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EARLY DIAGNOSIS OF LYMPHEDEMA USING MULTIPLE FREQUENCY BIOIMPEDANCE

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ABSTRACT

Multiple frequency bioelectrical impedance analysis (MFBIA) has previously been shown to provide accurate relative measures of lymphedema in the upper limb of patients (1). This paper reports the results of a three year prospective study to evaluate the efficacy of MFBIA to predict the early onset of lymphedema in patients following treatment for breast cancer.

Bioelectrical impedance measurements and circumferential measurements of each upper limb were recorded in healthy control subjects (n=60) to determine the normal range of the ratio (dominant/non-dominant) of extracellular and total limb volumes respectively. Patients undergoing surgery for the treatment of breast cancer were recruited as the study group; MFBIA and circumferential measurements were recorded pre-surgery, one month post-surgery and then at two month intervals for 24 months.

One hundred and two patients were recruited into the study. Twenty patients developed lymphedema in the 24 months follow up period of this study. In each of these 20 cases MFBIA predicted the onset of the condition up to 10 months before the condition could be clinically diagnosed. Estimates of the sensitivity and specificity were both approximately 100%. At the time of detection by MFBIA, only one of the patients returned a positive test result from the total limb volumes determined from the circumferential measures. These results confirmed the suitability of the MFBIA technique as a reliable diagnostic procedure for the early detection of lymphedema.

Acquired or secondary lymphedema is a subcutaneous accumulation of protein-rich extracellular fluid resulting from damaged or blocked lymphatic vessels. Frequently its progression passes through three phases of development from, first, edema with pitting, which may be alleviated by simple limb elevation or massage therapy, through a firm non-pitting edema, possibly with inflammation and fibrosis, to a final stage characterized by hardening of the skin and overproduction of connective tissue (2). Swelling of the limb occurs, which may reach gross proportions and lead to loss of function. Even in the initial stages the patient may experience varying levels of pain and discomfort.

Secondary lymphedema is a relatively common consequence of treatment for different types of malignancy, including breast, uterine, ovarian and prostatic carcinoma. Surgery or radiotherapy to the axillary or inguinal areas brings with it a substantial risk of producing lymphedema of the arm or leg. This is brought about by coincident, unavoidable and irreversible damage to the lymphatic channels (3). The condition usually occurs in one limb and presents as enlargement and distortion of the limb, pain, recurrent infection, reduced mobility and impaired function. The reported incidence of lymphedema following treatment, (surgical plus radiotherapy), for breast cancer has been reported to be as high as 25 to 38% (3-6).

Lymphedema is incurable, often progressive, disfiguring, disabling and has considerable adverse psychosocial effects. However the condition can be successfully treated and the advancement of the condition arrested. There has been a variety of treatments for the condition over past years including microsurgery and drug therapy. The current, accepted and preferred method of treatment is complex physical therapy: a regimen of exercises, compression bandaging and massage (7). As this severely debilitating condition is both incurable and progressive, the earlier it can be detected and treatment commenced, the sooner its progression can be arrested resulting in a minimization of the physical and psychological debilitations of the condition (4,8).

Current diagnosis of lymphedema is performed by a health professional and usually incorporates the identification of the symptomatic characteristics (*viz.* a firm non-pitting swelling). However, while this can positively identify the presence of lymphedema it will only yield a positive test result when the condition has progressed to the second stage where the physical symptoms are externally noticeable. A method of reliably and objectively diagnosing the condition in its earliest stage is needed if the treatment and management of the disorder is to result in the optimum outcome for the patient.

Objective measures of lymphedema

Several methods have been used to measure the extent of lymphedema. None of these methods provides an absolute measure of lymphedema but rather a comparison of the affected limb with that of the unaffected limb or some other reference value such as a pre-surgery measurement value. These techniques include:

1) Total limb volume measurement by water displacement (9), conic geometry (10) or perometry (11). In the normal healthy person the volume of the extracellular subcompartment is approximately 25% of the total volume. Hence these methods which measure total limb volume inherently suffer from a sensitivity four times less than any technique which measures extracellular volumes directly.

2) The measurement of tissue changes by tonometry (12). Lymphedema is not simply an increase in volume but also an alteration of the dermal and subcutaneous tissues accompanying the increase in protein concentration of the extracellular fluid. Such changes alter the resistance of the tissue to compression and a measure of this resistance can be used to reflect the extent of the changes. While this technique provides valuable information complementary to volume measurements, it is information about changes associated with lymphedema after the initial stages and as such may not useful in the early diagnosis of the condition.

3) Extracellular fluid volume measurement by magnetic resonance imaging (MRI) or computer tomography (CT). These techniques have also been used to determine the cross-sectional composition of the limb at small increments along the limb length (13,14). However, practical application of the procedure is severely limited due to both cost and availability. For a more detailed review of the above methods the reader is referred to Stanton et al. (15)

4) Extracellular fluid volume measurement by Bioelectrical Impedance Analysis. Bioelectrical impedance analysis (BIA), a method first used to assess body composition by nutritionists (16) has also been used successfully to quantify lymphedema (17,1) and is the subject of this report.

Bioelectrical impedance analysis (BIA) is a noninvasive technique first used in 1969 to measure the total water content of the body (18). 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 capacitive effect of the membrane decreases and the current passes through both the ECW and ICW.

Until the early 1990s, almost all BIA measurements were recorded at a single frequency of 50 kHz. At this frequency the current easily penetrates the cell membrane and the measured impedance is due to that of both ECW and ICW. Hence the BIA measurement (combined with the length of the body) can be used to estimate the total volume of water (ICW + ECW) within the body.

In recent years the BIA technique has been further developed to measure the impedance over a range of frequencies, typically 4 kHz to 1000 kHz. By 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* (19)]. This value cannot be measured directly as an electrical current of zero frequency (DC) cannot, in practice, 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.

We have previously demonstrated that MFBIA can be used to quantify the amount of lymphedema by comparison of MFBIA measures for the affected and non-affected limbs. The MFBIA technique was used to monitor the efficacy of treatment for lymphedema in patients following surgery for breast cancer (1). The technique was shown to be significantly more sensitive than circumferential measurements and able to detect very small differences in the extracellular volumes between the arms of any individual. The sensitivity demonstrated by the MFBIA technique suggested that the procedure permits the diagnosis of lymphedema in the first stage of its progression and hence before current techniques of diagnosis. The hypothesis tested in the present study was that multiple frequency bioelectrical impedance analysis (MFBIA) can be used for the early diagnosis of unilateral lymphedema (i.e., before the condition can be clinically diagnosed) resulting from treatment for breast cancer. To test this hypothesis a recent study was designed to monitor patients for a period of two years after their diagnosis and treatment for breast cancer.

METHODS AND SUBJECTS

One hundred and two patients (age 25 to 82 years) were recruited, and completed, the research program. A group of 60 female volunteers in a similar age range acted as a control group, and limb volume and bioimpedance measurements were recorded to determine the variation of these measurements in the healthy population. These measurements were also recorded, on a subset of the control group (n=25), after an interval of approximately 2.2 years to determine any drift in measurements over time. All patients diagnosed with breast cancer at the Wesley Breast Clinic, and living within 50 km of central Brisbane, were identified and after

TABLE 1
Characteristics of the Patient and Control Groups

	Patients (n = 102)	Controls (n = 60)
Age – median (range)	51 (25-82) yrs	53 (27-84) yrs
Dominant limb (L/R)*	10/92	0/60
Left arm at risk ‡ (Dom - L/R)	52 (8/44)	–
Right arm at risk ‡ (Dom - L/R)	50 (2/48)	–

*As defined by the subject.
‡Determined by the side receiving surgery

approval of their prospective surgeons were invited to join the study. This invitation included a detailed explanation of the aims and protocol of the study and information about arm lymphedema. A second tier of criteria was applied, after surgery, for continuation of volunteers in the study; these included pathology confirmation that the tumor was malignant and that surgery included axillary dissection. In this group of patients, the measurements described below were recorded prior to surgical intervention, one month post surgery, then every two months up to 24 months. All inductees to the program gave full, written, informed consent and the research project was conducted with the approval of the Ethics Committee of the Wesley Hospital, Brisbane.

The volunteer acceptance rate into the study was exceptionally high with over 85% of patients approached joining the study. A total of 107 patients, having satisfied all selection criteria, were accepted into the study. However, five patients were subsequently excluded due to further medical complications unrelated to lymphedema, leaving a study cohort of 102 subjects.

Limb Volume Measurement

Total limb volume was determined by the established procedure using the measured circumference at fixed intervals along the limb. 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. The accuracy and validity of this procedure has been reported as being equivalent to that of water displacement techniques (10).

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 seated, arms outstretched on a foam cushion and level with the shoulders 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 (1). These

TABLE 2
Measurements From the Control Group
Mean Values (SD)

		Volume* (by circ.)	Resistance at zero freq.
t = 0	Dominant arm (right)	1792 (340) [ml]	289 (32) [Ω]
n=60	Non-Dominant arm (left)	1741 (350) [ml]	299 (34) [Ω]
	Ratio (Dom. / Non-Dom)	1.03 (0.047)	0.964 (0.034)
A subset of these 60 controls were remeasured after approximately 2.2 years.			
t = 0	Dominant arm (right)	1700 (250) [ml]	285 (27) [Ω]
n=25	Non-Dominant arm (left)	1632 (240) [ml]	296 (28) [Ω]
	Ratio (Dom. / Non-Dom)	1.041 (0.043)†	0.962 (0.029)‡
t = 27 mths	Dominant arm (right)	1697 (250) [ml]	293 (26) [Ω]
n=25	Non-Dominant arm (left)	1630 (240) [ml]	303 (29) [Ω]
	Ratio (Dom. / Non-Dom)	1.043 (0.0475)†	0.964 (0.032)‡

*Volume of the 40 cm length of the arm from the wrist.
†Ratio at t = 27 not significantly different from that at t = 0, (paired t-test [two-tail] P > 0.9).
‡Ratio at t = 27 not significantly different from that at t = 0, (paired t-test [two-tail] P > 0.9).

electrode sites were chosen in preference to the standard shoulder to wrist sites (20) 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 hence the relative extracellular fluid volume of each (1). For each of the volume measures (ECW by MFBIA and total limb volume by circumference), volume of the 'at risk' limb was expressed as a ratio of the volume of the opposite limb.

Data Analysis

At each post-surgery measurement time the patient's ECW ratio and limb volume ratio were compared with the corresponding pre-surgery value which was used as a reference value. A ratio value greater than 3 standard deviations (as determined from the control group) from this reference value was deemed predictive of the onset of lymphedema and the measurement repeated one week later. When the second measurement yielded a 'positive' test result, the patient was referred to her physician for clinical confirmation and possible treatment.

RESULTS

Table 1 details the relevant characteristics of the control and patient groups.

The descriptive statistics of limb volume

TABLE 3
Summary of the Analysis of the Data From the Patient group

Number of patients monitored	102
axillary dissection	34
axillary dissection plus radiotherapy	68
Number of patients clinically diagnosed with lymphedema:	20
axillary dissection only	7
axillary dissection plus radiotherapy	13
time between surgery and onset of disorder	mean 10 months (range 3 to 21 months)
Number of patients with lymphoedema first identified by:-	
— positive result by MFBIA test	22*
— positive test result by limb volume test (circumference)	1†
Mean (SD) value of MFBIA ratio at first positive MFBIA test	1.20 (0.09)
Mean (SD) value of volume ratio at first positive MFBIA test	1.09 (0.06)
Time of clinical confirmation (cf MFBIA positive test)	
(a) immediately following MFBIA test	8
(b) 1 month following MFBIA test	3
(c) 2 months following MFBIA test	4
(d) 4 months following MFBIA test	3
(e) 6 months following MFBIA test	1
(f) 10 months following MFBIA test	1

* 20 of these 22 patients were those who developed lymphedema (see comment in discussion).
† at the time of detection by MFBIA.

and MFBIA measurements recorded in the control group are summarized in *Table 2*. The standard deviation of each of these measures was used to determine the threshold variation for the early detection of the disorder. This threshold was set as three standard deviations from the baseline measures recorded for each patient. Hence an MFBIA measured ratio greater than 0.102 from the patient's pre-surgery measurement was deemed indicative of the early onset of lymphedema. Similarly a volume (by circumference) ratio greater than 0.139 from the patient's pre-surgery measurement was deemed a 'positive' test result.

A two tailed, paired t test was used to test for any significant changes in the volume or impedance ratio in a subset ($n = 25$) of the control group. No statistically significant difference was found, ($P > 0.9$).

A summary of the data analysis from the patient group is presented in *Table 3*. As indicated in *Table 3* only one patient of the

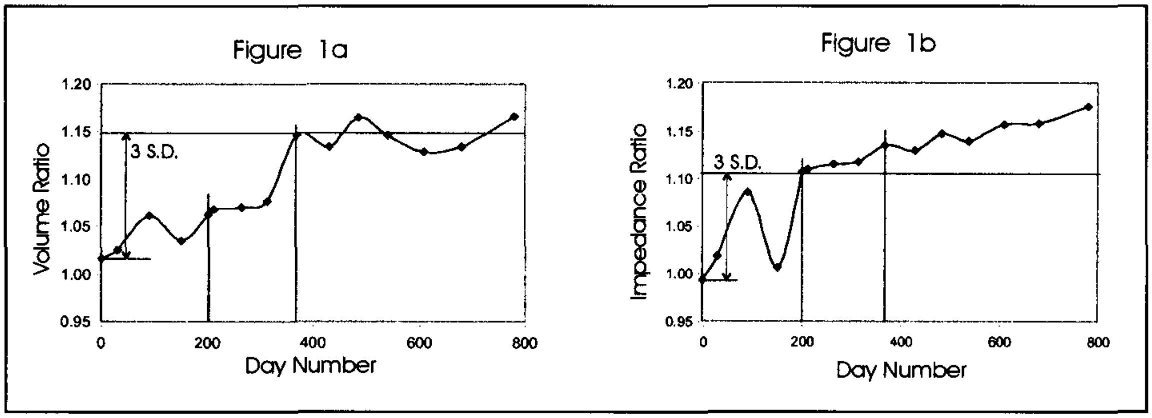

Figure 1. Variation in volume ratio (a), and impedance ratio (b), over the two year period for patient (code "T1O").

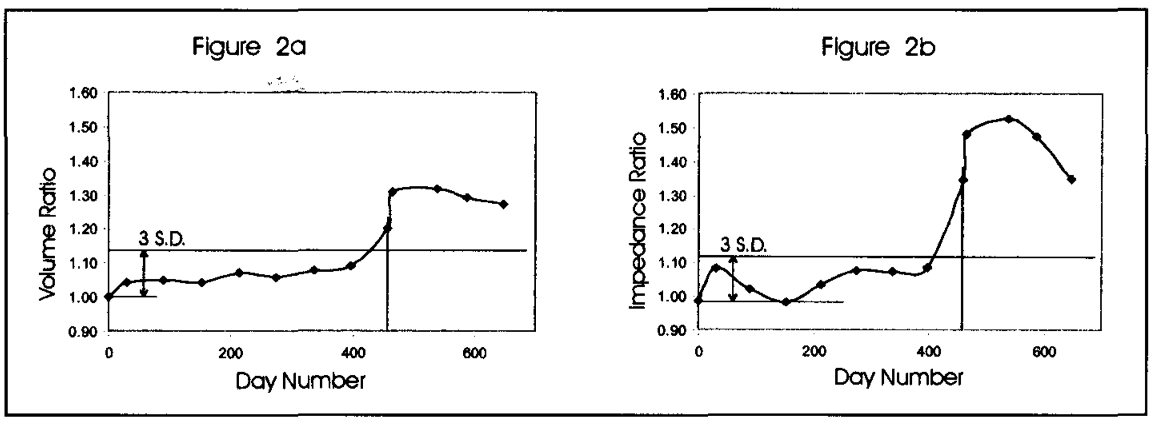

Figure 2. Variation in volume ratio (a), and impedance ratio (b), over the two year period for patient (code "S2T").

20 developing lymphedema was identified, at the time of detection by MFBIA, using the volume determined by circumferential measurements. This particular patient received clinical confirmation of the disorder (by her physician) immediately following the research project visit. No patient at any time yielded a 'positive' volume measurement together with a 'negative' MFBIA measurement.

Figs. 1 and 2 show the variation in the measurements over the two year period for two of the patients who developed lymphedema. Patient number T1O was the particular individual in which both the circumferential volume test and the MFBIA test returned a positive test result at the same time, (t=458 days); this was followed by clinical confirmation at t=463 days. Patient number S2T yielded a positive MFBIA test result at day number 203 and again at t=214 days. However, clinical examination at day numbers 218 and 280 failed to confirm the presence of lymphedema. At day 370 the circumferential volume yielded a positive test result, and the presence of lymphedema was subsequently confirmed clinically at day 372. *Fig. 3* shows the variation in measurements of a patient (number B2E) in the study who did not develop lymphedema within the timeframe of the study.

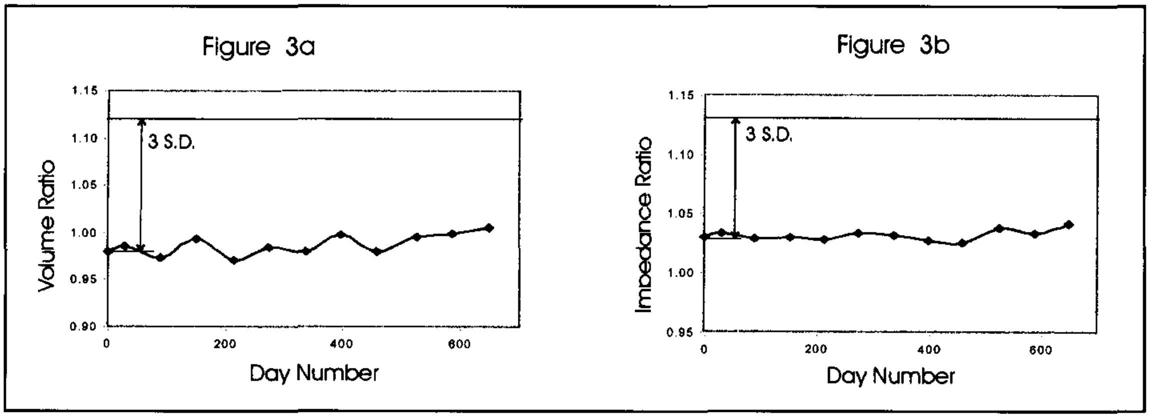

Figure 3. Variation in volume ratio (a), and impedance ratio (b), over the two year period for patient (code "B2E").

DISCUSSION

The exceptionally high acceptance rate of volunteers is indicative of the significant impact this disorder can have upon patients and also their family and friends. The incidence of lymphedema developing within the first two years after treatment for breast cancer in this study was 20%. This value may be even greater if the patients were monitored for a period greater than 24 months. This rate of incidence is in agreement with the results cited in the review of Petrek & Heelan (6) which found the incidence to be as high as 30%. The mean time between surgery and onset of the disorder was found to be 10 months in this group of patients. This is considerably shorter than the mean delay time of 3.5 years reported previously (7). The most probable reason for the much shorter development time noted in this study is a direct result of the early detection of the disorder achieved by the MFBIA technique which resulted in referral for clinical assessment.

The time lag between the early detection of the condition and clinical confirmation varied between 0 and 10 months. It should be noted that in the patients where a zero time lag was recorded, this clinical confirmation was sought as a result of the positive MFBIA test result. Without this stimulus the clinical diagnosis of lymphedema in these patients may well have been considerably later in the progression of the condition. There were five patients where clinical diagnosis, although sought approximately every two months, was not confirmed until 4 to 10 months after the early detection by MFBIA. This demonstrates the good sensitivity of the MFBIA technique although an alternative explanation for this may be that in these patients the condition was developing very slowly or quite possibly the patient may well have commenced some form of early prevention strategy such as exercise, etc.

The zero false negative rate of the MFBIA technique is indicative of an exceptional sensitivity (100%), ([true positives/true positives + false negatives] 21) . This compares with (in this study) a sensitivity of only 5% for the circumferential technique for the purpose of early diagnosis. The most probable reason for this considerable difference in sensitivity is the fact that the MFBIA technique provides a measure of the difference in extracellular fluid only; whereas the circumferential technique compares only total limb volumes.

Two patients in the study yielded positive results for the MFBIA test on consecutive occasions but showed no apparent clinical signs of lymphedema. Measurements from subsequent visits yielded negative test results. These two incidents have been classified as false positive results for the purpose of this study. However, they may well have been examples where the onset of lymphedema regressed without treatment. Despite these two false positive results the specificity of the MFBIA test is 98% ([true negatives/true negatives + false positives] 21) .

CONCLUSION

This study has confirmed that multiple frequency bioelectrical impedance analysis is an extremely sensitive and reliable technique for the early detection of lymphedema. The 100% sensitivity of the MFBIA technique demonstrated is a vast improvement on the presently used circumferential technique which proved to have a sensitivity of only 5%, for the purpose of early detection. The MFBIA technique is completely noninvasive, highly reproducible (22), can be repeated as frequently as desired and the entire measurement procedure takes approximately 2 minutes. The technique does not require special operator skills and has minimal inter-operator variability. These features combined with its demonstrated efficacy in the detection of lymphedema make it an invaluable diagnostic tool for the monitoring of patients at risk of developing lymphedema following treatment for breast cancer. The application of the MFBIA technique in the monitoring of breast cancer patients will enable the implementation of early treatment for lymphedema thus providing for the first time the opportunity for an objective evaluation of the benefits resulting from early treatment intervention.

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Editor's Note:

For more information on this subject, the reader may wish to consult the following additional references:

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