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TISSUE DIELECTRIC CONSTANT RATIOS AS A METHOD TO CHARACTERIZE TRUNCAL LYMPHEDEMA

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ABSTRACT

Truncal lymphedema is one possible complication of breast cancer treatment. It affects many women and is diagnosed based on symptoms and clinical assessment. Because changes occur late in the process, it is useful to have a quantitative assessment that is applied earlier to detect more subtle changes and quantitively assess treatment progress. Our goal was to describe a possible method to accomplish this via measurements of tissue dielectric constant (TDC). TDC was measured at lateral thorax, anterior forearm, and biceps in 120 women awaiting surgery for breast cancer. Inter-side TDC ratios were defined as values measured on the at-risk (cancer-side) lateral thorax divided by TDC values measured on contralateral thorax, forearm, and biceps. These ratios, designated as thorax-thorax, thorax-forearm, and thorax- biceps were (mean ± SD) 1.017 ± 0.121, 1.138 ± 0.223, and 1.263 ± 0.255 respectively. Corresponding truncal lymphedema thresholds were determined by adding 2.5SD to each mean yielding thresholds of 1.32, 1.70 and 1.90. For these thresholds, 99.4% of patients would have inter-side ratios less than the threshold value. Thus, from assessments in a non-lymphedematous patient-group a set of reference threshold-ratios are now available against which patients surgically treated for breast cancer may be prospectively compared.

Keywords: truncal lymphedema, truncal edema, tissue dielectric constant, detecting truncal lymphedema, measuring truncal lymphedema, breast cancer

Early work pointed out the that truncal edema associated with breast cancer related treatment was not only uncomfortable and painful for the patient but also could negatively impact treatment of co-present arm lymphedema (1). These descriptions were among the first to attempt to provide objective quantitative assessments of truncal edema using skinfold caliper measurements (1,2). Further it has been noted that with breast cancer related lymphedema (BCRL) of the arm, clearance of truncal edema plays a role in facilitating lymphatic drainage from affected limbs by achieving suitable pressure gradients and reducing lymphatic network resistance (3). Although the incidence of truncal edema associated with BCRL is unclear, it has been properly emphasized that this condition is associated with physical and psychological impacts (4) prompting the evaluation and comparison of targeted treatments (5). Because of the location of truncal lymphedema, it is not amenable to most measurement methods that have been used to assess upper or lower extremity limb lymphedema such as water displacement (6,7), girth measurements with or without volume calculations (8-10), and bioimpedance spectroscopy (11,12). However, one previously used method based on tissue dielectric constant (TDC) measurements (13,14) may have such potential since its value is largely dependent on localized tissue water and the TDC measurement can be made on any anatomical location. Prior TDC measurements on women with unilateral lymphedema have successfully used inter-side ratios to try to assess the presence or change in lymphedema extent (15-17). However, these studies have mainly focused on assessing arm lymphedema. The question of the suitability of TDC measures to detect early truncal lymphedema or its change with treatment remains open. Progress in this direction depends in part on establishing standardized reference values for truncal inter-side TDC ratios of women free of breast cancer treatment but sufficiently similar in demographics to women who are at-risk for lymphedema development. Thus, the main goal of this research report is to provide such data as a first step toward developing a practical noninvasive, quantitative assessment of truncal lymphedema.

METHODS

Participants

This research reports on a total of 120 women who had been diagnosed with unilateral breast cancer and were evaluated prior to their receiving treatment (surgical or radiation) for their condition. All were evaluated within two weeks prior to a planned surgery after signing a university institutional review board approved informed consent. Because of the possible but unknown role of body mass index (BMI) on measured TDC values, especially as it relates to the lateral thorax of the trunk, the total population was initially divided into two sub-groups such that half of the patients had BMI values greater than the overall median BMI and half had BMI values that were less than the median. The overall median BMI (N=120) was determined to be 26.8 Kg/m^2 and BMI group assignments were denoted as low and high BMI groups as shown in *Table 1*. These two groups did not differ with

TABLE 1
Tissue Dielectric Constant (TDC) Values and Inter-Side Ratios

	Low BMI (N=60)	High BMI (N=60)	ALL (N=120)	Thresholds
BMI (Kg/m^2)	23.6 ± 2.2	33.4 ± 6.1		
AGE (years)	60.0 ± 12.9	61.6 ± 12.5	60.8 ± 12.6	
TDC Absolute Values				
Thorax	30.1 ± 6.5	29.6 ± 7.7	29.9 ± 7.1	
Forearm	26.9 ± 4.5	26.6 ± 5.3	26.8 ± 4.9	
Biceps	23.9 ± 4.7	24.6 ± 5.6	24.2 ± 5.1	
Inter-Side RATIOS (At-Risk/Contralateral)				
Thorax/Thorax	1.024 ± 0.109	1.010 ± 0.132	1.017 ± 0.121	1.32
Thorax/Forearm	1.144 ± 0.203	1.133 ± 0.243	1.138 ± 0.223	1.70
Thorax/Biceps	1.308 ± 0.272	1.218 ± 0.229	1.263 ± 0.255	1.90

Table values are mean ± SD. Except for the significant difference in BMI between high and low BMI groups ($p<0.001$), no other values statistically differed between groups ($p>0.05$). Thresholds for ratios are computed based on overall mean values (N=120) to which is added 2.5 times the overall SD rounded up and expressed to three significant digits. All Inter-side ratios and absolute TDC values differ significantly from each other ($p<0.001$).

respect to age and had an overall age (mean ± SD) of 60.8 ± 12.6 years. To be considered eligible for inclusion, participants needed to be free of any present or past upper extremity major trauma, skin condition, edema, or lymphedema.

Measurements

TDC was measured bilaterally in triplicate at three anatomical sites using the MoistureMeterD (Delfin, Kuopio, Finland) as illustrated in *Fig. 1*. The average of the triplicate measurements was used as the value for each site. Measurements were done in the following order: 1) anterior forearm (6 cm distal to the antecubital fossa); 2) anterior biceps (8 cm proximal to the antecubital fossa); and 3) at the lateral thorax (10 cm inferior to the axilla). All TDC measurements were done using a probe with an effective measurement depth of 2.5 mm with subjects in a supine position. Measurements began after the subject had been resting in this position on a padded examination table for about 10 minutes. Each TDC measurement takes about 10 seconds and is triggered when the probe contacts the skin. The device has a display that reads the dielectric constant value, also called relative permittivity, from 1 to 80. For reference, water's dielectric constant is about 76 at 32°C. Calibrations are done by measuring the dielectric constant of various concentrations of ethanol-water solutions and comparing against known dielectric values. The physics of this method is well described in the literature (18,19). Briefly, a probe *(Fig. 1)* in contact with skin acts as a coaxial transmission line through which a 300 MHz signal is transmitted to the tissue. Some signal is absorbed and some reflected back to be processed by the control unit. Reflected energy depends on the tissue's complex permittivity which depends on signal frequency and on the dielectric constant (real part of the complex permittivity) and tissue conductivity. At 300 MHz the contribution of the conductivity to permittivity is small and the dielectric constant is mainly determined by water molecules (free and bound). Consequently, the device includes and analyzes only the tissue dielectric constant (TDC) that is directly proportional to tissue water content. This method has been used extensively in a variety of applications (13,15,16,20-29) with the method's validity evaluated on arms (19) and on legs (30).

Analysis

As noted, the main focus herein is on the possibility of assessing truncal lymphedema using TDC measures. To test the possibility that BMI might be a confounding factor in developing a suitable threshold, the total of the 120 patients were divided in half as two sub-groups according their BMI being below or above the overall median. For each of these

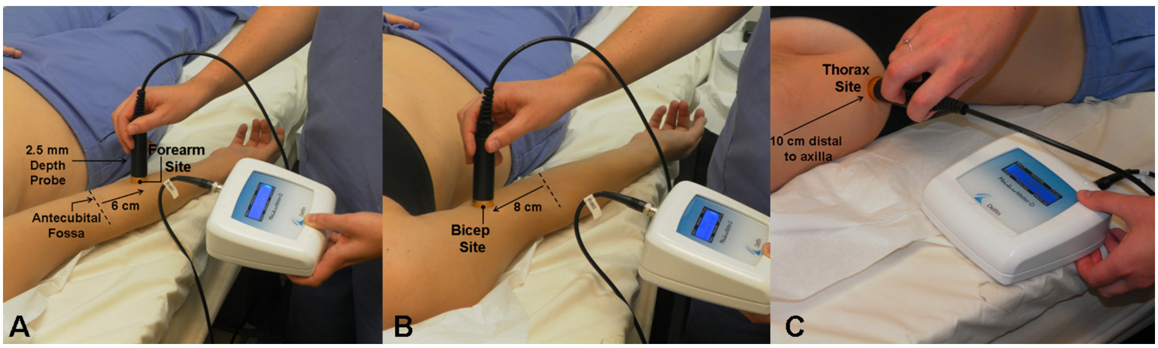

Fig. 1A-C. Sites at which the Tissue Dielectric Constant (TDC) was measured. TDC was measured bilaterally at each site in triplicate using a probe with an effective measurement depth of 2.5 mm.

groups, absolute TDC values as measured at the forearm, biceps, and thorax were compared. In addition, three inter-side TDC ratios of potential diagnostic use were calculated. These were the ratio of the at-risk thorax side (cancer side) to 1) the contralateral thorax (THX_{RSK}/THX_{CON}), 2) the contralateral forearm (THX_{RSK}/ARM_{CON}) and 3) the contralateral biceps (THX_{RSK}/BIC_{CON}). All parameters were tested to determine if they were normally distributed using the Shapiro-Wilk test. For the inter-side ratios, the Shapiro-Wilk test indicates the distribution was not statistically different from Gaussian and independent T-tests were used to assess differences. All other parameters could not be assumed to be Gaussian and differences were analyzed using the non-parametric Mann-Whitney test. If no statistical difference between groups was found ($p>0.05$) then the total data set was used to calculate values representative of absolute TDC values and inter-side ratios. Potential threshold ratios to aid in detecting truncal lymphedema were calculated for each of the three ratios of interest by adding to their overall mean a quantity equal to 2.5 times their overall standard deviation (SD). This rationale for this approach is that for a normally distributed data-set the addition of 2.5 SD to the overall mean implies that non-lymphedematous inter-side ratios would be less than this value in 99.4% of cases. Thus, persons without lymphedema would exceed the threshold so determined in only 0.6% of cases. The choice of adding 2.5 SD is somewhat arbitrary and could be less conservative by considering a threshold of mean + 2 SD or more conservative by considering a threshold of the mean + 3SD.

RESULTS

Comparisons of TDC values between at-risk sides and contralateral sides revealed very close agreement with no significant differences between sides as measured on thorax, forearm and biceps. Consequently, both sides were included (N = 120 per group) in the overall assessment of absolute TDC values at these sites for comparison as shown in Table 1. Except for the expected difference in BMI between high and low BMI groups ($p<0.001$), no TDC value or inter-side TDC ratio statistically differed between high and low BMI groups ($p>0.05$). However, all absolute TDC values and Inter-side ratios differed significantly from each other ($p<0.001$). Absolute TDC values (mean ± SD) at thorax had the largest value (29.9 ± 7.1) whereas the least TDC value was measured at biceps (24.2 ± 5.1). Contrastingly, among the three inter-side TDC ratios of interest, THX_{RSK}/THX_{CON}, THX_{RSK}/ARM_{CON} and THX_{RSK}/BIC_{CON}, the least inter-side TDC ratio and the one with the least SD, was determined to be THX_{RSK}/ THX_{CON} (1.017 ± 0.121) for which the overall distribution of values is shown in *Fig. 2*. For each inter-side ratio, a threshold can be calculated such that a patient measured value greater than this threshold would likely indicate the presence of truncal lymphedema. These thresholds, calculated for the three ratios of interest, are shown in *Table 1*. They are calculated by adding 2.5 SD to the corresponding mean inter-side ratio. Under the assumption of a normally distributed data-set of ratios, 99.4% of all values would be less than these thresholds which for the THX_{RSK}/THX_{CON} is 1.32 as rounded up and expressed to three significant digits. This threshold is calculated using the overall mean and SD for ratio (THX_{RSK}/THX_{CON}) in *Table 1* by adding to the mean (1.017), 2.5 times its SD (0.121) as $1.017 + 2.5 \times 0.121 = 1.017 + 0.302 = 1.3195$ which when rounded up is 1.32.

DISCUSSION

The present data indicate that among possible inter-side TDC ratios potentially suitable to detect or quantify truncal lymphedema it is the thorax-to-thorax ratio that has a ratio closest to unity and also the smallest standard deviation among those evaluated. This combination leads to a 2.5 SD ratio threshold for de-

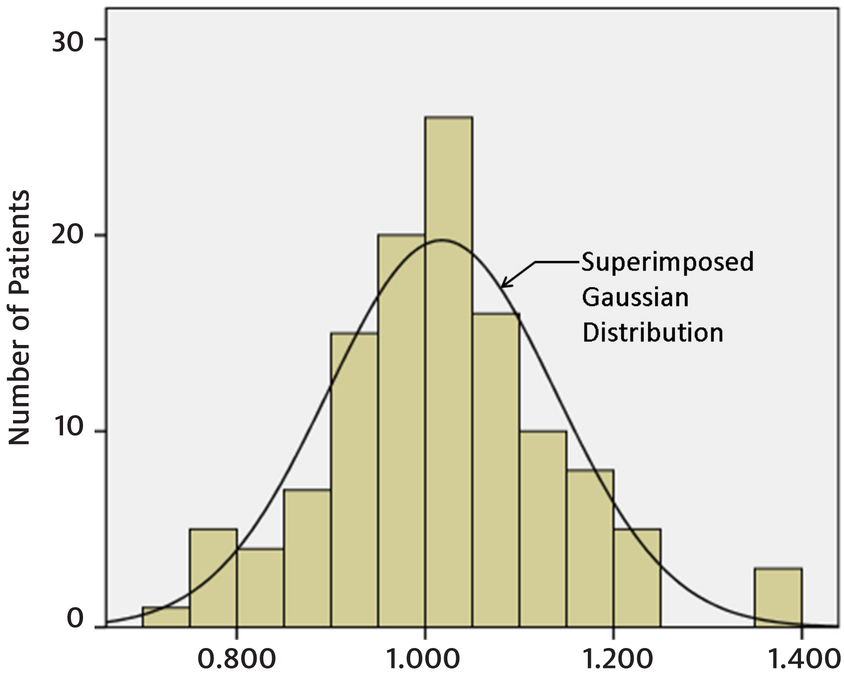

Fig. 2. Inter-side TDC ratios as measured on the lateral thorax THX_{RSK} and THX_{CON} are TDC values measured on the at-risk thorax and contralateral thorax. The median value of the distribution is 1.012 with a standard deviation of 0.120. The Shapiro-Wilk test indicates the distribution is not statistically different from Gaussian.

tection of 1.32. This is the least of those ratios measured. However, what is unclear from the present analysis is whether the thorax-to-thorax ratio would be the best discriminator in persons actually having truncal lymphedema. The worry is that truncal edema on the breast cancer at-risk side may spread resulting in some degree of contralateral side edema. In cases where this were true the measured thorax-to-thorax ratio might be artificially reduced thereby being a less sensitive detection parameter. This concern is precisely the reason for including inter-side ratios from at-risk thorax to contralateral forearm and contralateral biceps. The logic was that it seemed more unlikely for these arm contralateral targets to be affected by lymphedema on the at-risk side. Because very little if anything is known about the temporal and spatial course of truncal lymphedema, it may be that the thorax to arm ratios may turn out to be better discriminators despite their higher ratios as summarized in Table 1. The purpose of the present work was not to answer such questions but rather to provide reference ratios against which persons with lymphedema may be compared. This has been achieved for three practical at-risk to contralateral ratios; thorax-to-thorax, thorax-to-forearm, and thorax-to-biceps.

A potential limitation of the method is related to the fact that well defined (Fig. 1) but single anatomical sites were used to generate the reference ratios. If a patient's truncal lymphedema were manifest at sites not affecting the lateral thorax then it is unlikely that the ratios herein determined would be useful. According to information available from the National Lymphedema Network, truncal lymphedema can be manifest at breast, chest, lateral trunk, armpit, or back but the relative frequency of involvement of one site vs. the other is not very well known. Further work in delineating such information would be useful for choosing additional sites to characterize via TDC or other methods in future studies. For now, however, it is suggested that the most pressing need is to evaluate the presently described ratios in patients with confirmed lymphedema. One anticipated difficulty with such an approach is the absence of a truly gold standard. Evaluations would in the first instance need to rely on patient symptoms and clinical assessments that include palpation for fibrosis, pitting, and tissue quality. But this approach may prove to be challenging since according to a recent review such clinical assessments of the trunk have not been studied with respect to diagnostic utility (31).

In summary, methods for quantitative assessment of truncal lymphedema are needed and the present report provides a possible set of reference values that may prove to be useful for that purpose. A full judgment of the method's usefulness awaits future research with the threshold values being assessed in the presence of documented truncal lymphedema.

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CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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