Original Article

Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients

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Abstract

Background. Recent studies suggest that increased peritoneal membrane permeability is associated with higher morbidity and mortality in peritoneal dialysis patients. It is not known, however, whether the difference in clinical outcome among different peritoneal transport groups is due to differences in peritoneal fluid and solute removal. In the present study, we compared the peritoneal fluid and solute transport and clinical outcome in CAPD patients with high (H), high–average (H–A), low–average (L–A) and low (L) peritoneal transport patterns.
Design. A 6-h dwell study was performed in 46 patients with frequent dialysate and plasma samples using 2 1 of 3.86% glucose dialysate with ^{131}I albumin as an intraperitoneal volume marker. The patients were divided into four transport groups according to their D/P of creatinine at 240 min.
Results. The results showed that high transporters had significantly lower peritoneal fluid and small-solute removal but high glucose absorption and high protein loss during a 6-h exchange. The serum albumin was lower and blood pressure and triglycerides were higher in high transporters compared with the other groups. Two-year patient survival from the start of CAPD treatment was significantly lower for high transporters (64, 85, 90 and 100% for H, H–A, L–A and L respectively, $P < 0.01$). The 1-year patient survival from the dwell study was also significantly lower in high transporters (16, 63, 90 and 100% for each group, $P < 0.01$).
Conclusion. Our results suggest that high transporters remove less fluid and small solutes and have higher protein loss and increased glucose absorption. These alterations may contribute to fluid overload, malnutrition and lipid abnormalities that perhaps contribute to the increased mortality among the high transporters.

Key words: CAPD, adequacy, peritoneal transport, mortality

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Introduction

The accumulated experience and significant improvement in technology of peritoneal dialysis over the past decade have established peritoneal dialysis as a successful replacement therapy in the management of end-stage renal failure patients. Currently, there are over 105 000 patients alive world-wide on this treatment, representing some 15% of the global dialysis population [1]. Several studies have concluded that, in the short–medium term, CAPD assures similar patient survival as does hemodialysis [2]. However, to date, the ability of peritoneal dialysis to provide long-term dialysis is limited to a small number of patients [1] and the patient and technique survival after 2 years of PD treatment is still quite low [3,4]. In recent years, several risk factors have been identified for technique failure and mortality in CAPD patients, in particular cardiovascular disease (CVD) [5], low residual renal function and small-solute clearances [6,7], and impaired nutritional status [7–10].

It is generally accepted that there is a correlation between total (peritoneal + residual renal) small-solute clearances (Kt/V_{urea} and creatinine clearance) and clinical outcome in peritoneal dialysis patients [7,11]. Furthermore, most of the studies to date have found that residual renal function (RRF) was the strongest determinant of differences in Kt/V_{urea} and creatinine clearance among different patients and different times on dialysis [12,13]. RRF, but not peritoneal clearance, was reported as a strong predictor of patient survival [14]. High residual renal function was associated with better clinical outcome. All these findings might suggest that CAPD is not a suitable long-term treatment for most ESRD patients, as most of them have negligible urine output after 3 years of peritoneal dialysis [15,16].

More recently, however, several reports have indicated that the patient's peritoneal transport pattern has a significant impact on their clinical outcome including patient and technique survival [17–21]. The Canadian–USA (CANUSA) prospective, multi-center cohort study showed that a patient's peritoneal transport category according to the peritoneal equilibration

test (PET) result has an independent effect on patient survival. Increased peritoneal transport rate was associated with lower patient survival [21]. One possibility is that the differences in clinical outcome among different peritoneal transport groups may relate to differences in peritoneal fluid and solute removal. Therefore, a detailed investigation on how the peritoneal transport pattern affects peritoneal fluid and solute removal is of important clinical value.

Thus, the aim of the present study is to provide detailed information on how different peritoneal transport patterns affect the peritoneal fluid and solute removal as well as how the transport pattern may affect patients' clinical outcome.

Methods

A 6-h dwell study with an intraperitoneal volume marker (^{131}I-human albumin, RISA) and frequent blood and dialysate sampling was carried out in 46 CAPD patients using 2 l of 3.86% glucose dialysis fluid (Dianeal, Baxter-Travenol, Deerfield, IL, USA). These dwell studies were performed as part of a long-term follow-up of CAPD patients or as part of studies on alternative osmotic agents and some of the dwell studies reported here have been partly analysed before [22,23]. In this study, we only used the first dwell study (using glucose solution) for each patient. These dwell studies were performed during 1982–1990 and the patients were followed up until the end of 1996. Prior to the dwell study, 24-h dialysate and urine were collected to calculate the weekly peritoneal Kt/V_{urea} and creatinine clearance.

The patients were divided into four transport categories according to the modified peritoneal equilibration test (PET, see below): low (L), low–average (L–A), high–average (H–A) and high (H) transport with 6, 13, 20, 7 patients in each group. As our dwell study is different from the standard PET (3.86% glucose solution was used, and in addition we used the concentration of the solutes in plasma water rather than plasma concentration) we modified the criteria proposed by Twardowski *et al.* [24]. The limits of D/P creatinine at 4 h used for patient classification were 0.68 ± 0.12 (mean $\pm$ 1SD), as established in our clinically stable patients.

The 6-h dwell study was carried out using 2 l of 3.86% glucose dialysis fluid as described previously [22]. Briefly, the patients were studied in the morning after an overnight oral fast. Fresh dialysis fluid was prewarmed to 37°C and prepared with a priming dose of 0.2 g of human serum albumin to minimize the adhesion of RISA to the surface of the plastic material. Radioisotopically labelled albumin [185 kBq ^{131}I-human serum albumin (RISA), Institutt for Energiteknikk, Kjeller, Norway] was added and the fluid was then infused through an infusion set (CAPD Solution Transfer-set, Travenol Laboratories). Fresh dialysis fluid samples were taken (in triplicate in most cases) from the bag halfway through infusion. Dialysate samples (15 ml) were taken through a three-way stop-cock (Viggo, Connecta, Helsingborg, Sweden) and the Tenckhoff catheter at 3, 15, 30, 60, 90, 120, 180, 240 and 360 min after the complete infusion of the dialysis fluid. Prior to each sampling, 10 ml of the dialysate was flushed back and forth five times through the stop-cock. Blood samples were drawn at 0, 180 and 360 min. After 360 min, the dialysate was drained in the supine position and the volume was recorded. The peritoneal cavity was then rinsed for 5 min with 1 l of fresh 1.36%

glucose dialysis fluid (without RISA) to provide data for calculation of the residual volume at 360 min.

Blood and dialysate samples were analysed for RISA activity on an Intertechnique CG Gamma Counter (Intertechnique, Plaisir, France). Glucose, urea, creatinine and total protein concentration were measured with an IL 919 system (Instrumentation Laboratory, Milan, Italy) and sodium and potassium concentration with an IL 743 flame photometer (Instrumentation Laboratory).

Intraperitoneal dialysate volumes (V_D) were estimated from the dilution of RISA with corrections applied for the elimination rate of RISA from the peritoneal cavity (K_E, ml/min) and sample volumes. K_E was used for estimating the peritoneal fluid absorption rate [25]. Intraperitoneal dialysate volumes (V_D) were estimated from the dilution of RISA with corrections applied for the elimination rate of RISA from the peritoneal cavity (K_E, ml/min) and sample volumes. The dialysate concentration (C_D) over plasma concentration ratio, D/P, during the dwell study was calculated by dividing the dialysate concentration of a solute by the plasma water concentration of the investigated solutes. Total solute removal was calculated using intraperitoneal volume times the dialysate solute concentration at a certain time minus the solute amount at 3 min. The clearance of solute (K) was calculated as the total removal ($V_D(t)C_D(t) - V_3^* C_3$) divided by the time interval and the time-average blood concentration of the solute.

Weekly peritoneal Kt/V_{urea} and creatinine clearance (Ccr) were calculated using total urea and creatinine clearances (24-h dialysate collection) divided by the urea distribution volume in blood which was calculated using the Watson *et al.* equation [26] (for Kt/V_{urea}), or divided by the patient's normalized body surface area, which was calculated using the Du Bois and Du Bois equation [27] (for Ccr). The mean urea distribution volume and body surface area in these 46 patients were 36.7 l (range 29–46.5 l) and 1.74 m² (range 1.36–2.13 m²), respectively.

Analysis of variance (ANOVA) for single and repeated measurements was used to compare the difference in fluid and solute transport data and clinical characteristics among the different transport categories. When ANOVA showed significant differences, Scheffe's F-test was used to analyse the difference between the groups further. In addition, actuarial survival rates were determined by the Kaplan–Meier method. A log-rank test was used to compare the different survival curves. Transplantation, technique failures and loss to follow-up were censored observations for the patient survival analysis. Cox proportional hazards model was also used in this study to classify possible risk factors for patient mortality. Data are expressed as mean $\pm$ SD unless otherwise noted. Statistical significance was accepted if $P < 0.05$.

Results

Clinical characteristics

The clinical characteristics of the patients are summarized in Table 1. There were no significant differences in patient age, gender, height, time on PD treatment, peritonitis rate and urine volume among these four groups. However, the diastolic blood pressure in the H group was higher compared with the H–A and L–A group ($P < 0.05$) and the body weight also tended to be higher in the H group ($P = 0.07$). The serum triglyceride concentration was significantly higher in the

Table 1. Clinical characteristics of the 46 patients

	n	Age (years)	Sex (f/m)	T_{PD} (months)	Height (cm)	BW (kg)	S_{alb} (g/l)	TG (mmol/l)	SBP (mmHg)	DBP (mmHg)	V_{urine} (ml/24 h)	Weekly Ccr* (l/1.73 cm²)	Weekly Kt/V_{urea} *
H	7	59±13	1/6	25±17	175±11	75±3	29±5[a]	6.1±2.7[b]	161±38	88±12[c]	109±206	52.9±6.8	1.48±0.16[a,d]
H–A	20	60±12	11/9	12±16	168±10	66±14	30±4[a]	3.4±2.1	138±38	78±12	94±163	49.7±6.4	1.56±0.19[a,d]
L–A	13	56±14	7/6	15±12	166±11	59±14	33±4	3.5±2.1	131±15	73±9	96±172	50.6±7.1	1.77±0.23
L	6	50±12	3/3	13±15	171±10	62±6	37±5	2.4±1.0	139±35	83±10	14±18	43.1±5.3	1.89±0.17

Abbreviations: T_{PD}, time on PD treatment before the dwell study; BW, body weight; S_{alb}, serum albumin; TG, serum triglycerides; SBP, systemic blood pressure; DBP, diastolic blood pressure. V_{urine}, 24-h urine volume. [a] $P < 0.05$, compared with L group; [b] $P < 0.05$, compared with the other groups; [c] $P < 0.05$, compared with H–A and L–A groups; [d] $P < 0.05$ compared with L–A group. *Peritoneal clearances.

H group compared with the other groups ($P<0.01$). Serum albumin in the H and H–A groups was significantly lower compared with the L group ($P<0.05$). The primary renal disease and the history of CVD (defined as previous myocardial infarction, angina, peripheral vascular disease or cerebrovascular disease) before starting peritoneal dialysis are summarized in Table 2. Although diabetes and CVD seemed to be more common in the high transport group, the differences were not statistically significant.

Fluid transport in the different groups

The intraperitoneal volume was significantly lower in the high transporters compared with the other groups (ANOVA repeated measurements, $P<0.01$) (Figure 1). It was also significantly lower in the H–A and L–A groups compared with the L group ($P<0.01$). The intraperitoneal volume at 360 min was 2420 ± 222, 2849 ± 254, 2918 ± 275 and 3277 ± 248 ml for the H, H–A, L–A and L groups respectively. The fluid absorption rate estimated as the RISA disappearance rate (K_E) was 2.3 ± 0.4, 2.1 ± 0.5, 1.7 ± 0.6 and 1.5 ± 0.6 ml/min for the H, H–A, L–A and L groups respectively, and was significantly higher in the H group compared with the L and L–A groups ($P<0.05$) and in the H–A group compared with the L group ($P<0.05$). The average transcapillary ultrafiltration rate during 3–360 min was significantly lower in the H group compared with other groups, 2.8 ± 0.7, 3.5 ± 0.5, 3.6 ± 0.6 and 3.6 ± 0.7 ml/min for the H, H–A, L–A and L groups respectively.

Solute transport in the different groups

The D/D_0 for glucose was significantly lower in the H and H–A groups compared with the L and L–A groups ($P<0.05$, Figure 2). The total amount of absorbed glucose was significantly higher in the H group compared with the H–A, L–A and L groups ($P<0.01$) (Figure 2). As expected, the D/P values for sodium, potassium, urea, creatinine and protein were higher among the high transporters (data not shown). However, the total removal of sodium and potassium at 360 min was significantly lower compared with the other groups ($P<0.05$) (Figure 3). The removal of urea was lower in the H group compared with the L–A and L groups ($P<0.05$) and lower in the H–A group compared with the L group ($P<0.05$) (Figure 3). There was a slight decrease in removal of small solutes in the H group after 240 min of the dwell (Figure 3), in contrast to the other groups. There were no significant differences in the plasma sodium, potassium or urea concentrations, therefore the clearances of these solutes showed a pattern similar to the total removal. However, the plasma creatinine concentration

Table 2. Underlying renal disease and history of cardiovascular disease (CVD) before starting peritoneal dialysis

	H n (%)	H–A n (%)	L–A n (%)	L n (%)
Glomerulonephritis	0 (0%)	6 (30%)	6 (46.2%)	2 (33.3%)
Interstitial nephritis	0 (0%)	4 (20%)	3 (23.1%)	0 (0%)
Polycystic kidney	1 (14.3%)	0 (0%)	1 (7.7%)	1 (16.7%)
Nephrosclerosis	2 (28.6%)	3 (15%)	0 (0%)	2 (33.3%)
Diabetes	3 (42.9%)	3 (15%)	2 (15.4%)	1 (16.7%)
Other	1 (14.3%)	4 (20%)	1 (7.7%)	0 (0%)
CVD*	4 (57.1%)	7 (35%)	3 (23.1%)	2 (33.3%)

*CVD was defined as previous myocardial infarction, angina, peripheral vascular disease or cerebrovascular disease.

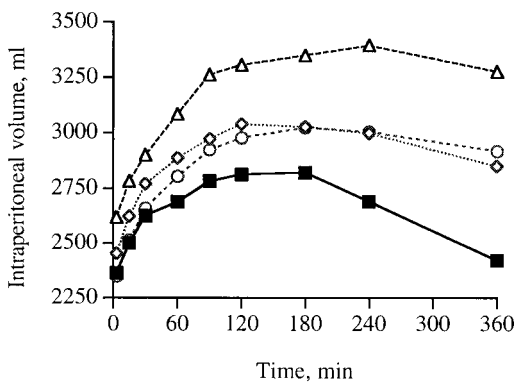**Fig. 1.** Intraperitoneal dialysate volume vs dwell time. ■, high transport group ($n=7$) ◇, high–average transport group ($n=20$); ○, low–average transport ($n=13$); △, low transport group ($n=6$).
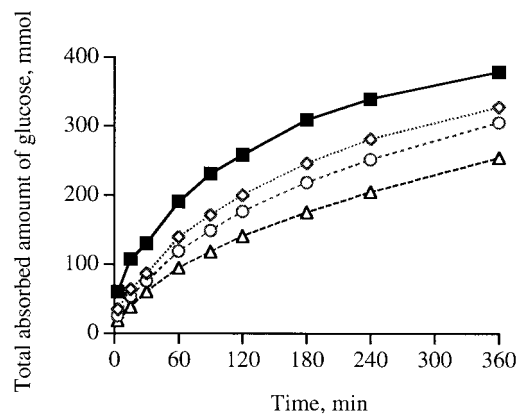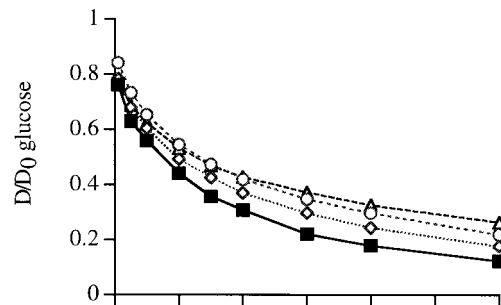

Fig. 2. Ratio of dialysate glucose concentration (D) to fresh dialysate glucose concentration (D_0) (upper panel) and total absorbed glucose (lower panel) vs dwell time. Symbols are as in Figure 1.
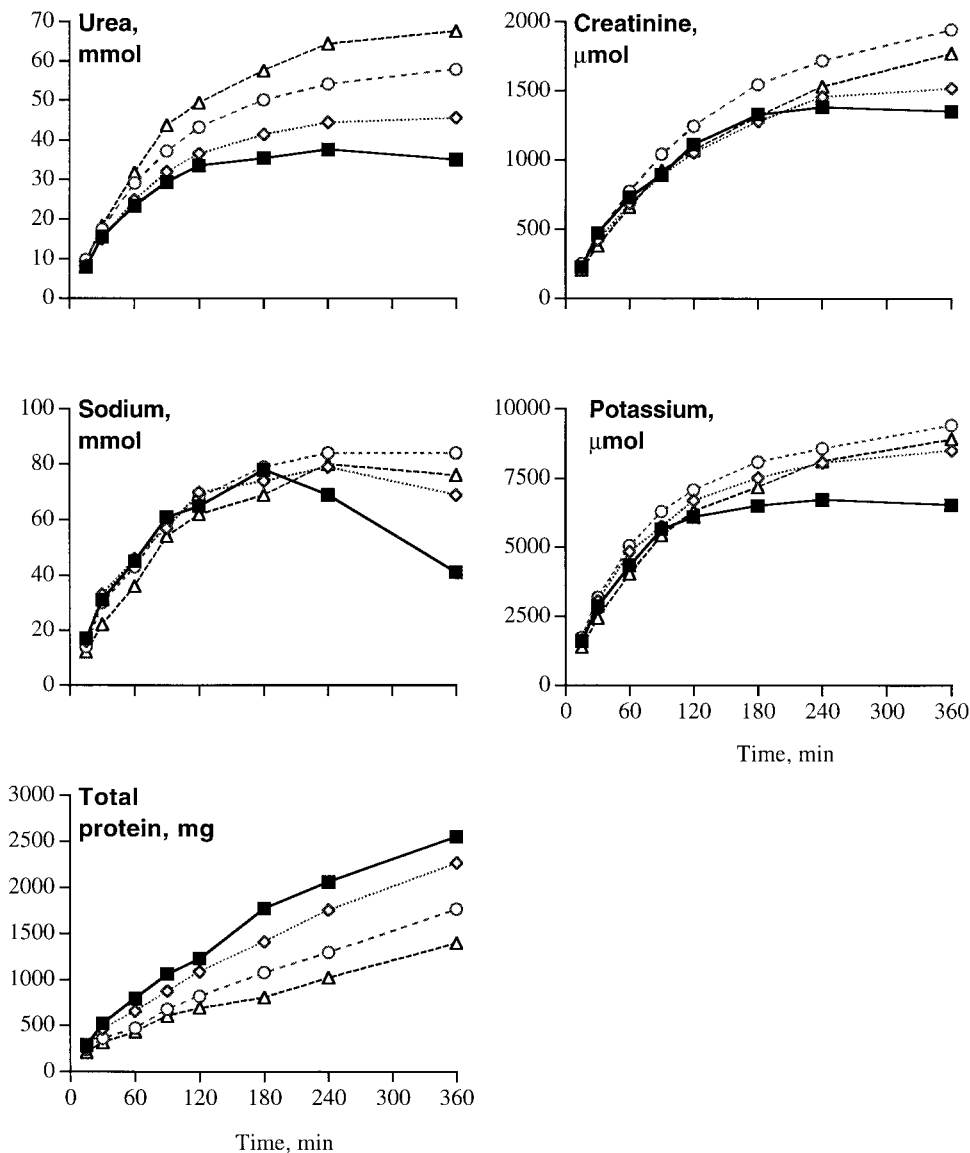
Fig. 3. Total removal of urea, creatinine, sodium, potassium and total protein *vs* dwell time. Symbols are as in Figure 1.

was significantly lower in the H group compared with the other groups ($P<0.05$). Thus, despite a lower removal of creatinine in the H group ($P=0.09$), a slightly higher creatinine clearance was observed in the H and H–A groups compared with the L group ($P=0.06$). The total removal and clearance of protein was higher in the H and H–A groups compared with the L group ($P<0.05$) (Figure 3). The weekly peritoneal Kt/V_{urea} and total Kt/V_{urea} (peritoneal + renal) were significantly lower in the high transporters as compared with the other groups (Table 1). No significant difference was found in weekly peritoneal Ccr or total Ccr among the four groups, although Ccr in the L group tended to be lower compared with the other groups (Table 1).

Patient survival in the different groups

Two-year patient survival from the start of CAPD treatment was significantly lower for the high trans-porters (64, 85, 90 and 100% for the H, H–A, L–A and L groups respectively, $P<0.01$) (Figure 4). The 1-year patient survival from the dwell study was also significantly lower in the high transporters (16, 63, 90 and 100% for each group, $P<0.05$) (Figure 4). The clinical outcome of these 46 patients is shown in Table 3. All the deaths among the high transporters were caused by cardiovascular diseases (Table 3). When using age, sex, time on PD and serum albumin as covariants to a Cox proportional hazards model, we found that only transport category had a significant effect on patient survival evaluated both from the dwell study ($P<0.01$) and from the start of CAPD treatment ($P<0.05$) with a higher peritoneal transport rate being associated with a higher risk of death. We also included the primary renal disease (diabetics *vs* non-diabetics) and CVD history in the Cox analysis and found that, besides the peritoneal transport category, CVD (but not diabetes) was also a strong predictor of mortality
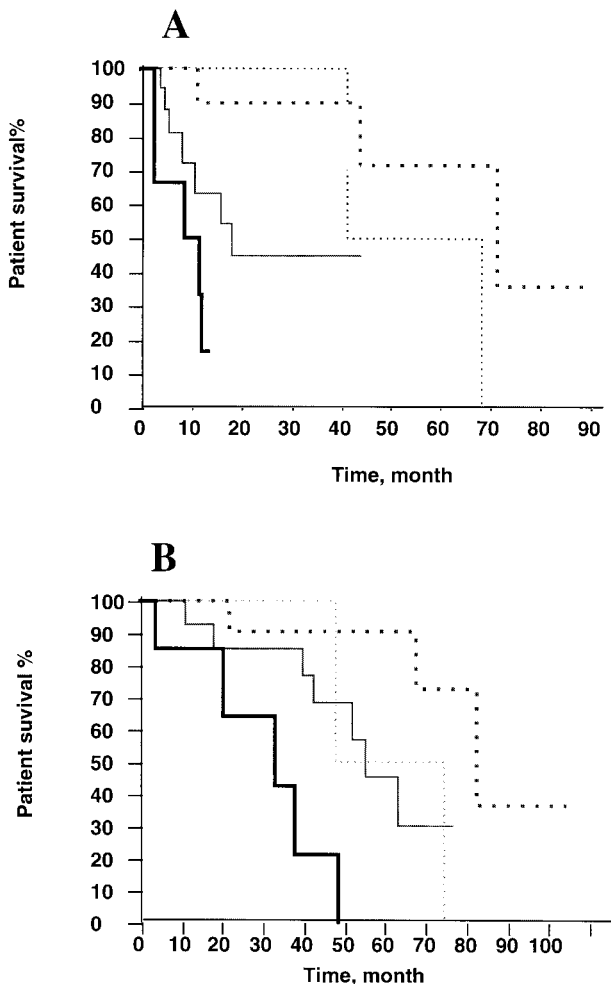
A

B

Fig. 4. Peritoneal transport patterns and patient survival (Kaplan–Meier curve). (**A**) From the dwell study; (**B**) from the start of CAPD. Thick solid line, high transport group; fine solid line, high–average transport group; thick dashed line, low–average transport group; fine dashed line, low transport group.

Table 3. Clinical outcome of the 46 CAPD patients

	n	Death* (n)	Transplant (n)	Transfer to HD (n)
H	7	5 (5)	1	1
H–A	20	7 (5)	4	9
L–A	13	3 (2)	5	5
L	6	2 (2)	2	2
Total	46	17 (14)	12	17

*Numbers in bracket are death due to cardiovascular diseases.

rate, calculated both from the dwell study and from the start of peritoneal dialysis (both $P < 0.05$).

Discussion

The present study shows that CAPD patients who were high (peritoneal) transporters had lower fluid, sodium, potassium, urea and creatinine removal but had higher protein loss and higher glucose absorption. In addition, the patients with a high peritoneal transport rate had a markedly higher mortality.

It is a general experience that increased peritoneal transport rate is associated with lower fluid removal [12,28–30]. The present study showed that the lower fluid removal during a single CAPD exchange in high transporters was not only a result of a decrease in the ultrafiltration rate but also a result of an increase in the peritoneal fluid absorption rate in these patients. The decrease in ultrafiltration rate in high transporters is likely to be due to a rapid decrease in the osmotic gradient because of an increased absorption of glucose (by diffusion) from dialysate. The increased fluid absorption rate may be the result of increased peritoneal interstitial hydraulic conductivity [31,32], as the peritoneal hydrostatic pressure gradient (which also affects the peritoneal fluid absorption) is unlikely to be higher in the high transporters. The decreased fluid removal in the high transport group may contribute to the higher blood pressure and higher body weight in these patients. Our results show that even with short dwell time treatments as in CCPD (dwell time 2–3 h [33]), fluid removal may still not be enough in high transporters when conventional glucose dialysates are used. Therefore, high transporters are at high risk of developing fluid overload. In fact, in the present study, three patients in the high transport group had some symptoms of overhydration such as pronounced oedema, and were classified as ultrafiltration capacity loss due to increased peritoneal diffusive transport [23].

Although there was an increased transport rate (higher D/P values) for all the small solutes investigated in the high transporters, the total removal of these solutes at the end of the dwell (at 6 h) was lower in this group. This was due to peritoneal fluid absorption which plays an important role in fluid and solute removal during long time dwell [34]. Interestingly, the solute removal did not show any significant differences among the four groups at 4 h of the dwell; this may, at least partially, explain why we found lower solute removal in high transporters (after 6 h) while a previous report (using PET results) did not [12]. Note that during the last 2 h of the dwell the total removal of fluid and all the small solutes investigated were in fact decreased in high transporters. This suggests that a long dwell time may be especially harmful to high transporters concerning the net removal of fluid and small solutes. However, in CAPD, the most common dwell time is 4–6 h during the day and 8–10 h during the night (in CCPD it is 10–14 h during the day). Thus, it is not surprising that the night-time dwell has been shown to have a dramatic impact on patients' fluid balance [35]. The significantly lower sodium removal in the high transporters may also contribute to the fluid imbalance and high blood pressure.

Although creatinine clearance was higher in high transporters, the total removal of creatinine was lower in this group because of the significantly lower serum creatinine concentration in this group, which is in

accordance with some previous reports [30,36]. Nolph *et al.* [30] found that the higher transporters had significantly lower serum creatinine and creatinine removal (dialysate + urine) compared with the low transporters and suggested that this may be a result of reduced muscle mass and represent malnutrition in high transporters. Furthermore, serum albumin, often used as a nutritional marker [37,38], was significantly lower in the high transport group in the present study; this is in agreement with some previous studies [7,39]. Thus, our results suggest that high transporters may have a worse nutritional status. However, in a recent cross-sectional study, Harty *et al.* [40] found that despite a significantly lower serum albumin level in high transporters, no significant relationship was demonstrated between D/P creatinine, body fat, lean muscle mass and dietary protein intake. They suggested that the hypoalbuminemia in high transporters may be a result of fluid overload rather than being due to malnutrition. Therefore, further studies in this area are needed.

The increases in dialysate total protein loss and glucose absorption in high transporters are in agreement with previous studies [30,41,42]. These changes may contribute to the higher triglycerides in the high transport rate group.

The significantly lower patient survival in the high transporter group is in accordance with previous reports [18,20,21]. In the CANUSA study, the peritoneal transport pattern had an independent impact on patient- and technique survival [21] and 2-year patient survival for the H, H–A, L–A and L transporters were 71, 72, 80 and 91%, respectively [21]. In the present study, analysis using Cox proportional hazards model also shows that the peritoneal transport pattern affects patient survival independently. The 1-year survival after the dwell study in the high transporters was only 16%, significantly lower than those of the other groups. In particular, CVD was the only cause of death among the high transporters. Note that the present study is not a controlled prospective study, the number of the patients is rather low, and the complex case-mix factors may also have an impact on the high mortality rate in the high transporters. The strong association between increased mortality rate and increased peritoneal transport rate (both for 1 year from the dwell and for 2 years from the start of peritoneal dialysis) may lead us to speculate that the higher mortality rate with increased peritoneal permeability may be directly related to the fluid status in these patients.

The higher mortality in high transporters, and the lower mortality in low transporters (at least in the short term), should be studied further as it seems to have a major implication for peritoneal dialysis. Although it is still under debate whether middle molecular weight uraemic toxins would affect patients' clinical outcome, it is commonly suggested that low transporters may not remove enough uraemic toxins [28,42]; and this may be a major limit and fundamental problem for peritoneal dialysis. Patients with an increased peritoneal transport rate have a high

clearance of those solutes whose molecular weights are higher than creatinine. Indeed our results show that high transporters have higher creatinine and total protein clearance than low transporters. In consequence, more attention should be given to the removal of small solutes and fluid. Note that adequacy of dialysis is not only a matter of reaching target Kt/V_{urea} or Ccr, but is also, and maybe even more importantly, a matter of removing enough fluid and sodium [43]. Furthermore, it is well known that the removal and clearance of small solutes such as urea also reflect fluid removal (flow dependent) during peritoneal dialysis. However, inadequate fluid removal and inadequate blood pressure control are common problems in CAPD patients [44,45], and may contribute to the unacceptably high rates of technique failure and mortality among these patients. In fact, in the CANUSA study, 75% of the deaths during the 2-year study period were cardiovascular in nature [7]. This is similar to the present study (82%). For haemodialysis patients, it has been suggested that efficient fluid removal and blood pressure control are crucial for the prevention of cardiovascular mortality among haemodialysis patients [43,46]. Our results suggest that efficient fluid removal is as important among peritoneal dialysis patients. However, in the present study, four of the six patients in the low transport groups were censored before the first death in this group: two patients were transplanted, and the other two were transferred to hemodialysis as shown in Table 3. It has long been a general perception that low transporters might remove insufficient uraemic toxins and therefore might not be best treated with long-term peritoneal dialysis [24,42]. Whether the high dropout rate in the low transport group seen in the present study suggests that sufficient removal of uraemic toxins (mid-sized or large molecules rather than small solutes and fluid) is also important for long-term peritoneal dialysis needs to be addressed in the future.

In summary, our study shows that high peritoneal transport is associated with lower levels of fluid and small-solute removal but higher levels of protein loss and glucose absorption. These alterations may result in fluid overload, inadequate dialysis and malnutrition which may contribute to the higher mortality seen among high transporters. Overall, these results suggest that adequate fluid balance is a crucial part of adequate peritoneal dialysis.

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