Original Article

Extracellular fluid volume determined by bioelectric impedance and serum albumin in CAPD patients

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Abstract

Aim. To investigate the relationship between serum albumin and extracellular fluid volume, as measured by multifrequency bioelectrical impedance, in stable patients treated by CAPD.

Method. Fifty-nine stable CAPD patients were assessed. Serum albumin (bromocresol green) and CRP, age, dialysate to plasma (D/P) creatinine ratio, normalized protein catabolic rate (nPCR), daily urine and peritoneal protein losses, and extracellular fluid volume (Vecf) were measured in each patient. Vecf was calculated as a percentage of actual body weight (Vecf% ABW), of lean body mass derived from anthropometry (Vecf% LBM) and of total body water (Vecf% Vtbw). Comparisons between those with a normal serum albumin ($\geqslant 37$ g/l) and those with a low serum ajbumin (< 37 g/l) were made by Mann–Whitney U test. Correlations with serum albumin were sought by Pearson's test.

Results. The D/P creatinine ratio, daily peritoneal and urine protein losses, and extracellular fluid volume (Vecf% LBM and Vecf% Vtbw) were all significantly greater in patients with serum albumin < 37 g/l as compared to those $\geqslant 37$ g/l; $P < 0.05$. Age, CRP, and nPCR were not different. Serum albumin was negatively correlated with Vecf% LBM, $r = -0.25$; $P = 0.05$, Vecf% Vtbw, $r = -0.39$; $P = 0.002$, and daily urinary albumin loss, $r = -0.25$, $P = 0.06$.

Conclusion. Hypoalbuminaemia is partly dependent on subclinical overhydration in CAPD patients. Serum albumin is negatively correlated with increased extracellular fluid volume and the proportion of Vecf to Vtbw is increased in hypoalbuminaemic patients. Multifrequency bioelectrical impedance is able to identify these abnormalities.

Key words: multifrequency bioimpedance; fluid overload/overhydration; hypoalbuminaemia

Introduction

In patients treated with continuous ambulatory peritoneal dialysis, a persistently low serum albumin has been attributed to poor nutritional intake [1], advanced age [2], a high dialysate to plasma (D/P) creatinine ratio [2], the presence of diabetes mellitus [2], increased urine and peritoneal protein loss [3], inflammation [4], and fluid overload [5]. Each of these factors can be assessed by simple clinical or laboratory testing with the exception of fluid overload, which may be present even in the absence of clinical signs. The plasma volume of CAPD patients may be expanded [5] and subclinical fluid overload has been suggested as a major factor in the development of left ventricular hypertrophy and cardiac failure in this group [6].

Multifrequency bioelectrical impedance is a simple-to-use and reproducible technique for measuring total body water (Vtbw) and extracellular fluid volume (Vect) [7]. We have used this technique to measure Vecf in CAPD patients with apparent optimal fluid status, in order to investigate the relationship between serum albumin and subclinical hypervolaemia,

Subjects and methods

Fifty-nine stable CAPD patients were investigated. All had been on CAPD for a minimum of 3 months. None had had peritonitis or a known active inflammatory disorder within the preceding 3 months. All patients were free of peripheral oedema, had no elevation of jugular venous pressure, and had clear lung fields on clinical examination. Patient age, time on CAPD, the presence of diabetes mellitus, and actual body weight (patient weight in underclothes with abdomen empty of dialysate and no clinical evidence of fluid overload) were recorded. Serum albumin (bromocresol green method), 24-h urine/peritoneal protein loss, protein catabolic rate (normalized to actual body weight [8]), D/P creatinine ratio (from 24-h pooled dialysate), C-reactive protein, and skinfold thicknesses at four sites were measured.

Extracellular fluid volume and total body water were determined by whole-body bioelectrical impedance measured at 25 frequencies logarithmically spaced in the range 5–500 kHz (Xitron 4000B, Xitron Technologies). Paired electrodes were placed on the dorsa of the right hand and foot, with the current-injecting electrode placed distally. Peritoneal dialysate was left in the abdomen during measurements. Estimates of extracellular fluid volume were derived using a two-stage analysis using data analysis software (Xitron Product Literature 1993); the first stage entailed fitting the

observed frequency dependence of the whole-body impedance to a three-element circuit model of the electrical properties of tissue [9]. The electrical resistances R_e and R_i of the extracellular and intracellular fluid current paths were given by this analysis. The second stage of the analysis used a mixture model of the extracellular and intracellular volumes to relate R_e to the extracellular volume, Vecf, [9], which is given by an equation of the form:

$$V_{ecf} = k \left(\frac{L^2 W^{1/2}}{R_e} \right)^{2/3}$$

where k is a factor related to the geometry of the body [10], and W and L are patient mass (kg) and height (cm) respectively. The total body water is given by using the same analysis from the equation

$$V_{tbw} = V_{ecf} + V_{icf}$$

where

$$\left(1 + \frac{V_{icf}}{V_{ecf}} \right)^{5/2} = \left(\frac{R_e + R_i}{R_e} \right) \left(1 + \frac{r V_{icf}}{V_{ecf}} \right)$$

and Vicf denotes the intracellular fluid volume and r is a constant determined by the ratio of the conductivities of the intra- and extracellular fluids [10].

Lean body mass was derived from skinfold thickness and dry weight [11]. Extracellular fluid volume (Vecf) was calculated as percentage of actual dry body weight (Vecf% ABW), percentage of the lean body mass derived from anthropometry (Vecf% LBM), and percentage of Vtbw (Vecf% Vtbw).

Median, and 25th and 75th centiles were calculated for each variable and comparisons between two patient groups defined by either normal or low serum albumin (serum albumin <37 g/l, the lower limit of the reference range for our laboratory, on two occasions two months apart) by the Mann–Whitney U test. Correlations with serum albumin were sought by Pearson's test.

Results

The 59 patients (37 males, 22 females) had been maintained on CAPD for 14 (5–41) months. Insulin-dependent diabetes mellitus was present in 10. Median and 25th and 75th centiles for each parameter, including age and serum albumin, are shown in Table 1. The D/P creatinine ratio, daily peritoneal and urine protein losses, and extracellular fluid volume as a percentage of actual body weight, lean body mass, and total body water volume were all significantly greater in patients with serum albumin <37 g/l as compared to $\geqslant 37$ g/l; $P<0.05$ (Figure 1, Table 2). Median age, nPCR, and actual Vecf were not different.

There was a significant negative correlation between serum albumin and Vecf (as % LBM), $r = -0.25$, $P = 0.05$, and Vecf (as %Vtbw), $r = -0.39$, $P = 0.002$ (Figure 2). There was a marginally significant negative correlation between serum albumin and daily urinary albumin loss, $r -0.25$, $P = 0.06$, but not with any other variable. Residual renal function ($r = -0.36$, $P = 0.006$), daily urinary albumin loss ($r -0.30$, $P = 0.02$), and nPCR ($r -0.27$, $P = 0.03$) were correlated with time on CAPD, but serum albumin and Vecf were not.

Table 1. Median values (with 25th and 75th percentiles) of parameters associated with hypoalbuminaemia in 59 stable CAPD patients

	n	Median	25th centile	75th centile
Albumin (g/l)	59	36	34	38
Age (years)	59	53	41	66
Body weight (kg)	59	66.5	60.5	73.2
CRP (mg/l)	59	67.5	0	16.35
D/P ratio creatinine	59	0.64	0.57	0.71
nPCR (g/kg/day)	59	0.95	0.77	1.15
24-h PD protein (g/day)	59	5.86	4.56	8.27
24-h urine protein (g/day)	59	0.22	0.00	0.85
Vecf (litres)	59	19.0	16.3	21.6
Vecf% body weight	59	29.9	25.5	32.2
Vecf% lean mass	59	39.0	35.3	41.0
Vecf% Vtbw	59	53.9	50.3	56.9

D/P ratio, dialysate to plasma creatinine ratio; nPCR, normalized (to actual body weight) protein catabolic rate; PD, peritoneal dialysate; Vecf, extracellular fluid volume; Vtbw, volume of total body water.

Discussion

Hypoalbuminaemia is strongly associated with decreased patient and technique survival in patients maintained on CAPD [12,13]. A number of factors contribute to hypoalbuminaemia in otherwise stable CAPD patients. Protein–calorie malnutrition has been emphasized as important, and correlations between dietary protein intake estimated from either food diaries [14] or protein catabolic rate [3] and serum albumin have been reported. An increased protein loss via the peritoneum has also been correlated with serum albumin [3], and an high dialysate:plasma creatinine ratio in a peritoneal equilibration test (consistent with an increased transmembrane transport and increased peritoneal protein loss) is also predictive of hypoalbuminaemia [2]. Patients with well-preserved residual renal function may continue to have nephrotic-range proteinuria with hypoalbuminaemia. In haemodialysis patients, an uncharacterized inflammatory response associated with elevated acute-phase and suppressed negative-phase proteins has been demonstrated [4]. This finding has not been reported in CAPD patients. Each of these contributory factors can be measured by simple clinical or laboratory testing.

The relationship of any biological variable to any number of independent factors is best assessed by multifactorial regression analysis. In this study, only one parameter was significantly correlated with serum albumin in univariate analysis, and multivariate analysis is inappropriate. This may reflect an insufficient sample number. However, the correlation between serum albumin and protein intake or dialysate protein loss has not been consistent [2,15] and protein catabolic rate normalized to actual body weight has been discredited as a nutritional marker [16].

There is evidence to suggest that CAPD patients are overhydrated. During the investigation of albumin homeostasis in CAPD patients, Kasyen and
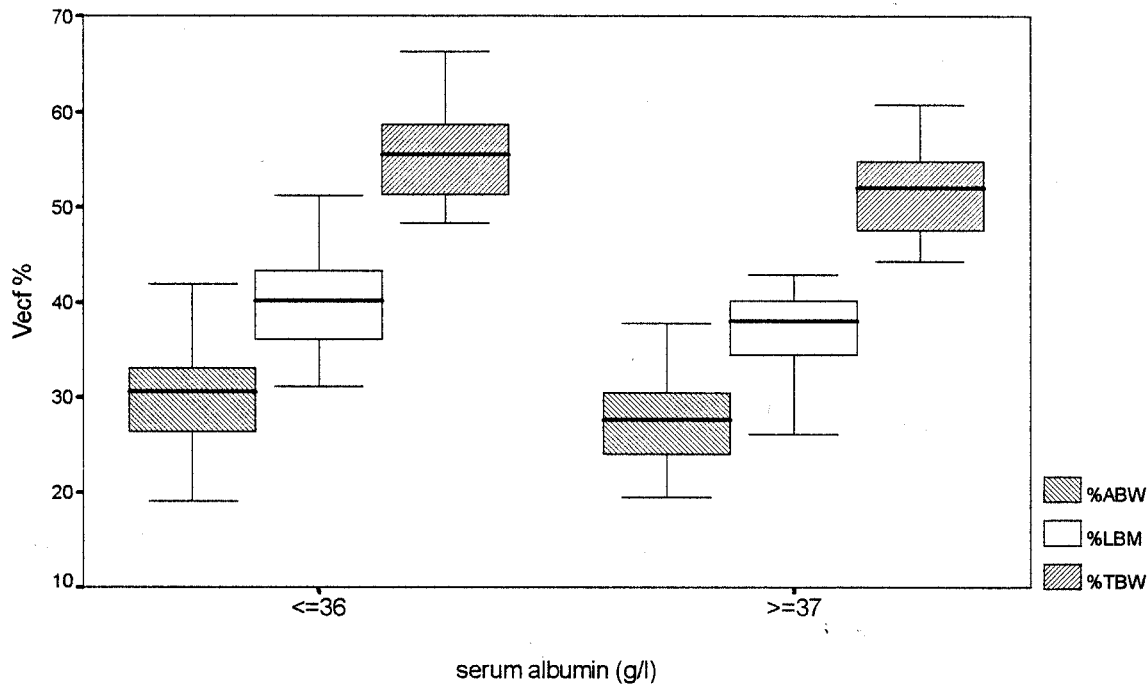
Fig. 1. Box plot (median, 25th and 75th centiles, and range) of extracellular fluid volume (Vecf) as a percentage of actual body weight (ABV), of lean body mass determined by anthropometry (LBM), and of total body water (TBW), comparing CAPD patients with a normal (*n*=25) or low serum albumin (*n*=34). The difference between groups is significant (*P*<0.05) for all three comparisons (Mann–Whitney U test).

Table 2. Comparison of median values (25th–75th percentiles) between CAPD patients with normal or persistently low serum albumin (⩾37 g/l vs ⩽36 g/l, median serum albumin=36 g/l) by Mann–Whitney U test (*P*<0.05 taken as significant)

Serum albumin	⩾37 g/l *n*=25	25th–75th	⩽36 g/l *n*=34	25th–75th	*P*
Albumin (g/l)	39	38–40	35	31–36	
Age (years)	53	34–66	55.5	48–66	n.s.
Body weight (kg)	65.5	61.5–73.0	67.8	60.5–76.0	n.s.
CRP (mg/l)	7.2	5.1–14.1	6.3	0–16.5	n.s.
D/P ratio creat	0.59	0.54–0.67	0.68	0.58–0.73	0.02
nPCR(g/kg/day)	0.90	0.79–1.03	0.97	0.76–1.15	n.s.
24-h PD protein (g/day)	4.73	3.87–6.36	6.31	5.22–8.57	0.03
24-h urine protein (g/day)	0.07	0.0–0.32	0.33	0.0–1.10	0.04
Vecf (litres)	18.9	16.3–19.8	20.0	16.0–23.1	n.s.
Vecf% body weight	27.5	24.6–30.3	30.6	26.4–33.0	0.03
Vecf% lean mass	38.1	34.5–40.2	40.2	36.1–43.4	0.03
Vecf% Vtbw	56.1	47.6–54.6	55.0	51.7–58.7	0.009

D/P ratio, dialysate to plasma creatinine ratio; nPCR, normalized (to actual body weight) protein catabolic rate; PD, peritoneal dialysate; Vecf, extracellular fluid volume; Vtbw, volume of total body water.

Schoenfield [5] noted an increased plasma volume, as determined by radiolabelled albumin dilution, in CAPD patients as compared to healthy controls (although this did not reach statistical significance). The plasma albumin mass was normal, suggesting that a dilutional hypoalbuminaemia was present. Secondly, the mean pulmonary artery pressure is higher in CAPD than in haemodialysis patients being prepared for renal transplantation [17]. Thirdly, transfer from CAPD to haemodialysis is accompanied by a considerable fall in 'dry' weight [18], and finally, CAPD patients require more antihypertensive medication than age-, gender-

and renal-disease-matched controls on haemodialysis [6]. The association between a high D/P creatinine ratio and hypoalbuminaemia might also be explained by poor ultrafiltration and consequent fluid retention in patients with a highly permeable peritoneal membrane.

There has been no simple clinical test for assessing volume status in patients who do not have clinically overt volume overload. The 'gold standard' method of measuring total body water (deuterium oxide dilution) is time consuming and requires complex analysis. Bioelectrical impedance has been used to assess total
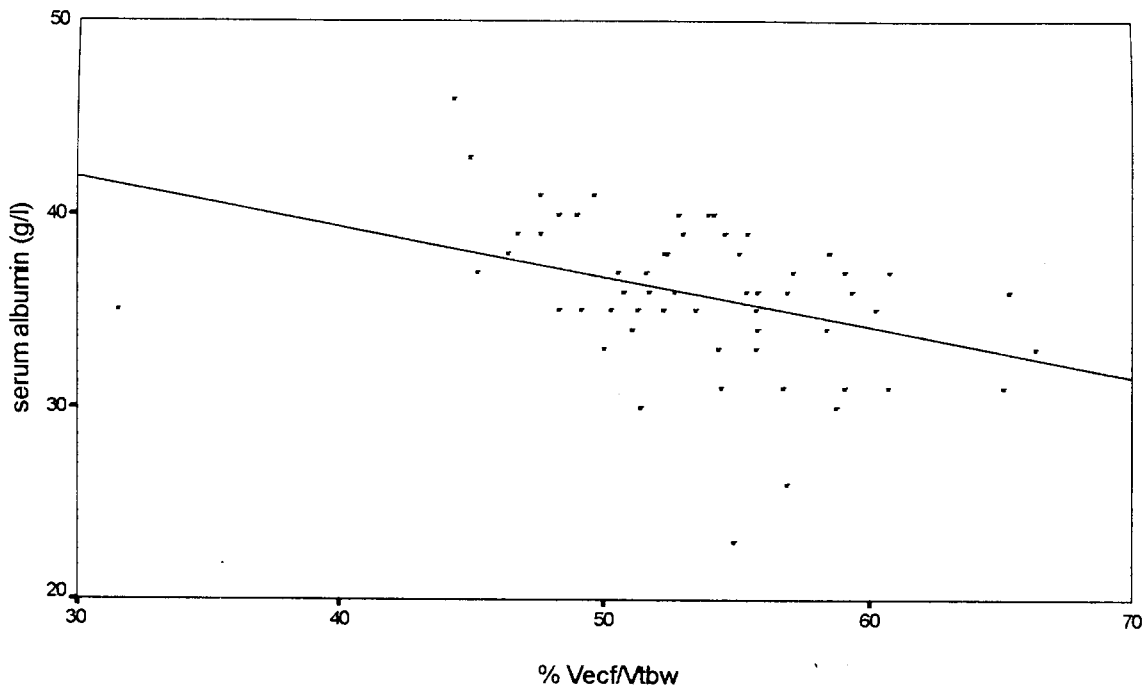
Fig. 2. Relationship between serum albumin (g/l) and extracellular fluid volume (Vecf) as a proportion of total body water (Vtbw); $r = -0.39$, $P = 0.002$.

body water and lean body mass, derived from total body water, in haemodialysis and CAPD patients [19,20]. Bioimpedance measurements have been closely correlated with total body water by deuterium oxide in CAPD patients with peritoneal dialysate *in situ* [21] and with the abdomen empty [22], although the limits of agreement between the two methods were wide. Single-frequency bioelectrical impedance, which has been used in most of these studies, depends on models that assume a fixed relationship between extracellular and intracellular water [23]. Abnormal hydration may thus lead to inaccuracy of estimation of the distribution of total body water between the intra- and extracellular spaces. The use of single-frequency techniques has been criticized in this context [24]. Multifrequency imped-ance can overcome this problem and is inherently more accurate when measured over the range of frequencies 10 kHz to 1 MHz [25]. In normal individuals, bioe-lectrical impedance is mainly dependent on limb length and circumference, with a less than 5% contribution from the thorax and abdomen [26]. Bioimpedance is insensitive to free peritoneal fluid [27] and even large-volume paracentesis in cirrhotic patients (mean volume 6.9 litres) resulted in minimal change in impedance estimates of either TBW or Vecf [28]. The presence of intraperitoneal dialysate in CAPD patients should therefore have little effect on impedance measurements and this is the case during peritoneal filling/emptying [29].

As fat is anhydrous, Vecf as a fraction of actual body weight may appear normal in obese individuals, where excess fat mass will disguise overhydration of lean mass. Vecf as a proportion of lean body mass

(measured by anthropometry) or total body water (measured by bioelectrical impedance) will reveal the true fluid status in such individuals. The normal pro-portion of extracellular to total body water is approxi-mately 30%. Abnormal body water distribution, as assessed by bioimpedance, has been reported in critic-ally ill patients with trauma and sepsis [30], and in patients with cirrhosis [28]. In both of these groups, bioimpedance correlated with dilution measurements and the Vecf/TBW ratio approached 50%. Our study was intended to compare extracellular water between patients with low and normal serum albumin and not with a control population. However, the range of Vecf/TBW ratios obtained suggests that many patients are overhydrated, including those with a serum albu-min in the normal range (Figure 1). This could reflect a systematic error of bioimpedance in the CAPD population, although the agreement with the abnormal ratio in other disease populations would be against this interpretation. The negative correlation between Vecf proportion and serum albumin would be consist-ent with the observation that hypoalbuminaemia in CAPD patients is associated with an increased risk of developing left ventricular dilatation and *de novo* or recurrent cardiac failure [31]. Chronic hypervolaemia has been associated with the development of an increased left ventricular mass in CAPD patients [32]. This issue is therefore important and tight control of circulating volume is an important part of assessing adequacy of CAPD therapy. A simple technique to monitor fluid status is required to allow effective monitoring. Whether or not the limits of agreement of measurements made by a 'gold standard' technique

and a clinically applicable technique are high is less important than whether the latter can detect important differences between 'adequately' or 'inadequately' treated patients.

We have found that CAPD patients with hypoalbuminaemia have an increased extracellular fluid volume as measured by multifrequency bioimpedance. In patients with unexplained or multifactorial hypoalbuminaemia, it may be possible to identify those patients with persistent hypervolaemia using this technique. Bioimpedance is simple, painless, quick to perform, non-invasive, and reproducible. Whether it could be used to monitor progressive reduction in fluid weight in response to clinical intervention and whether such reduction would lead to a rise in serum albumin requires further study.

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