Whole-body Bioelectrical Impedance Analysis in Assessing Upper-limb Lymphedema After Breast Cancer Therapy

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Abstract. *Aim: The purpose of this prospective study was to evaluate single-frequency whole-body bioelectrical impedance analysis (BIA) as a predictor for the onset of edema of the upper limb in patients undergoing treatment for breast cancer. Materials and Methods: Whole-body BIA was performed before surgery, as well as at two days, and one, three, six and twelve months after surgery. Results: Sixty women undergoing breast cancer surgery were examined, with loss of follow-up of 18 patients. Seven patients (14.3%) developed an edema of the upper limb within the first 12 months after surgery. Resistance (R) using whole-body BIA showed a fairly good performance in terms of sensitivity (85.71%) and specificity (97.4%) at predicting edema. The positive predictive value of 54.6% was unsatisfactory, whereas the negative predictive value was 97.4%. Conclusion: Resistance in whole-body BIA can be used to rule-out a developing edema of the upper limb.*

As breast cancer mortality rates in the Western world have significantly declined throughout recent years due to advances in diagnostic and therapeutic approaches, the necessity for adequate management of treatment-related side-effects, which may have a severe impact on quality of life, is evident. Breast cancer-related lymphedema is an important sequela, whose early detection seems to have a beneficial impact on treatment outcomes and may prevent progression of edema itself (12, 13). Bioelectrical impedance analysis (BIA) is a highly standardised technique which is fast and easy to perform, non-invasive and therefore well-tolerated by patients. BIA instruments are affordable devices, especially single-frequency instruments as the ones used in this study (11). These have been proven to be eminently suitable for non-laboratory settings (11). Until the 1990s, only single-frequency BIA (SFBIA) instruments were available, measuring impedance at 50 kHz. These instruments have been further developed, so that measurements can be performed over a range of frequencies. Whole-body SFBIA remains state-of-the-art for various indications (9). This is why these instruments are arguably most frequently and widely used in clinical routine (9). The physical properties of BIA, its measurement variables (resistance, reactance, phase angle) and their significance have been described in many investigations (1, 10, 11). Resistance (opposition to the electrical current from fluids of the body) is used to analyze edema. Resistance can be measured over a range of frequencies. Classic whole-body SFBIA, as the one used in this study, applies a current at 50 kHz alternating current (AC) that penetrates cell membranes, and leads to the measurement not only of extracellular but also of intracellular water (14). Hence, previous investigations, except for one smaller study performed by our department, analyzing edema of the upper limb, have always used segmental low-frequency SFBIA or bioelectrical impedance spectroscopy (BIS) (3, 15). Using this methodology, only extracellular water of the corresponding body segment is measured. The question is if these new measurement procedures, implicating the need for the acquisition of new, more expensive measurement devices and with the necessity of additional technical know-how, are more accurate compared to SFBIA. As whole-body SFBIA using the classic electrode sites is a technically simple and clinically widespread diagnostic method, our aim was to evaluate if this traditional diagnostic approach is capable of sensitively

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and specifically capturing edema of the upper limb. In a previous study, we investigated early edema of the upper limb (within the first three months after breast cancer surgery) using whole-body BIA and designed the presented investigation with a larger study collective (n=60) and a longer observation period of 12 months in order to achieve more reliable results (3).

Materials and Methods

Whole-body BIA was performed before surgery, as well as at two days, and one, three, six and 12 months after surgery. A standardized questionnaire was used for patients and treatment characteristics taking the following items into account: The patient characteristics: age, body mass index (BMI), side of dominance/handedness; treatment characteristics: type of surgery, number of removed lymph nodes, radiotherapy and chemotherapy. An SFBIA device (Biacorpus RX 4000, Medical GmbH, Karlsruhe, Germany) was used in this study. This instrument is a fully digital, phase-sensitive, 4-channel impedance measuring device. Each channel applies a 50 kHz AC current to precisely measure resistive impedance. By means of its four capturing interfaces, resistive impedance was measured taking the side of dominance into account: Right half of body (right arm, right foot: RARF); left half of body (left arm, left foot: LALF). The patient was placed in a supine position, limbs slightly abducted and palms pronated flat on the examining table covered with a non-conducting surface. Eight electrodes were attached to the patient´s hands and feet. After cleaning the skin with alcohol swabs where the electrodes were about to be attached, the measurement electrodes were placed on the dorsal surface of the wrist and ankle at the level of the process of the radial and ulnar, fibular and tibial bones. Signal electrodes were attached to the dorsal surface of the third metacarpal bone of the hands and feet, such that at least a 5 cm distance was maintained between signal and measurement electrodes (5). The resulting measurements were automatically transferred to a computer, where they were duly interpreted by the software. The manufacturer's software (BodyComp V 8.3) was used. When applied to the quantitative analysis of lymphedema, the extent of pathological accumulation of extracellular fluid is mirrored by a decrease in the measured impedance values. Ratios of resistance (R) of both body halves (LALF, RARF), taking the side of dominance into account, were calculated as follows every time SFBIA was carried out:

$$\frac{\text{R unaffected body half (left or right)}}{\text{R affected body half (left or right)}}$$

In this way, the ratio values obtained for each patient were related to the individual preoperative ratio, so that each patient served as their own control, subtracting each post-surgery impedance ratio from the individual pre-surgery ratio (changes of ratios were based on six individual measurements per patient, yielding five ratio differences to baseline for 42 patients, hence 210 observations). Ratios for patients who developed an edema of the upper limb were then compared to those who did not. In order to objectify the presence of established lymphedema, upper limb volumes were calculated by circumferential limb measurements according to Kuhnke (8). A total of 60 female patients with breast cancer were recruited after study approval by the Ethics Committee II of the Mannheim Medical Centre of Heidelberg University (2011-341N-MA). Written informed consent was obtained upon recruitment. All data were recorded in an Excel datasheet and transferred into the SAS® environment (Statistical Analysis System, Release 9.2; SAS Institute Inc, Cary, NC, USA) for statistical analysis. Quantitative data are presented as mean with standard deviation and median with range. Qualitative data are given as frequencies. Confidence intervals for the average change in impedance ratios were computed. The respective limits for the lymphedema and non-lymphedema group were used to generate a cut-off value. The group-wise comparison between the case group and non-case group also included a two-sample *t*-test of significance. The findings obtained in the univariate approach were confirmed by a receiver operating characteristic (ROC) analysis with corresponding area under the curve (AUC) computation and significance testing. A *p*-value less than 0.05 was considered significant.

Table I. *Patients' characteristics (edema collective: n=7, non-edema collective: n=35); data are given as the mean±SD.*

	Edema (%)	No edema (%)
Age (years)	60.29±10.59	60.40±11.26
Body mass index	27.97±7.69	26.07±7.69
Affected breast		
Left	2 (28.57)	21 (60.00)
Right	5 (71.43)	14 (40.00)
Handedness		
Left	0 (0.00)	6 (17.14)
Right	7 (100.00)	29 (82.86)
Type of surgery		
Mastectomy	0 (0.00)	2 (5.71)
Mastectomy, SNB	0 (0.00)	4 (11.43)
Mastectomy, AD	3 (42.86)	2 (5.71)
Wide excision, SNB	1 (14.29)	21 (60.00)
Wide excision, AD	3 (42.86)	6 (17.14)
Number of lymph nodes removed		
1-5	1 (14.29)	25 (71.43)
6-10	1 (14.29)	3 (8.57)
11-15	2 (28.57	3 (8.57)
>16	3 (42.86)	4 (11.43)
Chemotherapy		
Yes	5 (71.43)	28 (80.00)
No	2 (28.57)	7 (20.00)
Radiotherapy		
Yes	6 (85.71)	29 (82.86)
No	1 (14.29)	6 (17.14)

AD: Axillary lymph node dissection, SNB: sentinel node biopsy, SD: standard deviation.

Results

Sixty women were recruited, with a loss of follow-up of 18 (30%) patients. The characteristics of the 42 women analyzed are shown in Table I. A total of 86% were right-handed, and in 45%, cancer was located in the right breast. Seven (14.29%) patients developed a lymphedema of the upper limb. Three of these women had had a wide excision

Table II. *Changes of resistance ratios (based on six individual measurements per patient, yielding five ratio differences to baseline for 42 patients=210 observations).*

	Mean	SD	*p*-Value+	Median	*p*-Value*
No edema	0.0031	0.0434	<0.0001	–0.0016	<0.0001
Edema	0.1598	0.1400		0.1249	

SD: Standard deviation, +*t*-test, **U*-test.

Table III. *95%Confidence limits (CL) for the mean of impedance ratios stratified by edema group (based on six individual measurements per patient, yielding five ratio differences to baseline for 42 patients=210 observations).*

	Mean	SD	Lower 95%CL for mean	Upper 95%CL for mean	Cut-off
No edema	0.0031	0.0434	–0.0030	0.0092	0.0441
Edema	0.1598	0.1400	0.0790	0.2407	

SD: Standard deviation.

of the tumour with axillary lymph node dissection of levels 1 and 2 (AD), one had a wide excision with sentinel node biopsy (SNB), and three underwent a mastectomy with AD. Changes of BIA ratios compared to the individual baseline ratio (R ratio before surgery) were computed. Subsequently, descriptive statistics (mean, standard deviation, median, range) were calculated. In Table II, the corresponding values are shown comparing the edema to the non-edema collective. For the non-edema group, changes were centered around zero. The edema group on the other hand showed pronounced changes at a level of 0.079 to 0.241. These findings underline the statistical sustainability of whole-body BIA monitoring of developing edema of the upper limb. Differences of the ratio changes comparing both groups were tested with a two-sample *t*-test as a parametric approach, as well as with the *U*-test as a non-parametric approach. The results were significant and consistent (Table II). Based on 95% confidence intervals, a threshold value was computed with the arithmetic mean of the lower confidence level for the edema group and the upper confidence level for the non-edema group (see Table III):

$$\frac{\text{Upper 95\% limit no edema + lower 95\% limit with edema}}{2} = 0.0441$$

Classification tables were then used to calculate common diagnostic measures, such as sensitivity, specifity and predictive values: Resistance gave fairly good performance in terms of sensitivity (85.71%) and specificity (97.37%). The positive predictive value was 54.55%, the negative predictive value was 97.37%. Finally, the ROC analysis, implemented as logistic regression, confirmed the univariate results: The likelihood ratio test was significant (*p*-value <0.0001). The respective AUC was significantly above the 0.5 reference line at 0.966.

Discussion

In clinical practice, water displacement volumetry, and in particular calculation of limb volume by using segmental circumferential measures seem to be the most utilized methods to measure lymphedema (6, 16). A disadvantage of these techniques is the necessity for a clinically manifested disease, not allowing insight into early dysfunctions. Moreover, values might be biased due to changes of total arm volume caused by obesity or exercise-induced hypertrophy *i.e.* irrespective of how limb volume is determined, it provides only an indirect measurement, as other tissues including fat, muscle and bone contribute to the measurement (4). Due to this unsatisfactory clinical situation, BIA has been increasingly investigated and was proven to provide accurate relative measures of lymphedema, as well as functional parameters concerning the emergence of edema of the upper limb (6).

To our knowledge, except for two publications from our department, previous investigations analyzing edema of the upper limb have always used segmental low-frequency SFBIA or BIS measurements of the upper limb (2, 3). As placement of electrodes on feet and arms as stated above is an easier, and in clinical routine is the more established measurement technique, our aim was to show that the presented method is sensitive and specific for detection of early upper limb lymphedema before its clinical manifestation. Reviewing the literature, most investigations involving BIA use whole-body BIA and are conducted in the fields of nutritional and internal medicine (9). At our University Hospital, only whole-body BIA devices are available. Therefore we were interested to find out if these conventional instruments are sufficient for the detection of upper-limb lymphedema, or if new devices need to be purchased, being well aware of the fact that segmental BIS and low-frequency SFBIA are, in general, more accurate at assessing extracellular water. Foster and Lukaski showed that the largest contributors to whole-body resistance are the forearm (28%) and the lower leg (33%), which contribute only 1-2% to the fat-free mass and 1.5-3% to the body weight compared with the trunk, which contributes 9% to the total R and >50% to the fat-free mass and body weight (7). Reviewing the literature, there is no disagreement that the limbs account for most of the whole-body impedance but only a minor fraction of the body volume (7). For these reasons our aim was to evaluate if whole body BIA (instead of segmental BIA), analyzing both body halves (left and right), is capable of detecting edema of the upper limb. Results of this investigation are comparable with results of the earlier study at our department (3). A developing edema of the upper limb can be ruled out with a high certainty, as the negative predictive value was 97%. The positive predictive value was 55%, indicating insufficient predictive quality regarding an establishing edema. Concerning these results, it has to be considered that measurements were performed only up to 12 months after surgery. Therefore false-positive cases may have been included in this investigation due to the limited observational period, in which, in the course of time, patients may develop an edema of the upper limb. The capability to exclude an established edema constitutes an important result regarding patients' psychological reassurance, as well as therapeutic strategies.

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