

Role of handedness on forearm skin tissue dielectric constant (TDC) in relation to detection of early-stage breast cancer-related lymphedema

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Summary

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skin tissue dielectric constant (TDC) measurements help assess local skin water to detect incipient early-stage lymphedema subsequent to breast cancer treatment-related lymphedema. However, presurgery measurements are not always obtained and assessments for evolving lymphedema are only made after surgery. Thus, subsequent TDC assessments may be biased in an unknown way dependent on a patient's handedness in relation to the at-risk arm. We investigated this issue by comparing TDC values in dominant and non-dominant volar forearms of 31 left-handed women and 31 right-handed women (age range 24–84 years). Body fat and water percentages were assessed by bioimpedance at 50 KHz. Results showed that TDC values of dominant versus non-dominant arms did not significantly differ for left-handers or for right-handers. There was also no statistically significant difference in absolute TDC values between left- and right-handers or a statistically significant difference in dominant-to-non-dominant arm ratios between left- and right-handers. For the composite data set ($N = 62$), TDC values for dominant and non-dominant arms were, respectively, 30.0 ± 4.6 and 29.6 ± 4.2 and the dominant-to-non-dominant arm TDC ratio for combined left- and right-handers was 1.015 ± 0.075 . These results suggest that handedness is not a major factor when assessing lymphedema status in women who have previously been treated for breast cancer but for whom pretreatment TDC values have not been obtained. Moreover, these results suggest that threshold ratios of incipient subclinical unilateral lymphedema based on interarm TDC ratios apply independent of a patient's handedness for the site and tissue depths herein measured.

Introduction

The measurement of skin tissue dielectric constant (TDC) has been advocated and used as a way to assess local skin water content and its change in a variety of situations (Mayrovitz et al., 2012, 2013a,b; Nuutinen et al., 1998; Papp et al., 2007; Petaja et al., 2003). One of its most clinically relevant applications is its use to detect increased skin water in arms or legs as a method for the early detection of incipient early-stage oedema or lymphedema (Lahtinen et al., 2015; Mayrovitz, 2007; Mayrovitz et al., 2009a,b; Mayrovitz et al., 2015a,b). This detection is possible because TDC is largely dependent on tissue mobile and bound water content. In the case of its use in the potential early detection of lymphedema stemming from complications of breast cancer-related treatment, the goal is to obtain TDC values on both arms prior to treatment from which subsequent changes in the treated side arm may be

compared (Mayrovitz, 2009). However, often such presurgery measurements are not obtained and assessments for evolving lymphedema are only made some time after surgery. Various reports that have utilized other ways to assess lymphedema evolution, including measurement of arm volume changes and whole-arm bioimpedance, are based on whole-arm measurements that include muscle and bone and may not be as sensitive to local changes in water. Further, a number of workers have emphasized that there are differences in arm volume that is dependent on patient handedness (Godal & Swedborg, 1982; van Velze et al., 1991). Thus, without presurgery measurements, subsequent assessments may be biased in an unknown way. Various efforts have attempted to account for the differences in volume and impedance of dominant versus non-dominant arms (Ancukiewicz et al., 2011; Avila et al., 2015). Similarly, in the case of TDC assessments it is important to know if such handedness bias is present so that it

might be accounted for when presurgical measurements are not available. The goal of the present research was to investigate this issue by evaluating TDC in dominant and non-dominant arms of persons who were classed as left-handed and also in persons who were classed as right-handed. Because the breast cancer-related lymphedema for which TDC is used primarily affects women, all volunteer participants in this study were women.

Methods

Subjects

A total of 62 female adults volunteered for participation, and each signed an institutional review board approved informed consent. Half of the volunteers were left-handed (group LH) and half were right-handed (group RH). The method for assigning dominant handedness was as previously reported (Van Strien, 1992). Participants were asked to refrain from applying any lotions or creams or doing any vigorous exercise on the day of their evaluations. Characteristic features of the two groups are summarized in Table 1 in which it can be seen that the groups were well matched with respect to age, body mass index (BMI), total body fat percentage (FAT), total body water percentage (TBW) and arm fat percentages (AFP) of dominant and non-dominant arms with no significant differences in any of these features.

Tissue dielectric constant (TDC) measurement

Tissue dielectric constant (TDC) was measured bilaterally on anterior forearms of seated subjects at marked sites five cm distal to the antecubital fossa using a commercially available compact version of an open-ended coaxial probe (Nuutinen

et al., 2004; Stuchly et al., 1982) operating at 300 MHz (MoistureMeterD Compact, Delfin Technologies, Kuopio, Finland). Care was taken to avoid placing the probe over large veins, and the presence of hair in the intended measurement area in these female participants was not an issue. Effective measurement depth, defined as the depth at which the excitation field is diminished to $1/e$ of its value, is approximately 2 mm (Mayrovitz et al., 2015a,b). Measurements are done in triplicate using the hand-held probe and subsequently averaged. Each measurement is achieved by touching the probe to the skin with gentle but firm pressure for about five-s. The dielectric constant or relative permittivity is a dimensionless number equal to the ratio of tissue permittivity to vacuum permittivity. For reference, the dielectric constant of distilled water at 32°C is approximately 76. Because TDC values mainly depend on tissue water, they provide quantitative indices of skin water content. As TDC is measured at 300 MHz, its value is sensitive to both free and bound water (Pennock & Schwan, 1969). Inclusion of the bound water contribution is important. As up to 80–90% of young adult skin water content is bound (Gniadecka et al., 1998). The measurement device generates and transmits a very low power 300 MHz signal into a coaxial probe in contact with the skin that acts as an open-ended coaxial transmission line (Stuchly et al., 1982). Part of the signal is absorbed, mainly by tissue water, and part is reflected back to a control unit where the complex reflection coefficient is calculated (Lahtinen et al., 1997; Lan et al., 2007) from which the dielectric constant is determined (Alanen et al., 1998). Reflections depend on the complex permittivity of the tissue, which depend on signal frequency and the dielectric constant (the real part of the complex permittivity) and the conductivity of the tissue with which the probe is in contact. At 300 MHz, conductivity contributes little to the overall value of the permittivity and TDC is mainly determined by free and bound water molecules. Further details including prior uses for skin assessments, validation and repeatability data are described in the literature (Jensen et al., 2012; Mayrovitz et al., 2009a,b, 2013a,b; Nuutinen et al., 2004). Each probe is calibrated against various ethanol–water mixture concentrations each of known dielectric constant values (Mayrovitz, 2015).

Measurement Protocol

All measurements were done during lunch hours between 11:00 a.m. and 1:00 p.m. in an isolated quiet room in which room temperature was $23.1 \pm 1.2^\circ\text{C}$ and relative humidity was $54.5 \pm 3.9\%$. TDC was measured while participants were comfortably seated with their arms resting palms up on a supporting padded surface. TDC measurements began after a five-min seated rest interval and were made in triplicate alternating between the dominant and non-dominant arm. After completion of these measurements, the participant removed their shoes and socks and stood on a scale to measure their weight and body composition parameters via bioimpedance

Table 1 Participant characteristics.

	Left-handers (N = 31)	Right-handers (N = 31)	P-value
Age (years)	38.0 ± 18.8 (25–78)	39.5 ± 20.3 (24–84)	0.762
BMI (Kg m ⁻²)	25.4 ± 5.5 (18.2–37.0)	25.5 ± 5.4 (19.1–38.1)	0.929
Body water (%)	51.2 ± 5.7 (40.4–57.8)	51.0 ± 6.0 (38.4–60.9)	0.887
Body fat (%)	31.4 ± 8.3 (20.4–46.8)	30.7 ± 8.3 (19.0–47.6)	0.795
Dom arm fat (%)	33.9 ± 9.9 (22.1–51.7)	30.6 ± 9.2 (8.3–47.7)	0.255
Non-dom arm fat (%)	34.2 ± 9.7 (20.7–50.7)	31.7 ± 8.4 (17.2–47.8)	0.355

Data entries are mean ± SD with ranges in parenthesis. There was no significant difference in any parameter between left- and right-handers. The P-values are based on independent t-tests between subjects classified as left- or right-handers.

measurements at a frequency of 50 KHz (InnerScan Body Composition Monitor, Tanita model BC558). Participants stood barefoot on the scale for about 10 s while they gripped a handle electrode in each hand. Parameters measured were FAT, TBW and AFP, all determined by device proprietary algorithms based on measured impedance values.

Statistics

Tests for dominant versus non-dominant side differences was done using paired t-tests with a P-value<0.05 taken as representing a statistically significant difference.

Results

Tissue dielectric constant values by handedness and dominance

Tissue dielectric constant values of dominant versus non-dominant arms did not significantly differ for left-handers or for right-handers (Table 2). There was also no statistically significant difference in absolute TDC values between left- and right-handers or a statistically significant difference in dominant-to-non-dominant arm ratios between left- and right-handers. For the composite data set (N = 62), TDC values for dominant and non-dominant arms were, respectively, 30.0 ± 4.6 and 29.6 ± 4.2 , $P = 0.148$. The average dominant-to-non-dominant arm TDC ratio for combined left- and right-handers (N = 62) was 1.015 ± 0.075 .

Figure 1 shows the individual regression relationships for right- and left-handers with dominant arm TDC values (TDC_{dom}) as a function of non-dominant TDC values (TDC_{ndom}) in Fig. 1a and for non-dominant arm TDC values as a function of dominant arm TDC values in Fig. 1b. These regression equations may be used to estimate the increase in TDC values in suspected oedematous affected arms based on TDC measurements in the other non-affected arm. For convenience, the four regression equations are presented in Table 3 along with the conditions of their use. These regression equations allow estimation of the TDC value that would apply to

Table 2 Tissue dielectric constant (TDC) values by handedness and dominance.

	Dominant arm	Non-dominant arm	Dom/Non-dom ratio
Left-handers (N = 31)	29.7 ± 4.2	29.4 ± 4.0	1.011 ± 0.082
Right-handers (N = 31)	30.3 ± 5.0	29.7 ± 4.5	1.019 ± 0.070

Data entries are mean \pm SD. TDC values of dominant versus non-dominant arms did not significantly differ for left-handers or for right-handers. There was also no significant difference in TDC values or ratios between left- and right-handers.

the non-lymphedematous arm based on a TDC measurement of the non-affected arm. As an example of their use, suppose a right-handed patient was seen 6 months after her surgery and reports a feeling of fullness in her left arm, which is the side of her previous breast cancer. If her right arm TDC was measured to be 30, then the predicted left arm value is $TDC_{LEFT} = 0.821 \times TDC_{RIGHT} + 4.89$. From this calculation, one can then determine the deviation from the actually measured left arm TDC value.

Tissue dielectric constant dependence on body mass index and body composition parameters

Although there was the expected positive correlation between a participant's total body (FAT) and their BMI, which for the current group was expressed as $FAT = 1.43 \text{ BMI} - 3.81$, $r = 0.847$, $P < 0.0001$, there was essentially zero correlation between TDC values and BMI when tested for the entire group or left- and right-handers separately.

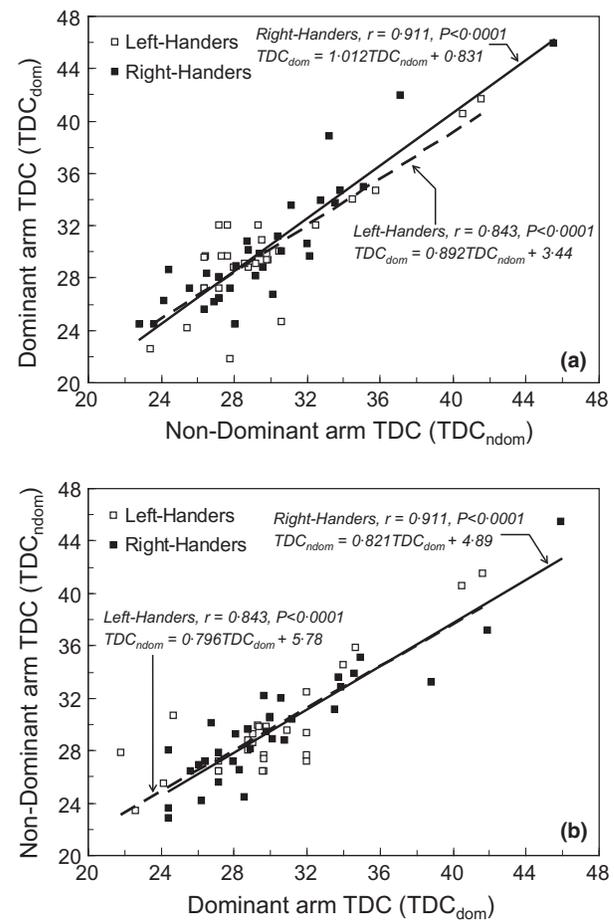


Figure 1 Dominant versus Non-dominant arm tissue dielectric constant (TDC) Relationships. Data are TDC values for dominant and non-dominant arms of right-handers (closed squares) and left-handers (open squares). Lines are linear regression lines with associated equations as shown in the inset of the Figure. (a) Dominant versus Non-Dominant Arms, (b) Non-Dominant versus Dominant Arms.

Table 3 Tissue dielectric constant (TDC) Prediction Equations.

Handedness	At-risk arm	Prediction equation for non-oedematous arm TDC value
RIGHT	RIGHT	$TDC_{RIGHT} = 1.012 \times TDC_{LEFT} + 0.831$, $r = 0.911$
RIGHT	LEFT	$TDC_{LEFT} = 0.821 \times TDC_{RIGHT} + 4.89$, $r = 0.911$
LEFT	LEFT	$TDC_{LEFT} = 0.892 \times TDC_{RIGHT} + 3.44$, $r = 0.843$
LEFT	RIGHT	$TDC_{RIGHT} = 0.796 \times TDC_{LEFT} + 5.78$, $r = 0.843$

Equations allow estimation of the TDC value that would apply to the non-lymphedematous arm based on a TDC measurement of the non-affected arm. At-risk arm is the arm on the side of the assumed treated breast cancer. The non-affected arm is the other arm. The non-lymphedematous arm TDC value is the predicted TDC value of the at-risk arm in the absence of lymphedema.

Discussion

The primary goal of this research was to determine if there is a handedness bias with respect to skin TDC values as reflective of skin water. The main purpose of this inquiry was to determine if handedness needs to be taken into account in a variety of clinical assessment efforts, which include those that utilize TDC to assess or detect early oedema or lymphedema development. Fortuitously from that perspective, the present findings indicate that handedness is not a significant factor. This result implies that handedness need not be considered a major factor when assessing lymphedema status in women who have previously been treated for breast cancer but for whom pretreatment TDC values have not been obtained. However, such pretreatment measurements are clearly the best approach. Moreover, the present results suggest that threshold ratios of incipient sub-clinical lymphedema based on interarm TDC ratios (Mayrovitz, 2007; Mayrovitz et al., 2009a,b, 2014) would seem to apply independent of the patient's handedness. If minor differences in TDC values associated with handedness are of interest, these can be suitably handled using the supplied regression equations as set out in Table 3. However, it should be emphasized that there are several aspects of the present outcome that need to be considered prior to a generalized acceptance.

One aspect relates to the fact that a single tissue depth was interrogated with the compact TDC device herein used. Prior reports (Mayrovitz et al., 2015a,b) have indicated that this device has an effective penetration depth between 1.5 and 2.5 mm and thus includes in its measurement volume epidermis, dermis and some amount of hypodermis with its largely low-water-content fat. Because prior forearm TDC measurements made to other skin depths have conclusively shown TDC values to decrease with increasing tissue depth (Mayrovitz et al., 2008, 2017), the present results apply to the one depth herein measured. Although it is likely that interarm ratios are less dependent on depth than are absolute TDC values, further research in which such data are obtained is needed to clarify this point.

A second aspect relates to the fact that the present findings apply most directly to the anterior forearm. Although this is a commonly measured area and is an area prone to demonstrate early signs of oedema associated with breast cancer treatment in those women who go on to develop lymphedema, recent

unpublished observations suggest that medial arm sites may be more likely to demonstrate early lymphedema. Given that TDC values have been shown to vary depending on anatomical site on the arm (Mayrovitz & Luis, 2010), it would seem relevant for future research to investigate the properties of medial TDC values and their interarm ratios.

A third aspect not explored in the present study is a possible relationship of TDC values and their ratios to functional aspects as might be measured by hand grip strength or other modalities. Although the questionnaire used to assess handedness is quite thorough, it relies on participant responses. For the measurement depths herein used, it is unlikely that differences in muscle-related water content would greatly influence the present TDC values. However, if deeper measurements are to be made, such differences may be greater and it may be worthwhile to examine this possible connection in a future study.

The present finding of essentially no difference in TDC values that are related to participant handedness should be considered in the context of other arm-related differences reported to be dependent on handedness. In a group of 60 self-reported right-handed women, right and left arm volumes were found to be 2031 ± 301 ml and 2000 ± 304 ml, respectively (Godal & Swedborg, 1982). Using regression analysis, these authors were able to provide prediction equations to estimate the non-oedematous arm volume based on measurements of the other, non-lymphedematous arm similar to what is presented in Table 3 for TDC values. According to these workers, if a right-handed woman had lymphedema of her right arm, then her right arm non-oedematous volume (VR_{NE}) is predicted as $VR_{NE} = 0.98VL + 71$ ml where VL is the volume of the non-affected left arm measured together with the oedematous right arm. Contrastingly, if the right-handed woman had lymphedema of the left arm, then the non-oedematous left arm volume (VL_{NE}) is predicted as $VL_{NE} = 1.00VR - 31$ ml where VR is the volume of the non-affected right arm measured together with the oedematous right arm. More recently, arm volumes of a group of 250 persons of which 100 were right-handed women were measured with water displacement volumetry (Gebruers et al., 2007). Regression equations corresponding to VR_{NE} and VL_{NE} were $VR_{NE} = 0.979LV + 96.7$ and $VL_{NE} = 0.991VR - 33.3$, respectively. However, neither of these studies provided specifically

dominant/non-dominant arm volume ratios that can be estimated from their regression equations using the average arm volume of the right and left arms of 2015 ml (Godal & Swedborg, 1982). Doing the calculation reveals dominant/non-dominant arm volume ratios of 1.016 (Godal & Swedborg, 1982) and 1.026 (Gebruers et al., 2007) which encompass the ratio found for the present TDC ratio of 1.019 as shown in Table 2 for right-handers. Corresponding ratios for left-handers are not otherwise available in the literature with sufficient numbers of included subjects either for volume or for TDC ratios. These ratios along with their associated standard deviations are potentially useful to establish thresholds above which the presence of early-phase lymphedema would be suggested. As an example of a conservative estimate, one could define a threshold to be the mean ratio + 3SD. From the data of Table 2, this means that a left-handed woman with her left arm at risk has a threshold of 1.257 and a right-handed woman with a right arm at risk has a threshold

of 1.229. A less conservative estimate based on a 2SD threshold would be more sensitive to detect early lymphedema but would admit more false positives. The choice of a specific threshold is a clinical decision and would need to be prospectively evaluated.

In summary, the present results, which are among the first obtained for equal numbers of left-handers and right-handers, suggest that interarm TDC ratios are essentially independent of handedness when assessed at the commonly used anterior forearm site for an effective tissue depth of approximately 2.0 mm. If further fine-tuning is needed, then the supplied regression equations and interarm ratios may be useful for assessing unilateral lymphedema.

Conflict of interest

All authors declare no conflict of interest of any kind.

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