

Original Article

Comparison of body fluid distribution between chronic haemodialysis and peritoneal dialysis patients as assessed by biophysical and biochemical methods

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Abstract

Background. The control of extracellular volume is a key parameter for reducing hypertension and the incidence of cardiovascular mortality in dialysis patients. In recent years bioimpedance measurement (BIA) has been proven as a non-invasive and accurate method for measuring intracellular and extracellular fluid spaces in man. In addition, plasma atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) concentrations have been shown to reflect central venous filling. Using these methods, we compared body fluid status between stable patients on haemodialysis and peritoneal dialysis.

Methods. Thirty-nine chronic haemodialysis patients, 43 chronic peritoneal dialysis patients and 22 healthy controls were included in the study. Multifrequency BIA was performed using the Xitron BIS4000B device (frequencies from 5 to 500 kHz were scanned and fitted) in patients before and after haemodialysis. Peritoneal dialysis patients were measured after drainage of the dialysate. Plasma ANP and cGMP levels were measured in plasma using a ¹²⁵I solid phase RIA. Serum albumin concentrations and serum osmolality were measured in all patients. The body fluid data were analysed in relation with the clinical findings.

Results. Total body water (TBW) was 0.471 ± 0.066 l/kg before haemodialysis and 0.466 ± 0.054 l/kg after haemodialysis. Peritoneal dialysis patients had a TBW (0.498 ± 0.063 l/kg) that was greater than the before and after dialysis values of haemodialysis patients. The extracellular body fluid (V_{ecf}) was increased pre-haemodialysis. It was even greater in peritoneal dialysis patients compared with patients both pre- and post-haemodialysis (pre $0.276 \pm$

0.037 l/kg; post 0.254 ± 0.034 l/kg; peritoneal dialysis 0.293 ± 0.042 l/kg, $P < 0.05$). However, plasma ANP concentrations (representing intravascular filling) in peritoneal dialysis patients were comparable with post-haemodialysis values (284 ± 191 pg/ml vs 286 ± 144 pg/ml). The correlation coefficient between sysRR and V_{ecf} was $r = 0.257$ in haemodialysis ($P = 0.057$) and $r = 0.258$ in peritoneal dialysis ($P < 0.05$). A significant negative correlation was found between serum albumin and V_{ecf}/TBW in peritoneal dialysis patients ($r = -0.624$).

Conclusion. Body fluid analysis by BIA demonstrated that TBW and V_{ecf} were increased in peritoneal dialysis patients, and were comparable or even greater than values found before haemodialysis. However, plasma ANP levels indicated that intravascular filling was not increased in peritoneal dialysis. The ratio of V_{ecf} to TBW was correlated to systolic pressure and negatively to serum albumin in peritoneal dialysis patients.

Keywords: ANP; bioimpedance analysis; body fluid; body water; cGMP; extracellular water; haemodialysis; hypertension; intravascular filling; peritoneal dialysis; serum albumin; total body water

Introduction

Overhydration is significantly linked to hypertension and the development of cardiovascular disease in dialysis patients [1,2]. However, the clinical assessment of correct 'dry weight' is difficult to perform and standard methods such as e.g. X-ray are insensitive and cannot be repeated frequently. A sensitive bedside method that allows repeated measurements of intracellular and extracellular fluid volumes may help to detect overhydration and to define an optimum dry weight in dialysis patients.

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The measurement of total body water (TBW) using an isotopic dilution method (for example using deuterium or ^{18}O -labelled water) represents the gold standard [3], but is not practical in clinical routine. Deuterium requires an equilibration time of at least 3 h and necessitates subtle laboratory analysis. Multi-frequency bioimpedance analysis (BIA) measurement has been shown to be a simple, safe, and inexpensive method to measure the different water compartments of the human body [4]. The method is based upon a model describing the human body as a circuit consisting of capacitors and resistors lying in an electric field [5]. BIA, when compared with standard isotopic dilution methods, has been shown to be a precise and reproducible technique for determining TBW and extracellular body fluid (V_{ecf}) [5].

The aim of this study was to investigate and compare total body water and the extracellular fluid compartment, including intravascular filling, in patients treated with haemodialysis and peritoneal dialysis. As BIA cannot differentiate between interstitial and intravascular fluid within the extracellular space, we additionally measured atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP), which have been shown to be sensitive markers of changes in body fluid status in end-stage renal disease patients [6]. The release of ANP depends on right atrial wall tension and it is significantly correlated with central venous filling or central venous pressure [7]. cGMP is the second messenger of ANP and has also been used as a marker of venous filling [8].

A recent study with haemodialysis patients in Tassin (France) assessing fluid status by BIA supported the hypothesis that improved control of fluid volume (V_{ecf}) was responsible for the low incidence of hypertension and was probably linked to the outstanding high survival rate of the Tassin patients [9]. Previous studies using biopsies or tracer dilution techniques (muscle biopsies, ^{18}O -labelled water) to measure body fluid in dialysis patients showed that subjects receiving peritoneal dialysis were often chronically fluid overloaded [10]. However, there is a lack of data comparing body fluid between peritoneal dialysis patients and haemodialysis patients.

Hypoalbuminaemia and a 'high' transport capacity of small solutes in the so-called 'peritoneal equilibration test' (PET) have been correlated with patient survival in peritoneal dialysis [11]. Because hypoalbuminaemia may be linked to body fluid status, we also examined the relationship between serum albumin concentration and body fluid distribution in haemodialysis and peritoneal dialysis patients.

Subjects and methods

Patients

Thirty-nine stable haemodialysis patients (HD patients/group) were recruited from three dialysis centres. Measurements of urea distribution volume were performed in a subgroup of 18 patients using the GeniusTM dialysis system. Forty-three stable peritoneal dialysis patients (PD patients/group) were also recruited. Twenty-two healthy individuals (15 men and seven women) served as controls. Patients in the HD and the PD groups were matched for weight, height, gender and residual diuresis (Table 1). The mean ultrafiltration rate was 2075 ± 1114 ml/dialysis session in haemodialysis and 881 ± 661 ml/day in peritoneal dialysis (difference n.s. per week).

Cardiac disease was assessed regularly by X-ray, electrocardiogram, and echocardiography. Coronary angiography was performed in patients with overt signs of ischaemia. An increased cardiothoracic ratio (CTR >0.5), atrial and/or ventricular dilatation, hypertrophy, ventricular dysfunction, and signs of ischaemia were classified as indicators of cardiac disease. Subgroups with and without heart failure were defined in both the HD and PD groups. However, the prevalence or severity of cardiac disease did not differ between the groups. Residual diuresis was not significantly different between the PD and HD groups (HD 0.63 ± 0.68 l/day, PD 0.93 ± 0.82 l/day). Serum creatinine in the HD group was 8.5 ± 2.2 mg/dl (mean value between pre- and post-dialysis measurements) and 10.8 ± 3.6 mg/dl in the PD group ($P < 0.05$). The corresponding serum urea-N concentration was 68.1 ± 25.2 mg/dl in the HD group and 56.7 ± 15.8 mg/dl in the PD group ($P < 0.05$).

To examine relationships between measured hydration data and clinical indicators of hydration, we performed further analysis on the PD group because they had a stable

Table 1. Anthropometric data and clinical findings of the patients investigated

Characteristics	Group 1 healthy subjects		Group 2 HD patients		Group 3 PD patients	
	Men <i>n</i> = 15	Women <i>n</i> = 7	Men <i>n</i> = 28	Women <i>n</i> = 11	Men <i>n</i> = 30	Women <i>n</i> = 13
Age (year)	36.4 ± 14.8	36.9 ± 16.5	61.4 ± 14.2	66.3 ± 13.0	49.0 ± 9.9*	43.0 ± 10.9*
Weight (kg)	77.8 ± 11.1	57.4 ± 6.7	75.3 ± 14.8	60.5 ± 10.6	76.9 ± 11.8	72.0 ± 18.3
Height (cm)	178.4 ± 8.0	163.6 ± 7.3	172.5 ± 7.6	164.5 ± 7.9	178.6 ± 8.5	166.2 ± 7.4
Body mass index (kg/m ²)	24.4 ± 3.4	21.4 ± 2.2	25.3 ± 4.4	22.4 ± 4.2	24.1 ± 3.4	25.9 ± 5.8
Time on dialys. (months)			36.3 ± 22.0	34.5 ± 30.4	29.7 ± 26.6	23.8 ± 19.2
Serum creatinine (mg/dl)			9.1 ± 2.1	7.5 ± 2.1	11.1 ± 3.3	9.9 ± 4.0
Serum BUN (mg/dl)			71.0 ± 24.5	63.2 ± 27.5	58.8 ± 15.3	52.0 ± 16.4
Cardiac disease (<i>n</i> , %)			18 (64%)	4 (36%)	18 (60%)	2 (15%)

Significant differences between groups 2 and 3 are indicated by asterisk ($P < 0.05$). * $P < 0.001$ haemodialysis vs peritoneal dialysis.

hydration status. These patients were subdivided into groups according to their fluid measurement data according to the limits of the Gaussian distribution: (i) below mean−1 SD 'low hydration'; (ii) between mean−1 SD to mean+1 SD 'average hydration'; and (iii) above mean+1 SD 'high hydration'. These groups were then assessed for differences in oedema, blood pressure, residual diuresis, and the use of antihypertensives.

Body surface area of the patients was calculated according to the Boyd formula.

Instruments

Bioelectrical spectroscopy was carried out using the BIS4000B analyser (Xitron Technologies, San Diego, CA, USA). Four skin electrodes (Xitron) were placed on the dorsal surfaces of the left hand and foot. Measurements were made after the subjects had been supine for at least 20 min. Fifty frequencies were measured ranging from 5 to 500 kHz. Data were collected and analysed with software supplied by Xitron Technologies. The Cole–Cole model and the Hanai equation were used for computation [12]:

$$Z_{\text{obs}} = \left(\frac{R_E}{R_E + R_I} \right) \left(R_I + \frac{R_E}{1 + (j\omega C_M (R_E + R_I))^\alpha} \right) (e^{-j\omega T_D})$$

Z_{obs} is the observed complex impedance, R_E , R_I , and C_M are the component values of the circuit, ω is frequency in radians/sec ($= 2\pi \times \text{frequency}$).

TBW was calculated as:

$$\text{TBW} = V_{\text{ecf}} + V_{\text{icf}}$$

Only measurements with a fit(r)>0.9965 were used (based on the data delivered at different frequencies). Repeated measurement coefficient of variation (same patient, same set up) was 0.234% for V_{ecf} and 0.814% for TBW ($n = 20$). Day to day coefficient of variation was additionally determined by measuring the same patient on two subsequent dialysis sessions at the same dry weight. Coefficient of variation (including the inaccuracy of weight measurement and potential fluid shifts) was 3.0% for V_{ecf} and 3.1% for TBW ($n = 24$). The Spearman correlation coefficient between weight loss on HD and the change of V_{ecf} was $r = 0.72$.

The urea distribution volume of one HD group is a well-established parameter for measuring TBW. In a closed dialysate tank system (e.g. Genius[™] dialysis system), it can easily be derived from the following equation:

$$V_{\text{urea}} = (V_{\text{Tank}} \times \text{Urea}_{\text{Tank}} + \text{UF} \times \text{Urea}_{\text{UF}} - \text{UF} \times \text{Urea}_{\text{pre}}) / (\text{Urea}_{\text{pre}} - \text{Urea}_{\text{post}})$$

V_{urea} is the urea distribution volume, V_{Tank} is the tank volume, UF is the ultrafiltration volume, $\text{Urea}_{\text{pre/post}}$ is the serum urea concentration before and after dialysis, Urea_{UF} is the urea concentration in the ultrafiltrate.

This technique was used to confirm the accuracy of BIA measurement. The Bland–Altman analysis was used to compare the two methods. The coefficient of correlation showing the differences between methods (urea distribution volume measured in the dialysate tank system and TBW measured by BIA) and the mean of all methods was 0.081 with a bias of −1.5 l and a 95% confidence interval of −3.50 to 0.50 l, indicating that the values of BIA fell near the identity line.

Blood samples for ANP measurement were collected from the arterial line in HD group before and 15 min after haemodialysis. Plasma was separated in chilled EDTA tubes. ANP was extracted from plasma using Sep-pak-C18 columns and quantified with a ¹²⁵I solid phase RIA (Laboserv GmbH, Giessen, Germany). cGMP levels were measured after acetylation with ¹²⁵I RIA using a second antibody coupled to magnetic beads (lower detection limit 0.5 pmol/ml, Amersham Buchler, Braunschweig, Germany).

Serum albumin was measured by the BCT methods (Brominecresol purple) on a Beckmann autoanalyzer. Osmolality was measured by freezing point depression (Knauer GmbH, Bad Homburg, Germany).

Peritoneal transport characteristics of the PD group were classified according to a 4 h standard PET test.

Statistics

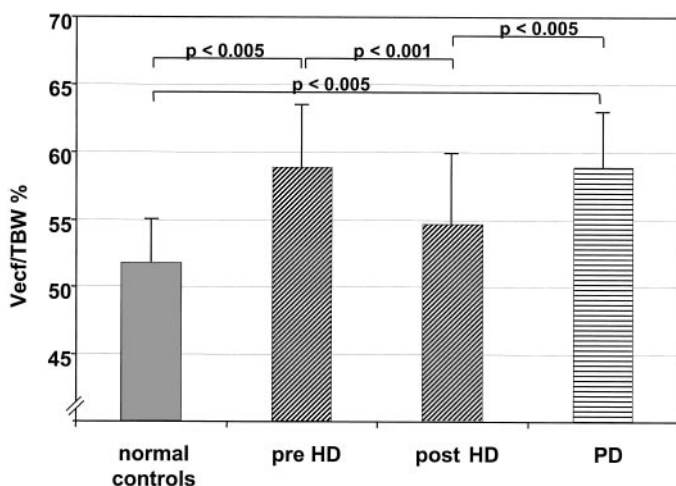
Results are expressed as means ± SD. Statistical analysis was performed using *t*-tests for unpaired or paired samples. An alpha error <0.05 was considered significant. Linear regression analysis was performed according to Spearman. A normal distribution of V_{ecf} and TBW in dialysis patients was confirmed by the Anderson–Darling normality test. Differences between more than two (sub)groups were analysed using ANOVA and post hoc Scheffé test (SPSS, v. 9.01, SPSS Inc., Chicago, IL, USA).

Results

TBW and V_{ecf} in HD and PD groups

In HD patients, TBW per kg body weight before dialysis was 0.471 ± 0.066 l/kg. After dialysis TBW dropped to 0.466 ± 0.054 l/kg (both n.s. vs normal controls 0.481 ± 0.037 l/kg). In PD patients, TBW was 0.498 ± 0.063 l/kg, and was greater than in normal controls and HD patients both before and after haemodialysis ($P < 0.05$). In HD patients, the V_{ecf} weight was 0.276 ± 0.037 l/kg before dialysis ($P < 0.05$ vs controls 0.261 ± 0.021 l/kg). After haemodialysis V_{ecf} dropped to 0.254 ± 0.034 l/kg ($P < 0.01$ vs pre HD). This value was slightly lower than in healthy controls (0.261 ± 0.021 l/kg, n.s.). PD patients had greater V_{ecf} (0.293 ± 0.042 l/kg) than normal and HD patients both before and after haemodialysis ($P < 0.05$). The differences in body fluid between HD and PD patients remained significant when body fluid was related to body surface area (TBW and V_{ecf} pre-HD vs PD, $P < 0.05$; post-HD vs PD, $P < 0.01$).

The ratio of V_{ecf} /TBW was calculated to determine the relative degree of extracellular fluid expansion. This value was increased in the PD group ($58.9 \pm 4.8\%$) compared with healthy controls ($52.2 \pm 3.0\%$, $P < 0.005$) (Figure 1). This ratio in PD patients corresponded with the findings in HD patients before dialysis ($58.7 \pm 5.2\%$). Ultrafiltration in HD patients reduced the ratio of V_{ecf} /TBW to $54.7 \pm 5.3\%$ ($P < 0.001$), which was significantly lower than in PD patients ($P < 0.005$). But also in HD the post-haemodialysis V_{ecf} /TBW fluid ratio, remained slightly elevated compared with normal controls ($P < 0.05$).



R_{ecf} [Ω]	669 ± 95	599 ± 90* [§]	693 ± 104 [#]	548 ± 104 [§]
R_{icf} [Ω]	1261 ± 278	1524 ± 388 [§]	1453 ± 330	1372 ± 347
R_{inf} [Ω]	459 ± 70	426 ± 66	466 ± 58 [#]	387 ± 66 [§]

Level of significance $p < 0.05$ or better: [§] HD or PD vs. Controls, * pre HD vs. post HD, [#] post HD vs. PD

Fig. 1. Ratio of V_{ecf}/TBW in HD patients (measured pre- and post-dialysis), in PD patients, and in healthy subjects. Measurements were performed after 20 min in the supine position using multifrequency bioimpedance. Raw data from BIA measurement are indicated in the table below: R_{ecf} = resistance at zero frequency reflecting extracellular fluid, R_{icf} = resistance of intracellular fluid reflecting intracellular water, R_{inf} = resistance at infinite frequency corresponding to TBW.

Parameters of intravascular filling

Plasma ANP concentration. Healthy volunteers had a mean supine plasma ANP concentration of 62 ± 30 pg/ml that ranged from 28 to 139 pg/ml (Figure 2). In the dialysis patients, the lowest plasma ANP levels were measured after the haemodialysis session (286 ± 144 pg/ml). Before haemodialysis, ANP concentrations were markedly higher (536 ± 324 pg/ml, $P < 0.005$). Plasma ANP levels were clearly decreased by ultrafiltration but remained unchanged in patients with isovolaemic haemodialysis. In the subgroup of HD patients showing signs of heart failure, higher plasma ANP levels were found (pre-HD 623 ± 354 pg/ml; post-HD 218 ± 72 pg/ml) compared with HD patients without heart failure (pre-HD 421 ± 245 pg/ml; post-HD 384 ± 168 pg/ml, n.s.). The mean plasma ANP concentration in the PD group was 284 ± 191 pg/ml, and it fell to a level near that of HD patients after dialysis. The subgroups of PD patients with and without signs of heart failure were comparable with the HD patient subgroups after dialysis. There was a significant correlation between plasma ANP levels and the ratio of V_{ecf}/TBW both in HD and PD patients ($r = 0.372$, $P < 0.005$ and $r = 0.469$, $P < 0.001$).

Plasma cGMP concentration. Healthy controls had a mean plasma cGMP level of 4.8 ± 2.3 pmol/l. As with ANP, the highest cGMP plasma levels were found before haemodialysis (HD group 29.6 ± 12.8 pmol/l). After haemodialysis, cGMP dropped to 12.4 ± 4.0 pmol/l ($P < 0.001$). In PD patients, cGMP levels

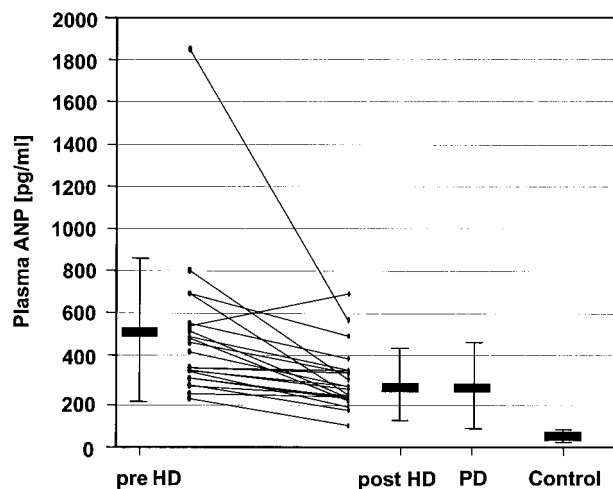


Fig. 2. Plasma ANP concentrations in patients pre- and post-haemodialysis compared with patients on peritoneal dialysis and healthy controls. Means \pm SD are indicated and the individual course of pre- and post-dialysis plasma ANP during haemodialysis is shown.

were intermediate to the values found before and after haemodialysis (24.9 ± 7.8 pmol/l). However, post-haemodialysis cGMP levels underestimated the true volume status because cGMP itself (a small molecule) was partly removed by dialysis. In contrast to ANP, cGMP markedly decreased in patients with isovolaemic HD. As found for ANP, there was a significant correlation between cGMP levels and V_{ecf}/TBW ratio ($r = 0.565$, all patients).

TBW and V_{ecf} related to clinical signs of overhydration

Pre-dialysis mean arterial blood pressure (MAP) was 105.5 ± 14.9 mmHg in PD patients and 100.5 ± 11.1 mmHg in HD patients (n.s.), systolic pressure was 146.2 ± 22.0 mmHg in PD and 143.5 ± 18.1 mmHg in HD patients, and diastolic pressure was 85.1 ± 14.0 and 79.0 ± 10.4 mmHg ($P < 0.05$) respectively. The rank correlation coefficient between systolic pressure and V_{ecf} was significant in PD patients ($r = 0.258$, $P < 0.05$) and was $r = 0.257$ ($P = 0.057$) in HD patients. There were more classes of antihypertensive drugs prescribed for PD patients than for HD patients (1.9 ± 1.1 vs 1.1 ± 0.9 , $P < 0.005$). The ratio of $V_{\text{ecf}}/\text{TBW}$ was negatively correlated to the amount of residual diuresis in the PD group ($r = -0.323$, $P < 0.05$).

As described in the methods section, the PD group was subdivided into three groups according to body fluid compartment measurements (from a low to high extracellular hydration status). Arterial pressure, antihypertensive medication, and the incidence of clinical signs of overhydration (oedema *and/or* increased jugular vein filling *and/or* increased interstitial pulmonary fluid according to chest X-ray) were evaluated. Of these parameters, the ratio of $V_{\text{ecf}}/\text{TBW}$ revealed the most clinically significant findings (Table 2). Measurements of single body fluid compartments showed a higher degree of variation and less significance.

The incidence of clinical signs of overhydration was lower in subgroup 1 than in subgroup 3 ($P < 0.01$). Systolic pressure increased with extracellular volume expansion ($P < 0.05$). The number of classes of prescribed antihypertensive drugs was highest in subgroup 3, which also had the most elevated $V_{\text{ecf}}/\text{TBW}$ ratio (n.s.).

Relation between body fluid distribution, serum albumin concentration and peritoneal transport properties

Serum albumin concentration did not differ between the HD and PD groups (PD 3.8 ± 0.8 g/dl; pre-HD 3.7 ± 0.3 g/dl; post-HD 3.9 ± 0.4 g/dl).

A negative correlation between serum albumin levels and $V_{\text{ecf}}/\text{TBW}$ was found in PD patients ($r = -0.624$, $P < 0.001$) (Figure 3), but not in the HD group ($r = -0.099$). PD patients with serum albumin levels below 3.5 g/dl had significantly higher ratios of $V_{\text{ecf}}/\text{TBW}$ compared with patients having serum albumin above 3.5 g/dl (60.5 ± 4.2 vs $57.1 \pm 4.9\%$, $P < 0.05$). A negative correlation between serum albumin level and plasma ANP was also revealed ($r = -0.367$, $P < 0.05$).

Body fluid status was not related to the peritoneal transport characteristics measured by the PET test (dialysate/plasma ratio of creatinine). PD patients showing a high peritoneal transport rate (D/P ratio $> 75\%$) did not differ from patients with a low transport rate ($< 75\%$) concerning TBW, V_{ecf} , $V_{\text{ecf}}/\text{TBW}$, or plasma ANP. The groups also had similar serum albumin concentrations.

Serum osmolality was lower in PD patients compared with HD patients after dialysis (PD 265.1 ± 22.4 mosmol/kg; pre-HD 277.8 ± 25.8 mosmol/kg; post-HD 281.0 ± 14.2 mosmol/kg, $P < 0.05$). Serum osmolality was not correlated with TBW, V_{ecf} , or $V_{\text{ecf}}/\text{TBW}$ in either group.

Discussion

Tracer dilution studies using the D_2O dilution space have shown that multifrequency BIA accurately predicts TBW [4]. Measurements of V_{ecf} and TBW by BIA have also been validated in renal transplant patients, and correlations with tracer techniques as well as X-ray absorptiometry were excellent [3]. Multifrequency BIA has, therefore, been proposed as an appropriate method for estimating of dry weight in dialysis patients [9].

However, variation in results may occur because of a lack of standardization, the type of device used, the skin electrodes used, and the mathematical model applied for curve fitting and computation. An individual control or set-up for each centre is, therefore,

Table 2. PD patients were divided into three subgroups according to their extracellular fluid balance (ratio of $V_{\text{ecf}}/\text{TBW}$)

	Group 1 [$V_{\text{ecf}}/\text{TBW}$: $< X-1$ SD] $n = 9$	Group 2 [$V_{\text{ecf}}/\text{TBW}$: $> X-1$ SD, $< X+1$ SD] $n = 26$	Group 3 [$V_{\text{ecf}}/\text{TBW}$: $> X+1$ SD] $n = 8$	Level of significance
Clinical signs of overhydration (%)	11.1 ± 33.3	53.9 ± 50.8	87.5 ± 35.3	$P < 0.01$
Classes of antihypertensive drugs (number)	1.8 ± 1.0	1.8 ± 1.2	2.3 ± 1.2	n.s.
Mean arterial pressure (mmHg)	113 ± 15	114 ± 16	124 ± 16	n.s.
Systolic pressure (mmHg)	139 ± 19	148 ± 30	162 ± 21	$P < 0.05$
Residual diuresis (l)	1.15 ± 0.97	0.83 ± 0.72	0.53 ± 0.60	n.s.
Plasma ANP (pg/ml)	167 ± 45	307 ± 163	346 ± 293	$P < 0.05$

The data were related to clinical findings known to be dependent on hydration status. Clinical signs of overhydration were defined as: aedema *and/or* increased jugular vein filling *and/or* increased interstitial pulmonary fluid according to X-ray. Level of significance between groups was determined by ANOVA. Post Hoc Scheffé tests indicated significant differences between groups 1 and 3 (for signs of overhydration, systolic pressure, ANP) and between groups 2 and 3 (for signs of overhydration).

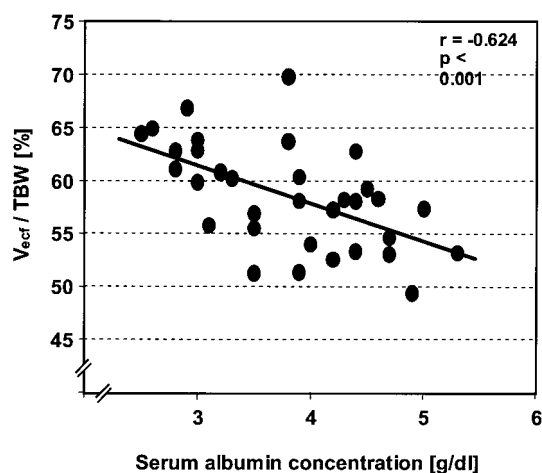


Fig. 3. Correlation between serum albumin concentration and the ratio of V_{ecf}/TBW in PD patients.

recommendable. To evaluate the accuracy of BIA, we compared TBW measured by BIA with the urea distribution volume calculated in HD patients from the dialysate and plasma urea concentration in a closed system (Genius[®] tank dialysis system). The Bland–Altman analysis showed that the bias was small with BIA values falling close to the identity line. A recent study called into question the accuracy of intradialytic volume changes assessed by BIA because of orthostatically (pre-HD) induced spurious volume changes during haemodialysis [13]. To minimize this effect we performed all measurements after the subjects had been supine for at least 20 min. Indeed, we found that the acute changes in TBW during ultrafiltration haemodialysis were more difficult to detect than shifts within the extracellular space. The correlation coefficient between weight loss on haemodialysis and the change in V_{ecf} was 0.72 (data not shown). In a recent study, Zhu *et al.* [14] demonstrated similar findings when comparing ΔTBW and ΔV_{ecf} with the actual ultrafiltration volume in dialysis patients. The extracellular fluid, which is mostly represented by an Ohm resistance is probably measured with higher accuracy by BIA than TBW measurement which is deduced from an Ohm and a capacitive resistance. An additional modified method, the so-called segmental BIA, found even higher correlations between ΔV_{ecf} and ultrafiltration volume than with whole body BIA [14]. The discrepancy in results between whole body BIA and segmental BIA has been attributed to the large difference in extracellular resistance in different segments of the body [14]. According to Zhu *et al.* [14], the limbs account for more than 90% of whole body resistance; however, they contribute to only 28% of total V_{ecf} . We used whole body BIA as it is the more common method, and because it is simple to use and less time consuming. Reliable comparisons of single body fluid compartments between individuals should be normalized for body weight, body surface area, or fat distribution. However, to avoid these calculations, it is possible to use the ratios of different compart-

ments. The ratio of V_{ecf}/TBW is a dimensionless value that sensitively reflects extracellular fluid expansion. This measure was best correlated to clinical signs of overhydration in our study.

While multifrequency BIA can measure extracellular water, it cannot differentiate between the interstitial and intravascular compartments. It has been shown that the plasma concentration of ANP that depends on right atrial wall tension correlates with intravascular volume and central venous pressure [7]. However, as a biochemical parameter, ANP only allows a relative estimation of central venous filling and is also dependent on cardiac function. Nevertheless, we found in previous studies very sensitive ANP responses to ultrafiltration and to intermediate changes in dry weight [6]. ANP can, therefore, be helpful to assess the filling state of the intravascular space [6].

Before haemodialysis, the extracellular fluid space was increased in HD. PD patients had both higher TBW and V_{ecf} compared with controls. PD patients had TBW which was even greater than in HD patients before dialysis. The increase in TBW in PD patients was also reflected by an expansion of the extracellular fluid space with a V_{ecf}/TBW ratio that surpassed the values of HD patients after dialysis and was in the range of the pre-haemodialysis values. Rottembourg [15] found a higher mean pulmonary artery pressure in CAPD patients compared with HD patients [15]. Lameire *et al.* [16] described a considerable fall in dry weight after transferring CAPD patients to haemodialysis.

PD patients, having a more constant level of hydration were subdivided into three groups according to their hydration status in order to study correlations between BIA and clinical findings. As mentioned previously, the ratio of V_{ecf}/TBW focuses attention on extracellular volume expansion. This ratio was better correlated with clinical findings of overhydration than with single body fluid compartments. Prevalent oedema, increased jugular vein filling, and interstitial pulmonary fluid indicated by X-ray were correlated with this quotient. Increased systolic blood pressure in PD patients was correlated with the ratio of V_{ecf}/TBW . The use of antihypertensive drugs tended to be more frequent in the group showing BIA indicated extracellular fluid overload. Even in the group having the highest V_{ecf}/TBW ratio there were still 12.5% of patients that did not demonstrate any clinical signs of overhydration. This illustrates the insensitivity of standard clinical parameters for estimating body fluid status. It has been demonstrated that with an increasing extracellular fluid space blood pressure ‘slowly’ increases over weeks to months [17]. However, short-term changes in extravascular and intravascular filling did not actually change blood pressure. In a follow-up investigation, Katzarski and Charra *et al.* [9] have demonstrated that reductions in dry weight were accompanied by slow decreases in blood pressure over several months. This finding in dialysis patients supports the concept that not hypervolaemia *per se* but a rise in peripheral vascular

resistance may trigger the induction of hypertension. The biochemical or pathophysiological links between V_{ecf} and peripheral vascular resistance, however, are still unclear.

Plasma ANP levels were significantly elevated in all dialysis patients, and they were even increased at post-haemodialysis. Contrary to V_{ecf} in PD patients, which was slightly above the level in HD patients before haemodialysis, plasma ANP concentrations in PD patients corresponded to post-haemodialysis values. This supports the concept that extracellular fluid expansion in PD patients occurs predominantly in the interstitial space whereas intravascular filling is not increased to the same degree.

In the PD group, cGMP increased to a similar degree as did ANP. Contrary to the ANP findings, cGMP in PD patients surpassed the post-haemodialysis values in the HD group. However, the rather low post-haemodialysis cGMP levels can be attributed to the significant diffusional removal of this small molecule during haemodialysis. Plasma cGMP consecutively decreases also during isovolaemic haemodialysis and thereby 'underestimate' post-dialysis hydration [18].

Metabolic changes during dialysis may be related to fluid status. We found a significant negative correlation between serum albumin levels and the $V_{\text{ecf}}/\text{TBW}$ ratio in PD patients. No such correlation was found in the HD group, which may be a result of the more intermittent type of dialysis. Lower serum albumin levels may result from extracellular 'dilution' in cases of overhydration. Whether a low serum albumin concentration *per se* favours extracellular fluid expansion, especially in the interstitial space, is a matter of debate. Because the effective oncotic pressure gradient does not change between the intravascular and interstitial spaces during hypalbuminaemia (as a result of albumin equilibration between both compartments) an oncotic mechanism is unlikely to cause fluid expansion. Interestingly extracellular fluid status, serum albumin, and arterial pressure have been linked in previous studies. In clinical trials, dialysis patients with 'refractive' hypertension that were treated with longer dialysis sessions or with daily haemodialysis at home showed a fall in dry weight, an increase in serum albumin levels and reductions in mean arterial blood pressure [19]. However, the role of solute clearance and the time factor in dialysis need further clarification to understand their link to hydration status in this setting.

The large prospective CANUSA study indicated that increased mortality in PD patients might be attributed to high peritoneal transport rates [11]. It was speculated that high transporters produced more rapid reductions in dialysate osmotic pressure, causing reduced ultrafiltration in CAPD with the risk of subsequent fluid overload. Hypertension and left ventricular hypertrophy could then develop resulting in increased mortality. In the present study, we did not detect differences in body fluid distribution in patients having low (<75%) or high (>75%) peritoneal

transport rates. We found no correlation between the D/P ratio of creatinine in the peritoneal equilibration test and V_{ecf} , TBW, or $V_{\text{ecf}}/\text{TBW}$. This finding may be explained by fact that we closely adapted the dialysis regimen to changes in ultrafiltration. High transporters having a loss of ultrafiltration were typically switched to regimes with shorter dwell times using automated peritoneal dialysis. In a retrospective analysis that included 238 patients from our centre, we did not find a negative impact of high peritoneal transport rate on patient or system survival [20]. However, when reduced ultrafiltration because of high peritoneal transport is not adequately compensated by the dialysis regime, overhydration may occur thereby worsening patient outcome.

The current body fluid distribution findings in dialysis patients support a more general use of BIA for the assessment and repetitive control of dry weight, especially in PD patients. The data highlighted the links between extracellular fluid expansion and elevated systolic pressure in PD patients. Closer monitoring of dry weight and an adaptation of dialysis regimen may, therefore, be key for the improvement of long-term survival.

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