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ORIGINAL ARTICLE

A method for the detection of post-operative lymphoedema after operation for breast cancer: multifrequency bioelectrical impedance analysis

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Summary
Lymphoedema, a pathological accumulation of extracellular water (ECW), is a severe post-operative complication. Multifrequency bioimpedance analysis (MFBIA) is a method for the detection of changes in ECW. Our aim is to establish the methodology of MFBIA and to apply it on to group of patients undergoing breast cancer surgery.

We measured a control group of 60 women, another group of 5 women with pronounced lymphoedema and a group of 36 patients undergoing breast cancer surgery during a 9-month period after surgery using MFBIA and circumferential measurements for recording volume changes in the upper limb. Different linear extrapolations from 1, 5, 50, 100, 200 kHz were determined to find resistance at 0 Hz for each patient; ratios of R_0 were evaluated for non-dominant/dominant and non-operated/operated limbs. Pearson's correlation coefficient was used to compare the correlation between the results and patient characteristics.

Extrapolation using 5, 50, 100 kHz had the lowest standard deviation. Within the patients with pronounced lymphoedema, bigger differences were found by MFBIA as compared with circumference measurements. A stronger correlation between limb volumes calculated from circumference measurements with weight and BMI as compared with MFBIA was found. Lymphoedema was found in 14 women in the tested group. The best association between patients' subjective symptoms was with the MFBIA measurement.

Key words: lymphoedema – post-operative complication – multifrequency bioelectrical impedance analysis – breast cancer

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INTRODUCTION

Lymphoedema is a severe post-operative complication after the treatment of numerous malignancies when lymphadenectomy is performed. Lymphoedema is due to the mechanical destruction of lymphatic vessels and to a failure of

the innervation of arteries and veins. Both of these factors tend to increase hydrostatic pressure and thus lead to the development of lymphoedema, i.e. – an accumulation of extracellular water (ECW) in the limbs. Several methods have been established to detect lymphoedema, including limb circumference measurement, tissue tonometry, water displacement volume measurement and lymphoscintigraphy. Most of these methods, however, measure only the total limb volume (TLV), are costly, or require sophisticated manipulation (Gerber 1998). Multifrequency bioelectrical impedance analysis (MFBIA) is a method that can precisely evaluate ECW (Cornish et al. 1993). It uses a measurement of the resistance of the tissue to electric current using different frequencies. The resistance is indirectly proportional to the TLV, which represents the ECW and intracellular water (ICW) together. The fluid is a conductor while the cell membrane is an insulating material. When the frequency is near zero, the cell membranes act as an insulator, where measured resistance corresponds to the resistance of the ECW. At higher frequencies ($\geq$ 50 kHz), the current passes through cell membranes, measuring the ECW and ICW. Because it is not possible to measure resistance at f=0 Hz or infinitive frequency, it is necessary to extrapolate these values (Cornish and Ward 1998). The ratio of the extrapolated R_0 of a dominant and non-dominant limb is determined and the standard deviation of these values is used to construct a reference range for future patients (Cornish et al. 2001).

There are certain aspects of the methodology that are not clearly defined. Extrapolation could be carried out using 1, 5, 50, 100, 200 kHz or even higher frequencies. Results obtained at lower frequencies than 5 kHz exhibit the high skin impedance of contact electrodes (Cornish et al. 1993). It is not clear which frequencies should be used for the extrapolation. For the reference range, several models can be used: (a) the interval from the control group is applied to the tested women (Cornish et al. 1996), (b) the pre-operative value of a concrete patient + 1.96 x $S.D_C$ (the standard deviation obtained from a control group) and (c) the pre-operative value of a concrete patient + 1.96 x $S.D_P$ (the standard deviation obtained from pre-operative values of tested women) (Box et al. 2002). For the reference range, a range of ± 2 or 3 S.D. is always applied, but we know that when lymphoedema is present, a rise in the ECW or TLV occurs. This means that only the reference range from a one-tailed confidence interval can be used.

The definition of the diagnosis of lymphoedema is heterogeneous: for instance, the difference in circumference at single circumferences more than 2 cm; the difference of the sums of circumferences of each limb over 5 cm; or the difference of volumes calculated from the circumferences over 200 ml (Box et al. 2002; Cornish et al. 1996; Kissin et al. 1986).

The goal of the present study was to evaluate different methodologies for the MFBIA examination of an upper limb in order to determine the reliability of MFBIA and to apply it to a group of patients undergoing breast cancer surgery.

MATERIAL AND METHODS

Between August 2004 and February 2006, we evaluated three groups of women. Group A consisted of 60 healthy women (control group) whose limb volume was recorded by circumferential measurements and MFBIA 1-100 kHz. A subgroup (A1) of 7 women underwent, in addition to circumference measurements and MFBIA, an examination by water displacement in order to determine the correlation between circumference and water displacement. Another subgroup (group A2) of 20 women had an additional measurement using MFBIA at 200 kHz. These women were chosen from those who were visiting their relatives that were hospitalised in our department. Group B consisted of 5 women with pronounced lymphoedema. These women were measured to determine the correlation between circumferential measurements and MFBIA in the affected limbs. Group C was made up of 36 patients undergoing breast cancer surgery. These patients were examined in 3-month intervals over a period of 9 months post-surgery. Surgery of the breast was either radical modified mastectomy or segmentectomy. Two techniques of lymphadenectomy were performed: sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND). After the signing of an informed consent form, circumference measurements of the upper limbs and measurement by MFBIA were performed on both hands. Circumference measurements were made at 10 cm intervals (altogether 40 cm segments), starting from the wrist, followed by calculation of the upper limb volume. The shape of the upper limb was simplified to four cylinders: an average circumference between two measured circumferences was calculated, followed by calculation of the volume of the cylinder. Finally, by adding the volume of the four cylinders, the total volume of the limb was obtained. Examination by MFBIA (Impmeter, Papouch©, Prague, Czech Republic) was performed on both upper limbs. The patients were asked to lay supine with their arms slightly outstretched and palms down. Inductive electrodes were then placed 40 cm apart, measuring electrodes in distances of 5 centimetres from the inductive electrodes. Data concerning weight, height, age and limb dominance were collected.

Using Pearson's correlation coefficient, a correlation was observed between water displacement and volume calculated using circumference measurements. To find resistance at theoretical zero frequency we used linear extrapolation from frequencies 1, 5, 50, 100 kHz (R01100d, R01100nd); from 5, 50, 100 kHz (R05100d, R05100nd); from 1, 5, 50, 100, 200 kHz (R01200d, R01200nd); from 5, 50, 100, 200 kHz (R05200d, R05200nd) each for the dominant (d) and non-dominant limb (nd) and for the operated (o) and non-operated (no) limb in the tested group. Ratios of extrapolated resistances of both limbs were established: nd/d in controls as well as in patients (in order to determine the initial, pre-operative value) and no/o after surgery (for the detection of lymphoedema). Because of the indirect proportion of volume V and resistance R, it is important to take into account the fact that the ratio of the estimated volume from MFBIA (V_o/V_{no}) is replaced by the ratio of the extrapolated resistance of R_{no}/R_o. The relationships between the measured data and the characteristics of the study group were determined using Pearson's correlation coefficient. The detection of lymphoedema in the group of patients who had undergone surgery was established by following five detection methods: (1) the difference of the sums of the circumferences (Ci) of each limb over 5 cm, (2) the difference of the volumes calculated from the circumferences (Vi) of each limb over 200 ml, (3) the ratio of MFBIA resistances no/o extrapolated from 5, 50 and 100 kHz outside of the range over 2 one-tailed interval calculated from the control group, added to the nd/d ratio calculated from the control group (MFBIAcont), (4) MFBIA ratio outside of the range over 2 one-tailed interval calculated from the control group added to the pre-operative ratio of the actual patient (MFBIApre), and (5) using the patient's symptoms (Ps). We choose to use only the 2 one-tailed interval to establish the range in the detection of lymphoedema, which entails higher sensitivity and lower specificity. In the case of a pathological finding we performed a control examination one week later. The patient was referred to the lymphatic massage sessions in case of subjective swelling of the arm confirmed by at least two methods. For the association between patient's symptoms and each of the methods, we used the association coefficient.

For statistical evaluation the SAS 9.1 Software® was used. The project was approved by the ethical committee of the 2nd Medical Faculty of the Charles University in Prague, Czech Republic.

RESULTS

Group characteristics are summarised in Table 1. The correlation between water displacement and volume, as calculated by circumferential measurements in group A1, was statistically significant: for the right limb the correlation was 0.9436 and for the left hand 0.9396.

Table 1. **Characteristics of the two patient and control groups**

Variable	Mean (min-max)	N	S.D.
Group A	Control group		
Age	40.20 (22-75)	60	14.34
Weight	65.92 (44-100)	60	10.99
Height	167.77 (154-180)	60	6.26
BMI	23.48 (16.79-34.6)	60	4.09
Group B	Patients with lymphoedema		
Age	63.30 (55-78)	5	7.25
Weight	68.80 (60-80)	5	8.07
Height	161.80 (146-170)	5	9.28
BMI	26.26 (23.62-28.15)	5	1.82
Group C	Patients undergoing surgery		
Age	60.00 (37-76)	36	9.87
Weight	73.81 (51-115)	36	14.27
Height	164.39 (148-175)	36	6.17
BMI	27.29 (18.70-37.98)	36	4.88

BMI – body mass index
N – number of patients
S.D. – standard deviation

The results of the comparison between extrapolated ratios and the ratios of volume calculated from the circumferences in groups A and C are presented in Table 2. The best results – (i.e. the lowest S.D.) exhibit ratios derived from 5, 50 and 100 kHz of 0.0827, whereas the worst results were from 5, 50, 100 and 200 kHz of 0.1041. Based on the results of the control group, we further used 5, 50 and 100 kHz extrapolations. The results of patients with pronounced lymphoedema (group B) are given in Table 3. The correlation between the calculated data and the characteristics of the women in group A are shown in Table 4. As can be seen in this table, a stronger correlation was found between the volume, as calculated from circumferences, with weight and BMI as compared with the correlation between volumes, as calculated from MFBIA, with weight and BMI. From MFBIA extrapolations, the best results are obtained with frequencies 5, 50 and 100 kHz. A one-tailed confidence interval (1.138) was calculated rather than the two-tailed confidence interval (1.164) for the ratios. Lymphoedema was detected by at least one of the methods in 14 patients (39%), at least 2 of the methods in

8 patients (22%), at least 3 or 4 of the methods in 4 patients (11%) and all 5 methods in 2 patients (6%). In three patients (8%) subjective determination of lymphoedema was confirmed by at least two other methods. Table 5 presents the success of each method regarding the detection of lymphoedema. The association coefficients were 0.04 for the Ci method, 0.00 for the Vi method, 0.26 for MFBIApre and 0.41 for MFBIAcont. In 43% of the cases lymphoedema was found in patients with SLNB (the mean number of lymph nodes was 3.3) and in 67% of the cases lymphoedema was detected in patients with ALND (the mean number of lymph nodes was 14.8).

Table 2. **Comparison between extrapolated ratios and ratios of volume calculated from the circumferences for the controls and patients undergoing surgery**

Variable	Minimum	Mean	Maximum	N	S.D.
Group A: Control group					
Vd/Vnd	0.9324	1.0372	1.2548	60	0.0644
Nd/d R01100	0.7873	1.0096	1.2199	60	0.0925
Nd/d R05100	0.8024	1.0002	1.2454	60	0.0827
Nd/d R01200	0.8670	0.9938	1.1938	20	0.0831
Nd/d R05200	0.8389	0.9963	1.2855	20	0.1041
Group C: Patients undergoing surgery					
Vd/Vnd	0.9314	1.0357	1.1478	36	0.0558
Nd/d R01100	0.7761	1.0159	1.1979	36	0.0846
Nd/d R05100	0.8130	1.0218	1.1823	36	0.0666
Vo/Vno	0.8713	0.9951	1.1363	36	0.0628
No/o R01100	0.8360	1.0195	1.2885	36	0.0877
No/o R05100	0.8458	0.9989	1.2300	36	0.0704

S.D. – standard deviation
N – number of patients
d – dominant limb
nd – non-dominant limb
o – operated limb
no – non-operated limb
V – volume calculated from circumferency
R01100 – R_0 extrapolated from 1, 5, 50, 100 kHz
R05100 – R_0 extrapolated from 5, 50, 100 kHz
R01200 – R_0 extrapolated from 1, 5, 50, 100, 200 kHz
R05200 – R_0 extrapolated from 5 50, 100, 200 kHz

Table 3: **Patients with lymphoedema**

Variable	Minimum	Mean	Maximum	N	S.D.
Vo/Vno	1.2206	1.3830	1.7334	5	0.2254
No/o R05100	1.2484	1.7334	3.0235	5	0.7292

S.D. – standard deviation
N – number of patients
o – operated limb
no – non-operated limb
V – volume calculated from circumference
R05100 – R_0 extrapolated from 5, 50, 100 kHz

Table 4: **Correlation coefficient between calculated data and characteristics of the control patients (group A) and patients undergoing surgery (group C)** (P values for the test of independence are in brackets).

	N	Weight (kg)	BMI
Group A	Control group		
Vd	60	0.8070 (<.0001)	0.84702 (<.0001)
Vnd	60	0.7629 (<.0001)	0.8397 (<.0001)
R05100d	60	0.3165 (0.0137)	0.2636 (0.0418)
R01100d	60	0.3364 (0.0086)	0.2797 (0.0304)
R01100nd	60	0.2211 (0.0896)	0.1906 (0.1450)
R05100nd	60	0.2197 (0.0915)	0.1651 (0.2073)
R01200d	20	0.0027 (0.9910)	0.0438 (0.8585)
R01200nd	20	-0.0140 (0.9546)	0.0332 (0.8926)
R05200d	20	-0.0281 (0.9091)	0.0004 (0.9984)
R05200nd	20	-0.0261 (0.9153)	0.0173 (0.9437)
Group C: Patients undergoing surgery			
Vd	36	0.8201 (<.0001)	0.8092 (<.0001)
Vnd	36	0.7764 (<.0001)	0.7945 (<.0001)
R05100d	36	0.4864 (0.0026)	0.4387 (0.0074)
R01100d	36	0.4374 (0.0076)	0.3772 (0.0233)
R01100nd	36	0.3641 (0.0290)	0.3194 (0.0575)
R05100n	36	0.5280 (0.0009)	0.4916 (0.0023)

BMI – body mass index
N – number of patients
d – dominant limb
nd – non-dominant limb
V – volume of the limb calculated from circumference
R01100 – R_0 extrapolated from 1, 5, 50, 100 kHz
R05100 – R_0 extrapolated from 5, 50, 100 kHz
R01200 – R_0 extrapolated from 1, 5, 50, 100, 200 kHz
R05200 – R_0 extrapolated from 5 50, 100, 200 kHz

DISCUSSION

The control group, in comparison with the study group, consists of younger women with lower BMI. Because we used a ratio of one limb to another for all relevant calculations, the differences are compensated.

The calculation of volume from circumferences is a very precise measurement as indicated by the fact that even with only 7 patients, the correlation was statistically significant.

The results of extrapolation from 1, 5, 50 and 100 kHz in the patient group were 273 Ω for the dominant limb and 276 Ω for the non-dominant limb. These findings are comparable with those of Cornish who reported the following results: R_0 for the dominant limb = 289 Ω, R_0 for the non-dominant limb = 299 Ω and the MFBIA ratio = 0.964 (S.D. = 0.034) (Cornish et al. 2001). In the present study the best results were found using only 5, 50 and 100 kHz. These results correspond with the finding that resistance at 1 kHz exhibits high skin impedance (Cornish et al. 1993).

The detection of lymphoedema in patients with pronounced lymphoedema was most obvious with the ratio obtained from the no/o limb derived from the MFBIA measurement, which shows that MFBIA is more sensitive to ECW changes.

Pearson's correlation coefficient revealed a stronger correlation between volume from

circumferences and weight and BMI than MFBIA measurements, indicating that the MFBIA measurement is less dependent on the characteristics of the patients.

The examination by MFBIA is fast (1–2 minutes), painless and can be achieved anywhere with minimal cost and easy reproducibility (Ward et al. 1997). Furthermore, the method has 100% sensitivity and 98% specificity (Cornish et al. 2001). The possibility of detecting lymphoedema by comparing the results before and after surgery independently of the second limb is another advantage of the MFBIA method that other methods cannot offer (Cornish et al. 2002).

Table 5. **Patients with detected lymphoedema**

	Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Lymphadenectomy	S	A	S	S	S	A	S	A	A	S	A	A	A	A
	Number of LN	5	13	3	3	5	11	1	21	25	3	16	16	10	7
	Number of positive LN	1	0	0	0	1	0	0	5	3	3	1	1	3	1
Method	Ci	1	1		1	1				1	1		1	1	1
	Vi	1	1	1	1						1	1		1	
	MFBIAcont	1			1						1			1	
	MFBIApre				1	1	1	1	1		1			1	
	Ps	1						1	1		1			1	1

S – SLNB
A – ALND
LN – lymph node
Ci – detected by circumference measurements
Vi – detected by volume calculated from circumference measurement
MFBIAcont – detected by MFBIA based on control group
MFBIApre detected by MFBIA based on pre-operative value
Ps – detected based on patient‘s symptoms

The detection rate of lymphoedema in our study group depended on the particular method selected. MFBIAcont was found to be the most precise method in that it showed the highest association with subjective symptoms. This finding is in agreement with those of other studies (Armer 2005). A notable finding in our study was the presence of lymphoedema in 43% of patients undergoing only SLNB, with significantly fewer lymph nodes being extirpated. These patients need to be followed up.

Several variables affect the impedance measurements, including exercise, skin temperature, hydratation, time of the day, menstruation and pregnancy (Mikes et al. 1999). Most of the variables (hydratation, menstruation and pregnancy) mainly influence the trunk of the body, i.e. influence on the limb is only minor. We tried to diminish the influence of the other variables by performing the measurement in a quiet room where the patient was lying comfortably. Further, we recorded the weight of each patient. Some authors tried to develop new equations used by MFBIA (Dittmar and Reber 2001, Hayes et al. 2005) to improve diagnostics. Based on our results, we recommend extrapolation from 5, 50 and 100 kHz, the use of a one-tailed interval for the detection of lymphoedema and detection by the MFBIA ratio based on the control group (MFBIAcont). In conclusion, MFBIA is a sensitive and promising method that could be used to detect post-operative lymphoedema.

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