

DIALYSIS – TRANSPLANTATION

Bioelectric impedance vector distribution in peritoneal dialysis patients with different hydration status

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Background. In continuous ambulatory peritoneal dialysis (CAPD), total body water (TBW) is estimated by functions of body weight, and by equations of bioelectric impedance analysis (BIA). These procedures may be biased with abnormal tissue hydration. We validated vector BIA (BIVA) patterns of hydration in CAPD patients, based on direct measurements of resistance (R) and reactance (Xc) (RXc graph) without knowledge of the body weight.

Methods. Cross-sectional study in 200 adult CAPD patients from two groups: 149 patients (77 males and 72 females) without edema (BMI 24.3 kg/m²), and 51 (29 males and 22 females) with pitting edema (BMI 24.6 kg/m²). Single frequency (50 kHz), whole-body impedance vector was measured with both empty and filled peritoneal cavity. Vector distribution was compared with that from 726 healthy subjects, 1116 hemodialysis patients, and 50 nephrotic patients, all with a same BMI. The performance of BIVA was compared with indications of four anthropometry and four conventional BIA equations for TBW.

Results. TBW estimates from anthropometry (Watson, Hume and Weyers, Chertow, and Johansson formulas) were misleading, indicating the same hydration in edema. TBW estimates from BIA equations indicated a 10% excess TBW in edema. BIVA were very sensitive to fluid overload, as both R (by 10%) and Xc (by 40%) were reduced in patients with edema (regardless of peritoneal filling). The vector distribution of individual CAPD patients without edema was superposable to that of the healthy, gender-specific, reference population (50%, 75%, and 95% tolerance ellipses, RXc graph) and close to the hemodialysis, pre-session distribution. Vectors from patients with edema were displaced downward on the RXc graph, out of the 75% ellipse (88% sensitivity and 87% specificity), and close to vectors from nephrotic patients.

Conclusion. CAPD prescription would keep or bring vectors of patients back into the 75% reference ellipse (border for progression from latent to apparent overhydration across the lower pole) regardless of body weight. Whether CAPD patients with vector within the target ellipse have better outcome needs longitudinal evaluation.

Key words: bioelectric impedance analysis, continuous ambulatory peritoneal dialysis, total body water, edema, anthropometry, uremia.

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Continuous ambulatory peritoneal dialysis (CAPD) often results in bringing the patient either to dehydration (decrease in residual urine output and peritoneal ultrafiltration) or to fluid overload (pitting edema with worsening of hypertension and impair of peritoneal ultrafiltration). Maintaining euhydration and euvolemia in CAPD patients is recommended in order to minimize cardiovascular risk and to maximize ultrafiltration in the long term [1]. Edema is not usually detectable until the interstitial fluid volume has risen to about 30% above normal (4 to 5 kg of body weight), while severe dehydration can develop before clinical signs [2].

The routine evaluation of hydration status based on body weight and blood pressure changes over time can be misleading, since changes are not uniquely determined by body fluid volume variations. Formulas based on anthropometry are recommended for estimation of total body water (TBW) at the bedside, not only in dialysis prescription [3–8]. Measurement of central venous pressure is invasive and only evaluates the volemic status, that is, an indirect indicator of soft tissue hydration [9]. Vena cava diameter is also based on the same principle.

At the top of TBW measurement, routine utilization of diluimetry (e.g., tritium and deuterium) is implemented in unique centers evaluating plasma activity 3 to 4 hours after isotope ingestion [8, 10]. But estimates are obtained with a relevant within-subject measurement error (about 10%) even in the absence of delayed gastric emptying [8, 10], and three available isotopes measure different water spaces (by 3% to 4%) [11]. Finally, an abnormal hydration status (hydration constant other than 73%) propagates errors in body compartment prediction of reference methods, including diluimetry [11]. Therefore, diluimetry cannot be considered an optimal method for monitoring of hydration in any clinical condition.

Bioelectric impedance analysis (BIA) is a property-based method of body composition specifically detecting soft tissue hydration with a 2% to 4% measurement error [11], comparable to routine laboratory tests. Contribution of bone to impedance is negligible, and lean contributes more than fat soft tissue because adipocyte droplets of triacylglycerols are nonconductors [12–14]. Whole-body

impedance, a complex number represented in the real-imaginary plane by the Z vector [12, 13], is a combination of resistance (R) (i.e., the opposition to flow of an alternating current through intra- and extracellular ionic solutions, representing the real part of Z) and reactance (X_c) (i.e., the capacitive component of tissue interfaces, and cell membranes and organelles, representing the imaginary part of Z). The arc tangent of X_c/R is called the phase angle. In simple biologic conductors without cells (e.g., saline, urine, ascites, and dialysate) no X_c component can be measured [12, 13]. Because current flows more easily through extracellular spaces, the impedance of a tissue with a same number of cells but with a larger (smaller) extracellular volume will decrease (increase) in both R and X_c components [12, 13]. The impedance (ohm) of a cylindrical conductor is proportional to its specific impedivity and to its length, and is inversely proportional to its cross-sectional area (body impedance is determined by limbs up to 90% and by trunk up to 10%) [12, 13]. The height (H) is used as a measure of the human conductor length [12, 14]. Vector normalization by the subject's stature (Z/H , in ohm/m) controls for the different conductor length [15–18].

The standard BIA technique, with tetrapolar measurement on hand and foot (whole-body) and 50 kHz current frequency provides the best information at a body level because it maximizes the signal-to-noise ratio and minimizes both frequency-dependent errors and variability of electric flow path of multifrequency BIA [12, 13, 19–21].

With multifrequency BIA, despite promising theory in suspended cells, it is impossible to estimate the extracellular electric volume of tissues (and of intracellular by difference from the total volume) because an unknown and variable amount of low-frequency current passes through cells (tissue anisotropy), particularly through muscle fibers (parallel direction) [12, 13]. Differences in compartment estimates obtained with multifrequency as opposed to single-frequency BIA are caused by different, arbitrary constants of electric models [19].

Hundreds of excellent validation studies have established a solid relation between whole-body impedance at 50 kHz, through the impedance index H^2/R , and body fluid volume through isotope dilution [22–26]. However, because criterion methods for TBW have their own errors and intersubject variability of hydration is high, the standard error of the estimate of the best BIA regression equations is too large to be useful in the clinical setting (95% prediction interval for an individual subject greater than ± 6 to 8 L) [2, 26–28]. The prediction error of BIA equations is the sum of five errors, namely the impedance measurement error, the regression error against the reference method, the intrinsic error of the reference method, the electric-volume model error, and the biologic variability among subjects. Furthermore, bi-

ased BIA estimates of TBW are obtained in patients with either severe obesity or severe edema [8, 10, 28–31].

Clinical utility of BIA can be achieved by following the methodology of electrocardiogram interpretation, that is, as a stand-alone procedure based on clinically validated patterns of direct impedance measurements [19] and taking care of two unavoidable errors (i.e., the impedance measurement error and the biologic variability of subjects [9, 15–18, 32–34]). Vector BIA (bioelectric impedance vector analysis) (BIVA) considers combined changes in R and X_c components of Z on the RX_c graph (probability graph), where the intersubject variability of Z is represented with the bivariate normal distribution (i.e., with elliptical probability regions on the R - X_c plane, which are confidence and tolerance ellipses for mean and individual vectors, respectively [15, 18, 35, 36]). An individual vector reading can then be compared with the reference 50%, 75%, and 95% tolerance ellipses calculated in the healthy population of a same race, gender, body mass index (BMI), and age class [16, 18]. After transformation of vector components of the RX_c graph into bivariate Z scores, the *bivariate Z score graph* can be used with any analyzer in any population [18].

In this study, we evaluated the performance of BIVA patterns for interpreting hydration of CAPD patients with different fluid volumes and a same body weight.

For comparison of methods, we also considered TBW predictions based both on anthropometry and conventional BIA regression equations that are recommended in the literature.

METHODS

Study design

This observational (cross-sectional) multicenter, clinical validation study was designed to establish (1) whether fluid status of CAPD patients was associated with a definite BIVA pattern (which could be utilized in dialysis prescription), (2) whether dialysate drainage from abdomen was associated with impedance vector displacement (which could support timing preferences for measurements), and (3) whether fluid status indicated by BIVA pattern was in agreement with either anthropometry or conventional BIA formulas of guidelines and literature.

Study populations

CAPD patients. We studied 200 patients (age 18 to 85 years old) undergoing standard CAPD (2000 mL glucose solution changed four times daily), selected from 14 dialysis units participating in the Italian CAPD-BIA Study Group. All patients had two impedance measurements, one with empty peritoneal cavity (immediately after drainage) and one with filled peritoneal cavity

(immediately after inflow of 2000 mL dialysate), making a total of 400 measurements. All subjects gave their informed consent to the study, following approval of local ethical committees.

Inclusion criteria. Uremic patients, adult Caucasian of both genders, with $16 < \text{BMI} < 31 \text{ kg/m}^2$ (body weight divided by the squared stature) undergoing CAPD from 2 months or longer were eligible for the study.

Exclusion criteria. Patients with amputations or metal implants, with cardiac (New York Heart Association class III or higher), pulmonary, or hepatic failure, with cancer, or with previous kidney graft failure were not considered. The study population actually did not include diabetic patients, although they were not excluded by selection criteria.

CAPD groups. Apparent, pitting edema was considered the clinical criterion identifying patients with fluid overload and leading to classification of patients into two CAPD groups, with edema versus without edema. A sampling grid was provided to centers in order to balance the sample size for CAPD groups (25% with edema and 75% without edema), and by gender and age within the CAPD groups.

The group of patients without edema consisted of two subgroups. One subgroup (65%) was formed by selecting patients who were free from edema with any residual urine output and using any combination of glucose concentration (high-glucose group) and the other one (35%) was formed with patients who only used 1.36% glucose concentration and whose residual urine output was greater than 1000 mL/24 hours (low-glucose group).

Protocol variables. Age, dialytic age, stature, blood pressure, and average daily ultrafiltration volume in the last week before the study were recorded the day of study. Body weight immediately before and after abdominal drainage was recorded. BMI was calculated from the body weight after dialysate drainage.

Laboratory. Hemoglobin, albumin, total plasma protein concentration, and C-reactive protein were determined by routine methods of clinical chemistry in the week of the study. The plasma oncotic pressure was calculated from albumin and total protein concentration [37].

Bioimpedance. In every center, impedance measurements was conducted by the same operator with an impedance analyzer which emitted 800 μA and 50 kHz alternating sinusoidal current (BIA-101) (RJL Systems/Akern, Clinton Twp, MI, USA) and was connected to surface electrodes (standard, tetrapolar placement on the hand and foot) strictly following the method reported elsewhere [14, 22–26]. Electrodes were not removed during dialysate outflow and inflow. The mean coefficient of variation was 1.5% for paired intraindividual repeated measurements. The external calibration of the instrument was checked with a calibration circuit of known impedance value ($R = 470 \text{ ohm}$, and $X_c = 90 \text{ ohm}$, error

1%). According to the RXc graph method of vector BIA, we standardized impedance measurements by the height (H) of the subjects, thus expressing both R/H and X_c/H in ohm/m.

Comparison populations

Body impedance measurements collected in CAPD patients were compared with measurements previously performed with the same method in the following populations, from the same geographic area, with normal or disordered fluid status, whose data are available in the literature.

Healthy subjects. As reference, normal population for impedance measurements we considered 726 healthy Italian subjects, 354 males and 372 females ($15 < \text{age} < 85$ years old, and $16 < \text{BMI} < 31 \text{ kg/m}^2$) [16].

Hemodialysis patients. As a uremic population with a cyclical fluid status control, we considered 1116 uremic patients (680 males and 436 females) undergoing maintenance hemodialysis without hypotension [33].

Nephrotic patients. As a comparison population with fluid overload without uremia, we considered 50 edematous patients (25 males and 25 females) with the nephrotic syndrome [17].

Equations for TBW

TBW volume was estimated by regression equations recommended in the literature, on the basis of either anthropometry data, known as the body weight fraction [4], Watson, Watson, and Batt [5], Hume and Weyers [6], Chertow et al (hemodialysis-specific) [7], and Johansson et al (CAPD-specific) [8] formulas, or through conventional BIA equations, indexed in the following as BIA-a TBW [23], BIA-b TBW [24], BIA-c TBW [25], and BIA-d TBW [26].

In all the equations, TBW is measured in liters, age in years, H in centimeters, postdrainage body weight in kilograms, and R in ohms. For an easy comparison of results, we expressed TBW of different methods as body hydration fraction, that is, as the percentage of body weight (i.e., TBW in liters/body weight in $\text{kg} \times 100$). The relative ($\times 100$) difference of TBW between edema and nonedema groups was calculated as TBW in edema group minus TBW in nonedema group, divided by TBW in nonedema group (Fig. 1). The relative difference of TBW as body weight fraction was not calculated, as it was zero by definition.

Anthropometry. The following anthropometric equations were used:

$$\begin{aligned} \text{Body weight fraction, TBW, males} &= 0.6 \text{ weight} \\ \text{Body weight fraction, TBW, females} &= 0.5 \text{ weight} \\ \text{Watson, TBW, males} &= 2.447 - 0.09516 \text{ age} + 0.1074 \text{ H} \\ &+ 0.3362 \text{ weight} \end{aligned}$$

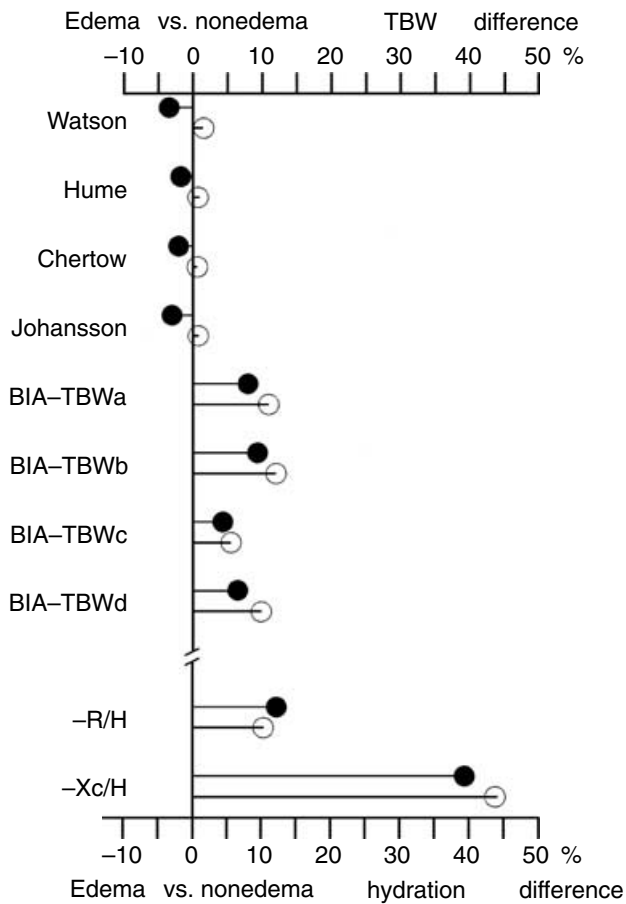


Fig. 1. Two versions of hydration. Top, Hydration is expressed as a relative difference (%) of total body water (TBW) between edema and nonedema groups, that is, as $100 \times (\text{TBW edema} - \text{TBW nonedema})/\text{TBW nonedema}$. TBW estimates are from four anthropometry formulas, Watson, Watson, and Batts [5], Hume and Weiers [6], Chertow et al [7], and Johansson et al [8], and four convention bioelectric impedance analysis (BIA) equations, a [23], b [24], c [25], and d [26]. Bottom, hydration is expressed as a relative difference (%) of the two impedance vector components, that is, as $100 \times (\text{Z/H edema} - \text{Z/H nonedema})/\text{Z/H nonedema}$ (with the minus sign accounting for the inverse relationship between impedance and dehydration). Solid and open points indicate males and females, respectively. Abbreviations are: H, height; R, resistance; Xc, reactance; Z, impedance.

Watson, TBW, females = $-2.097 + 0.1069 H + 0.2466 \text{ weight}$
 Hume, TBW, males = $-14.013 + 0.1928 H + 0.2968 \text{ weight}$
 Hume, TBW, females = $-35.270 + 0.3445 H + 0.1838 \text{ weight}$
 Chertow, TBW = $-0.07494 \text{ age} - 1.01768 \text{ gender} + 0.12703 H - 0.04012 \text{ weight} + 0.57895 \text{ diabetes} - 0.00067 \text{ weight}^2 - 0.03486 (\text{age} \times \text{gender}) + 0.11263 (\text{weight} \times \text{gender}) + 0.00104 (\text{weight} \times \text{age}) + 0.001861 (\text{weight} \times H)$
 Johansson, TBW, males = $-10.759 - 0.078 \text{ age} + 0.192 H + 0.312 \text{ weight}$
 Johansson, TBW, females = $-29.994 - 0.0004 \text{ age} + 0.294 H + 0.214 \text{ weight}$

Conventional BIA. The following equations were used to determine BIA estimates of TBW:

BIA-a, $\text{TBW} = 1.726 + 0.556 H^2/R + 0.095 \text{ weight}$
 BIA-b, $\text{TBW} = 0.040 + 0.590 H^2/R + 0.065 \text{ weight}$
 BIA-c, $\text{TBW} = 4.65 + 0.377 H^2/R + 0.14 \text{ weight} - 0.08 \text{ age} + 2.90 \text{ gender}$ (0 females and 1 male)
 BIA-d, TBW, males = $1.203 + 0.449 H^2/R + 0.176 \text{ weight}$
 BIA-d, TBW, females = $3.747 + 0.450 H^2/R + 0.113 \text{ weight}$

BIVA

The BIVA software [38] was used for vector analysis with the RXc graph method.

Group vector analysis. Using the bivariate normal distribution of R/H and Xc/H, we calculated the bivariate 95% CI for mean impedance vectors of the different CAPD groups (i.e., the ellipse containing both R and Xc, or both the magnitude and the phase angle of the mean vectors, with 95% probability). The average of R/H and Xc/H was plotted as arrowhead line segment with the 95% confidence ellipse, that is as a “RXc mean graph” (Figs. 2 and 3). Separate 95% confidence ellipses of mean vectors indicate a statistically significant difference in vector position on the R-Xc plane, which is equivalent to a significant ($P < 0.05$) Hotelling’s T^2 test for unpaired data [36, 38, 39].

Individual vector distribution. We drew the gender-specific, bivariate 50%, 75%, and 95% tolerance intervals of the impedance vector in the reference healthy Italian population (i.e., the ellipses within which the vector of the individual subject falls with a probability of 50%, 75%, and 95%, respectively) that was available in literature [16].

Then we plotted on the reference ellipses the distribution of individual vectors measured in either group of CAPD patients, which allowed the comparison of the bivariate, intersubject variability of impedance in CAPD patients versus healthy subjects (nonedema group in Fig. 4).

Statistical methods

The programs of the statistical package BMDP [39] were used for standard calculations, including the Student t test, the Hotelling’s T^2 test for vector analysis (Program 3D), the two-way analysis of variance (ANOVA, Program 7D), and the linear correlation coefficient r (Program 6D). Analysis of frequencies, including sensitivity and specificity of BIVA patterns, was performed with CIA software [40]. A test P level of less than 0.05 was considered as statistically significant.

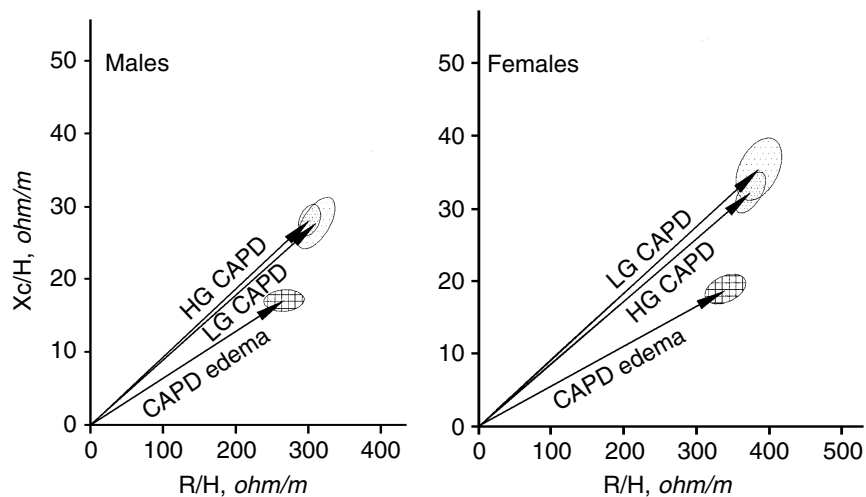


Fig. 2. RXc mean graph by gender. Males (A) and females (B), with mean vectors (arrows) and the 95% confidence ellipses from three continuous ambulatory peritoneal dialysis (CAPD) groups: low-glucose (LG), high-glucose (HG), and edema (net-hatched ellipse) group. Abbreviations are: R, resistance; Xc, reactance; H, height.

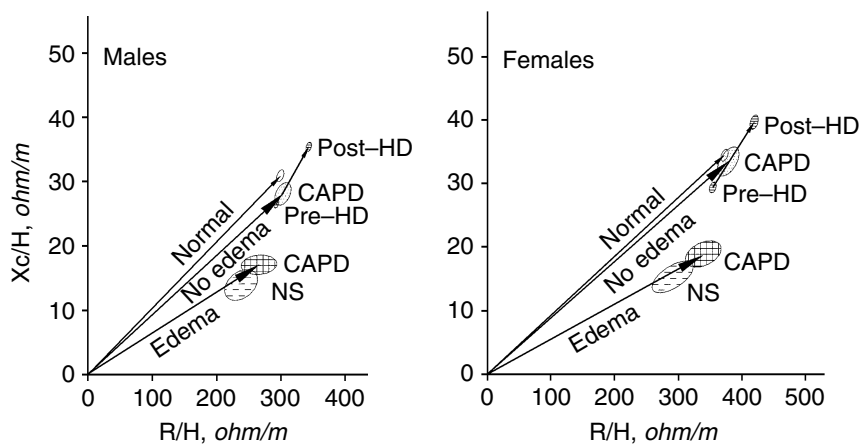


Fig. 3. RXc mean graph by gender. Males (A) and females (B), with mean vectors and the 95% confidence ellipses from edema and nonedema continuous ambulatory peritoneal dialysis (CAPD) groups, compared with the reference, healthy population (normal) [16], asymptomatic hemodialysis (HD) population, pre- and posthemodialysis session [33], and edematous patients with the nephritic syndrome (NS) [17]. Abbreviations are: R, resistance; Xc, reactance; H, height.

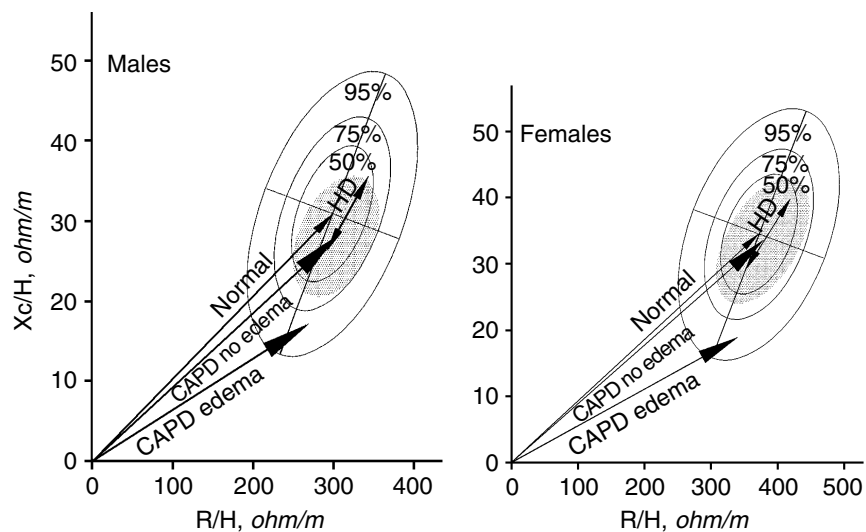


Fig. 4. Dotted ellipses represent the distribution of 50% of impedance vectors from individual continuous ambulatory peritoneal dialysis (CAPD) patients without edema, plotted on the reference, gender-specific (A) males and (B) females, 50%, 75%, and 95% tolerance ellipses of the healthy population [16]. Two big arrows indicate mean vectors of CAPD groups (edema and no edema). Double-headed arrows represent the mean vector of hemodialysis patients before (lower arrowhead) and after a hemodialysis (upper arrowhead) [33]. Abbreviations are: R, resistance; Xc, reactance; H, height.

RESULTS

We studied 200 CAPD patients, 149 without edema (50 in the low-glucose subgroup and 99 in the high-glucose subgroup) and 51 with edema.

Results of continuous variables are reported as mean \pm SD.

Average, daily ultrafiltration in the week before the study was comparable by gender (909 ± 727 mL in males

and 921 ± 756 mL in females, $t = 0.01$) and by hydration status (798 ± 724 in low-glucose, 976 ± 657 in high-glucose, and 910 ± 890 mL in edema group, $F = 1.0$).

Urine volume (24 hours) was comparable by gender (791 ± 601 mL in males and 703 ± 560 mL in females, $t = 1.1$). It was significantly larger in the low-glucose group (1309 ± 338 mL, range 1000 to 2400 mL) versus high-glucose (522 ± 467 mL, range 0 to 2000 mL) and edema groups (641 ± 617 mL, range 0 to 2500 mL) ($F = 45.7$, $P < 0.01$).

Following abdomen drainage, body weight decreased by 2.2 ± 0.3 kg in males and by 2.1 ± 0.3 kg in females ($t = 2.7$, $P < 0.05$). It decreased significantly more in high-glucose versus low-glucose and edema groups (2.3 ± 0.3 kg, 1.9 ± 0.3 kg, and 2.1 ± 0.3 kg, respectively, $F = 16.7$, $P < 0.01$).

Dialysate infusion and impedance. Impedance vector displacement before and after peritoneal dialysate infusion was within the measurement error, that is, 0.5% for R/H (1.74 ± 5.8 ohm/m, $t = 4.3$, $P < 0.05$) and 0.9% for Xc/H (0.25 ± 2.7 ohm/m, $t = 1.3$, P , NS).

In the following, impedance data are those measured after abdomen drainage (empty peritoneal cavity).

CAPD without edema, low- versus high-glucose subgroups

In low-glucose versus high-glucose subgroups of the CAPD group without edema, there was a significantly higher urine output in either gender (1348 ± 357 mL versus 571 ± 510 mL, respectively, $t = 6.4$, in males, and 1281 ± 327 mL versus 459 ± 402 mL, respectively, $t = 9.2$, in females), and a significantly smaller abdomen drainage (2.0 ± 0.4 kg versus 2.3 ± 0.3 kg, respectively, $t = 3.7$, in males, and 1.9 ± 0.3 kg versus 2.2 ± 0.3 kg, respectively, $t = 3.8$, in females), which reflected patient selection criteria (i.e., low-glucose group with residual urine output greater than 1000 mL versus high-glucose group with any urine output).

Mean values of all other protocol variables, including impedance vectors (Fig. 2), were comparable between low-glucose versus high-glucose subgroups (details not reported). Therefore, we present pooled results of both subgroups into one group of CAPD patients without edema.

CAPD without edema versus edema groups

In Tables 1 and 2 we reported comparisons of average protocol variables by gender and CAPD fluid status (no edema versus apparent edema). Impedance vector data are reported in rectangular coordinates, as direct measures (R and Xc), as measures normalized by the stature (R/H and Xc/H), and with the phase angle for the alternative expression of vector in polar coordinates [i.e., vector

magnitude = $\sqrt{(R^2 + Xc^2)}$ or $\sqrt{((R/H)^2 + (Xc/H)^2)}$ and phase angle = $\arctan(Xc/R)$].

There was no significant interaction between gender and fluid status for protocol variables, with the exception of Watson TBW, indicating that data variability was independently influenced by gender and fluid status (two-way ANOVA, interaction test F_{ExS}) (Table 2). Significant differences by sex were documented in average height, body weight, hemoglobin, oncotic pressure, mean arterial pressure, TBW, and impedance vector position of the same CAPD groups. A significant gender effect on impedance was observed in all groups, with longer and less steep impedance vectors in females, as previously documented in different races, ages, and other clinical conditions [9, 15–18, 33]. Hence, vector distributions were analyzed separately by gender.

CAPD patients with edema had a comparable dialytic age, BMI, C-reactive protein, TBW by the four anthropometry formulas, systolic, and mean blood pressure as patients without edema. Mean values of both R/H and Xc/H, phase angle, hemoglobin, albumin, oncotic pressure, and diastolic blood pressure were significantly lower in patients with edema than in those of the same gender without edema. In contrast, pulse pressure, and TBW of the four conventional BIA equations were significantly higher in patients with edema than in those of the same gender without edema.

Edema and TBW estimates. An increase in interstitial fluid volume above 30% ($>12\%$ in TBW) was expected following Guyton's pressure-volume curve in edema group [2].

As shown in Table 2 and Figure 1, TBW estimates provided by anthropometry, through Watson, Hume and Weyers, Chertow, and Johansson formulas were misleading since predictions of TBW were either equal (0.7% to 1.6% in females) or lower (-1.7% to -3.4% in males) in edema. Indeed, the body hydration fraction in males was between 56% and 61% in nonedema group, and between 54% and 60% in edema group. In females it was between 49% and 54% in either CAPD group. Of note, different formulas of different complexity estimated the hydration of males lower than 60% and the hydration fraction of females higher than 50%, regardless of fluid status.

TBW estimates of the four conventional BIA equations were moderately sensitive to fluid overload, indicating an excess TBW of 4% to 9% in males and 6% to 12% in females, with a variable hydration fraction of different formulas, from 52% to 63% in edema versus 50% to 58% in nonedema group in males, and from 43% to 58% in edema versus 41% to 52% in nonedema group in females.

In fact, direct impedance measurements were very sensitive to fluid status, as both vector components were reduced in patients with edema compared with those without edema, precisely by 10% (in females) to 12%

Table 1. Mean values with standard deviation (SD) of protocol variables. Details are reported elsewhere, for healthy [16] and hemodialysis [33] populations

Population	Healthy		Hemodialysis before		CAPD, no edema		CAPD, edema		CAPD, two-way ANOVA		
	M	F	M	F	M	F	M	F	F _{Edema}	F _{Gender}	F _{E×G}
Gender <i>male, female</i>											
Sample size <i>number</i>	354	372	680	436	77	72	29	22			
Age <i>years</i>	49	48	58	60	59	58	64	67	13.5 ^a	0.1	0.9
SD	17	18	14	14	14	13	12	13			
Dialytic age <i>months</i>	—	—	72	72	27	25	26	33	0.4	0.6	0.3
SD	—	—	72	60	29	24	30	27			
Height <i>cm</i>	170	158	169	157	168	158	170	157	0.1	126.2 ^a	2.2
SD	8	7	8	7	7	6	8	7			
Body mass index <i>kg/m²</i>	24.9	24.5	23.6	23.5	24.2	24.4	25.1	24.0	0.2	0.6	1.4
SD	2.9	3.3	2.9	3.1	2.7	3.7	3.2	4.3			
Weight <i>kg</i>	72.6	61.5	68.6	59.4	68.8	60.9	72.8	58.9	0.4	42.8 ^a	3.2
SD	11.5	9.5	10.0	9.1	9.6	10.0	10.8	11.4			
R <i>ohm</i>	507.0	587.4	492.9	554.1	509.5	596.3	451.6	529.4	22.1 ^a	38.4 ^a	0.1
SD	77.7	78.7	65.7	66.1	71.1	89.5	92.2	70.0			
R/H <i>ohm/m</i>	298.6	371.9	292.6	353.6	303.0	377.9	265.9	338.8	20.0 ^a	75.2 ^a	0.1
SD	43.2	49.0	40.6	44.9	44.9	58.2	56.6	49.0			
Xc <i>ohm</i>	52.3	54.3	44.4	45.9	47.1	52.6	28.9	29.3	159.5 ^a	3.2	2.4
SD	14.0	14.1	10.0	11.6	10.3	12.0	5.5	5.5			
Xc/H <i>ohm/m</i>	30.8	34.4	26.3	29.3	28.0	33.4	17.0	18.8	150.1 ^a	11.7 ^a	2.9
SD	7.2	7.7	5.8	7.3	6.3	7.9	3.0	3.6			
Phase angle ^o	5.88	5.28	5.16	4.75	5.32	5.07	3.79	3.20	107.3 ^a	6.5 ^a	1.1
SD	1.26	1.21	1.12	1.09	1.09	1.03	0.93	0.65			
r (R,Xc)	0.47	0.41	0.32	0.38	0.41	0.52	0.10	0.39	—	—	—
Hemoglobin <i>g/L</i>	—	—	103	98	118	109	111	101	8.2 ^a	11.0 ^a	0.1
SD	—	—	15	14	17	16	16	17			
Albumin <i>g/L</i>	—	—	39.6	40.5	38.1	37.6	35.9	34.3	11.0 ^a	1.8	0.5
SD	—	—	5.9	5.3	5.6	4.7	4.7	4.2			
Oncotic pressure <i>mm Hg</i>	—	—	19.1	18.6	19.6	18.8	18.0	16.0	17.2 ^a	6.5 ^a	1.2
SD	—	—	3.1	3.2	3.1	3.3	3.9	2.2			
C-reactive protein ^b <i>mg/L</i>	—	—	—	—	0.8	0.7	0.8	0.8	0.1	0.1	0.1
SD ^b	—	—	—	—	2.6	2.9	3.4	2.6			
Systolic blood pressure <i>mm Hg</i>	—	—	—	—	141	141	147	143	1.5	0.7	0.5
SD	—	—	—	—	17	18	18	23			
Diastolic blood pressure <i>mm Hg</i>	—	—	—	—	85	83	83	78	4.7 ^a	3.7	0.9
SD	—	—	—	—	9	10	10	12			
Mean blood pressure <i>mm Hg</i>	—	—	—	—	103.6	102.4	104.2	99.6	0.4	2.6 ^a	0.9
SD	—	—	—	—	10.0	11.5	10.8	12.7			
Pulse pressure <i>mm Hg</i>	—	—	—	—	56.5	57.7	64.3	64.3	7.7 ^a	0.1	0.1
SD	—	—	—	—	15.9	13.9	15.8	21.9			

Abbreviations are: CAPD, continuous ambulatory peritoneal dialysis; ANOVA, analysis of variance; R/H, resistance/height; Xc/H, reactance/height; r(R,Xc), correlation coefficient between R and Xc. Data are precession in hemodialysis and postdrainage in CAPD patients; body mass index in hemodialysis is the mean of pre- and postvalues.

^a $P < 0.05$; ^bAntilog values.

(in males) in the R/H component, and by 39% (in males) to 44% (in females) in the Xc/H component.

Impedance patterns in CAPD groups. As indicated by separate 95% confidence ellipses, significantly shorter and more down-sloping mean impedance vectors were observed in CAPD patients with edema compared to those without edema of the same gender (Figs. 2 and 3).

The mean impedance vector of CAPD patients without edema was half-way between the mean vectors of the healthy population and the hemodialysis population before the hemodialysis session, with some difference by gender. Indeed, it was closer (with overlapping confidence ellipse) to the prehemodialysis vector in males and to reference vector in females. It was far from posthemodialysis mean vector in either gender.

Mean impedance vector position of CAPD patients with edema was comparable (overlapping 95% confidence ellipse) to that of edematous patients of the same gender with the nephrotic syndrome [17] (Fig. 3).

Individual vector distributions. To derive on the RXc graph the target region of optimal tissue hydration of individual subjects, we plotted the vectors recorded from single patients undergoing CAPD without edema on the reference 50%, 75%, and 95% tolerance ellipses of the healthy population of the same gender. The intersubject variability of CAPD vectors was comparable to that of healthy people, as shown in Figure 4 where the dotted area containing 50% of CAPD vectors was apparently superposable to that containing 50% of reference vectors (as were other percentiles not shown). The 50% vector distribution in CAPD females was closer than males

Table 2. Mean values with standard deviation (SD) of total body water (TBW) estimates, expressed as hydration fraction (%) of body weight (TBW, L/weight, kg) \times 100

Gender <i>male, female</i>	CAPD, no edema		CAPD, edema		Two-way ANOVA		
	M	F	M	F	F _{Edema}	F _{Gender}	F _{E\timesG}
Sample size number	77	72	29	22	—	—	—
Body weight <i>kg</i>	68.8	60.9	72.8	58.9	0.4	42.8 ^a	3.2
SD	9.6	10.0	10.8	11.4			
Weight fraction [4], TBW %	60.0	50.0	60.0	50.0	—	—	—
Watson, Watson, and Batt [5], TBW %	55.7	49.5	53.8	50.3	0.8	63.9 ^a	4.9 ^a
SD	3.9	3.7	2.4	4.5			
Hume and Weyers [6], TBW %	57.4	50.5	56.4	50.9	0.1	75.6 ^a	1.0
SD	3.3	5.0	3.6	6.1			
Chertow et al [7], TBW %	60.7	53.8	59.5	54.2	0.5	81.5 ^a	1.3
SD	3.3	4.8	3.2	5.4			
Johansson et al [8], TBW %	56.3	48.9	54.6	49.3	1.0	92.1 ^a	2.4
SD	3.7	4.3	2.9	5.2			
BIA-a [23], TBW %	58.3	52.0	63.0	57.7	22.2 ^a	27.6 ^a	0.2
SD	6.6	6.6	7.9	6.3			
BIA-b [24], TBW, %	55.6	48.6	60.8	54.5	23.4 ^a	34.0 ^a	0.1
SD	6.9	6.7	8.4	6.4			
BIA-c [25], TBW, %	49.6	41.0	51.8	43.3	6.8 ^a	99.0 ^a	0.0
SD	5.3	5.1	5.8	4.9			
BIA-d [26], TBW %	56.7	49.6	60.5	54.5	21.8 ^a	51.0 ^a	0.3
SD	5.3	5.7	6.4	5.6			

Abbreviations are: CAPD, continuous ambulatory peritoneal dialysis; ANOVA, analysis of variance; BIA, bioelectric impedance analysis. Data are postdrainage. ^a $P < 0.05$.

to the gender-specific, 50% reference ellipse, and it was also more centered than males with respect to the pre- and posthemodialysis vector migration trajectory (double headed arrows, backward down, and forward up).

The distribution of shorter and more down-sloping vectors of CAPD patients with edema was displaced downward, along the direction of the major axis of reference tolerance ellipses, close to the vector distribution of nephrotic patients (Figs. 2 to 4). As the lower pole of the 75% tolerance ellipse has been found to behave as a threshold for apparent edema in nephrotic patients [17], we calculated sensitivity and specificity for edema using the lower half of the reference 75% tolerance ellipse as a test border (with vector falling outside as a positive test result).

In CAPD patients without edema, the frequency of vectors falling out of the lower half of the 75% reference ellipse was 12.8% (false positive rate, 95% CI 7% to 18%), close to the expected frequency of 12.5% in healthy subjects, without significant difference by gender (13.0% in males and 12.5% in females). The frequency of vectors falling either within the lower half of 75% reference ellipse or in the upper half regions was 87.2% (specificity, 95% CI 82% to 93%), without significant difference by gender (87.0% in males and 87.5% in females).

In CAPD patients with edema, the frequency of vectors falling out of the lower half of the 75% reference ellipse was 88.2% (sensitivity, 95% CI 79% to 97%), without significant difference by gender (86% in males and 91% in females), while the frequency of vectors falling within the lower half of the 75% reference ellipse or in the upper

half regions was 11.8% (false negative rate, 95% CI 3% to 21%, all vectors within the lower half 75% ellipse), without significant difference by gender (14% in males and 9% in females).

Therefore, regardless of the body weight of CAPD patients, the vector displacement along the direction of the major axis of tolerance ellipses supported a BIVA pattern of progressive fluid overload associated with shortening and down-sloping vectors (as indicated by edematous patients), and of progressive dehydration associated with longer and steeper vectors (as indicated by posthemodialysis vector migration) (Figs. 3 and 4). In the absence of a definite clinical criterion of dehydration, we did not perform sensitivity and specificity analysis of the 10.1% vectors falling out of the upper half of the 75% tolerance ellipse.

Blood pressure. Patients did not undergo a wash-out period from their antihypertensive therapy before impedance measurements.

Systolic blood pressure was higher, although not significantly, in CAPD group with edema (by 6 and 2 mm Hg in males and females, respectively). Diastolic blood pressure was significantly lower (by 2 mm Hg in males to 5 mm Hg in females) in CAPD patients with edema, in whom pulse pressure was also higher (by 8 and 7 mm Hg in males and females, respectively). In contrast, mean blood pressure was significantly higher in males (Table 1).

Hence, different ways of combining small differences in systolic and diastolic blood pressure led to different statistical results.

Relationships among variables

With the available sample size by gender (106 males and 94 females), any correlation coefficient $r > 0.20$ was statistically significant ($P < 0.05$) although its squared value ($r^2 = 0.04$) indicated that only 4% variability of one variate could be explained with the other correlated variate. So, both r and r^2 values are reported in results of correlation.

The two components of the impedance vector were significantly linearly correlated each other in CAPD patients, with the exception of edematous males, and with r values in the same order of healthy subjects and hemodialysis patients (Table 1).

The correlation coefficients between either vector components and age, dialytic age, BMI, hemoglobin, plasma albumin, oncotic pressure, and blood pressure reached significant levels in particular combinations of groups, with highest values of $r < 0.44$, indicating that less than 19% of the variability of vector components was associated to the variability of other protocol variables.

Correlation with body mass. The correlation between BMI and the four TBW estimates of anthropometry formulas was very high, with $-0.98 < r < -0.96$ in males and $-0.98 < r < -0.76$ in females, indicating that 57% to 96% of TBW estimates was determined by the BMI value (as expected by the structure of formulas).

The correlation between BMI and the four TBW estimates of conventional BIA equations was moderate in females, $-0.68 < r < -0.58$, and low in males, $-0.35 < r < -0.27$, indicating that 7% to 46% of TBW estimates was determined by the BMI.

As previously documented in different populations [16–18], a negative, weak correlation ($r^2 < 18\%$) was documented between BMI and R/H values both in males ($r = -0.43$) and females ($r = -0.36$), without any significant correlation between BMI and Xc/H ($r = -0.18$ in males, and $r = -0.09$ in females).

Correlation among TBW estimates. The four anthropometry TBW estimates were tightly correlated each other, with $0.91 < r < 1.00$ in females and $0.80 < r < 0.97$ in males, particularly between Hume and Weyers, Chertow, and Johansson's formula ($r = 0.98$ to 1.00 in females, and $r = 0.92$ to 0.97 in males).

The four TBW estimates of conventional BIA reached a nearly perfect mutual correlation between them, with $0.94 < r < 1.00$ in males and $0.92 < r < 1.00$ in females.

The cross correlation between TBW estimates of anthropometry and of conventional BIA was moderate in females, $0.56 < r < 0.67$, and low in males, $0.26 < r < 0.52$.

In short, the correlation analysis indicated that comparable (strongly correlated) estimates were obtained by any of the formulas of a same anthropometry or BIA set, but different (uncorrelated) estimates were obtained from anthropometry versus conventional BIA formulas.

Performance of methods in monitoring of hydration

The clinical validation criterion based on pitting edema demonstrated that (1) hydration assessment obtained with four anthropometry formulas detected no difference in TBW between edema and nonedema CAPD groups (because the BMI was the same in either group); (2) four conventional BIA formulas detected a 10% more TBW in edema group (because they were function of H^2/R in addition to BMI); (3) a decreased tissue impedance (increased tissue hydration) by 40% was documented in edema group using BIVA without anthropometry data (because both R and Xc vector components were simultaneously considered); and (4) short impedance vectors falling below the lower pole of the 75% reference ellipse indicated apparent edema with 88% sensitivity and 87% specificity, which can be utilized as a border to keep away in preventing progression from latent to apparent overhydration in individual CAPD patients.

DISCUSSION

Literature and Dialysis Outcomes Quality Initiative (DOQI) Guidelines for CAPD prescription recommend that body fluid volume be estimated using one of the anthropometry formulas for TBW, such as those of Watson or of Hume and Weyers [1, 3, 27], although their poor performance has been reported in literature [8, 29, 30, 41]. TBW estimates based on conventional BIA equations are not recommended by guidelines [3], although they proved to be accurate, on average, in stable CAPD patients [28, 29, 41, 42]. Following identification of BIVA patterns in hemodialysis patients [33], we designed this study to establish whether fluid status of CAPD patients was associated with a definite BIVA pattern that could be utilized in dialysis prescription. To our knowledge, this is the largest CAPD population described in BIA literature.

We used pitting edema as a clinical, indisputable indicator of fluid overload. Based on Guyton's theory, fluid overload is detectable as apparent edema when interstitial pressure becomes positive due to an increase of interstitial fluid volume above 30% (meaning increase >4 to 5 kg body weight, or $>12\%$ TBW) [2]. As a derived working hypothesis, we believe that a progressive shortening and down-sloping of the impedance vector corresponds to a progressive increase in the interstitial fluid pressure, as depicted in Figure 5. In the normal subject (40 L TBW), the interstitial fluid volume is 15 L in a gel form and with a negative interstitial pressure of -2 mm Hg, the blood volume is 5 L, and tissue impedance is normal (Z vector in the center of the 75% tolerance ellipse). When the interstitial fluid pressure rises above zero, most of the extra fluid is free fluid allowing the appearance of pitting edema and bringing the impedance vector out of the lower pole of the 75% tolerance ellipse (established BIVA threshold for apparent edema). Fluid overload is

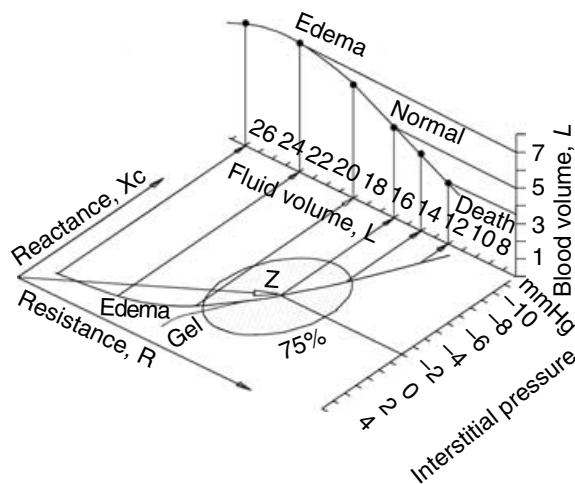


Fig. 5. Interpretation of tissue impedance based on interstitial pressure-volume curve (on the floor) and interstitial volume-blood volume curve (on the wall) following Guyton's theory [2]. In the normal subject [40 L total body water (TBW)], the interstitial fluid volume is 15 L in a gel form and with a negative interstitial pressure of -2 mm Hg, the blood volume is 5 L, and tissue impedance is normal (Z vector in the center of the 75% tolerance ellipse). When the interstitial fluid pressure rises above zero, most of the extra fluid is free fluid, allowing the appearance of pitting edema and bringing the impedance vector out of the lower pole of the 75% tolerance ellipse (established threshold for apparent edema). Fluid overload also increases the blood volume up to a plateau of 7 L. Vector migration from the lower to the upper pole of the 75% tolerance ellipse indicates a progressive loss of interstitial fluid from the gel meshwork and a progressive decrease in interstitial pressure, which lowers the blood volume. Vector migration along the major axis of 75% tolerance ellipse detects changes in tissue hydration before the appearance of clinical signs of fluid overload (edema, lower pole) or dehydration (hypovolemia, upper pole).

also associated with an increase in blood volume up to a plateau (7 L, or 40% increase) where the interstitial spaces for free fluid become an overflow release valve for the circulatory system. Although severe dehydration can develop before clinical signs, we demonstrated that dehydration [15, 18] and fluid removal with hemodialysis [33] are associated with vector migration from the lower to the upper pole of the 75% tolerance ellipse, indicating a progressive loss of interstitial fluid from the gel meshwork and a progressive decrease in interstitial pressure, which lowers the blood volume. Hence, vector migration along the major axis of 75% tolerance ellipse can be utilized in monitoring tissue hydration before the appearance of clinical signs of fluid overload (edema, lower pole) or dehydration (hypovolemia, upper pole).

Among patients without edema we also selected a group of patients with "optimal hydration" who were likely free from latent overhydration because they were free from edema only using 1.36% glucose concentration and had a residual urine output greater than 1000 mL/24 hours (low-glucose subgroup).

By using direct whole-body impedance measurements, we obtained eight important clues for the routine

monitoring of hydration in CAPD irrespective of the patient's body weight. First, the impedance vector distribution of most CAPD patients without edema was close to the gender-specific reference intervals calculated in the healthy population, which allowed the identification of patients with full versus partial restoration of normal tissue electrical properties that are associated with soft tissue hydration. This result cannot be compared with literature where impedance measurements in CAPD patients are not reported with both components (R and X_c) by gender, nor are compared with their reference populations. However, a comparable deuterium-TBW has been reported in CAPD patients without edema and control subjects [30].

The finding that vector distribution in compensated, dry CAPD patients is the same as in healthy subjects can be envisaged as speaking either against sensitivity of vector BIA in detecting tissue hydration or in favor of CAPD technique in restoring and keeping hydration close to normal. We do not derive that a same tissue hydration necessarily leads to the same blood pressure both in subjects with a normal kidney function and in uremic patients, due to a variable adaptation of vascular resistance and cardiac output [2].

However, BIVA patterns can be utilized at the bedside as exclusion criteria for mechanisms of hypertension and hypotension. In hypertension, a BIVA pattern of tissue dehydration excludes fluid overload as the cause, but a BIVA pattern of tissue fluid overload cannot exclude causes other than hypervolemia. In hypotension, a BIVA pattern of tissue dehydration is consistent with hypovolemia as a cause, whereas a BIVA pattern of tissue hyperhydration indicates causes of hypotension other than hypovolemia.

It would be very interesting to compare clinical outcomes on the basis of impedance vector distribution: perhaps longer vectors, close to the upper pole of the 75% tolerance ellipse (indicating dehydration) could be more safe in uremic patients.

Second, vector distribution in patients without edema who only used 1.36% glucose concentration and whose residual urine output was greater than 1000 mL/24 hours was comparable to that of patients that were free from edema using higher glucose concentration with any residual urine output. This finding demonstrated that in this population with an average dialytic age of 25 to 33 months, a same tissue hydration could be achieved with different dialysis prescriptions. We could not further stratify the population by dialytic age to establish whether vector migration toward overhydration occurred over longer periods after a progressive falling of residual renal function.

Third, CAPD patients with apparent edema were characterized by shorter (10% decrease in R/H), less steep (40% decrease in X_c/H) vectors than patients without

edema with a same BMI. Vector distribution below the lower pole of the reference 75% tolerance ellipse was comparable to that of nephrotic patients without uremia, with sensitivity and specificity in the order of 90% [17].

The different vector position of CAPD patients with edema was associated with lower oncotic pressure, lower albumin and hemoglobin concentration, compared to patients without edema. We have no additional data (e.g., independent nutritional evaluation) supporting causes other than hemodilution for these findings. A flawed interpretation of these laboratory parameters of malnutrition [43] is prevented if they are only used in patients with normal hydration (vectors within the 75% tolerance ellipse). Age (64 to 67 years old in edema versus 58 to 59 years old in nonedema groups) can be ruled out, as impedance was comparable to that of nephrotic patients aged 50 to 57 years old [17].

The sharp decrease in phase angle ($<4^\circ$) of vectors from edematous patients should dissuade from interpreting a small phase angle independent on the vector length, as an indicator of malnutrition and poor prognosis [44–46], which is prone to the ridiculous conclusion that nutrition and prognosis improve after hemodialysis because the phase angle increases with fluid removal (Fig. 3). As reviewed elsewhere [18], with respect to the reference tolerance ellipses, long vectors with a small phase angle (increased R with decreased Xc) are associated with malnutrition, whereas short vectors with a small phase angle (decreased R with decreased Xc) are associated with fluid overload and edema not only in renal patients [9, 15–18, 33, 34, 47, 48, 50]. Symmetrically, long vectors with a high phase angle (increased R with increased Xc) are observed in dehydration of healthy subjects [32], of cholera [15, 18], at the end of a hemodialysis session [33], and following enhanced fluid removal in peritoneal dialysis [49]. In obese subjects, including obese hemodialysis patients, vectors are short but with a normal or increased phase angle [17, 18]. Therefore, changes in body composition can be continuously monitored without confusion on the RXc graph, and vector displacements can be ranked with respect to their distance from the mean.

The positive correlation coefficient between vector components indicates that factors modifying R values are expected to modify also Xc values, and vice versa, because soft tissues are anisotropic media where fluids are allowed to increase and decrease with a definite adaptation of tissue mass and structure [2, 12, 13, 17–19]. This correlation has been documented in large populations of different races [18], and may flaw statistical conclusions obtained from univariate analysis of individual components. Due to tissue anisotropy, separate estimates of intra- and extracellular volumes cannot be obtained from impedance measurements [19]. Instead, profiles over time of both serum osmolality and sodium concentration are reliable indicators of fluid shift between intra- and extracellu-

lar compartments [4], which, however, is a rare event in CAPD [1].

Contrary to expectation, the difference in blood pressure between edema and nonedema groups was small and dependent on the way of expressing blood pressure. For instance, in the group with edema the systolic blood pressure and the pulse pressure were higher (in the order of 2 to 8 mm Hg), whereas the diastolic blood pressure was lower. These small differences between edema and nonedema groups possibly reflect an effective antihypertensive treatment at the time of the study. In the protocol we did not include a wash-out period, which only would have allowed the evaluation of blood pressure as a function of vector distribution. The study was designed to establish BIVA patterns of different fluid status independent on its effect on blood pressure or antihypertensive treatment. The power of the study with 200 subjects would have been very low with respect to blood pressure (level or treatment) because the sampling grid already considered eight + two subgroups of patients (two genders \times two classes of age \times two groups of edema, plus two additional groups of dialysate glucose level in the group without edema).

Fourth, impedance vector displacement before and after abdomen filling was negligible (although statistically significant for the R/H component), within the measurement error (0.5% for R/H, and 0.9% for Xc/H), which allows taking impedance measurements at the operator's convenience, either with empty or filled peritoneal cavity. The random nature of these changes in R/H and Xc/H, by 1.7 and 0.3 ohm/m, respectively, is apparent when they are compared with the increase by 55 and 10 ohm/m, respectively, that followed 2500 mL of fluid removal with hemodialysis [33]. In other words, the sensitivity in detecting removal of a same volume of fluid from soft tissue with hemodialysis is 30 to 40 times greater than removal from peritoneal cavity.

The indifference of whole-body impedance to the abdominal drainage is a confirmatory result of other studies in CAPD patients and in patients with ascites [50–52] due to the 10% contribution of trunk versus 90% of limbs to the whole-body impedance [12, 13]. The clinical usefulness of impedance in body composition analysis is based on this property that reflects the composition of homogeneous soft tissues of limbs (skin, muscles, and adipose tissue) and makes it negligible the heterogeneous electric contribution of the trunk (skin, muscles, adipose tissue, mediastinum, lungs, pleural effusions, heart, big vessels, liver, pancreas, spleen, bladder, intestine, peritoneum, ascites, etc.). Furthermore, free fluid within the trunk (effusions, ascites, urine, etc.) does not contribute to the Xc component of impedance.

On the other hand, segmental BIA for body composition analysis cannot be validated with dilution methods nor provided better performance than whole-body

measurements in edema [53] and in CAPD at any frequency [10]. In CAPD patients, the best estimation of peritoneal fluid volume (2100 mL, with bias 130 ± 300 for drained fluid to 190 ± 400 mL for infused fluid) was obtained with segmental BIA of the trunk using several arbitrary assumptions on body geometry (three different k values), fluid volume distribution (double for limbs versus trunk, with different powers of the impedance index) and changes in dialysate conductivity, and using smoothed mean values of the “extracellular R” (i.e., R value extrapolated to zero frequency from fitting a Cole-Cole model) [54]. In fact, removing the effect of these assumptions in volume estimation, extracellular R values changed little, within the measurement error range, up to 6 ohm after draining and filling [50, 54].

Fifth, vector distribution in CAPD patients without edema when compared to that of asymptomatic hemodialysis patients was closer to pre- than postsession distribution, particularly in males (Figs. 3 and 4) [33]. This indicated a greater average tissue hydration in CAPD without edema versus hemodialysis in the interdialytic period. A similar conclusion was reached by others based on fluid volumes estimated by multifrequency BIA in CAPD patients with variable fluid status [28, 55]. Different levels of overhydration (either apparent or latent) could also have been associated with outcome of ADEMEX trial, where overhydration effect on outcome was excluded using tertiles of the unreliable TBW estimates by Watson formula to classify patients, several of whom died with congestive heart failure [56].

Sixth, the study was not designed with the aim to validate BIVA patterns versus clinical signs of dehydration, for which we were not able to identify a definite criterion. The vector distribution of CAPD patients without edema, from both low-glucose and high-glucose groups, was scattered on the R-Xc plane as that of healthy subjects, including a 10% of long vectors (out of the upper half of the 75% tolerance ellipse) that likely were measured in dehydrated, still asymptomatic patients (Fig. 5). Interestingly, it has been reported that the switch from 2.27% glucose to 7.5% icodextrin in automated peritoneal dialysis caused a lengthening (increase in R by 10%) and steepening (increase in Xc by 20%) of impedance vectors at any current frequency (5, 50, and 200 kHz). Following this vector displacement (toward the upper poles of their vector distribution), hypotension was observed in 50% of patients (as predictable from Guyton’s theory and working hypothesis in Fig. 5) [49].

Seventh, anthropometry is misleading and should no longer be recommended in guidelines. TBW estimates of anthropometry formulas (functions of body weight and stature) detected no difference between edema versus nonedema groups. Chertow’s formula, that was more accurate than Watson and Hume and Weyers’ formulas in hemodialysis patients [7], and Johansson’s formula

that was derived in CAPD patients [8], did not perform better than other formulas (Fig. 1). Anthropometry formulas, which also resulted insensitive to different central venous pressure levels [9], may be useful in epidemiology of healthy people, but not in monitoring of body hydration at the bedside [8, 10]. The same conclusion applies to other related formulas for TBW based on a fixed constant of body weight (e.g., 58%, either gender [27–30, 41], or 50% in females and 55% in males [1]).

Finally, TBW estimates of the four conventional BIA formulas that are functions of H^2/R and body weight, detected some 10% more TBW in edema group, which is a little below the expected value of 12% [2]. The variability among formulas was greater than 10%. In the clinical setting, the consequence of a small difference with a high variability is a poor discrimination between different fluid status. The tight correlation between the four equations indicates a comparable performance at the individual level. BIA equations produce TBW estimates with high accuracy but with a large prediction error for the individual subject (± 6 to 8 L), which can be more useful in epidemiology than at the bedside [22, 26, 28, 29, 42]. No reduction in prediction error has been obtained with multifrequency BIA in CAPD patients [10].

Of note, a sequential application of the RXc graph method before conventional BIA equations can increase the usefulness of both methods. On one hand, accuracy of TBW-functions of impedance means validity for BIVA patterns. On the other hand, BIA-TBW estimates obtained in patients with normal hydration, that is, with vectors within the 75% tolerance ellipse of the RXc graph, are more valid because those patients are comparable to subjects recruited for validation of BIA equations.

CONCLUSION

Estimation of TBW with anthropometry formulas is misleading and should be avoided. Evaluation of hydration with conventional BIA equations for TBW is less sensitive than with BIVA patterns. Our results support a new operative definition for the optimal hydration in CAPD patients. The definition of optimal includes impedance vectors lying within the 75% tolerance ellipse of the reference healthy population where tissue electrical properties of uremic patients are restored. The feedback adjustment of dialysis prescription based on BIVA pattern indications, allows the hydration of the individual patient be kept close or brought back to the reference target of the healthy people. Vector displacements parallel to the major axis of tolerance ellipses indicate changes in tissue hydration, namely, dehydration with lengthening and steepening of vectors, and overhydration with shortening and down-sloping of vectors. Percentiles of reference, tolerance ellipses allow ranking and classifying of vector displacements in either directions. Only

longitudinal studies will establish whether patients with vectors within the target ellipse have better outcomes than those with vectors out of the target ellipse.

APPENDIX

The Italian CAPD-BIA Study Group consisted of the following investigators (with dialysis unit, Italy): P. Allaria (Busto Arsizio), G. Amici (Treviso), R. Bergia (Biella), E. Coppola (Fano), F. Caputo (Palermo), G. Giacchetta (Senigallia), G.M. Iadarola (Torino), A. Malagoli (Padova), S. Mastrosimone (Camposampiero), A. Piccoli (Padova), R. Piperno (Firenze), G. Quintaliani (Perugia), R.A. Rocca (Roma), R. Scanziani (Desio), R. Zani (Brescia).

Formulas for calculation of confidence and tolerance ellipses

Confidence and tolerance ellipses of a bivariate normal distribution [35, 36] can be calculated using common statistics of the simple linear correlation analysis [15, 16, 18]. Given n pairs of observations x and y , with standard deviation s_x and s_y , and correlation coefficient r , for a fixed α probability level, take the Snedecor's F_α value with 2 and $n-2$ degrees of freedom.

In the RXc graphs, the semiaxes L_1 and L_2 and the slopes b_1 and $b_2 = -1/b_1$, of the axes of the $100(1-\alpha)\%$ confidence and tolerance ellipses (e.g., $\alpha = 0.05, 0.25$, and 0.50 for the 95th, 75th, and 50th percentile, respectively) are calculated using equations (1a) and (2a), respectively.

In the RXc-score graph, parameters of tolerance ellipses of bivariate Z-scores can be calculated using equations (1b) and (2b) [18].

$L_1, L_2 =$

$$\sqrt{K} \cdot \sqrt{(n-1)(s_x^2 + s_y^2) \pm \sqrt{[(n-1)(s_x^2 + s_y^2)]^2 - 4(n-1)^2(1-r^2)s_x^2s_y^2}} \quad (\text{equation 1a})$$

$$L_1, L_2 = \sqrt{K} \cdot \sqrt{2(n-1) \pm 2r(n-1)} \quad (\text{equation 1b})$$

Where $K = F/n \cdot (n-2)$ for confidence ellipses, and $K = F \cdot (n+1)/n \cdot (n-2)$ for tolerance ellipses.

$b_1, b_2 =$

$$(b, -1/b) = (s_y^2 - s_x^2)/2rs_x s_y \pm \sqrt{1 + [(s_y^2 - s_x^2)/2rs_x s_y]^2} \quad (\text{equation 2a})$$

$$b_1, b_2 = \pm 1 \quad (\text{equation 2b})$$

Free software available for RXc graphs and vector BIA at apiccoli@unipd.it

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