Breast Cancer Research and Treatment 38: 169-176, 1996. @ 1996
Kluwer Academic Publishers. Printed in the Netherlands.

Report

Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes

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Key words: lymphoedema, bioimpedance monitoring, treatment, post-mastectomy

Abstract

The treatment of lymphoedema includes a combination of massage, compression bandaging, and exercise. To date the most common technique of assessing the efficacy of treatment has involved estimating the total limb volume from circumferential measurements at fixed intervals along the limb. This study investigated the application of multiple frequency bioelectrical impedance analysis, MFBIA, to monitor the volume of lymphoedema in the upper limb of patients who developed this disorder following surgery for cancer of the breast. Daily measurements of both circumference and impedance of both the affected and unaffected limbs were recorded for 20 patients throughout their 4 week treatment programmes. Twenty control subjects were also monitored daily over a similar 4 week period. Prior to the commencement of treatment the bioimpedance technique detected a significant ($P < 0.01$) asymmetry between the two limbs of the control subjects, associated with handedness ($P < 0.001$). Circumferential estimates of limb volumes in the control group detected no asymmetry. Impedance measures of extracellular fluid showed all of the patients to lie outside the 95% confidence interval determined from the data of the control group. The trends of the impedance measures and the circumferential estimates of volume throughout the 4 week program were found to be significantly different ($P < 0.05$); MFBIA exhibiting a greater sensitivity in the detection of lymphoedema. The results demonstrate that MFBIA is significantly more sensitive than circumferential measurement both in the early diagnosis of lymphoedema and in monitoring change.

Introduction

Lymphoedema is a condition characterised by excess protein and oedema in the tissues caused by reduced lymphatic transport capacity and/or reduced tissue proteolytic capacity in the presence of a normal lymphatic load. Lymphoedema normally occurs in the limbs. Apart from enlargement and distortion of the limb, patients suffer pain, reduced mobility, and impaired limb function.

Lymphoedema is an incurable, progressive, often disfiguring and physically-disabling disorder, the course of which can, however, be arrested by intervention, preferably at the earliest opportunity. While 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 [15]. Complex physical therapy, a regimen of ex-

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ercises, compression bandaging, massage, and other physical techniques is reported to be effective in reducing limb volume [7,3], and in improving the quality of life, function, and body image of patients [2,12].

Although lymphoedema has been thoroughly described in physiological and biochemical terms, no published literature has been found describing a recognised sensitive, quantifiable, and scalable measure of the severity of the condition or its response to therapy. At present, the best index appears to be an estimate of the excess size of the affected limb compared with that of the unaffected limb as measured either by circumferential measurements or immersion [9]. Both methods have difficulties. Circumferential measurements are time consuming (5-7 min) and require a series of measurements to be made at precisely defined locations along the length of the limb. Immersion is messy, undignified, and even more time consuming. Both procedures measure total limb volume and only indirectly the actual hydrostasis of the limb. Indeed, in some individuals the disparity in limb size may be due in part simply to hand-use preference.

We have previously shown [16] that multiple frequency bioelectrical impedance analysis (MFBIA) has the capability to determine quantitatively the degree of fluid accumulation in the arms of postmastectomy patients having lymphoedema. The MFBIA technique is a non-invasive procedure which involves passing a very small AC current through the body segment and measuring the impedance to the flow of current at frequencies from 4 kHz to 1 MHz. From this impedance spectrum the resistance at zero frequency, R_o, and the impedance at the characteristic frequency, Z, can be -determined [4]. Previous research has demonstrated that total body water (TBW) and extracellular water (ECW) are inversely proportional to Z_c, and R_0, respectively [14], and Z_c and R_O have been shown to be reliable predictors of TBW and ECW [5,6]. The MFBIA instrument is relatively inexpensive, is simple to apply, and measurements can be readily performed after a short period of training by non-technical staff Details of our procedure in the measurement of the severity of lymphoedema have been provided previously [16].

This present study extended our earlier work [16] and investigated the application of MFBIA as a monitoring tool of the efficacy of treatment of lymphoedema of the arm of post-mastectomy patients.

Experimental

Subjects

The subjects were 20 female patients, randomly chosen from those attending the Lymphoedema Management Program of The Wesley Clinic for Haematology and Oncology. All patients had developed at least grade two lymphoedema of the upper limb characterised by firm, non-pitting oedema, following surgery and/or radiotherapy for carcinoma of the breast (unilateral, either side). A group of 20 female volunteers from the clinic and university staff acted as the control group. Clinical and anthropometric data are presented in Table 1. The purpose of the study was fully explained to all participants and written consent obtained. The study was ap-

Table 1. Clinical and anthropometric data of all participants. Values expressed as median (range)

	Patients (n = 20)	Controls (n = 20)
Age (years)	60(32- 78)	40(29- 56)
Weight (kg)	81 (50-100)	64(47- 90)
Height (cm)	167 (153-180)	170 (156-180)
BMI’ (kg m-’)	27.2 (19.5-38.1)	22.5 (18.1-29.7)
Oedematous limb (L/R)	13/7	-
Dominant limb (UR)*	1/19	2118

#Body Mass Index = body weight/height^2

* As defined by the subject.

proved by the Human Ethics Committees of the Queensland University of Technology, the University of Queensland, and the Wesley Hospital.

Method

The program [12] for the treatment of lymphoedema provided by the clinic aims at the self-management of the condition by the patient but begins with an intensive daily schedule that includes compression therapy, massage, and compression bandaging for the first four weeks. During these four weeks the patient is educated in the self-management of her condition and encouraged to maintain the treatment. Subsequent to this four week intensive therapy period, quarterly clinical reviews are conducted to advise patients of their progress in the self-management of the condition. This study involved the daily comparison of impedance with the circumferential measurement technique of estimating limb lymphoedema during the initial phase of the treatment. The method of determining the total limb volume was 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 [9]. 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.

Impedance measurements of each limb were recorded, after a short period of rest, using a swept frequency bioimpedance meter (model SFB2, SEAC Brisbane, Australia) with the subject supine, limbs slightly abducted and palms flat on the couch. The two measurement electrodes were placed at either end of the 40cm length over which the circumference measurements were made. These electrode sites were chosen in preference to the standard shoulder to wrist sites [13], so that direct comparisons could be made between the volumes measured by the circumference method and by the MFBIA predictors.

Body water volumes of limbs or individual body segments cannot be determined by isotope dilution techniques and without any direct measure of TBW and ECW, algorithms for prediction of segmental water volumes using impedance of the limb cannot be determined. However, the ratios of segmental water volumes can be readily obtained from the impedance measures and are given by equations 1 and 2, assuming the resistivities of the limbs and constituent fluids are the same.

$$\frac{\text{TBW}_{\text{affected limb}}}{\text{TBW}_{\text{unaffected limb}}} = \frac{Z_c}{Z^*_c}$$

$$\frac{\text{ECW}_{\text{affected limb}}}{\text{ECW}_{\text{unaffected limb}}} = \frac{R_o}{R^*_o}$$

where * denotes the impedance of the affected limb.

Intracellular water (ICW), is an accurate index of fat-free mass and can be calculated from the difference between TBW and ECW Hence an expression for the limb ratio for ICW can be obtained (equation 3).

$$\text{ICW} = \text{TBS} - \text{ECW}$$

$$\frac{\text{ICW}_{\text{affected limb}}}{\text{ECW}_{\text{unaffected limb}}} = \frac{(R^*_O - Z^*_c)}{R^*_O\, Z^*_c} \times \frac{R_O\, Z_c}{(R_O - Z_c)}$$

Results and discussion

As shown in Table 1, both groups were similar in height, but the controls were younger, weighed less, and had a lower body mass index (BMI). No attempt was made in this study to match controls to patients on these parameters as both the circumferential and impedance measurements of the affected limb were expressed as a ratio of the unaffected limb, i.e. each individual acted as their own control. To assess the consistency of the impedance measurements daily measurements were made on the control subjects over the four week period. The mean standard deviation of the impedance measures for a single limb was 9? , corresponding to approximately 3% of the measured value. However,

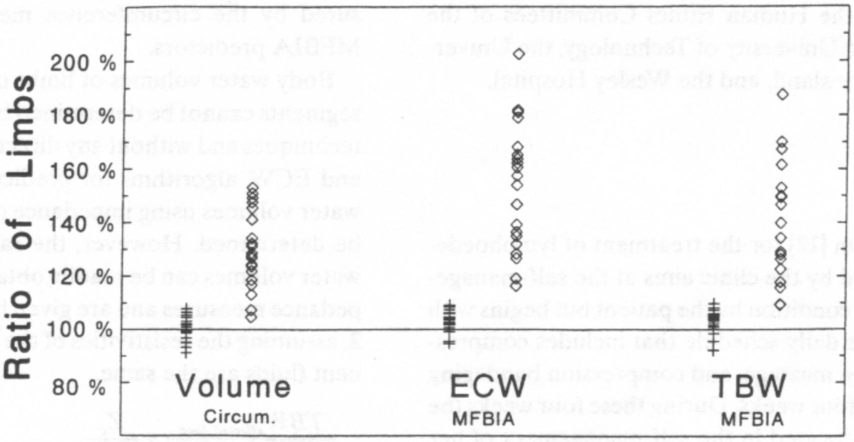

Fig. 1. Comparison of MFBIA estimates and volume measurements for control and patient groups. Values are the ratio of the two limbs, (+ controls, (dominant/non-dominant); ?patients, (affected/unaffected)).

when the ratio of the impedance of the two limbs was calculated, this variation was reduced to less than 1.5%.

The results of the impedance and volume measures of both controls and patients recorded on ’day one’ of the study are represented in Fig. 1. A Mann Whitney two-sample test for group comparisons was applied. No significant asymmetry in circumferential estimates of volume was observed between the two limbs of individuals of the control group. However, a small but significant asymmetry was detected in the impedance-predicted values of their TBW and ECW ratios (both $P < 0.01$). A binomial test of the impedance predictors, Z, and R, indicated that this asymmetry was significantly associated ($P < 0.001$) with their hand-use preference (dominant limb). Applying the Mann-Whitney test [11] to the data of the patient group showed the circumferential estimates of the volume of the lymphoedematous limb was significantly greater ($P < 0.005$), than that of the contralateral, unaffected limb.

There was also a significant asymmetry detected in the impedance-predicted values of the TBW and ECW ratios of the *patient* group ($p < 0.005$). However, in the *patient* group this result was not attributable to hand-use preference. Using the data from the control group the 95% confidence interval (dominant/non -dominant), was determined: $- 3.3\% < \text{ECW ratio} < 10.5\%$. Applying this confidence interval to the patient group all subjects would be classified as outside the ’normal’ range of variation in the ECW ratio. A similar analysis of the circumferential measurements resulted in a confidence interval of $- 7.5\% < \text{Volume ratio} < 12.5\%$, and applying this interval to the patient group resulted in 17 out of the 20 subjects classified as outside the normal range, thus indicating the greater diagnostic potential of MFBIA. The use of the 95 % confidence interval of the ratio (dominant/non-dominant) established in the control group, is a more stringent criterion than an arbitrary right/left limb ratio and in fact is more likely to result in ’false negatives’ in the patient group.

A caveat is that the ubiquity of these confidence limits needs to be confirmed before this mode of diagnosis can be adopted in clinical situations. In particular the validity of these confidence intervals to individuals with large differences in muscle mass between the limbs (e.g. athletes who practise unilateral exercise, squash and tennis players, archers, etc.) needs to be determined.

The ratio of ECW and ICW measures of the limbs (expressed as a ratio of the unaffected limb), were calculated for each participant over a period of four weeks. The daily variations of these ratios for typical subjects from both the patient and control groups are shown in Fig. 2.

The procedure of Bland and Altman [1] was used to analyse the agreement between the two mea-

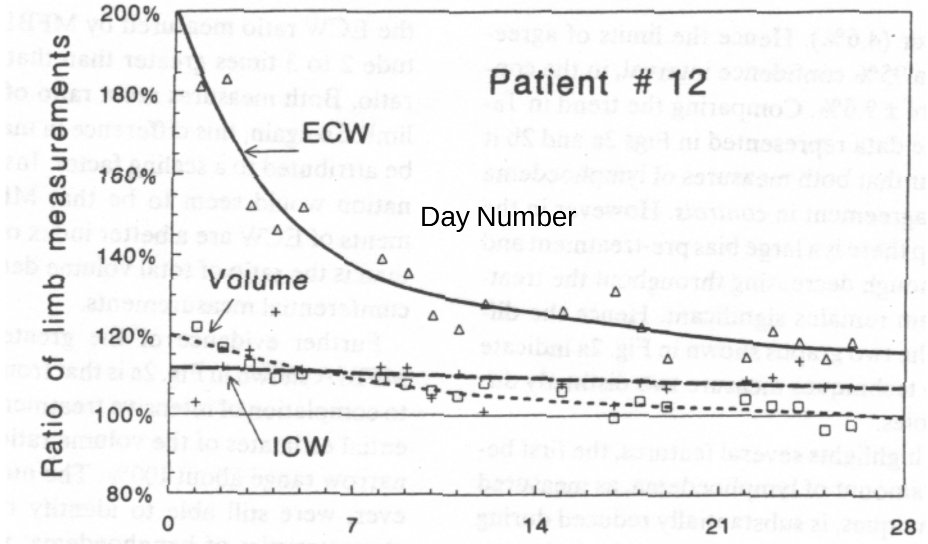

Fig. 2a.Trends in the measured quantities for a typical patient during the 4 week treatment period. ? = ECW ratio (by MFBIA); + = ICW ratio (by MFBIA); ? = Volume ratio (by circumference).

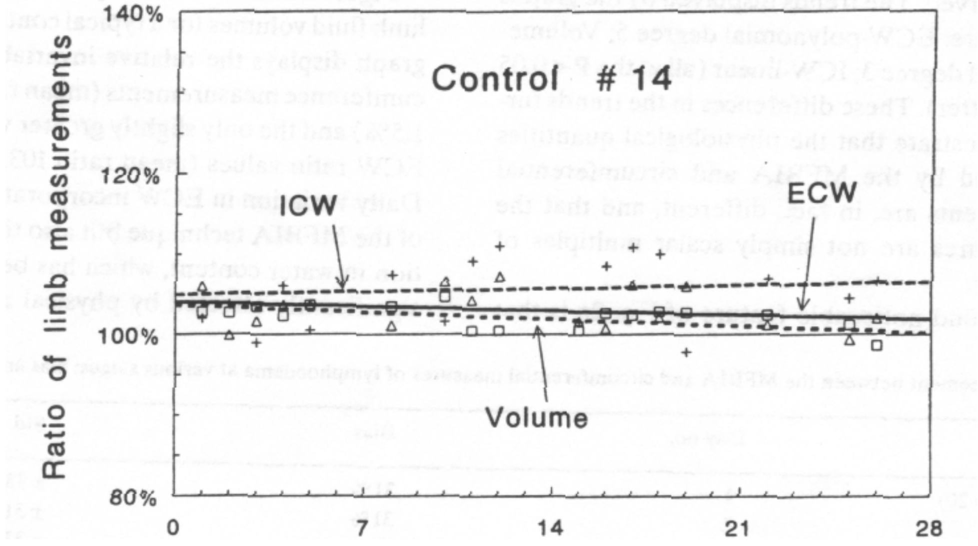

Fig. 2b.Trends in the measured quantities for a typical control subject during a 4 week period, A = ECW ratio (by MFBIA); + = ICW ratio (by MFBIA); ? = Volume ratio (by circumference).

sures of lymphoedema (viz. the ECW ratio by MFBIA and the volume ratio by circumference measurements). Table 2 shows the bias (an indication of the agreement between the two methods) and the standard error of the bias between the two measures at various stages throughout the four week program.

The reasonably close agreement between the two measures in the group of controls is indicated by a small bias (3.1%), but more importantly a small standard error (4.6%). Hence the limits of agreement, using a 95% confidence interval, in the control group are ± 9.6%. Comparing the trend in Table 2 with the data represented in Figs 2a and 2b it would appear that both measures of lymphoedema are in close agreement in controls. However in the patient group there is a large bias pre-treatment and this bias although decreasing throughout the treatment program remains significant. Hence the differences in the two graphs shown in Fig. 2a indicate that the two techniques measure two distinctly different variables.

Figure 2a highlights several features, the first being that the amount of lymphoedema, as measured by both techniques, is substantially reduced during the 4 week treatment regime. The method of curvilinear regression analysis was applied to investigate the trends displayed by the loci shown in Fig. 2. An F-test [10] was used to statistically determine the lowest order polynomial which best quantifies the trend observed. The trends displayed by the graphs in Fig. 2a are: ECW-polynomial degree 5; Volume-polynomial degree 3; ICW-linear (all at the $P < 0.05$ level or better). These differences in the trends further demonstrate that the physiological quantities represented by the MFBIA and circumferential measurements are, in fact, different, and that the two measures are not simply scalar multiples of each other.

The second noticeable feature of Fig. 2a is that the ECW ratio measured by MFBIA has a magnitude 2 to 3 times greater than that of the Volume ratio**.** Both measures are a ratio of the unaffected limb. So again, this difference in magnitude cannot be attributed to a scaling factor. Instead, the explanation would seem to be that MFBIA measurements of ECW are a better index of lymph volume than is the ratio of total volume determined by circumferential measurements.

Further evidence of the greater sensitivity of MFBIA shown in Fig. 2a is that from day 16 through to completion of intensive treatment the circumferential estimates of the volume ratio fluctuated in a narrow range about 100%. The nursing staff, however, were still able to identify the symptomatic characteristics of lymphoedema; viz: a firm, non-pitting swelling. The MFBIA measure of the ECW ratio continued to detect the presence of lymphoedema, although decreasing in magnitude, up to day 26.

Figure 2b shows the daily variation in measured limb fluid volumes for a typical control subject. This graph displays the relative invariability of the circumference measurements (mean ratio 102.2%; s.d. 1.5%) and the only slightly greater variability in the ECW ratio values (mean ratio 103.1%; s.d. 2.4%). Daily variation in ECW incorporates not only that of the MFBIA technique but also the diurnal variation in water content, which has been shown to be significantly affected by physical activity and diet

Table 2. Agreement between the MFBIA and circumferential measures of lymphoedema at various stages; bias and standard error

	Day no.	Bias	Std.Error
Patients (n =20)	1	31%	± 33%
	2	31%	± 31%
	3	20%	± 23%
	5	14%	± 19%
	8	17%	± 20%
	10	17%	± 21%
	12	14%	± 16%
	15	16%	± 18%
	17	15%	± 12%
	19	16%	± 10%
	22	15%	± 14%
	24	13%	± 10%
	26	15%	± 12%
Controls (n 20)		3.1%	± 4.6%

[8]. The regression line of the ICW data has a relatively constant value (105%). This result is not unexpected in active subjects given that the data are expressed as a ratio of dominant/non-dominant limb, and limb dominance is usually associated with a greater muscle mass.

Conclusion

The MFBIA procedure determines the resistance at zero frequency, R_o, of each limb and hence differences in ECW In the present work it has been shown to be a better index of lymphoedema than circumference-derived measures of total limb volume. ECW occupies approximately 25% of the total body [13]. Thus, a 40% increase in ECW of a body segment would lead to only a 10% increase in its total volume. It is not surprising, therefore, that a technique such as MFBIA, which measures actual ECW, will have greater sensitivity and precision in detecting changes than one which measures total segment volume. Another advantage of MFBIA is that a measure of ICW, which is very closely correlated with muscle mass, can be obtained. While the precision of this measure is less than that of the ECW measurement, its trend may provide the clinician with valuable information which may reflect changes in mobility and exercise of the limb.

MFBIA offers a technique in the diagnosis and management of lymphoedema which has been shown in this and previous papers to be more sensitive to lower levels of lymphoedema and particularly to treatment response. In particular the technique offers a means of discrimination between low levels of lymphoedema where arm and hand dominance may conceivably cause confusion through increased muscle bulk in circumferential measurements and offers a technique which reflects the true physiological status of the underlying arm better than an external circumferential measurement and that the results obtained are not simply a scalar phenomenon but reflect true underlying physiological change.

In the diagnosis of overt, severe lymphoedema, the advantages beyond this of MFBIA may not be immediately obvious. However in response to treatment, there is a clear advantage of the MFBIA over circumferential measurements which will allow the effect of various treatment modifications to be measured and further may allow earlier termination of intensive therapy with resource saving. This study confirms that MFBIA is more sensitive than circumferential measurement at low levels of lymphoedema, and remains effective and discriminatory at times where circumferential measurements have difficulty in discriminating between affected and non-affected arm. There is clinical benefit in the consequent ability using MFBIA to better document the incidence of post-mastectomy lymphoedema as well as to assess those factors which influence lymphoedema persistence or regression and in particular to determine if simple preventive techniques in the early stages of lymphoedema will prevent the more severe lymphoedema evolving which in our experience is

Acknowledgement

The financial support of the Queensland Cancer Fund is gratefully acknowledged.

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