

BIOIMPEDANCE ANALYSIS IN THE ASSESSMENT OF LYMPHOEDEMA DIAGNOSIS AND MANAGEMENT

Stanley Rockson

Lymphoedema can pose diagnostic challenges, particularly in its early stages. Conventional assessment measures suffer from varying degrees of invasiveness and imprecision. In this context, the potential current and future applicability of multifrequency bioimpedance analysis (MFBIA) is discussed. This accurate, reproducible and non-invasive method detects alterations in extracellular fluid volume and is applicable to both unilateral and bilateral disease. Changes in bioimpedance may antedate the appearance of clinically identifiable disease, thereby facilitating identification of at-risk individuals.

Key words

MFBIA
Extracellular fluid volume
Oedema detection
Lymphoedema

Lymphoedema is a chronic debilitating disease that is frequently misdiagnosed, treated too late or not treated at all (Rockson, 2006a). Lymphoedema can be surprisingly difficult to diagnose, especially in its early stages. Without a proper diagnosis, therapy can be delayed, allowing secondary fibrosis and lipid deposition to take place. Early treatment often results in rapid clinical improvement and may prevent progression to the chronic phase of the disease (Szuba et al, 2003).

The field of lymphatic imaging is evolving (Barrett et al, 2006). At present, clinical approaches encompass indirect radionuclide scintigraphy (Szuba et al,

2003) and the use of modalities such as magnetic resonance imaging (MRI) to undertake the assessment of tissue composition (Szuba and Rockson, 1998). Nevertheless, non-invasive or minimally invasive imaging techniques with the capacity to evaluate lymphatic function accurately, either in health or disease, are still largely lacking (Pain et al, 2004).

Since the occurrence of oedema reflects the presence of underlying dysfunction, in clinical practice an increase in measured limb volume is often utilised as a functional surrogate for the direct quantitation of changes in lymph transport rates (Pan et al, 2006). One widely used approach, at least in research settings, is water displacement volumetry. The affected extremity is submerged in a cylinder filled with water. The amount of water displaced by the submerged limb is equivalent to its volume (Kaulsar Sukul et al, 1993). In clinical practice, perhaps the most commonly utilised technique is to calculate limb volume, with the principles of solid geometry, using measured values of limb circumference and length (Ward, 2006). These equilinear segmental circumferential measures have been the most consistently utilised, largely reflecting the ease with which repetitive assessments can be made, the negligible cost of the interventions and their ability to generate reliable

quantitative data (Mortimer, 1990; Bunce et al, 1994; Gerber 1998). Nevertheless, a review of outcome indicators in human clinical lymphoedema suggests a lack of consistency and rigour in such methods of oedema quantification (Sitzia et al, 1997). Furthermore, such methodology presupposes the presence of established disease, providing little insight into disease risk or the presence of early, functionally negligible impairments. It is within the context of these clinical shortcomings within current approaches to lymphoedema evaluation and management that multifrequency bioimpedance analysis (MFBIA) has been increasingly investigated.

Multifrequency bioimpedance analysis

MFBIA has been applied historically to the assessment of body composition (Thomas et al, 1998). When an alternating current, conventionally of 200–800 mA, is applied to the body's exterior through a set of cutaneous electrodes, it is transmitted through the aqueous component, that is, the path of least electrical resistance, within the tissues. The current flow through biological tissue is frequency-dependent. Nearly all of the current that passes through the extracellular fluid is of low frequency; at higher frequencies, the current passes through both the extracellular and intracellular fluid

Stanley Rockson is Director, Stanford Center for Lymphatic and Venous Disorders, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA

spaces as the reactance of the cell membranes decreases.

Thus, for MFBIA, measurements of the flow of applied current through the body are utilised to accurately quantify the fluid composition (Cornish, 2006). A negligible magnitude of alternating current is applied externally so that the resistance to current flow (impedance) can be measured. Historically, MFBIA has been used to quantitate a variety of physiological attributes, including fat-free mass (Jaffrin et al, 2006), tumour detection (Lee et al, 1999), tissue characterisation (Rigaud et al, 1996), assessment of lung oedema (Shochat et al, 2006) and the measurement of cardiac output (Albert et al, 2004). When applied to the quantitative analysis of lymphoedema, the pathological accumulation of extracellular fluid is mirrored by a decrease in the measured impedance, in proportion to the degree of extracellular fluid accumulation.

Since MFBIA can be used to distinguish extracellular fluid volume, as a component of total fluid volume (for example, of a limb), it can be used to directly quantitate this volume. Comparisons can also be made between a limb of interest and an unaffected limb, expressing the measured impedance of the two limbs as a ratio. Since impedance declines as extracellular fluid volume increases, the measured values of bioimpedance are conventionally expressed as the ratio of the normal limb/abnormal limb. In the absence of segmental excess fluid volume accumulation, this ratio should approximate one; as lymphoedema severity increases, the measured ratio rises proportionately.

To measure bioimpedance, the patient assumes a supine position on a non-conducting surface. The limbs are placed in slight abduction, with the upper extremities pronated (palms down). After cleansing of the skin sites with alcohol, four cutaneous electrodes are positioned on the surface of the patient: the two measurement electrodes are placed at the distal end of the extremities to be assessed (hand

or foot), and the two drive electrodes are placed distally. For the measurement of the upper limbs, measurement electrodes are positioned on the dorsal surface of the wrists at the level of the process of the radial and ulnar bones. Drive electrode sites are at least 5 cm distal on the dorsal surface of the third metacarpal bone of the hands and on the foot (Cornish, 2006).

To minimise intra-operator and inter-operator variability, variations in the placement of electrodes should be minimised by ensuring a reproducible method for identifying the exact location of the electrode placements, relative to superficial anatomic landmarks. Using such precautions, a standard deviation of 2.4% in daily impedance ratios has been reported for unilateral upper extremity lymphoedema (Cornish et al, 2001).

MFBIA for the detection of lymphoedema

Based on the theoretical and practical principles already discussed, the potential use of MFBIA in the detection of extremity lymphoedema can be considered. The application of this technology is based on several implicit assumptions (Ward, 2006). MFBIA is a variable that reflects measured volume, if measured at a low frequency the extracellular fluid is detected and the increase in the volume of the extracellular fluid compartment will reflect the contribution of lymph accumulation when the subject under scrutiny is at risk of developing lymphoedema. Using these assumptions, the measurement of impedance ratios between normal and at-risk zones of the body can be considered for the detection of lymphoedema in the extremity (Ward, 2006).

In a first application of these principles, a cohort of 15 patients and controls with breast cancer-associated unilateral lymphoedema was compared with a comparable group of control subjects (Ward et al, 1992). Measurement of impedance was correlated to direct limb volume assessment, calculated from circumference quantitation. Subsequently, the same investigators documented the fact that the impedance ratios accurately discriminated the lymphoedema-affected

individuals from the controls; in contrast, the ratios of volume measurements overlapped (Cornish et al, 1996). These observations underscore the potential implicit in this methodology for earlier definitive diagnosis (Ward et al, 1992).

As an extension of these observations, a prospective evaluation has been undertaken of the predictive efficacy of bioimpedance determinations for the early onset of lymphoedema in patients at risk by virtue of prior breast cancer therapies (Cornish et al, 2001). Bilateral upper extremity MFBIA and limb circumference were recorded in healthy control subjects to establish the normal range of extracellular and total limb volume ratios. The study subjects were patients scheduled for breast cancer surgery. MFBIA and circumferences were measured before surgery and at intervals thereafter for 24 months. Of the 102 patients recruited into the study, 20 developed lymphoedema; in each of these, MFBIA predicted the onset of lymphoedema up to 10 months before clinical diagnostic criteria would allow identification of pathology. 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.

While a similar study by Box et al (2002) did not mirror these observations of diagnostic sensitivity (with a 67% detection rate), the findings may have been influenced by the greater variability observed in the reference population, leading to a much higher threshold for disease detection by MFBIA. Nevertheless, because changes in measured bioimpedance precede changes in any of the other measurements, at least in one highly conclusive study (Cornish et al, 2001), these results support the suitability of the MFBIA technique as a reliable diagnostic procedure for the early detection of lymphoedema.

MFBIA for assessment of lymphoedema treatment

The applicability of repetitive quantitation of MFBIA to assess the impact of therapy in lymphoedema patients has

also been investigated (Cornish et al, 1996). In this study, daily measurements of circumference and impedance of both the affected and unaffected limbs were recorded for a cohort of 20 lymphoedema patients throughout a four-week treatment programme. As expected, both volumes and impedance ratios declined during active treatment. Perhaps more notably, although volume ratios completely normalised by day 28 of treatment, the measured impedance ratio remained detectably elevated. This observation can be interpreted to reflect a potentially greater sensitivity for impedance when compared with direct volumetric techniques, such as quantitation from simple circumferential measurements. The sensitivity of the impedance technique was approximately three to four times greater (Ward, 2006). Thus, MFBIA conceivably possesses greater discriminating capacity than direct volume assessment both in early detection and in monitoring therapeutic impact.

What about bilateral lymphoedema?

The presence of bilateral lymphoedema poses particular challenges with regard to the use of MFBIA. As we have seen, unilateral lymphoedema can be monitored and quantitated through the use of the contralateral normal limb as a reference with which to construct the bioimpedance ratio. For the assessment of bilateral lymphoedema, the quantitation of intracellular fluid volume can serve as a suitable alternative reference (Ward, 2006). In theory, since intracellular fluid volume should be virtually unaffected by the advent or progression of lymphoedema (Cornish et al, 2001), a ratio for extracellular-to-intracellular (ECF/ICF) volume can be constructed from the measured MFBIA.

To evaluate the validity of these assumptions, a preliminary study has been performed to investigate the relative accuracy of the ECF/ICF volume ratio in detecting unilateral lymphoedema (Cornish et al, 2002). Twenty patients with breast cancer were monitored before surgical intervention and after a clinical diagnosis of lymphoedema was established. Total limb volume by circumferential measurements and

MFBIA measurements of both limbs were serially recorded. An ECF/ICF index was calculated for both the affected and unaffected limbs at both measurement times. In this study, the established techniques of total limb volume and extracellular fluid volume normalised to the unaffected contralateral limb were accurate in the detection of lymphoedema. In addition, comparison of the ECF/ICF index of the affected limb post-diagnosis with that of the baseline measurement showed a substantial, highly significant increase. The results of this pilot study have been interpreted to suggest that the ECF/ICF ratio obtained through MFBIA has a diagnostic sensitivity comparable with, or greater than, the other techniques for lymphoedema detection. As this index does not require normalisation to another body segment, it can therefore be used to detect bilateral lymphoedema, where the absence of a contralateral, normal limb precludes the application of the previously described bioimpedance calculations. Further substantiation of the technique's utility must be derived from direct study of bilaterally affected individuals.

Future clinical applications

The potential utility of MFBIA in the diagnosis of lymphoedema and in assessing its response to therapy has already been addressed. Perhaps the most promising future application of this technology resides in its potential for defining and managing lymphoedema risk (Rockson, 2006b).

Lymphoedema is a disease that is prevalent, yet its prevalence is likely underestimated (Szuba et al, 2003). In its early stages, lymphoedema can be surprisingly difficult to diagnose and often remains unperceived by the patient. In one published series, while 25% of a breast cancer-survivor population manifested objective increases in the volume of the arm at risk, only 14% of the patients subjectively acknowledged the presence of swelling (Kissin et al, 1986).

Beyond the difficulties with the detection of early pathology, one must acknowledge that an even more challenging clinical aspect of the disease

is its propensity for protracted clinical latency (Rockson, 2006b). Published studies of the incidence of breast cancer-associated lymphoedema underscore the importance of this phenomenon. With an aggregate estimated risk of 15–20%, the accrual pattern of new cases of lymphoedema typically displays an early exponential rise, with subsequent more gradual new case identifications with no identifiable time limit beyond which new clinical disease might appear (Herd-Smith et al, 2001; Clark et al, 2005). Compounding this inherent difficulty in identification of impending disease are the elusive properties of biological predisposition to lymphoedema. Many clinical and disease-treatment variables, paradoxically, have no identifiable bearing on lymphoedema risk (Kissin et al, 1986; Rockson, 1998).

It is imperative to accurately define risk and to diagnose early disease because, once established, lymphoedema tends to progress in severity and disease duration has been identified as an important factor in the likelihood that the disease will worsen (Casley-Smith, 1995). The inability to define lymphoedema risk accurately has been identified as a source of fear and frustration by breast cancer survivors and others who face the threat of this complication. MFBIA is a new, developing technology, whose attributes suggest substantial utility in this realm. Increasing use of MFBIA is likely to facilitate the objective documentation of disease and permit the detection of early and subclinical involvement. The utility of MFBIA in future epidemiologic investigations of lymphoedema is self-evident.

Conclusion

In prospective evaluations to date, the assessment of lymphoedema by MFBIA has been found to be rapid, accurate, consistent, and well accepted by patients and practitioners. Its utility is increasingly acknowledged (Moseley et al, 2002). The commercial availability of MFBIA spectrometers designed for specific lymphoedema application (Ward et al, 2001) should encourage more widespread use, both in research and in practice. As discussed, MFBIA is

likely to occupy a central role in the future approaches to lymphoedema risk management, diagnosis and therapeutic monitoring. **JL**

References

- Albert NM, Hail MD, Li J, Young JB (2004) Equivalence of the bioimpedance and thermodilution methods in measuring cardiac output in hospitalized patients with advanced, decompensated chronic heart failure. *Am J Crit Care* 13(6): 469–79
- Barrett T, Choyke PL, Kobayashi H (2006) Imaging of the lymphatic system: new horizons. *Contrast Media Mol Imaging* 1(6): 230–45
- Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM (2002) Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema. *Breast Cancer Res Treat* 75(1): 51–64
- Bunce IH, Mirolo BR, Hennessy JM, Ward LC, Jones LC (1994) Post-mastectomy lymphoedema treatment and measurement. *Med J Aust* 161(2): 125–8
- Casley-Smith JR (1995) Alterations of untreated lymphedema and its grades over time. *Lymphology* 28(4): 174–85
- Clark B, Sitzia J, Harlow W (2005) Incidence and risk of arm oedema following treatment for breast cancer: a three-year follow-up study. *QJM* 98(5): 343–8
- Cornish B (2006) Bioimpedance analysis: scientific background. *Lymphat Res Biol* 4(1): 47–50
- Cornish BH, Bunce IH, Ward LC, Jones LC, Thomas BJ (1996) Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. *Breast Cancer Res Treat* 38(2): 169–76
- Cornish BH, Chapman M, Hirst C et al (2001) Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology* 34(1): 2–11
- Cornish BH, Thomas BJ, Ward LC, Hirst C, Bunce IH (2002) A new technique for the quantification of peripheral edema with application in both unilateral and bilateral cases. *Angiology* 53(1): 41–7
- Gerber LH (1998) A review of measures of lymphedema. *Cancer* 83(12 Suppl): 2803–4
- Herd-Smith A, Russo A, Muraca MG, Del Turco MR, Cardona G (2001) Prognostic factors for lymphedema after primary treatment of breast carcinoma. *Cancer* 92(7): 1783–7
- Jaffrin MY, Fenech M, Moreno MV, Kieffer R (2006) Total body water measurement by a modification of the bioimpedance spectroscopy method. *Med Biol Eng Comput* 44(10): 873–82
- Kaulesar Sukul DM, den Hoed PT, Johannes EJ, van Dolder R, Benda E (1993) Direct and indirect methods for the quantification of leg volume: comparison between water displacement volumetry, the disk model method and the frustum sign model method, using the correlation coefficient and the limits of agreement. *J Biomed Eng* 15(6): 477–80
- Kissin MW, Querci della Rovere G, Easton D, Westbury G (1986) Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 73(7): 580–4
- Lee BR, Roberts WW, Smith DG et al (1999) Bioimpedance: novel use of a minimally invasive technique for cancer localization in the intact prostate. *Prostate* 39(3): 213–18
- Mortimer P (1990) Investigation and management of lymphoedema. *Vasc Med Rev* 1: 1–20
- Moseley A, Piller N, Carati C (2002) Combined opto-electronic perometry and bioimpedance to measure objectively the effectiveness of a new treatment intervention for chronic secondary leg lymphedema. *Lymphology* 35(4): 136–43
- Pain SJ, Purushotham AD, Barber RW et al (2004) Variation in lymphatic function may predispose to development of breast cancer-related lymphoedema. *Eur J Surg Oncol* 30(5): 508–14
- Pan D, Han J, Wilburn P, Rockson SG (2006) Validation of a new technique for the quantitation of edema in the experimental setting. *Lymphat Res Biol* 4(3): 153–8
- Rigaud B, Morucci JP, Chauveau N (1996) Bioelectrical impedance techniques in medicine. Part I: Bioimpedance measurement. Second section: impedance spectrometry. *Crit Rev Biomed Eng* 24(4–6): 257–351
- Rockson SG (1998) Precipitating factors in lymphedema: myths and realities. *Cancer* 83(12 Suppl): 2814–16
- Rockson SG (2006a) Lymphedema. *Curr Treat Options Cardiovasc Med* 8(2): 129–36
- Rockson SG (2006b) Addressing the unmet needs in lymphedema risk management. *Lymphat Res Biol* 4(1): 42–6
- Shochat M, Charach G, Meyler S et al (2006) Internal thoracic impedance monitoring: a novel method for the preclinical detection of acute heart failure. *Cardiovasc Revasc Med* 7(1): 41–5
- Sitzia J, Stanton A, Badger C (1997) A review of outcome indicators in the treatment of chronic limb oedema. *Clin Rehab* 11: 181–91
- Szuba A, Rockson SG (1998) Lymphedema: classification, diagnosis and therapy. *Vasc Med* 3(2): 145–56

Key Points

- ▶▶ Lymphoedema is a chronic debilitating disease that is frequently misdiagnosed, treated too late or not treated at all (Rockson, 2006a).
- ▶▶ Since MFBIA can be used to distinguish extracellular fluid volume, as a component of total fluid volume (for example, of a limb), it can be used to directly quantitate this volume.
- ▶▶ MFBIA conceivably possesses greater discriminating capacity than direct volume assessment, both in early detection and in monitoring therapeutic impact.
- ▶▶ Increasing use of MFBIA is likely to facilitate the objective documentation of disease and permit the detection of early and subclinical involvement.

Szuba A, Shin WS, Strauss HW, Rockson S (2003) The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med* 44(1): 43–57

Thomas BJ, Ward LC, Cornish BH (1998) Bioimpedance spectrometry in the determination of body water compartments: accuracy and clinical significance. *Appl Radiat Isot* 49(5–6): 447–55

Ward LC (2006) Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. *Lymphat Res Biol* 4(1): 51–6

Ward LC, Bunce IH, Cornish BH, Mirolo BR, Thomas BJ, Jones LC (1992) Multi-frequency bioelectrical impedance augments the diagnosis and management of lymphoedema in post-mastectomy patients. *Eur J Clin Invest* 22(11): 751–4

Ward L, Piller N, Cornish B (2001) *Single or multiple frequency bioelectrical impedance analysis for the assessment of lymphedema?* XI International Conference on Electrical Bio-Impedance. Oslo, Norway