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Relations between malnutrition–inflammation–atherosclerosis and volume status. The usefulness of bioimpedance analysis in peritoneal dialysis patients

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Abstract

Background. Chronic fluid overload (FO) is frequently present in peritoneal dialysis (PD) patients and is associated with hypertension and left ventricular hypertrophy and dysfunction, which are important predictors of death in dialysis patients. In the present study, we investigated the relationship between nutrition, inflammation, atherosclerosis and body fluid volumes measured by multifrequency bioimpedance analysis (m-BIA) in PD patients. In addition, we analysed the relationship of extracellular volume values by m-BIA to echocardiographic parameters in order to define its usefulness as a measure of FO.

Methods. Ninety-five prevalent PD patients (mean age 50 ± 13 years, 10 of them diabetic) were enrolled. Extracellular water (ECW), total body water (TBW), dry lean mass (DLM) and phase angle (PA) were measured by m-BIA. Volume status was determined by measuring left atrium diameter (LAD) and left ventricular end-diastolic diameter (LVEDD). Measurement of carotid artery intima-media thickness (CA-IMT) was used to assess the presence of subclinical atherosclerosis. Serum albumin was used as a nutritional marker, and serum C-reactive protein (CRP) was used as an inflammatory marker.

Results. Mean ECW/height was 10.0 ± 1.0 L/m for whole group and 9.3 ± 0.6 L/m in patients with normal clinical hydration parameters. In correlation analysis, markers of nutrition, inflammation and atherosclerosis correlated well with m-BIA parameters. When we used echographically measured LAD (>40 mm) or LVEDD (>55 mm) as a confirmatory parameter, a cut-off value of 10.48 L/m ECW/height (78% specificity, with a sensitivity of 77% for LAD and 72% specificity, with a sensitivity of 70% for LVEDD) was found in ROC analysis for the diagnosis of FO. Patients with FO were older and had higher systolic blood pressure, cardiothoracic index, serum CRP level and mean CA-IMT than patients without FO. Patients with inflammation had higher CA-IMT values. In multivariate analysis, only two factors—low urine output and ECW/height—were independently associated with the presence of inflammation.

Conclusions. FO defined by m-BIA is significantly correlated with markers of malnutrition, inflammation and atherosclerosis in PD patients. The indices obtained from

m-BIA, especially ECW/height, correlated well with volume overload as assessed by echocardiography and might be a measure worth testing in a properly designed clinical study.

Keywords: bioimpedance analysis; fluid overload; inflammation; malnutrition; peritoneal dialysis

Introduction

Chronic fluid overload (FO) and hypertension are well recognized factors contributing to the high mortality in dialysis patients [1]. Recently, malnutrition, inflammation and atherosclerosis (the so-called MIA syndrome) have also been proposed as the main causes of mortality in end-stage renal disease patients [2–4].

In peritoneal dialysis (PD) patients, inflammation has been related to extracellular fluid volume expansion [5–7]. This relationship seems to be bidirectional. It has been proposed that expanded extracellular volume, due to inadequate water and sodium removal, acts as an inflammatory stimulus in these patients [8,9]. On the other hand, the inflammatory process itself may promote extracellular water (ECW) expansion, as seen in patients with peritonitis.

In the general population, serum C-reactive protein (CRP), considered to be a marker of inflammation, is a powerful risk factor for ischaemic heart disease and peripheral atherosclerosis [10]. Zoccali *et al.* found that CRP is also a strong independent predictor of the severity of atherosclerosis in dialysis patients [11].

The multi-frequency bioelectrical impedance analysis technique (m-BIA) is a tool to measure body fluid. Application of this non-invasive, inexpensive and simple method is not only helpful in determining the degree of FO but also to evaluate the condition of the body cells and may highlight parameters of malnutrition [12].

Only one study has assessed ECW with m-BIA in a limited number of mixed haemodialysis (HD) and PD patients [13] and reported lower values in patients who were not clinically overhydrated than in normal controls.

The aims of the present study were to investigate (i) the relationship between nutrition, inflammation, atherosclerosis and FO in PD patients by using multi-frequency bioimpedance analysis and (ii) to evaluate the usefulness of ECW/height in assessing the hydration state of these patients.

Materials and methods

Ninety-five prevalent PD patients treated at the Ege University Dialysis Center were enrolled in the study between November 2006 and December 2008. Of these patients, 72 received continuous ambulatory peritoneal dialysis (CAPD) and 23 automated peritoneal dialysis (APD). Ten of these patients had diabetes. The centre has a strict volume control strategy which has been in place for 15 years. This consists of dietary salt restriction and ultrafiltration in order to reach blood pressure levels below 140/90 mm Hg and cardiothoracic index below 0.48. This has resulted in a relatively low prescription (15%) of antihypertensive drugs. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Systolic and diastolic blood pressure were measured at the time of m-BIA investigation and presented as the mean of at least three measurements. We used mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) for analyses.

The following variables were obtained from patient charts: age, gender, diabetes, duration of PD, body weight and height, presence of anuria (diuresis <100 mL/day), serum albumin, CRP, ferritine, phosphorus, creatinine, peritoneal equilibration test (PET), weekly total Kt/V urea and weekly total creatinine clearance (CCr). Peritoneal transport status was analysed as a categorical variable according to the four groupings of D–P Cr 4-h values defined by Twardowski *et al.* (low, <0.50; low average, 0.50–0.64; high average, 0.65–0.80; and high, ≥0.81) [14]. Based on PET, we described low and low average as low transporters and high and high average as high transporters.

Bioimpedance analysis

All patients underwent tetrapolar multi-frequency bioelectric impedance analyses (Bodystat Quadscan 4000, Isle of Man, British Isles) with empty peritoneal cavity to evaluate body composition. To allow for equilibration of body fluids, patients were positioned supine for at least 15 min before the start of measurements with m-BIA. The impedance values were obtained at frequencies of 5, 50, 100 and 200 kHz. The following variables were measured: ECW, total body water (TBW) and phase angle (PA) at 50 kHz.

The principle of measuring the flow of current through the body (impedance) is dependent on the frequency applied. At low frequencies, the current cannot bridge the cellular membrane and will pass predominantly through the extracellular space.

At higher frequencies, penetration of the cell membrane occurs and the current is conducted by both the extracellular water (ECW) and intracellular water (ICW).

By measuring the impedance at 5 kHz and 200 kHz and by applying predictive equations, it is possible to estimate both ECW and TBW. By measuring the impedance at 50 kHz and applying the unique Bodystat® equation, body fat, lean mass and dry lean mass can be assessed. ICW was assessed as TBW − ECW and dry lean mass (DLM) as lean body mass − total body water. Total body weight, height, age and gender are required by the predictive equations used in the hardware unit to display the results on the LCD screen. Bioimpedance analysis has been correlated most frequently against either hydrostatic weighing or isotope dilution as the 'gold standard' [15]. All values were adjusted for height. m-BIA was also performed in 47 healthy controls. A measurement made by the same observer and intra-observer variability was below 2%.

Echocardiography

All echocardiographical measurements were performed according to American Society of Echocardiography recommendations [16,17] at the time of m-BIA investigation. The following measurements were taken: left atrium diameter (LAD), left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD), right ventricular end-diastolic diameter, thickness of the posterior wall and the interventricular septum. Left ventricular mass (LVM) was calculated using the equation described by Devereux [18]. Left ventricular mass index (LVMI) was calculated by dividing LVM by body surface area; LV hypertrophy was defined as LVMI >131 g/m^2 in males and 100 g/m^2 in females [19]. LAD was adjusted for height. Left ventricular systolic function was assessed by left ventricular ejection fraction and fractional shortening. Measurements were made by the same cardiologist.

Cardiothoracic index

Cardiothoracic index (CTI) was calculated as the percentage of the largest horizontal diameter of the heart by the largest internal diameter of the thorax wall on the chest X-ray. It was measured in all patients at the time of other investigations.

Atherosclerosis

Common carotid artery intima-media thickness (CA-IMT) was assessed by using high-resolution colour Doppler ultrasound unit (HDI 5000, Philips, Bothell, WA, USA) equipped with 5–12-MHz broadband electronic

Table 1. Demographic and clinical characteristics of the study patients

Variable	Mean ± SD
Gender (male/female) (*n*)	42/43
Age (years) (range)	50 ± 13 (18–80)
Diabetes mellitus (*n*) (%)	10 (10.5%)
Duration of PD (months) (range)	38 ± 31 (1–173)
APD (*n*) (%)	23 (24.2%)
BMI (kg/m^2)	26.0 ± 3.9
CTI (%)	44.9 ± 4.6
SBP (mm Hg)	118 ± 22
DBP (mm Hg)	76 ± 12
Use of antihypertensive drugs	
No drug (*n*)	42
Diuretics (*n*)	49
ACE inhibitors (*n*)	1
Calcium-channel blockers (*n*)	2
β-Blockers (*n*)	1
PET results	
High (*n*)	5
High average (*n*)	20
Low average (*n*)	35
Low (*n*)	35
Weekly total Kt/V_{urea}	2.40 ± 0.63
Weekly total CCr (L/1.73 m^2)	75 ± 37
Peritoneal ultrafiltration (mL/day)	1154 ± 641
Total sodium removal (mmol/day)	171 ± 105

PD, peritoneal dialysis; APD, automated peritoneal dialysis; BMI, body mass index; CTI, cardiothoracic index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CCr, creatinine clearance; PET, peritoneal equilibration test.

linear array transducer. CA-IMT was measured using the double echogenic line of arterial wall visualized. The inner echogenic line represents the lumen–intima interface. The CA-IMT measurement included the total thickness of the inner echogenic line and adjacent hypoechoic layer, excluding the outer echogenic line, which represents the media–adventitia interface. The intra-observer variability of measurement was 4% (mean difference, 0.02).

Laboratory data

Total sodium removal (TNaR) was calculated from the 24-h dialysate and urine samples TNaR = $[(V_{Out} \cdot D_{NaOut}) - (V_{in} \cdot D_{NaIn})] + [\text{urine volume} \cdot \text{urine}_{Na}]$ (V is the volume of PD solution expressed in litres and D_{Na} the dialysate sodium concentration expressed in mmol/L).

Blood samples for biochemical measurements were taken at the time of m-BIA and echocardiographic investigation. Serum albumin was used as a nutritional marker, CRP was used as an inflammatory marker, LAD and LVEDD measured by echocardiography [20] and ECW/height assessed by m-BIA were used as markers of the volume status.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Proportions were compared by Chi-square analysis. Student *t*-test, analysis of variance and Mann–Whitney tests were used for group comparison. Correlation analysis was performed using Spearman's correlation coefficient. We sought the best cut-off threshold value for ECW/height for FO using the ROC curve. Multivariate stepwise linear regression analyses were used to define independent predictors of volume, nutrition, inflammation and atherosclerosis. Stepwise multiple logistic regression analysis was used to define the predictors of the presence of inflammation. A P-value of <0.05 (two-sided) was regarded as statistically significant. SPSS (Chicago, Illinois) for Windows (Version 15.0) was used for statistical analysis.

Results

Demographic and clinical characteristics of patients are shown in Table 1. Mean age was 50 ± 13 years, duration of PD 38 ± 31 months, percentage of male 44% and prevalence of diabetes 10.5%. Blood pressure was below 140/90 in most (77%) of the patients. In 71% of the patients CTI was below 0.48. Thirty-eight percent of patients were anuric and twenty-five patients were classified as high transporters according to PET.

Table 2. Comparison of body composition parameters of peritoneal dialysis patients with healthy controls

	Male		Female	
Variables	Healthy	PD	Healthy	PD
Age (years)	52.6 ± 8.8	53.1 ± 12.2	50.0 ± 9.6	49.2 ± 14.5
Gender (male/female)	21	42	26	53
Height (cm)	169.2 ± 5.6	167.4 ± 6.6	154.3 ± 5.0	153.9 ± 7.1
Weight (kg)	78.5 ± 13.0[b]	70.6 ± 8.9	69.6 ± 15.1[c]	63.2 ± 11.3
BMI (kg/m^2)	27.3 ± 4.0[a]	25.2 ± 3.3	29.0 ± 5.3[c]	26.6 ± 4.2
BSA (m^2)	1.93 ± 0.18[b]	1.79 ± 0.12	1.74 ± 0.22[d]	1.60 ± 0.15
ICW (L)	25.5 ± 2.5[b]	23.2 ± 2.0	18.2 ± 3.1[c]	16.6 ± 2.2
ECW (L)	18.9 ± 1.8[b]	17.6 ± 1.5	15.7 ± 2.0[c]	14.8 ± 1.7
TBW (L)	44.4 ± 4.3[b]	40.8 ± 3.4	33.9 ± 5.2[c]	31.4 ± 3.9
ECW/height (L/m)	11.1 ± 0.9[b]	10.5 ± 0.8	10.1 ± 1.1[c]	9.6 ± 0.9
ECW/BSA (L/m^2)	9.81 ± 0.42	9.85 ± 0.63	9.02 ± 0.30	9.22 ± 0.52
ECW/TBW	0.42 ± 0.00[a]	0.43 ± 0.01	0.46 ± 0.01[c]	0.47 ± 0.01
DLM (kg)	14.6 ± 2.7[a]	12.7 ± 3.4	8.7 ± 2.8	8.0 ± 2.8
PA (°)	6.5 ± 0.6[b]	5.8 ± 1.4	6.1 ± 0.6	5.7 ± 1.0

BMI, body mass index; BSA, body surface area; ICW, intracellular water; ECW, extracellular water; TBW, total body water; DLM, dry lean mass; PA, phase angle at 50 kHz.
[a]P < 0.05 level (two-tailed) between male healthy controls and PD patients.
[b]P < 0.01 level (two-tailed) between male healthy controls and PD patients.
[c]P < 0.05 level (two-tailed) between female healthy controls and PD patients.
[d]P < 0.01 level (two-tailed) between female healthy controls and PD patients.

Table 3. Correlation analysis between nutrition, inflammation, volume and atherosclerosis markers and bioimpedance analysis parameters

m-BIA parameters	Volume parameters			Nutritional parameters		Inflammation	Atherosclerosis
	LAD/h	SBP	CTI	Albumin	Creatinine	CRP	CA-IMT
TBW/h	0.327[a]	0.366[a]	0.140	0.064	0.099	0.196	0.469[a]
ICW/h	0.250[b]	0.377[a]	0.082	0.135	0.141	0.134	0.459[a]
ECW/h	0.439[a]	0.332[a]	0.223[b]	−0.079	0.017	0.287[a]	0.448[a]
DLM/h	−0.172	0.137	−0.099	0.271[a]	0.349[a]	−0.029	0.093
PA°	−0.165	0.093	−0.221[b]	0.440[a]	0.239[b]	−0.330[a]	−0.245[b]

h, height; CRP, C-reactive protein; CA-IMT, carotid artery intima-media thickness; LAD, left atrium diameter; CTI, cardiothoracic index; SBP, systolic blood pressure; DLM, dry lean mass; ECW, extracellular water; ICW, intracellular water; TBW, total body water; PA, phase angle at 50 kHz.
[a]Correlation is significant at the 0.01 level (two-tailed).
[b]Correlation is significant at the 0.05 level (two-tailed).

We compared the body composition determined by m-BIA of patients with that of 47 healthy controls matched for age and sex showed in Table 2. The PD patients had significantly lower ICW, ECW, TBW, ECW/height values and higher ECW/TBW ratio than healthy controls.

Markers of nutrition, inflammation, volume and atherosclerosis were significantly correlated with m-BIA parameters (Table 3). Serum albumin level was positively correlated with serum levels of creatinine, cholesterol and phosphorus and ultrafiltration volume and negatively correlated with serum CRP level. Serum CRP level was positively correlated with age, CTI, LAD, LVESD, LVEDD and CA-IMT. CA-IMT was positively correlated with age, SBP, LAD, LVEDD and LVM. Furthermore, we performed stepwise linear regression analysis to examine which of m-BIA parameters were independent predictors of volume, nutrition, inflammation and atherosclerosis. For albumin, significant predictors were PA (t: 3.13; P = 0.002), ECW/TBW (t: −2.91; P: 0.005), Ca × P product (t: 5.35; P < 0.001) and CRP (t: −2.37; P: 0.020). For CA-IMT, significant predictors were age (t: 7.89; P: 0.000) and female gender (t: −4.43; P < 0.001). For CRP, significant predictors were PA (t: −4.17; P < 0.001) and diabetes mellitus (t: 3.46; P: 0.001). For LAD, significant predictors were ECW/height (t: 4.45; P < 0.001), Kt/V (t: −2.26; P: 0.026) and diabetes mellitus (t: 2.05; P: 0.043). All other tested variables were not significant and have been excluded (Table 4).

We identified a cut-off value for ECW/height by drawing ROC curves to discriminate patients with FO and those without, using LAD (>40 mm) or LVEDD (>55 mm) measured by echocardiography as confirmatory parameters. The area under the curve was 0.80 ± 0.04 for LAD and 0.78 ± 0.05 for LVEDD in the study group (P < 0.0001 and P < 0.01, respectively). An ECW/height cut-off value of 10.48 L/m resulted for LAD and LVEDD in 78 and 72% specificity, respectively, and with a sensitivity of 77 and 70%, respectively, for the diagnosis of FO, for the overall group (Figure 1). In males, an ECW/height cut-off value of 10.59 L/m for LAD and LVEDD resulted in 67 and 60% specificity, respectively, for the diagnosis of FO, with sensitivity of 75 and 83%, respectively. In females, cut-off value of 9.86 L/m for LAD and LVEDD resulted in 75 and 74% specificity, respectively, for the diagnosis of FO, with a sensitivity of 83 and 100%, respectively.

Diabetic patients had a significantly higher ECW/height than non-diabetics (10.6 versus 9.6 L/m, respectively, P < 0.05).

We then evaluated the new cut-off value for ECW/height by dividing non-diabetic patients into two groups: those

Table 4. Multivariate linear regression analysis (stepwise) for independent predictors of volume, nutrition, inflammation and atherosclerosis markers in PD patients

Variables	Model 1 (LAD)		Model 2 (Albumin)		Model 3 (CRP)		Model 4 (CA-IMT)	
	t	P	t	P	t	P	t	P
Age	1.55	0.124	0.48	0.632	−0.52	0.599	7.89	<0.01
Female gender	1.29	0.197	0.78	0.433	−0.16	0.874	−4.43	<0.01
Diabetes mellitus	2.05	<0.05	−0.77	0.441	3.46	<0.01	−0.22	0.820
CRP	1.27	0.205	−2.37	<0.05			1.24	0.219
Weekly total kT/V	−2.26	<0.05	−0.62	0.532	−0.89	0.376	0.19	0.848
Ca × P product	0.163	0.871	5.35	<0.01	0.81	0.417	−1.84	0.069
ECW/height (L/m)	4.45	<0.01	−1.80	0.075	0.36	0.716	1.09	0.277
ECW/TBW	0.94	0.346	−2.91	<0.01	−0.24	0.807	−0.009	0.993
PA (°)	−0.29	0.768	3.13	<0.01	−4.17	<0.01	−0.82	0.411

Included variables: age, gender, diabetes mellitus, BMI, duration of PD, systolic blood pressure, cholesterol, triglyceride, ceratinine, Ca × P product, albumin, C-reactive protein (CRP), weekly total kT/V, weekly total CCr, PA, ECW/ICW, ECW/height, ECW/TBW, ICW/height, TBW/height and DLM/height.
LAD, left atrium diameter; CRP, C-reactive protein; CA-IMT, carotid artery intima-media thickness; ECW, extracellular water; ICW, intracellular water; TBW, total body water; PA, phase angle at 50 kHz; DLM, dry lean mass; BMI, body mass index; PD, peritoneal dialysis.

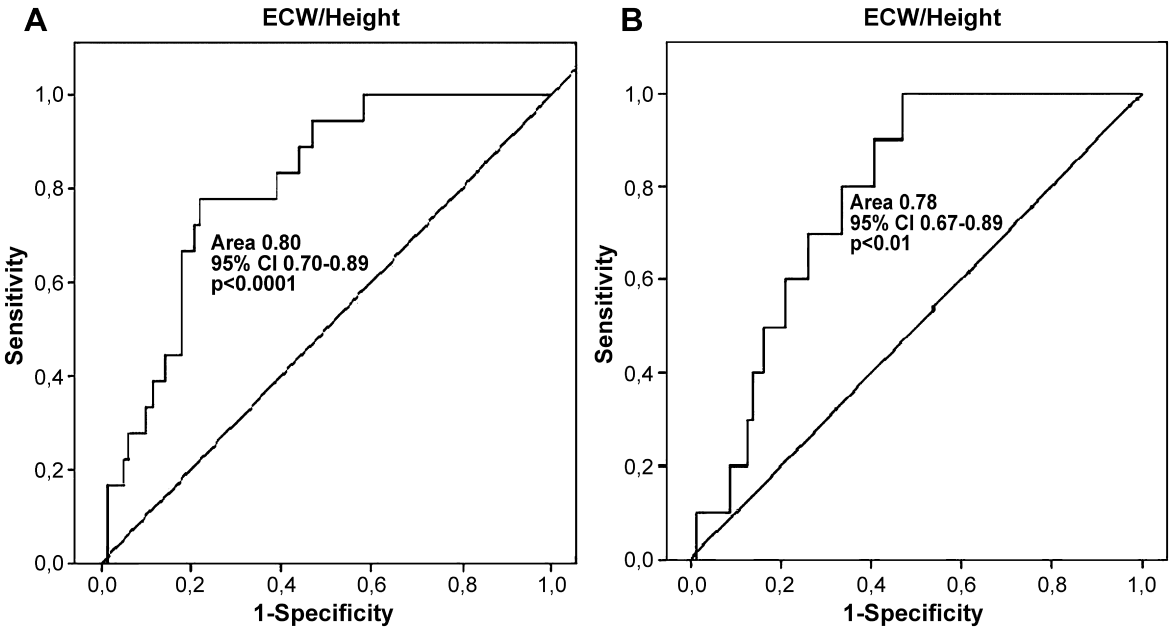

Fig. 1. Receiver operating characteristic (ROC) curves for ECW/height cut-off value of 10.48 L/m in predicting fluid overload using left atrium diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) measured by echocardiography as confirmatory parameters for the overall group. (**A**) LAD >40 mm; (**B**) LVEDD >55 mm. 276 × 138 mm (600 × 600 DPI).

with ECW/height values which were above the cut-off values (fluid overloaded, $n = 31$) and those with ECW/height values which were below the cut-off values (normal fluid volume, $n = 54$). Gender-specific cut-offs used for identification of fluid status (ECW/height) were 10.59 L/m for males and 9.86 L/m for females. When comparing these groups (Table 5), patients with FO were older and had higher SBP, CTI, serum CRP levels, mean CA-IMT value and higher total sodium removal than those without FO. Patients with FO also had significantly lower fractional fibre shortening by echocardiography than those without.

Serum CRP was above the upper limit of normal (0.5 mg/dL) in 40 (42%) of the 95 patients. CA-IMT was measured in 82 patients. When divided into two groups according to

Table 5. Comparison of patients with fluid overload and those without according to bioimpedance analysis

	Patients with FO ($n = 31$)	Patients without FO ($n = 54$)	P
Age (years)	55 ± 10	46 ± 14	P < 0.01
Duration of PD (months)	45 ± 27	37 ± 35	ns
SBP (mm Hg)	128 ± 22	116 ± 27	P < 0.05
CTI (%)	46 ± 4	43 ± 4	P < 0.01
Serum albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.5	ns
Serum CRP (mg/dL)	1.1 ± 1.4	0.5 ± 0.7	P < 0.05
Weekly total Kt/V_{urea}	2.34 ± 0.65	2.44 ± 0.62	ns
Weekly total CCr (L/1.73 m^2)	71 ± 28	74 ± 38	ns
Urine volume (mL/day)	650 ± 898	550 ± 721	ns
Peritoneal ultrafiltration (mL/day)	1247 ± 502	1140 ± 734	ns
Urine sodium removal (mmol/day)	49 ± 75	29 ± 47	ns
Peritoneal sodium removal (mmol/day)	162 ± 76	125 ± 87	P = 0.05
Total sodium removal (mmol/day)	211 ± 134	154 ± 81	P < 0.05
PA (°)	5.5 ± 1.3	6.0 ± 1.0	P = 0.05
ECW/height (L/m)	10.9 ± 0.6	9.3 ± 0.6	P < 0.01
LAD (mm)	37 ± 5	31 ± 6	P < 0.01
LAD/h (mm/m)	23 ± 3	19 ± 4	P < 0.01
LVEDD (mm)	50 ± 6	44 ± 4	P < 0.01
LVMI (g/m^2)	116 ± 25	103 ± 38	ns
EF (%)	60 ± 12	65 ± 13	ns
Fractional shortening (%)	27 ± 7	31 ± 8	P = 0.05
Mean CA-IMT (mm)	0.70 ± 0.18	0.59 ± 0.17	P < 0.05

PD, peritoneal dialysis; CTI, cardiothoracic index; SBP, systolic blood pressure; CRP, C-reactive protein; CCr, creatinine clearance; PA, phase angle at 50 kHz; ECW, extracellular water; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; EF, ejection fraction; CA-IMT, carotid artery intima-media thickness; ns, non-significant.

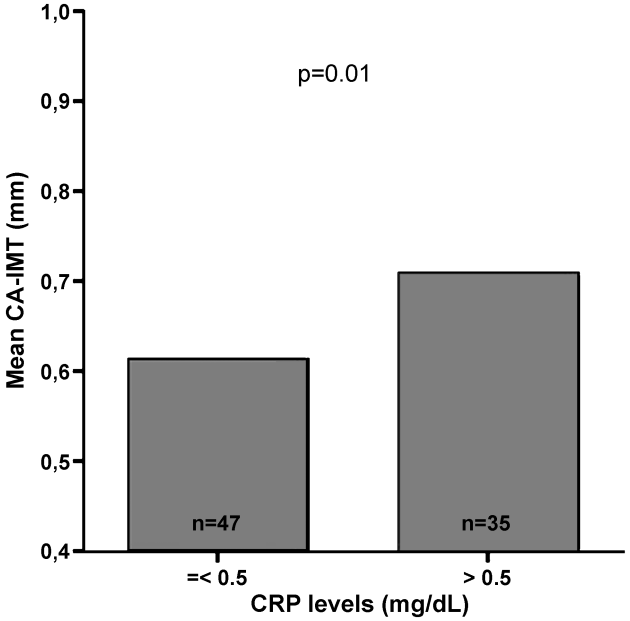

Fig. 2. Carotid artery intima-media thickness (CA-IMT) values in patients with and without elevated CRP. 158 × 115 mm (600 × 600 DPI).

the serum CRP level (≤0.5 mg/dL and >0.5 mg/dL), patients with inflammation (CRP >0.5 mg/dL) had significantly higher CA-IMT values (Figure 2).

In logistic regression analysis (using a model including age, PD duration, diabetes, gender, SBP and DBP, serum albumin, weekly total Kt/V, weekly total CCr, total sodium removal, urine volume and ECW/height, ICW), only urine volume (OR = 0.40, 95% CI: 0.20–0.81, P = 0.011) and ECW/height (OR = 2.30, 95% CI: 1.39–3.79, P = 0.001) were associated with the presence of inflammation (CRP > 0.5 mg/dL).

We also evaluated fluid status of patients with respect to residual renal function and peritoneal transport status. Among the 36 patients with anuria, 11 were on APD. Anuric patients (n = 36) had lower SBP, serum albumin level, weekly total Kt/V, weekly total CCr, total sodium removal and higher serum CRP level and longer duration of PD than patients with residual renal function. Anuric patients also had lower PA and had higher ECW/TBW than patients with residual renal function (Table 6).

When we compared high transporters (high and high average) (n = 25) with low (low and low average) transporters (n = 70), high transporters had longer duration of PD, lower serum albumin, higher serum CRP level and lower total sodium removal than low transporters. Volume parameters obtained by m-BIA were not different between groups, but lower PA was found in high transporters (Table 7).

Discussion

FO is common in PD patients but assessment of hydration is not easy particularly if blood pressure is within normal limits. There is obviously a need for a practical method for routine clinical assessment of FO, and thus 'dry weight'. m-BIA technique offers an easily repeatable, economical and non-invasive method of body composition analysis [21–23]. The indices obtained from m-BIA are useful for both the evaluation of hydration status (ECW) and nutritional status (e.g. ICW and PA). In normal subjects, values of ECW found by this method match well with those obtained by isotope dilution methods, which are considered as a 'golden standard'. However, body composition of dialysis patients may differ from normal. Indeed, van de Kerkhof *et al.* reported that ECW/height in normovolaemic dialysis patients was 2.5 L lower than in normal controls. We also found lower values in our patients with normal left atrium diameters and left ventricular end-diastolic diameters (ECW/height 10.3 ± 0.9 for males and 9.4 ± 0.9 L/m for females).

The criteria for 'clinically normovolaemic' are somewhat arbitrary. Blood pressure may decrease in overhydrated patients with cardiac failure, while dilated heart will not immediately 'remodel' when the ECW is reduced.

Table 6. Comparison of anuric patients with those with residual renal function

	Anuric patients (n = 36)	Patients with RRF (n = 59)	P
Age (years)	48 ± 12	52 ± 13	ns
Duration of PD (months)	54 ± 37	28 ± 22	P < 0.01
SBP (mm Hg)	105 ± 21	127 ± 19	P < 0.01
DBP (mm Hg)	69 ± 12	81 ± 11	P < 0.01
Serum albumin (g/dL)	3.7 ± 0.5	3.9 ± 0.4	P < 0.05
Serum CRP (mg/dL)	1.5 ± 2.9	0.5 ± 0.8	P < 0.05
Weekly total Kt/V_{urea}	2.21 ± 0.44	2.51 ± 0.70	P < 0.05
Weekly total CCr (L/1.73 m^2)	54 ± 8	89 ± 42	P < 0.01
Peritoneal ultrafiltration (mL/day)	1210 ± 597	1121 ± 668	ns
Peritoneal sodium removal (mmol/day)	146 ± 76	127 ± 89	ns
Total sodium removal (mmol/day)	146 ± 76	186 ± 116	P < 0.05
PA (°)	5.3 ± 1.4	6.1 ± 0.9	P < 0.01
ECW/height (L/m)	9.8 ± 1.1	10.1 ± 0.9	ns
ECW/TBW	0.46 ± 0.02	0.44 ± 0.02	P < 0.01

PD, peritoneal dialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; CCr, creatinine clearance; PA, phase angle at 50 kHz; ECW, extracellular water; TBW, total body water; ns, non-significant.

Table 7. Comparison of high (high and high average) transporters with those with low (low and low average) transporters

	High transporters (n = 25)	Low transporters (n = 70)	P
Age (years)	49 ± 10	51 ± 14	ns
Duration of PD (months)	51 ± 34	34 ± 29	P < 0.05
SBP (mm Hg)	116 ± 23	119 ± 22	ns
DBP (mm Hg)	74 ± 12	77 ± 13	ns
Serum albumin (g/dL)	3.7 ± 0.4	3.9 ± 0.4	P < 0.05
Serum CRP (mg/dL)	1.6 ± 3.2	0.7 ± 1.1	P < 0.05
Weekly total Kt/V_{urea}	2.33 ± 0.61	2.42 ± 0.63	ns
Weekly total CCr (L/1.73 m^2)	66 ± 45	78 ± 33	ns
Peritoneal ultrafiltration (mL/day)	978 ± 492	1218 ± 679	ns
Urine sodium removal (mmol/day)	10 ± 20	48 ± 65	P < 0.01
Peritoneal sodium removal (mmol/day)	102 ± 80	143 ± 83	P < 0.05
Total sodium removal (mmol/day)	112 ± 86	191 ± 103	P < 0.01
PA (°)	5.3 ± 1.2	6.0 ± 1.1	P < 0.05
ECW/height (L/m)	10.1 ± 0.9	9.9 ± 1.0	ns
ECW/TBW	0.45 ± 0.01	0.45 ± 0.02	ns

PD, peritoneal dialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; CCr, creatinine clearance; PA, phase angle at 50 kHz; ECW, extracellular water; TBW, total body water; ns, non-significant.

However, when both blood pressure and cardiac dimensions are within normal limits, a normal ECW may be assumed, while hypertension and/or dilated cardiac cavities do not rule out the existence of a normal volume. On the other hand, dilated cardiac cavities may not only be caused by overhydration but can also reflect cardiac damage. This concerns particularly LAD, since diastolic dysfunction (stiffness of the left ventricle) may hamper atrial emptying during diastole. However, there was little difference in the relations of LAD and LVEDD and volume assessed by m-BIA. With these restrictions in mind, we established normal ECW values for m-BIA and compared the patients who fell within this normal range with those elevated values in Table 5.

In our study, ECW/height of clinically normal patients was 10.59 in males and 9.86 in females, values matching well with those given by van de Kerkhof *et al.* (10.96 and 9.13, respectively) [13] who used LVEDD as reference technique. These authors investigated a mixed group of HD and PD patients, only 12 of whom were considered normovolaemic. The mean LVEDD of these patients was 47.4 ± 6.6 mm, while we found a value of 44 ± 4 mm in our patients without FO. This suggests that volume control in our patients was slightly better.

The results show that in PD patients, FO established by m-BIA is well correlated with markers of nutrition (serum albumin), inflammation (serum CRP) and atherosclerosis (CA-IMT) confirming results of previous studies [24–29].

We found significant correlations between ECW/height and LAD, LVEDD and LVMI. ECW/TBW ratio has been used as an index of hydration [30]. An elevated ECW/TBW ratio may, however, occur in malnutrition as well as in overhydration [31]. In our study, we found that patients with higher ECW/TBW also had significantly lower serum albumin levels.

The importance of fluid management in PD patients is attracting more attention in recent years. In one study, there is an association between hypervolaemia and inflammation in PD patients [5]. The same group found that the ratio of ECW/TBW was greater in inflamed compared with non-inflamed male patients. In multivariate analyses, only the ratio of ECW/TBW was significantly (P = 0.04) and independently associated with the presence of an elevated CRP [9]. We also found a relationship between CRP (inflammation) and ECW/height. Using multivariate analysis, only low urine output and ECW/height were independently associated with the presence of inflammation (P = 0.01 and P = 0.001, respectively).

Many studies have confirmed a close association between cardiovascular disease (CVD) and inflammation in dialysis patients. Wu *et al.* found a strong linkage between inflammation (CRP ≥8 mg/L) and CVD in their PD population [32]. Similarly, Stenvinkel *et al.* found strong relationships between malnutrition, elevated CRP levels and the prevalence of CVD in patients starting PD [33].

We also found a clear relation between inflammation and atherosclerosis measured by CA-IMT as well as between CA-IMT and volume parameters obtained by clinical examination (e.g. SBP), echocardiography (LAD, LVEDD, LVM) and m-BIA (ECW/height).

Residual renal function plays an important role in maintaining fluid balance by fluid and sodium removal in PD patients [34]. Chung *et al.* reported that the decline in residual renal function was correlated with an increase in peritoneal transport status. They suggested that the peritoneal transport rate during a patients' first year on PD may be linked with inflammation and declining residual renal function [35]. We found that anuric patients and patients with high membrane transport had significantly higher serum CRP levels. In this regard, loss of residual renal function may initiate the inflammatory state via reduced renal clearance of inflammatory markers.

Our patients with anuria had lower SBP and lower total sodium removal. This is similar to the findings of the study by Cheng *et al.* who reported that patients with residual renal function had higher blood pressure and higher sodium

and fluid removal. These findings are a little surprising since residual renal function tends to preserve fluid balance. Cheng *et al.* suggested that the higher blood pressure in patients with urine output >400 mL might be due to the higher salt intake. In our PD patients, salt and fluid restriction was apparently more effective in anuric patients than patients with residual renal function. This implies that patients with residual renal function had relaxed for compliance in salt and fluid restriction. Despite instructions, our patients' compliance with salt restriction apparently was not sufficient, although better than in some other series [36,37].

In PD patients, the normal value for the ECW/height appears to be lower than in normal healthy subjects. In malnutrition, which is often seen in PD patients, the dry lean mass is also negatively affected. Since muscle and fat masses of our PD patients were low, their extracellular fluids could be lower. Indeed, van de Kerkhof *et al.* also reported that the dialysis patients who were considered as normovolaemic had lower ECW/height ratios compared to healthy population.

In our study, we used height instead of weight as denominator for ECW because of its significant relationship with echocardiographic and clinical volume parameters (such as LAD, LVEDD, systolic and diastolic blood pressure and cardiothoracic index). The ECW/height ratio was not related to age in our healthy control subjects. In contrast to height, weight cannot be used as a reference for hydration because body composition varies greatly between individuals. Most water is located in fat-free mass while adipose tissue contains little water. In this regard, a new technique developed by Chamney may have advantages. In this model, excess fluid can be identified by using three whole-body measurements: weight, ECW and ICW [38]. Accordingly, the sum of normally hydrated lean tissue and normally hydrated adipose tissue provides a hydration reference against which excess fluid can be identified. Therefore, one of the limitations of our study may be that the use of height as denominator could underestimate the relative contribution of ECW to body weight in patients with a significant decline in body cell mass (such as malnutrition). Unlike the Chamney model, we used the ECW to measure FO in our patients and we did not take into account the effects of differences in body fat. Adipose tissue has much lower water content but a higher ratio of ECW to ICW than lean tissue. Despite these shortcomings, ECW/height cut-off values detected in our study correlated well with LAD, one of the most sensitive markers of the volume status. Thus, ECW/h values may be useful for management of fluid status of PD patients in routine clinical practice [39].

Conclusion

We found a close relationship between ECW/height measured by m-BIA and markers of poor nutrition, inflammation, atherosclerosis and FO in PD patients. Patients who were not overhydrated as judged by echocardiography had lower than normal ECW/height values. The indices obtained from m-BIA, especially ECW/height, seem to be useful in the management of PD patients and deserve further testing in properly designed clinical validation study.

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