

Body Composition Assessment in Clinical Studies: Considerations and Applications

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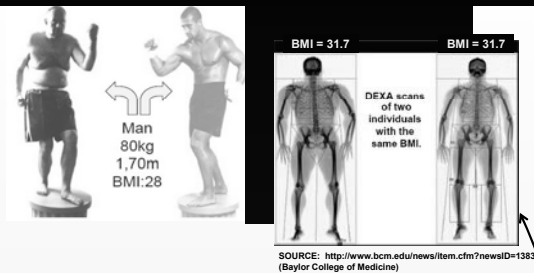
March 18, 2011

Presentation Objectives

- To understand
 - The relevance of body composition to clinical research: focus on body cell mass (BCM) and fluid
 - How to measure BCM and fluid compartments
 - “Reference” methods vs. “field” methods
- To gain insight into:
 - The theory and limitations of bioimpedance methods in clinical populations
 - Issues and considerations in interpretation of validation studies
 - Applications of bioimpedance in clinical settings
 - Future directions and research needs

Why Measure Body Composition?

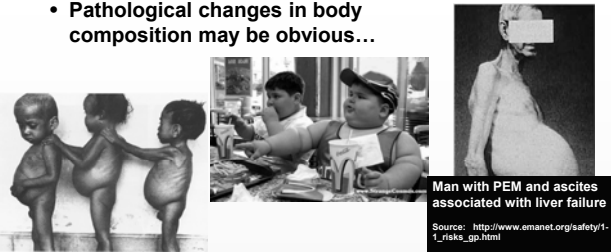
- Standard anthropometric tools problematic
 - Body Mass Index (weight/height²), weight alone



This man has twice the body fat as the other

Why Measure Body Composition?

- Pathological changes in body composition may be obvious...



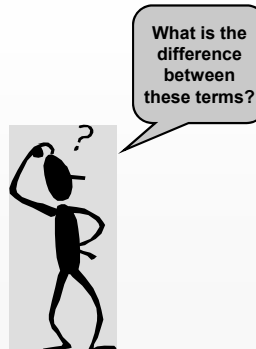
Man with PEM and ascites associated with liver failure

Source: http://www.emanet.org/safety/1-1_risks_gp.html

- Or they can be more subtle...
 - Loss of lean tissue can occur before overt weight loss in individuals with HIV infection and other chronic illness
 - Loss of lean tissue with normal aging

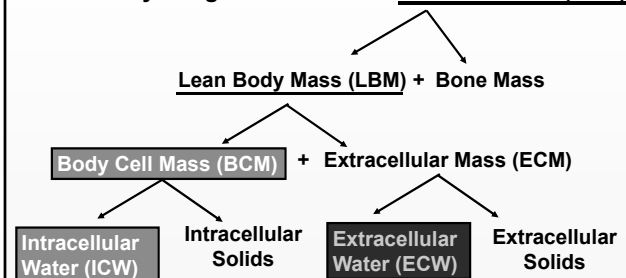
There Are Several Terms for Lean Tissue:

- Fat-free mass (FFM)
- Lean body mass (LBM)
- Body cell mass (BCM)



Body Composition Basics

$$\text{Body Weight} = \text{Fat Mass} + \text{Fat-Free Mass (FFM)}$$



Clinical Relevance and Implications

- **Body cell mass (BCM)**
 - Metabolically active, functional tissue (Moore and Boyden, 1963)
 - Key parameter of nutritional status
- **Fluid distribution:**
 - Detecting fluid overload or dehydration (ECW)
 - Early detection of malnutrition (loss of BCM)
 - Loss of BCM (ICW) with concomitant expansion of ECW could cause TBW and body weight to remain constant, thus masking malnutrition

Reference Methods for BCM and Fluid Compartments in Clinical Research

- 'Reference' methods for body cell mass
 - Total body potassium counting (TBK)
 - Neutron activation analysis (TBN – total body nitrogen)
 - Multiple dilution (ICW)
 - Deuterium dilution: total body fluid (TBW)
 - Bromide dilution: extracellular fluid (ECW)
 - $TBW - ECW = ICW$
 - Fluid distribution between ECW and ICW compartments
 - Time-consuming, expensive, not practical
 - Useful as reference methods against which field methods can be validated

Reference Methods for FFM and LBM in Clinical Research

- 'Reference' methods
 - Air displacement plethysmography (BodPod)
 - $Wt = Fat\ Mass\ (FM) + FFM$
 - Dual energy X-ray absorptiometry (DXA)
 - $Wt = FM + FFM$
 - $FFM = Bone + LBM$
 - *DXA is a reference method for both FFM and LBM
 - Deuterium dilution
 - Deuterium dilution: total body fluid (TBW)
 - From TBW, derive fat-free mass (FFM)
 - $FFM = TBW \cdot 0.73$
 - Time-consuming, expensive, not practical
 - Useful as reference methods against which field methods can be validated

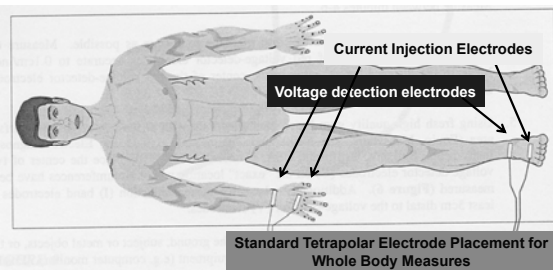


Bioimpedance is a Field Method that May Be Used in Clinical Research

- Single-frequency bioimpedance analysis (SF-BIA)
- Multiple-frequency bioimpedance analysis (MF-BIA)
- Bioimpedance spectroscopy (BIS)
- All are safe, easy, noninvasive, relatively inexpensive
- Key differences in underlying theory, potential applications, and validity in clinical populations



Bioimpedance Basics



- Introduce weak alternating current to body, measure impedance of tissues to flow

Single-Frequency BIA is Based on the 2-Component Model

- **Body Weight = Fat Mass + Fat-Free Mass (FFM)**
 - **Single-frequency BIA:** Field method for FFM
 - Measure impedance, predict total body water (TBW)
 - From TBW, derive FFM
 - $FFM = TBW \cdot 0.73$
 - Assumption: FFM is constantly hydrated at 73%

Single-Frequency Bioelectrical Impedance Analysis (SF-BIA)

- Fixed single frequency (typically 50 kHz)
- $V = \rho L^2/R$
 - Regression equation developed by regressing Ht^2/R against TBW measured by dilution methods
 - Empirically derived equations are *population-specific* and must then be cross-validated
- $TBW(L) = m Ht^2/R + c$
 - m and c correspond to empirically derived slope and intercepts of the regression analysis

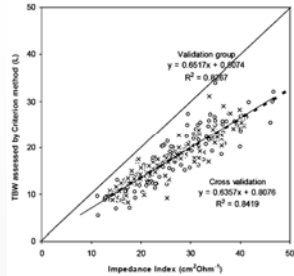
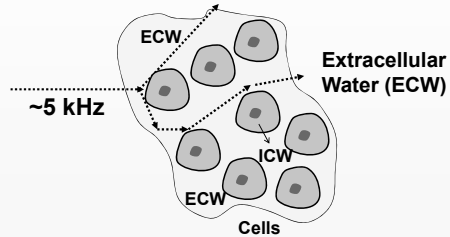


Figure 1 Association between TBW (l) assessed by criterion method (D₂O) and impedance index (cm²/Ω). Solid line represents validation group, dashed line represents cross-validation group.

Wickramasinghe et al. Eur J Clin Nutr 62: 1170-1177, 2008.

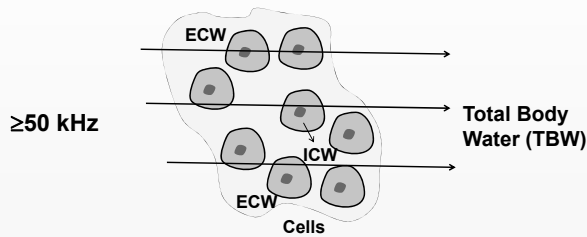
Theoretical Basis of Bioimpedance

- Theory:
 - Apply current at low frequency: ECW



Theoretical Basis of Bioimpedance

- Theory:
 - Apply current at low frequency: ECW
 - Apply current at higher frequencies: TBW



Body Composition Basics

Single-frequency BIA:
Field method for FFM

$$\text{Body Weight} = \text{Fat Mass} + \text{Fat-Free Mass}$$

$$\text{Lean Body Mass (LBM)} + \text{Bone Mass}$$

$$\text{Body Cell Mass (BCM)} + \text{Extracellular Mass (ECM)}$$

$$\text{Intracellular Water (ICW)} + \text{Intracellular Solids} + \text{Extracellular Water (ECW)} + \text{Extracellular Solids}$$

MF-BIA and BIS: Possible field methods for ICW (& BCM), ECW

Multiple-Frequency BIA (MF-BIA) Goes Beyond the 2-Component Model

- Fixed low and high frequency
 - 1 or 5 kHz to measure ECW
 - 50, 100, 200, or 500 kHz to measure TBW
- (Thomasset, 1963; Deurenberg et al., 1995; Hannan et al., 1994, 1998)

$$V = \rho L^2/R$$

Regression of Ht^2/R (or other) measured at low and high frequency against ECW and TBW measured by dilution methods

- Equations are *population-specific* and must then be cross-validated

$$\text{Ex: } TBW(L) = m Ht^2/R_{200} + c$$

$$\text{Ex: } ECW(L) = m Ht^2/R_5 + c$$

$$\text{Ex: } TBW - ECW = ICW$$

- Theoretically able to differentiate ECW vs. ICW, and to quantify BCM

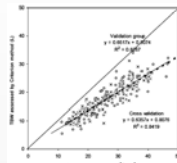


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Wickramasinghe et al. Eur J Clin Nutr 62: 1170-1177, 2008.

Bioimpedance Spectroscopy (BIS) Goes Beyond the 2-Component Model

- Range of frequencies (~5 - 1000 kHz)

Biophysical modeling

- Impedance data over the spectrum is fit to the Cole model through nonlinear least squares curve fitting

- Cole model terms can then be:

- Regressed vs. dilution volumes to derive equations (Cole)

- Once cross-validated these equations can be used to estimate volumes

- Applied to equations based on Hanai mixture theory (Cole/Hanai)

- Theoretically able to differentiate ECW vs. ICW, and to quantify body cell mass (BCM)

- ICW ~ BCM

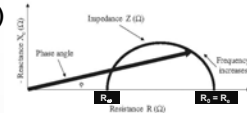


Figure 3 Diagram of the graphical derivation of the phase angle; its relationship with resistance (R), reactance (Xc), impedance (Z) and the frequency of the applied current.

Kyle et al. Clin Nutr; 23: 1226-1243, 2004.

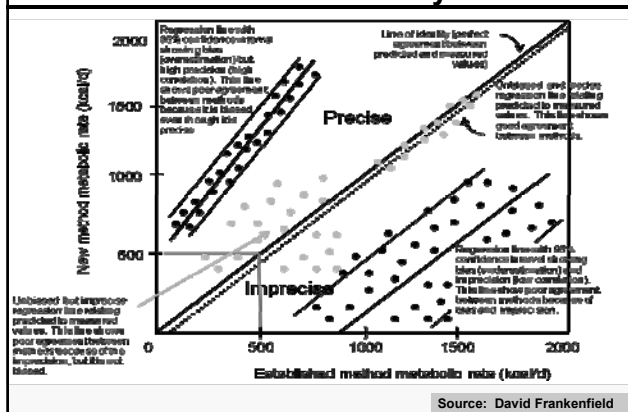
Comparison to References: "Validation"

- BIA measures are compared to reference method
 - Dilution methods for fluid volumes, BCM
 - TBK for BCM, ICW
 - DXA or BodPod for FFM
- Paired t-tests (or other mean level methods)
- Correlational analysis
 - Linear regression (correlation and SEE statistics)
- Bland-Altman analysis
- Ways to describe error in the measurements
 - 95% confidence intervals
 - Root mean squared error (RMSE), mean absolute difference
 - Limits of agreement (mean \pm 2SD)
 - Standard error of the estimate (SEE)

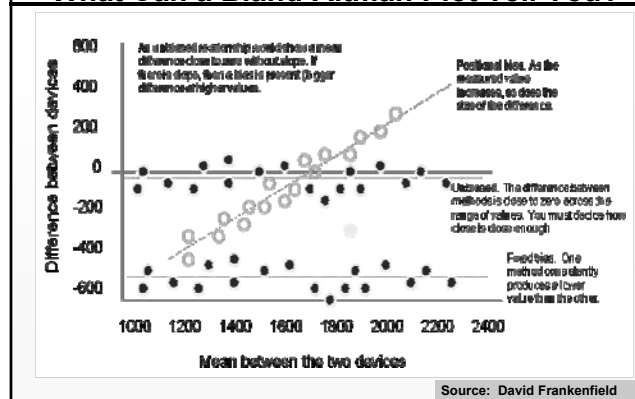
Considerations for Validation of Methods

- "Validity" is typically defined as
 - No significant difference between BC measures by the field and reference method by a paired t-test
 - But negative errors can cancel positive errors
 - High correlation in BC measures by the 2 methods
 - Tight cluster of values around the mean in Bland-Altman plots
- Considerations
 - What can a significant paired t-test tell you?
 - What can a high correlation tell you?
 - What about Bland-Altman plots?
- Caution when interpreting validation studies!

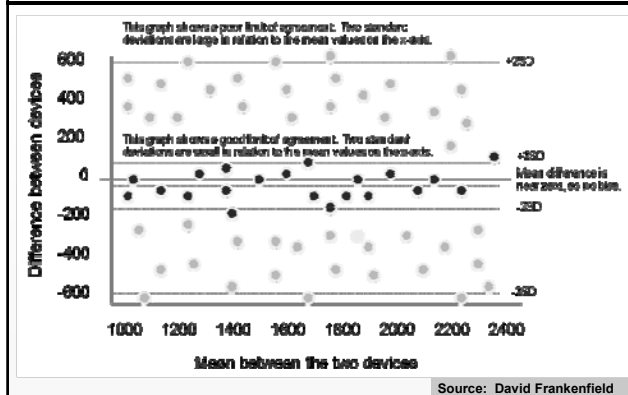
What Can Correlational Analysis Tell You?



What Can a Bland-Altman Plot Tell You?



What Can a Bland-Altman Plot Tell You?



Precision and Accuracy

- Precision
 - Most commonly defined as repeatability of the measurement
 - Degree of agreement among measurements obtained by one method
- Accuracy
 - May be termed validity or bias
 - Degree of agreement of a set of measurements by a field method with the 'true' values by a reference method
 - Two schools of thought:
 - Accuracy = strong group average agreement, regardless of the closeness of each individual measurement (low bias, no concern for precision)
 - Accuracy = strong individual level agreement (low bias, high precision)

Precision and accuracy

TABLE 13. Precision, accuracy, and detectable changes for an individual using various body composition measurement techniques

Body Composition Compartment (Method)	Measurement		Minimum Detectable Change for an Individual
	Precision,* %	Accuracy,† %	
TBK (⁴⁰ K counting)	1-3	5	150 meq (4%)
TBW (D ₂ O dilution)	1-2	2	2 liters (5%)
ECW (Br dilution)	2-3	2-4	2 liters (10%)
TBN (Prompt-γ)	2-4	3	130 g (7%)
TBCa (Delayed-γ)	1-2	5	55 g (5%)
FFM (UWW/ADP)	1-2	2-3‡	4 kg (9%)
FFM (BIA/BIS)	1-2		2-4 kg (7%)
DXA			
BMC (g)	1-2	2-10§	160 g (4%)
LTM (kg)	2-3	5	4 kg (7%)
Fat (kg)	3-4	5-10	1 kg (10%)
VAT (MRI/CT)	5-10		

TBK, total body potassium; TBW, total body water; ECW, extracellular water volume; TBN, total body nitrogen; TBCa, total body calcium; FFM, fat-free mass; DXA, dual-energy X-ray absorptiometry; VAT, visceral adipose tissue; BMC, bone mineral content; LTM, lean tissue mass; MRI, magnetic resonance imaging; CT, computed tomography. Estimates of minimum detectable change for an individual were based on ICRP-23 Reference Man model. *Reproducibility for repeat measurements. †Accuracy error for absolute mass or volume estimate. ‡Dependent on choice of model used. §Error tends to increase if specific bone site is measured.

Ellis KJ. Human Body Composition: In Vivo Methods. PHYSIOLOGICAL REVIEWS 2000;80(2): 649-680

BIS Cole/Hanai (Xitron 4000B device) to Measure ECW Changes in Critically-Ill Patients

Table 1. Extracellular water measurements (l) in 37 patients over 10 days by bromide dilution and bioimpedance spectroscopy (mean ± s.d.)

	Day 0	Day 10	10-Day loss	P value*
Bromide	26.02 ± 6.56	21.58 ± 6.49	4.43 ± 4.84	< 0.0001
BIS	24.53 ± 5.29	20.11 ± 5.53	4.42 ± 4.25	< 0.0001
P value*	0.014	0.012	0.96	
r†	0.85	0.85	0.87	

*Paired t-test.
†Pearson correlation coefficient.

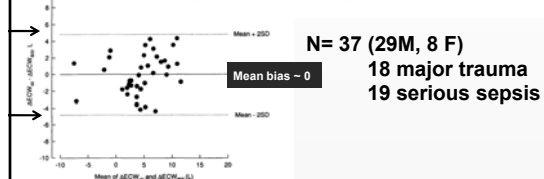


Fig. 1. Agreement between 10-day loss in extracellular water volume measured by bromide dilution (ΔECW_{Br}) and bioimpedance spectroscopy (ΔECW_{BIS}) in 37 critically ill patients.

Plank et al. Appl Radiat Isot. 1998;49:481-3.

Evaluation of Bioimpedance Techniques to Measure ICW (BCM) Changes in HIV Patients Undergoing Anabolic Therapy

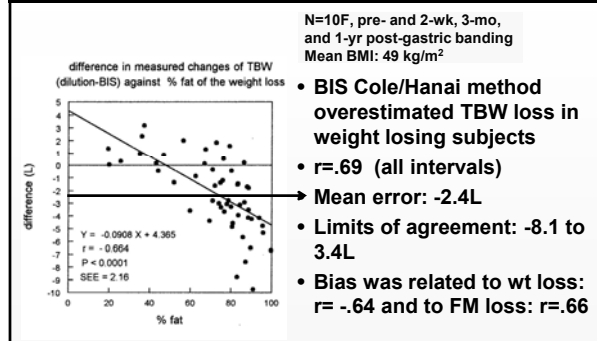
Method	Change, liters	r	E_{avg} , liters	P (n=10)	RMSE, liters	RMSE/√n, liters	-E _{lim} , liters	+E _{lim} , liters
Total body water								
7H	2.8 ± 2.4							
BIS	3.5 ± 2.3	0.73	0.65	0.020	1.71	0.37	1.02	0.28
TBW _{500kHz}	1.9 ± 1.3*	0.81	-0.84	0.002	1.45	0.32	-0.62	-1.26
TBW _{2000kHz}	1.7 ± 1.3*	0.82	-1.12	0.003	1.48	0.32	-0.80	-1.44
TBW _{5000kHz}	2.6 ± 2.0	0.82	-0.24	0.472	1.35	0.30	0.06	-0.54
Intracellular water								
7H - Br	2.4 ± 1.8							
BIS	2.7 ± 1.8	0.59	0.22	0.570	1.63	0.36	0.58	-0.14
ICW _{500kHz}	1.3 ± 0.8*	0.64	-1.16	0.002	1.47	0.32	-0.84	-1.48
ICW _{2000kHz}	1.4 ± 1.1*	0.63	-1.04	0.004	1.43	0.31	-0.73	-1.37
TBW _{500kHz} - ECW _{500kHz}	1.0 ± 0.7*	0.68	-1.42	0.000	1.47	0.32	-1.10	-1.74
TBW _{2000kHz} - ECW _{2000kHz}	1.9 ± 1.4*	0.67	-0.54	0.063	1.38	0.30	-0.24	-0.84

Change values are means ± SD. E_{avg} , the difference between the predicted and measured average change; RMSE, root mean squared error computed by subtracting the average error of the measured change from the error of each individual measurement, squaring each value, then computing the mean and its square root. E_{lim} , systematic error computed as $E_{avg} \pm RMSE/\sqrt{n}$. *Significantly different from criterion, $P < 0.10$.

67% of subjects' BIS Cole/Hanai values and 52% of subjects' MF-BIA (Hannon 500 KHz TBW - Hannon 5 KHz ECW) values fell within ±1.5L of reference-measured Δ ICW

Earthman et al. J Appl Physiol. 2000;88:944-956.

Errors in BIS Cole/Hanai Method are Related to Degree of Weight and Fat Loss



N=10F, pre- and 2-wk, 3-mo, and 1-yr post-gastric banding
Mean BMI: 49 kg/m²

- BIS Cole/Hanai method overestimated TBW loss in weight losing subjects
- $r = .69$ (all intervals)
- Mean error: -2.4L
- Limits of agreement: -8.1 to 3.4L
- Bias was related to wt loss: $r = -.64$ and to FM loss: $r = -.66$

Cox-Reijnen et al. JPEN. 2002;26:120-127.

Limitations of SF-BIA for Assessment of BCM and Fluid Volumes in Clinical Populations

- Single-frequency BIA (SF-BIA)
 - Fixed single frequency, 50 kHz
 - Assumed high enough to cross cell membranes to measure TBW
 - Requires statistically-derived population-specific equations
 - With use of appropriate equation, can be used to estimate TBW and FFM in healthy, normally hydrated individuals, but questionable in clinical populations
 - As with all bioimpedance methods, SF-BIA lacks sensitivity to detect small changes
 - Cannot distinguish between ICW and ECW
 - Cannot measure BCM
 - Cannot measure fluid distribution

Sources of Error in All Bioimpedance Methods

- Inappropriate selection of prediction equation (SF- or MF-BIA) or resistivity constants (BIS)
- Lack of standardization in measurement conditions and methodology
- Limitations of the reference method used in validation; differences between devices
 - Errors can simply be due to scaling differences
- Violation of body geometry and hydration assumptions
- Biological variability of humans

Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations

María Cristina G. Barbosa-Silva^a and Aluísio J.D. Barros^b

Purpose of review

The bioelectrical impedance analysis is not a direct method for estimating body composition. Its accuracy depends on regression equations, and recent papers have suggested that this approach should not be used in several clinical situations. Another option is to obtain information about the electrical properties of tissues by using raw bioelectrical impedance measurements, resistance and reactance. They can be expressed as a ratio (phase angle) or as a plot (bioelectrical impedance vector analysis). This review describes their use in clinical practice.

Abbreviations

BCM body cell mass
BIA bioelectrical impedance analysis
BIVA bioelectrical impedance vector analysis
BMI body mass index
ECW extracellular water
PA phase angle
SGA subjective global assessment
SFA standardized phase angle

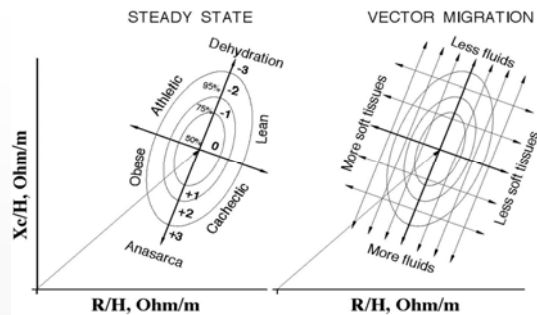
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 1363-1950

Current Opinion in Clinical Nutrition and Metabolic Care 2005;8:311-317.

Bioimpedance as an Outcome Measure

- Regardless of absolute volume accuracy, BIA parameters may be useful as prognostic indicators or as indicators of disease severity, hydration status, or malnutrition
 - Bioelectrical impedance vector analysis (*SF-BIA*, 50 kHz)
 - Phase angle (*SF-BIA*, 50 kHz)
 - Lower PA, worse outcomes
 - Impedance ratio (*MF-BIA* or *BIS*, 200/5 kHz)
 - Higher impedance ratio, worse outcomes

Bioelectrical Impedance Vector Analysis

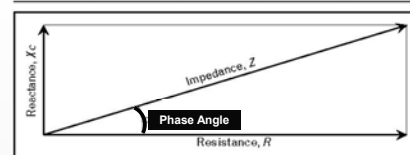


Piccoli A. Nutrition 2002;18:520-521.
 Piccoli et al. Kidney Int 1994;46: 534-539.

Phase Angle

What is the phase angle?

Figure 1. Graphical representation of impedance and phase angle



Their values can be calculated as $Z = \sqrt{X_c^2 + R^2}$ and phase angle (PA) = arc-tangent (X_c/R) $\times 180^\circ/\pi$.

> Opposition of a body to an alternating electric current (i.e. bioimpedance) has 2 components, R (resistance) and Xc (capacitance reactance)

> Part of the electric current is stored by the cell membranes, creating a phase shift (quantified as the PA)

> The PA depends on the capacitive effect of the tissues and their pure resistive properties, and membrane permeability

Barbosa-Silva and Barros. Current Opinion in Clin Nutr and Metabol Care 2005;8:311-317.

Bioimpedance as an Outcome Measure



Martinez et al. Nutrition. 2007;23:412-18.

NUTRITION

Nutrition 23 (2007) 412–418

www.elsevier.com/locate/nut

Applied nutritional investigation

Bioelectrical impedance and strength measurements in patients with heart failure: comparison with functional class

Lilia Castillo Martínez, M.Sc., Eloísa Colín Ramírez, M.Sc., Arturo Orea Tejada, M.D.*, Enrique Asensio Lafuente, M.D., Laura Paola Bernal Rosales, B.Sc., Verónica Rebolter González, M.D., René Narváez David, M.D., and Joel Dorantes García, M.D.

- N=243 patients with heart failure
 - 101 NYHA functional class I-II (56M, 45F)
 - 39 NYHA functional class III-IV (15M, 24F)
 - In the Class III-IV compared to Class I-II group, by gender:
 - Phase angle (50 KHz) was lower, impedance ratio (200/5 KHz) was higher, impedance vector was shorter and more downsloping and handgrip strength was lower

Bioimpedance as an Outcome Measure

- Phase angle (50 kHz):
 - Is not in strong agreement with SGA score for malnutrition, but predicts post-operative complications in GI surgery patients (Barbosa-Silva et al. Nutr 2003;19:422-426, Barbosa-Silva et al. Clin Nutr 2005;24:830-838.)
 - Is a strong prognostic indicator in patients with advanced pancreatic cancer (Gupta et al. 2004;92:957-962.) and amyotrophic lateral sclerosis (Desport et al. Amyotrophic Lateral Sclerosis 2008;9:273-278.)
 - Normative data has been published for phase angle in healthy German (Dittmar. Am J Phys Anthropol 2003;122:361-370, Bony-Westphal et al. JPEN 2006;30:309-316.), Swiss (Kyle et al. Nutrition 2001;17:534-541, Kyle et al. Clin Nutr 2004;23:758), and diverse American populations (Barbosa-Silva et al. Am J Clin Nutr 2005;82:49-52.)
- Impedance ratio (200/5 kHz): may predict disease severity
 - In 38 patients undergoing major abdominal surgery, Z_{200}/Z_5 was significantly higher in the 20 subjects who developed post-operative edema (Itobi et al. Br J Surgery 2006;93:354-361.)

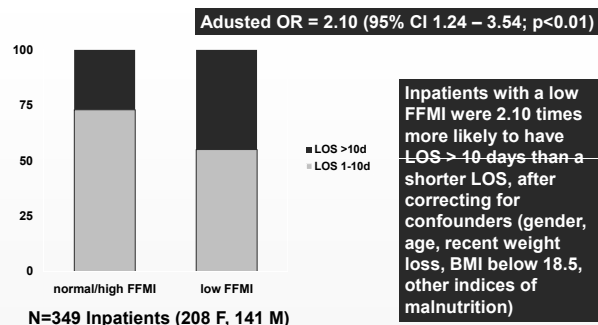
Other Novel Applications of Bioimpedance

- **Monitoring fluid status in dialysis patients**
 - Segmental BIS (Cole/Hanai with segment specific resistivity constants) can be used to detect fluid volume changes in peritoneal and hemo-dialysis patients
Zhu et al. Kidney Int 2000;57:299-306; Zhu et al. J App Physiol 2006;100:717-724.
 - Segmental lower leg MF-BIA to obtain impedance at 200 and 5 KHz (Z_{200}/Z_5) has been used to predict dry weight post-HD
Zhou et al. Am J Nephrol 2010;32:109-116.
 - Model using wrist-ankle BIS ECF and predicted population ECF to achieve dry weight, with further refinements
Chamney et al. Kid Int 2002;61:2250-8, Chamney et al. AJCN 2007;85:809.
- **Evaluating lymphedema**
 - The BIS Cole method has been validated against electro-optical perometry to evaluate lymphedema in women
Ward et al. Breast Cancer Res Treat 2009;117:541-547.

FFM Index May be Useful for Assessment

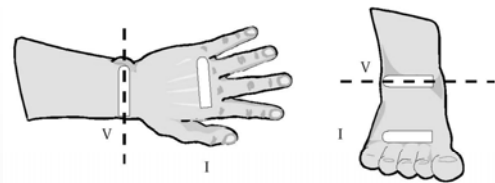
- FFM differs with height, weight, age, and gender
- **FFM Index (FFMI) = kg FFM/m² by SF-BIA**
 - Assuming validity of measurement, FFMI can provide a height-independent way to evaluate nutrition status, compare inter-study results, develop standard tables for interpretation
(Kyle et al. Nutrition 2003;19:597-604.)
- Normative data has been published for FFMI by SF-BIA in healthy Swiss Caucasians
(Schutz, Kyle, and Pichard. Int J Obesity 2002;26:953-960.)

FFM Index May be Useful for Assessment



PJM Weijs, HM Kruijzenga, JAE Languis, MAE van Bokhorst-de van der Schueren
Dept Nutrition and Dietetics, Vumc, Amsterdam, The Netherlands

Optimizing the Measurement



- Clean skin surface well with alcohol; subject should not use lotion or oils prior to measurement
- Electrodes should be placed ≥ 5 cm apart
- Measure and record distance between electrodes to ensure consistency in placement for follow-up measurements

Optimizing the Measurement

- If SF- or MF-BIA: Choose an appropriate, validated equation
- For longitudinal measures, same conditions and same technician
- **Ideal testing conditions**
 - No caffeine, alcohol, and exercise – 24 hours before testing
 - FAST (NPO except water) 8 hours before testing
 - Remove metal from clothing and body
 - Void bladder
 - Arms separated from trunk by $\sim 30^\circ$, legs separated by $\sim 45^\circ$
 - Measurements recommended to be taken at 10 minutes after assuming a supine position; *most important to standardize timing for longitudinal measures*

Summary

- Although SF-BIA and MF-BIA (with an appropriate equation) and BIS techniques can provide reasonably accurate whole body measures in healthy normal-weight people, there have been mixed results in clinical populations
 - Variability at individual level particularly problematic for clinic use
- Caution in using any bioimpedance method for measuring whole body volumes or mass
 - Choose validated equation carefully
 - Recognize limitations of the method
 - Utilize multiple parameters as clinical outcomes

Future Directions and Research Needs

- **Additional validation work**
 - Compare bioimpedance to reference measures in various clinical populations
 - Segmental measurements may improve MF-BIA and BIS Cole/Hanai estimates in patients with abnormal body geometry or hydration
 - Population-specific resistivity constants and other adjustments may improve accuracy of the BIS Cole/Hanai method
- **Additional outcomes-based research**
 - Impedance ratio Z_{200}/Z_5 for assessing dry weight?
 - Phase angle, impedance ratio Z_{200}/Z_5 , FFM index for identification of malnutrition and evaluating response to nutrition? What cutpoints to use?
- **With refinement, bioimpedance methods can provide information that the dietitian can use to enhance nutritional assessment and monitoring**