

1 *Review*

2 **Classification of hydration: two approaches using** 3 **bioimpedance**

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15 **Abstract:** Although the need to assess hydration is well recognized, laboratory tests and clinical
16 impressions are impractical and lack sensitivity to be clinically meaningful. Different approaches use
17 bioelectrical impedance measurements to overcome some of these limitations and aid in classification
18 of hydration status. One indirect approach utilizes single or multiple frequency bioimpedance in
19 regression equations and theoretical models, respectively, with anthropometric measurements to
20 predict fluid volumes (bioelectrical impedance spectroscopy; BIS) and estimate fluid overload based
21 on deviation of calculated to reference extracellular fluid volume. Alternatively, bioimpedance vector
22 analysis (BIVA) uses direct phase-sensitive measurements of resistance and reactance, measured at
23 50 kHz, normalized for height, then plotted on a bivariate graph, resulting in a vector with length
24 related to fluid content normalized by standing height, and direction with phase angle that indexes
25 hydration status. Comparison with healthy population norms enables BIVA to classify (normal,
26 under- and over-) and rank (change relative to pre-treatment) hydration independent of body weight.
27 Each approach has wide-ranging uses in evaluation and management of clinical groups with
28 overhydration with an evolving emphasis on prognosis. This review discusses the advantages and
29 limitations of BIS and BIVA for hydration assessment with comments on future applications.

30 **Keywords:** fluid overload; resistance; reactance; bioelectrical impedance vector analysis;
31 bioelectrical impedance spectroscopy; malnutrition.

32

33 **1. Introduction**

34 Routine assessment of the hydration status to support patient care persists as a challenge. The
35 preponderance of methods suffers from impracticality and insensitivity [1,2]. Historically, hydration
36 assessment was synonymous with the use of tracer dilution methods to estimate total body water
37 (TBW), extracellular water (ECW) and plasma volume (PV) with calculation of intracellular water
38 (ICW) (ICW = TBW – ECW). This approach is invasive, time-consuming, costly and prone to
39 ambiguous interpretations of hydration status because of reliance on the assumption of constant TBW
40 to body weight (%TBW), which is prejudiced by inter-individual differences in body composition
41 (adipose, muscle mass or cachexia), or TBW to fat-free mass (%TBW/FFM) that requires an

42 independent determination of FFM [3-6]. Thus, the measurement of fluid volumes to assess human
43 hydration status has limited value.

44 Laboratory tests of plasma or serum constituents (osmolality, sodium, natriuretic peptide, and
45 other promising proteins), urine characteristics (osmolality, specific gravity, conductivity, 24-hr
46 output), saliva and tear composition (osmolality) have inadequate feasibility and lack sensitivity.
47 Imaging techniques (radiography, ultrasound) and invasive procedures (catherization) are costly and
48 fail to identify early disturbances in hydration. Simple assessments such as self-reported thirst,
49 patient history and physical examination are subjective and lack sensitivity [2,7]. Thus, the need
50 persists for a method that is non-invasive, valid (accurate and sensitive), practical, cost-effective, and
51 provides real-time discrimination within the spectrum of hydration status. Classification of hydration
52 as normal, less or greater than normal, is a practical and valid approach that can overcome these
53 limitations. Burgeoning evidence supports bioelectrical impedance as a unique and promising
54 method to classify the hydration status of an individual.

55 Bioimpedance (BI) is the general term describing the safe, non-invasive measurement of the
56 passive electrical characteristics of an organism after introduction of a painless, low-level alternating
57 current into the body [8-10]. Bioimpedance analysis (BIA), however, augments BI measurements with
58 theoretical biophysical models and statistical (regression) equations contributing to “black box”
59 predictions of fluid volumes that can be unreliable and imprecise. Bioimpedance *per se* offers direct,
60 uncomplicated measurements that facilitate a practical and valid approach to monitor hydration.

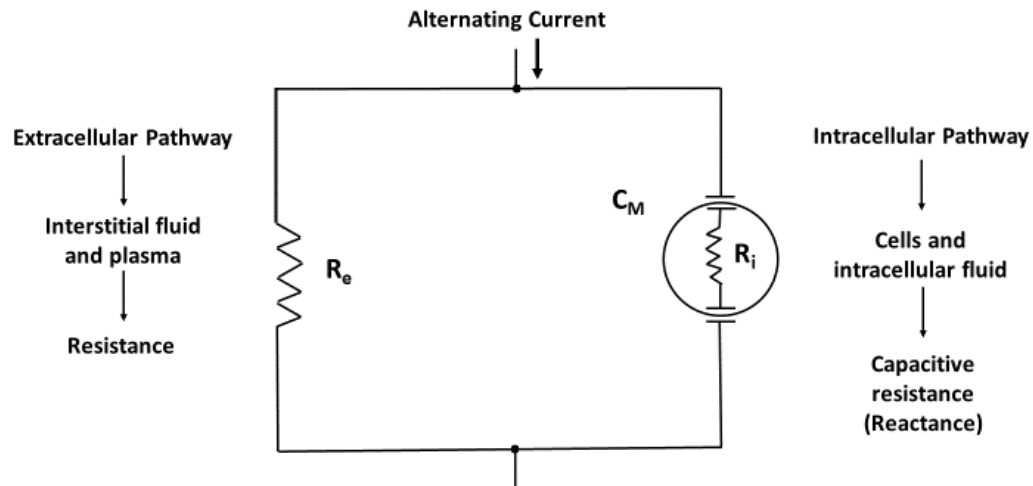
61 This review emphasizes the use of BI to classify hydration. It describes the biophysical basis of
62 the BI method, summarizes different technical approaches and their limitations to estimate fluid
63 volumes, discusses advantages of BI measurements compared to calculated fluid volumes, highlights
64 clinical applications of BI emphasizing its emerging role in prognosis, and provides
65 recommendations to improve and expand use of BI in clinical applications.

66 2. Bioelectrical Impedance

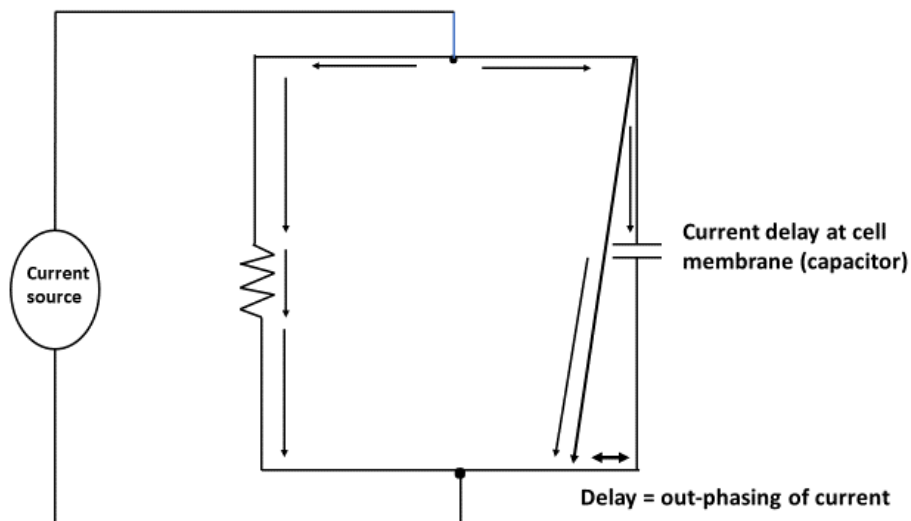
67 2.1. Bioimpedance Basics

68 The physical basis of the BI method is the awareness that the human body is a network of resistors
69 and capacitors [8]. Physiological fluids behave as resistors and cell membranes act as capacitors
70 (Figure 1). Thus, the body may be represented as a parallel resistor-capacitor (RC) equivalent circuit
71 (Figure 2) in which the introduced alternating current divides into resistive (fluid and electrolytes)
72 and capacitive (cell membranes and tissue interfaces) pathways. The lower specific resistivity of body
73 fluids and tissues containing water and electrolytes compared to intact lipid-laden cell membranes
74 [11] enables frequency-dependent impedance measurements [12]. A low-level alternating current
75 continuously passes predominantly through the resistive component but concurrently delayed
76 (temporarily stored) by capacitive elements in tissues and tissue interfaces. Importantly, a variable
77 amount of very low-frequency current, regardless at which frequency the current is introduced, can
78 penetrate the membranes of muscle cells, particularly when the current is parallel to the muscle fiber
79 [13]. Cell membranes are capacitive elements surrounding the intracellular fluid (ICF) in a series
80 circuit that exists in parallel with the water-containing interstitial gel or extracellular fluid (ECF). Any
81 alternating current will penetrate the capacitive component (reactance, X_c) of the cell membrane in
82 proportion to the frequency of the applied current. Reactance is inversely related to frequency (f) and

83 capacitance (C, Farads): $X_c \text{ (ohm, } \Omega) = 1/[(2\pi \cdot F \cdot C)]$. Capacitance is the ability of a system or circuit
 84 to store an electrical charge.
 85



86
 87 Figure 1. Illustration of the body as a network of resistors and capacitors in a parallel configuration.
 88 The alternating current usually exceeds 1 kHz and typically is 50 kHz. C_M is membrane capacitance
 89 and R_e and R_i are extracellular and intracellular resistance, respectively.
 90

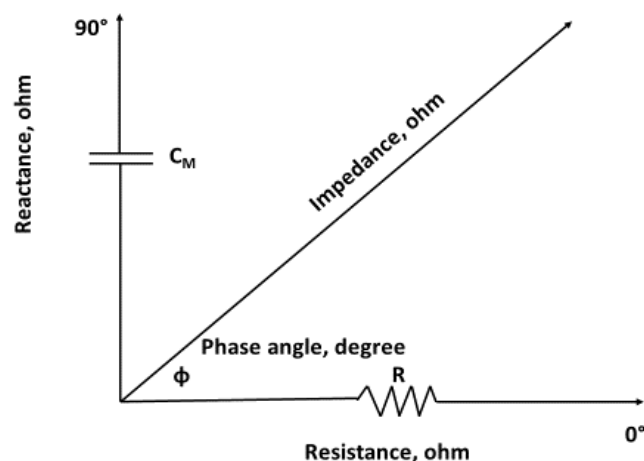


91
 92 Figure 2. Representation of the body as a parallel resistor-capacitor (RC) equivalent circuit. Delay of
 93 current penetration at the cell membrane causes an out-phasing of current.
 94

95 At low frequencies (e.g., 1 to 5 kHz), alternating current flows largely in the ECF but not in a
 96 direct or fixed proportion relative to the ICF. Similarly, at 50 kHz alternating current does not
 97 distribute in proportion to fluid distribution (extra- to intra-cellular fluid volume) but relative to
 98 capacitive elements. Thus, phase angle (PhA) is frequency-dependent, principally due to the amount
 99 of X_c , and is an index of the amount of applied current that penetrates the capacitive element or cell
 100 membranes. Current that is restricted or delayed at (intact) cell membranes becomes out-phased from
 101 the voltage drop that occurs at the cell.

102 Impedance (Z) is the broad term describing the opposition to the flow of alternating current by
 103 any biological conductor, and is defined by the type of electrical current introduced to a circuit. When
 104 direct current is applied, the total conductor is termed resistance (R) whereas when alternating
 105 current is introduced, it is called Z . Direct current passes only through resistive elements but
 106 alternating current flows through resistive and capacitive elements. The resistive (R) component of Z
 107 is independent of frequency so it has the same measurement value (Ω) when either direct or
 108 alternating current is used. The capacitor in a biological circuit serves as an insulator and may be
 109 envisioned as an imaginary component of Z when direct current is introduced. However, when
 110 alternating current is present, the imaginary component acts as a poor conductor with capacitive
 111 resistance and is termed reactance (X_c), which is frequency-dependent. Thus, Z is a complex number,
 112 $Z^2 = R^2 + X_c^2$, and characterizes the specific fluid and cellular components of an organism. Impedance
 113 is a vector with length and position on the bivariate RX_c plot (Figure 3). The PhA describes the
 114 position of Z and is the angular transformation of X_c to R [$\arctan(X_c/R) \cdot (180^\circ/\pi)$] expressed in
 115 radian degrees.

116



117
 118 Figure 3. Geometric relationships among resistance, reactance (capacitance, C_M), impedance, and
 119 phase angle.

120

121 2.2 Measurement of Bioelectrical Impedance

122 Assessment of whole-body hydration uses surface, gel (silver-silver chloride) or modern
 123 hydrogel electrodes and tetrapolar electrode placements. Whole-body BI measurements employ

124 traditional limb placements with paired current-introducing (source) and voltage-drop-sensing
125 (detector) electrodes placed on the distal wrist and ankle [8,10].

126

127 3. Volume Quantification in Hydration Assessment: Limitations and Imprecision

128 A primary factor for reliable hydration assessment is the technical validity of the BI
129 measurement. It includes the accuracy of the instrument, which is determined with a precision
130 (<1%) circuit of a resistor and a capacitor in a parallel circuit, and precision or reproducibility that
131 requires repeated measurements of a validation circuit and repetitive *in vivo* measurements. The
132 technical validity should be <2% for all BI measurements [9]. Similarly, the validity of the reference
133 tracer dilution methods must be assessed with technical accuracy and precision determined to be
134 <2%. Inter-individual biological sources of error for the tracer dilution methods, including
135 hydrogen exchange and anion (bromine-chlorine) shifts that >4% [14,15], directly affect the
136 variability of fluid volume estimates.

137

138 3.1 Single-Frequency Bioimpedance

139 Clinical investigators applied different BI approaches to estimate fluid volumes as indicators of
140 hydration. They mostly used phase-sensitive single-frequency (50 kHz) BI because of the high
141 signal-to-noise ratio [9,16] or multiple-frequency (5 kHz to 1 MHz) measurements coupled with
142 either multiple regression equations or theoretical biophysical models to predict fluid volumes
143 [10,17-19]. Each of these approaches has notable concerns that limit their general application in
144 estimation of fluid volumes. The electrical volume model adapted from Ohm's Law is the physical
145 basis for estimation of fluid volumes with single- and multiple-frequency BI measurements [10].
146 The volume (V) of a conductor (fluid plus electrolytes) depends on the length (L) and cross-
147 sectional area (A) of a cylindrical conductor with constant geometry and composition (specific
148 resistivity or ρ), so that $V = \rho(L^2/R)$. Standing height (Ht) is a biological surrogate for L, so $V =$
149 $\rho(Ht^2/R)$. The assumptions of this model, which include the body is a uniform cylinder of constant
150 chemical composition (e.g., water content) of the conductor, are open to criticism [18]. Specifically,
151 the body consists of five cylinders (two arms, two legs and the thorax) with different geometry
152 (varying length and diameter) and different chemical composition (specific resistivities of different
153 tissues) including a disputed constant hydration of the fat-free body (73%). Researchers exploited
154 this bioelectrical volume model, together with various anthropometric information [Ht, weight
155 (Wt), age, and gender], to develop and validate multiple regression prediction equations using
156 single- and multiple-frequency measurements for TBW estimates in healthy and ill adults [18].

157 A technical issue exists with any application of these regression models. The independent
158 variable is R and not Z. Thus, only phase-sensitive BI instruments should be used in application of
159 specific single-frequency prediction models using R as an independent variable. Although Z and R
160 are highly correlated ($R^2 > 0.9$), the magnitude of Z is greater than R (1 to 2%) because Z includes the
161 value of X_c , which is not negligible (~10% of R) and includes biologically important information for
162 hydration classification [9,10]. Similarly, predictions based on multi-frequency BI measurements
163 should ensure that appropriate devices are used to obtain the required Z or R measurements.

164 Critical evaluation of a population-based model to predict TBW highlights a practical
165 limitation to the use of BIA to estimate fluid volume. Sun et al. [20] derived and validated TBW
166 prediction equations in a large sample of healthy adults of diverse ethnicity:

167

168 Males: $TBW (L) = 0.87 + 0.43 (Ht^2/R) + 0.20 Wt$ 169 Females: $TBW (L) = 3.27 + 0.45 (Ht^2/R) + 0.12 Wt$

170

171 Cross-validation of these equations revealed a large predictive error [standard error of estimate
 172 (SEE)] of 3.8 and 2.6 L, for the males and females, respectively. The magnitude of these prediction
 173 errors is too large (e.g., imprecise) to estimate TBW or to identify change in TBW of an individual
 174 and, therefore, limits these equations to observational or epidemiological studies.

175

176 3.2 Bioelectrical Impedance Spectroscopy (BIS)

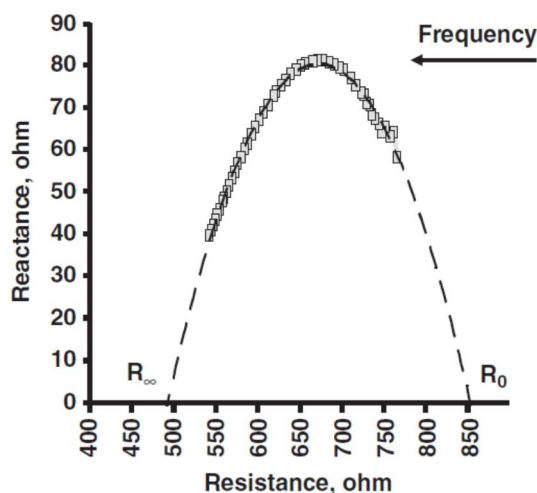
177 Some BI instruments measure Z over a wide range of frequencies (e.g., 5 kHz up to 1 MHz), report
 178 various measurements and then use programmed software to estimate fluid volumes [17]. Certain
 179 non-phase-sensitive devices only measure Z and provide the ratio of Z at low and high frequencies
 180 (Z_{low}/Z_{high}) that is equivalent to PhA at 50 kHz. Similarly, they also use the Z_{low}/Z_{high} to compute phase
 181 and cannot perform valid calculations to form the impedance modulus for the Cole plot.

182 The BIS method relies on the assumption that low-frequency current flows through the ECF and
 183 high-frequency current penetrates ECF and ICF. These assumptions are open to criticism largely
 184 because they were derived from *in vitro* studies of cells suspended in fluid and ignore the cell-cell
 185 interfaces that occur in tissues [10]. Additionally, investigators agree that at lowest frequencies some
 186 current penetrates cell membranes (e.g., extracellular and intracellular paths) and that at highest
 187 frequencies current does cross all cells (e.g., extracellular and intracellular paths) [11,21-23].

188 The BIS method uses non-linear least-square (polynomial) modelling of limited phase-sensitive
 189 multi-frequency measurements of Z and X_c , calculated from PhA, then extrapolate these values to
 190 generate a Cole plot (Figure 4). This mathematical model [24] calculates theoretical resistivity values
 191 that are used to approximate fluid volumes. The extrapolated (modeled) variables are R_0 , also termed
 192 as R_e (the resistance of the extracellular fluid or interstitial resistivity), and R_∞ (resistance associated
 193 with the sum of extracellular and intracellular fluids), critical frequency (f_c) or the frequency at which
 194 X_c is maximal, and membrane capacitance (C_m). The value of calculated C_m depends on another
 195 fitted variable, time delay (T_d), that represents the effect of cell membrane and orientation on current
 196 transmission in the body. These resistance parameters are used to calculate intracellular resistance
 197 (R_i) as $1/R_i = 1/R_\infty - 1/R_e$.

198 Mixture theory uses these calculated resistance parameters with anthropometric measurements
 199 and some wide-ranging assumptions to estimate fluid volumes [17,25,26]. It relies on a theoretical
 200 model that estimates apparent conductivity in a heterogenous entity composed of conductive (water
 201 and ions) and non-conductive (anhydrous materials such as bone, fat and cell membranes)
 202 components such as the body. Fluid volumes, ECW and ICW, are predicted separately and summed
 203 to obtain TBW. Calculation of ECW and ICW depends on the estimated Cole resistance parameters,
 204 body scalar factors calculated from the Ht and Wt of an individual, an assumed body density value
 205 derived from body mass index (BMI), empirically derived gender-specific resistivity values, and
 206 other assumptions. Extracellular fluid volume (V_{ECF}) is calculated as $V_{ECF} = k_{ECF} \cdot (Ht^2 \cdot Wt^{0.5}/R_e)^{2/3}$
 207 with $k_{ECF} = 10^{-3} \cdot (K_B^2 \cdot \rho_{ECF}^2/D_b)^{1/3}$, where K_B is a body geometry factor that relates relative volume of
 208 the legs, arms and trunk, ρ_{ECF} is the resistivity of the extracellular fluid, and D_b is total body density.
 209 Intracellular fluid volume (V_{ICF}) also is calculated from the derived Cole resistance variables and

210 gender-dependent resistivities of the ECW and ICW. These calculations are performed with software
 211 provided by the manufacturers of the different BIS instruments, and are subject to change.
 212



213
 214 Figure 4. Plot of reactance and resistance of a healthy male obtained with a Xitron 4200 and derived
 215 using non-linear curve-fitting software based on the Cole model. Note that the majority of values
 216 (dashed lines) is estimated. R_0 and R_∞ are calculated and they approximate resistance at 0 and highest
 217 frequency, respectively.
 218

219 Uncertain basic assumptions and constants of the original BIS approach [26-29] resulted in errors
 220 in the predictions of fluid volumes. Specifically, significant errors in estimation of TBW (2 L) and
 221 ECW (~1 L) in individuals with increasing adiposity, characterized using BMI, were explained as the
 222 effect of increasing adipose tissue on the assumed resistivity of ECW [30-32]. A proposed remedy to
 223 this limitation was the use of BMI as a proxy for adiposity [33].

224 A multi-center validation trial [33] of this revised BIS approach included healthy adults and dialysis
 225 patients and found that this change improved the sensitivity of the revised ECW predictions by
 226 decreasing the variability of the ECW estimate by 24% (0.6 L) in healthy and dialysis patients and
 227 reducing the variability of TBW prediction in adults with BMI values of less than 20 and greater than
 228 30 kg/m². Although no significant differences between tracer dilution reference measurements and
 229 BIS predictions of TBW, ECW and ICW were found, there were wide limits of agreement (95%
 230 confidence intervals; 95% CI). Specifically, the mean differences were small with wide limits of
 231 agreement for prediction of TBW [-0.2 L (95% CI: 4.6 L)], ECW [-0.4 L; 95% CI: 2.9 L] and ICW [0.2 L
 232 (95% CI: 4.1 L)]. These wide limits of agreement contribute to poor sensitivity of ECW and TBW
 233 estimates estimated with BIS for individuals.
 234

235 3.3 Comparison of Fluid Volumes Estimated with Single-Frequency Bioimpedance and Bioelectrical Impedance 236 Spectroscopy

237 Although a common opinion is that BIS, compared to a single-frequency BIA, provides more
 238 accurate estimates of fluid volume [23], experimental data fail to confirm this supposition. Impedance
 239 predictions of TBW and ICW were equally accurate in comparison to isotope dilution estimates but
 240 included a significant bias (error) in single-frequency and BIS prediction of ECW in steady-state
 241 hemodialysis patients [34]. Both impedance methods had a proportional error in estimation of ICW

242 largely due to assumptions of the BIS model and the single frequency equation used to predict ICW
243 with calculations from total body potassium, a specific marker for body cell mass. Similar findings
244 came from another study of hemodialysis patients [35]. A consistent observation is the wide limits of
245 agreement between the impedance and reference methods that cautions against the use of these
246 methods for individual assessment of fluid volumes [36].

247 Other research supports these findings. In adults receiving growth hormone replacement therapy,
248 TBW was determined using isotope dilution and predicted from BI measurements, collected with the
249 same multi-frequency instrument, using 50 kHz values and four published equations and the Hanai
250 mixture [25] model with and without adjustment for BMI [37]. Measured and predicted TBW values
251 were significantly and similarly correlated for linearity and concordance ($r>0.9$). Comparisons of
252 measured and predicted TBW values revealed limits of agreement with slightly greater variability
253 (0.9 to 2.7 L or 4 to 7%) for the 50 kHz predictions compared to variability estimates (0.6 to 0.9 L or 1
254 to 2%) from the BIS predictions. Thus, both the single frequency prediction equations and BIS models
255 performed equally well in predicting TBW at the population level.

256 Follow up analyses determined the comparability of these different approaches to estimate TBW at
257 the level of an individual [38]. The mean absolute error of BIS was slightly improved compared to
258 multiple regression equations using 50 kHz values (5 vs 7% or 2 vs 3 L). These findings indicate that
259 the precision of these BIA approaches may be appropriate for group comparisons but is too large for
260 monitoring changes in TBW in clinical conditions.

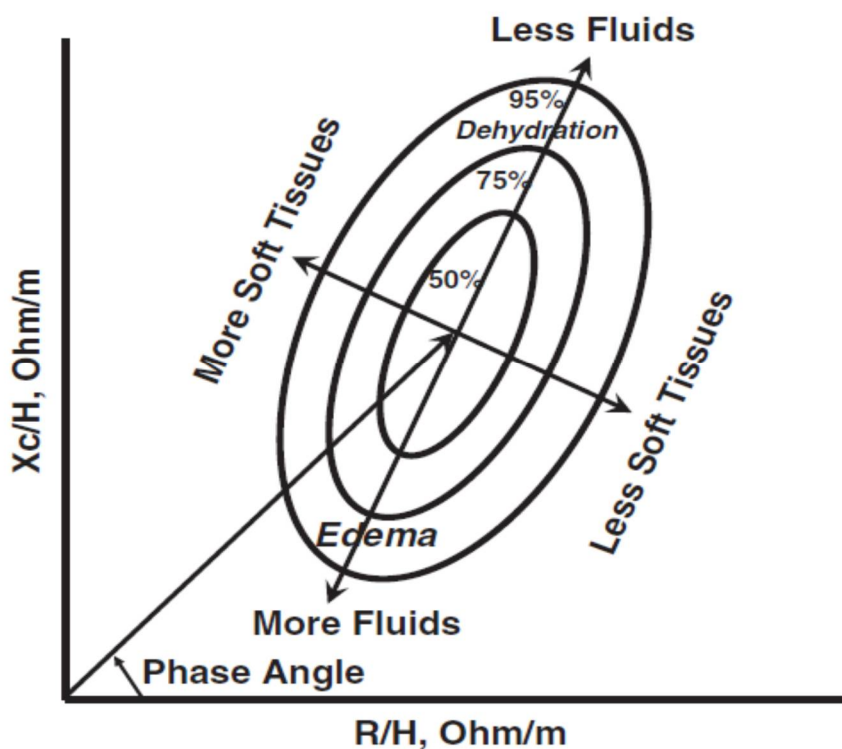
261 Any comparison of BIA-predicted fluid volumes with tracer dilution reference measurements
262 suffers from technical and biological limitations. Sources of error include the validity (accuracy and
263 precision) of the impedance measurement, error of prediction from the regression equation, intrinsic
264 error of the reference method (technical accuracy and reproducibility, biological errors in
265 assumptions of the dilution method), electrical-volume errors (anisotropy and body geometry), and
266 biological variability (inter-individual differences in the diameter of body segments, limb lengths,
267 and variation in body fatness) [36]. Use of the Cole model depends on the reliability of the fitting of
268 the impedance data. Review of recent BIS and BCS publications reveals that individual subjects are
269 removed from analyses because of failure to achieve acceptable tolerances (>99% reproducibility) of
270 repeated the time delay estimates derived from curve fitting [34,35]. This observation indicates
271 significant imprecision in calculation of the current delay at membranes. Finally, use of different
272 single-frequency mathematical prediction equations complicates comparisons. As suggested by
273 Seone et al. [37,38], volume prediction models that include more independent variables than Ht^2/R
274 and weight tend to produce greater errors in estimated TBW that indicates a specificity of that
275 regression equation and, thus, excludes its application in any sample or individual differing in
276 characteristics from the original sample in which the regression model was developed. These factors
277 as well as the imprecision of the prediction models, single-frequency and BIS, impedes their use in
278 point-of-care individual assessments of hydration.

279

280 **4. Classification of Hydration with Bioelectrical Impedance Vector Analysis (BIVA)**

281 In contrast to the use of mathematical modeling of limited BI measurements, theoretical and
282 regression prediction models, classification of hydration only requires precise BI measurements and
283 reference values [39]. A 50 kHz phase-sensitive BI instrument directly measures R and X_c , which are
284 normalized for standing height to achieve a standard resistivity and plotted on the RX_c graph (Figure

285 5). The vector (Z) has length that is inversely related to TBW and its position, described as the PhA,
 286 provides information on tissue hydration.
 287



288
 289 Figure 5. Resistance-reactance (RXc) plot with tolerance ellipses from healthy Caucasian males.
 290

291 Bioelectrical impedance vector analysis (BIVA) enables classification (under-, normal and over-
 292 hydration) and ranking of change in hydration (more or less than before treatment), as well as
 293 classification (more or less) of soft tissue mass, by comparing vector position of an individual or a
 294 group to a healthy ethnicity-, age- and gender-matched population [39]. Compared to single-
 295 frequency BIA and BIS predictions of fluid volumes, BIVA only has minimal error associated with BI
 296 measurement and reproducibility (1-2%) whereas fluid volume predictions include additional
 297 sources of error including regression error of prediction equation (~10%), technical error in the
 298 reference method (~4%), limitations of the bioelectrical volume model (i.e., anisotropy of tissues and
 299 geometry), and biological variability (i.e., inter-individual body composition differences) that
 300 propagate. Therefore, for an individual, classification and ranking of hydration is more precise and
 301 accurate than is quantification of fluid volume because BIVA is independent of regression equations
 302 and theoretical models that are acquired with limited and specific samples and, thus, are not robust
 303 in the assessment of hydration outside of the group in which they were developed, and are adversely
 304 affected by illness.

305 The RXc graph (Figure 5) is a probability distribution that classifies a vector according to its
 306 distance from the mean healthy vector. The variability of the impedance vector is represented in the
 307 bivariate normal distribution with elliptical probability areas (50, 75 and 95%) in the tolerance or
 308 reference ellipses. Vectors displacements parallel to the major axis indicate changes in hydration
 309 (more or less fluids). Vectors within the 50% tolerance ellipse are considered to be at normal

310 hydration whereas lengthening of vectors from the 51 to 75% and >76% percentile of the upper range
311 of percentiles indicate moderate and severe dehydration, respectively. Conversely, shortening of
312 vectors from the 51 to 75% and >76% percentile reference ellipses in the lower range indicate
313 increasing fluid overload. Vectors positioned to the left of the major axis reflect increasing cell mass
314 and vectors to the right indicate decreasing cell mass, respectively. Thus, BIVA uses patterns of
315 impedance vector distribution without the need for prediction equations, body weight or reliance on
316 the assumption of stable composition (water content) of the FFM. BIVA enables detection and ranking
317 of changes in tissue hydration status of < 500 mL in real-time [39].

318 Appropriate derivation and implementation of the RXc graph to classify hydration requires
319 some important technical considerations. All measurements should be acquired with a phase-
320 sensitive (e.g., phase angle directly measured) BI instrument. Failure to use a phase-sensitive device
321 results in significant errors in R (10 Ω) and Xc (10-12 Ω) measurements [40] contributing to 8-10%
322 repositioning of reference and patient vectors. Additionally, use of high-impedance electrodes can
323 lead to misclassification of hydration [41].

324

325 4.1 Clinical Applications of BIVA

326 A focal application of BIVA is the assessment of hydration status in patients with fluid overload
327 and evaluation of effects of therapeutic procedures designed to achieve homeostasis without
328 undesirable side effects. Kidney disease and hemodynamic impairments are the principal conditions
329 in which BIVA is used to classify hydration and to monitor changes in response to treatments.
330 Traditional approaches to assess hydration in these patients are unreliable because they rely on body
331 weight to designate excess fluid and are insensitive to fluid overload in the presence of edema [42].

332

333 4.1.1 Hydration Assessment in Hemodialysis (HD)

334 Dialysis, particularly HD, is amenable to BIVA because of the need for fluid removal and post-
335 dialytic fluid retention. Routine evaluation of hydration includes monitoring of body weight and
336 blood pressure changes that are not reliably determined by fluid volume. Edema is not usually
337 detectable until interstitial fluid volume increases of 30% over normal levels (4 to 5 kg gain in body
338 weight) and severe dehydration can occur before appearance of clinical signs. Thus, traditional
339 indicators of over- and under-hydration in patients with renal disease are insensitive and inadequate
340 [39].

341

342 4.1.2 Hydration Changes and Vector Patterns During the HD Cycle

343 The objective of HD is to remove excess fluid without complications for the patient. Estimation
344 of volume of fluid for removal is subjective and generally related to previous post-dialytic body
345 weight, which may be unreliable [42]. Fluid removal occurs during HD. It can be symptomatic or
346 uncompensated with episodes of hypotension, malaise and cramps or asymptomatic (compensated).
347 Fluid overload can occur during the inter-dialytic period and is symptomatic with edema,
348 exacerbated hypertension and pulmonary congestion. Dry weight is a general term associated with
349 the post-dialytic body weight at which most of the excess fluid has been removed. The optimal "dry
350 weight" is determined clinically and operationally as the weight at which a patient can tolerate HD
351 without adverse intra-dialytic symptoms, notably hypotension. Body fluid volumes, however,

352 change continuously during the inter-dialytic period so that euhydration occurs only for a brief
353 period.

354 Serial BI measurements and examination of vectors before and after HD reveal a classic pattern
355 of fluid removal and repletion during a standard 3-d HD cycle. Fluid removal via ultrafiltration (UF)
356 accompanies vector lengthening parallel to the mean vector of healthy adults [43]. Within the first 2-
357 hr post HD, vectors are relatively stable near the post HD vector. During the next 24, 48 and 72 hr,
358 however, vectors progressively shorten within the 50 to 75% tolerance ellipse and reflect fluid
359 repletion of 1.4, 2.6 and 3.4 L. Thus, BIVA is specific and sensitive to monitor fluid during the wet
360 and dry cycle of HD.

361

362 4.1.3 Vector Trajectories: Adequacy of Ultrafiltration (UF)

363 Measurement of the electrical properties of tissues enables the classification of vectors as
364 abnormal and identification of HD patients at risk of intra-dialytic problems. Observational findings
365 indicate that BIVA can identify potential symptomatic HD patients. Before dialysis, HD patients,
366 compared to healthy controls, exhibit evidence of fluid overload with shorter vectors and lesser phase
367 angles [43,44]. Pre-HD vector position discriminated unstable (symptomatic), compared to stable
368 (asymptomatic), HD patients with significantly longer vectors and smaller phase angles regardless
369 of gender. Vector displacement caused by fluid removal (2.4 to 2.6 L) further differentiated the HD
370 groups with significantly shorter and less steep vectors among the unstable compared to the stable
371 patients. Patients with vectors cycling within the 75% tolerance ellipse had no symptomatic response
372 during the HD session. However, patients with vectors exceeding the 75% tolerance ellipse (e.g.,
373 longer and flatter) were at significantly greater risk for hypotension. This finding provides an
374 operational definition for use of BIVA in HD [45].

375 Trajectory of an individual vector during UF provides insight into efficacy in HD. Exceeding the
376 75% tolerance ellipse, longer vectors indicate fluid loss or dehydration (dry vector) and shorter
377 vectors designate fluid overload (wet vector). Vector displacements to the left, compared to the right,
378 of the major axis reveal more versus less cell mass, respectively. A troublesome vector displacement
379 during UF is flat vector displacement to the right associated with an increase in R/H without a
380 proportional increase in X_c/H due to a loss of cells in soft tissue. This pattern is seen in patients with
381 malnutrition or cachexia [44].

382

383 4.2 BIVA in Peritoneal Dialysis (PD)

384 Chronic ambulatory peritoneal dialysis (CAPD) is a procedure that performs UF of the lower
385 abdomen by infusion of hypertonic glucose or icodextrin and exchange every 6 hr. The process is
386 continuous rather than cyclical as in HD with the objective to obtain adequate UF and thus achieve
387 normal hydration of the patient. CAPD can result in dehydration or excess fluid removal (decrease
388 in residual urine volume and peritoneal UF) or fluid overload (FO; pitting edema, exacerbation of
389 hypertension and impairment of UF).

390 Comparisons of BIVA plots from healthy, HD and CAPD patients reveal differences in tissue
391 electrical properties [46]. Group vectors for pre-HD asymptomatic patients were shorter and flatter
392 (e.g., smaller PhA) within the lower 50% ellipse and lengthened into the 75% ellipse after HD.
393 Whereas mean vectors of non-edematous (compensated) CAPD patients were midway between the
394 vectors of healthy controls and pre-HD values (e.g., overlapping and within the 50% ellipse), it was

395 shorter than the post-HD mean vector. The group vector for edematous (uncompensated) CAPD
396 patients was significantly shorter with smaller PhA in the 95% ellipse. Infusion of dialysate solution
397 (1 L) did not affect R/H, Xc/H or PhA (0.5%) principally because the thorax only contributes
398 minimally (<10%) to total body Z and thus is relatively insensitive to acute changes in fluid volume.
399 BIVA discriminated FO among the CAPD patients. Specifically, 88% of CAPD patients with pitting
400 edema exceeding the 75% tolerance compared to 12% of non-edematous patients. This observation
401 of a shortened down-sloping vector is consistent with the excess accumulation of interstitial fluid in
402 pitting edema.

403 Characteristics of an individual vector from a dialysis patient provides an important example of
404 relationships among BI measurements and tissue hydration in relation to FO. Edema, which is an
405 acknowledged sign of FO, is present with increased interstitial pressure due to an expansion of the
406 interstitial fluid volume with concomitant gains in body weight and TBW. In a normal hydration,
407 fluid is partitioned between the capillaries and the interstitial compartment that consists of a
408 gelatinous matrix and has a negative interstitial pressure; this condition is characterized with an
409 impedance vector within the 50% tolerance ellipse. Fluid overload is detectable as edema when
410 interstitial pressure changes from negative to positive due to an increase in interstitial fluid volume
411 (30%) and a concomitant gain in body weight (4 to 5 kg) [47]. Piccoli [46] hypothesized that edema
412 may be expressed with the shortening of the pre-HD vector and displacement in a downward
413 direction toward the lower margin of the 75% tolerance limit corresponding to the increased
414 interstitial fluid pressure. When interstitial fluid pressure increases, most of the fluid increase is free
415 fluid allowing the appearance of pitting edema and bringing the vector outside of the 75% tolerance
416 ellipse, which is defined as the operational threshold for apparent edema. Fluid overload results in
417 an increase in blood volume so the gain in free fluid in the interstitial space is a release to control
418 blood pressure. Conversely, movement of the vector from the lower to the upper 75% tolerance ellipse
419 indicates a progressive loss of interstitial fluid from the gel meshwork and a decrease in interstitial
420 fluid pressure that reduces blood volume.

421

422 *4.3 BIVA in Critically Ill Patients*

423 Determination of fluid status in the intensive care unit is difficult because of the need for real-
424 time assessments. In the critical care setting, central venous pressure (CVP) measurements are
425 obtained invasively with either a CVP catheter or more invasive hemodynamic monitoring devices
426 to guide fluid infusion. In general, low CVP values designate true or relative hypovolemia and high
427 CVP measurements indicate true or relative hypervolemia or FO.

428 BIVA was evaluated as an index of fluid status and compared to CVP measurements in intensive
429 care unit (ICU) patients [48]. Both components of the Z vector (R/H and Xc/H) were significantly,
430 linearly and inversely correlated with CVP. A progressive increase in CVP matched the shortening
431 and downward displacement of the Z vector out of the lower pole of the 75% tolerance ellipse. Low
432 CVP values were associated with normal or lengthened vectors into the 75% tolerance ellipse, which
433 is indicative of dehydration.

434 The combination of assessment of peripheral tissue hydration with BIVA and central filling
435 pressure with CVP provides a useful clinical tool for evaluation and planning fluid therapy for
436 patients with low CVP. A different response or tolerance to fluid infusion in dehydrated compared

437 to well hydrated patients with the same CVP in which BIVA could identify patients with reduced,
438 preserved of excess fluid.

439 Among patients admitted to an ICU, BIVA classified 70% as overhydrated [49]. Fluid overloaded
440 patients had a longer stay on the ICU due to persistent fluid retention. Average hydration was a
441 significant ($p < 0.05$) predictor of mortality during the 5-d stay on the ICU [odds ratio (OR) 1.19 (95%
442 CI:1.04-1.37)] or the 60 d after discharge (OR 1.17, 95% CI:1.03-1.33).

443 In a clinician-blinded observational study [50], patients admitted to the ICU were assessed for
444 hydration status with BIVA [51] with concomitant determinations of cumulative fluid balance (input
445 – output) during a 72-hr observation period. Patients classified as dehydrated gained 3.4 L whereas
446 over-hydrated patients had a net cumulative fluid balance of -4.5 L. Severe over-hydration was the
447 only significant predictor of mortality on the ICU (OR 22.9, 95% CI:2.38-220; $p < 0.01$).

448 The presence of AKI in critically ill patients is related to increased mortality with over-hydration,
449 estimated by fluid balance, an independent contributor to decreased survival [52]. Survivors of AKI
450 in the ICU had longer and steeper group vectors, characterized by greater ($p < 0.05$) R/H and χ_c/H
451 values, compared to non-survivors diagnosed with AKI [53]. Overhydration, estimated as mean fluid
452 balance (fluid retention) calculated from diagnosis of AKI until recovery, discharge from ICU or
453 death, was greater ($p < 0.001$) in the non-survivors compared to the survivors (6.9 vs 1.6 L,
454 respectively).

455 Iatrogenic AKI can occur in patients undergoing coronary angiographic procedures with
456 iodinated contrast media. Prevention strategies include pre-procedural saline infusion to overcome
457 plasma volume depletion. However, identification of patients with low ECF would improve efficacy
458 and outcome of this strategy. Although intravenous volume expansion is a general preventive
459 strategy, a safe, practical and valid means to identify low hydration status of patients is needed.

460 Stable coronary artery disease (CAD) patients with low BIVA-assessed hydration status
461 presented with a significant risk of CI-AKI [54]. Pre-procedural R/H values were greater in patients
462 with CI-AKI than those without CI-AKI (395 vs 352 Ω/m for women, $p < 0.001$; 303 vs 279 Ω/m , $p < 0.009$
463 for men) indicating lower fluid volume in patients with CI-AKI. Stratification of patients according
464 to R/H values revealed a significantly higher risk of CI-AKI in patients with higher R/H values (OR
465 2.9, 95% CI:1.5-5.5; $p < 0.002$). Optimal ROC threshold analysis determined R/H values for prediction
466 of CI-AKI risk were 380 and 315 Ω/m for women and men, respectively. R/H values exceeding these
467 values were found to be significant and independent predictors of CI-AKI (OR 3.1, 95% CI:1.8-5.5;
468 $p < 0.001$).

469 Pre-procedural BIVA determinations were used to classify patients as low or normal hydration
470 status [55]. Based on the previously determined R/H thresholds for increased risk of CI-AKI [53],
471 patients with low hydration status were randomized to receive a standard (1 mL/kg/hr) or double (2
472 mL/kg/hr) saline infusion for 12 hr before and after the procedure. The incidence of AKI was
473 significantly lower [11.5 vs 22.3%; OR 0.45, 95% CI: 0.24-0.85; $p < 0.015$) in the patients receiving double
474 compared to single saline volume. Thus, evaluation of hydration with BIVA in patients with stable
475 CAD at admission allows identification of hypohydration and adjustment of intravascular fluid
476 volume expansion resulting in lower incidence of CI-AKI after angiography.

477

478 *4.4 BIVA in Congested Heart Failure (HF)*

479 The pattern of BIVA changes in response to therapy among dialysis patients should be
480 comparable in congestive heart failure patients. Similar to the HD cycle, heart failure is characterized
481 by a cyclical fluid overload (pulmonary and peripheral congestion) and removal (diuretics and
482 extracorporeal fluid removal with dialysis). Despite current therapy, the high rate of readmission
483 emphasizes that current guidelines for discharge, typically based on clinical impressions, is
484 inadequate for patient stabilization.

485 Current practice relies on a blood biomarker, N-terminal pro-B-type natriuretic peptide (NT-
486 proBNP), to assess overhydration in the diagnosis of heart failure (HF). An adaptation of BIVA
487 tolerance ellipses yields the hydration index (HI) that corresponds to soft tissue hydration as hyper-
488 (>74.3%), normo- (72.7 to 74.3%) and hypo-hydration (<72.7%) [51]. Patients diagnosed with HF had
489 significantly greater NT pro-BNP levels, lower R/H and Xc/H values and greater hydration (81 vs
490 74%) than non-HF patients evaluated in the emergency-outpatient department [56]. Massari et al. [57]
491 reported that overhydration was a significant predictor of length of stay in hospital (LOS). Patients
492 with a normal hydration index (72.8 to 74.2%) had a shorter LOS [7.36 d (interquartile range or IQR:
493 7.34 to 7.39 d); $p < 0.05$] than other patients classified as overhydration [9.04 d (IQR: 8.85 to 9.19 d).
494 Multivariate regression analysis demonstrated that BNP and hydration index were significant
495 predictors of LOS ($p < 0.0001$). Hydration index and BNP levels were significantly and inversely
496 related. Importantly peripheral edema was not a predictor of LOS. Thus, congestion determined with
497 BIVA is a important predictor of LOS in HF patients with acute decompensation.

498 Fluid overload is a risk factor for heart failure patients. Hydration status can be determined from
499 BIVA tolerance ellipses. Nunez et al. [58] classified 369 heart failure patients at discharge and found
500 after 12 months an increased risk of mortality [hazard ratio (HR) 2.08, 95% CI:1.21-3.58; $p < 0.008$] for
501 over-hydrated patients as well as a linear risk of re-admission of heart failure (HR 1.06, 95% CI:1.03-
502 1.10; $p < 0.001$).

503 The combination of admission BNP and discharge BIVA allows prediction of 90-d mortality risk
504 in HF patients [59]. In a prospective multi-center study, survivors had significantly lower BNP levels
505 (515 vs 838 pg/L) and lower hydration (hydration index: 74 vs 85%), and greater R/H (503.6 vs 445.3
506 Ω/m) and Xc/H (37 vs 26.7 Ω/m). BIVA was a significant predictor of 90-d mortality [area under the
507 curve (AUC) 0.715, 95% CI: 0.65-0.76; $p < 0.004$] with Xc/H (AUC 0.712, 95% CI: 0.655-0.76; $p < 0.007$) a
508 stronger predictor of mortality than R/H (AUC 0.65, 95% CI: 0.29-0.706; $p < 0.025$). Together BNP and
509 BIVA have greater prognostic power for cardiovascular mortality (AUC 0.74, 95%CI:0.69-0.76;
510 $p < 0.001$).

511 Dyspnea is a consequence of congestion in HF patients. However, differential diagnosis of acute
512 dyspnea relative to hydration is challenge. Clinicians blinded to BIVA diagnosed patients presenting
513 with acute dyspnea as cardiac (54%) or non-cardiac etiology based on standard examination criteria.
514 BIVA positions outside the 50% tolerance ellipse (specifically Xc/H) identified peripheral congestion
515 (edema). BIVA measures (vector positions on the RXc plot) accurately discriminated cardiac and non-
516 cardiac dyspnea (69% sensitivity and 79% specificity with 80% AUC analysis) [60].

517

518 **5. Bioelectrical Impedance Spectroscopy (BIS)**

519

520 *5.1 BIS in Dialysis*

521 The prediction of fluid volumes with BIS is another approach to classify hydration with an
522 emphasis on estimation of excess fluid volume [60]. Chamney et al. [62] proposed a model based on
523 body composition that estimates hydration (fraction, %) of lean and adipose tissue (AT) to estimate
524 FO. They used dual x-ray absorptiometry and tracer dilution and derived fixed values for normal
525 hydration fraction of lean (0.703) and AT (0.197) with different fluid distributions (ECW/ICW, %) in
526 normal lean (0.630) and AT (1.88) to calculate FO, equivalent to excess ECW, from measurements of
527 body weight and BIS-derived estimates of total body ECW and ICW and pre-HD body weight [62].
528 This approach, termed the physiological tissue model, relies on the assumption of a constant
529 ECW/TBW to identify over-hydration and guide dialysis.

530 The criteria for designation of FO is variable and generally dependent on some clinical
531 measures. A pre-HD hydration classification of hydration was a graded FO as normal (-1 to +1 L),
532 mild (+1 to <2.5 L) and gross (> 2.5 L) and under-hydration (-1 to -2.0 L). The goal of HD was to
533 reach normo-hydration range of fluid excess and remove fluid to reach within 1 L of excess ECW.
534 Application of this model in 500 HD patients revealed only 19% had normo-hydration with systolic
535 BP <140 mm Hg, 33% had >2.5 L ECW with BPs <150 mm Hg, 15% had >2.5 L ECW and systolic BP
536 >150 mm Hg [63]. In contrast, 15% patients were hypertensive with FO of 1 L and 10% had systolic
537 BP <140 mm Hg and FO >2.5 L. Mean over-hydration was greater (+2.95 vs +1.35 L, $p<0.05$) in
538 patients who died of cardiac causes than patients with non-cardiac deaths [64]. Similarly, significant
539 FO was an independent predictor of survival [HR 1.83, 95% CI:1.19-2.82, $p<0.001$] in PD patients
540 [65].

541 An alternative index of hydration is relative fluid overload (RFO) that is the expression of the
542 predicted ECW a percentage of the age- and gender-specific normative ECW [61,62]. Recalculation
543 of RFO from Wabel et al. [66] reveals an RFO of 15% is equivalent to excess ECW >2.5 L. A follow
544 up study of diabetic HD patients found that gross or excess hydration (RFO >15%) was associated
545 with an elevated risk of mortality [HR 2.102, 95% CI:1.389-3.179; $p<0.003$] [67]. A few other patients
546 had a decrease in PhA (HR 1.74, 95% CI:1.37-2.21; $p<0.001$) independent of age and co-morbidities
547 that predicted mortality of end-stage kidney disease patients [68].

548 Randomized controlled studies revealed that BIS-guided UF resulted in better outcomes for
549 patients whose UF was directed by conventional approaches. Hur et al. [69] found a significant
550 decrease in time-average FO during a 1-yr period that lead to significant decreases in myocardial
551 function measures, blood pressure, and antihypertensive medications with BIS-managed UF as
552 compared to control patients. However, patients with BIS-guided UF had significantly decrease
553 urine output and an increase in the proportion of patients with anuria. Another study reported
554 decreased mortality ($p<0.03$) among patients randomly assigned to BIS-predicted UF [70].

555 Results of large-scale, international, multi-center observational studies of PD patients treated
556 with both PD modalities, CAPD and automated peritoneal dialysis, reveal important factors related
557 to the estimation of over-hydration using BIS. Unmodifiable patient characteristics (age, male
558 gender, diabetes, and low BMI) and dialysate composition (hypertonic glucose) predicted FO in PD
559 patients in the EuroBCM Study [71]. Clinical judgement predicted FO less frequently than BIS in the
560 IPOD-PD Study [72]. Inconsistency was observed between BCM hydration assessment and systolic
561 blood pressure (BP) despite its strong relation to FO [63]. Fifty-six percent of the patients were
562 designated with FO (>1.1 L) of which 24.5% had systolic BP <140 mm Hg whereas 38.7% were
563 normo-hydrated and 28.2% had systolic BP >140 mm Hg, and among 4.9% classified as dehydrated,

564 3.4% had elevated systolic BP. Among the PD patients assessed as normally hydrated by clinical
565 judgement, >30% appeared FO with BIS. These findings indicate a limitation of BIS to adequately
566 detect fluid in the trunk, which is consistent with the inability of the applied current to enter the
567 peritoneum and the relatively low contribution of the trunk to total body BI measurements [12,73].

568 Consensus on the ability of BIS to detect sequestered fluid in the peritoneum is lacking. Siphai
569 et al. [74] measured FO before and after removal of peritoneal dialysate and found a non-significant
570 240 mL difference. Parmentier et al. [75] similarly reported a negligible (50 mL) difference in FO
571 estimated before and after PD session. Arroyo et al. [76], however, found that FO measured after
572 infusion of dialysate was greater (180 mL; $p < 0.043$) than after removal of dialysate, and concluded
573 that BIS prediction of FO should be performed after drainage of the abdomen. Age, severity of end-
574 stage renal disease (ESRD), nutritional status and different sample sizes affect the interpretation of
575 the results. However, the modest differences in apparent FO confirm the limitation of BIS to reliably
576 detect fluid in the truck and specifically the abdomen.

577 Recent findings indicate no benefit of BIS-guided fluid management among non-anuric PD
578 patients on residual renal function (RRF) and cardiovascular function. Oh et al. [77] studied 137
579 adults who had no differences age, gender ratio, cause of kidney failure, duration of PD, glomerular
580 filtration rate (GFR), or peritoneal transport type for one year. Use of BIS resulted in no differences
581 in net changes in estimated overhydration or ECW/TBW, echocardiographic parameters or arterial
582 stiffness.

583 Tabinor and Davies [78] conclude that the usefulness of BIS to guide fluid management in
584 dialysis is not well defined. They remark that BIS can monitor fluid change but the need is to link
585 BIS-estimated fluid changes with intermediate variables (blood pressure, cardiac dynamics and
586 morphology) with a goal to preserve residual kidney function; evidence of relationships with
587 mortality is lacking. Additional research with more coordinated and consistent research designs is
588 needed.

589

590 **6. BIVA in Nutrition Assessment**

591 Patients with kidney disease are progressively at risk for impaired nutritional status,
592 exacerbation of renal function and protein energy wasting. Surveys reveal both suboptimal intakes
593 of macro- and micro-nutrients with increased losses of micronutrients associated with metabolic
594 acidosis, hormonal dysregulation and inflammation that increase mortality risk in patients with
595 chronic kidney disease (CKD) and can lead to ESRD [79,80]. Protein energy wasting is
596 acknowledged to cause muscle loss and potentially precipitate intra-dialytic complications [62].

597 Identification of altered body composition with BIVA comes from early observation of CKD
598 patients referred for treatment. Compared to healthy, age- and gender-matched adults, CKD
599 patients had a shorter and downward sloping mean vector at the lower boundary of the 75%
600 tolerance ellipse [81]. Patients had significantly decreased R/H, Xc/H and PhA values. PhA
601 decreased in relation to the severity of CKD. Furthermore, diabetic CKD patients had the shortest
602 and most downward vector displacements. Whereas differences in PhA globally indicate
603 proportional losses of body cell mass, provided that hydration is considered [82], they importantly
604 reflect differences in the fluid distribution. Specifically, a decrease in PhA designates an increase in
605 ECW/ICW due to disproportionate loss of muscle and thus an indication of fluid overload.

606 BIVA distinguishes fluid excess and nutritional status in uremic HD patients. Undernutrition,
607 assessed with the Subjective Global Assessment (SGA), significantly affected vector displacements
608 before and after an HD session [83]. Before dialysis, the mean vector of HD patients classified with
609 normal nutritional status (SGA-A) was within the 50% tolerance ellipse. In contrast, the mean
610 vectors of the patients with moderate and severe malnutrition (SGA-B and C) decreased into the
611 75% and outside the 95% tolerance ellipses, respectively, indicating progressive fluid accumulation
612 and excess. Importantly, the contributions of X_c progressively decreased ($A < B < C$). Fluid removal
613 (2400 mL) resulted in a lengthening of the mean vectors due to large changes in R/H for the normal
614 nutrition and moderately malnourished patients, indicating fluid removal, and similar changes in
615 X_c/H . In contrast, the mean vector of the severely malnourished patients flattened with a smaller
616 change in R/H associated with less fluid removal (1800 mL), due to complication during the dialytic
617 session, and a negligible change in X_h/H consistent with reduced body cell mass. Thus, BIVA
618 discriminates fluid excess from nutritional status and identifies deficit in muscle mass in
619 malnourished HD patients.

620

621 7. Equivalence of Bioimpedance Measurements

622 There is a paucity of data comparing BIVA and BIS patterns in the same subjects. Piccoli et al.
623 [84] performed simultaneous phase-sensitive 50 kHz BI and phase-sensitive BIS measurements on
624 renal patients before and during an HD session. A pattern of congruence between groups vectors
625 on the RX_c graph and the peak of each Cole plot (F_c or critical frequency) emerged indicating
626 equivalence of information from these two BI approaches. Specifically, the Cole plots progressively
627 enlarged and moved to the right on the RX_c graph during the 180 min dialytic session with F_c
628 nearly identical to the X_c at 50 kHz so that the Z vector tracked dialytic fluid removal similarly as
629 the Cole plots. The X_c values at 5 kHz, which were expected to be 0Ω if conduction was only
630 extracellular, were 70% of the maximum (F_c) indicating intracellular current flow at low frequencies
631 and suggesting anisotropy. Additionally, correlation coefficients relating R and X_c at 50 kHz with
632 all other frequencies were 0.96 to 0.99 and 0.65 to 0.99, respectively, demonstrating an equivalence
633 of BI measurements. They observed similar findings in a comparison of the same BI instruments in
634 body builders and non-resistance training men [85]. Notably, the ratio of X_c values at 5 kHz to F_c
635 were 70 and 64% for the body builders and control men, respectively, indicating a substantial
636 intracellular flow of current in both groups. The R and X_c measurements at 50 kHz were highly
637 correlated with same measurements at frequencies ranging from 0 to infinity and ranged from 0.94
638 to 1.0. Thus, there was equivalence of information provided by the vector components of R and X_c
639 at 50 kHz compared with the measurements from BIS. This equivalence persists with fluid removal
640 and expanded ICW with increased muscularity.

641 An important question is the equivalence of BI measurements obtained from various
642 impedance instruments in the same subjects. Phase angle measured in patients before an HD
643 session with a phase-sensitive BIS compared to a phase-sensitive 50 kHz device was significantly
644 less (4.2° vs 4.7° , respectively) with no difference in R (515 vs 510 Ω , respectively). This difference in
645 PhA values indicates that BIS can underestimate X_c presumably as a result of the mathematical
646 modelling of the T_d factor as well as anisotropy in tissues [86]. These findings reaffirm previous
647 observations that BI instruments do not provide similar values of R , X_c and PhA and conclude that
648 BI devices should not be used interchangeably [83].

649

650 8. Summary and Conclusions

651 Bioimpedance measurements are gaining interest to assess and monitor hydration status in
652 dialytic and critically ill patients because they overcome many of the limitations of traditional
653 methods of hydration assessment. Whereas two approaches use of BI measurements, each has
654 specific advantages and certain limitations.

655 Use of direct 50 kHz, phase-sensitive BI measurements in the BIVA model for hydration
656 assessment is progressing in a variety of clinical conditions. BIVA illustrates a vector whose
657 position is evaluated relative to healthy reference ranges and is interpreted as normal or abnormal
658 hydration based on distance from the mean healthy vector. Migration of the vector (shortening or
659 lengthening) in response to progression of a physiological process, pathology or an intervention
660 indicates changes in hydration (gain or loss of fluids). Classification of hydration status (normal or
661 abnormal) avoids insensitivities (>10% variability and imprecision for individual estimations)
662 associated with regression equations and unproven biophysical models, and does not rely on body
663 weight to assess hydration. Use of BIVA improves the prescription of UF in dialysis by monitoring
664 the backward-forward displacement of vectors in relation to the wet-dry cycle of HD. It further
665 enhances decision-making in dialysis by facilitating interpretation of alterations in blood pressure
666 relative to hydration status and, thus, adjusting UF. Among critically ill patients, BIVA is
667 significantly and inversely correlated with CVP. On the RXc graph, impedance vectors of patients
668 with low, normal and high CVP move downward and outside of the 75% tolerance level with
669 increasing CVP, which indicates excess fluid accumulation. Identification of hypohydration in
670 stable CAD patients before angiographic procedures enabled rehydration with appropriate
671 volumes of saline to attenuate risk of CI-AKI. Use of BIVA in assessment of malnutrition, notably in
672 illnesses with muscle loss when hydration is altered, is increasing.

673 Phase-sensitive multi-frequency BIS measurements coupled with biophysical models indirectly
674 estimate ECW that is compared with projections of normal ECW to calculate excess ECW described
675 as FO. The estimates of ECW, adjusted for BMI, are derived from regression equations using
676 gender, height and body weight as independent variables with wide limits of agreement and, hence
677 imprecision for an individual ECW estimate. Estimates of FO >2.5 L or >15% predicted ECW are
678 associated with increased morbidity in dialysis patients but the prognostic value for mortality is
679 lacking.

680

681 9. Future Directions

682 Advancement of the use of BI measurements to aid in fluid management of dialysis patients
683 requires prospective controlled studies with more focus on outcomes [78,87-89]. Early efforts were
684 descriptive emphasizing proof-of-principle research. Adequate confirmation of positive findings
685 related to validity BIVA and BIS is available. New research should critically evaluate the benefit of
686 these BI approaches in patient care. Importantly, there is a need for more consistency and scrutiny
687 in research design with appropriate sample sizes to test hypotheses and comparability in reporting
688 of results. Some topics include the ability to predict intra- and inter-dialytic complications and
689 mortality of HD patients; measure the effects of therapeutic interventions on changes in hydration
690 and fluid status on preservation of renal function; evaluate the specificity and sensitivity of
691 available and putative clinical markers of hydration; determination of changes in body composition

692 as well as nutritional status/intake relative to longevity of dialysis and effect of interventions to
693 preserve muscle mass on survival. The goal is to provide findings that can be applied practically to
694 improve patient outcomes.

695

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