Bioimpedance in the clinic

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Introduction

The medical profession is continually on the search for new diagnostic tools, which will provide convenient, inexpensive and accurate descriptions of the physiological state of the patient. Bioimpedance analysis (BIA) is already being used to provide a variety of measurements in the clinic, and more applications of this methodology are sure to follow in the future. This article provides a brief description of the physical principles underlying its operation and some illustrations of its use in the clinic.

There are a number of advantages in the use of BIA as a diagnostic tool. It is non-invasive, relatively inexpensive, convenient for clinical use, and not uncomfortable for the patient. Other, competing diagnostic methods lack one or more of these features.

In body composition analysis dual-energy x-ray absorptiometry exposes the patient to radiation, requires a specialized setting and is expensive. Isotopic dilution is invasive, and hydrostatic immersion is inconvenient. Both of these require a special setting for administration and neither can measure body composition in a local region, such as a limb.

Cardiac output, stroke volume and other heart-related measurements can be made invasively employing hemodynamic thermodilution or the direct Fick-oxygen principle. Although sometimes considered noninvasive, transesophageal Doppler echocardiography requires the insertion of an ultrasonic probe into the esophagus under general anaesthesia in a specialized setting by a trained operator.

In breast cancer, mammographies can be quite uncomfortable for the patient, and their interpretation can be problematic for women who are young and/or women with dense breast tissue. Biopsies are unpleasant for the patient, and their results are not immediately available to the clinician. Both procedures are expensive, as are most of the other competing diagnostic methods mentioned above.

Clearly there is a role for a different diagnostic technique in these areas. BIA can be performed in an ordinary clinical environment by staff that do not require extensive additional training. Hence, it is less expensive than alternate tests. The software associated with the devices can provide rapid analysis. The electrodes are noninvasive and can be applied to localized areas of the body. Patients are not sedated and may stand or recline on a table.

Prior to its adoption in the clinic a new technology must meet certain criteria. It should provide either a simpler or more ac-

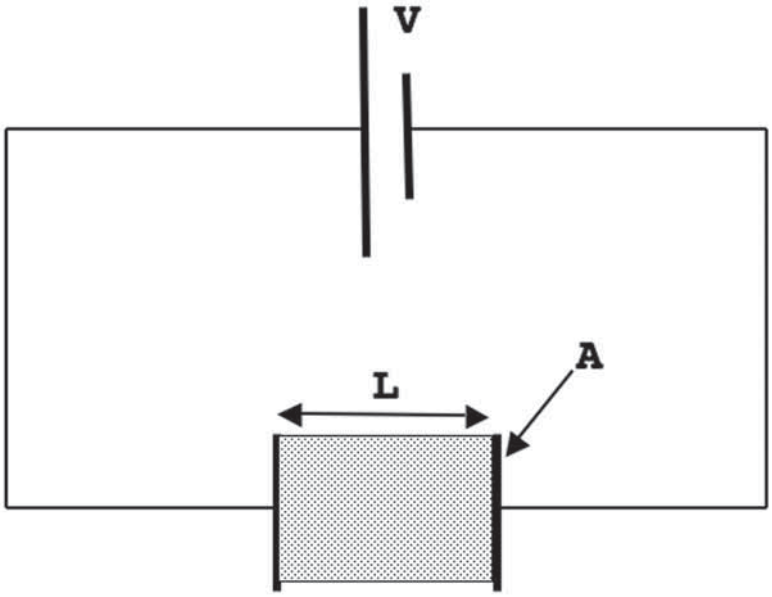

Figure 1: A sample of material with length L connected to a battery of voltage V. The sample has an area A, perpendicular to the plane of the page.

curate determination of a clinical measurement or laboratory value. If not, then the new technology should be much simpler or less expensive to use. Otherwise, there is no reason to use it. Furthermore, its application should be covered by insurance. But most of all, it must be shown to be clinically effective by comparison, preferably under blinded conditions, with previously established methods for measuring the same quantity. As noted above, bioimpedance methods are generally easier and less expensive to use than many other techniques. However, the prime concern with it is under what conditions are its results fully trustworthy and under what conditions should they be viewed with some suspicion.

This review is certainly not exhaustive with regard to clinical applications or devices. It describes the basic principles involved in several major applications and discusses their representative uses in the clinic. Other applications that use similar principles may not be covered. Similarly, it does not attempt to discuss the many devices currently on the market, but describes a few in some detail to illustrate the basic methodology.

Readers interested in more detailed coverage of particular aspects of bioimpedance analysis can find information in several reviews. Ivorra[1] has provided a detailed review of bioimpedance monitoring which emphasizes in detail some of the basic electrical concepts involved. The general principles determining the electrical properties of tissue are described at length by Miklavcic et al..[2] The basic electrical properties of a variety of tissues are summarized and analyzed in great detail in a three-part article.[3–5] Some other review articles are noted throughout this article.

Physical principles

Electrical properties can be associated with any material object, including biological tissue. If a battery is connected to a material sample, as illustrated in Figure 1, charge will flow from the battery toward the sample. The sample is in the form of a rectangular solid with cross-sectional area A (perpendicular to the plane of the page) and length L. Some of that charge may pass through the sample to produce an electric current while other charge may be trapped or stored at interfaces within the sample.

Two parameters are commonly used to describe these responses. The resistance, R, of the material is a measure of its tendency to restrict the flow of current due to collisions of the charges (ions in tissue) with atoms of the sample. The capacitance, C, is a measure of the trapping of the charges at interfaces, such as the cell membranes. For the sample shown in Figure 1 the resistance is $R = L/gA$, and its capacitance is $C = eA/L$, where g and e are the conductivity and permittivity, respectively, of the sample material. The extracellular fluid and the cytosol are examples of materials for which electric current flows relatively freely. In that case the resistance dominates and the capacitance can be neglected. The cell membrane is an example for which the resistance is so high that charge cannot flow and is stored at the surfaces. In that case the capacitance dominates.

Figure 2 illustrates the Fricke circuit model commonly used for tissue. The dashed line indicates the cell with the membrane represented as a pure capacitance, C, and the cytosol in the cell interior as a pure resistance Ri. The extracellular medium is represented as a pure resistance Re. Re and Ri are determined primarily by the water content of the tissue. Re serves as a measure of the extracellular

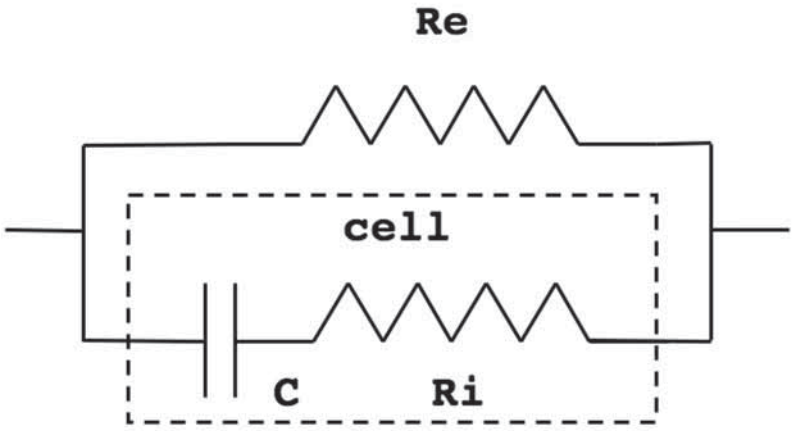

Figure 2: Circuit diagram for the Fricke model. The dashed line encloses the body of the cell. C represents the transmembrane capacitance and Ri is the resistance of the intracellular medium. Re is the resistance of the extracellular medium.

water (ECW) and Ri, the intracellular water (ICW). The sum of ECW and ICW is the total body water (TBW).

BIA does not use direct current, such as is produced by a battery, Instead, it applies a current which varies sinusoidally with time, like a smooth, repeating wave. The frequency of repetition, f, is measured in units of Hertz (Hz). In Europe and most of the world the power grid provides electricity with a frequency of 50 Hz, whereas the power frequency in the United States is 60 Hz. Frequencies in the thousands of Hertz (kilohertz or kHz) are used to electrically refresh the screens of televisions and computer monitors. Even higher frequencies in the millions of Hertz (MegaHertz or MHz) are used for radio transmission and some cellular phones. R and C are found from the application of a current at a frequency f and the measurement of the resulting voltage.

How well current flows through a tissue depends on its R and C as well as on the frequency of the applied signal. To compare the relative effects of R and C on the passage of current, a parameter X, the reactance, is used to measure the effective resistance offered by the capacitance to the flow of current. Because $X = \frac{1}{2}\pi fC$, as frequency increases the reactance offered by the capacitance becomes smaller. Increasing the length or decreasing the cross-sectional area of a sample increases its resistance and reactance.

Consider the tissue model illustrated in Figure 2. At low frequencies the reactance offered by cell membranes is so large that current cannot enter the cell, but must flow around it in the extracellular space. At higher frequencies the reactance offered by the cell membranes is sufficiently lowered so that current can flow through the cell as well as around it. The relative importance of X and R is described by a phase angle; $\tan \phi_1 = X/R$ (tan is the trigonometric function, the tangent).

This model illustrates one of the main features of bioimpedance analysis. At low frequencies the current is determined primarily by the ECW. For sufficiently high frequencies at which the capacitance does not significantly restrict its flow, the current is determined by both Re and Ri; i.e., by the TBW.

Clinical devices generally avoid the use of very low and very high frequencies. Frequencies below about 1 kHz are avoided so that patients will not sense the application of the signal. In addition, for some systems a residual impedance at the electrode-tissue interface might begin to dominate the current flow at low frequencies. Frequencies above about 1 MHz are avoided because electrical interactions between the wires lead to the introduction of artifacts in the signal.

Many bioimpedance systems use 50 kHz as a frequency at which the capacitor's reactance becomes relatively small so that the current is determined primarily by the TBW. It should be noted that measurements made on tissue[3,6] consistently indicate that membrane reactance does not really become negligible until frequencies significantly higher than 100 kHz. Consequently, measurements made at 50 kHz should underestimate ICW. Jaffrin et al.[7] have analyzed this issue in some detail. They conclude that the simple Fricke model cannot adequately represent the complexity of tissue. Instead, a more complex "Cole-Cole" analysis is required. Based on the results of such an analysis the 50 kHz values may be adjusted to obtain Ri, Re and thus the TBW.

Some bioimpedance systems, however, do not use R and X to characterize the tissue, but related quantities, an impedance, Z, and a different phase angle, ϕ_2. There are two parts to Z. One is referred to as the real part, ReZ; the other, the imaginary part, ImZ. $Z^2 = ReZ^2 + ImZ^2$ and $\tan \phi_2 = ImZ/ReZ$. The terms 'real' and 'imaginary' refer to how the

wave corresponding to the current is shifted in time compared to the wave corresponding to the voltage. It should be noted that ϕ_1 and ϕ_2 are different and should not be confused.

Current must be applied through two electrodes in order to measure either X and R or ImZ and ReZ. However, the interface between each current electrode and the skin has electrical properties that can be described by the circuit elements discussed above. The presence of these interface elements could distort the interpretation of the data. For this reason two other, voltage-measuring electrodes that do not pass significant current are attached close to, but in between the current electrodes. In such a "four-electrode" system the effects of the electrode-skin interfaces are minimized.

For example, one current-voltage electrode pair could be applied at an ankle and the other pair at a wrist. There are three segments in that current path, each with its own resistance and reactance: the leg, the trunk and the arm. Because the trunk has such a large cross-section compared to the other two segments, it contributes relatively little to the total resistance or reactance for this electrode placement. To measure the characteristics of the trunk, one should place the four electrodes on it. Placing the four electrodes on one leg would measure the characteristics of that limb well, but those results might not be generalized to the trunk. With these configurations the patient is frequently supine and time is required for the fluids to redistribute in the body. A convenient measuring system involves scales in which a current-voltage electrode pair is inserted in each foot receptacle. The standing position and simultaneous weight-measurement make this system easy to use.

It must be emphasized that at any one frequency, such as 50 kHz, only two electrical parameters can be obtained, either R and X or Z and ϕ_2. Additional information must be provided or assumptions made to generate clinically useful empirical relationships from the measured electrical parameters. A wide variety of empirical equations have been proposed to calculate TBW and fat-free mass (FFM) from these two parameters. Jaffrin has summarized some of these equations in a recent review.[8]

The electrical properties of tissue that determine R and C (conductivity and permittivity) are not constant, but vary with frequency.[3] For frequencies below about 50 kHz both R and C increase; R increases only by a small amount. For frequencies above about 100 kHz R and C decrease significantly, with the variation depending on tissue type.

Some bioimpedance devices measure R and X (or, alternatively, Z and ϕ_2) at a number of frequencies. Such instruments are generally more expensive than single-frequency models, but can provide more reliable information. There are two varieties of these devices. In one case X and R values are obtained at several frequencies (multi-frequency BIA or MF-BIA), and their individual values are used to obtain better fits for physiological values. For example, at a frequency well above 50 kHz the X from a membrane capacitance is more easily neglected so that the tissue can be well represented by a parallel combination of just Re and Ri, (refer to Figure 2). The resulting resistance, denoted here as Rhi, should provide a much better estimate for TBW than a single measurement at 50 kHz. On the other hand, at a frequency well below 50 kHz the membrane capacitance completely blocks current flow into the cells so that the tissue is well represented by just Re. The resulting resistance, denoted here as Rlo, should provide a much better estimate for ECW than a single measurement at 50 kHz. The combination of these values would yield a good estimate for ICW. Examples of such instruments are the Bodystat 1500MDD (Bodystat, Douglas, Isle of Man, UK) which uses two frequencies, 5 kHz and 50 kHz and the Bodystat Quadscan 4000 (Bodystat, Douglas, Isle of Man, UK) which uses four frequencies: 5, 50, 100 and 200 kHz. The latter instrument would be expected to provide a better estimate of Rhi.

In the second case (BIS or Bioimpedance Spectroscopy) X and R are measured for a large number of frequencies and X is plotted vs R. Examples are the SFB7 (Impedimed, San Diego, CA, U.S.A.) which scans 256 frequencies between 4 kHz and 1 MHz and the Xitron Hydra 4200 (also Impedimed, San

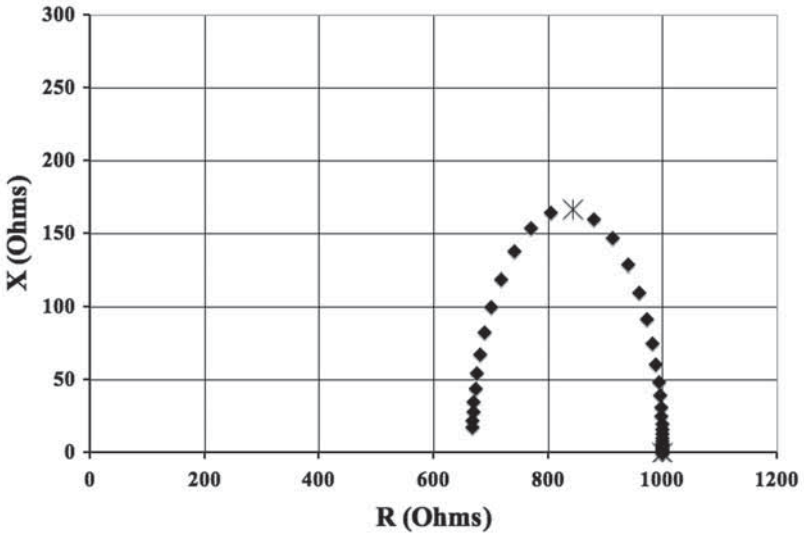

Figure 3: Idealized "Cole-Cole plot" for the circuit shown in Figure 1 with generic values: Re =1000 Ohms, Ri =2000 Ohms and C = 1 nanoFarad.

Diego, CA, U.S.A.) which scans 50 frequencies between 5 kHz and 1 MHz. Figure 3 is such a "Cole-Cole plot" for the circuit shown in Figure 2 with generic values: Re =1000 Ohms, Ri =2000 Ohms and C = 1 nanoFarad. In this idealized representation Rhi and Rlo are determined from the ends of the arc. Here Rlo is about 1000 Ohms, which agrees with Re and would represent the ECW. Rhi is about 650 Ohms, which agrees well with the value for a parallel combination of Re and Ri and would thus represent the TBW. The * represents the value at 50 kHz with an R value (R50) about midway between Rlo and Rhi. In these devices a curve-fitting routine is used to determine Rlo and Rhi as well as the overall shape of the curve. In Figure 3 the difference between R50 and Rlo is about 15%, which is somewhat larger than would be found in healthy adults.

There are two fundamental impedance-analysis strategies. In one, as used in body composition measurements or breast cancer diagnosis, the values of X and R, or equivalently Z and f, are determined at one or more frequencies. The impedance values, per se, are the objects of software analysis. In the other, as used in blood flow and breathing measurements, it is the time rate of change of the impedance that is the object of software analysis.

Body composition

Suppose that a MF-BIA or BIS measurement has provided values for Re and Ri. Empirical scaling relationships involving the height, H, and weight, W, of the patient along with factors such as body shape can then be used to determine the ECW, the ICW and thus the TBW mass. In healthy individuals the TBW mass is known to be about 72% of the FFM. With the fat-free weight and total weight known, the weight of the fat alone and thus the percentage body fat can be determined. The empirical relationships have been validated by comparison with standard body composition methods, such as dual X-ray absorptiometry (DXA), underwater weighing, and isotope dilution. BIA is certainly more convenient and less expensive than these standard methods. Knowledge of percentage body fat, especially when determined in a convenient manner, would be very useful in a weight-management program. It must be emphasized, however, that the empirical relationships have been validated primarily for healthy subjects.

Electrode placement is an important factor in body composition measurements. As noted previously, the resistance/reactance offered by the trunk is small compared to that produced by the limbs because of their smaller cross-sectional area. Different empirical relationships are used depending on whether the current/voltage electrode pairs are placed on the ankle and wrist or both ankles. A combination of a scales with impedance measurement uses a current/voltage pair in contact with the sole of each foot. Some companies, such as Tanita (Tokyo, Japan), offer a system with a wide variety of electrode-placement options. The Tanita BC-418 provides separate body mass readings for each arm, each leg and the trunk. Lozano-Nieto[9] discussed in detail problems in body composition analysis related to electrode placement and patient posture.

The ability to distinguish between ECW and ICW is important clinically for the management of dialysis to monitor shifts between extracellular and intracellular fluid levels or for the presence of extracellular edema. Electrodes can be placed at various positions to

determine the local fluid balance, provided that the proper empirical relationships have been validated.

Multifrequency techniques require relatively complicated and expensive instruments. A less expensive alternative would be the use of a single, 50 kHz measurement. In that case, however, an empirical relationship must be established to obtain Rlo and Rhi from R50, and use may be made of X50 as well. As illustrated in Figure 3, Rlo might be assumed to be a small percentage higher than R50 and Rhi, a small percent lower for healthy people. Sometimes R50 is even assumed to be Rhi.

Jaffrin and his colleagues have applied Hanai's mixture theory in conjunction with 50 kHz measurements to extend the capabilities of single-frequency instruments in this way. For example,[10] the Xitron Hydra 4200 BIS system (Impedimed, San Diego, CA, U.S.A.) was used to obtain relatively accurate measures of the ratio Rlo/R50. That ratio was then used with measurements made by a single frequency meter, the BodyExplorer (Juwell Medical, Gauting, Munich, Germany), to obtain similar Rlo values.

Jaffrin et al.[11] also compared the ability of a foot to foot electrode system (Tefal Bodymaster, Tefal SAS, Rumilly, France), the Xitron Hydra 4200 BIS system (Impedimed, San Diego, CA, U.S.A.), and a DXA system to measure ECM and FFM. They also reviewed results obtained with two single-frequency instruments, the Tanita 105 and the Tanita 625 (Tanita, Tokyo, Japan). The Bodymaster uses 114 kHz square waves and proprietary software to determine the parameters of interest. Although the Bodymaster sometimes is viewed as a single-frequency instrument, a square wave is actually a combination of many frequencies so that the Bodymaster should be regarded as a multi-frequency device. Their conclusion is that foot-to-foot devices provide accurate results for healthy individuals and are convenient to use. However, because such devices emphasize the legs in their measurements, errors would result for persons with leg edema.

Readers interested in more detailed evaluations of the clinical use of bioimpedance for body composition determination should consult the two-part review by Kyle et al.[12,13] sponsored by ESPEN (The European Society for Clinical Nutrition and Metabolism). In the first part they review the basic principles of clinical bioimpedance and the empirical equations validated for the determination of ECW, ICW and TBW. In the second part they review the various parameters that affect bioimpedance measurements and its use to determine water and fat values for persons who are not healthy. Buchholz et al.[14] also extensively reviewed the clinical use of BIA. They determined that this methodology was useful for monitoring body composition changes in individuals over time, but not for a single measurement on a patient. There is also some concern in extending its use beyond young, relatively healthy adults. Jaffrin[8] has reviewed recent developments for calculating body composition parameters and the impedance meters used to measure them. The website Choice (www.choice.com.au/) has a review of commercial body fat scales

Blood flow and breathing

Measurement of the electrical impedance, Z, at a single frequency across the thorax can be used to monitor blood flow and/or breathing. Electrode placement can vary; for example, strip electrodes can be placed on the back and chest or electrode discs can be placed just on the chest. There are three basic contributions to the inter-electrode impedance: the soft tissue, air space in the lungs, and blood flow. Although the contribution from soft tissue impedance may be large, it is constant in time whereas the air in lungs and blood flow vary. The change in impedance due to the increase and decrease in the effective air space of the lungs is slower than that due to blood flow changes; hence, the two can be separated. A significant problem, however, is that patients, particularly babies, can move during the measurements and introduce artifacts. Some companies have proprietary software that eliminates motion artifacts. One possible technique for their elimination is the use of multiple frequencies in the signal.

Breathing rate is measured by the periodicity of the longer duration variations;

change in lung volume, by the magnitude of the impedance change. Empirical equations may be used to obtain other information. One of the main applications of this method is the monitoring of sleep apnea. For example, the CASMED 511 Cardio-Respiratory Monitor (CAS Medical Systems, Branford, CT, U.S.A.) utilizes a single frequency of 28 kHz to monitor impedance changes. A filter removes the more rapid blood flow variations. The electrocardiogram (ECG) is measured at the same time. Problems can arise due to patients' shallow breathing and poor electrode placement.

There are two methods for obtaining blood flow parameters from the rapid impedance changes. Both are based on the calculation of the rate of change in impedance with respect to time. This change rate varies during the course of the cardiac cycle. The methods differ in their modeling of this change. Both use other physiological parameters in conjunction with impedance change to determine a variety of hemodynamic measures, such as stroke volume and cardiac output, with the use of empirical equations. Electrodes are typically applied at the base of the neck and the base of the thorax although other sites have been used.[15]

Impedance cardiography (ICG) analyzes the change in impedance as due to the increase in volume of the aorta and the velocity of the blood flow. For example, the BioZ (Cardiodynamics, a subsidiary of Sonosite, Bothell, WA, U.S.A.) uses a 60 kHz signal and regards the maximum rate of change of the impedance as a measure of blood velocity. Concerns have been expressed, however,[16] that the overall performance of this method needs improvement. On the one hand, Taler et al.[17] have found ICG to be useful in the management of hypertension, and Packer et al.[18] have found it valuable in the identification of decompensation in heart-failure patients. On the other, this method was not successful in the measurement of stroke volume index with patients suffering from chronic heart failure.[19]

A newer method, Electrical Cardiometry (EC) or Electrical Velocimetry, interprets the maximum rate of change of impedance to be a measure of aortic blood acceleration. When the aortic valve is opened the orientation of the blood cells changes from random to aligned with the flow, and this alignment increases the electrical conductivity of the blood. For example, the Aesculon monitor (Osypka Medical, Berlin, Germany) uses a 50 kHz signal and standard ECG electrodes. It relates quantities such as stroke volume to the ratio of the maximum impedance rate change to the base impedance value. Unlike traditional ICG, Electrical Velocimetry seems to be capable of effective use with children[20] although there are some conflicting reports.[21]

Breast cancer

Impedance spectroscopy has been suggested as a potential diagnostic tool for the detection of tumors. Because of the disorganized structure of many tumor types their electrical conductivity is increased. They offer less resistance to the passage of current and may be detected by impedance measurements. Laboratory measurements have confirmed that tumors can be detected in this way under controlled conditions. The problem has been the effective translation of this capability to a clinical environment.

Breast cancer would be an important application of this technology. There is a need for an improved screening system for women in the ages 30 to 39, especially those with relatively dense tissue. Ionizing radiation might identify tumors, but it should not be used routinely, especially for women in this age group.

The T-Scan 2000 (Mirabel Medical Systems, Austin, TX, U.S.A.) has been approved for more than a decade by the U. S. Food and Drug Administration (FDA) for use as an adjunct to mammography for women of any age with somewhat equivocal mammograms (ACR BIRADS Category 3 or 4). According to Sumkin et al.[22] the T-Scan measures capacitance and conductivity (the reciprocal of resistivity) at seven frequencies in the range 100 Hz to 5 kHz. These quantities are combined into an "admittance", which is the reciprocal of impedance. Like impedance, admittance can be expressed in terms of real and imaginary parts as well as a magnitude

and phase angle. A 64 pad-electrode array (8x8 square) is applied to the chest and a "source" electrode is held in the hand. The algorithm used to analyze the data emphasizes the phase angle and the frequency at which the imaginary part of the impedance is a maximum.

In 2006 the FDA declined[23] to approve Mirabel's newer T-Scan 2000 ED model which was designed to evaluate breast cancer risk for women in the 30 to 39 year age group, who do not otherwise seem to be at risk. It would be used in conjunction with a clinical breast examination, rather than as an adjunct to a mammogram. Concern was expressed regarding the sensitivity of the instrument. Mirabel could modify the empirical relationships used to identify tumors from the impedance measurements or even use additional electrical measurements to improve the device's sensitivity and eventually obtain FDA approval. There appears to be a definite need for such a diagnostic device.

Impedance spectroscopy is also used in the post-surgical treatment of breast cancer. One of the main complications can be lymphedema, i.e. the swelling of the extremities due to the buildup of excess lymph fluid. This buildup can occur following breast cancer surgery or radiation therapy. This use of impedance measurements is thus an application of body fluid measurements discussed earlier. For example, the Imp XCA (Impedimed, San Diego, CA, U.S.A.) measures X and R at a single frequency below 30 kHz. At present it has FDA approval for the assessment of lymph in the arms and may receive approval for other areas.

Future applications

The application of BIA to the skin could be quite useful in the clinic for the monitoring of transdermal drug delivery, the measurement of moisture levels and the identification of tumors. The outer layer of the skin, the stratum corneum, does not permit significant charge flow and thus behaves as a capacitance under ordinary conditions. As with the cell membrane the impedance offered by this layer decreases with increasing frequency. At frequencies in the high kiloHertz range the signal can effectively penetrate to the epidermis and dermis. Electrode placement also determines the depth of signal penetration. The signal from closely separated electrodes is transmitted close to the surface. As electrode separation increases, the signal penetrates more deeply. Hence, low frequency signals applied usng closely spaced electrodes yield primarily the properties of the stratum corneum whereas high frequency signals applied with widely-spaced electrodes yield information regarding the lower epidermis and the dermis. Because a wide variety of factors (such as body location, age, gender, cigarette smoking, recent exercise, nervousness, tanning, etc.) can affect skin impedance, it may be difficult to assign changes in the impedance to one particular factor.

The DPM 9003 (Nova Technology, Gloucester, MA, U.S.A.) has been used successfully in laboratory environments to measure skin moisture levels. At present, as noted on the company's website, this instrument is for research use only, not for diagnostic procedures. Application for approval for clinical use is presumably underway. Instruments for the detection and identification of skin tumors are currently under various stages of development.

BIA already provides some relatively safe and convenient measurement systems for the clinic. In the future more sophisticated applied signals and empirical relationships should provide improved diagnostic accuracy as well as the extension of BIA to the monitoring of other conditions. Laboratory measurements have indicated that BIA is capable of providing accurate physiological measurements under controlled conditions. Extending this accuracy to the population at large in a clinical environment is the challenge for BIA. Furthermore, it might prove to be effective in the laboratory for some clinical purpose, but there may not be many patients with the corresponding condition. In that case there probably would not be sufficient economic demand for a company to invest in the development and production of an easily-used device.

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