

Local tissue water assessed by tissue dielectric constant: anatomical site and depth dependence in women prior to breast cancer treatment-related surgery

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Summary

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Assessing local tissue water using tissue dielectric constant (TDC) values is useful to evaluate oedema/lymphoedema features and their change. Knowledge of anatomical site and tissue depth dependence of TDC values could extend this method's utility. Our goal was to compare TDC values obtained at anatomically paired sites and to investigate their depth dependence. In 22 women (12 awaiting surgery for breast cancer and 10 cancer-free control subjects), four sites (mid-forearm, mid-biceps, axilla and lateral thorax) on both body sides were measured with a 2.5-mm sampling depth probe. Also, at forearm, four different probes with sampling depths of 0.5, 1.5, 2.5 and 5 mm were used. TDC values range between 1 for zero water to 78.5 for 100% water. Site comparisons showed TDC values (mean \pm SD) to be largest at axilla (36.4 ± 8.9), least at biceps (21.6 ± 3.5) and not different between forearm and thorax (24.3 ± 4.0 versus 24.8 ± 5.0). Group comparisons showed slightly greater values in patients at forearm and biceps ($P < 0.05$) but no group difference at other sites. Dominant-non-dominant side comparisons showed no significant difference in paired-TDC values in either group at any site. Forearm TDC values decreased with increasing depth from 36.4 ± 4.8 at 0.5 mm to a minimum of 21.4 ± 3.9 at 5.0 mm, with a sharp decline between 1.5 and 2.5 mm. The composite findings suggest that TDC measurements have the necessary features for usefully assessing oedema/lymphoedema and its change on limbs and at body sites not routinely amenable to assessment by other techniques. The depth dependence feature provides additional flexibility to investigate oedematous or lymphoedematous conditions.

Introduction

A variety of methods are available to assess overall limb oedema. These include metric and volume measures (Casley-Smith, 1994; Sander et al., 2002; Karges et al., 2003; Mayrovitz, 2003; Meijer et al., 2004; Mayrovitz et al., 2005, 2006, 2007a), automated methods (Mayrovitz et al., 2000b; Moseley et al., 2002; Stanton et al., 1997; Tierney et al., 1996) and electrical impedance-type methods (Cornish et al., 1998, 2001, 2002; Ward, 2006). However, these methods are not generally suitable to determine local oedema or oedema in body parts other than the limbs. Quantitative assessment of local tissue oedema could provide useful information not previously available to help initially detect, to assess and to track oedema or lymphoedema progression in many body parts or anatomical regions. Recent work indicates that local tissue water measurements based on a tissue dielectric

constant (TDC) method allows the quantification of localized tissue water in arms of patients with cancer treatment-related lymphoedema, thereby providing useful discrimination for the presence of lymphoedema in these patients (Mayrovitz, 2007). It has also been used to evaluate possible hormone-related changes in localized arm tissue water in pre- and postmenopausal women (Mayrovitz et al., 2007b).

The method's working principle is based on the fact that tissue electrical properties depend on water content, which in turn affects the value of the TDC (Nuutinen et al., 2004). Measurement of the TDC at a suitable frequency thus provides an index of the relative tissue water (Stuchly et al., 1981, 1982; Aimoto & Matsumoto, 1996; Alanen et al., 1998, 1999; Nuutinen et al., 1998). As previous applications of this method have mainly used the volar (ventral) forearm, it was our belief that knowledge of anatomical site and tissue depth dependence

of TDC values could provide reference comparative data and also help to extend the utility of this method. Thus our goal was to determine and compare TDC values obtained at anatomically paired sites and to investigate tissue depth dependence. Because one of the eventual uses of this type of measurement is to potentially detect developing lymphoedema at an early stage, we carried out the measurements on a group of women awaiting surgery for breast cancer at anatomical sites likely to be at risk for developing breast cancer treatment-related lymphoedema. Measurements were also carried out at corresponding sites in a control cancer-free group of women.

Methods

Subjects

A total of 22 women with ages (mean \pm SD) of 53.0 \pm 15.7 years (range 27 to 82 years) were evaluated after signing an Institutional Review Board approved informed consent. Of the 22 participants, 12 were in a patient group who had recently (within one month) been diagnosed with breast cancer and were awaiting breast cancer surgery (age: 62.3 \pm 11.8 years) and 10 were cancer-free subjects in a control group who had no previous diagnosis of breast cancer (age: 41.9 \pm 12.3 years). The patient group, as compared to the control group, was similar in height (1.64 \pm 0.05 versus 1.63 \pm 0.07 m, NS), weight (76.7 \pm 15.4 versus 73.0 \pm 14.4 kg, NS) and body mass index (28.7 \pm 5.9 versus 27.5 \pm 5.8 kg m⁻², NS) but was significantly older ($P < 0.001$).

Tissue dielectric constant measurement device

The device used in this study to measure the TDC was the MoistureMeter-D (Delfin Technologies Ltd, Kuopio, Finland, <http://www.delfintech.com>). It consists of a cylindrical probe connected to a control unit that displays the TDC when the probe is placed in contact with the skin. The physics and principle of operation has been well described (Stuchly et al., 1981, 1982; Aimoto & Matsumoto, 1996; Alanen et al., 1998, 1999). In brief, a 300-MHz signal is generated within the control unit and is transmitted to the tissue via the probe that is in contact with the skin. The probe itself acts as an open-ended coaxial transmission line (Stuchly et al., 1982; Alanen et al., 1999). 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 1–80. The effective penetration depth depends on the probe dimensions, with larger spacing between inner and outer conductors corresponding to greater penetration depths. In this study, four different dimension probes were used to characterize depth dependence at the forearm site having effective penetration

depths of 0.5, 1.5, 2.5 and 5.0 mm. Corresponding (maximum) probe diameters were 10, 20, 23 and 55 mm with conductor spacing of 1, 3, 5 and 17 mm respectively. For the anatomical site-dependence evaluations at forearm, biceps, axilla and thorax, only the 2.5 mm depth probe was used.

Tissue dielectric constant measurement procedure

All measurements were carried out with subjects supine on a padded examination table.

Measurements were made on four paired standardized measurement sites as follows: both volar forearms 6 cm distal to the antecubital crease, both medial biceps 6 cm proximal to the antecubital crease, both axilla and both lateral thorax 8 cm below the axilla. Except for the axilla, these points were first marked with a dot using a surgical pen for reference. The dot served as the centre point for probe placements. For the axilla, the probe was placed in the centre. Measurements were begun after the subject had been comfortably lying for 10 min. Depth measurements at the forearm site were carried out first. For these measurements, probes were placed in contact with the skin and held in position using gentle pressure. 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 1-min wait between changing probes. The time required to obtain a single measurement, once the probe was placed in contact with the skin, was about 10 s. Preliminary work showed that repeated measurements taken at 15 s intervals for 600 s resulted in a coefficient of variation of only 2.8%, indicating a good short-term repeatability of the technique (Mayrovitz, 2007). For the different site evaluations, only the 2.5-mm depth probe was used. These site-dependent measurements were also carried out in triplicate pairs, alternating between one body side to the other. This alternating between body sides method, used for all measurements, was employed as a measure to help obtain paired values as close in time as possible. At each site, the three measurements were averaged and used to characterize the site average TDC value.

Arm volume measurements

Circumferences of both arms were measured with a calibrated spring-loaded tape measure (Gulick-type, <http://www.fitnessmart.com>) starting at the wrist with measurements repeated at 4 cm intervals extending up the arm to the axilla. Arm volumes were calculated using circumference values in a truncated-cone model with calculations made using an automated software algorithm (Limb Volumes Professional 4.0, <http://www.limbvolumes.org>). In this method, a segmental volume V_s is 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 4 cm. The arm total volume is then determined by the sum of all

segment volumes. This method of estimating limb volume has been extensively tested and validated (Casley-Smith, 1994; Latchford & Casley-Smith, 1997; Mayrovitz et al., 2000a,b, 2007a; Karges et al., 2003; Mayrovitz, 2003). For comparison purposes, arms were designated as either dominant or non-dominant depending on the handedness of the subject. For the present group, one subject, who was in the patient group, was left-handed; all other subjects were right-handed. For consistency, the axilla and thorax sites on the dominant-hand side are also designated as the dominant sides.

Analysis

Site comparisons

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Differences in TDC values between groups among sites (forearm, biceps, axilla and thorax) were tested for using the non-parametric Kruskal–Wallis test for independent samples (Table 1). Differences in TDC values among sites were tested for using analysis of variance (ANOVA) of data for all sites and both groups (Table 1 – combined). Differences between dominant and non-dominant sides were tested for using the non-parametric Wilcoxon signed-rank test (Table 2). For all analyses, the criterion for acceptance of statistically significant differences was set at $P < 0.05$.

Forearm depth-dependent comparisons

Comparisons of TDC values obtained on forearms at different depths were made using a general linear model (GLM) for repeated measures with depth as the within factor (Table 4). Analyses were made for each group separately and for both groups combined. Comparisons between TDC values for

different depths were made using a one-way ANOVA with depth as the dependent variable and group as the independent factor. Differences between dominant and non-dominant arm volumes were tested for using a GLM with arm as the dependent factor and group as the independent factor (Table 3).

Results

Group and site dependence of tissue dielectric constant values

Group and site comparisons are summarized in Tables 1 and 2; results being given as mean \pm SD throughout. As may be seen in Table 1, TDC values for the patient group tended to be larger than for the control group in all but the thorax with average differences ranging between about 8.5% and 10%. Arm site TDC values (forearm and biceps) were statistically significantly greater for patients ($P < 0.05$). In comparing differences among sites, the most clearly evident difference was the significantly larger TDC value at the axilla. This was greater than measured at all other sites ($P < 0.001$). The lowest TDC value was found at the biceps that was significantly less than all other sites ($P < 0.001$). There was no significant difference in TDC values between the forearm and thorax. Although there were some significant differences among sites, there were no significant differences in TDC values between paired dominant and non-dominant body sides at any site (Table 2).

Depth dependence of arm tissue dielectric constant values

Arm volumes did not significantly differ between groups or between dominant and non-dominant arms (Table 3). Contrastingly, TDC values monotonically decreased with increasing depth in both control and patient groups (Table 4, Fig. 1) with

Table 1 Tissue dielectric constant values between groups and among sites.

| | Forearm | | Biceps | | Axilla | | Thorax | |
|----------|----------------|-----------------|------------------|-----------------|-------------------|-----------------|----------------|----------------|
| | Controls | Patients | Controls | Patients | Controls | Patients | Controls | Patients |
| Groups | 22.9 \pm 3.8 | 25.4 \pm 3.7* | 20.4 \pm 3.2 | 22.6 \pm 3.5* | 34.6 \pm 7.0 | 37.8 \pm 10.1 | 24.8 \pm 5.0 | 24.8 \pm 4.9 |
| Combined | 24.3 \pm 4.0 | | 21.6 \pm 3.5** | | 36.4 \pm 8.9*** | | 24.8 \pm 5.0 | |

Table entries are mean \pm SD of tissue dielectric constant (TDC) values obtained with a probe sampling to a depth of 2.5 mm. Group comparison shows small but statistically different arm values between patients and controls ($*P < 0.05$). Combined data of controls and patients show that axilla TDC values were significantly greater than for forearm, biceps and thorax ($***P < 0.001$). TDC values at the biceps were significantly less than at all sites ($**P < 0.001$).

Table 2 Body side comparisons of tissue dielectric constant values.

| Forearm | | Biceps | | Axilla | | Thorax | |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Dominant | Non-dominant | Dominant | Non-dominant | Dominant | Non-dominant | Dominant | Non-dominant |
| 24.2 \pm 3.6 | 24.3 \pm 4.4 | 21.9 \pm 3.3 | 21.3 \pm 3.6 | 37.6 \pm 8.4 | 35.1 \pm 9.4 | 25.0 \pm 5.1 | 24.6 \pm 5.0 |

Tissue dielectric constant values did not significantly differ between dominant and non-dominant sides at any site. Table entries are mean \pm SD.

Table 3 Arm volumes.

| Arm | Controls | Patients |
|---------------------------------|------------|------------|
| Dominant (cm ³) | 2424 ± 547 | 2313 ± 589 |
| Non-dominant (cm ³) | 2382 ± 551 | 2306 ± 639 |
| Combined (cm ³) | 2403 ± 535 | 2309 ± 601 |

Arm volumes were not significantly different between control and patient groups or between dominant and non-dominant arms. Table entries are mean ± SD.

Table 4 Tissue dielectric constant depth dependence.

| Depth (mm) | Control group (N = 20) | Patient group (n = 24) | Combined groups (n = 44) |
|------------|------------------------|------------------------|--------------------------|
| 0.5 | 34.8 ± 4.4 | 37.8 ± 4.7* | 36.4 ± 4.8 |
| 1.5 | 32.8 ± 5.3 | 35.6 ± 4.4* | 34.3 ± 4.9 |
| 2.5 | 22.5 ± 3.9 | 25.8 ± 4.1* | 24.3 ± 4.3 |
| 5.0 | 20.9 ± 3.5 | 21.8 ± 4.2 | 21.4 ± 3.9 |

Tissue dielectric constant values decreased with depth in both groups similarly with values at each depth being significantly different from all others ($P < 0.001$). Patient group values were significantly greater than control group values for all but the 5-mm depth. * $P < 0.05$.

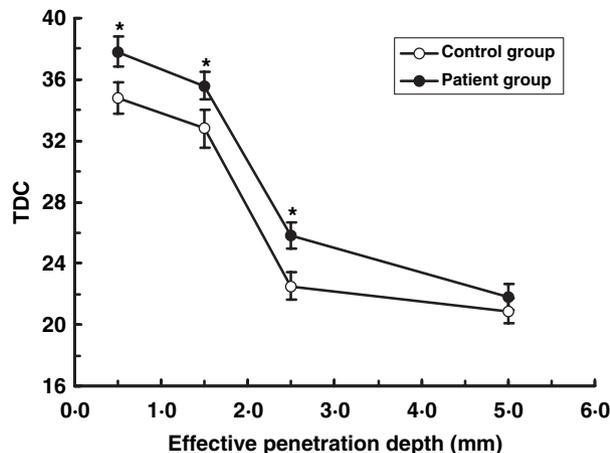


Figure 1 Tissue dielectric constant values as a function of effective penetration depth for each probe at the volar forearm. * denotes patient group values significantly greater than control group values ($P < 0.05$). Values at each site differed significantly ($P < 0.001$) from all other sites for both groups.

TDC values at each depth being significantly different from all others ($P < 0.001$). Patient group TDC values were significantly greater than corresponding control group TDC values ($P < 0.05$) for all depths except 5 mm.

Discussion

This study is the first to investigate the possibility of using this TDC method and device to characterize localized tissue water at multiple sites that are 'at risk' regions for lymphoedema

development in women exposed to breast cancer treatment surgery, radiation or both. As most breast cancers are unilateral, one goal of this initial study was to not only characterize TDC values at these sites but also to compare TDC values between body sides in women already diagnosed with breast cancer and women free of breast cancer. In essence, the measurements carried out on these women would constitute 'baseline' presurgery values that would be made if one were planning to track changes in these women following their cancer treatment process.

One main finding demonstrated despite significant differences in TDC values among the various anatomical sites, the differences in TDC values between corresponding body sides were small and not significant for any measured site. This similarity of dominant–non-dominant side baseline TDC values is a feature that would enhance the ability to interpret changes in local tissue water that might occur in an affected body side subsequent to breast cancer treatment. This is especially relevant to the vast majority of cases for which treatment is unilateral.

A second finding relates to the absolute TDC values at the different anatomical sites and the differences among sites. Values obtained at the forearm and thorax were very similar to each other whereas values at biceps were significantly lower and values at axilla were significantly greater. Lower values at biceps may reflect a larger contribution of low water content of the subcutis in this area. Higher values at the axilla may be due to the fact that this area is a portal for lymphatic drainage that would give rise to higher TDC values. The possibility is that differences in skin thickness among these sites, however, cannot be ruled out as a contributing factor to the differential TDC values (Mellor et al., 2004).

A third finding relates to TDC differences between patient and control groups. Except for the thorax, patient group values tended to be greater than for controls, with arm TDC values (forearm and biceps) being about 10% greater. We do not have a specific explanation for the slightly larger values in the patient group. Previous comparisons of arm TDC values between groups of healthy (cancer-free) pre- and postmenopausal women revealed no differences in arm TDC values (Mayrovitz et al., 2007b). We may speculate that the presence of the cancer in the current patient group some how may have contributed to the higher TDC values measured. Differences in skin thickness, as discussed subsequently, probably are not responsible as ageing tends to be associated with reduced skin thickness of the forearm (Tsukahara et al., 2001b), and thus a reduced relative water content would be anticipated if thickness had a significant effect on the presently observed differences.

Other major findings relate to the characterization of the dependence of TDC values on tissue depth. These data (Table 4, Fig. 1) consistently demonstrated a significant decrease in TDC values with increasing depth in both controls and patients. Such dependence is consistent with the variation in tissue constituents and their water content with depth below the skin surface. As effective measurement depth is determined

by the depth of electromagnetic field penetration (Lahtinen et al., 1997), 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 (Alanen et al., 1999).

An additional interesting and related depth-dependent feature is the large decrease in TDC that is observed to occur between a depth of 1.5 and 2.5 mm (Fig. 1). We believe that this finding is also linked to and explainable by considering skin thickness features in relation to measurement penetration depth. Measurements of skin thickness on the volar (ventral) forearm of women using high-frequency ultrasound indicate that skin depth to the subcutis interface ranges between 0.75 and 1.25 mm (Eisenbeiss et al., 1998; Tsukahara et al., 2001a,b; Moore et al., 2003; Mellor et al., 2004). These data are consistent with and would largely explain the great difference observed between the 1.5- and 2.5-mm probes, yet the much smaller difference between the 2.5- and 5.0-mm probes for the following reason. The 2.5- and 5.0-mm probes include in their sampling volumes both skin (epidermis and dermis) and portions of the subcutis that contain relatively less water content than the dermis, whereas 0.5- and 1.5-mm probes include mostly or exclusively skin. Further, as subcutis depth, measured from dermal-subcutis interface to fascia, is about 7.5 mm in ventral forearms (Mellor et al., 2004), the slightly less TDC value recorded by a 5.0-mm probe compared to a 2.5-mm probe is explained by the relatively greater proportion of low water content subcutis included in the 5.0-mm probe sampling volume.

The composite results of site and depth dependence have several potential clinical implications. First, as TDC measurements can be tailored to reflect changes to a depth of between 0.5 and 5.0 mm whereas standardly used indices of limb oedema or lymphoedema based on girth or limb volume (Mayrovitz et al., 2000a,b; Armer & Stewart, 2005) reflect conditions of the entire cross-section, it is likely that TDC assessments are more sensitive and flexible for detecting early developing oedema or lymphoedema. This is an important feature as it is well established that early detection of incipient lymphoedema is a major factor to controlling this condition (Casley-Smith, 1994, 1995). A second important aspect of the TDC approach to characterizing oedema/lymphoedema is the fact that assessments can be made in any body area or part, as the measurement method is not limited to limbs as are most if not all other methods. Thus it should be possible to assess localized oedema/lymphoedema and their change in the hand, finger, head, neck, genitalia, thorax and so on. Assessments of these possibilities need to be investigated and validated with further clinical research.

Finally based on the present data, it would be important in any potential clinical assessment or research protocol to initially consider and take into account both the anatomical site and depth-dependence features that might be expected when choosing a probe and site for use in any specific study.

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