in vivo *26*: 863-868 (2012)

Comparing Bioelectrical Impedance Values in Assessing Early Upper Limb Lymphedema after Breast Cancer Surgery

SEBASTIAN BERLIT[1], JOACHIM BRADE[2], BENJAMIN TUSCHY[1], AMADEUS HORNEMANN[1], HANS LEWELING[3], VANESSA EGHARDT[1] and MARC SÜTTERLIN[1]

[1]Department of Obstetrics and Gynecology and [3]Fourth Department of Medicine, University Medical Center Mannheim, and
[2]Department of Biostatistics, Heidelberg University, Mannheim, Germany

Abstract. *Aim: The purpose of this prospective study was to evaluate resistance (R) and phase angle (Pa) determined by single-frequency whole-body bioelectrical impedance analysis (BIA), as predictors for the early onset of edema of the upper limb in patients undergoing surgical treatment for breast cancer. Materials and Methods: Whole-body BIA was performed before surgery, as well as at two days, at one and three months after surgery. Results: A total of 33 women undergoing breast cancer surgery were examined. Four patients developed an edema of the upper limb within the first three months after surgery. Both analyzed parameters showed a fairly good performance in terms of sensitivity (R=75%, Pa=75%) and specificity (R=86%, Pa=83%). The positive predictive values of 43% (R) and 38% (Pa) were unsatisfactory, whereas the negative predictive values were 96% for both parameters. Conclusion: Pa, as well as R, 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 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 the edema itself (1, 2).

Bioelectrical impedance analysis (BIA) is a highly standardized technique which is fast, non-invasive and therefore well-tolerated by patients. BIA instruments are affordable devices, especially the single-frequency instruments, as the ones used in this study (3). These have been proven to be eminently suitable for non-laboratory settings (3). Until the 1990s, only single-frequency BIA (SFBIA) instruments were available for 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 remain state-of-the-art instruments for various indications. This is why these instruments are arguably most frequently and widely used in clinical routine practice (4). The physical properties of BIA, its measurement variables (resistance, reactance, phase angle) and their significance have been described in many investigations before (3, 5, 6). Resistance (R, opposition to the electrical current from fluids of the body) is used to analyze edema. The phase angle (Pa) in this context is clinically interesting as it reflects different electrical properties of tissues that are affected in various ways by hydration status and cellular membrane integrity, without algorithm-inherent errors or requiring assumptions such as constant tissue hydration (7). Pa is an indicator of the distribution of body water between intra- and extracellular spaces (8). A high Pa corresponds to a low extra- to intracellular water ratio (6). Lower Pa suggests cell death or decreased cell integrity, whereas a higher Pa suggests a high proportion of intact cell membranes (9). Pa has been used to predict clinical outcome in various ailments (see below) (10-12). To our knowledge, Pa has not yet been investigated to predict emergence of edema of the upper limb after breast cancer treatment. Moreover whole-body SFBIA, in this context, has not been used. Resistance can be measured over a range of frequencies. Classic whole-body SFBIA, as used in this study, applies a current at 50 kHz AC, thus penetrating cell membranes, and leads to the measurement of not only extracellular but also intracellular water (13). Hence recent investigations of lymphedema use segmental *i.e.* measurements of only the upper limbs, multi-frequency BIA (MFBIA) devices, so that only extracellular water is measured

Correspondence to: Sebastian Berlit, MD, University Medical Center Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1–3, D-68167 Mannheim, Germany. Tel: +49 6213832286, Fax: +49 6213835074, e-mail: sebastian.berlit@umm.de

Key Words: Single-frequency bioelectrical impedance, lymphedema of the upper limb, breast cancer, phase angle, resistance.

due to AC in the low-frequency range being used (14). The question is if these new measurement procedures, implicating the acquisition of new, more expensive measurement devices, with the necessity of additional technical know-how are so much more accurate compared to SFBIA. As whole-body SFBIA, using the classic electrode sites is a technically simple and constitutes a clinically wide-spread diagnostic method, our aim was to evaluate if R and Pa of this traditional diagnostic approach are capable of sensitively and specifically capturing early edema of the upper limb.

Materials and Methods

A standardized questionnaire was used for patients and treatment characteristics taking the following items into account: Patients' characteristics: age, body mass index, side of dominance/handedness; treatment characteristics: type of surgery, number of removed lymph nodes. An SFBIA device (Biacorpus RX 4000, idiag GmbH, Bad Säckingen, 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 as well as Pa. By means of its four capturing interfaces, resistive impedance and Pa were 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 is 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 are to be attached, the measurement electrodes are placed on the dorsal surface of the wrist and ankle at the level of the process of the radial and ulnar, and fibular and tibial bones. Signal electrodes are attached to the dorsal surface of the third metacarpal bone of the hands and feet, such that at least a 5-cm distance is kept between signal and measurement electrodes (15). The resulting measurements (R and Pa) are automatically transferred to a computer, where they are duly interpreted by the software. The manufacturer's software (BodyComp v8.3) 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 R and Pa values of both body halfs (LALF, RARF), taking the side of dominance into account, were calculated as follows every time SFBIA was carried out:

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

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 four individual measurements per patient, yielding three ratio differences to baseline for 33 patients hence 99 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 (16). A total of 33 female patients with breast cancer were examined after study approval by the Ethics Committee II of the Mannheim Medical Center of Heidelberg University. 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) for statistical analysis. Quantitative data are presented as the 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. These analyses were performed separately for each predictor (R and Pa in whole-body SFBIA) and were used for comparison.

Table I. *Patients' characteristics*

	Total	Percentage
Age, years		
Mean	59.9	
Range	51-78	
Standard deviation	9.26	
Body mass index		
Mean	26	
Range	18-34	
Standard deviation	5.05	
Breast operated		
Left	19	57.58
Right	14	42.42
Handedness		
Left	4	12.12
Right	29	87.88
Type of surgery		
Mastectomy	2	
Mastectomy, SNB	3	
Mastectomy, AD	4	
Complete local excision, SNB	15	
Complete local excision , AD	9	
No. of lymph nodes removed		
1-5	20	
6-10	3	
11-15	3	
>15	5	

SNB: Sentinel node biopsy; AD: axillary lymph node dissection.

Results

The characteristics of the 33 patients participating in the study are shown in Table I. 88% were right-handed, and in 42%, cancer was located in the right breast. Four (12%) of patients developed a lymphedema of the upper limb, as diagnosed by circumferential limb measurements. Three of

Table II. *Changes of ratios (based on four individual measurements per patient, yielding three ratio differences to baseline for 33 patients=99 observations)*

	No edema				Edema				*p*-Value		
Parameter	N	Mean	Std	Median	N	Mean	Std	Median	*t*-test	*U*-test	Cut-off
R	87	0.0031	0.0606	0.0000	12	0.1305	0.0782	0.1304	0	0	0.0484
Pa	87	0.0090	0.1190	–0.0133	12	0.1450	0.1227	0.1216	0.0004	0	0.0507

R: Resistance; Pa: phase angle; Std: standard deviation.

Table III. *95%-Confidence limits for the mean of impedance ratios stratified by edema group*

	N	Lower 95% confidence limit	Upper 95% confidence limit
Resistance			
No edema	87	–0.0098	0.0160
Edema	12	0.0808	0.1802
Phase Angle			
No edema	87	–0.0164	0.0343
Edema	12	0.0671	0.2230

Table IV. *Sensitivity and specificity of single frequency bioelectrical impedance analysis.*

Parameter	Sensitivity	False-negative	Specifity	False-positive
R	75.00	25.00	86.21	13.79
Pa	75.00	25.00	82.76	17.24

R: Resistance; Pa: phase angle.

Table V. *Prevalence and predictive values of single frequency bioelectrical impedance analysis.*

Parameter	Prevalence	Positive predictive value	Negative predictive value
R	12.12	42.86	96.15
Pa	12.12	37.50	96.00

R: Resistance; Pa: phase angle.

Table VI. *Receiver operating characteristic (ROC) analysis.*

Parameter	Likelihood ratio	Area under the curve
R	0.0006	0.9310 (<0.0001)
Pa	0.0193	0.9224 (<0.0001)

R: Resistance; Pa: phase angle.

these women had had wide excision of the tumour with axillary lymph node dissection (level 1 and 2), one had a mastectomy with sentinel node biopsy. Changes of BIA ratios compared to the individual baseline ratio (impedance ratio before surgery) were computed separately for R and Pa. 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 0.13 to 0.22 (median values are comparable). 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 for both parameters (Table II). Based on 95% confidence intervals, a threshold value was computed as 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). As expected, for the non-edema group the confidence limits include zero, whereas those for the edema group have values that indicate a profound increase of bioimpedance ratio. This cut-off served as the decision criterion to allocate each patient to one of the two groups. Classification tables were then used to calculate common diagnostic measures, such as sensitivity, specifity and predictive values. Both parameters analyzed showed fairly good performance in terms of sensitivity (R=75%, Pa=75%) and specificity (R=86%, Pa=83%). Positive predictive values were 43% and 38% for R and Pa respectively, the negative predictive value was 96% for both parameters (see Tables IV and V). Finally the ROC analyses, implemented as logistic regressions, confirm the univariate results: All likelihood ratio tests had highly significant *p*-values (see Table IV). The respective AUCs were significantly above the 0.5 reference line, with 0.93 for R and 0.92 for the Pa (see Table VI).

Discussion

The bioelectrical Pa has consistently been shown to have prognostic relevance regarding morbidity and mortality in various diseases (17-20). Pa has been interpreted as an indicator of membrane integrity and water distribution between the intra- and extracellular spaces (8). As previous investigations have shown, a reduced Pa is associated with an impaired outcome in malignant and infectious diseases such as breast, lung, colorectal and pancreatic cancer, as well as HIV/AIDS (10, 17-19). Furthermore, the prognostic relevance of the Pa has been demonstrated in malnutrition, prolonged physical inactivity and inflammation (11, 21, 22). 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 (23, 24). 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 (25). Due to this unsatisfactory clinical situation, BIA has increasingly been investigated and has been proven to provide accurate relative measures of lymphedema, as well as functional parameters concerning the emergence of edema of the upper limb (23).

To our knowledge, previous investigations analyzing edema of the upper limb have always used segmental SFBIA or bioelectrical impedance spectroscopy (BIS) measurements of the upper limb, *via* attaching electrodes to the hands and shoulders of both affected and unaffected arms. As placement of electrodes on feet and arms, as stated above, is an easier, and in clinical routine the more established measurement technique, especially for obese patients, our aim was to show that the presented measurement technique is sensitive and specific for the detection of early upper limb lymphedema before its clinical manifestation. Reviewing of the literature, revealed that most investigations involving BIA use whole-body BIA and are conducted in the fields of nutritional and internal medicine. At our University Hospital, only whole-body BIA devices are available, hence we were interested to find out if these traditional instruments are adequate for the detection of early upper limb lymphedema or if new devices need to be purchased. Furthermore, Pa in this context has not been analyzed before, as far as we know.

Foster and Lukaski showed that the largest contributors to whole-body R 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 (26). Reviewing of the literature, revealed that there is no disagreement that the limbs account for most of the whole-body impedance but only a minor fraction of the body volume (26). 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 early edema of the upper limb. Results show that a developing edema of the upper limb can be ruled out with a high certainty, as the negative predictive value for both parameters was 96%. The positive predictive values were 43% and 38% for R and Pa, respectively, implicating insufficient predictive qualities regarding an established edema. Concerning these results, it has to be considered that measurements were performed only up to three months after surgery, as we planned to detect early edema of the upper limb after breast cancer surgery. Therefore false-positive cases may have been included in this investigation due to the limited observational period, which, in the course of time 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. As diagnostic methods for breast cancer detection improve, there is a greater need for analyzing the prevalence and morbidity of upper limb edema in population-based studies that are stratified by the method of surgical intervention. It has to be emphasized that the presented results should be considered as exploratory due to the small number of patients who developed an edema and the limited observation period. For this reason, at this point, a concluding statement concerning an impedance cut-off value cannot be made. Differences in the analyzed parameters are only marginal, yet they could be more pronounced on a larger-scaled study. As a technically simple and affordable tool for the clinician, whole-body SFBIA appears to be a suitable device for monitoring edema in patients after surgical treatment of breast cancer.

References

1 Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH and Soballe P: Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer *15;112(12)*: 2809-2819, 2008.

2 Szuba A and Rockson SG: Lymphedema: classification, diagnosis and therapy. Vasc Med *3(2)*: 145-156, 1998.

3 Ridner SH, Dietrich MS, Deng J, Bonner CM and Kidd N: Bioelectrical impedance for detecting upper limb lymphedema in nonlaboratory settings. Lymphat Res Biol *7(1)*: 11-15, 2009.

4 Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J: Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr *23(6)*: 1430-1453, 2004.

5 Lukaski HC, Johnson PE, Bolonchuk WW and Lykken GI: Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr *41(4)*: 810-817, 1985.

6 Baumgartner RN, Chumlea WC and Roche AF: Bioelectric impedance phase angle and body composition. Am J Clin Nutr *48(1)*: 16-23, 1988.

7 Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M and Gomez JM: Bioelectrical impedance analysis – part I: review of principles and methods. Clin Nutr *23(5)*: 1226-1243, 2004.

8 Goovaerts HG, Faes TJ, de Valk-de Roo GW, ten Bolscher M, Netelenbosch JC and van der Vijgh WJ: Extra-cellular volume estimation by electrical impedance – phase measurement or curve fitting: A comparative study. Physiol Meas *19(4)*: 517-526, 1998.

9 Selberg O and Selberg D: Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. Eur J Appl Physiol *86(6)*: 509-516, 2002.

10 Schwenk A, Beisenherz A, Romer K, Kremer G, Salzberger B and Elia M: Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. Am J Clin Nutr *72(2)*: 496-501, 2000.

11 Schwenk A, Ward LC, Elia M and Scott GM: Bioelectrical impedance analysis predicts outcome in patients with suspected bacteremia. Infection *26(5)*: 277-282, 1998.

12 Toso S, Piccoli A, Gusella M, Menon D, Bononi A and Crepaldi G: Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. Nutrition *16(2)*: 120-124, 2000.

13 Thomasset A: Bio-electric properties of tissues. Estimation by measurement of impedance of extracellular ionic strength and intracellular ionic strength in the clinic. Lyon Med *209*: 1325-1350, 1963 (in French).

14 Ward LC, Dylke E, Czerniec S, Isenring E and Kilbreath SL: Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy. Lymphat Res Biol *9(1)*: 47-51, 2011.

15 Cornish B: Bioimpedance analysis: scientific background. Lymphat Res Biol *4(1)*: 47-50, 2006.

16 Kuhnke E: Statistical demonstration of the effectiveness of the Vodder-Asdonk method of manual drainage of lymph. Experientia Suppl *33*: 33-46, 1978 (in German).

17 Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG and Grutsch JF: Bioelectrical impedance phase angle in clinical practice: Implications for prognosis in advanced colorectal cancer. Am J Clin Nutr *80(6)*: 1634-1638, 2004.

18 Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL and Grutsch JF: Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. BMC Cancer *8*: 249, 2008.

19 Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL and Grutsch JF: Bioelectrical impedance phase angle in clinical practice: Implications for prognosis in stage IIIB and IV non-small cell lung cancer. BMC Cancer *9*: 37, 2009.

20 Ott M, Fischer H, Polat H, Helm EB, Frenz M and Caspary WF: Bioelectrical impedance analysis as a predictor of survival in patients with human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol *9(1)*: 20-25, 1995.

21 Piccoli A, Pittoni G, Facco E, Favaro E and Pillon L: Relationship between central venous pressure and bioimpedance vector analysis in critically ill patients. Crit Care Med *28(1)*: 132-137, 2000.

22 Nescolarde L, Piccoli A, Roman A, Nunez A, Morales R and Tamayo J: Bioelectrical impedance vector analysis in haemodialysis patients: relation between oedema and mortality. Physiol Meas *25(5)*: 1271-1280, 2004.

23 Cornish JL and van den Buuse M: Regional expression of c-Fos in rat brain following stimulation of the ventral tegmental area. Neurosci Lett *220(1)*: 17-20, 1996.

24 Ward LC, Essex T and Cornish BH: Determination of Cole parameters in multiple frequency bioelectrical impedance analysis using only the measurement of impedances. Physiol Meas *27(9)*: 839-850, 2006.

25 Casley-Smith JR: Measuring and representing peripheral oedema and its alterations. Lymphology *27(2)*: 56-70, 1994.

26 Foster KR and Lukaski HC: Whole-body impedance – What does it measure? Am J Clin Nutr *64(3 Suppl)*: 388S-396S, 1996.

Received April 27, 2012
Revised June 30, 2012
Accepted July 2, 2012