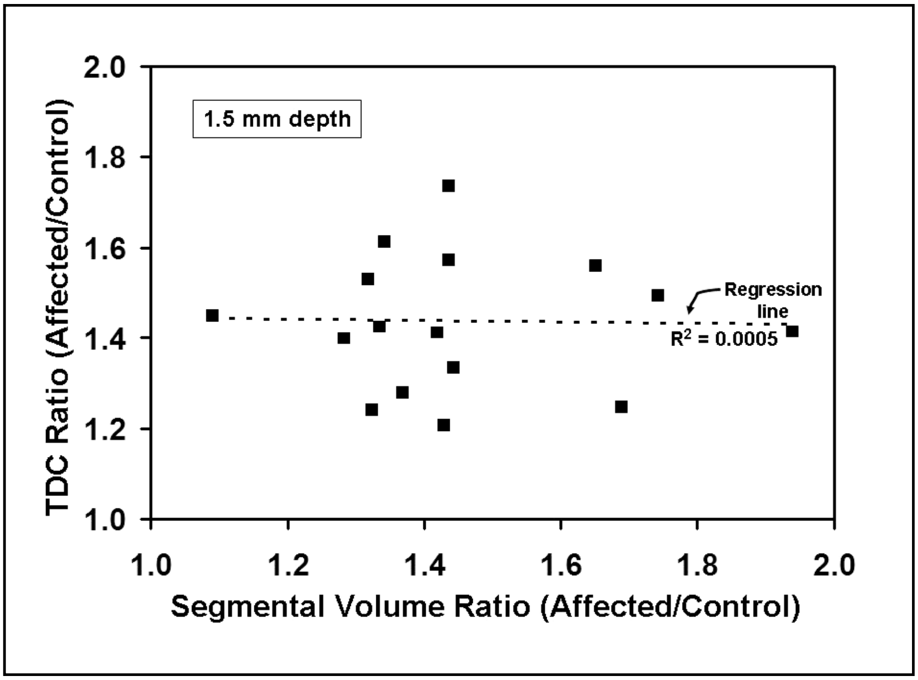

Fig. 4. Segmental Volumes Compared to Tissue Dielectric Constant. Arm segment volumes and tissue dielectric constants are shown as ratios between the affected arm and contralateral control arm for all patients. No significant relationship is observable between these ratios. The dashed line is the linear regression line. Data are shown for a depth of 1.5 mm. Results obtained for other depths were similar.

Using regression analysis, we detected no discernible relationship between the amount of edema in the lymphedematous arm and the TDC ratio. This is illustrated for a measurement depth of 1.5 mm in Figure 4 that shows the TDC ratio as a function of the segmental volume ratio. Thus, despite significantly greater TDC values obtained in the patient's edematous arm segments compared to their contralateral arms, no significant correlation was found between the TDC values and the amount of excess volume of the edematous segments. This finding is consistent with the fact that TDC values reflect water content within the effective measuring depth, which in this study was not greater than 5 mm. In comparison, the effective arm radius included in the volumetric assessment of edema for the patients averaged 45.8±4.8 mm, with a range of 37 to 53 mm. Thus, similar values of TDC could occur despite substantial differences in arm segment volumes. However, the absence of a correlation between excess volume and TDC values indicates that the method does not quantify edema extent when used as a single time-point measurement.

DISCUSSION

The present study is the first to investigate the possibility of using this tissue dielectric constant method and device to evaluate local tissue edema in patients with lymphedema. In the reference volume of edematous arms of patients, the TDC values, and by extension the relative tissue water, exceeded those in non-affected contralateral arms of all patients.

Results *(Table 1 and Fig. 2)* demonstrate a dependence of the absolute TDC value on the effective depth of the measurement. This was true in edematous tissue and in normal tissue in patients and in both control groups. Such dependence is consistent with the known variation in tissue constituents and their water content with depth below the skin surface. Since effective measurement depth is determined by the depth of electromagnetic field penetration (23), larger diameter probes result in an increased effective measurement depth. Thus, net TDC values are increasingly influenced by deeper tissue constituents such as subcutaneous fat and its lower relative water content (19) . Despite this variation, highly significant differences in TDC were detected between edematous and normal limbs at every depth.

In patients, a comparison of the TDC ratio between edematous and non-affected arms proved to be informative. The average ratio ranged between 1.44 to 1.65 depending on the measuring depth. Further, the TDC ratio in every patient evaluated exceeded the highest TDC ratio in all control subjects. This finding suggests that the use of this ratio may be diagnostic for the presence of lymphedema.

This concept is speculative since all patients evaluated had established lymphedema with already measurable changes in arm volumes. However, since the method detects fluid accumulation within a small distance from the skin surface it is likely that it would be sensitive to early manifestations of incipient clinical edema. In support of this notion is the fact that the normally large compliance of the interstitial space and subcutaneous fat (24) should allow for considerable fluid volume expansion without visible or perceived swelling. Further, tissue pressure and compliance has been reported to not correlate with the duration of edema and correlate only very weakly with clinical edema volume (25). Thus, we would hypothesize that the increase in measured TDC is a threshold-like indicator in the sense that once excess fluid has filled the tissue volume within the measurement depth, little further increase in TDC would be expected despite the subsequent onset of visible swelling and lymphedema progression. The absence of a defined relationship between the TDC ratio and the segment volume ratio between patients, shown in figure 4, is consistent with this hypothesis. However, this finding does not rule out the possibility that the TDC value and its ratio in a given patient might not decrease during or following therapy. This aspect has not yet been studied since all patients have been evaluated prior to the start of their treatment programs.

Based on the fact that no patient's TDC ratio was as low as 1.2 and no control subject's TDC ratio was as great as 1.2, we suggest that a critical TDC ratio of 1.2 or greater would be a good discriminator for the presence of lymphedema in patients with unilateral limb lymphedema risk. This early detection criteria needs to be evaluated prospectively.

Conclusions

Results suggest that this method may serve as a rapid quantitative assessment procedure to document lymphedema.

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