Bioimpedance Spectroscopy and Multifrequency Bioimpedance Approaches for Fluid Compartment Assessment: Theory and Clinical Applications

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Presentation Objectives

• To understand
  – The underlying theoretical basis of:
    • Bioimpedance spectroscopy (BIS)
    • Multifrequency bioelectrical impedance analysis (MF-BIA)
  – How estimates of fluid volumes by these methods compare to dilution (reference) in various populations

• To gain insights into:
  – The limitations and possibilities of the methods
  – Future research needs

Body Composition Basics

Body Weight = Fat Mass + Fat-Free Mass

Lean Body Mass (LBM) + Bone Mass

Body Cell Mass (BCM) + Extracellular Mass (ECM)

Intracellular Fluid (ICF) + Extracellular Fluid (ECF)

Intracellular Solids + Extracellular Solids
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

### BIS Devices

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacturer</th>
<th>Country</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydra 4200</td>
<td>Xitron Technologies</td>
<td></td>
<td>5, 50, 100, 200 KHz</td>
</tr>
<tr>
<td>ImpediMed SFB7</td>
<td>ImpediMed*</td>
<td>Pinkenba, Australia &amp; San Diego, CA</td>
<td>5, 50, 100 KHz</td>
</tr>
</tbody>
</table>

### MF-BIA Devices

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<th>Country</th>
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<tr>
<td>QuadScan 4000</td>
<td>Bodystat Ltd.</td>
<td>Isle of Man, UK</td>
<td>5, 50, 100 KHz</td>
</tr>
<tr>
<td>Data Input Body Composition</td>
<td>Bodystat Ltd.</td>
<td>Darmstadt, Germany</td>
<td>5, 50, 100 KHz</td>
</tr>
<tr>
<td>Body Comp MF</td>
<td>Akern Srl</td>
<td>Potassieve, Italy</td>
<td>5, 50, 100 KHz</td>
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Bioimpedance Basics

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

Theoretical Basis of Bioimpedance

- Theory:
  - Apply current at low frequency: ECW

  ~5 kHz Extracellular Water (ECW)

- Theory:
  - Apply current at higher frequencies: TBW

  ≥50 kHz Total Body Water (TBW)
Multiple-Frequency Bioelectrical Impedance Analysis (BIA)

- 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)

\[ V = \frac{p L^2}{R} \]

- 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
  Ex: \( TBW (L) = m Ht^2/R_{200} + c \)
  Ex: \( ECW (L) = m Ht^2/R_5 + c \)
  Ex: \( TBW - ECW = ICW \)

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

Bioimpedance Spectroscopy (BIS)

- 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 ECF vs. ICF, and to quantify body cell mass (BCM)
  - ICF ~ BCM

BIS: Step 1 - Cole Modeling

- Key Cole model terms:
  - \( R_c \): Represents ECW resistance and is renamed \( R_e \)
  - \( R_w \): Represents TBW resistance

Figure 3: Diagram of the graphical derivation of the phase angle; its relationship with resistance \( R_e \), resistance \( R_w \), impedance \( Z \), and the frequency of the applied current.

BIS: Step 1 - Cole Modeling (Cole)

- Raw impedance data fit to the Cole model (using nonlinear least squares curve fitting)
  - When R and Xc data at all the frequencies are plotted against each other, an impedance locus plot is created
- BIS device software generates Cole model, characteristic frequency, and other terms

BIS: Step 2 – Mixture Theory (Cole/Hanai)

- Cole model terms can be applied to equations derived from Hanai mixture theory:
  - Assumptions must be made:
    - The body is a conducting medium of water, electrolytes, and lean tissue, in addition to nonconductive material within it (e.g. bone, fat); and effects of non-conducting tissues in ECW and ICW increases their 'apparent' resistivity
    - The body has a constant density
    - Human body = 5 cylinders (arms, legs trunk) so a shape factor (Kb) developed from anatomical measures must be applied
  - R_i can be computed as: 1/ R_i = 1/R_\infty - 1/R_e, but it is not solely representative of ICW resistance because of cell membrane (cm) capacitance

Comparison of BIS/MFBI to References

- Reference for fluid volumes or BCM
  - Deuterium or tritium dilution for TBW
  - Bromide dilution for ECW
  - TBW – ECW = ICW

- Paired t-tests (or other mean level methods)
  - Mean error NS may be deemed good agreement
    - But negative errors can cancel positive errors

- Correlational analysis
  - Linear regression (correlation and SEE statistics)

- Bland-Altman analysis
  - Ways to describe error in the measurements
    - 95% confidence intervals
    - RMSE, mean absolute difference
    - Limits of agreement (mean ± 2SD)
    - SEE
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 terahertz spectroscopy (mean ± SD)

<table>
<thead>
<tr>
<th>Method</th>
<th>Change (L)</th>
<th>r</th>
<th>z value</th>
<th>P valuea</th>
<th>Brønstead</th>
<th>BIS</th>
<th>P valuea</th>
<th>r</th>
<th>z value</th>
<th>P valuea</th>
</tr>
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<tr>
<td>Day 1</td>
<td>31.0 ± 7.5</td>
<td>0.73</td>
<td>6.65</td>
<td>0.0001</td>
<td>36.1 ± 6.4</td>
<td>36.9</td>
<td>4.43</td>
<td>0.0001</td>
<td>6.85</td>
<td>0.0001</td>
</tr>
<tr>
<td>Day 10</td>
<td>31.0 ± 7.5</td>
<td>0.73</td>
<td>6.65</td>
<td>0.0001</td>
<td>36.1 ± 6.4</td>
<td>36.9</td>
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<td>18-Day loss</td>
<td>31.0 ± 7.5</td>
<td>0.73</td>
<td>6.65</td>
<td>0.0001</td>
<td>36.1 ± 6.4</td>
<td>36.9</td>
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*N= 37 (29M, 8 F)
18 major trauma
19 serious sepsis

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

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<tr>
<th>Method</th>
<th>Change (L)</th>
<th>r</th>
<th>z value</th>
<th>P valuea</th>
<th>Mean BMI (kg/m²)</th>
<th>MFBIA (Hannon 500 kHz TBW – Hannon 5 KHz ECW)</th>
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<tr>
<td>Day 1</td>
<td>0.1 ± 1.2</td>
<td>0.91</td>
<td>1.71</td>
<td>0.0001</td>
<td>39.2 ± 8.1</td>
<td>0.58 ± 0.15</td>
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67% of subjects’ BIS Cole/Hanai values and 52% of subjects’ MFBIA (Hannon 500 kHz TBW – Hannon 5 KHz ECW) values fell within ±1.5L of reference-measured ΔICW

Errors in BIS Cole/Hanai Method are Related to Degree of Overweight...
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

- 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

Correction for BMI Improves Estimates by BIS: Body Composition Spectroscopy

| Table 4. Agreement between TBW_{est} and TBW_{BCS} for each centre. |
|------------------------|-----------------|-----------------|
| Centre                 | r²               | Mean ± SD (L)   |
| Kiel                   | 0.91             | -0.27 ± 2.18    |
| NY                     | 0.59             | 1.18 ± 2.56     |
| Oldenburg              | 0.94             | -1.56 ± 1.50    |

All 32 were Dialysis pts

Comparing Cole/Hanai method vs. BCS:
SEE for TBW decreased by 0.6 L for all subjects, and by 1.2L for 24 subjects with extreme BMIs (<20 or >30)

Unique Applications of MF-BIA and BIS

- 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
  - 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
  - Model using wrist-ankle BIS ECF and predicted population ECF to achieve dry weight, with further refinements

- Predicting 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

- Evaluating lymphedema
  - The BIS Cole method has been validated against electro-optical perometry to evaluate lymphedema in women
Summary: Clinical Applications

- Although MF-BIA (with an appropriate equation) and BIS techniques can provide reasonably accurate whole body fluid measures in healthy normal-weight people, there have been mixed results in clinical populations (variability at individual level particularly problematic for clinic use)

- BIS Cole/Hanai method
  - Has best potential, but needs refinement particularly for populations with abnormal body geometry (e.g. obesity)
  - May be better for measuring changes (>2 kg) in patients with stable fluid and electrolyte balance, e.g. HIV
  - Improved results with BMI-correction (body composition spectroscopy)

- Both MF-BIA and BIS are being used by some dialysis centers for monitoring fluid status and dry weight

Future Directions

- Further refinement of the BIS Cole/Hanai method needed
  - Population-specific resistivity constants and other adjustments may improve the accuracy of the BIS Cole/Hanai method
  - Segmental approach may improve estimates in patients with abnormal body geometry or hydration status

- Additional research is needed to evaluate use of the impedance ratio \(Z_{200}/Z_2\) for assessing dry weight and for predicting disease severity

- Development and validation of algorithms for using MF-BIA or BIS data to identify malnourished patients (e.g. Fuzzy Logic System, Wieskotten et al, 2008. Physiol Meas. 29:639-654)

- With refinement, these methods can provide information that may be used to enhance nutritional assessment

Bioimpedance in Clinical Practice

Bioelectrical impedance analysis—part II: utilization in clinical practice

If 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 ~30°, legs separated by ~45°
  – Measurements recommended to be taken at 10 minutes after assuming a supine position; most important to standardize timing for longitudinal measures

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

Thank you!