

BIOELECTRICAL IMPEDANCE ANALYSIS REVISITED

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ABSTRACT

Although total limb volume measurements are used to track the progress of lymphedema and its treatment, these measurements can be confounded by changes other than fluid excess namely muscle or fat gain. Bioelectrical impedance analysis (BIA) is a technique that specifically quantifies both total body fluid and extracellular fluid in extremities. Whereas BIA has potential as a quick, inexpensive, and quantitative technique to measure directly fluid gain or loss from lymphedema, it also has certain shortcomings that must be addressed before it can be validated. This paper examines the background that explains why measuring total limb volume is insufficient to quantify the extent of peripheral lymphedema and explores the advantages and drawbacks of using BIA for this purpose.

Lymphedema is a chronic swelling of an extremity from an accumulation of tissue fluid and lymph in the extravascular interstitium. Lymphedema may be congenital or acquired as a complication of surgery, radiation therapy, or infection of lymphatics and lymph nodes. Lymphedema limbs can be heavy, awkward, and disfiguring. Moreover, patients with lymphedema are susceptible to life-threatening extremity infection, to an ingrowth of fibrosclerotic tissue, and to other musculoskeletal disabilities.

Although complete elimination of lymphedema is seldom possible, patient quality of life can be improved with treatment. In order to determine if treatment is effective, one needs to measure changes in lymph fluid volume within an affected limb. Usually, this is accomplished indirectly by total limb volume measurement. Commonly the volumes of the affected and unaffected limbs are compared to verify when excess fluid has been diminished. Other methods compare pre- and post-treatment volume measurements in a single limb.

A basic assumption underlying the measurement of limb volume in determining the progress or regression of lymphedema is that a change in limb volume uniformly signifies a change in lymph fluid volume. However, other compartments within a limb, including fat, muscle, bone and blood, may alter limb volume. Therefore, it is not assured that a change in limb volume can be attributed solely to a change in lymph fluid volume.

Problems with Limb Volume Measurement

It is useful to consider measuring lymph volume more directly (1). Total limb volume measurements do not distinguish tissue fluid volume changes from those due to left-right dominance (1), weight gain, muscle atrophy, or the deposition of fibrosclerotic tissue. Furthermore, total limb volume measure-

ments are not reliable for measuring small changes in lymph volume or in detecting early (Stage I) lymphedema (2). Differences in muscle volume due to right or left limb dominance may exist prior to the onset of lymphedema. For example, a right-handed person's right arm may have larger and more developed muscles than the left. If a patient's non-dominant limb is affected with lymphedema, it may measure to be the same size as the unaffected limb and yet still contain excess fluid (3). Alternatively, a patient might simply have increased muscle mass from exercise. Total limb volume measurements may suggest that limb lymphedema has remained static or even worsened whereas in actuality lymphedema volume has improved. A similar situation arises when a patient gains weight as fat and fears the return of lymphedema. Measuring lymph fluid volume directly would help distinguish among the various agents of total limb volume change.

Several studies have attempted to quantify the relative change in limb compartments as a result of lymphedema (4-7). One study suggests that muscle in the affected limb hypertrophies (4). Another shows a small, but significant, decrease in density, but no notable difference in cross-sectional area in the muscle and bone compartments (5). These studies have focused on the lower limbs, however, while post-mastectomy lymphedema develops in the upper limbs. Muscle volume change in the arms in conjunction with lymphedema is largely unknown.

Excess protein-rich lymph causes other compositional changes within a limb. One such change, termed the "honeycomb" effect, is seen with proliferation of fibrosclerotic tissue (6-8). Neither total limb volume measurements nor lymph volume measurements distinguish new cellular growth from residual fluid. Subjective measurements of limb compliance are needed for determining whether tissue overgrowth has occurred.

Measuring lymph volume directly has

several distinct advantages over using limb volume changes to quantify lymph fluid changes, as it can distinguish among the gain or loss of fluid from fat and muscle. It may also allow the detection of lymphedema earlier because smaller changes can be quantified. Thus, any increase in lymph fluid volume represents a higher proportion of extracellular fluid of total limb volume. Earlier detection of lymphedema should make treatment easier and likely less expensive. Finally, direct lymph volume measurement would simplify when fluid has been entirely evacuated and treatment is therefore complete.

Lymph Volume Measurement

Although many techniques qualitatively determine that excess fluid is present within a limb, few accurately calculate the volume of tissue/lymph fluid. Techniques that attempt to measure lymph volume directly include bioelectrical impedance analysis (BIA) (2,3,9,10), mechanical impedance (11), CT-scans, MRIs (4-7), total body electrical conductivity (TOBEC) (12,13), tissue resonance impedance monitoring (TRIM) (12,13), and deuterium tracing (14). Of these, BIA is perhaps the most promising because of its low cost, portability, and speed.

Principles of Bioelectrical Impedance Analysis

The principle behind BIA is that an electrical signal changes as it passes through different materials. These changes can be traced back to the properties of these materials. In the situation of lymphedema, the impedance of a limb or body segment at certain frequencies can be correlated with the volume of conductive fluid contained within that limb or body (2). Thus, to understand the basic principles behind BIA one must first examine body components and their electrical properties. Fat and bone act as insulators, whereas lean tissues and electrolytic fluids conduct electricity. Therefore, an electrical

current passes through only lean tissues (muscle) and electrolytic fluid (blood and lymph). In addition, each muscle cell has a membrane (perimysium) that separates intracellular fluid from the extracellular space. A low frequency alternating current is unable to be transmitted across such a cell membrane (Fig. 1), and passes only through highly conductive extracellular fluid. At high frequencies, however, such a current crosses the cellular membrane and passes through both intra- and extracellular fluid, thereby enabling measurement of total fluid impedance.

Bioelectrical Impedance Analysis

Mathematically, one can model different parts of the body as different electrical components in order to derive a relationship between impedance and volume. The electrical properties of the extracellular fluid, mainly blood and other electrolyte-containing fluids, are first examined. Opposition to the flow of current in circulating cells in extracellular fluid is purely reactive (R_e). Fixed cells containing fluid, however, act as both capacitors and resistors. The capacitance (C) is a measure of the opposition to current flow across a cell membrane caused by charge built up on one side of the bilayer of polar proteins and phospholipids; current cannot cross the core of nonconductive lipids (15). There is also a small resistance (R_i) associated with the intracellular fluid. Both extra- and intracellular fluids are accounted for in the equivalent circuit model that is displayed in Fig. 2. Here the extracellular resistivity is arrayed in parallel with the intracellular resistivity and capacitance (in series) of the cell membrane.

The total tissue impedance for the equivalent circuit depicted in Fig. 2 can be calculated from:

$$\frac{1}{Z} = \frac{1}{R_e} + \frac{j\omega C}{1+R_i j\omega C} \quad 1$$

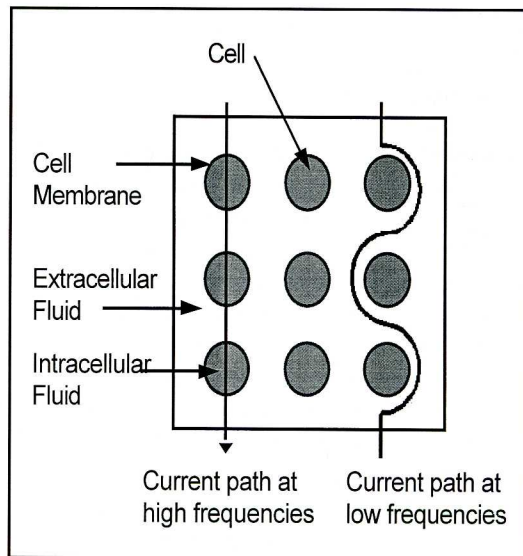


Fig. 1. The working of BIA at the cellular level.

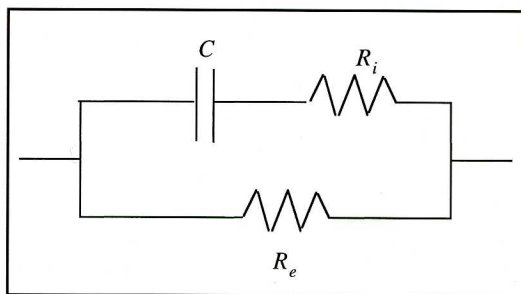


Fig. 2. The equivalent circuit used in BIA modeling.

where Z is total tissue impedance, j represents the phase shift between resistance (R) and reactive ($j\omega C$) components, and ω is the frequency (in radians) of the applied current. The complex impedance itself is expressed by:

$$Z = \frac{R_e(1 + R_i j\omega C)}{1 + (R_i + R_e)j\omega C} \quad 2$$

At high frequencies, $j\omega C$ becomes large, and in the limit of $\omega \rightarrow \infty$, the impedance of the limb goes to $\frac{R_e R_i}{R_e + R_i}$ (16,17). Thus, a high

frequency current passes through both intra- and extracellular fluid, making it possible to measure total body fluid (TBF). At low frequencies, $j\omega C$ becomes small, resulting in a vanishing-frequency limit of $Z=R_e$. Therefore, the only resistance to a low frequency current is across the ECF, which includes blood and lymph (3).

Because it is virtually impossible to inject current either at an infinite frequency or at zero frequency (i.e., a direct current), it is necessary to measure the impedance at many frequencies and then extrapolate these results to either zero frequency or infinite frequency (16-19). Many studies have simplified this procedure by either conducting studies using single frequency BIA (SFBIA) or using multi-frequency BIA (MFBIA), where it is safe to assume that high frequencies can be defined as $\omega > 500$ kHz and low frequencies as $\omega < 1$ kHz (20).

The application of the BIA equivalent circuit model to the human body hinges on three major assumptions. The first is that any segment of the body can be modeled as an isotropic conductor, assuming a uniformly distributed current density within the body segment. The second assumption is that the specific resistivity (ρ) of the medium is constant. The third is that the body segment can be approximated as a three dimensional object that has a volume, V , or

$$V=AL \quad 3$$

where L is the length of the conductor and A is its cross-sectional area. The volume of this body segment is related to the total impedance of an isotopic conducted by (15,21,22):

$$Z = \frac{\rho L}{A} = \frac{\rho L}{V/L} \quad 4$$

from which the following relationship between the volume and impedance of an isotropic conductor is obtained:

$$V = \frac{\rho L^2}{Z} \quad 5$$

For a given body segment, both L and ρ are constant. Hence, the volume of the body segment is simply inversely proportional to its impedance. Since BIA devices measure applied voltage (E) at a given current (I), and since basic circuit analysis stipulates that $E=IZ$, it follows that the volume of fluid—and extracellular fluid in particular—measured is proportional to IL^2/E .

BIA Studies

Several studies have examined the applicability of BIA to measuring fluid distribution in humans. These studies have focused on fluid disturbed patient populations. These include patients on dialysis (23-25) and patients with diabetes (20,26), cancer (27), and cirrhosis of the liver (28-31). The results of these studies have varied, but this shortcoming may be a consequence of how BIA was applied.

Most studies that use BIA attempt to measure the whole-body impedance at 50 kHz. Unfortunately, 50 kHz is neither high enough to pass through both intra- and extracellular fluid, nor low enough to pass through only the extracellular fluid component (16,17,23).

A second problem with measuring whole-body impedance is that one generates a current at the wrist and measures the voltage drop from wrist to ankle, assuming that the path length (L) is somewhere around body height.

Further, the approximations and assumptions discussed previously do not apply to the torso at all (15,17,23,30-34). First, the torso has a much larger volume than the limbs, which means that its impedance is disproportionately low. Second, the specific resistivity of tissue is inconstant throughout the body; it varies greatly from the limbs to the torso. Current parallel to muscle experiences frequency-independent

resistance, whereas current perpendicular to the muscle fibers experiences frequency-dependent resistance. When current passes through an extremity, where the muscle fibers have an obvious orientation, resistivity is constant over the length of the limb. This is not true for the torso, however, which contains many visceral organs and a variety of oriented muscle fibers. Thus, measuring whole body impedance is only practical if segmental measurements of each limb and of the trunk are summed.

In most cases, segmental measurements are sufficient to detect fluid gain, and BIA is sensitive to changes in distribution between intra- and extracellular fluid (16,17). Further, both the equivalent resistivity of extracellular fluid, and the ratio of intracellular fluid to extracellular fluid are good indicators of edema (35,36). Others have also demonstrated the validity of BIA in predicting total body fluid in both healthy adults and patients with altered metabolic function (19,23,36-38). It is likely that further research will demonstrate that BIA, when applied segmentally and at a high enough frequencies, is an accurate method for predicting TBF.

BIA is also a fairly robust system of measurement. Extensive research has been conducted in order to determine which physiological variables can affect impedance measurements. These variables include: exercise (16,17,25,39), general fitness (16,17), skin temperature (40,41), electrolyte content (39), sweat gland activity (41,42), hydration levels (25,39), food intake (25,39), time of day (25,39), menstruation (43), and pregnancy (43). Most of these variables are negligible, while others can generally be taken into account and controlled.

Heavy exercise can also increase the resistivity of both ICF and ECF by approximately 5% and 12%, respectively, due to the shift in the distribution of fluid within the body, from arms to legs (16,17). Thus, impedance measurements should, like most physiological measurements, be performed when the patient is resting. However, because

only strenuous exercise has this profound distribution effect, it is only necessary for a patient to rest for a few minutes before BIA measurements are performed.

Fitness level also has a notable effect on resistivity levels. With a decrease in body weight, as after exercise, the resistivity of the intra- and extracellular fluids in an average "fit" patient actually falls by 1% and 9%, respectively (16,17).

Skin temperature also affects impedance measurements. Thus, in the range of 20-40 °C, the basal impedance of the human skin changes by approximately 3% per °C (41). Electrolyte content (except in extremely malnourished or severely diabetic individuals) changes impedance measurements by only $\pm 0.4\%$. Food intake can also alter basal impedance measurements by $\pm 1.7\%$, but diurnal variations are insignificant.

Impedance measurements are also affected by sweat gland activity, hydration levels, and time of day, but these changes are negligible. Skin resistance values are thus at a maximum when sweat gland activity is at a minimum, and vice versa. Maximum resistivity due to electrolyte content are on the order of 0.1%. Each of these variables can be controlled by making sure that the area of skin that comes in contact with the electrodes is dry and that patients do not change their drinking patterns, fast for a period of time before each measurement, and schedule their appointment at the same time of day.

The most significant variations of an individual's impedance are seen during pregnancy and at different intervals in the menstrual cycle. The primary change that occurs during pregnancy is a large weight gain, the vast majority of which is fluid retention (fetus, placenta, amniotic fluid, maternal blood volume, etc.). The mean increase is about 7.75 liters (43). Changes in fluid distribution and content associated with the menstrual cycle have similar effects, though at significantly lower levels of magnitude. Experimental evaluation has shown that the change in resistivity can be as

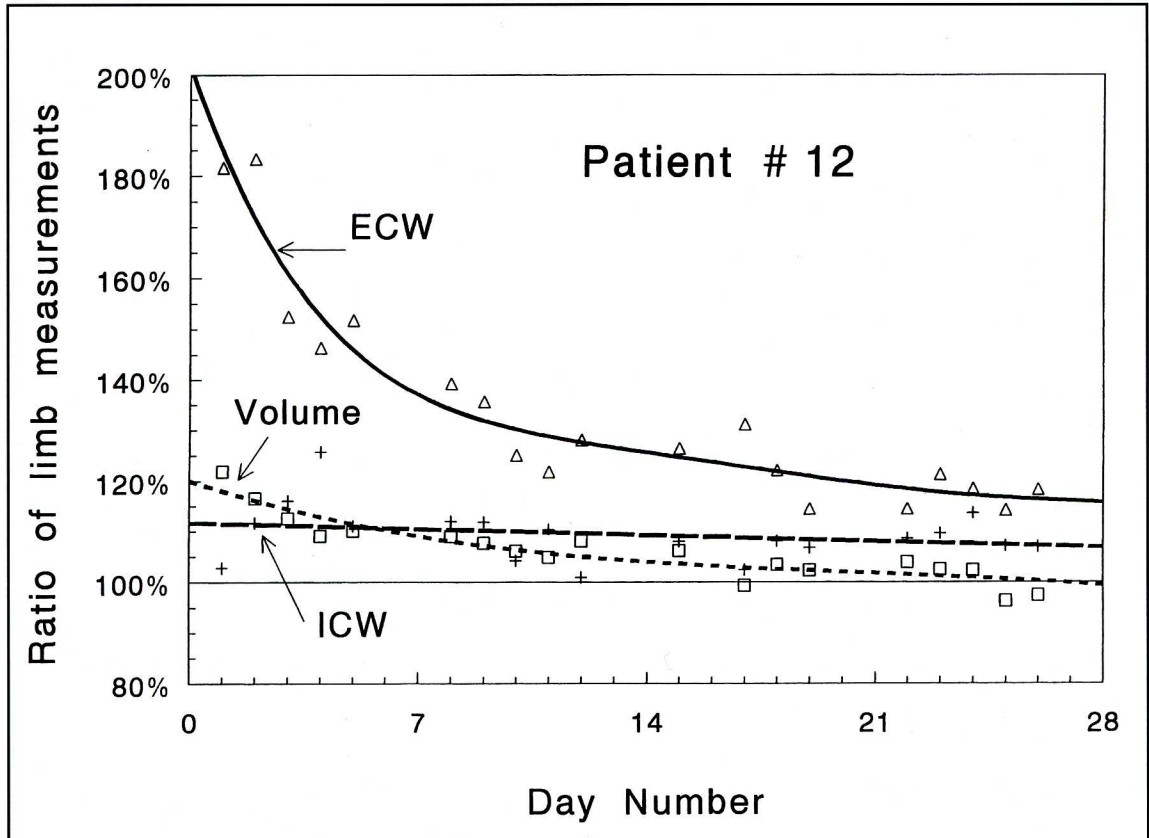


Fig. 3. Trends in the measured quantities for a typical patient during the four week treatment period. (Reprinted with permission, 15).

high as an 18% increase over average levels or as low as no increase, with no steady baseline other than one related to the individual metabolism and body type of the patient (43). Most of these changes occur in the trunk, and do not notably affect limb measurements. There is as yet, however, no way to compensate for fluid changes due to menstruation and pregnancy.

Using BIA to Measure Lymphedema

Fig. 3 is taken from Cornish et al's 1996 paper on using BIA to measure lymphedema and shows the results of some preliminary experiments (2). The results, which were qualitatively verified by trained therapists,

suggest that this technique is more sensitive to small changes in tissue fluid/lymph volume than are circumferential measurements (2). BIA could determine that there is still excess fluid in the arm even though total limb volume measurements, when compared with the unaffected limb, indicate that edema has regressed.

Fig. 4 is reproduced from the same paper and demonstrates that BIA can also more accurately distinguish the ratio of extracellular fluid to intracellular fluid in healthy subjects and patients with lymphedema more accurately than total limb volume measurements (1,2). This finding has important implications for earlier and less costly therapy.

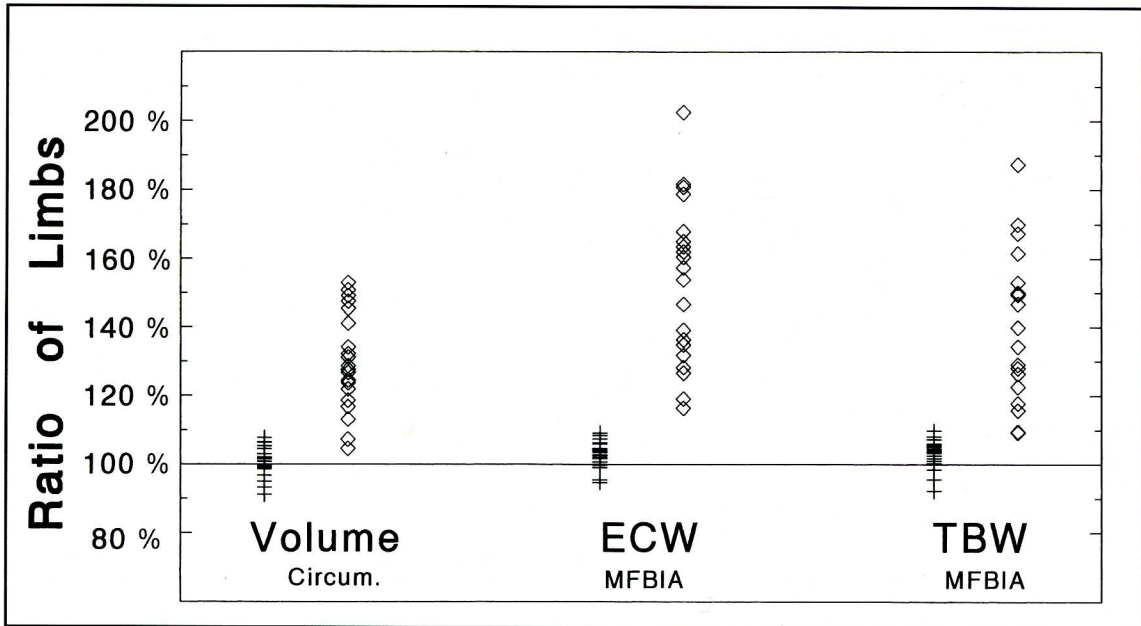


Fig. 4. A comparison of BIA and volume measurements as diagnostic tools. (Reprinted with permission, 15).

Disadvantages of Using BIA to Measure Lymphedema

Critics of using BIA to measure lymphedema have raised several valid concerns (44). Extracellular fluid is not necessarily the only parameter to measure in assessing the progress of lymphedema. Several studies suggest that an increase in interstitial fluid is often accompanied by a considerable increase in the solid elements (44). Besides fibrous tissue deposition associated with advanced lymphedema, there may be an increase in the blood and lymph vasculature in the affected limb. Since BIA only measures fluid resistance, it cannot register the presence of excess cellular material. This limitation means that impedance measurements have to be interpreted carefully because BIA measures only detect fluid gain or loss.

As previously discussed, BIA has often been applied to the whole body, rather than to small segments of a limb or the whole limb.

This error has been compounded by use of frequencies that are neither high enough nor low enough to traverse both cells and fluid, or fluid alone. Although there are promising preliminary results (1,2), more investigation is needed to determine if BIA is uniformly successful for indicating limb fluid volume.

Another concern is that, although good correlations exist between impedance results and other estimates of extracellular fluid, there are only low correlations (-0.614) between the resistance and the cross-sectional area of the limb. In another study, the correlation between resistance and limb size was only 0.7, Ward and Cornish have attributed the poor correlation to lack of algorithms relating body segment impedance to fluid volume (1). It should be apparent, however, that it is the correlation between ECF volume and limb volume that is low. Therefore, there must be agents of limb volume change other than lymph-tissue fluid. BIA offers the advantage that it measures fluid change alone, so one can not expect

impedance measurements to correlate perfectly with limb volume measurements.

Finally, BIA exhibits a similar shortcoming as do all other lymphedema measurement techniques: it is necessary to compare impedance values to a normal in order to determine the endpoint of treatment. Unless the ratio of extracellular fluid to intracellular fluid is more constant among people than is limb size, which seems unlikely, it is necessary to make this comparison. The advantage of measuring only a single compartment (fluid, for example) is that the measurements are not as easily confounded by changes in the other compartments.

CONCLUSIONS

If the shortcomings of BIA can be appropriately addressed, BIA has many advantages over traditional limb volume measurements as a diagnostic and monitoring technique for quantifying lymphedema. It is quick, potentially more sensitive to the presence of excess lymph and interstitial fluid than total limb volume measurements, and easy to administer. Furthermore, it addresses the fact that changes in total limb volume do not always signify changes in limb lymph and interstitial volume.

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