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Bioimpedance at the Bedside: Current Applications, Limitations, and Opportunities

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Abstract

The loss of muscle mass is a defining characteristic of malnutrition, and there is ongoing interest in the assessment of lean tissue at the bedside. Globally, bioimpedance techniques have been widely appreciated for their noninvasiveness, safety, ease of use, portability, and relatively low cost compared with other clinically available methods. In this brief update, we review the 3 primary types of commercially available bioimpedance devices (single- and multiple-frequency and spectroscopy) and differentiate the underlying theory and current applications of each. We also address limitations and potential opportunities for using these devices at the bedside for clinical assessment. Mixed reports in the validation literature for all bioimpedance approaches have raised questions about absolute accuracy to estimate whole body composition in clinical populations, particularly those with abnormal fluid status and/or body geometry in whom underlying method assumptions may be violated. Careful selection of equations can improve whole body estimates by single- and multiple-frequency techniques; however, not all devices will allow for this approach. Research is increasing on the use of bioimpedance variables including phase angle and impedance ratio as potential markers of nutrition status and/or clinical outcomes; consensus on reference cut-points for interpreting these markers has yet to be established. Novel developments in the bioimpedance spectroscopy approach are allowing for improved fluid management in individuals receiving dialysis; these developments have implications for the clinical management of other conditions associated with fluid overload and may also provide enhanced whole body estimates of lean tissue through new modeling procedures. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

electrical impedance; body composition; spectroscopy; lean body mass; nutrition assessment; total body water; fat-free mass; body cell mass

The new consensus malnutrition framework[1] features the loss of muscle mass as one of the key characteristics defining malnutrition. The loss of muscle mass is also a key characteristic of sarcopenia, which is a core defining characteristic of cachexia.[2] From a therapeutic standpoint, lean tissue is an important concept for appropriate drug dosing, given the risk of toxicity with certain drug therapies in individuals with lean tissue depletion.[3-5] Furthermore, the current American Society for Parenteral and Enteral Nutrition critical care guidelines recommend that protein delivery in individuals with extreme obesity should be based on ideal body weight,[6] but it is likely that a more effective strategy would be to dose protein on the basis of lean tissue given what we know about the relationship between the two.[7-10] For these reasons, there has been ongoing interest in the assessment of body composition (and in particular lean tissue) at the bedside. Globally, bioimpedance techniques have been widely appreciated for their noninvasiveness, safety, ease of use, portability, and relatively low cost compared with other clinically available methods (eg, dual-energy X-ray absorptiometry [DXA]),[11,12] and various applications of bioimpedance across the lifespan were presented in a recent supplement of the *European Journal of Clinical Nutrition*.[13] Three primary categories of devices are available: single-frequency, multiple-frequency, and spectroscopy. Although single-frequency devices were the first to be made commercially available and are the most abundant in the marketplace, multiple-frequency and spectroscopy devices are becoming more readily available.

Thorough reviews of the validation literature for whole body composition estimates have been published previously.[14,15] Although many available bioimpedance devices have been shown to be relatively valid for estimating fat-free mass (FFM) and other body composition compartments in healthy normal-weight individuals, studies in various clinical

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populations are much less abundant and tend to yield mixed results regardless of approach. All bioimpedance approaches have been shown to be largely erroneous for whole body composition estimates in individuals with obesity.[16-19] Although refinements in bioimpedance techniques have led to important advancements in the management of individuals receiving dialysis, the clinical applications for whole body lean tissue assessment require additional development. Validation studies in clinical populations have typically reported good mean-level agreement between bioimpedance and reference methods based on correlation and paired *t*-test statistics, but poor accuracy at the individual level (ie, wide limits of agreement by Bland-Altman analysis) raises doubts about the capacity of bioimpedance techniques to accurately quantify whole body compartments. Each reference method has a certain amount of inherent error, and it can be argued that the aforementioned statistical techniques used to prove validity do not effectively take into account the errors associated with the reference.[20] Furthermore, prediction equations are scaled to a particular reference method and can produce error when evaluated against a different reference method. For example, a bioimpedance equation that was developed for FFM from DXA may produce substantial scaling errors when compared against total body water (TBW) measures generated by deuterium dilution in a different study. Studies that focus on evaluating a bioimpedance method's ability to measure changes in volume or mass may be less affected by this kind of systematic error, given that the calculation of changes over time would potentially minimize the impact of scaling error. In addition, differences in measurement protocol can also contribute error and yield variable results across validation studies. Although in many cases the errors in estimates generated from bioimpedance techniques at the individual level probably are truly significant, it is certainly possible that at least some of the time bioimpedance techniques have been unfairly judged to be erroneous due to these limitations inherent to body composition validation studies.

Nevertheless, there remains significant global interest in the applications of bioimpedance techniques for bedside assessment of nutrition status either through the evaluation and monitoring of whole body lean tissue or through the interpretation of some bioimpedance-derived variable independent of whole body mass or volume. Indeed, given the difficulties associated with the validation of bioimpedance techniques, there is growing interest in new applications of bioimpedance for the clinical setting that go beyond quantifying whole body composition. In addition, new developments in the field for whole body fluid volume management in dialysis hold promise for improving the capacity to estimate whole body lean tissue. In this brief update, we review the 3 primary types of commercially available bioimpedance devices and differentiate the underlying theory and current applications of each. We also address limitations and potential opportunities for using these devices at the bedside for clinical assessment.

Principles of Bioimpedance

The 3 general categories of bioimpedance devices available commercially are single-frequency, multiple-frequency, and spectroscopy devices. Regardless of the device, bioimpedance involves the administration of a weak, alternating electrical current at one or more radiofrequencies through leads attached to surface electrodes in order to characterize the conductive and nonconductive tissue and fluid components of the body.[11,21] The applied current flows at various rates depending on the composition of the body; the current is well conducted by water- and electrolyte-rich tissues such as blood and muscle and is poorly conducted by fat, bone, and air-filled spaces.[12,21,22] The voltage decrease of the current as it passes through the body is detected through the current sensing electrodes, and the impedance data are recorded by the bioimpedance device.

Bioimpedance measurements are typically taken with the patient in the supine position following standardized protocol.[14,15,22] Electrodes can be attached to the body in several different arrangements. The most common approach for generating whole body composition estimates is the standard tetrapolar arrangement (also termed *wrist-ankle*), which involves the placement of 2 electrodes on the hand (one on the bony protuberance that forms the wrist, ie, the styloid process of the ulna, and the other just behind the meta-carpals), and 2 electrodes on the foot (one on the ankle placed midline between the medial and lateral malleoli, ie, the styloid process of the radius, and the other just behind the metatarsals). A less common option used by select devices (eg, the InBody segmental multiple-frequency devices; BioSpace, Inc, Cerritos, CA) involves the placement of 8 electrodes in a tetrapolar arrangement on both hands and both feet. Segmental approaches require the placement of electrodes in various arrangements depending on the limb or segment to be measured.[11,21]

Several excellent reviews provide a comprehensive discussion of bioimpedance and the assumptions that underlie available technologies.[11,12,21] However, it is useful to review the core concepts here. In brief, *impedance* (Z) is the frequency-dependent opposition by the conductor (ie, the body) to the flow of electric current.[23,24] Geometrically, impedance is the vector composed of 2 frequency-dependent parameters—*resistance* (R) and *reactance* (Xc).[21,24] Resistance is the opposition to the flow of current when passing through the body.[21,24] Reactance is the delay in conduction caused by cell membranes, tissue interfaces, and nonionic substances.[12,21,22,24] *Capacitance* is a function of reactance that arises when cell membranes store a portion of the current for a brief time.[11] This temporary storage of charge creates a phase shift or *phase angle* (PA), quantified as the ratio of the arc tangent of reactance to resistance (arc tangent [Xc/R] × [180°/π], expressed in degrees).[12] At very low (or theoretically approaching zero) frequencies, virtually no conduction occurs because a higher cell membrane capacitance permits the current to only pass through (and therefore quantify) the extracellular water (ECW).[15,21] At very high

(or theoretically approaching infinity) frequencies, total conduction occurs through cell membranes, thus allowing for the quantification of TBW.[15,21] The difference between the TBW and ECW further determines the intracellular water (ICW) volume, which theoretically can be used to estimate body cell mass (BCM) based on the assumption that cells are comprised of 70% water.[25] Therefore, the potential applications available depend on the nature of the device at hand, including the number and range of frequencies, software capacity, quality of circuit board, and other factors. It is useful to consider the general framework, underlying assumptions, and strengths and limitations for each of the 3 general approaches for estimating whole body fluid volumes and lean and fat tissue masses.

Bioimpedance for Estimating Whole Body Composition

Single-Frequency Bioelectrical Impedance Analysis

Single-frequency bioelectrical impedance analysis (SF-BIA) using a 50-kHz single-frequency device and wrist-ankle tetrapolar electrode placement is the most widely used bioimpedance approach to estimate whole body composition (Table 1). Most typically, impedance data measured at 50 kHz are used to estimate various body compartments through application to regression-derived equations previously derived from reference data. For example, an equation for predicting TBW would typically be developed by measuring TBW using deuterium dilution as the reference method in a homogeneous sample from a study population. Bioimpedance data obtained from the study sample would then be regressed against TBW reference measures in order to develop an equation that can be used to predict TBW from bioimpedance data. The new equation must then be cross-validated in a separate independent sample of individuals with similar characteristics. Once TBW is predicted from SF-BIA generated impedance data applied to such an equation, then FFM can be derived through the assumption that FFM is constantly hydrated at 73.2%. By this method, fat mass (FM) can then be derived through subtraction of FFM from body weight. Thus, it can be appreciated that SF-BIA inherently is based upon the 2-component model of body composition (FM + FFM = Body Weight). Alternatively, regression equations have been developed based on other appropriate reference methods for directly predicting FM, FFM, and other compartments from 50-kHz data; these have been well reviewed by Kyle et al.[11] Ideally, an equation that is appropriately matched to the characteristics of an individual should be chosen to provide optimal body composition estimates. However, in the clinical setting there are significant barriers to this approach and underlying assumptions to SF-BIA are frequently violated.

First and foremost, the SF-BIA approach relies on an assumption that the body is a uniform conductor with constant geometry and composition and that resistance (R, ohms) is directly related to the product of specific resistivity (ρ, ohm-cm) and conductor length (L, cm) and indirectly related to conductor cross-sectional area (A, cm^2), such that $R = \rho (L/A)$.[11,12,21] Rearranging these variables allows for the prediction of volume from what has been termed the *impedance quotient* (L^2/R), which is essentially $Height^2/R$ (Ht^2/R), with an appropriate adjustment factor (ρ) that accounts for the lack of uniformity in the conductivity of the body. In this way, impedance data can be used to predict the volume (V, cm^3) of TBW as follows: $V = \rho (Ht^2/R)$, also referred to as the *volume conductor model*.[11,12]

The presumption underlying the whole body SF-BIA approach—that the human body is a single, symmetrical cylinder with homogenous composition and uniform cross-sectional area—is not physiologically accurate, as the body can be better described by having 5 distinct cylinders (2 arms, 1 trunk, and 2 legs).[22,26] Furthermore, the SF-BIA approach is based on the assumptions that the ICW to ECW ratio remains constant and that specific resistivity (ρ) is constant across all tissues of the body so that the bioelectrical current is conducted uniformly.[22] However, ρ is related to factors such as electrolyte concentration (inverse relation) and temperature (direct relation),[15,22,23] and the distribution of fluid between the intra- and extracellular compartments (and consequently the electrical properties) of various tissues varies with disease state and nutrition status.[14] These factors, and the fact that SF-BIA relies solely on the utility of just 1 frequency, make it highly improbable that SF-BIA can accurately differentiate between ICW and ECW based on static assumptions; the validation literature bears that out.[14,22,27] Indeed, clinicians should be wary of reports generated by SF-BIA devices that provide values for ICW, ECW, BCM, and even bone mass, as they are highly questionable.

Even the generation of TBW by SF-BIA in clinical populations is potentially erroneous due to the assumption that 50 kHz is a high enough frequency to overcome membrane capacitance to completely quantify both ICW and ECW. Studies have demonstrated that in certain disease states, much higher frequencies are required in order to fully quantify TBW.[28,29] At 50 kHz frequency, the method is actually measuring the weighted sum of ECW and ICW resistivities rather than TBW; therefore, it estimates TBW without distinguishing between or measuring the individual ECW and ICW volumes.[11,22] In addition, FFM is typically derived from TBW following the assumption that FFM is constantly hydrated at 73.2%[26]; the hydration of FFM has been demonstrated to be significantly higher in individuals with obesity[30,31] and fluid overload.[32,33] Indeed, predictions of FFM have been reported to be overestimated in cardiac and renal settings, where ECW volume expansion is common.[14,22] This has also been shown among patients with advanced lung and gastrointestinal cancer, where FFM was overestimated (1.88 ± 7.66 kg) with wide limits of agreement between an SF-BIA device (TBF-300A, Tanita, Arlington Heights, IL) and DXA (Lunar Prodigy Advance, GE Healthcare, Madison, WI).[34]

Table 1. Selected Commercially Available Bioimpedance Devices (Listed Alphabetically by the Device Manufacturer).[a]

Manufacturer	Device	Method	Price Range[b]	Frequencies Measured
BioSpace, Inc, Cerritos, CA, USA	InBody770	S-MF-BIA	$15,000–$20,000	1, 5, 50, 250, 500, and 1000 kHz
	InBody720	S-MF-BIA	$15,000–$20,000	1, 5, 50, 250, 500, and 1000 kHz
	InBody570	S-MF-BIA	$5000–$10,000	5, 50, and 500 kHz
	InBody370	S-MF-BIA	$5000–$10,000	5, 50, and 250 kHz
	InBody230	S-MF-BIA	$5000–$10,000	20 and 100 kHz
Bodystat Ltd, Douglas, UK	Bodystat 1500	SF-BIA	$500–$1500	50 kHz
	Bodystat 1500 MDD	MF-BIA	$1500–$5000	5 and 50 kHz
	QuadScan 4000	MF-BIA	$5000–$10,000	5, 50, 100, and 200 kHz
	BBis~MultiScan 5000	BIS	$10,000–$15,000	50 frequencies from 5 to 1000 kHz
Data Input, Pöcking, Germany	Nutribox	SF-BIA	$1500–$5000	50 kHz
	Nutriguard-MS	MF-BIA	$1500–$5000	5, 50, and 100 kHz
Fresenius Kabi AG, Bad Homburg, Germany	BodyScout[c]	BIS	NA	50 frequencies from 5 to 1000 kHz
Fresenius Medical Care, Bad Homburg, Germany	Body Composition Monitor[c]	BIS	NA	50 frequencies from 5 to 1000 kHz
ImpediMed, Carlsbad, CA, USA	DF50	SF-BIA	$1500–$5000	50 kHz
	SFB7	BIS	$15,000–$20,000	256 frequencies between 4 and 1000 kHz
	Hydra 4200 (Xitron Technologies)[d]	BIS	NA	50 frequencies from 5 to 1000 kHz
	Xitron 4000B (Xitron Technologies)[d]	BIS	NA	50 frequencies from 5 to 1000 kHz
Maltron International Ltd, Essex, UK	BF-900	SF-BIA	<$500	50 kHz
	BIOSCAN 920-II	MF-BIA	$10,000–$15,000	5, 50, 100, and 200 kHz
RJL Systems, Inc, Clinton Township, MI, USA	Quantum II	SF-BIA	$1500–$5000	50 kHz
	Quantum III	SF-BIA	$1500–$5000	50 kHz
	Quantum IV	SF-BIA	$1500–$5000	50 kHz
	Quantum X	SF-BIA	$1500–$5000	50 kHz
	Quantum Desktop	SF-BIA	$5000–$10,000	50 kHz
Tanita Corporation of America, Inc, Arlington Heights, IL, USA	MC-780U	MF-BIA	$5000–$10,000	5, 50, and 250 kHz
	SC-331S	SF-BIA	$1500–$5000	50 kHz
	BC-418	S-SF-BIA	$5000–$10,000	50 kHz
	SC-240	SF-BIA	$500–$1500	50 kHz
	SC-240IM	SF-BIA	$5000–$10,000	50 kHz
	TBF-410GS	SF-BIA	$1500–$5000	50 kHz
	TBF-310GS	SF-BIA	$1500–$5000	50 kHz
	TBF-300A	SF-BIA	$1500–$5000	50 kHz
	TBF-300WA	SF-BIA	$1500–$5000	50 kHz
	BF-350	SF-BIA	$500–$1500	50 kHz
Valhalla Scientific, Inc, Poway, CA, USA	G61-S	SF-BIA	$1500–$5000	50 kHz
	G62-S	SF-BIA	$1500–$5000	50 kHz
	G63-S	SF-BIA	$1500–$5000	50 kHz
	G6 Duo	SF-BIA	$1500–$5000	50 kHz
	BCS-1	SF-BIA	$1500–$5000	50 kHz
	BCS-2	SF-BIA	$1500–$5000	50 kHz
	BCS-3	SF-BIA	$1500–$5000	50 kHz

BIS, bioimpedance spectroscopy; MF-BIA, multiple-frequency bioelectrical impedance analysis; NA, not applicable; S-MF-BIA, segmental multiple-frequency bioelectrical impedance analysis; S-SF-BIA, segmental single-frequency bioelectrical impedance analysis; SF-BIA, single-frequency bioelectrical impedance analysis.

[a]This is not a complete list; it describes devices for which the pricing and other information was most readily available. Due to space constraints, we have not attempted to identify which devices provide raw data and/or the prediction equations used in their devices. Clinicians are advised to take these issues into consideration and obtain up-to-date information on the technical capacities before purchasing any bioimpedance device.

[b]Approximations based on the current retail price of the devices as of October 2014.

[c]Device not currently commercially available in the United States as of October 2014.

[d]Device no longer commercially available in the United States as of October 2014.

Finally, it is important to remember that the SF-BIA approach generates whole body volumes and masses by using statistically derived, population-specific equations (typically height, weight, age, gender, and ethnicity specific) that have mostly been validated among healthy and normal-weight individuals under highly controlled conditions.[11,14] Obtaining optimal results for whole body compartments even in healthy people depends on the selection of an appropriate prediction equation. In reality, many devices do not specify the equation programmed into their software, considering that information to be proprietary, and clinicians rarely have the time or inclination to search the literature to find an equation appropriate to the individual being measured. Furthermore, some devices do not provide the raw impedance data (ie, resistance, reactance, impedance, phase angle), thus making it impossible to recalculate body composition compartments using an appropriate equation. This critique can also be made of many multiple-frequency devices.

There is a growing body of literature investigating the utility of 50-kHz derived bioimpedance data to either enhance nutrition assessment or independently predict nutrition status and/or clinical outcomes, without relying on predictions of whole body volumes or masses.[35,36] Specifically, phase angle can be compared with population-specific reference values.[37-40] The 50-kHz data can also be used to generate FFM index (FFMI), a height-corrected index of FFM that can be calculated by a standardized equation and compared with reference data.[41] Another parameter that can be generated from 50-kHz data is derived from a graphical procedure called *bioelectrical impedance vector analysis* (BIVA); this method involves the plotting of resistance and reactance standardized for height to create a vector that can then be compared with gender- and race-specific reference values from healthy population samples.[42,43] The use of BIA data in this way is theoretically advantageous in situations where bioimpedance assumptions are not valid to estimate body composition. The BIVA method presents some logistical challenges for clinical application given that few devices are programmed with software appropriate to calculate it. BIVA has been reviewed elsewhere[14,35]; PA and FFMI are discussed further in a subsequent section.

Multiple-Frequency Bioelectrical Impedance Analysis

The most commonly applied multiple-frequency bioelectrical impedance analysis (MF-BIA) approach for the determination of whole body masses and volumes involves measuring impedance using the wrist-ankle tetrapolar electrode placement and then applying the data obtained at 2 or more frequencies to regression-derived population-specific prediction equations.[11,15] Although a bioimpedance spectroscopy (BIS) device can be used to generate data that can be applied to MF-BIA prediction equations, it is most common to take this approach using an actual MF-BIA device. Typically, MF-BIA devices apply the current at 1 very low frequency (eg, 5 kHz) and several higher frequencies (eg, 50, 100, 200, 500 kHz; see Table 1). Thus, theoretically, MF-BIA is able to differentiate between the ECW and ICW compartments, because at lower frequencies the impedance to current flow allows for the determination of the ECW, while at higher frequencies the impedance can be used to determine the TBW; ICW can be derived by subtracting ECW from TBW.[11,22] This represents one potential advantage of MF-BIA over SF-BIA approaches, although the efficacy of selecting one specific high frequency to completely quantify TBW across all clinical populations is somewhat questionable, particularly in those with fluid overload. A number of validation studies of various equations to predict whole body composition in healthy and clinical populations can be found in the literature and have been reviewed previously.[11] The same challenges described for the SF-BIA validation literature are evident in the MF-BIA validation literature, typically with good population-level agreement but large individual variability being reported. Furthermore, with the exception of the assumption regarding the static ratio of ICW to ECW, the same underlying assumptions inherent to SF-BIA hold true for MF-BIA, thus potentially limiting its applications for whole body composition assessments in clinical populations.[36]

Although MF-BIA was first explored using a 50-kHz SF-BIA device,[44] there has been increasing interest in the use of segmental measurements with MF-BIA to potentially produce more accurate whole body composition estimates.[45] Unlike whole body wrist-ankle bioimpedance measurements that relate Ht^2/R to estimate TBW based on the volume conductor model (as discussed previously), segmental BIA recognizes the body as having 5 distinct cylinders with different resistivities over which impedances are measured separately.[46] One of the criticisms that can be made of whole body wrist-ankle measurements is that the trunk contributes very little to whole body resistance (~10%) but comprises a substantial conductor volume (~50%).[11,21,47] Further, the assumption is made that any changes in fluid volume or adiposity within the trunk will have a minor influence on whole body measurements. These assumptions are quite likely violated in obesity and conditions associated with fluid overload (eg, heart or liver failure).[14] Thus, segmental measurements have been purported to provide more accurate whole body estimates. However, in order to get to whole body estimates from segmental measurements, the bioimpedance data obtained from limb and trunk measurements must still be applied to regression-derived prediction equations developed from reference data and have been shown to be erroneous in individuals with obesity; as has been observed with all other bioimpedance approaches, the errors tend to increase with increasing adiposity.[47] The true potential advantage of segmental measurements is most likely to be evidenced in determining fluid shifts and distribution in individuals with fluid overload and those on dialysis.[45] These applications are discussed later.

Similar to the discussion regarding the use of SF-BIA devices to generate 50-kHz PA and FFMI as potential parameters of nutrition status and/or clinical outcomes, there is growing interest in the application of an MF-BIA generated parameter, namely the ratio of impedance at 200 kHz to impedance at 5 kHz as a

potential indicator of nutrition status[48,49] and fluid overload.[50-52] The advantage of an MF-BIA device over an SF-BIA device is that the MF-BIA device can be used to generate all of these aforementioned parameters; these are discussed further in subsequent sections.

Bioimpedance Spectroscopy

The BIS approach for whole body measurements differs fundamentally from SF-BIA and MF-BIA. BIS devices have been commercially available since 1990, when Xitron Technologies (San Diego, CA) introduced the first one onto the market (4000B). Although Xitron is no longer manufacturing BIS devices, the company was pioneering in this field, and now several companies are producing these devices worldwide. These devices typically measure impedance at a minimum of 50 frequencies over a spectrum of frequencies from very low to ~1000 kHz (see Table 1). Most commercially available BIS devices are programmed with modeling software that generates volumes through Cole modeling and subsequently applies the generated terms to modified versions of mixture equations first developed by Xitron. Generally speaking, the software fits the impedance data (ie, resistance and reactance) to the Cole model,[53] a mathematical model shown to best describe this kind of physiologic data. With this procedure, nonlinear least-squares curve fitting yields an interrupted semicircle (or impedance locus) that generates Cole model variables, which can then be applied to equations to generate fluid volumes.[21] Cole model terms include R_0 (or R_e, resistance associated with ECW), R_∞ (sum of ECW and ICW resistances), C_m (cell membrane capacitance), and exponent α (accounts for distribution effects such as cell size and shape).[21] Cole model term R_i (resistance associated with ICW) can further be computed with R_∞ and R_e or R_0 variables using the following equation: $1/R_i = 1/R_\infty - 1/R_e$.[12,21] Characteristic frequency (fc), which is the frequency at which the effects of cell membrane capacitance are maximum, is also calculated with the C_m, R_e, and R_i terms as $1/(2\pi C_m [R_e + R_i])$[21] and is represented graphically as the point of maximal reactance in the Cole plot (ie, the top middle point of the semicircle). Ideally, the data around fc are weighted to provide the best overall fit for the model.[21] With this approach, ECW and ICW volumes are generated by applying Cole model terms to equations developed based on Hanai mixture theory, which describes how electrical properties of tissues are modified by mixture effects of conducting (water, electrolytes, lean tissue) and nonconducting (bone, fat) components of the body.[21,54] Theoretically, at zero frequency (with resistance R_0), no conduction occurs and impedance (Z) is a function of ECW; that is, $Z = R_0 = R_e$.[21] At infinite frequency (with resistance R_∞), pure conduction occurs and impedance is a function of TBW; that is, $Z = R_\infty$.[21] These concepts have been thoroughly reviewed elsewhere,[29,55] and the Xitron mixture theory-based BIS equations have been published previously.[54,56]

In general, BIS has several theoretical advantages over SF-BIA and MF-BIA in that BIS measures impedance over an entire range of frequencies and does not depend upon population-specific prediction equations to generate whole body volumes and masses. The BIS approach is the only one that allows for the possibility of computing (through mathematical modeling) the characteristic frequency (fc) that changes with shifts in fluid compartments and cell membranes; and by measuring impedance up to very high frequencies, BIS ensures that the characteristic frequency is reached, allowing for complete quantification of TBW. In addition, separate specific resistivity constants (derived from dilution references) for each of the fluid compartments (by gender) are applied to the volume equations; thus, the BIS mixture equation approach does not assume that ECW and ICW are uniformly distributed.[21] Therefore, this technique theoretically provides a more direct and individualized measure of ECW, ICW, and TBW compartments, compared with SF-BIA and MF-BIA approaches, which has potential advantages particularly in patient populations with altered fluid homeostasis.[15,21]

However, several underlying assumptions of the original Xitron mixture equation approach potentially introduce error to the volume estimates. Several constants are applied to the equations. Fixed (although separate) values for specific resistivity of the ECW and ICW compartments and constants for body density and shape are used in the equations. It is assumed that these constants are appropriate across the range of body composition, but this is unlikely to hold true, particularly in individuals with excessive adiposity and those with fluid imbalance associated with injury and disease. Indeed, it has been well-documented that overestimation errors in TBW and FFM produced by the Xitron BIS equations increase with increasing adiposity[16,18,19] and that much of this error is attributed to the impact that adipose tissue can have on the specific resistivity of ICW.[21,54] This limitation has been partially addressed by modifying the Xitron mixture equations with an adjustment for body mass index (BMI, kg/m^2).[54]

Moissl et al[54] introduced a BIS approach termed *body composition spectroscopy* (BCS) that involves the correction of the Xitron mixture equations for BMI, a surrogate for adiposity. The BCS approach was shown to improve volume estimates in individuals at the extremes of BMI. The BMI correction improved the standard error of the estimate for ICW by 24% for all subjects and by as much as 48% for the 24 subjects at BMIs <20 and >30.[54] That said, the BCS approach is still associated with significant error in whole body estimates, particularly at the individual level. In the Moissl study, wide limits of agreement were observed in all fluid compartment estimates. Interestingly, in malnourished individuals with advanced cancer, the BCS approach was shown to reduce the underestimation of errors in FFM generated using BIS by 35% (Hydra 4200, Xitron Technologies) compared with DXA (Lunar DPX-L and Lunar Prodigy, GE Healthcare); however, again, substantial variability at the individual level was observed.[57]

As stated previously for SF-BIA and MF-BIA, numerous validation studies in various healthy and clinical populations have been published on BIS (predominantly the original Xitron mixture equation approach), with similar findings of good

mean-level but poor individual-level agreement between reference methods and BIS; much of the literature has been reviewed previously.[11,15] Thus, although adjustment for BMI is an important advance for BIS, particularly in settings with extreme BMIs, further refinements are needed before it can be relied upon to accurately assess whole body masses and fluid volumes in the clinical setting. Nevertheless, the application of BIS (and MF-BIA) approaches for the monitoring of fluid status in individuals undergoing dialysis is an active and growing area. Developments in BIS technology for managing fluid balance are particularly promising and are discussed later. In addition, because BIS devices measure impedance data over the range of frequencies, they can easily be used to generate bioimpedance variables of interest including the 50-kHz PA and FFMI and the impedance ratio at 200/5 kHz (and potentially derivations unique to BIS: eg, ratio of impedance at infinity/zero). These novel applications are discussed next.

Novel Applications: Use of Bioimpedance Data for Clinical Assessment

Due to the questionable validity of bioimpedance approaches for the assessment of whole body composition estimates in clinical populations, there is growing interest in the utility of the raw bioimpedance data for its potential to contribute to bedside assessment of nutrition status and/or clinical outcomes. Bioimpedance-derived parameters (including 50-kHz measured PA, 50-kHz FFMI, and 200/5-kHz impedance ratio) have been investigated as potential prognostic indicators of mortality, disease severity, morbidity, hydration status, and malnutrition.[35,36] The use of such data has been purported to be mostly independent of regression equations (except for FFMI) and may be potentially useful in situations where assumptions for whole body composition estimates are likely to be violated. However, it should be noted that their application to predict outcomes or nutrition status also relies on a statistical relationship.

Phase Angle

PA is the ratio of the arc tangent of reactance to resistance and is purported to relate to important cellular characteristics, including membrane capacitance, integrity, and permeability, as well as overall size and hydration;[58,59] although the question of whether or not these relationships have a true physiologic basis has been questioned.[21] Although PA can be calculated at any frequency, the PA measured at 50 kHz has been the primary clinical parameter of interest due to the wide availability and predominance of SF-BIA devices. Moving forward, we will use the term "PA" to indicate PA measured at 50 kHz. A higher PA indicates a proportionally greater reactance for a given resistance, which has been interpreted to suggest more intact cell membranes and higher BCM.[35,60] In contrast, a lower PA has been interpreted to indicate cell loss and decreased cell integrity and BCM.[60] Clinically, a low PA has been studied as a prognostic indicator of disease and/or nutrition risk in HIV infection,[61,62] cirrhosis,[63] hemodialysis,[64] cancer,[58,65-67] chronic heart failure,[68] and geriatric settings,[69] where cell membrane integrity is likely to be compromised and fluid-based alterations are common.[35,59,67] Additionally, a low preoperative PA has been shown to be associated with poor nutrition and clinical outcomes among individuals undergoing cardiac[70] and gastrointestinal[71-73] surgeries. In one of the more recent reports, Kyle et al[59] observed that when compared with healthy controls, hospitalized patients had a lower PA (<5.0° in men, <4.6° in women, using an SF-BIA device [RJL-101, RJL Systems, Clinton Township, MI; no longer commercially available]) that was significantly associated with lower FFM and a higher percentage of body fat. Additionally, patients at moderate and severe nutrition risk (identified by Nutritional Risk Screening [NRS-2002] and Subjective Global Assessment [SGA]) were more likely to have low PA than healthy controls.[59] In this study, hospital length of stay (LOS) and nonsurvival were also associated with a lower PA.[59]

In a series of other investigations, Gupta and colleagues[58,65-67] reported that PA measured by an SF-BIA device (BIA-101Q, RJL Systems; no longer commercially available) was an independent prognostic indicator in individuals with advanced pancreatic (stage IV), advanced lung (stages IIIb and IV), advanced colorectal (stages II and IV), and breast cancer (stages I–IV). For example, using the nutrition assessment tool SGA, this research team identified various PA cut-points to identify well-nourished or malnourished individuals with advanced colorectal cancer.[66] Individuals classified as malnourished by the SGA had a significantly lower median PA score than well-nourished individuals (5.18° vs 6.12°, $P = .005$), and a modest but significant correlation was found between the SGA and PA scores ($r = 0.33$, $P = .004$).[66]

The primary challenge of using PA for clinical assessment is the lack of consensus on cut-points to be used to identify malnutrition (or poor clinical outcomes). Although several investigators around the globe have generated reference values for PA based on large population samples including healthy Swiss,[74] German,[38,39] and American[37] adults, notable differences have been observed. It is not entirely clear whether these differences are solely population dependent or whether differences among devices used are contributory. It has been observed[37] that PA reference values generated by the RJL-101 device from healthy US adults were higher than those generated for healthy Swiss adults using various devices including the RJL-101 and 109 (SF-BIA devices no longer commercially available) and the Xitron Technologies 4000B (a BIS device no longer commercially available),[74] even after adjustment for BMI and percentage FM. Although the use of different devices could have introduced some variation in these results, a more likely explanation is the ethnicity-specific differences in relative leg length, frame size, and body build.[14] Therefore, standardized population-specific reference data are likely to be necessary for optimal interpretation and application. For example, among individuals with

cancer (mostly with gastrointestinal tumors), Norman et al[40] evaluated PA measured by an MF-BIA device (Nutriguard M, Data Input, Pöcking, Germany; no longer commercially available) using the age-, sex-, and BMI-stratified data that were previously generated for the healthy German population.[38] In this way, a standardized PA value was generated for each patient. Individuals with a standardized PA value below the fifth percentile exhibited impaired nutrition and functional status, diminished quality of life, higher LOS, and a significantly higher 6-month mortality risk when compared with individuals with PA values above the fifth percentile.[40]

Additional research on the applications of standardized PA data for clinical assessment is vitally needed. It is unclear whether adjustments can be made to align reference data generated from different populations using different devices. Furthermore, additional research is needed to determine whether standardized PA can be used to identify muscle loss as one of the diagnostic markers of malnutrition.[1] With additional research in this area, it is certainly possible that standardized PA might prove to be a useful index of nutrition status in the clinical setting; however, its use as an assessment tool is limited by the lack of clear and consistent reference cut-points.

Impedance Ratio

Another bioimpedance parameter that has been proposed as a potential indicator of nutrition status and/or clinical outcomes is the ratio of impedance measured at 200 kHz to impedance measured at 5 kHz. This has been termed *impedance ratio* (IR) or *prediction marker* (introduced as such by Bodystat, Douglas, UK) and is designated in this discussion as IR. With impedance measurements at high (200 kHz) and low (5 kHz) frequencies, the IR parameter has been suggested to reflect the ratio of ECW/TBW fluid distribution. A limited number of published studies have investigated the clinical utility of IR. Although normal reference cut-points have not yet been established as they have for PA, IR values ≤0.78 in males and ≤0.82 in females have been observed in healthy individuals.[49] IR values approaching 1.0 suggest that the 2 measured impedances are approaching each other in value; higher IR values have been associated with postoperative edema,[50] worsening renal[51] and cardiac[52] function, and poor nutrition status.[48,49]

Several studies have evaluated IR as a surrogate marker for clinical outcomes associated with fluid overload. Among 38 individuals undergoing major abdominal surgery, preoperative IR measured by an MF-BIA device (QuadScan 4000, Bodystat) was significantly higher in the 20 participants who developed postoperative edema compared with individuals who did not develop edema later on (0.81 ± 0.03 vs 0.78 ± 0.02; $P = .015$).[50] In another observation, an IR value of >0.85 (QuadScan 4000) was found to be an independent predictor of worsening renal function among 80 patients hospitalized with decompensated heart failure.[51] Similarly, among 243 individuals with chronic heart failure, gender-adjusted IR values (QuadScan 4000) were significantly higher (eg, 0.85 vs 0.82 for females, 0.83 vs 0.80 for males) and gender-adjusted PA values were significantly lower (eg, 4.2 vs 5.1 for females, 4.9 vs 5.7 for males) in the class III–IV New York Heart Association (NYHA) functional classification group (indicative of more severe cardiac symptoms) compared with class I–II NYHA group (less severe cardiac symptoms).[52] These findings suggest that whole body MF-BIA derived IR may be useful in identifying individuals who already have or are at risk for developing fluid overload, which carries risk for poor clinical outcomes.

Other lines of investigation have evaluated IR as a potential marker for malnutrition. In one limited analysis of 316 hospitalized patients with IR values between 0.75 and 1.0 on admission measured using a BIS device (Hydra 4200S, Xitron Technologies; no longer commercially available), 27% of whom were malnourished, a higher IR was associated with greater risk for malnutrition (defined as weight loss >5% in 1 month or >10% in 6 months and/or BMI <18.5) and longer LOS in the hospital.[48] Specifically, for each 0.10 increase in IR above 0.75 at admission, the odds ratio of severe malnutrition was 5.8 (95% confidence interval [CI], 2.7–12.5; $P < .001$) and LOS increased by 4.2 ± 1.7 days ($P = .013$). Similar but less robust findings were observed for PA; for each 1.0-unit decrease in PA at admission, the odds ratio of severe malnutrition was 2.0 (95% CI, 1.2–3.6; $P = .011$) and LOS increased by 2.3 ± 1.2 days ($P = .056$).[48] In a similar observation among 109 individuals with gastrointestinal disorders, IR and PA (Xitron 4000B BIS device for IR, RJL BIA 101 SF-BIA device for PA) were evaluated for their ability to identify individuals with malnutrition assessed by neutron activation analysis derived total body protein measurements.[49] In this report, a higher IR (high IR defined as values >0.82 for females and >0.78 for males, from 151 healthy volunteers) was associated with a 4.15-fold higher odds of being malnourished, whereas the odds ratio for a lower PA was 1.55.[49] Additionally, from a total of 71 identified malnourished individuals, 56 were detected by IR, compared with 16 individuals identified by PA; each 0.10 increase in IR and each unit decrease in PA was associated with a 4.64-fold and a 1.55-fold increased odds of malnutrition, respectively.[49]

The limited research conducted to date seems to suggest that IR and PA may have clinical utility for identifying malnutrition at the bedside; however, additional research is needed to better identify standardized cut-points and to validate those cut-points in terms of current malnutrition criteria[1] and, ideally, against reference methods for lean tissue (ie, to establish whether clinicians can use PA and/or IR to identify individuals with muscle loss in addition to identifying individuals with overall malnutrition).

Fat-Free Mass Index

Schutz et al[41] and Kyle et al[75] proposed the use of FFMI, determined as the ratio between FFM calculated from their published 50-kHz bioimpedance equation[74] and height (kg/m^2), as a

standardized, height-independent nutrition assessment method. Although FFMI is not in the same category as PA and impedance ratio (because it requires the use of a prediction equation for FFM), it has similarly been studied for its potential to predict nutrition status and/or clinical outcomes. The interest in FFMI has arisen in part due to the challenges described earlier for generating whole body FFM estimates by bioimpedance. Furthermore, from a theoretical perspective, it is challenging to interpret the absolute values of FFM in kilograms measured by any technique, as estimates increase with height and decrease with body weight, age, illness, and gender differences.[41,74,75] This group has published normative data for FFMI developed from measurements in healthy Swiss adults,[41] and FFMI cut-off values for various BMI categories have also been reported in this population.[75]

Several studies have investigated the clinical utility of FFMI. In a prospective observational study involving 325 cardiac surgery patients in the Netherlands, preoperative FFMI calculated from the 50-kHz data generated by a BIS device (BodyScout, Fresenius Kabi, Bad Homburg, Germany; not currently commercially available in the United States) was evaluated for various postoperative outcomes.[76] A low FFMI value was set at ≤14.6 kg/m^2 in women and ≤16.7 kg/m^2 in men using previously published normative Swiss population data.[75] It was reported that a low preoperative FFMI was independently associated with a higher occurrence of postoperative infections and longer LOS in the intensive care unit.[76] More recently, among 123 preoperative abdominal surgery patients in the Netherlands, FFMI estimates generated by 2 different devices were compared (BF-906, Maltron International Ltd, Essex, UK [an SF-BIA device], and BodyScout [a BIS device]).[77] In this study, the BIS device identified a larger proportion of patients with lower FFMI (47%) compared with the SF-BIA device (16%) ($P < .001$).[77] Limits of agreement between the 2 devices indicated that the SF-BIA device overestimated the values compared with the BIS device for both FFM (4.93 ± 6.22 kg) and FFMI (1.66 ± 2.25 kg/m^2).[77] These results point to the challenges inherent in applying FFMI as an indicator of nutrition status when potentially using a different device from that used to generate reference cut-points. As mentioned for PA and IR, additional research is needed to determine how FFMI might be used as a tool for nutrition assessment in the clinical setting.

Use of Bioimpedance Techniques for Evaluation of Lymphedema and Fluid Management in Dialysis

Beyond the potential role of bioimpedance in nutrition assessment, there has been substantial interest from the medical community in the application of bioimpedance for the assessment of various aspects of clinical care including wound healing,[78] neuromuscular disease progression,[79,80] cardiac output monitoring,[81-84] and conditions associated with expanded ECW.[85-87] The reader is referred to the excellent review by Lukaski[12] for a more complete description of these novel applications of bioimpedance. Here, we discuss the 2 most prominent examples of the application of bioimpedance for assessment of conditions associated with expanded ECW: the evaluation of lymphedema and the management of fluid balance in individuals receiving dialysis.

Evaluation of Lymphedema

Lymphedema is the swelling that occurs when protein-rich lymph fluid accumulates in the interstitial space,[88] resulting from damaged or blocked lymphatic vessels that inhibit the drainage of fluid from tissues. This subcutaneous accumulation of lymph fluid is associated with the expansion of ECW.[89] Secondary lymphedema of one or both arms or legs is a debilitating consequence of cancer or its treatment that is particularly prevalent among individuals with breast, uterine, ovarian, and prostate carcinomas and lymphomas or melanomas.[88] Although lymphedema is incurable, early detection through regular monitoring is one of the best ways to promptly manage lymphedema.[88,89]

Significant interest has arisen in the application of segmental BIS to monitor and detect early stages of lymphedema, particularly among individuals with breast cancer. Much of the early work in this area involved the application of a BIS device to generate an interlimb ratio of resistance values for an affected limb compared with an unaffected limb.[89-94] In brief, the BIS device is used to generate Cole model terms, and the resistance at 0 kHz (R_0) for the unaffected limb is divided by the R_0 for the affected limb. Among women diagnosed with unilateral arm lymphedema following breast cancer treatment, Ward et al[95] used the aforementioned ratio method to generate the ECW/ICW ratio and volume of the affected arm using a BIS device (SFB7, ImpediMed). The mean arm ECW/ICW ratio was 1.5:1 among those with lymphedema, compared with values between 0.85:1 and 1:1 in the group without lymphedema.[95] When compared with the reference method perometry (which provides more direct measures of limb volume), BIS showed proportional increases in arm size, and strong correlations were noted between the 2 measures for ECW, ICW, and TBW compartments ($r = 0.80–0.90$).[95] In a further evaluation of this technique among women with lymphedema and those with no history of lymphedema, Czerniec et al[90] reported that when compared with perometry-derived volume data, segmental BIS using the SFB7 device detected mild localized lymphedema; however, the limits of agreement between the 2 methods varied from 8.5% for the upper arm segment to 16.6% for the forearm segment, with increases in bias with the severity of lymphedema.[90] The authors have asserted that because BIS is sensitive to changes in the ECW volume, the method is able to detect mild localized lymphedema better than perometry. However, evaluation of the absolute accuracy of BIS-guided limb volume estimations is difficult to achieve due to

limitations inherent to perometry and other reference methods and the lack of segment-specific normative data for limbs. Regardless, this segmental BIS approach appears to hold promise for the early detection of lymphedema in its latent stages and therefore merits additional research.

Fluid Management in Dialysis

Overhydration characterized by expansion of the ECW is common among individuals receiving dialysis,[21] and bioimpedance techniques have been investigated for monitoring hydration status and adjusting dialysis treatment goals. The primary target of interest is the estimation of "dry weight," which has been defined as the lowest tolerable postdialysis weight at which the patient is as close as possible to a normal hydration state without experiencing symptoms associated with either overhydration or underhydration.[96,97] Dry weight is technically achieved through the removal of excess water during dialysis.[97] Estimates of dry weight are further used to calculate the ultrafiltration rate, or the rate at which the fluid is removed during the course of dialysis. Clinical assessment of dry weight is critical because an overestimation of dry weight could result in inadequate ultrafiltration and hypervolemia and its associated symptoms including arterial hypertension, left ventricular dilatation, and left ventricular hypertrophy.[96,97] An underestimation of dry weight, in contrast, could result in excessive ultrafiltration and hypovolemia, which could lead to hypotension, arrhythmias, reduced compliance to treatment, and an increased risk of vascular thrombosis.[97,98] The clinical estimation of dry weight has been conducted mostly through trial and error methods that involve parameters such as physical examination, changes in blood pressure or respiration rate, or presence of edema, without actually quantifying changes in fluid volume.[97,98] Thus, bioimpedance techniques have been explored for their ability to estimate dry weight in individuals receiving dialysis.

Segmental measurements. One approach that has been studied is the use of continuous segmental BIS measurements of the calf during hemodialysis. The assumption underlying this approach is that due to gravity effects, the calf is the last section of the body from which excess ECW is likely to be removed, and thus it has been identified as an ideal region to target for measurement given that the relative fluid volume of excess ECW would be expected to be higher in the calf region compared with the arms or trunk.[96,99] By this approach, the dry weight is identified when the ECW volume in the calf does not decrease further, despite ongoing ultrafiltration. Hence this method identifies the time-point during dialysis at which an individual is assumed to be at his or her dry weight and thus ultrafiltration should be stopped.[96,99] One of the limitations of this method is that it does not provide a whole body target volume to be removed at the initiation of dialysis, because the dry weight is identified during ongoing dialysis and the excess fluid removed at the whole body level is not quantified.[100]

In a derivation of this approach, Zhou and colleagues[98] used an MF-BIA device (QuadScan, Bodystat) to generate the IR from a segmental measurement of the calf to estimate dry weight in individuals receiving hemodialysis. Age-stratified calf impedance ratio values were obtained from healthy controls and set as target impedance ratios. In this study, calf IR was measured 30 minutes after the completion of a mid-week dialysis session, and dry weight was incrementally decreased at each subsequent dialysis session (or on a weekly basis) until the target calf IR was reached or symptoms of hypovolemia occurred. Achievement of target calf IR values in this study was associated with a significant reduction of blood pressure and use of antihypertensive medications.[98]

Wrist-ankle measurements. Significant recent advancements in BIS technology provide a novel and promising approach to the fluid management of individuals undergoing dialysis, with potential ramifications for other clinical populations. These developments involve the refinement of the whole body wrist-ankle BIS approach to incorporate a new model of body composition.[32] Essentially, the BMI-corrected mixture equations described earlier as the BCS approach[54] are used to generate ECW and ICW volumes that are then applied to model equations proposed by Chamney et al[32] that attempt to differentiate excess fluid from normally hydrated tissue. In this 3-compartmental model of body composition, the body is delineated into normally hydrated adipose tissue mass, normally hydrated lean tissue mass, and excess fluid mass.[32]

This new approach has been evaluated in several studies. Wizemann et al[101] used the Body Composition Monitor BIS device (Fresenius Medical Care, Bad Homburg, Germany; not currently commercially available in the United States), which incorporates the aforementioned approach into its software based on previous work,[32,102] to estimate overhydration and predict mortality among 269 chronic hemodialysis (HD) patients during a follow-up period of 3.5 years. The device software is programmed with expected normal values for ECW for a given body weight and composition based on healthy population data; absolute fluid overload is determined by the difference between the normal expected ECW and the actual measured ECW. The relative fluid overload is expressed as the ratio between the absolute fluid overload and the ECW. Wizemann et al[101] reported that the predialysis relative fluid overload was an independent predictor of mortality, with a hazard ratio of 2.1 (95% CI, 1.39–3.18; $P = .003$). In a similar study among 529 individuals on peritoneal dialysis, the Body Composition Monitor–derived relative fluid overload was also found to be an independent predictor of mortality (hazard ratio = 2.09, 95% CI, 1.19–2.82; $P < .001$).[103]

In a recent prospective randomized trial, Body Composition Monitor–derived ECW, ICW, and TBW volumes were used to adjust dry weight and prescribe ultrafiltration goals for HD patients over a period of 2.5 years.[104] A total of 131 patients were randomized into the "bioimpedance group" (n = 62), in

which target dry weight was prescribed based on the readouts from the BIS device, and a control group (n = 69), in which dry weight was determined based on the blood pressure value, presence of edema, and other physical parameters.[104] Compared with the control group, subjects in the bioimpedance group had significantly lower all-cause mortality, arterial stiffness, blood pressure, and relative fluid overload.[104]

Taken together, these study results are strongly supportive of the application of BIS, in particular the approach incorporated into the Body Composition Monitor software, for the clinical assessment of dry weight in individuals undergoing dialysis. Additional research is certainly warranted to investigate outcomes including morbidity and mortality in individuals with dialysis being managed with this approach. Furthermore, the apparent effectiveness of this new 3-compartment model BIS approach in the fluid management of individuals receiving dialysis carries great potential for application to other clinical conditions associated with fluid overload, including heart and other organ failure, sepsis, trauma, and other critical illness. Moreover, the ability to differentiate between excess fluid and this model's concept of normally hydrated lean tissue holds promise, particularly if it can be refined to provide meaningful estimates of lean tissue for purposes of nutrition assessment.

Summary and Conclusions

In this update, we have reviewed the 3 primary categories of bioimpedance techniques in terms of underlying assumptions, strengths, and limitations in order to orient clinicians to the differences between approaches and the potential opportunities for their application in the clinical setting. The global interest in these techniques to provide whole body estimates of lean tissue for bedside nutrition assessment has led to substantial validation research efforts to provide proof of their accuracy with mixed results. Predominant reports of large variability in individual estimates by bioimpedance and reference techniques have led to a general mistrust of bioimpedance methods to quantify whole body composition in clinical populations, particularly those with abnormal body geometry and fluid balance. Reliance on statistical methods that may not adequately account for errors in reference techniques and cross-validation of SF-BIA and MF-BIA equations originally developed from one reference method by comparison to a different reference method are just two of the limitations in the validation literature that may contribute to the inconsistencies regarding validity across studies. Thus, it remains somewhat unclear whether any bioimpedance technique can be proven to provide sufficiently meaningful whole body lean tissue estimates at the individual bedside to appropriately identify individuals with malnutrition and/or to effectively monitor lean tissue changes in response to nutrition interventions. The new developments in BIS technology that are being applied in individuals undergoing dialysis hold promise; the improvements in the ability of BIS devices to quantify excess fluid in these patients using new models of body composition could lead to further refinements for the assessment of lean tissue in other clinical populations.

The SF-BIA and MF-BIA approaches for whole body lean tissue assessment are likely to remain somewhat limited for use in the clinical setting. Although clinicians might optimize accuracy in whole body estimates generated by a particular SF-BIA or MF-BIA device by choosing an appropriate equation from the literature that matches the characteristics of their particular patient, it is not very practical to expect this to happen in the clinical setting. Many bioimpedance devices have a "black box" approach where programmed equations are kept as proprietary information so clinicians have no idea of what equation is being used. Furthermore, some devices do not provide the raw bioimpedance data, and thus clinicians have no way to recalculate their own estimates of body composition, even if they are able to find the time to identify an appropriate prediction equation. Taken together, these concerns have led to the pursuit of using raw bioimpedance data for the evaluation of nutrition status and/or clinical outcomes independent of whole body composition estimates. Although these applications appear promising, they are limited by their statistical foundation, and by the lack of consensus on reference cut-points. From the literature on PA and FFMI, it appears that there may be potentially important population- and device-specific differences in reference values; the ongoing turnover of devices in the market place is a significant consideration. Moreover, these applications require further study to determine whether they can be used to accurately identify individuals with malnutrition and to monitor response to nutrition interventions. There is clearly a need for additional research investigating the applications of bioimpedance for clinical assessment of malnutrition and response to nutrition interventions. Two specific questions that merit further investigation are these:

- Can the application of PA and/or IR be sufficiently refined (ie, with clear cut-points) to be useful for the diagnosis of sarcopenia (with and without the presence of obesity) and malnutrition in clinical settings?
- Can BIS-derived "normally hydrated lean tissue mass" as generated from the new BIS models being applied in dialysis be used to effectively identify malnutrition and evaluate responses to nutrition interventions at the bedside?

Obtaining answers to these questions will likely require the design of rigorous clinical trials that incorporate appropriate reference techniques and solid statistical design and the cooperation of the bioimpedance manufacturing industry.

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