LYMPHATIC RESEARCH AND BIOLOGY
Volume 4, Number 1, 2006

XX International Society of Lymphology Symposium on Bioelectrical Impedance Analysis in the Management of Lymphedema

The 20th Congress of The International Society of Lymphology was held in Salvador, Brazil in September, 2005. Among the many excellent presentations at that Congress was a special symposium entitled, "*Addressing the unmet needs in lymphedema risk assessment and therapeutic monitoring*". The particular focus of the presentations was the bioelectrical impedance analysis technique for the assessment of lymphedema, a topic that also received some attention elsewhere in the Congress. The symposium was chaired by Associate Professor Leigh Ward from the University of Queensland and included two other eminent speakers. Professor Stanley Rockson of Stanford University commenced the Symposium by providing the clinical background to the need for tools to measure lymphedema and how one can then use these tools in a clinical setting for the management of the condition. He was followed by Associate Professor Bruce Cornish from the Queensland University of Technology who has been one of the leading researchers in the field developing the impedance technology and of the application of this technology for the purposes of monitoring lymphedema. Dr. Cornish provided an overview of the theoretical basis on which the technique is based. The Symposium was concluded by Dr. Ward discussing available clinical trial data assessing the utility of the technique—in essence, answering the question, "*Does it actually work?*". The papers that follow represent the content of the presentations from this timely symposium.

LYMPHATIC RESEARCH AND BIOLOGY
Volume 4, Number 1, 2006

Addressing the Unmet Needs in Lymphedema Risk Management

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It is the purpose of this overview to underscore some of the clinical problems associated with the clinical assessment of lymphoedema to create a context in which to discuss the utility of bioimpedance analysis as a tool for diagnostic evaluation.

Initially, as a point of reference, it is appropriate to address the normal function of the lymphatic system. In healthy individuals, the lymphatic system subserves three vital functions: the maintenance of fluid homeostasis through the drainage of interstitial I fluid from the extracellular space; the absorption of lipids from the intestinal tract; and modulation of immune traffic through its obligate transport of immunocompetent cells from the periphery to the more central aspects of the immune system.[1]

A fairly simple classification scheme is usually applied to the functional categorization of patients with lymphedema.[1] As a first division, one conceives of the disease as either 'primary' (i.e., congenital, heritable, or without obvious antecedents), or 'secondary' (i.e., acquired). The category of acquired lymphoedema can then be further refined into subgroups with reference to the initiating factors for lymphedema develop, including traumatic or iatrogenic damage to the lymphatic structures, the latter encompassing both surgical interventions and radiation effects; infection; and obliteration of lymphatic transport capacity through either extrinsic compression or intraluminal invasion by tumor. In this context, it is useful to distinguish between 'benign' and 'malignant' forms of lymphedema, the former category reflecting, among other causes, the iatrogenic consequences of treatment for malignant diseases like breast cancer.

In health, normal lymphatic circulatory function reflects a balance between the lymphatic load (i.e., the quantity of lymph produced/unit time and the ability of the lymphatic circulatory structures to accommodate the transport requirements for that volume of fluid; Fig. 1). Lymphedema results in circumstances where the load is pathologically increased, where transport capacity is anatomically or functional deranged, or in situations where there is a relative distortion of both factors. A variety of pathological conditions can create an imbalance between load and transport capacity. The current discussion will center chiefly on those disease entities that reduce the transport capacity, typically through an acquired anatomic damage to the lymphatic circulation.

The net consequence of a lymphatic load/transport imbalance is the development of either latent or clinically-expressed lymphedema. This edematous condition represents a complex disease state that is characterized by a number of biological attributes: in addition to fluid accumulation, there is an elevation of interstitial protein content, chronic inflammation, recurrent infection, fibrosis, and the accumulation of adipose content.[1] Functionally, the patient experiences pain, swelling, and progressive immobility.

As a point of reference, as one considers risk assessment, it is appropriate to consider this

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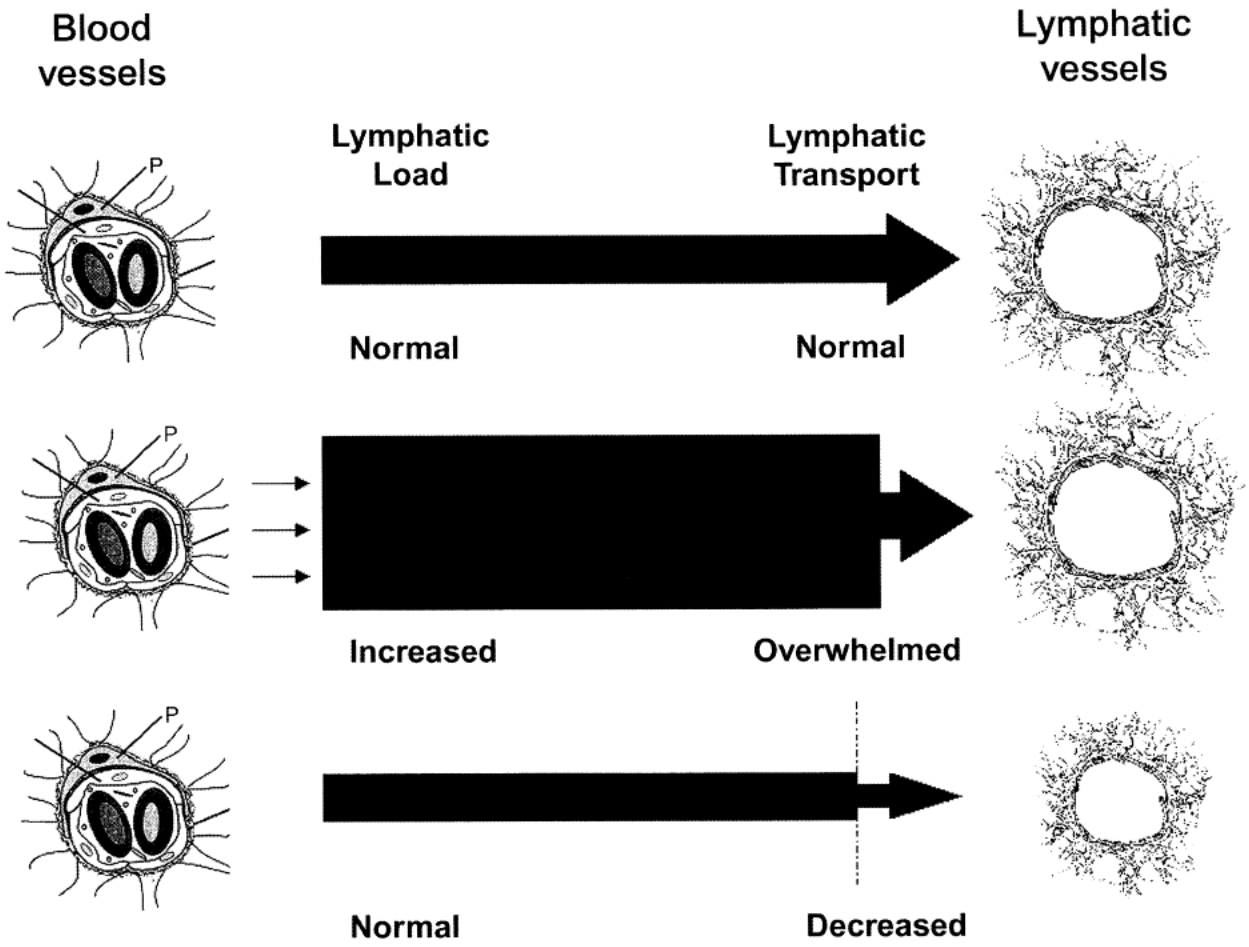

FIG. 1. Schematic representation of the pathogenesis of lymphedema. Normal lymphatic function is characterized by a balance between the formation of lymph and its transport into, and through, the lymphatic vasculature (*upper panel*). Lymphedema results when the formation of lymph exceeds the transport capacity of the circulation (*middle panel*) or when a normal lymph load cannot be accommodated by the vasculature that has been damaged (*lower panel*). Hybrid forms of disease also occur.

phenomenon in the context of breast cancer-associated lymphedema, perhaps the most extensively studied cause of acquired vascular insufficiency. Estimates of the incidence of breast cancer lymphedema vary in the medical literature from low values in the range of 9%–10% to those that exceed 50%. Incidence estimates depend on the methods employed to identify and enumerate cases.[3]

When lymphedema is clinically overt, it is a disease entity that is reasonably simple to recognize on clinical grounds. A trained clinician can assign the diagnosis of acquired lymphoedema with reasonable confidence. Paradoxically, however, with a relative lack of emphasis on this disease condition in prevailing medical practice, it is frequently overlooked or misdiagnosed.[4] In any event, one of the elusive attributes of this, and other, acquired forms of lymphedema is the poorly understood biology that predicates a strong tendency toward latency. In other words, the anatomic insult is incurred by the patient at a point in time that may precede by 5 years, or longer, the clinically recognizable, functional expression of disease. Published studies of the incidence of breast cancer-associated lymphedema illustrate this phenomenon well. For example, one study of 1278 breast carcinoma patients residing in a defined geographical region illustrates an aggregate 15% risk of lymphedema development.[5] Examination of the cumulative incidence reveals an early exponential increase in cases, followed by a more gradual, virtually linear ac-

crual; while the slope of this relationship incidence to time flattens progressively, it never attains a value of zero (Fig. 2). Another recent study has focused on similar events in the early months after the anatomic insult to the lymphatics after breast cancer therapy.[6] Here, with an aggregate 20% incidence in the population studied, despite a linear-to-exponential accrual of new cases over 36 months, one again observes a substantial delay from the anatomic insult to the clinical expression of disease. These examples illustrate the obstacle posed to risk assessment by the prominence of latency in the expression of this disease.

Another frustrating aspect of this problem is reflected in the difficulty with which one determines predisposition to heightened risk for the development of overt lymphedema. If one assumes, on average, that 20% of breast cancer survivor population is at risk, how are these individuals distinguished from the remaining 80% of the survivor population? Patient age, menopausal status, and most of the surgical variables have no statistically identifiable bearing on relative risk.[5] The most important disease variable, tumor classification and numbers of nodes examined bear an inconstant relationship to risk. Many other treatment-related factors, including drug therapy, time interval since presentation, and radiotherapy to the breast pose no increment of risk.[7] Those treatment variables that have been associated with enhanced risk (mastectomy with wide local excision, extent of axillary surgery, axillary radiotherapy; radiotherapy to the breast, nodal disease status) do not, alone, accurately distinguish the at-risk subpopulation.[8]

Thus, in using breast cancer-associated disease as a paradigm for acquired lymphedema, one can conclude that this chronic debilitating disease is frequently under-recognized or misdiagnosed; consequently, it can be said that it is usually treated too late and very likely will not be treated at all.[9] Lymphedema is a disease that is prevalent, yet its prevalence is likely under-estimated.[9] Thus, the availability of newer technology, that will facilitate the objective documentation of disease and permit the detection of early and subclinical involvement will undoubtedly ameliorate the clinical response to these patients and provide a much-needed link to foster epidemiologic investigations.

It must be recognized that the inability to reliably identify the risk-promoting and precipitating factors that cause lymphoedema to appear or to worsen has served to foster fear and frustration in patients who perceive themselves to be at risk or are told by their physicians and care providers that they are at risk. Unfortunately, the medical community has, historically, had no ability to identify or quantify the magnitude of that risk. The incidence of breast cancer in the United States is projected to increase to 420,000 per year in the next 20 years.[10] The greater incidence of breast cancer is likely to increase the incidence of lymphedema proportionally. It has been observed that, even

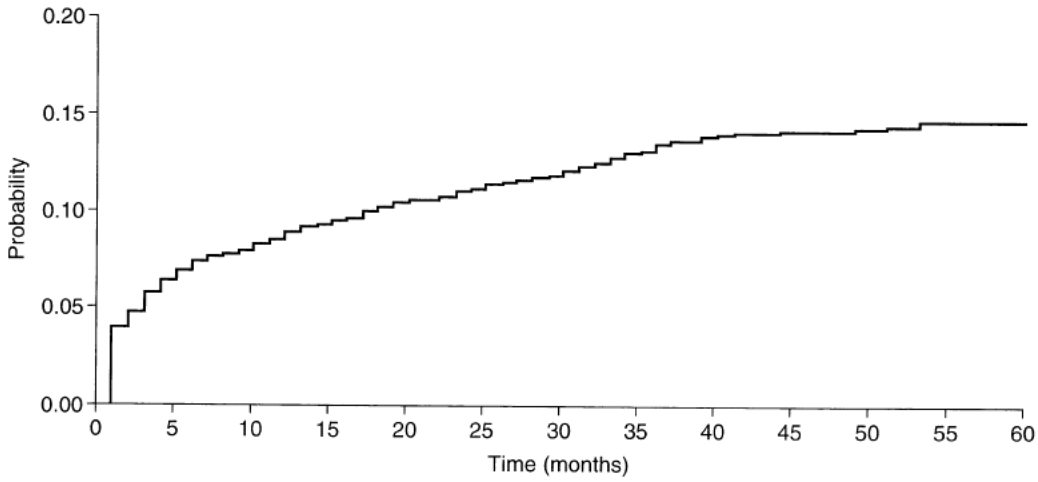

FIG. 2. Cumulative Incidence of lymphedema after breast cancer. Reprinted from Ref. 5 with permission of Wiley-Liss, Inc. a subsidiary of John Wiley & Sons, Inc.

with more conservative surgical techniques the problem of post-breast cancer treatment lymphoedema has certainly not been eliminated.[11,12] Therefore, the accrual of greater numbers of cases will predictably increase the case rate of lymphedema as well. In addition the enhanced survival of breast cancer patients is likely to occasion an increased prevalence of arm lymphedema which can develop, as we have seen, many years after the index breast surgery.

Beyond insufficient practitioner education, lymphedema can be surprisingly difficult to diagnose, especially in the early stages. Patients do not accurately perceive the presence of subtle disease. In one study, it has been demonstrated that only 14% of the patients complained subjectively of swelling yet, upon measurement of limb volume, it was established that fully 25% of that patient population had edema by objective analysis.[7] Thus, the clinician cannot rely upon subjective complaints to draw attention to the presence of early disease and, without a proper diagnosis, therapy is often delayed. When fully expressed disease is encountered, aggressive therapeutic interventions can readily by instituted. In circumstances where lymphatic insufficiency enters the differential diagnosis, indirect radionuclide lymphoscintigraphy can be performed to provide additional objectification.[9] Such diagnostic techniques are useful and reliable when applied in specific clinical circumstances, but are not necessarily suitable, or cost-effective, for widespread screening patients that may harbor latent or subclinical disease.

Why the imperative to establishing an early diagnosis in lymphedema? in clinical series that are available for analysis, it is readily recognized that, once established, lymphedema does have an inexorable tendency to progress and the temporal duration of the lymphedema appears to represent an additional factor that will contribute to the likelihood of progression.[13] In other words, earlier diagnosis and institution of appropriate therapeutic measures creates a theoretically greater potential to impact the tendency of the condition to progress or to produce functional impairment in the patient. In a study of 231 individuals with lymphedema, it was observed that the lymphedema had a significant tendency to increase with time, both in grade and in quantity; both patient age and duration of lymphoedema were significant factors for that progression, but the more important of these was, in fact, the duration of the disease.[14]

Many of the clinical attributes of lymphedema may bear a relationship to this duration-dependent behavior. The interstitial edema tends to be more protein-enriched than is the case in hydrostatic forms of edema. The relationship of this observation to the other attributes of the disease has not been established but, on clinical grounds, it is recognized that lymphedema patients are predisposed to fibrotic and sclerotic changes of the affected tissues, and the generalized effects of fibrosis lead to progressive functional impairment. Histologically, the skin of lymphedematous extremities is characterized by a marked increase in the thickness of the dermal/epidermal junction, with hyperkeratosis, parakeratosis, inflammatory infiltrates, and dilation of the microlymphatics. Furthermore, chronic lymphoedema leads to a poorly understood, but well-documented predilection to adipose deposition in the affected limb with the passage of time.[15] It is not clear to what extent an aggressive, early intervention might prevent this tendency, but this complex biology is clearly related to chronicity of disease and might therefore be amenable to therapeutic modulation. The tendency of these patients to manifest recurrent soft tissue infection is another attribute of lymphedema that may be beneficially modulated through early and effective therapeutic intervention.

It is believed, but not definitely ascertained yet, that early effective interventions in chronic lymphoedema will reduce the long term implications of lymphoedema, including the tendency to infection, predilection to fibrotic transformation, and the accumulation of excess adipose tissues. Therefore, tools that might permit the accurate identification of these patients at the earliest possible time point will facilitate the prospective studies that will allow assessment of efficacy. Risk stratification and aggressive early intervention may have the capacity to forestall, or even eliminate, the consequences of lymphedema. The elusive as-

pect of disease latency complicates the identification of high risk patients; therefore, the potential for effective strategies exists, but requires the ability to accurately identify these high risk individuals. Availability of accurate, noninvasive technology for the detection of latent or early disease may facilitate the implementation of preventive strategies.

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LYMPHATIC RESEARCH AND BIOLOGY
Volume 4, Number 1, 2006

Bioimpedance Analysis: Scientific Background

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In this section, the scientific principles which form the basis of the bioimpedance technology are explained. A thorough understanding of these principles is essential for understanding how the technology is applied so that one can appreciate what the limitations are and how best to interpret the measurements obtained in various applications.

Essentially the technology "bioelectrical impedance analysis" measures the response of the body to an applied electrical current. A low level alternating current is passed through the body and the impedance or opposition to this current flow is measured. The concept of using the electrical resistance or impedance to assess physiological aspects of the body was investigated as early as 1888 by Vigouroux. However it was the middle of the twentieth century when the first major advances in the technology were progressed. Researchers Nyboer, Thomasset, and Hoffer independently used bioelectrical impedance analysis (BIA) to estimate physiological parameters such as blood flow, body water, and fat-free mass. The first single frequency commercial instrument was produced by RJL in the 1980s, followed by multifrequency instruments in 1993. Although studies of electrical conduction through the body date back over 100 years, the period of intense research into the application of BIA commenced in 1985 with Hank Lukaski publishing his seminal article in the *American Journal of Clinical Nutrition*. The proliferation of research in the applications of BIA is demonstrated by over 2000 citations returned by a *PubMed* search using "Impedance" + "Body Composition". This proliferation of research is evidence of the numerous applications of BIA in the general area of human body composition.

PRINCIPLES OF BIA

An alternating electric current at a typical frequency of 50 kHz is passed through the body via ECG-type skin electrodes. The electric current, typically between 200 and 800 :A, is conducted along the path of least resistance which is the tissue with high water content. Measurement of the impedance is recorded, with an arithmetic transformation used to relate this to the physiological parameter of interest. The impedance (Z) is a two-dimensional vector quantity which can be expressed either as a magnitude (in Ohms) and phase angle (degrees) or as a resistance (R) and reactance (X). The resistance is the opposition to the current inherent in body conductors (fluids), while the reactance is the opposition to the current flow due to cell membranes and tissue interfaces.

The impedance of a conductor is related to its dimensions as well as the electrical properties of the material. In a cylindrical conductor the impedance is given by Equation 1.

$$Z = \rho \frac{L}{A} \qquad \text{Equation 1}$$

where ρ is the electrical resistivity of the material, and L and A are the length and cross-sectional area of the cylinder.

Using the relationship for the volume of a cylinder, Equation 1 can be rearranged to provide the relation between impedance and volume (Equation 2).

$$V = \rho \frac{L^2}{Z} \qquad \text{Equation 2}$$

Current flow in biological tissue is frequency dependent with almost all of the current passing through the extracellular fluid at low fre-

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quencies. At higher frequencies the reactance of the cell membranes decreases and the current passes through both the extra- and intracellular fluids. Ideally the best frequency is either zero or infinite depending on whether the extracellular fluid volume is being measured or that of the total fluid (extra- plus intracellular fluids). Unfortunately neither of these can be used due to practical limitations. One method of overcoming these limitations is to use fixed frequencies close to the ideals of zero and infinite, such as 5 kHz and 500 kHz. However a better solution is to use Bioelectrical Impedance Spectroscopy (BIS).

In the spectroscopy approach the impedance is measured at many frequencies in the range 5 to 1000 kHz. The resistance and reactance of the measured impedances are plotted and form a semicircular locus as shown in Figure 1.

By extrapolating the data along the theoretical circular locus, the values of R_0 and R_∞ (both of which are unable to be measured directly) can be determined. Using the relation in Equation 2, the impedance quotients H^2/R_0 and H^2/R_∞ can be used to estimate extracellular fluid and total body fluid volumes, respectively (height H is used as a surrogate measure of the conducting length).

APPLICATIONS OF BIOIMPEDANCE

There are numerous applications of BIA including tumour detection, tissue characterization, assessment of lung edema, and the measurement of cardiac output. However the main application discussed here is that of human body composition and, in particular, the measurement of lymphedema.

Whereas Equation 2 suggests a well-defined relationship between volume and the impedance quotient, the value of the electrical resistivity, ρ, varies significantly between tissue types. Equation 2 is also restricted to cylindrical conductors with a uniform cross-sectional area, quite unlike the human body. Hence, while the technology is based on a sound theoretical foundation, its application is an empirical approach requiring a calibration against known gold standards. In these calibrations a large cohort of subjects is measured by both BIA and an appropriate gold standard such as tracer dilution (for total body fluid) or Dual Energy X-ray Absorptiometry (for fat-free mass). A regression equation is then used to create a prediction algorithm which can then convert future BIA measurements into total body fluid volumes or fat free mass.

The resulting prediction algorithms can be applied with relatively high accuracy, achieving standard errors of between 3% and 10% in numerous validation studies. The electronic accuracy and precision of readily available instrumentation is less than 1–2% with a coefficient of variation for individual measurements generally less than 1%. However, the most important limitation on the technique is that any particular algorithm is only valid for the cohort

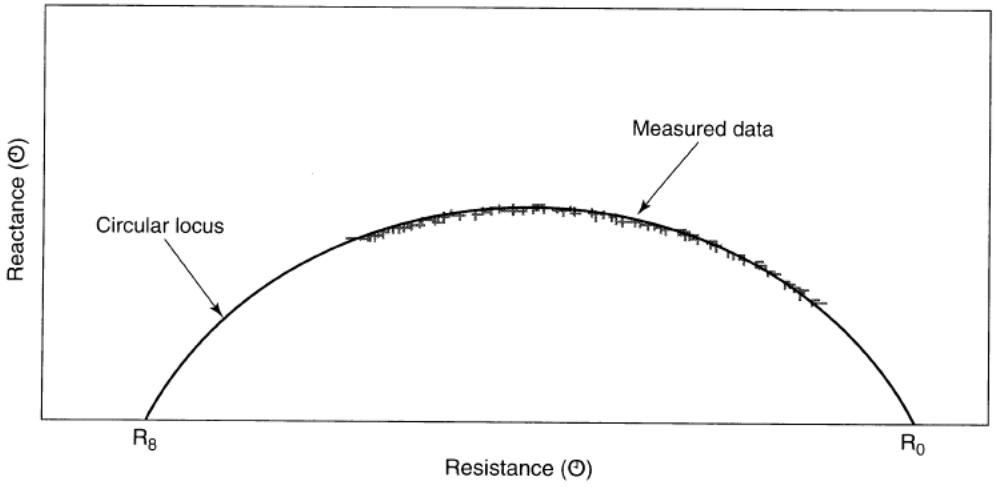

FIG. 1. Plotted resistance and reactance of the measured impedance.

of subjects in which it was developed. Hence different algorithms are needed for variations such as age groups, ethnicity, and various states of ill-health.

LYMPHEDEMA

Lymphedema is a chronic tissue swelling, usually in a limb, as a result of impaired lymph drainage. The measurement of the severity of the condition is an essential component of any treatment regimen. The lymphatic fluid is part of the extracellular fluid compartment which normally comprises approximately one-quarter of the total volume of the limb. Hence any technique, to quantify lymphedema, based on the measurement of total limb volume will be relatively insensitive to changes in the volume of lymphatic fluid.

Bioimpedance is one of the few techniques of body composition analysis which differentiates the extracellular fluid compartment from the total limb volume. However while a similar impedance quotient, L^2/R_0, can be used there is no gold standard technique of independently determining the extracellular volume of a single limb. Hence, unlike the approach described above to estimate fat-free mass, no algorithm to provide a volume in liters can be produced. Instead the ratio of the impedance measures from the affected and unaffected limbs provides an index which describes the increase in lymph volume, (Equation 3).

$$\frac{ECF_{affected\ limb}}{ECF_{unaffected\ limb}} = \frac{R_0}{R_0^*} \quad \text{Equation 3}$$

where R_0 is the impedance (at zero frequency) of the unaffected limb, and R_0^* is the impedance (at zero frequency) of the affected limb.

For a patient with clinical lymphedema, this index will be greater than 1.00; typically a patient with grade 2 lymphoedema would have an index of approximately 1.35. With the positive effect of intervention treatment, this index will decrease, demonstrating a decrease in lymph volume of the affected limb.

MEASUREMENT PROTOCOL

The BIA technique uses a tetrapolar electrode arrangement; with two measurement electrodes positioned one at each end of the segment to be measured, and two drive electrodes each positioned distal to the measurement electrodes. The low level current is passed between the two drive electrodes and the measurement electrodes record the impedance of the segment of interest. At first it would appear obvious and logical to select the wrist and shoulder as the sites of the measurement electrodes for the upper limb. However the poor reproducibility of locating the electrode at the shoulder results in up to 10% variation in the measurement. This

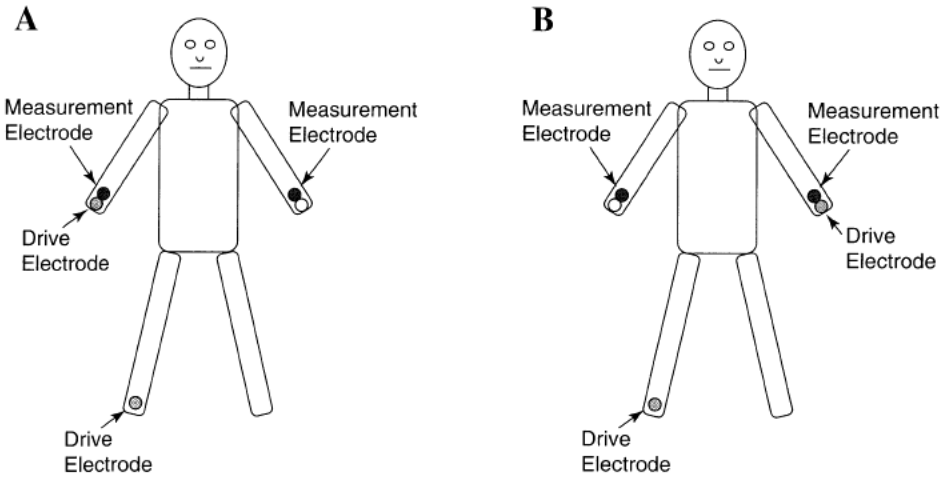

FIG. 2. Schematic representation of electrode sites.

variability is unacceptable when attempting to detect changes of a few percent in volume.

An important feature of the fundamental relation between the measured impedance and volume (Equation 2) is the impact of the length in the equation. As this parameter is squared in the equation, small variations in the measured length will have considerable impact on the estimated volume. While the length does not appear in the lymphedema index (Equation 3), it is essential that the length of the measured segment in each limb is identical. This requires a reliable and reproducible method of locating the sites of the measurement electrodes.

When driving the current through the whole body (e.g., right hand to right foot) no current passes along the contralateral limbs (i.e., left arm and left leg). Hence the entire length of the left arm has the same equipotential as the right shoulder (i.e., the left arm is 'electrically equivalent' to the right shoulder). Similarly the left leg is 'electrically equivalent' to the top of the right thigh. Therefore by using the contralateral limb as the site of the measurement electrode for the shoulder, the reproducibility of measurements both intra- and inter-operator is greatly improved.

RECOMMENDED ELECTRODE POSITIONING

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.

Electrode:	*To measure the right limb*	*To measure the left limb*
Drive	Right hand	Left hand
Measurement	Right wrist	Left wrist
Measurement	Left wrist	Right wrist
Drive	Foot (either side)	Foot (either side)

These electrode sites are represented schematically in Figure 2.

Other issues which should be addressed in the measurement protocol include standardizing all parameters which have the capacity to affect the impedance measurements, including avoiding excessive exercise or food and drink consumption immediately prior to the measurement. The positioning of the subject is of primary importance. The subject should be positioned supine on a nonconducting surface with limbs slightly abducted and palms facing down. All jewelery should be removed from the limbs being measured and electrode sites cleaned with an alcohol swipe. Using this measurement protocol the intra- and inter-operator variability can be limited to as little as 1%.

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LYMPHATIC RESEARCH AND BIOLOGY
Volume 4, Number 1, 2006

Bioelectrical Impedance Analysis: Proven Utility in Lymphedema Risk Assessment and Therapeutic Monitoring

LEIGH C WARD

Secondary lymphedema is a debilitating condition that afflicts many individuals world-wide. Professor Stanley Rockson in this symposium has eloquently illustrated the magnitude of the problem of lymphedema post breast cancer, arguing persuasively that early intervention will reduce the long-term consequences of the disease. Such a therapeutic strategy presupposes the availability of tools capable of identifying, at the earliest opportunity, those individuals at risk. Associate Professor B. Cornish has presented the theory underpinning bioelectrical impedance analysis (BIA) as a highly sensitive monitoring and assessment tool for early detection of lymphedema. It is now my task to present the evidence that BIA is indeed a sensitive and accurate instrument suitable for this purpose.

BIOELECTRICAL IMPEDANCE ANALYSIS IS A VOLUMETRIC METHOD

Bioelectrical impedance analysis has a long history in the field of nutrition where for the past 25 years it has been a popular method for the assessment of body composition.[1] Its use for the assessment of lymphedema is more recent; the earliest publication of which I am aware, was by Watanabe and colleagues who, in 1989, reported the application of impedance for measuring leg edema resulting from lymphatic obstruction.[2] Although research has continued since then, implementation of the technology in clinical practice has lagged. This has been primarily due to lack of commercially available instrumentation suitable for routine clinical use, a situation now remedied with the advent of BIA spectrometers specifically designed for assessment of lymphedema.[3] The wider acceptance and use of BIA is dependent upon its proven utility and that it exhibits advantages over existing assessment tools.

A wide variety of assessment methods for lymphedema and the detection of at-risk individuals exist. These include: assessment of tissue composition by imaging techniques such as magnetic resonance imaging; surrogate measures of tissue pressure by tonometry; changes in skin temperature although in practice measurement of limb volume is the most important.[4] This can be achieved in a number of ways: water displacement, optoelectronic volumetry, or by calculation using solid geometry from measurements of limb circumference and length. The latter method would be most commonly used in a clinic setting and has become the *de facto* reference method despite acknowledgement of a number of sources of error.[4] BIA is a volumetric measurement method but with a subtle difference, it should not be used to quantify lymphedema in absolute volume units (i.e., mL). The previous speaker (Dr. Cornish) showed that an impedance measurement (Z) is related to the volume of the limb by the equation

$$V = \rho \frac{L}{Z} \qquad \text{Equation 1}$$

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Unfortunately, for any given individual we do not know the value of Δ and hence cannot directly calculate volume. Empirically-derived relationships may be used to convert the measured value of impedance to volume, as is common in the body composition arena, but these are always subject to uncertainty and few such algorithms exist for limbs. Consequently, the raw impedance values are used as a surrogate index of volume according to the inverse relationship between impedance and volume

$$Z \propto \frac{1}{V} \qquad \text{Equation 2}$$

Also, as stated by Dr Cornish, when impedance is measured at a low frequency, ideally zero, the impedance is an index of extracellular fluid (ECF) of which lymph is a primary component. Therefore changes in impedance indicate changes in ECF, and hence lymph volume. It is necessary to reference the measured impedance or its changes to a normative standard. The wide range of impedances exhibited in the normal population make it impossible to set a cut-off or impedance threshold which can be deemed presumptive of accumulation of ECF in excess of normal. Consequently, internal standardization is used in which the impedance of an at-risk body region is indexed to that of an unaffected body region, typically the contralateral limb. Thus BIA assessment of lymphedema is based upon the following tenets:

a *that impedance is an index of the measured volume;*
b *that, if impedance is measured at a low frequency, the measured volume is that of the ECF;*
c *that lymph is a primary component of ECF;*
d *that accumulation of lymph in lymphedema will be reflected by a change (decrease) in impedance at a low frequency;*
e *that the ratio of impedances between body regions, normal to at-risk, can be used as index of lymphedema.*

CAN BIA DISCRIMINATE LYMPHEDEMA?

In 1992, Ward and colleagues published the results of a cross-sectional study of a cohort of women with postmastectomy unilateral lymphedema and a comparable group of control subjects in which both impedance and limb volume, calculated from circumferences, were measured.[5] Whereas their data showed that the

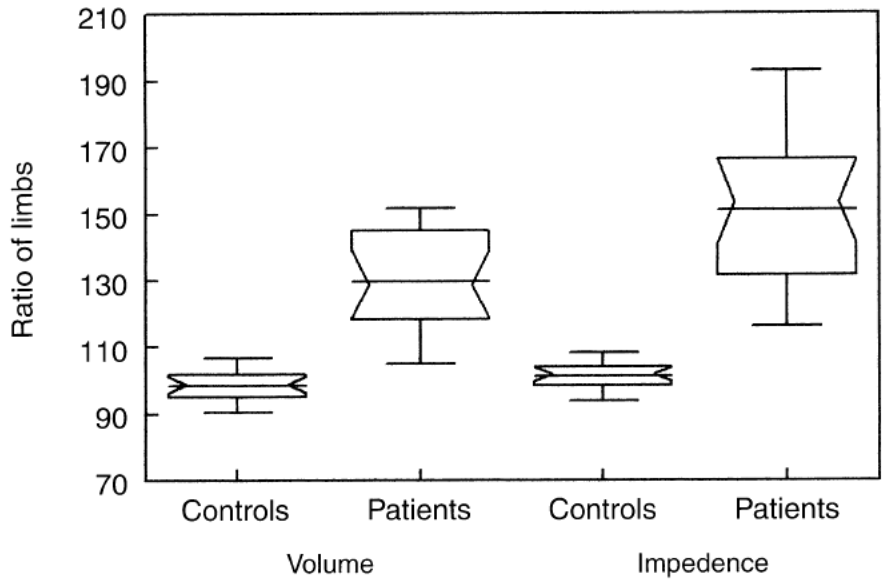

FIG. 1. Comparison of impedance and volume measurements of arms of controls and patients with lymphedema. Data are presented as the ratio of two limbs: controls, dominant to nondominant; patients, affected to unaffected. Legend: *line and bar*, mean ± 5th and 95th percentiles; *box*, 25th and 75th percentiles; *notch*, median and confidence interval. Data redrawn from Cornish et al.[6]

mean impedances of the two groups were significantly different, the overlap in individual impedance values did not discriminate totally between lymphedematous and control limbs. In a subsequent study,[6] they were able to demonstrate, however, that the *ratio* of impedances between limbs clearly discriminated the affected individuals from the controls while the ratio of volume measurements overlapped (Fig. 1). The subjects in this study were randomly selected from those presenting at a lymphedema treatment clinic for treatment of pre-existing lymphedema, grades I or II. Crucially therefore, these data were unable to assess the sensitivity of the impedance technique but the results implied that it was greater than that of circumferential measurement.

BIA FOR ASSESSMENT OF LYMPHEDEMA TREATMENT

In the same study, the subjects were followed during treatment of their lymphedema with serial measurements being made over 28days of treatment. Both volume and impedance ratios between limbs declined toward normal values (Fig. 2) with treatment but, notably, although by day 28 the volume ratio was indistinguishable from that for normal controls, the impedance ratio was still some 20% higher. This observation was interpreted as indicative of a greater sensitivity of impedance in detecting lymphedema than simple circumferential measurements, a view supported by the opinions of the nursing staff who were still able to identify the symptomatic characteristics of lymphedema although volume differences were no longer present. The increased sensitivity of the impedance technique was assessed as approximating three- to four-fold.

BIA AND EARLY DETECTION OF UNILATERAL LYMPHEDEMA

Emboldened by the encouraging results of these early studies showing the efficacy of BIA at monitoring pre-existing lymphedema, it was opportune to assess whether the sensitivity of the BIA method would allow early detection of lymphedema. A prospective study was designed (Fig. 3) in which subjects were recruited prior to surgery for breast cancer and would be monitored for 2 years following surgery.[7] Each subject was assessed presurgery, 1 month post-

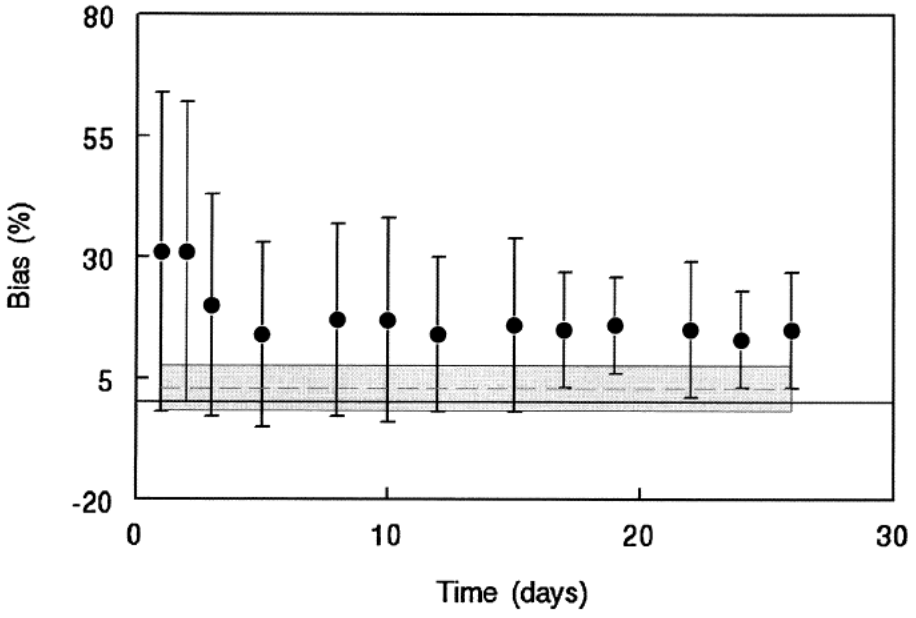

FIG. 2. Agreement between impedance and volume measurements of arms of controls and patients with lymphedema. Data are presented as the bias and associated standard error. Legend: ●, bias ± SE for patients; —, bias for controls; *box*, SE for controls. Data redrawn from Cornish et al.[6]

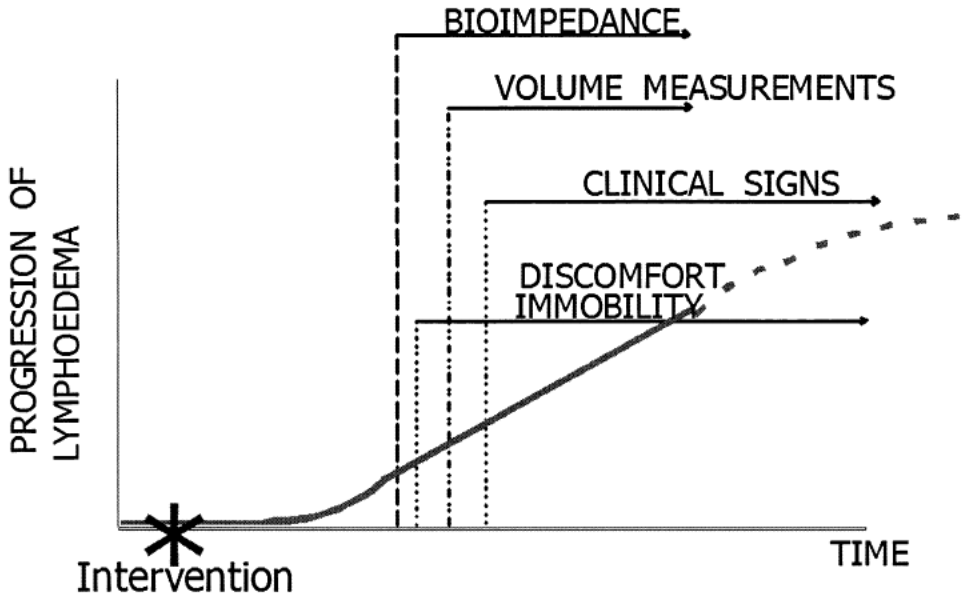

FIG. 3. Design of prospective study for early detection of lymphedema.[7] Patients were monitored pre-intervention (surgery for breast cancer) and subsequently for up to 2 years with different monitoring instruments for lymphedema. The hypothesis was that bioelectrical impedance would detect lymphedema prior to the other measurement tools.

surgery, and subsequently at 2-monthly intervals with retesting after 1 week if a positive test were recorded. A range of measurements was made at each time-point (Fig. 3) and the hypothesis to be tested was that significant change in bioimpedance would occur prior to changes in any of the other measurements. A significant change in impedance was one in which the BIA ratio between limbs fell outside the range (mean ± 3 SD) of impedances seen in a control population.

Within the 24-month study period, 22 patients out of 102 participants presented a ratio outside of the normal range on two consecutive measurements. Of these, 2 exhibited transient abnormal impedance ratios while the remaining 20 patients were subsequently confirmed to have lymphedema. Strikingly, in all of these cases, the abnormal impedance ratios, presumptive of impending lymphedema, were detected between 1 and 10 months *before* clinical diagnosis (Fig. 4) and in only one case was this accompanied by a positive difference in circumferential measurements. This study argues persuasively for the view that BIA is an accurate and sensitive early detection tool for those at risk of developing lymphedema. A similar study by Box and associates[8] was less supportive with only a 67% detection rate for BIA compared to a 200 mL volume difference as the criterion measurement, but it should be noted that in their study the BIA threshold was some 60% higher owing to a greater variability observed in the reference population.

BIA IN PRACTICE—SENSITIVITY AND RELIABILITY

Few formal studies of reliability of the technique with respect to lymphedema have been conducted. It is not unreasonable, however, to anticipate that reliability will be similar to that observed for BIA when used to assess body composition (i.e., better than 1%).[9] Cornish et al.[7] have quoted standard deviations of 2.4% in daily impedance ratios for unilateral lymphedema of the arm, while Hutson quotes variation for repeat measurements of 0.60 ± 15.4% compared to 2.1 ± 35% and 1.4 ± 31% for circumference and volume measurements (calculated geometrically), respectively.[10] Hutson also noted a low inter-rater variability in the use of BIA instrumentation and a greater speed

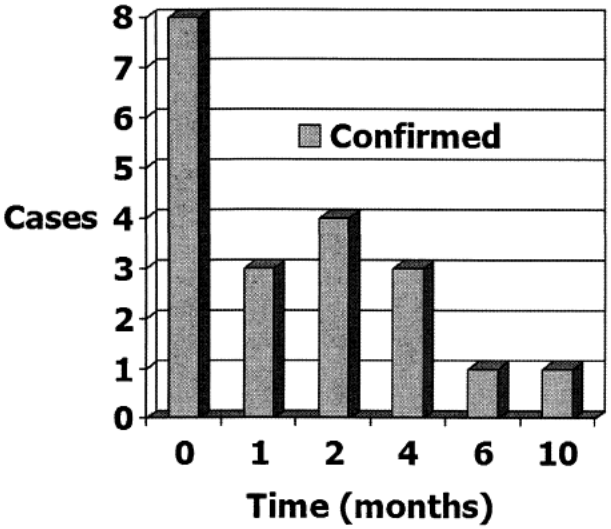

FIG. 4. Time of clinical confirmation of lymphedema compared to presumptive detection by bioelectrical impedance analysis. Legend: number of cases at each timepoint. Zero time is immediately following BIA testing, other times are months following BIA testing. Data redrawn from Cornish et al.[7]

of use in a clinical setting (1 min *vs.* 7 min for tape measurements). The sensitivities of the difference in sum of arm circumferences of greater than 5 cm or self-report as criteria of lymphedema compared to BIA have been reported as 35% and 65%, respectively. The corresponding specificities were 88.5% and 76.9%.[11]

WHAT ABOUT BILATERAL LYMPHEDEMA?

It is not possible to differentiate with certainty on the basis of absolute impedances a lymphedematous from a normal limb. This difficulty is circumvented in the case of unilateral lymphedema by the use of the contralateral normal limb as a reference. Clearly, in bilateral lymphedema this approach can not be used. Alternatively, since intracellular fluid (ICF) volume is largely unaffected by lymphedema,[7] which, by definition, is an accumulation of an extracellular fluid, reference of ECF may be made to ICF. Preliminary studies have shown that the ratio of impedance for ECF (R_0) to ICF (R_i) differs significantly between normal and affected limbs.[12] These data raise the possibility that comparison of this ratio for an affected limb with that of *some other* unaffected body region (i.e., obviating the need for a contralateral body region) may be capable of detecting and quantifying the degree of lymphedema in cases of a bilateral lymphedema. Research is currently underway to test this hypothesis.

IF YOU REALLY NEED THE SECURITY OF ABSOLUTE VOLUMES!

The preferred embodiment of the BIA method is to use impedance quotients as indices of the relative volumes of affected and normal body regions. By the use of appropriate BIA measurements (i.e.< at low frequency), such indices quantify, in both direction and magnitude, changes in ECF, and hence lymph, volume. Nonetheless, it is acknowledged that not all who work in lymphedema treatment are comfortable with such surrogate measurements. A volume difference of "200 mL" has a familiar meaning whereas a ratio of 1.23 does not! Impedances can be converted to absolute volumes by applying Equation 1 with an assumed value for Δ (taken from the literature) but these may not be accurate. User beware!

CONCLUSIONS

Assessment of lymphedema by BIA has been found to be faster, more consistent, and better accepted by clinicians, therapists, and patients than serial tape measurements or water displacement methods.[10] The equipment is highly portable, relatively inexpensive, and is easy to use by nonspecialist personnel. It is still a novel technique that is only now finding a place in the armoratorium of clinical practice. Its usefulness is acknowledged—"*This trial confirms that perometry and bioimpedance were both effective in independently showing a reduction in leg lymphedema . . . and that both methods can be reliably used to measure and follow leg lymphedema.*"[13] Undoubtedly, we will see more publications in the future attesting to its value in lymphedema assessment.

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