Is BIS ready for prime time as the gold standard measure?

Leigh Ward

Assessment of lymphoedema can pose challenges to the clinician. There is no universally accepted standardised method for measurement. In this, the first of two articles, Leigh Ward, a pioneer in the application of bioelectrical impedance spectroscopy (BIS) for assessment of breast cancer-related lymphoedema, makes a strong case that BIS technology now warrants consideration as the reference method for this purpose. In the second of this series, the counter arguments will be put and justification provided for alternative assessment methods. The challenge for all those involved in lymphoedema assessment is to reach agreement on this pressing issue of standardisation.

Key words

Lymphoedema detection
Bioelectrical impedance
spectroscopy (BIS)
Volume measurements

Lymphoedema is a chronic, debilitating condition characterised typically, although not exclusively, by oedematous swelling of the limbs, as a result of inadequate lymph drainage. The precise prevalence of the condition is uncertain, but it is relatively high (Rockson and Rivera, 2008) with estimates for its all cause prevalence in the range of 1.33 (Moffatt et al, 2003) to 1.44 per thousand (Petlund, 1990). Under-estimation of prevalence is likely since the condition is considered to be frequently under-recognised or misdiagnosed (Rockson and Rivera, 2008).

Diagnosis is typically based upon physical examination and clinical history, although direct assessment of lymphatic insufficiency by lymphoscintigraphy may be used (Szuba and Rockson, 1998). In practice, measurement of increase in

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limb size, as change in circumference or volume, is most commonly used as an aid to clinical judgement. Unfortunately, there is no universal consensus on the on the accepted method for measuring either circumference or volume or, indeed, an accepted criterion for a diagnosis of lymphoedema. For example, the International Society of Lymphology (ISL) grades minimal lymphoedema as a <20% increase in volume, Stillwell defined significant

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lymphoedema as >10% volume increase, while the American Physical Therapy Association uses a change in circumference-based grading system (Stillwell, 1969; ISL, 2003; Stout Gergich et al, 2008). This failure to gain agreement on an accepted method for the assessment of lymphoedema has profound consequences. As noted by Rockson and Rivera (2008), 'the reported incidence and prevalence estimates for lymphedema must be scrutinized with regard to the methods in which tissue oedema is sought,

identified, and quantitated', a point reinforced by Hayes et al (2008). It is also clear that if the condition does not have precise criteria for detection, patients may not receive appropriate treatment at the earliest opportunity.

Lymphoedema of the arm is a common sequela of treatment for breast cancer. Its incidence is reported to range from a low of 2–3% to as high as 56%, with 20–30% being typical (Warren et al, 2007). This wide range again reflects the problems associated with varied methods for detection and reporting. Nevertheless, breast cancer-related lymphoedema (BCRL) is an important clinical condition for which there is compelling evidence that early detection assists treatment outcomes (Stout-Gergich et al, 2008). It is also important to note, as again highlighted by Rockson and Rivera (2008), that there is little motivation for the biotechnology and pharmaceutical industries to invest heavily in the development of treatment modalities for conditions of uncertain prevalence and, hence, disease burden.

Lymphoedema assessment methods
Many techniques are available (see Weissleder and Brauer, 2008 for a recent review) and have been used for the diagnosis and detection of lymphoedema. In addition to clinical examination, they include direct methods such as lymphoscintigraphy, lymphangiography, capillary scintigraphy,

ultrasound, computed tomography, magnetic resonance imaging (MRI), nuclear medical imaging and indirect methods such as tonometry, volume estimation and bioelectrical impedance analysis. In most cases, detection of lymphoedema, particularly of the extremities, is achieved by the simple procedures of clinical examination and volume measurement without recourse to the more sophisticated and expensive imaging techniques (Weissleder and Brauer, 2008). It is therefore incumbent upon those who rely upon these procedures to detect lymphoedema, to ensure the validity of the techniques that they use and to have defined criteria for diagnosis and detection. At present, with regard to volume-related measurements, this is unfortunately not always so.

Problems with currently used procedures for volume measurement of peripheral lymphoedema

There are three principal techniques for measurement of leg and arm volumes:

▸ Geometrical calculation of volume based upon circumferential measurements performed with tape measure at pre-defined intervals, typically 4, 5 or 10cm along the limb; volume being calculated assuming a circular (Casley-Smith, 1994) or elliptical truncated cone geometry (Mayrovitz, 2003)

▸ Volume determined by water displacement (Lette, 2006)

▸ Volume determined from the 2-D silhouette cast by the limb when passed through an array of optoelectronic sensors, a technique referred to as perometry (Stanton et al, 1997).

Each of these methods has its own unique advantages and disadvantages. Geometric calculation is inexpensive as only a tape measure and calculator or nomogram are required. It is highly acceptable to a patient but is tedious and time-consuming to perform. Furthermore, there is no standardisation of the number of circumferential measurements (slices) that are required to provide a reasonably accurate measurement of volume. As a consequence, the method can lack

accuracy and precision (Weissleder and Brauer, 2008). Water displacement is equally inexpensive and can be less time-consuming but is messy for the patient, may be associated with infection control problems and is clearly not appropriate where the limb being measured has open wounds or skin conditions (Fu et al, 2009a). Perometry is rapid, accurate and precise and provides an immediate result for the attending clinical staff. Unfortunately, the equipment is expensive and only recently has become available as a portable unit.

Notwithstanding these practical issues, each of these methods aims to provide a measurement of total limb volume. This, in itself, is not fully informative. Lymphoedema is, at least in its early stages, an accumulation of lymph, an extracellular fluid. The total volume of an arm may change for other reasons. Obesity and work- or exercise-induced hypertrophy are cases in point, where a simple total volume measurement is not immediately related to the parameter of interest, i.e. lymph volume. If the aim of volumetric methods is the early detection of an increase in volume caused by the presence of lymphoedema, it is necessary to have volume standards against which we can compare test results and thresholds, or cut-offs established for a degree of swelling considered to be indicative of the presence of lymphoedema. It is analogous to the circumstances pertaining in clinical chemistry where a normal or reference range for a diagnostic parameter, e.g. fasting blood glucose concentration, is established (2.8–6mmol per litre) and values above a set threshold (a fasting venous blood concentration >6.7mmol per litre) are indicative of diabetes mellitus and prompt further investigation. It is recognised in clinical chemistry for such an approach to have diagnostic utility, where quality control of procedures is paramount and there are universally recognised and accepted standardised technical and data analytic protocols. Furthermore, interpretation of results should rest on a sound theoretical, objective and statistical footing. However, this does not appear to be the case for volume measurement

and its interpretation in lymphoedema assessment.

As an example, volume difference of 200ml between the arms is a widely used criterion to define unilateral lymphoedema following breast cancer treatment (Box et al, 2002). An exhaustive survey of the literature failed to find studies in which this criterion was determined or validated in a rigorous scientific manner. The 1986 paper of Kissin et al is widely quoted by later authors when referencing the 200ml criterion. Yet in that paper, with reference to volume difference between arms, Kissen et al (1986) state that, 'several cut-off points were chosen (these were of necessity arbitrary in nature but corresponded with some of those chosen by previous authors)'. Almost a decade earlier, the publication of Swedborg (1977) is also cited, but careful reading of the paper, while noting the need to account for normal difference in volume between arms due to dominance, a confounder not always accounted for, does not provide evidence for general acceptance of a 200ml cut-off. One of the earliest publications that makes reference to the use of volume for lymphoedema assessment is that of Stillwell (1969), who recommended that swelling be expressed as a percentage of the normal arm. This led Wilhelm et al (1974) to use a classification of a 'slight amount' of swelling as an 11–20% volume excess, 'moderate amount' as 21–40% volume excess, and a 'marked amount' as 41–80% volume excess. It is worth noting that these authors also recognised the difficulties stemming from an inadequate definition of lymphoedema: 'Variability in the definition of edema of the arm makes incident figures difficult to obtain'. It would seem, despite the three and a half decades of lymphoedema research that have passed since this statement was made, that we are still no further forward. We continue to use outmoded measurement methods and detection criteria of uncertain provenance.

Bioelectrical impedance spectroscopy (BIS) for detection and assessment of lymphoedema

It is now seventeen years since bioelectrical impedance spectroscopy

(BIS) was first used in a clinical setting to assess lymphoedema (Ward et al, 1992). In the intervening years, BIS instrumentation has been improved and data analysis has become more sophisticated, and yet the underlying principles for using BIS to assess lymphoedema remain unchanged (*Figures 1* and *2*). Briefly, BIS analysis measures the opposition (impedance) of the body tissues by the passage of an imperceptible alternating electric current over a range of frequencies. The magnitude of the impedance at zero frequency (Z0), determined by extrapolation from the impedances at the measured frequencies, is inversely proportional to the magnitude of the extracellular fluid volume. The impedance can be used, therefore, as a quantitative index of extracellular fluid volume which includes lymph. (For further details the reader is referred to Ward, 2006 and Ward et al, 2008.)

To recognise the normal variation in impedance values within the population, normalisation of data has been adopted. In the case of unilateral lymphoedema, this is achieved by using the ratio of impedance between the at-risk limb and the contralateral, unaffected limb, and for bilateral lymphoedema, by normalising the impedances of the at-risk or affected limbs to those of the unaffected limbs, e.g. affected legs are normalised to unaffected arms (Cornish et al, 2002). Clinical interpretation of these impedance ratios poses the same problems as beset interpretation of direct volumetric measures; namely, what ratio value should be taken as indicative of the presence of excess extracellular fluid or lymph? Unlike the arbitrary choice of a set volume difference as noted above, a statistical approach is adopted to determine cut-off values for lymphoedema. The normal distribution of ratios in the normal population was determined and cut-offs set at the population mean value plus three standard deviations (Cornish et al, 2001). Values greater than this in a patient at risk of lymphoedema flag the patient as requiring further investigation, while in patients with existing lymphoedema,

change in this value can be used to monitor progression. Alternatively, ratios may be converted to a linear scale as an L-dex score (Ward et al, 2009).

Why bioelectrical impedance spectroscopy should now be adopted as a reference method

It is necessary where there are competing methods of assessment to compare their performance against a common set of criteria. Again, we can take our lead from the long established quality control systems in analytical and clinical chemistry. Under these procedures preference should be given to methods of analysis or measurement, the reliability of which have been established with respect to:

▸▸ Specificity
▸▸ Accuracy
▸▸ Precision
▸▸ Repeatability both within and between centres
▸▸ Limits of detection
▸▸ Sensitivity and practicability
▸▸ Applicability under normal conditions of use (Wood et al, 1998).

The BIS approach fulfils these criteria.

Specificity
Unlike total volume measurement methods, BIS provides an index of what is actually changing in lymphoedema, i.e. lymph (an extracellular fluid) volume. In this regard, BIS can be considered as approaching the definition of a 'definitive method', as applies in clinical chemistry quality control as 'today's best approximation to the true value' (Stockl and Reinauer, 1993).

Accuracy
Bioimpedance analysers when correctly calibrated are exceedingly accurate electronic measuring instruments (Oldham, 1996). It is not possible to assess measurement accuracy for the human body since its true impedance is unknown. However, measurements on electrical circuits simulating the human body indicate accuracy of at least ±1% (Oldham, 1996).

Precision and reproducibility
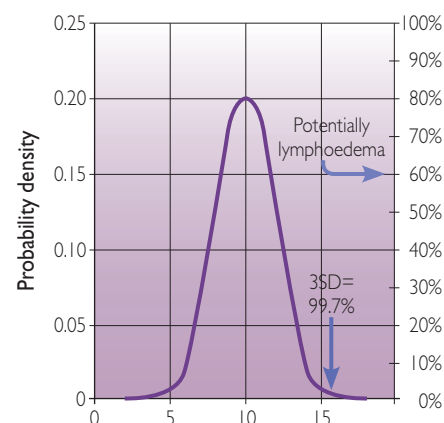An assessment of the performance of

Figure 1. BIS uses the normal distribution of inter-arm impedance ratios to set thresholds indicative of possible lymphoedema.
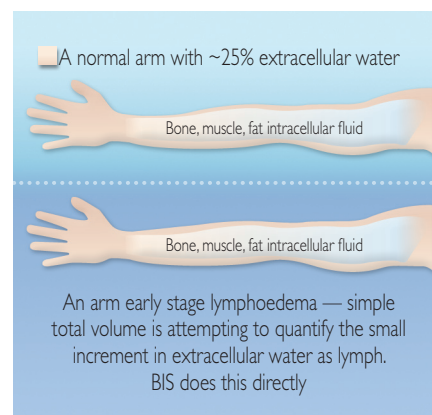

Figure 2. The principles of BIS. BIS measures the impedance of only the tissue compartment that changes in lymphoedema, not all the tissues of the limb.

early generation impedance analysers indicated precision of impedance measurements both on test circuits and in humans of better than 1%, with inter-operator bias, mainly due to operator input in data analysis, of up to 2.5% (Ward et al, 1997). More recently, Czerniec et al (2009) have reported high intra- and inter-rater reliabilities for BIS measurements of arm lymphoedema (intraclass correlation coefficients of 0.94 and 0.99). It is worth noting that current generation BIS spectrometers reduce markedly the inter-operator bias since much of the data analysis is now automated.

Limit of detection
The detection limit for BIS in lymphoedema is difficult to ascertain. Czerniec et al (2009) showed that a mean change in arm volume over

four weeks, measured by perometry, in BCRL patients was 57.5ml. The corresponding BIS ratio change was 0.06. In control subjects the four-week change was 36.3ml by perometer and 0.04 by BIS. Thus, we may assume that the detection limit is at least of this order. This corresponds to a detection limit of about 2% of total arm volume (Ward et al, 2008), a value comparable to a 3% change in volume measured by perometry that has been used successfully for the early detection of BCRL (Stout Gergich et al, 2008).

Sensitivity

An early study of Cornish et al (1996) measured the change in BIS ratio over a 28-day period in a cohort of women undergoing treatment for unilateral lymphoedema of the arm post-treatment for breast cancer. Change in arm volume, determined geometrically, was also monitored. At the end of the treatment period, lymphoedema was considered to be absent in some women on the basis of volume measurement but still present on the basis of BIS assessment. It was concluded that BIS was approximately four-fold more sensitive in detecting change in lymphoedema than simple volume measurement. In a later prospective study, the same group demonstrated that on the basis of an elevated BIS ratio, lymphoedema was detected up to 10 months before confirmed clinical diagnosis (Cornish et al, 2001). More recently, and again from the same research group, sensitivity and specificity data have been provided, suggesting that compared to the BIS method, set as 100%, the sum of arm circumference method had a sensitivity of 42% and a specificity of 88% (Hayes et al, 2005; 2008).

In contrast, Box et al (2002) found that BIS was unable to detect lymphoedema in 50% of women post-breast cancer treatment and at risk of lymphoedema, who demonstrated an increase of at least 200ml in the volume of the operated arm compared to the unoperated arm. However, in their study, the ratio cut-off for detection was not determined in an independent control population, but from baseline

measurements performed on the women immediately pre-operatively. The three standard deviation cut-offs reported by this group were higher than those reported in the earlier study of Cornish et al (2001). It is noteworthy that most recently, Ridner et al (2009) reported that original cut-offs determined by Cornish were capable of discriminating breast cancer survivors with lymphoedema from those without and a normal cohort, concluding that these 'limb index ratios (LIRs) can be used with confidence as markers for lymphoedema'.

Practicality

BIS measurement is simple to perform. The measurement technique is highly standardised, rapid (less than five minutes in total) (Ridner et al, 2009), painless and does not require the patient to disrobe. BIS instruments are relatively expensive and may be beyond the resources of smaller lymphoedema care centres. A less expensive, single, low-frequency instrument is available that has been found to be eminently suitable for use in non-laboratory settings and well tolerated by patients (Ridner et al, 2009). Indeed, these authors note that some participants in their study expressed interest in using such a device at home as an adjunct to their lymphoedema self-management programme. The BIS and single frequency devices have been cross-validated (York et al, 2009).

Is BIS ready for prime time as the method of choice for lymphoedema detection?

Many authors (Erickson et al, 2001; Galland et al, 2002; Hayes et al, 2008; Rockson and Rivera, 2008; Stout Gergich et al, 2008; Fu et al, 2009b) identify lack of standardisation for the detection and evaluation of lymphoedema as an impediment to lymphoedema care and therapy. This article asked the question, 'Is BIS ready for prime time as a gold standard for lymphoedema detection?'. To this question, my answer is a qualified 'yes'. A convincing argument can be made that on theoretical grounds, analytical and technical accuracy and precision and practicality in use, impedance technology is the method of choice when compared to competing technologies. The case is well made

Key points

» BIS has proven utility for the assessment of breast cancer related unilateral lymphoedema.

» BIS is founded on sound theoretical grounds and meets internationally accepted criteria for defining a reference method.

» The instrumentation is relatively inexpensive, easy and rapid to use and is well accepted by the patient.

» A strong case is made for its adoption as the reference method for lymphoedema assessment.

for its adoption for the assessment of lymphoedema post-breast cancer treatment. It should be acknowledged that impedance ratios, in common with the other assessment modalities, should not be considered as providing the definitive diagnostic criterion. They must always be considered alongside the clinical judgement of the clinician, lymphoedema practitioner or lymphologist. To quote Stanton et al (2006) in relation to BCRL: 'Careful examination of the arms of patients with breast cancer is vital. Comparison of arm volumes (or circumferences) alone, will not detect early BCRL and will result in an underestimate of its prevalence in studies of the complications of axillary surgery'.

Like all technologies, BIS is under constant development and refinement. Pressing needs are for optimisation and thorough validation of the method for quantification of bilateral lymphoedema. Its adoption awaits these further studies. The challenge for the lymphoedema research community is to undertake these studies at the earliest opportunity. JL

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