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A new technique for the quantification of peripheral oedema; with application in both unilateral and bilateral cases.

Bruce H. Cornish Ph.D.
Centre for Medical & Health Physics, Queensland University of Technology, Brisbane, Australia

Brian J.Thomas Ph.D.
Centre for Medical & Health Physics, Queensland University of Technology, Brisbane, Australia

Leigh C. Ward Ph.D.
Department of Biochemistry, University of Queensland, Brisbane, Australia.

Cherrell Hirst MBBS
The Wesley Breast Clinic, Brisbane, Australia.

Ian H. Bunce FRCPA
Haematology and Oncology Clinics of Australasia, Brisbane, Australia

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Corresponding Author:
Dr. Bruce H. Cornish
Centre for Medical & Health Physics
Queensland University of Technology
Brisbane 4001
Australia

ph: + 61 7 3864 1581
fax: + 61 7 3864 1521
email: b.cornish@qut.edu.au

Running title: Quantification of peripheral oedema

Abstract:

Current noninvasive techniques for the routine and frequent quantification of peripheral lymphoedema in patients are total limb volume measurement (by water immersion or by circumferential measurements) and bioelectrical impedance analysis (BIA). However both of these techniques require standardising the measurement using a contralateral measurement from the unaffected limb. Hence these techniques are essentially restricted to unilateral lymphoedema. This paper describes the results from a preliminary study to investigate an alternative approach to the analysis of the data from multiple frequency BIA to produce an index of lymphoedema without the need for normalisation to another body segment.

Twenty patients receiving surgical treatment for breast cancer were monitored prior to surgery and again after diagnosis with unilateral lymphoedema. The data recorded were total limb volume, by circumferential measurements, and BIA measurements of both limbs. From these measurements total limb volumes and extracellular fluid volumes were calculated and expressed as ratios of the affected limb to that of the unaffected limb (as described previously, Cornish *et al*, 1996). As well as these established techniques an index of the ratio of the extracellular fluid volume to the intracellular fluid volume was determined. This ECW/ICW index was calculated for both the affected and unaffected limbs at both measurement times.

Results confirmed that the established techniques of total limb volume and extracellular fluid volume normalised to the unaffected contralateral limb were accurate in the detection of lymphoedema ($P < 10^{-6}$). Comparison of the ECW/ICW index from the affected limb post

diagnosis with that from the pre-surgery measurement revealed a significant ($P < 10^{-6}$), and considerable (75%) increase.

The results of this pilot study suggest that by using multiple frequency bioelectrical impedance analysis an index of the ECW/ICW ratio can be obtained and this index appears to have an equal, or better, sensitivity as the other techniques in detecting lymphoedema. More importantly, this index does not require normalisation to another body segment and can be used to detect all types of peripheral oedema including both unilateral and bilateral lymphoedema.

Introduction

Swelling of tissue due to oedema is one of the earliest and classical signs of disease of varying aetiologies such as chronic venous insufficiency, kidney failure, burn injury or disturbed circulation of lymph or lymphoedema. Lymphoedema, also called 'lymphostatic disorder', is characterised by excess protein and oedema in the tissues which leads to chronic inflammation and fibrosis (1). Primary lymphoedema is relatively uncommon. However, secondary lymphoedema is a common sequela of either radiotherapy or surgery, particularly in the treatment of cardiac disorders and also different types of malignancy including breast, uterine, ovarian and prostatic carcinoma (2). It may occur in one or both arms or legs and presents as an enlargement and distortion of the limb(s) and usually accompanied by pain, recurrent infection, reduced mobility and impaired function.

Surgery or radiotherapy to the axillary or inguinal areas brings with it a substantial risk of producing lymphoedema of the arms or legs. This is brought about by coincident unavoidable and irreversible damage to the lymphatic channels. Whilst the true incidence of secondary lymphoedema is unknown the reported incidence of lymph stasis, for example after mastectomy varies from 25.5% to 38.3% depending on the type of surgery and whether or not the patient received radiotherapy (3,4). Treatment of breast cancer alone therefore, given the incidence of the disease, produces a large at-risk population.

Although the assessment of oedema is clearly of clinical importance relatively few objective and accurate techniques for its measurement exist (5,6,7) and these can be broadly classified into three categories.

Imaging techniques: including lymphoscintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) . However these procedures can only be conducted in major facilities using expensive equipment (8). The first two also deliver a small but significant radiation dose to the subject.

Total limb volume measurements: involve measuring the volume of the entire affected limb; and comparing the value with that of the contralateral unaffected limb, in the case of unilateral lymphoedema; or comparing the value with previously recorded measurements, in the case of bilateral lymphoedema. These techniques include volume measurement by perometry, water displacement and longitudinal circumferential measurements (6). However as previously reported (9), these techniques suffer an inherent and unavoidable loss in precision as they measure the volume of the entire limb in order to detect small changes in the volume of the extracellular fluid compartment (which comprises approximately 25% of the total volume).

Bioelectrical impedance analysis. In recent years the technique of bioelectrical impedance analysis (BIA) to detect body composition has been applied to the quantification of unilateral lymphoedema (10,11,12). For an independent review see Mikes *et al*, (13). The procedure involves passing an extremely small electrical current through the body and measuring the impedance (or resistance) to the flow of this current. The electrical current is primarily conducted by the water containing fluids in the body; this water is contained both within the cells, intracellular water (ICW), and external to the cells, extracellular water (ECW). While the total concentration of solute (osmolarity) of both compartments is equal, their electrical properties differ significantly. One important difference is due to the effect of the cell membrane which acts as an insulator at zero or low frequencies thus preventing the electrical current from traversing the ICW. However as the frequency of the current is increased the insulating effect of the membrane decreases and the current passes through both the ECW and ICW.

By measuring the impedance over a range of frequencies, (5 kHz to 1 MHz), using multiple frequency bioelectrical impedance analysis (MFBIA) and applying a theoretically based mathematical model to the measured data the impedance at zero frequency can be determined (for a full explanation see Cornish *et al*, 14). This value cannot be measured directly as an electrical current of zero frequency (DC) cannot traverse the skin / electrode interface. The importance of the impedance at zero frequency is that this value represents the impedance of the ECW fluid **alone** since as explained above the cell membrane acts as an insulator at DC. Hence by using multiple frequency bioelectrical impedance analysis (MFBIA) an estimate of the extracellular fluid volume alone can be obtained. Similarly, by application of the mathematical model the resistance at infinite frequency can be obtained, (10), and subsequently the resistance of the intracellular fluid (ICW).

We have previously demonstrated that MFBIA can be used to quantify the amount of lymphoedema by comparison of MFBIA measures for the affected and non-affected limbs. The MFBIA technique was used to monitor the efficacy of treatment for lymphoedema in patients following surgery for breast cancer (10). The technique was shown to be significantly more sensitive than circumferential measurements and able to detect small differences in the extracellular volumes between the arms of any individual. However an essential feature of the technique is the standardisation of the measurement using the impedance of the unaffected contralateral limb, and also (to a lesser extent) the comparison with the individual's baseline measurement rather than a population normative value.

The need for this individual normalisation of the bioimpedance measures is to account for the variation in anatomical measurement values (*eg* arm length and diameter) between subjects and also the biological variations with time for any given subject, due to diet, physical activity etc. These requirements limit the application of the technique to unilateral lymphoedema and preferably in situations where pre-surgery or pre-treatment measurements are known. The fact that the bioimpedance measures from any individual need to be normalised before comparison with any reference value appears to be an unavoidable necessity. However, if there was another reference measurement from the same subject which could account for these variations, these limitations would be eliminated thus enabling the technique to be applied to a much larger number of clinical cases including bilateral oedema in general, as may occur, for example, in chronic venous insufficiency. This paper presents the results of a preliminary study investigating an alternative concept in the analysis of the MFBIA data which may prove to considerably enhance and expand the application of the technique in the monitoring of all types of peripheral oedema.

Hypothesis: During the early stages of lymphoedema there is little change to the lean tissue mass (and therefore ICW) of the limb and only the volume of the extracellular fluid (ECW) increases. Hence, by normalising measures of ECW against ICW of the same limb, a reliable technique for the detection of lymphoedema can be obtained without relying upon measurements from another body segment.

Subjects and Methods

Twenty (20) patients who were treated for breast cancer and had subsequently developed lymphoedema had measurements (described below) recorded prior to surgery and again after clinical confirmation of the condition. All volunteers gave full, written, informed consent and the research project was conducted with the approval of the Human Research Ethics Committee of the Queensland University of Technology.

Limb volume measurement:

Total limb volume was determined by the established procedure using the measured circumference at fixed intervals along the limb. The accuracy and validity of this procedure has been reported as being equivalent to that of water displacement techniques (15). Circumferential measurements of the limb using a tape measure were recorded at 10 cm intervals from the pisiform prominence of the wrist up to a total distance of 40 cm. Volumes of each 10 cm segment of the limb were calculated using the average of two circumferential measures and assuming a simple cylindrical geometry. Total limb volume was calculated as the sum of the volumes of the four individual segments.

Total limb volume was calculated from the circumferential measurements for each individual, and the ratio of the limb volumes recorded.

$$\frac{Va}{Vu} = \frac{Volume\ \textbf{at risk limb}}{Volume\ \textbf{'normal' limb}} \qquad \text{Eqn 1}$$

Bioimpedance measurement:

Impedance measurements of each limb were recorded, after a short period of rest, using a multiple frequency bioimpedance meter (SFB3 bioimpedance monitor manufactured by

SEAC, Brisbane, Australia) with the subject lying supine, arms outstretched and slightly abducted from the body with the palms facing down. Two 'measurement' electrodes were placed at either end of the 40 cm length over which the circumference measurements were made and 'drive' electrodes were placed 8 to 10 cm distal to the measurement electrodes (10). These electrode sites were chosen in preference to the standard shoulder to wrist sites, (11), so that direct comparisons could be made between the volumes measured by the circumference method and by the MFBIA technique. The software supplied by the manufacturer was used to determine the resistance of the limbs at zero frequency and at infinite frequency (the explanation of theory underpinning this software is explained in Cornish *et al*, 14). The resistance of the intracellular fluid (R_i) was calculated as the parallel difference between the total resistance (at infinite frequency) and the resistance of the extracellular fluid (R_0, the resistance at zero frequency) (16).

The Volume of fluid measured is given by:

$$V = \frac{\rho l^2}{R} \qquad \text{Eqn 2}$$

where: Δ = resistivity of the fluid; l = length of segment; and R = measured resistance.

Given the length is constant for the ECW and ICW measurements of the same region, the ratio of ECW / ICW is then:

$$\frac{ECW}{ICW} = \frac{\rho_{ECW} \; R_i}{\rho_{ICW} \; R_o}.$$

Assuming that the resistivities of the extracellular and intracellular fluids are relatively constant (17,18), the ratio of the resistances can be used as an accurate 'index' of the ratio of the fluid compartments. Hence

$$\frac{R_i}{R_o} = \left[\frac{ECW}{ICW}\right]^{index} = \frac{\rho_{ICW}}{\rho_{ECW}}\frac{ECW}{ICW} = (constant)\frac{ECW}{ICW} \qquad \text{Eqn 4}$$

Results:

Characteristics of the subject group are listed in table I.

table I here

The volume of each limb was calculated from the circumferential measurements and the ratio of the volume of the at risk limb to that of the contralateral normal limb determined. The mean and standard deviation of these ratios were calculated for both measurement times (pre-surgery and after diagnosis of lymphoedema). The second measurement time was within one month after clinical confirmation of the disorder. Similarly the means and standard deviations for the ECW/ICW indicies for the at risk limb and contralateral normal limb were also found. For the purpose of comparison with the standard bioimpedance method, (as described by Cornish *et al*, 10), the ratio of the resistances at zero frequency R_o (normal limb) / R_o (at risk limb) were also calculated (note that resistance is inversely related to fluid volume, *cf.* equation 1). Table II summarises these data from the two measurement times.

table II here

Tests for the difference between means (paired *t* tests) were conducted to test for statistical significance between the pre-surgery and post diagnosis value. For the volume ratio, ECW/ICW index of the affected limb and the R_o ratio, all tests showed a significant increase

($P < 0.00001$). However there was no significant change in the ECW/ICW index for the contralateral normal limb ($P = 0.8$). The individual data (of each ratio described in table II) for each patient at each measurement time are represented in figure 1.

figure 1 here

Discussion:

The ECW/ICW index values determined pre-surgery were almost identical for the at risk and the contralateral normal limbs. This is in agreement with both the volume and impedance R_o ratios (both equal to 1.0). After clinical diagnosis of lymphoedema in the at risk limb both the volume ratio as determined by circumferential measurements and the bioimpedance ratio of R_o values were elevated and in excess of the diagnostic threshold used in previous studies (11). Hence both of these detection techniques supported the clinical diagnosis of lymphoedema. The ECW/ICW index recorded at this time was also considerably elevated, a mean of 4.39 compared with a mean value of 2.51 pre-surgery. This would strongly suggest that the ECW/ICW index could also be used as a detection technique for the early onset of the condition.

Two of the patients recorded a slightly elevated ECW/ICW index in the contralateral normal limb at time 2 (post diagnosis). A closer examination of the data revealed an expected decrease in the R_o value from the at risk limb (time 2 *cf* time 1); but also a similar, but somewhat smaller, decrease in the R_o value from the normal limb. The measured R_i values from both limbs at time 2 were not significantly different from those measured at time 1. Both of these patients had been clinically diagnosed with lymphoedema approximately 3 weeks prior to the time 2 measurement and had begun an exercise and massage regimen. One possible explanation for the elevated ECW/ICW index in the normal limbs of these patients is that the short term effect of exercise and massage, immediately prior to the measurements, is to shift some of the lymphatic fluid from the affected limb across to the unaffected limb. This is an interesting hypothesis and warrants further investigation.

The increase in the mean value of the ECW/ICW index with the onset of lymphoedema appears to be considerably larger than the concurrent increase in the volume ratio as determined by circumferential measurements and also the bioimpedance ratio of R_o values. This is also evident in figure 1, as is the much larger range of individual ECW/ICW values compared with the volume and R_o ratios at time 2. At first this may appear to suggest that the ECW/ICW index technique has a much greater sensitivity. However these effects may be simply a result of a scaling factor. As equation 1 describes the ECW/ICW index also incorporates a constant, the ratio of the resistivities of the body fluids. A further study is currently planned to monitor the measured values of the ECW/ICW index (together with other established techniques) during the treatment of subjects with lymphoedema. The results of this further research should help clarify this question of a possible increased sensitivity.

An important feature of this new ECW/ICW index is that it does not require normalisation of the measurement from the limb being assessed with a normal contralateral limb. The reference value used in this index is that of the intracellular fluid within the same measurement region. Hence the technique can be readily applied to bilateral lymphoedema. Indeed the technique should have application to the assessment of oedema in general in any body segment, such as that occurring in primary oedema or post-surgical oedema (19).

Conclusion:

There are a number of techniques which are used for the detection and monitoring of lymphoedema. However there are relatively few, low cost techniques which can be readily performed on subjects. These include total limb volume (by immersion or by circumferential measures) and bioelectrical impedance analysis. However both of these techniques require standardising the measurement using a contralateral measurement from the unaffected limb. Hence these techniques are essentially restricted to unilateral lymphoedema. The results of this pilot study suggest that by using multiple frequency bioelectrical impedance analysis an index of the ECW/ICW ratio can be obtained and this index appears to have an equal, or better, sensitivity as the other techniques in detecting lymphoedema. More importantly, this index does **not** require normalisation to another body segment and can be used to detect all types of peripheral oedema including both unilateral and bilateral lymphoedema.

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Table I. Subject Characteristics (n = 20).

Age – median (range)	52 (25 - 76) yrs
Dominant limb (L/R)*	1 / 19
Left arm lymphoedema (Dom - L / R)	12 (1 / 11)
Right arm lymphoedema (Dom - L / R)	8 (0 / 8)

* As defined by the subject.

Table II. Means and (SD) of the data collected pre-surgery and post diagnosis.

Measurement	time 1 Pre-surgery	time 2 lymphoedema diagnosed
$[ECW / ICW]^{index}_{normal\ limb}$	2.49 & (0.38)	2.48 & (0.68)
$[ECW / ICW]^{index}_{at\ risk\ limb}$	2.51 # (0.37)	4.39 # (1.55) [range 2.98 – 8.10]
$R_{O\ normal}$ / $R_{O\ at\ risk}$	1.01 $ (0.05)	1.26 $ (0.17)
$V_{at\ risk\ limb}$ / $V_{normal\ limb}$	1.00 * (0.03)	1.14 * (0.08)
Statistical differences: Paired t-tests *cf.* times 1 and 2 :- # $ * P < 0.00001 & P = 0.8		

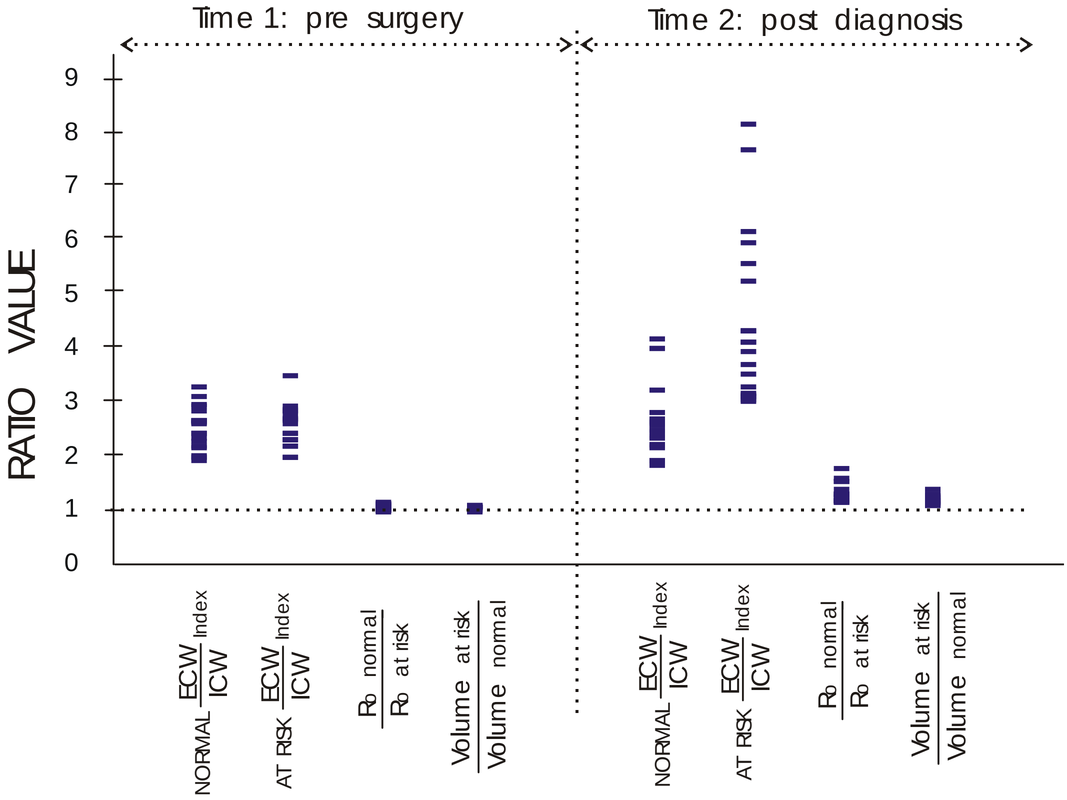
Time 1: pre surgery
Time 2: post diagnosis
RATIO VALUE
0
1
2
3
4
5
6
7
8
9
NORMAL ECW/ICW Index
AT RISK ECW/ICW Index
Ro normal / Ro at risk
Volume at risk / Volume normal
NORMAL ECW/ICW Index
AT RISK ECW/ICW Index
Ro normal / Ro at risk
Volume at risk / Volume normal

Figure 1.

Distribution of values (both pre-surgery and post diagnosis) of the ECW/ICW index for both limbs compared with that of the standard limb volume ratios and the previously reported bioimpedance ratio.