Lymphology 33 (2000) 122-135

NON-INVASIVE ASSESSMENT OF THE LYMPHEDEMATOUS LIMB

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ABSTRACT

Accurate assessment of the swollen limb is crucial to effective management, and usually consists of measurement of volume and assessment of skin condition. Here, we review the different methods available to measure volume, and their accuracy, together with other non-invasive methods available to assess the characteristics of the swelling. These include the measurement of fluid mobility by recording deformation of tissue by a mass (tonometry) and the step compression method; the measurement of truncal swelling by skinfold calipers; imaging techniques (magnetic resonance imaging, computed tomography, ultrasound) which provide information on size and other characteristics of the different tissue compartments; and measurement of impedance (amount of extracellular water and total water content). The varying quality of swelling, as well as its extent and distribution, indicates the need for objective methods of assessment other than simple limb volume measurement. Such detailed information should improve the understanding of peripheral lymphedema.

Lymphedema is increasingly recognized as a common side effect of cancer treatment, especially breast cancer (1-3), with filarial infection responsible for most cases worldwide. Management consists of careful treatment, particularly external compression, exercise, and manual lymph drainage, and accurate assessment of the response of the limb. Accurate measurement of limb volume is considered crucial to lymphedema management. We have previously reviewed outcome measures in lymphedema management (4).

Non-invasive methods that are available to assess the swollen limb are reviewed here. The severity of lymphedema is usually assessed on the basis of limb volume, but limb shape, skin condition and overall function are equally important. The tape measure is the most commonly used method to measure volume, but is prone to error. In this review, the tape method is critically appraised together with a number of other methods. Some of the other methods of assessment examined provide information on the composition of the limb or the relative size of different compartments within the limb, and on the physical characteristics of the skin and subcutaneous tissues. Whereas of less practical use to the therapist currently, these techniques are included because improved understanding of this chronic condition and more effective treatment should result from a better understanding of the nature of the swelling.

Accurate measurement of limb size is also important in studies on the pathophysiology of lymphedema, as demonstrated by recent research on postmastectomy edema in which unexpected relationships were revealed between arm volume and interstitial fluid protein concentration (5) and between skin surface area and capillary density (6).

When Is the Limb Swollen?

Normal differences between right and left

The degree of limb swelling is often expressed in relation to the size of the other limb (assumed to represent the pre-morbid size of the affected limb), if the contralateral limb is free of disease. It is known, however, that differences between right and left (or dominant and non-dominant) occur in health, and several authors have addressed this issue. In 91 right- and 5 left-handed healthy women over the age of 30 years, right arm volume (hand plus forearm) was 43 ± 50 ml (mean ± standard deviation, s.d.), or 3.9%, greater than left arm volume in the right-handed subjects, and left arm volume was 21 ± 22 ml (2.1%) greater than right in the left-handed subjects. Volumes were measured using water-displacement volumetry (7). Using optoelectronic volumetry, dominant forearm volume (hand excluded) was 3.6% greater than non-dominant forearm volume in a group of 14 healthy, mainly right-handed, men and women aged 18-49 years (8).

The dominant and non-dominant arms of healthy female subjects (aged 29-56 years) have been compared using multiple frequency bioelectrical impedance measurement (9). Interestingly, small but statistically significant differences were detected in parameters thought to reflect total water and extracellular water volume. These differences were significantly associated with handedness. Differences in volume determined from circumference measurements (taken at 10-cm intervals and using a cylinder formula) were not significant. Impedance analysis is considered in more detail later.

Differences between right and left leg volume in health are less commonly documented. In one study using water displacement (10), mean left leg volume (upper leg, lower leg and foot) was 1.5% greater than mean right leg volume in a group of 24 young men. The difference was greater in 23 young women (left leg 2.7% larger than the right). Dominance was not considered. Using computed tomography, Vaughan (11) measured the cross-sectional area of the muscle compartment at the same level of the upper calf of the right and left legs of 10 normal subjects (four male, six female, age and dominant side not given). He found an average difference of 2.9 ± 2.2%, corresponding to a difference in circumference of 1.4 ± 1.1 %. The right and left muscle compartments were larger in equal numbers of subjects.

The diagnostic threshold for swelling

Limb swelling is usually obvious, and the patient is usually the first to notice it (3). A quantitative threshold, above which limb swelling may be said to be present, is useful for the detection of mild cases, and for epidemiological and pathophysiological studies. Such a threshold requires that the opposite limb is normal in size, which is usually the case in lymphedema following breast cancer treatment. Kissin et al. (1) considered several possible cut-off points (differences in forearm and upper arm circumference and volume) in order to determine the most sensitive indicator of postmastectomy lymphedema. The most sensitive indicator was found to be a greater than 200 ml difference in arm volume (measured by water displacement to 15 cm above the epicondyle); none of the control group had a difference of this magnitude. Volume differences of greater than 500 ml and greater than 20% were also sensitive indicators. Percentage differences seem more universally applicable, and a difference in arm volume of 10% is considered an appropriate cut-off point, although lymphedema may be present at smaller differences (3). Intuitively, dominance would be expected to influence leg volume less than arm, and a smaller cut-off point could be applied, but the greater likelihood of bilateral swelling (see below) makes such a threshold less useful.

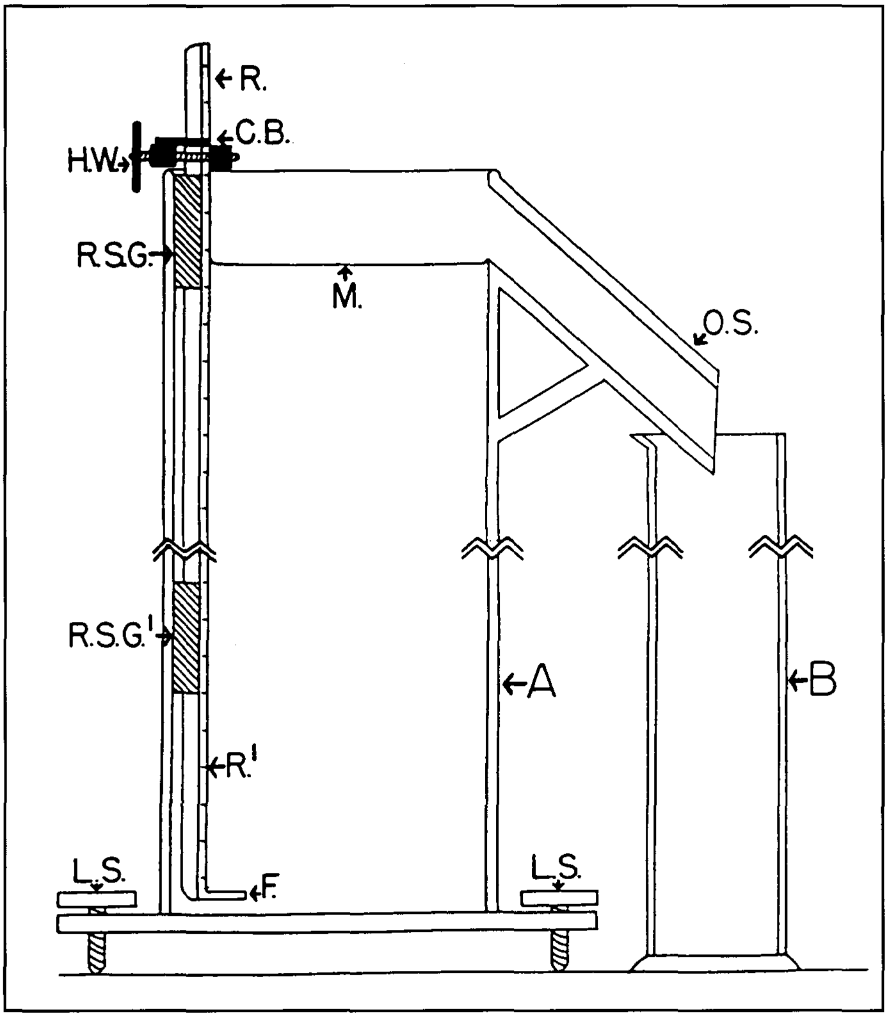

Fig. 1. Sectional diagram of water-displacement apparatus to measure limb volume (from ref. 7, with permission). The tank (A) is cylindrical, made from 1/4 inch Perspex, the base being 1/2 inch thick; B - graduated collecting cylinder; OS -overflow spout; LS - leveling screws; R - metal rule (slides up and down in housing, RSG, attached to wall of tank); F - adjustable shelf; HW - hand wheel (fixes rule and shelf in position); CB - cursor block; M - meniscus of water.

With tissue shrinkage associated with fibrosis or tissue loss by extensive resection, a lymphedematous limb may be smaller than the opposite normal limb (3). Other clinical signs may accompany the swelling, especially if longstanding and lymphatic obstruction is severe, e.g., enhanced skin creases, increased skin turgor, hyperkeratosis and papillomatosis (12). Extensive skin hardening is occasionally seen in very small limbs.

When swelling is bilateral

It is difficult to be always sure that the 'normal_ side is indeed normal, especially for the leg, and this limitation presents a special problem for assessing the degree of swelling. Thus, treatment of cancers affecting mid-line structures (e.g., cervix, prostate) can damage lymph drainage routes on both sides, but with one leg affected severely and the other only mildly. In addition, both sides are often affected in primary lymphedema. Repeated measurements of volume over time are useful in these cases. Aslem et al (13) considered this problem and have examined the relationship of leg volume to height, weight and body mass index using regression analysis. Body weight was found to be an independent predictor of lower leg volume but the method was too imprecise for clinical assessment of severity. The importance of recording the patient_s height and weight and calculating body mass index is useful, however, because leg volume can change for reasons other than lymphedema treatment. For patients at high risk (extensive extirpation of lymph nodes plus radiotherapy), baseline leg volume should be determined at an early stage, and the possibility of co-existing venous disease should always be considered.

Measurement of Limb Size and Shape

Water displacement volumetry

This method has been widely used to provide a direct measurement of arm and leg volumes and is sometimes thought of as the gold standard. Apparatus for the measurement of arms has been described in detail (7) (*Fig. 1*), and its reproducibility has been examined (7,14). In 10-15 observations on each of four normal arms (hand plus forearm) from three subjects, the relative standard deviation (r.s.d., s.d/mean x 100%) was 1.5-3.9% (7). There is close agreement (3% difference) between water displacement and an optoelectronic plethysmographic device, the Perometer, considered later (15).

Careful positioning of the extremity is essential. An adjustable shelf with which to touch the fingertip for arm measurement is one possible arrangement (*Fig. 1*). Use of a bony landmark as a reference point is useful, e.g., the styloid process of the ulna for hand measurement, and alignment with a fixed level is essential. When performed properly, water displacement is accurate but time-consuming and messy. It is, however, an easy way of determining hand and foot volume accurately and is also useful for comparing the accuracy of different methods to measure volume. No information, however, is provided on limb shape. Water displacement cannot readily be used in the postoperative period, when joint mobility is limited, and when skin ulceration is present. Together with general hygiene considerations, these constraints limit its routine clinical use.

The tape measure

Limb volume can be indirectly but conveniently calculated from circumference measurements made using a flexible tape measure, and distribution of swelling can be assessed by comparing the circumferences. Accuracy clearly depends on the spacing between and hence the total number of measurements. The greater the deviation of the limb from the theoretical shape being assumed in the formula for calculation of volume, the greater the potential for error for a given spacing of measurements. Many therapists use a measurement interval of 4 cm (16), with calculation of volume based on the formula for a frustum of a cone (i.e., a truncated cone), $V_{limb} = \sum(X^2 + Y^2 + XY)/3\pi$ (equation 1), or for a cylinder, $V_{limb} = \sum Z^2/\pi$ (equation 2). X is the circumference at one point on the limb (usually starting at the styloid process at the wrist or the medial malleolus at the ankle) and Y is the circumference at a point 4 cm up the limb from X; Z is the circumference of the 4-cm segment of limb taken from one point, preferably the mid-point. Equation 1 is therefore based on two measurements per segment and equation 2 is based on one. Measurements are made every 4 cm along the axis of the limb (not along the surface). The frustum and cylinder models have been compared against other methods. Close agreement has been reported for the tape/cylinder method (based on circumference measurements every 3 cm) and water

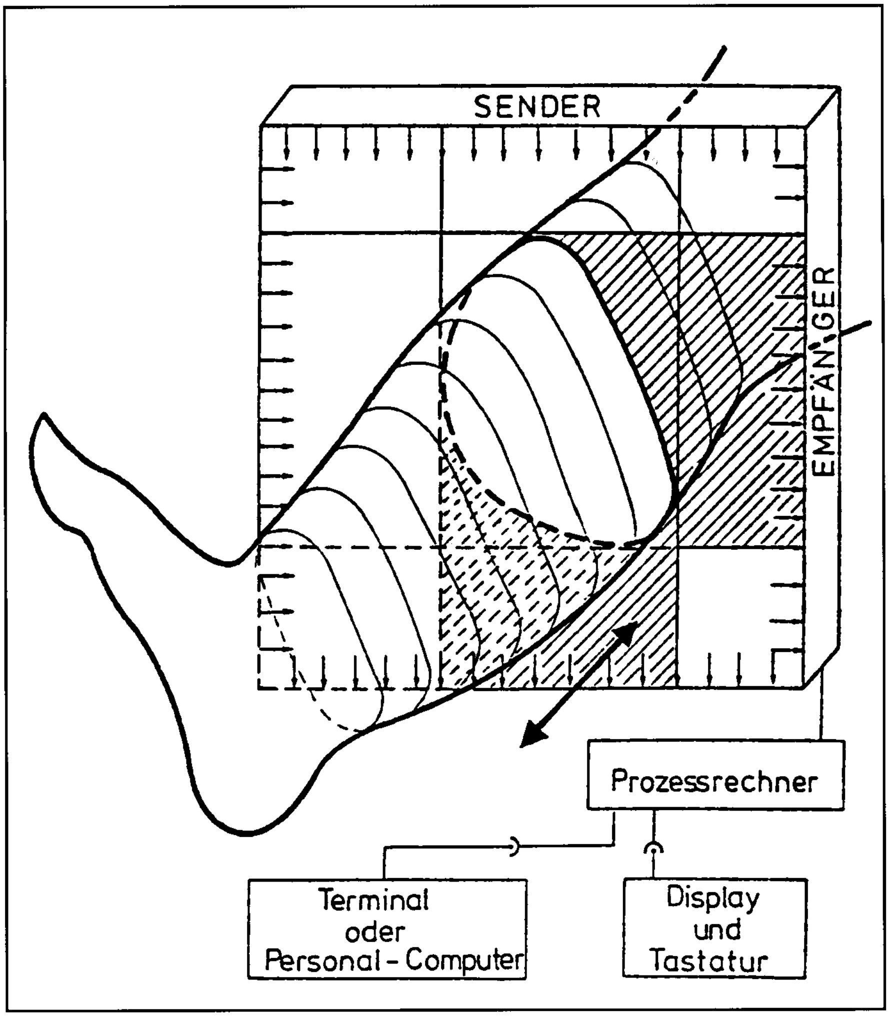

Fig. 2. Diagram of operation of the Perometer (reproduced with permission from Professor J-U Fischbach).

displacement for the healthy lower leg (17). The tape/cylinder method gave a volume 45 ± 39 ml (mean ± s.d.) (1.6%) greater than water-displacement. The tape/frustum method agreed less well with water-displacement but frustum volume was determined from only two circumferences for the entire lower leg. Tierney et al. (15) found greater variability in tape/frustum measurements when comparing this method with the cylinder model and with water displacement and the Perometer. In contrast, Sitzia (18) concluded that the frustum method was superior to the cylinder model. Clearly, the accuracy of each model depends on the shape of the segment of limb. Either method of calculation is sufficiently accurate, provided it is used consistently.

Hand and foot volume are best measured by water displacement, but size can be estimated from one or two tape measurements. The circumference of the hand and the foot are measured at a fixed distance from a suitable anatomical point. A formula for calculating foot volume which assumes a wedge shape, $V_{foot} = lCh/2\pi$ (equation 3), has

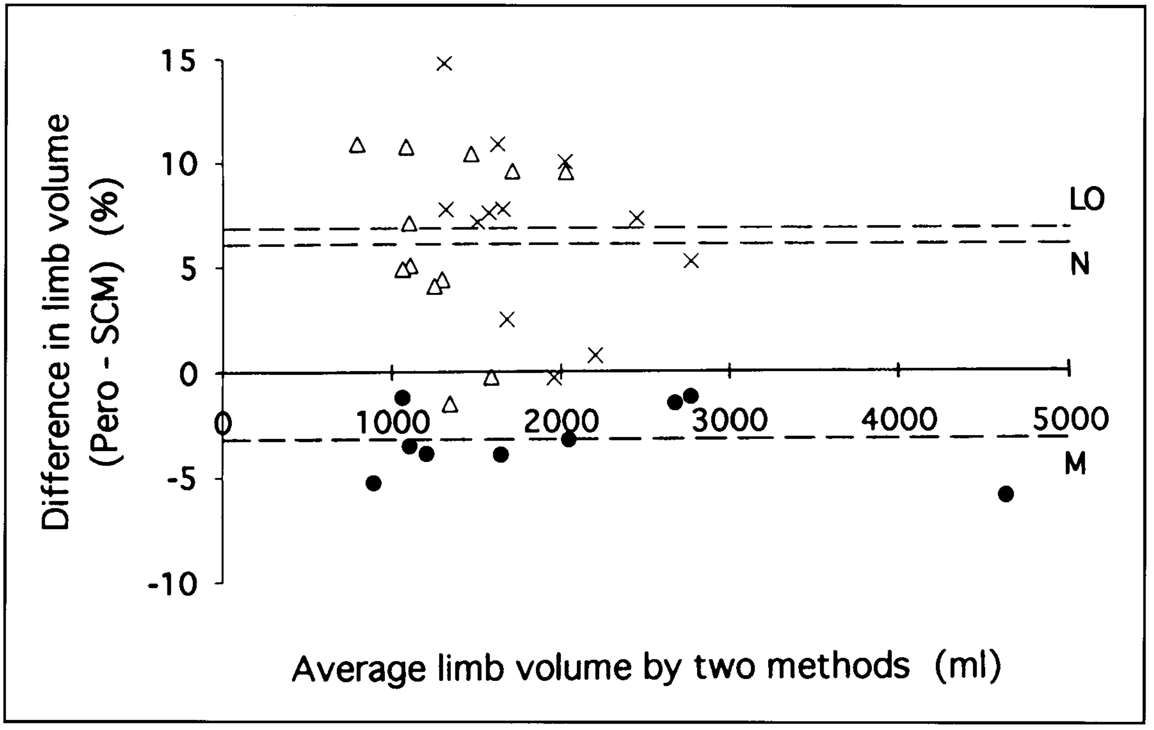

Fig. 3. Differences between the Perometer (Pero) and the sequential circumference method using a tape measure (SCM, tape/frustum method), in the measurement of normal (N, open triangles), lymphoedematous (LO, crosses) and mannequin (M, closed circles) limbs, plotted against the average volume of the two methods (Bland-Altman plot). Dashed lines - mean difference (from 20, with permission).

been proposed (19) but is little used. **l** is the length of the foot, C is the ankle circumference, h is the height of the foot from the sole to where C is measured.

Sources of error in the use of the tape method have been recently addressed (20), and arise from the assumption of circular cross-section of the limb (with either the frustum or cylinder formula), and from the way the operator uses it. The error deriving from the former assumption results from the area of cross-sections that deviate from the circular being less than that of true circles of equal circumference. Serial circumference measurements thus have an inherent tendency to overestimate. A controlled tension device has been used to minimize compression of tissues when wrapping the tape around healthy and swollen lower legs (15). In this study a surprisingly large overestimation of volume with the tape measure (by 8-12%) was obtained in comparison with water displacement or the Perometer. A smaller overestimation with the tape method (3.3%) when compared with the Perometer was obtained on mannequin limbs (not compressible by the tape) (20). Unless tension on the tape is minimal, compression of the soft tissues occurs readily and can result in underestimation of circumference. Other sources of error include failure to wrap the tape around the limb at right angles to its axis, inaccurate or inconsistent spacing of measurements, and errors in the position of the first measurement point. Old tapes can stretch, too. It can not be assumed that errors cancel each other. However, with good technique and when performed by the same operator, the tape method is sufficiently reliable to measure limb volume. Comparison of circumferences provides information on limb shape and localization of swelling.

Optoelectronic volumetry

The Perometer® (21) is one such opto-electronic device. Devices using this principle depend on the interruption of infrared light beams by the limb. The arm or leg is placed inside a vertically-oriented square measuring frame which contains rows of infrared light emitting diodes (LED) on two adjacent sides and rows of corresponding sensors on the opposite two sides (*Fig. 2*). The limb casts shadows in two planes, and on moving the frame along the length of the limb, its volume is automatically calculated from a large number of vertical and horizontal diameter measurements at 3.1-mm intervals. A circular or elliptical cross-section is assumed. In reality, all limbs deviate from this scheme but errors tend to cancel. The Perometer has been comprehensively evaluated (20).

Comparison of the Perometer with the tape measure (15,20) has demonstrated small but important differences between these methods with the tape method undoubtedly being the main source of error. These differences preclude the interchangeable use of the two methods. *Fig. 3* illustrates the individual differences in volume obtained using the two methods on 12 arms with postmastectomy edema. The Perometer is probably the most accurate method of limb volume measurement, and is becoming the new gold standard. It is also the best method to record limb shape. Drawbacks include (a) difficulty in measuring the full length of the arm or leg right up to the shoulder or hip because of the thickness of the frame and the necessary abduction of the limb required; (b) less accurate hand and foot measurement; (c) cost; (d) size of the equipment, rendering it difficult to use outside the clinic and precluding bedside use. Another application of the Perometer is the measurement of dynamic events in venous occlusion plethysmography (8,22).

A recent modification of the Perometer enables the detection of convex contours of the limb, i.e., volume is calculated from a large number of diameter measurements rather than just two at right-angles. The '3D-LED-scanner system' has been assessed under conditions of venous occlusion of the leg (venous capacity measurement) and for the measurement of legs for the fitting of compression hosiery (23), but is not necessarily more accurate in measuring volume than the earlier system.

Measurement of the Physical Characteristics of Oedematous Tissues

Tonometry

If the presence of edema is suspected in a patient, it may be sought by applying digital (thumb) pressure for one minute to a region where edema fluid is known to accumulate (e.g., behind the medial malleolus to test for the presence of ankle edema in cardiac failure). This test results in a depression, or pit, in the tissues if edema is present. The pitting test is essentially a subjective test for increased interstitial fluid mobility, and can be performed at various anatomical sites. Lymphedematous tissues of the arm or leg pit to applied pressure, but less easily if the swelling is 'brawny' (strictly, muscular or fleshy, but used to describe swelling that is firm or hard) or fatty in nature. Objective determination of the depth of soft tissue pitting in lymphedema has been described using a tonometer (24) which measures the depth of compression of tissues by an applied mass, and is read from a scale after a fixed time period.

An electronic device has been developed that records the initial almost instantaneous deformation of arm tissue following application of a mass, and the time constant of the subsequent slow indentation (25). Indentation curves are analyzed according to a spring and dashpot (Kelvin-Hooke) model. Although the initial deformation of the

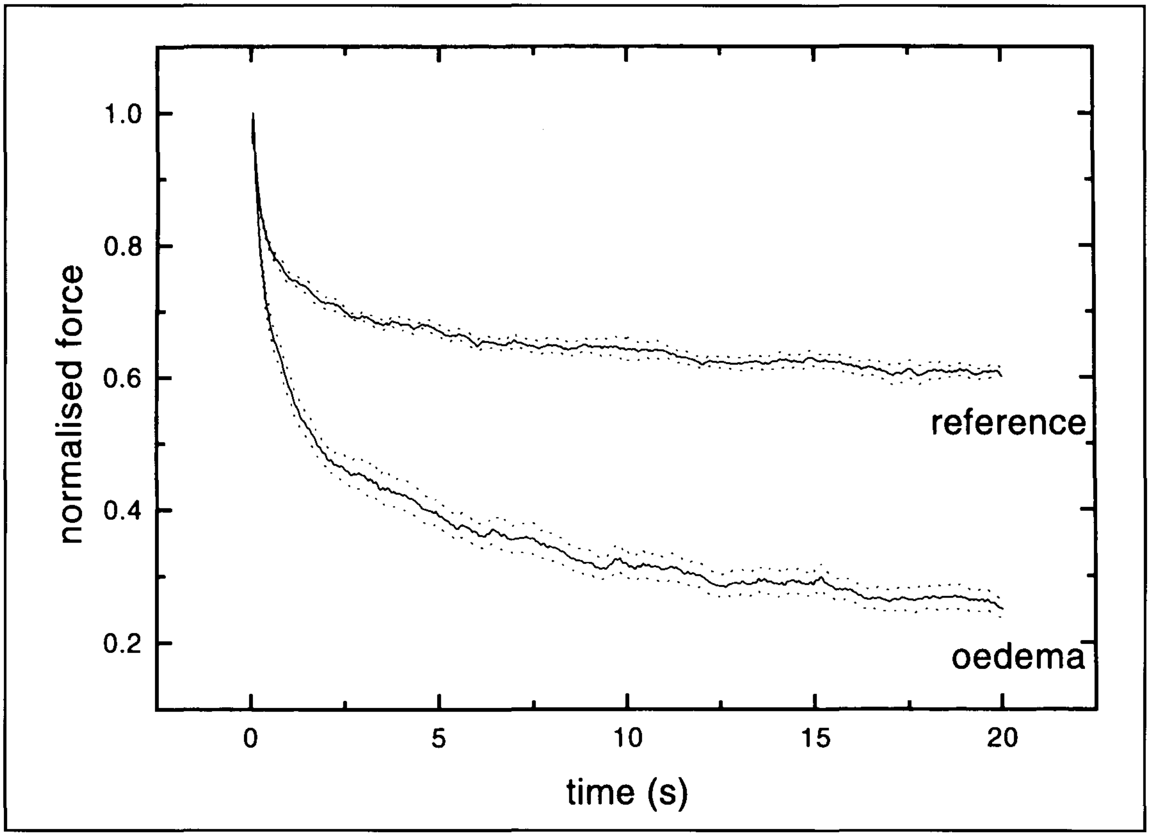

Fig. 4. Declining impression force curves from oedematous and the opposite, normal (reference) arms obtained using the instantaneous step impression method. Solid lines - mean, dotted lines - s.e.m., n = 7 (from ref. 27, with permission).

lymphedematous arm is the same as the opposite normal arm, the slow deformation is on average 4-fold greater in the swollen arm and the time constant 3-fold greater. Analysis of displacement versus time curves thus provides an objective means of quantifying pitting characteristics.

Other biomechanical approaches

Another approach in the assessment of interstitial fluid mobility in edema is the step compression method (26). With this method, the gradually decreasing resistive force of the tissue following quasi-instantaneous compression of constant depth (4 mm) is recorded as a function of time (*Fig. 4*). The decrease in resistance to the compression results from the displacement of fluid from the vicinity of the compressed region. A biexponential model based on the relative fractions of low-viscosity (gel-like) and high-viscosity (water-like) fluid is used to analyze the force curve data from normal and edematous tissue (26,27). The calculated volume of fluid displaced from the compressed region and the rate of fluid displacement are greater in edematous skin and varied with the degree of edema. The method has been used to study the effect of pneumatic compression in patients with lymphedema of the arm (28).

In a further biomechanical approach, mechanical pulse wave propagation velocity was studied in the arms of women with lymphedema (29). Velocity was lower in pitting, edematous tissues than in normal tissues. In two patients with non-pitting edema, velocity was higher, and this approach may be useful for brawny limbs in which fluid displacement cannot be studied. The same group has also developed a compact and portable spring-loaded tactile sensor to evaluate the stiffness and elasticity of human skin (30).

Measurement of Truncal Swelling

It is well known that lymphedema affecting a limb can also involve the adjacent trunk. This is often seen in association with postmastectomy edema. Truncal swelling is usually assessed in the clinic using the pinch test, where the right and left posterior axillary skinfolds are simultaneously pinched between finger and thumb and the thickness compared subjectively.

At this site it is impossible to detect edema using the biomechanical approaches outlined above. However, Roberts et al (31) described an objective assessment of posterior axillary fold edema by the use of modified Harpenden skinfold calipers. In a group of 14 women, three gave a history of swelling and two had clinically detectable swelling. Taking a 10% greater skinfold thickness on one side over the other as the threshold for truncal swelling, the calipers demonstrated swelling in eight of the 14 patients. Sustained application of the calipers demonstrated 'creep', i.e., decrease in measured thickness with time, the pressure of the caliper jaws causing displacement of interstitial fluid (at the slow indentation recorded by the electronic tonometer (25). A greater rate of creep was present in all 14 patients, suggesting that rate of creep represents an even more sensitive indicator of truncal edema than skinfold thickness alone. Careful and consistent positioning of the caliper jaws is essential, and the calipers cannot be used at other sites such as the forearm where the skin is tighter.

Imaging Techniques

Nuclear magnetic resonance

Magnetic resonance imaging (MRI) scans are radiological pictures similar to those of computed tomography. Little used in lymphedema, magnetic resonance imaging has been compared with computed tomography for the investigation of axillary symptoms, including swelling, following breast cancer treatment (32). Both methods have previously been used to demonstrate the normal and abnormal brachial plexus. Differences between the two methods in the differentiation of fibrosis from metastatic disease were small, and the choice of test did not appear to influence the patients' quality of life. It was noted that, even in centers where both tests are used, CT is the cheaper option and more readily available. Whereas no irradiation is administered to the patient with MRI, a disadvantage is that the confined space inside the scanner can be claustrophobic.

Computed tomography

Computed tomography (CT) has been used by several groups to assess arm and leg swelling. The overall cross-sectional area of the limb can be determined at any level, together with that of the constituent muscle and subcutaneous compartments. In primary and secondary lymphedema, CT has shown that the subcutaneous compartment increases in volume markedly, accounting for most of the increase in volume of the limb (*Fig. 5*) (33,34). The skin is also shown to be thickened, but the muscle is relatively unaffected (34,35). The density of the tissues can also be quantified (34). A characteristic, but not pathognomonic, CT appearance of the subcutaneous tissues is the 'honeycomb' pattern. Honeycombing was observed in 10 out of 12 patients with longstanding lymphedema, and is probably caused by thickened/fibrotic interlobular septa (33). A role for CT has been proposed in the

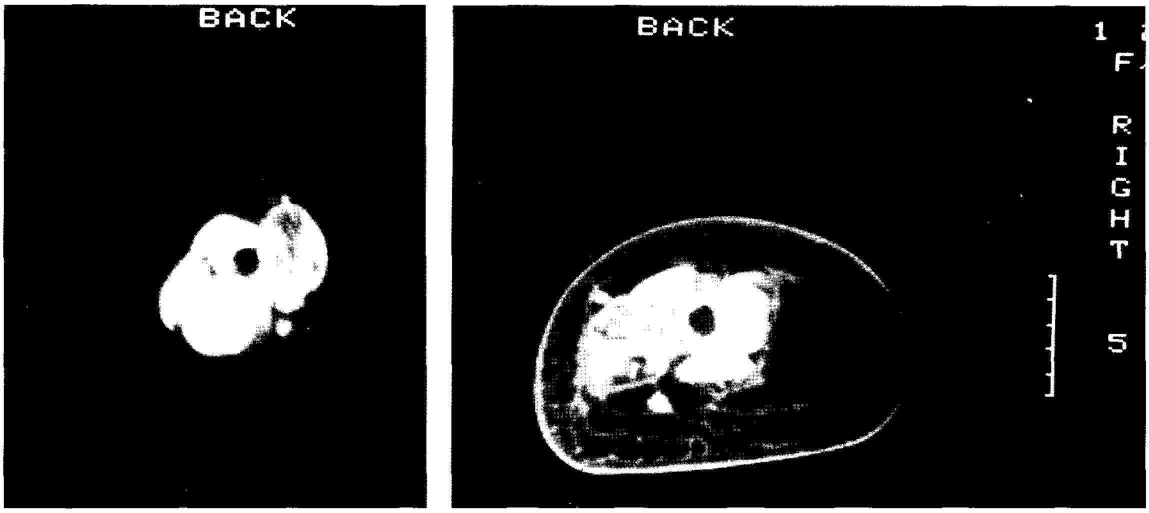

Fig. 5. CT scan of the left (normal) and right (lymphedematous) forearms of a patient with postmastectomy edema (reproduced with permission from Dr CD Collins).

differential diagnosis of the swollen leg, with different patterns occurring in lymphedema, deep vein thrombosis, chronic venous insufficiency, hematomas and popliteal cysts (11,33). The radiation dose is a particular drawback for the repeated use of CT. A similar criticism would apply to dual energy X-ray absorptiometry (DEXA) which has been used to study soft tissue composition (amount of fat and lean tissue) as well as bone mineral density (36).

Ultrasound

Although ultrasonography has been applied in the study of skin disease *per se* (37), it has been little used in lymphedema. It can be used to determine skin thickness, skin having well defined interface echoes towards air and subcutaneous fat. The thickness of the subcutaneous fat layer has been determined in several other conditions (see 38 for review). Doldi et al. (39) examined 91 patients with primary or secondary lymphedema of the arms and legs using ultrasound (3.5-10 MHz linear probes). Thickening of the subcutis was evident, but only minimal skin thickening was observed. Changes in the muscle compartment were less consistent, an increase in volume being present in 75% of patients with primary lymphedema, with the volume unchanged or decreased in 25%. In secondary lymphedema it was increased in 50% of patients but unchanged or decreased in the others. The degree of change in muscle volume was not stated.

The application of ultrasound systems in the assessment of skin tumors and inflammatory disease (in conjunction with histology) and the need for multi-frequency (5-100 MHz) equipment to study the different parts of the skin and subcutaneous tissues has been discussed (37).

Imaging techniques for leg swelling in children have been reviewed (40). These authors considered it mandatory to exclude an underlying vascular abnormality using ultrasound. The ultrasound development of color Doppler imaging has been used to demonstrate venous flow abnormalities in lymphedema (41).

Measurement of Impedance

The impedance spectrum to a small current passed through the body at a range of

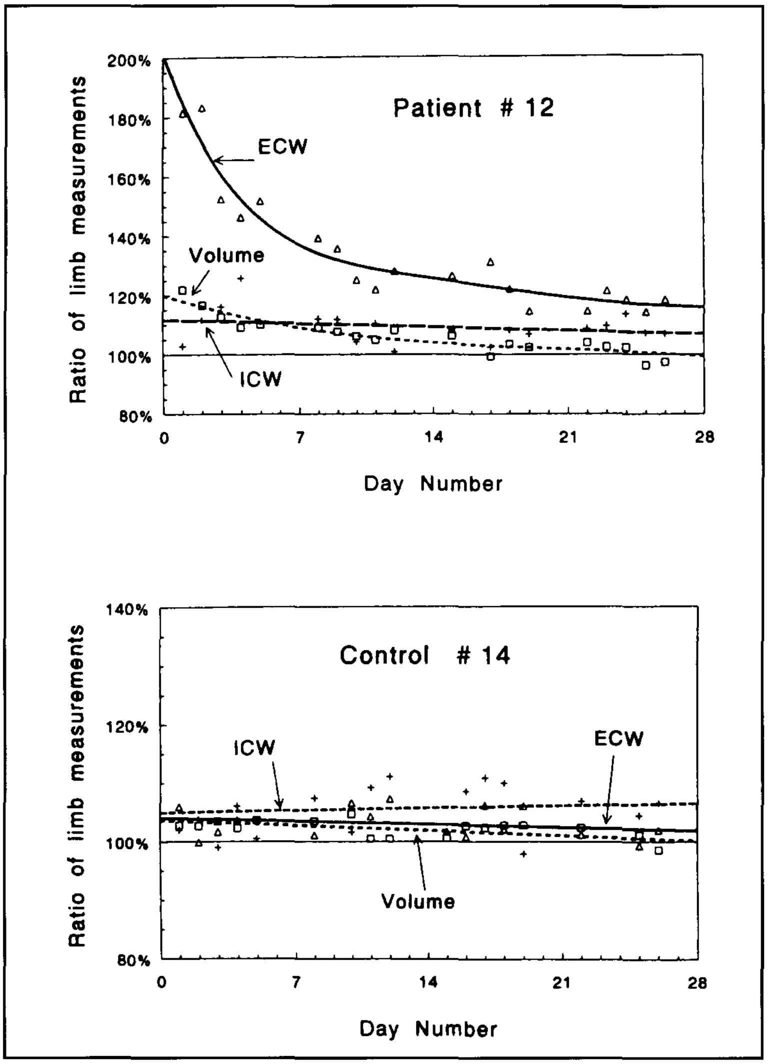

Fig. 6. Extracellular and intracellular water content (ratio of lymphedematous to normal arm), determined by impedance measurement, and arm volume during a 4-week period of treatment (upper panel). Results from the arms of a normal individual are also shown (lower panel; from ref. 9, with permission).

frequencies can be used to provide information on the amount of total body water and total extracellular water. The theory of impedance monitoring assumes that the extracellular and intracellular fluids act as a network of resistors (in series and in parallel), with the cell membranes behaving as an imperfect capacitor (42). Multiple frequency bioelectrical impedance analysis has been used to study the volume of fluid in lymphedematous limbs (43). Impedance at 50 kHz is indicative of total water content, not discriminating between compartments, whereas extrapolated impedance at 0 kHz is a measure of extracellular fluid only. The latter was found to be superior at distinguishing patients with clinically obvious lymphedema from control subjects.

In another study, the same group monitored the arms of women with lymphedema during a four-week program of compression therapy and massage (9) (*Fig. 6*). The lymphedema was described as firm and non-pitting. Significantly more impedance-determined total water and extracellular water was detected in the swollen arm than in the opposite normal arm, and this was not attributable to dominance. During the course of treatment, extracellular water volume responded (i.e., reduced) relatively more than arm volume. The extracellular water volume ratio (swollen arm/normal arm) was higher than the arm volume ratio, and in one patient was still elevated when arm volume had returned to normal at four weeks. Intracellular water volume, calculated from impedance-determined total water minus extracellular water, was increased in the swollen limb, but changed little during treatment. No correlation coefficients between impedances and arm volume were stated. As the authors point out, the availability of indicator dilution techniques to study whole-body water compartments has enabled the development of algorithms to relate total body impedance (Ω) to volume (ml), but such techniques cannot be applied to a body segment and no algorithms exist for the arm and leg. A further drawback is the inconsistency of impedance measurement between different makes of instrument (42).

Recently, impedance analysis has been compared with the step impression biomechanical approach to assess intercompartmental fluid shifts in patients with burns (44).

CONCLUSIONS

A variety of non-invasive methods is now available to assess volume, shape, interstitial fluid mobility, and composition of limbs in a patient with lymphedema, but not all of these methods are suitable for routine clinic use. These methods should enable the effect of new and existing therapies to be evaluated in terms of quality as well as quantity of edema. Lacking at present are longitudinal studies of suitable size to evaluate the quality of swelling over a period of time, e.g., to assess the degree of simple edema versus fibrosis, and its response to treatment by, for example, manual lymph drainage. Investigation of the limbs of patients treated for cancer but without swelling would be useful to study the changes induced by the surgery and radiotherapy *per se*, possibly leading to a means of detecting latent or incipient lymphedema. The biomechanical and impedance approaches would be appropriate here.

Quality of life issues have come to the fore in the management of patients treated for cancer, and lymphedema education and management is now given a higher priority than in the past. More detailed information on the limb and its response to treatment will aid the refinement of existing therapies and the development of new ones.

ACKNOWLEDGEMENT

AWB Stanton is supported by the Medical Research Council.

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