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ASSESSING LYMPHEDEMA BY TISSUE INDENTATION FORCE AND LOCAL TISSUE WATER

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ABSTRACT

Tissue water and mechanical property changes accompany lymphedema, however the relationship between these changes, if any, is unclear. Local tissue water is quantifiable using the tissue's dielectric constant (TDC), but a non-gravity dependent handheld clinical assessment tool to easily quantify corresponding local tissue properties is not widely available. Herein such a tool is described along with results obtained with it and with TDC measurements made in healthy legs and in lymphedematous legs before and after one manual lymphatic drainage (MLD) treatment.

Using the handheld device, tissue indentations to various depths could be completed and corresponding indentation forces (IF) recorded. Following tests in gels, foams, and 24 healthy human legs to confirm linearity and repeatability, IF and TDC were measured in 22 legs of 18 lymphedema patients prior to and after one MLD treatment. Results showed that pre-MLD both IF and TDC were significantly ($p<0.001$) greater in lymphedematous legs compared to healthy legs and that both IF and TDC significantly ($p<0.001$) decreased after MLD. However, no correlation was found between pretreatment IF and TDC nor between post-MLD changes. Thus, measurements of local IF and tissue water provide useful but apparently independent information as to lymphedematous status and its potential change with therapy.

Keywords: lymphedema measurement, edema measurement, lymphedema treatment, tissue dielectric constant, tissue water, leg lymphedema, manual lymphatic drainage, MLD, tonometry, tissue mechanical properties

Most methods available to evaluate limb edema and its change in patients treated for limb lymphedema assess changes in limb volume or electrical properties (1-8). These are quite useful but do not directly reveal any of the physical properties of the underlying lymphedematous tissue. In an effort to include an indicator of such physical properties as part of routine lymphedema assessments, Clodius and Piller developed a tonometer device to measure the resistance of tissue to compression (9,10). The operating principle of this tonometer is that if tissue is loaded by a fixed weight, the penetration of an indentor that is in contact with the skin will be greater in softer than harder tissue. Recording this penetration depth offers the potential for a quantitative indicator of tissue resistance. Modified versions of this device have subsequently been used in a variety of lymphedema-related studies (11-14).

Because this form of tonometer depends on gravity, it must be applied vertically to the body part of interest and the surface to which it is applied must be sufficiently flat to allow for it to be nearly free standing. Thus although the gravity- dependent device is in principle simple, portable, and designed to be

used routinely in a clinic, the requirements limit its utility in some patients and may create reliability issues (15). Other approaches to estimate tissue properties without a gravity dependent weight have been developed (16-18) as research tools, but are not generally suitable for routine clinical use.

Tonometry-like methods can provide valuable information about initial tissue hardness and changes associated with time or treatment (14,19). However, with respect to the lymphedematous condition, there are few published data that compare tissue indentation resistance to other relevant lymphedema-related parameters. During localized compressive loading of tissue, the resistance to indentation depends in part on mechanical properties of the skin, subcutaneous matrix, and interstitial fluid phase (20). In lymphedematous tissue, the relative importance of matrix and fluid components varies depending on the extent of solidification of the matrix phase which occurs with fibrosis and on amount of accumulated interstitial water. Because fluid accumulation is an initial and ubiquitous component in edematous and lymphedematous conditions, it is of both fundamental and clinical interest to know what, if any, relationship exists between tissue water and tissue resistance.

Thus, the goals of this research were two-fold. The first was to develop a simple portable handheld device that could be routinely used in the clinic to assess tissue indentation resistance in patients with lymphedema in a manner that circumvents the gravity and flatness limitations of other approaches. The second was to determine if a significant tissue water-tissue resistance relationship could be detected in patients presenting for, but prior to their subsequent manual lymphatic drainage (MLD) therapy (21-23) and to determine if changes in tissue indentation resistance occurred with a single MLD treatment as had been previously observed for changes in local tissue water (5).

MATERIALS AND METHODS

Tissue Testing Device

The specially designed device (*Fig. 1*) consists of force indicator rigidly coupled to a penetration depth indicator (PDI). The PDI has a circular 29.5 mm diameter base plate attached at the bottom with a central 10.5 diameter opening through which a 10 mm diameter indentor passes to indent the tissue. Contact areas for the base plate and indentor are 601 mm^2 and 78.5 mm^2 respectively. Indentation depth depends on the force applied and the resistance of the target tissue. The zero for the PDI is set with the device placed vertical on a hard (impenetrable) surface by rotating the PDI indicator bezel to indicate zero indentation. Accuracies of the force and penetration indicators are ± 5 g and ± 0.1 mm respectively. Calculated surface contact pressure of the indentor is 93.6 mmHg per 100 g applied force. For brevity, the complete tissue testing device (force indicator and PDI) will subsequently be referred to as tissue tester.

From a fundamental analytical point of view, the relationship between indentation force (F) and indentation depth (δ) for soft tissues with an overall soft tissue thickness H can be expressed as $F = \delta E D \kappa / (1-v^2$ in which E is the effective elastic modulus of the tissue, D the indentor diameter, v the Poisson's ratio for the tissue and a factor that depends on the ratio of both δ/H and D/H (24-26). Thus, measured force depends directly on penetration depth and soft tissue elastic modulus. If penetration depth is fixed as in the present study, then changes in force depend directly on changes in the tissue elastic modulus.

To evaluate the tissue tester performance under controlled conditions, its indentation-force characteristics were determined using gels of varying water content and consistency. Three gel concentrations were prepared by mixing gelatin (Knox™) with distilled water to achieve gelatin concentrations of 44 mg/ml, 70 mg/ml and 105 mg/ml. Freshly prepared, stirred, and fully dissolved gelatin of each

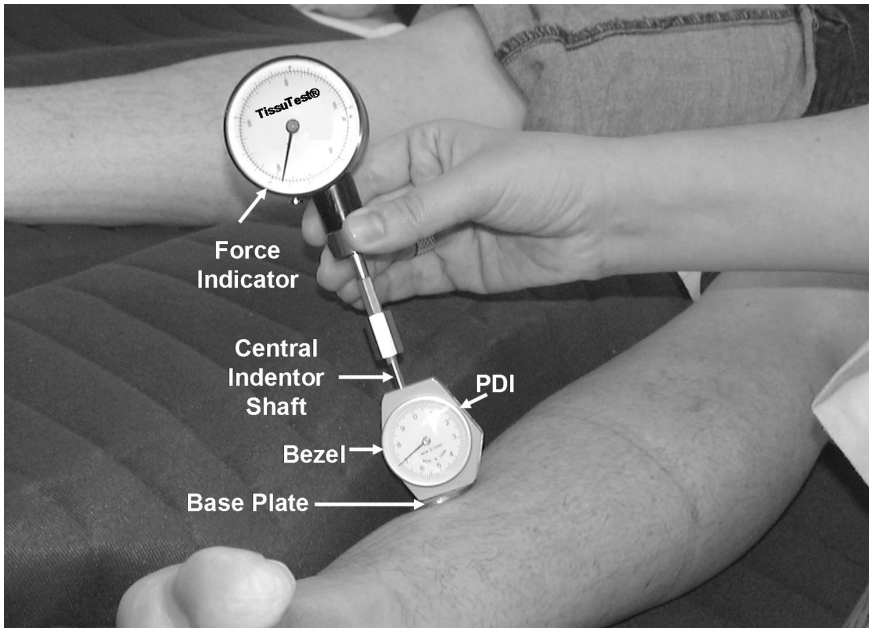

Fig. 1. Tissue Tester. The force indicator is rigidly coupled to a penetration depth indicator (PDI) that has a base plate attached at the bottom with a central opening through which a 10 mm diameter indentor passes to indent the tissue. Indentation depth depends on the force applied and the resistance of the target tissue. The zero for the PDI is set with the device placed vertical on a hard surface by rotating the PDI indicator bezel to indicate zero indentation. Accuracies of the force and penetration indicators are ± 5 g and ± 0.1 mm, respectively.

concentration was poured into eight 21 mm deep by 42 mm wide wells in a pan containing 24 individual wells. The total volume placed in each well was 25 ml. The pan was then placed in a refrigerator overnight at 4%C and removed after 12 hours for testing.

For each concentration, the tissue tester was used to produce indentations to a depth of 1.25, 2.0, 2.5, 3.25, 4.0 and 4.5 mm and the force for each was recorded. Each test was done on a separate well (6 wells per concentration) to avoid possible alterations of the gel due to a prior compression. Results of these tests indicate a linear dependence of force with indentation for each concentration (*Fig. 2A*) and with concentration for different indentation depths (*Fig. 2B*).

In addition to testing on gels, the tissue tester was evaluated on polyurethane foam blocks of different indentation force displacement (IFD) ratings as specified by the American Society of Testing Materials (ASTM) standard. This rating is based on measurements of force required to compress the material 25%. Tissue tester evaluations were done using 2.5 cm thick, 4 by 4 cm square blocks with IFD ratings of 0.3, 0.5, 0.7 and 1.3 psi where higher ratings correspond to greater compression force requirement. Indentation tests to 4.0 mm were done on each IFD rating 12 times to assess both linearity and variability. Results showed indentation force linear with IFD rating (r=0.994) with coefficients of variation for all IFD ratings less than 5% (*Fig. 3*).

Tissue Dielectric Constant

Local tissue water was assessed using a tissue dielectric constant (TDC) method (MoistureMeter-D, Delfin Technologies Ltd, Kuopio, Finland). The working principle of this method is based on the fact that tissue electrical properties depend on water content,

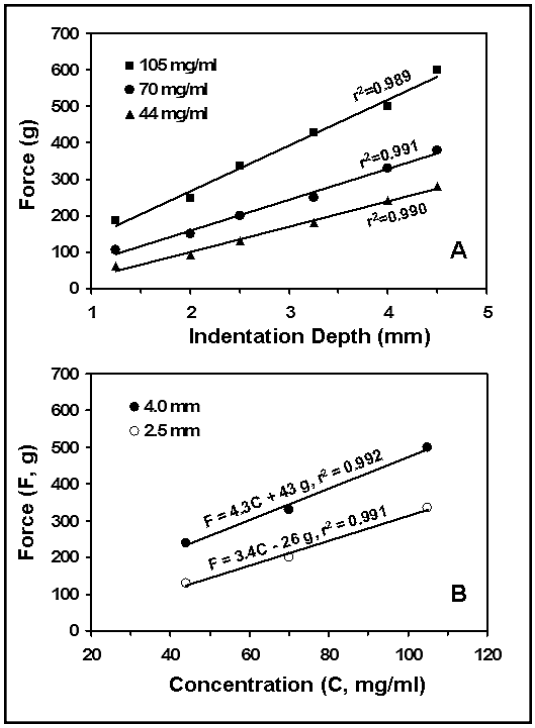

Fig. 2. Indentation Force-Depth for Gels. A) Indentation force as a function of indentation depth for three different gel concentrations. B) Indentation force as a function of gel concentration for two different indentation depths. Solid lines are linear regression lines. Linearity between indentation depth and force is demonstrated for each case.

which in turn affects the value of the tissue dielectric constant (27) with pure water having a value of 78.5. Since the dielectric constant is the ratio of electrical permittivity of the tissue to that of vacuum, it is a dimensionless quantity. Measurement of TDC at a suitable frequency, in this case 300MHz, provides an index of relative tissue water (28,29) based on the portion of the incident wave that is reflected and subsequently processed by the device's control unit. The utility of this device to evaluate tissue water and its change has been previously reported (5,27,30-33). Effective penetration depth, which defines the depth of tissue sampled, depends on probe dimensions in contact with the skin, with larger spacing between inner and outer conductors causing greater penetration. In this study a probe with a maximum diameter of 23 mm and conductor spacing of 5 mm was used to achieve an effective penetration depth of about 2.5 mm.

Patients and Control Subjects

All participants (patients and normal volunteers) signed an informed consent approved by the University Institutional Review Board. Patients (N=18, 10 female) who were included in this study were previously diagnosed by a referring physician as having lower extremity secondary lymphedema and were now about to receive lymphedema therapy that included MLD at a lymphedema treatment clinic. Measurements in these patients were done prior to and after a single MLD treatment that was administered by an LANA certified lymphedema therapist. The treatment session was about one hour. In four patients, two lymphedematous legs were treated and evaluated yielding a total of 22 lymphedematous legs treated and evaluated. Average patient age (mean ± SD) was 72.4 ± 18.6 years (range 39 to 97 years). Self reported duration of lymphedema ranged from 4 months to 30 years.

In addition to measurements of patients, for reference and comparison purposes, both legs of 12 control subject volunteers (age range 40-70 years) who had no history of lower extremity abnormalities were also evaluated with respect to their TDC values and indentation force resistance. For purposes of estimating measurement variability, multiple measurements were also made at an anterior forearm site in two volunteer subjects and at an anterior thigh site of one these subjects.

Control Subject Measurement Procedure

In the 12 volunteers, leg measurements were done at a standardized site on the calf located 10 cm proximal to the medial malleolus. TDC values were determined in

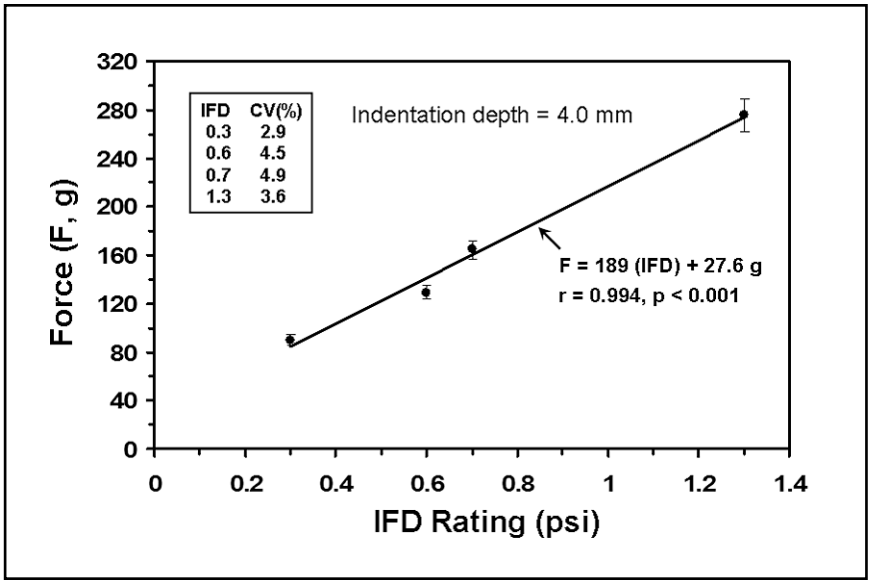

Fig. 3. Indentation Force for Polyurethane Foams. Data points show mean ± SD of 12 indentation force trials when foam blocks with different standardized indentation force ratings (IFD) were indented to a depth of 4 mm. Inset shows coefficients of variation for force for each of the four test blocks used. Solid line is linear regression.

triplicate and indentation force was determined for penetration depths of 2, 3 and 4 mm. All measurements were done with subjects supine and were obtained after 10 minutes of lying at rest. Forearm and thigh measurements of one volunteer were made over an indentation range of 3 to 5 mm in 0.5 mm steps with each indentation depth at each site repeated 10 times to estimate short term variability in measured values. For these tests, the forearm test site was 8 cm distal to the antecubital crease and the thigh test site was 15 cm proximal to the knee with the subject supine. Time between repeated depth measurements at each site was 60 seconds. In another volunteer, to estimate repeatability of sequential measurements over a longer time span, measurements were made at 4 minute intervals over a 60 minute test period at an anterior forearm site 6 cm from the antecubital crease. These measurements included, TDC, indentation force, and skin temperature (via noncontact infrared) all measured at the same site.

Patient Measurement Procedure

TDC and tissue resistance measurements were made on the calf at a site visually identified as having the greatest swelling. The girth (circumference) of this site, TDC values, and tissue indentation force were measured prior to and after completing the leg MLD treatment procedure. Initial measurements began after the patient had been lying supine for 10 minutes. TDC was measured in triplicate and the average of the three readings used to characterize the target site's tissue water. Each TDC measurement takes about 10 seconds once the probe is touched to the skin. Tissue resistance was then measured at the same site using the tissue tester by indenting to a standardized indentation depth of 4 mm and recording the force required to achieve this indentation. The force meter holds the indentation force value for easy reading. Although lesser (or greater) penetration depths are possible with the device, a 4 mm depth was chosen for this initial study

TABLE 1
Result Summary

	Subjects (28 Legs)	Patients (22 Legs)		
		Pre-treatment	Post-treatment	% Change
Force (g)	316 ± 38	401 ± 123	331 ± 98**	-21.5 ± 17.1
TDC	28.6 ± 1.6	35.9 ± 8.3	32.6 ± 8.0**	-9.1 ± 6.9
Girth (cm)		35.3 ± 7.3	34.3 ± 7.2**	-3.0 ± 2.3

Values are mean ± SD. † $p<0.001$ compared to subjects , ** $p<0.001$ compared to pre-treatment.

to achieve force levels within the optimal meter reading range of 50 to 500g which correspond to forces of about 0.5 to 5 Newtons (N). In addition to the biophysical measurements, the circumference (girth) of the leg at the test site was measured before and after MLD using a constant tension tape measure.

Analysis

Indentation force and TDC values at measured leg sites were compared using regression analysis. In volunteer subjects, the goal was to determine if these two biophysical quantities were related. In patients, it was used to test for a possible pre- treatment relationship between tissue water and tissue resistance. To assess the potential of the tissue tester to detect changes in tissue indentation resistance and to test for changes in TDC associated with MLD treatment, post treatment values obtained within 5 minutes of completing the leg MLD procedure were compared to pre-treatment values using a nonparametric Wilcoxon signed rank test since the distributional assumptions that underlie the paired *t*-test were not verified for the present measurement set.

RESULTS

TDC and Tissue Indentation Resistance in Control Subjects

TDC values (mean ± SD) for left and right legs were 28.4 ± 1.8 and 28.7 ± 1.4 respectively with no significant difference between paired-legs ($p>0.4$). The overall TDC value considering all 24 legs was 28.6 ± 1.6. Indentation force for left and right legs were 311 ± 41 g and 321 ± 37 g respectively with no significant difference between paired legs ($p>0.5$). The overall indentation force considering all 24 legs was 316 ± 38 g (*Table 1*). Indentation force was found to be linear with respect to indentation depth as indicated by the high linear correlation coefficient (0.996) (*Fig. 4*). The arm and thigh measurements (*Fig. 5*) also indicate a linear dependence of force with indentation depth for each site. Calculated coefficients of variation among the 10 repeated force measurements at each site and depth were all less than 5%. Coefficients of variations of indentation force and TDC values over a one hour period were 2.3% and 1.15%, respectively (*Fig. 6*).

TDC and Tissue Indentation Resistance in Patients – Pre MLD Treatment

TDC values for lymphedematous legs (n=22) was 37.8 ± 10.1 which was significantly

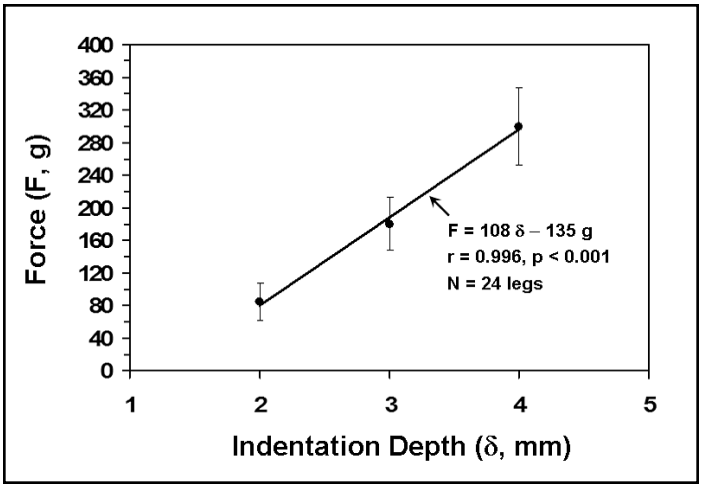

Fig. 4. Indentation Force-Depth for Healthy Legs. Data points show mean ± SD of indentation force as a function of indentation depth for 24 legs measured at the medial gaiter area. Solid line is linear regression.

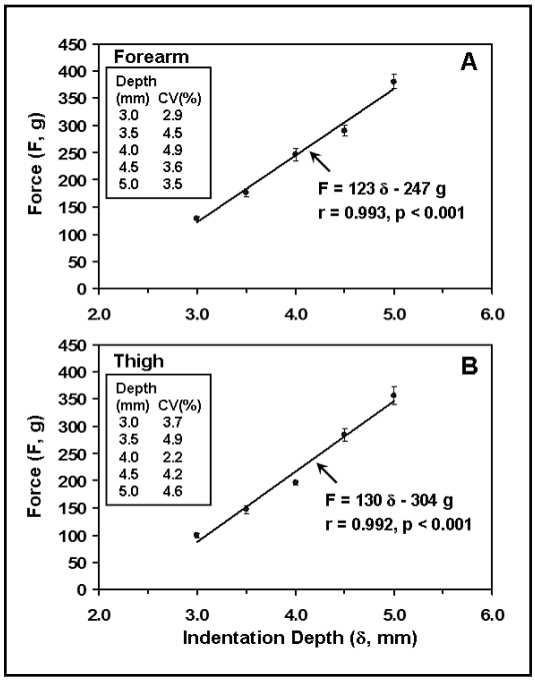

Fig. 5. Short Term Repeatability and Linearity at Different Tissue Sites. Data points show mean ± SD of 10 indentation force trials on one subject's anterior forearm and thigh. Time between repeated depth measurements at each site was 60 seconds. Results indicate a linear dependence of force with indentation depth for each site. Calculated coefficients of variation among the 10 repeated measurements at each depth are shown in the inset.

greater ($p<0.001$) in comparison to TDC values for normal subject legs. Indentation force for lymphedematous legs was 417 ± 134 g which was also significantly greater ($p<0.001$) than for normal subject legs.

TDC and Tissue Indentation Resistance in Patients – Post MLD Treatment

After the single MLD treatment, indentation force was significantly reduced from its pre-treatment value of 417 ± 134 g to 348 ± 110 g ($p<0.001$) and TDC was reduced from its pre- treatment value of 37.8 ± 10.1 to 34.3 ± 9.6 ($p<0.001$). Examination of individual responses showed that indentation force was reduced in every patient, with percentage reductions ranging from 1.2 to 62% and an overall 20.7 ± 16.7% reduction. TDC values were found to be reduced in all but one patient, and ranged from 1.7 to 28% with an overall reduction of 9.2 ± 6.7%.

Indentation Force – TDC Relationship

Despite treatment-related reductions in both indentation force and TDC there was no correlation between the changes in these parameters as assessed via Pearson's correlation value ($r= -0.067$).

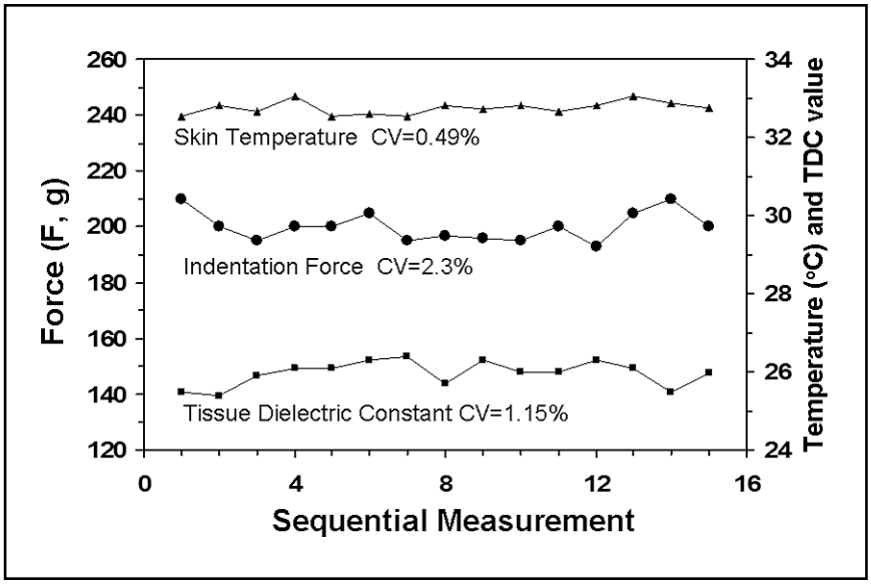

Fig. 6. Variation of Force and Tissue Dielectric Constant Measurements. Data points show sequential values of indentation force for a 4 mm indentation depth together with TDC and skin temperature values measured at 4 minute intervals on the anterior forearm of one subject. CV is the coefficient of variation over the 60 minute test period.

There was also no discernible correlation between indentation force and TDC values for either the control subjects or for the patients.

DISCUSSION

Tissue Tester Device

The tissue tester was demonstrated as a rather simple handheld device which can easily be used in the clinic to rapidly assess tissue resistance to localized compression and provide an index of underlying tissue mechanical properties. Typically, measurement can be done in less than 10 seconds and does not depend on gravity for operation. This allows it to be applied to tissue at any orientation and, in principle, can be used on any lymphedematous body part without need for a significantly large flat area.

The *in vitro* gel evaluations of the tissue tester demonstrate that the force recorded for varying penetration depths is linear with indentation depth and that for varying gel concentrations that simulate differing tissue properties, the force is linear with concentration. Similar linear dependencies were shown using standardized polyurethane foams that had differing indentation force ratings and for normal leg tissues. Further, estimates of measurement repeatability *in vitro* and *in vivo* indicate a coefficient of variation of less than 5% which is a value that in most cases is suitable for clinical assessments. Although the tissue tester device was specially designed for this study, it is not difficult to construct and the author would be willing to provide guidance to other investigators in that task should there be interest.

Effects of Leg Lymphedema on Measured Parameter

As compared to legs of subjects without lymphedema, presence of leg lymphedema was associated with 1) a significantly greater tissue resistance as judged by the indentation force and 2) a greater local tissue water as judged by the greater tissue dielectric constant.

TDC values for normal legs in this study (28.6 ± 1.6) were similar to TDC values measured in normal arms of patients with unilateral upper extremity lymphedema secondary to breast cancer related treatment (25.2 ± 2.7) (30) and similar to TDC values measured in the forearms of a previously measured normal control group (25.8 ± 3.9) (30). TDC values for lymphedematous legs of the present study group (37.8 ± 10.1) were similar to TDC values measured previously on lymphedematous arms (41.2 ± 7.9) (30) and bilateral lymphedematous legs (42.1 ± 3.7) (5). No corresponding measurements of tissue resistance have been previously reported.

Effects of MLD therapy

With respect to the effects of therapy, the present data showed that a single MLD treatment of lymphedematous legs resulted in a significant reduction in tissue resistance as judged by the reduced indentation force and also resulted in a significant reduction in local tissue water as judged by the reduction in tissue dielectric constant. Such a single-session MLD-related tissue softening as determined by tonometry has been previously observed (34). In addition, although previous studies have shown that a single MLD therapy session causes a decrease in local tissue water in lymphedematous legs of 9.7 ± 5.45% (5) compared with 9.2 ± 6.7% herein determined, the percentage reduction in indentation force in the present study (20.7 ± 16.7%) was greater than for the tissue water reduction . Since both tissue resistance and tissue water were found to be reduced with treatment, we investigated whether there was evidence that these were related phenomena. Analysis showed that the correlation between these two changes was virtually zero suggesting that the measured changes were largely independent of each other. A similar absence of a tissue resistance-water relationship was found when the relationship was tested for control legs and for pre-treatment values in the patient group. Although previous studies showed an increase in relative tissue water in lymphedematous limbs (5,30,32), the present result is the first to measure both parameters thereby allowing a test of such a possible association.

Interpretation of Findings

When considering the reasons that lymphedematous changes might affect indentation resistance, several factors need to be considered. In principle, tissue resistance measured by indentation force reflects the mechanical properties of skin and subcutaneous tissues with the interstitial space composed of fluid, solid (collagen and elastin), and gel-like substances such as mucopolysaccharides. In lymphedema, the fluid phase is increased and if edema volume rises sufficiently, resultant increase in interstitial pressure might be expected to cause an increase in net tissue indentation resistance. If increase in measured tissue water in lymphedematous tissue were the dominant factor affecting the presently measured tissue resistance, then a direct relationship between TDC and indentation force might be expected. A similar correlation might be expected for changes in these parameters with treatment.

That such relationships were not demonstrated may be explained if the average tissue fluid pressure rise associated with the present lymphedematous group had a minor effect. Supporting this view is the finding that in significantly lymphedematous arms with an average 33% increase in limb volume, average interstitial pressure increased by just 3.5 mmHg (35). Although this magnitude of pressure increase may affect transcapillary fluid transfer, it is unlikely to significantly contribute to the increased indentation force herein measured since its magnitude is much less than indentor pressures achieved during testing. So, our interpretation of the present findings is that an MLD-related tissue softening accounts for the force reduction whereas fluid movement out of the interstitial space accounts for the TDC reduction. These

findings suggest that measurements of both local tissue resistance and tissue water can provide useful independent information as to the lymphedematous status and its potential change with therapy.

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