Peritoneal Fluid and Solute Transport: Influence of Treatment Time, Peritoneal Dialysis Modality, and Peritonitis Incidence

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Abstract. The integrity of the peritoneal membrane in peritoneal dialysis (PD) is of major importance for adequate dialysis and fluid balance. However, alterations in peritoneal fluid transport, such as ultrafiltration failure, often develop during long-term PD. To investigate peritoneal solute and fluid transport and to analyze the influence of treatment time, peritonitis incidence, and PD modality (continuous ambulatory PD [CAPD] or automated PD [APD]), a cross-sectional study with an extended peritoneal transport test that used dextran 70 in 2 L of glucose was performed in 23 nonselected chronic PD patients. Compared were long-term (>40 mo) with short-term PD patients (<40 mo), CAPD with APD patients, and those with a peritonitis incidence of >0.25/yr to those with an incidence of <0.25/yr. Dialysate/plasma (D/P) ratio and mass transfer area coefficient of creatinine, lymphatic absorption rate (LAR), transcapillary ultrafiltration, and effective ultrafiltration were measured. Long-term PD patients had higher D/P ratio of creatinine ($73.5 \pm 2.3\%$ *versus* $65.9 \pm 2.2\%$; $P < 0.01$) and higher LAR (243 ± 69 ml/4 h *versus* 96 ± 31 ml/4 h; $P < 0.03$), both resulting in lower effective ultrafiltration (242 ± 35 ml/4 h *versus* 324 ± 30 ml/4 h; $P < 0.05$). D/P ratio ($r = 0.66$) and LAR ($r = 0.67$) were positively correlated to PD duration. Patients on APD compared with those on CAPD and patients with a history of peritonitis compared with those without did not differ in terms of D/P ratio, mass transfer area coefficient, LAR, transcapillary ultrafiltration, and effective ultrafiltration. Lower ultrafiltration after long-term PD is both the result of increased small solute transport and increased lymphatic absorption. APD or CAPD modality and peritonitis incidence do not have a significant influence on small solute transport or fluid kinetics.

In peritoneal dialysis (PD), adequate peritoneal transport characteristics and fluid kinetics are of major importance for establishing the optimal treatment modality (1,2), and they play a pivotal role for patient's clinical outcome (3). Data by Davies *et al.* (3) showed that patients with increased small solute transport (dialysate/plasma ratio of creatinine [D/P_{crea}]) had a worse clinical outcome. D/P_{crea} turned out to be an independent predictor of death. On the basis of the individual peritoneal membrane properties, the optimal PD regimen must be found to optimize the fluid balance and to ensure adequate clearance targets. Both are even more important and challenging in anuric PD patients, as numerous studies have stressed (2,4,5). Data from the Canada-USA study (5) demonstrated that adequate total creatinine and urea clearance are strong predictors for the survival of chronic PD patients and are the basis for the clearance targets recommended by the Dialysis Outcome Quality Initiative guidelines (6). Optimal fluid balance is also an important factor for patient's clinical outcome because the incidence of ultrafiltration failure in PD, especially in anuric long-term PD patients, determines not only the system survival

of PD, but also the patient's mortality (3,7,8). Long-term PD patients often develop an increase in small solute transport and therefore experience decreased ultrafiltration capacity.

Macromolecule transport is reported to be stable (9–12). It is hypothesized that the incidence of ultrafiltration failure and altered transport characteristics with time on PD may reflect the chronic damage of the peritoneal membrane by the long-term influence of the "unphysiologic" solution (13). It is speculated that low pH, glucose (14), and the formation of advanced glycosylation end products (14–16) influence transcapillary and transcellular (aquaporins) water transport in PD patients (17). The importance of glucose in this regard is underlined by the histologic findings of diabetes-like alterations in the peritoneal capillaries of PD patients (18–20). Although the influence of PD treatment time and peritonitis episodes on transport characteristics is under debate (9,21), little is known about the influence of the PD modality (continuous ambulatory PD [CAPD] or automated PD [APD]) on peritoneal transport. If the effect of pH, glucose, and advanced glycosylation end products on the peritoneal membrane and transport properties is as negative as it is speculated to be, then it can be hypothesized that APD, with larger volumes of solution and more frequent contact times with fresh and unphysiologic dialysate, may enhance the negative effect of the solution. Because the usage of automated PD has steadily increased as a result of higher dialysis efficiency, lower rates of infections, and higher quality of life, this hypothesis is of clinical relevance (22–24).

Intraperitoneally applied dextran as a volume marker allows the exact calculation of peritoneal fluid kinetics (25–27). Dextran 70 is a macromolecule, and its disappearance rate corre-

lates to the lymphatic absorption rate (LAR). Transcapillary ultrafiltration (TCUF) is calculated from the dilution of dextran corrected for the amount disappeared by lymphatic absorption. The final effective ultrafiltration is the difference of TCUF and LAR.

In this study, we calculated detailed fluid kinetics and transport properties in chronic PD patients via an extended transport analysis with intraperitoneal dextran 70. We subsequently investigated peritoneal fluid kinetics in chronic PD patients and analyzed the influence of treatment time, PD modality, and peritonitis incidence.

Materials and Methods
Patients

After providing informed consent, 23 PD patients in our unit were subjected to an extended peritoneal transport analysis. Excluding any special selection criteria, the transport analysis was performed within 6 mo in patients who otherwise would have had a routine peritoneal equilibration test. The patients were stable on PD, had not changed from CAPD to APD or *vice versa* during the last year, and had been free of peritonitis for at least 3 mo before the transport analysis.

Baseline sociodemographic data and clinical characteristics of the patients assessed in this study are listed in Table 1. Average treatment time was 43.4 ± 9 mo, and peritonitis incidence was low, at 0.25/yr. Treatment time did not differ between APD and CAPD patients (40.3 ± 9.2 mo *versus* 48.2 ± 8.3 mo; NS) as a condition for a valid interpretation of the data. Only 2 of the 14 APD patients started PD treatment with CAPD for a shorter period of time (50 and 36 mo) compared with the final APD treatment (73 and 50 mo). At the day of transport analysis, both of these patients were on APD for more than 4 yr. The design of the study was prospective, nonrandomized, and cross sectional.

For treatment time, the patient group was divided into 2 groups of equal number by using the statistical median of 40 mo PD treatment time. For peritonitis, we first compared those patients with one or more peritonitis episodes in their history to those without peritonitis episodes. Because treatment time was significantly higher in patients

with an episode of peritonitis, we also looked for the peritonitis incidence, and we compared patients with a peritonitis incidence higher than the average of >0.25/yr with those with a lower incidence (<0.25/yr) and adjusted for equal treatment time ($n = 14$) by excluding patients with very short (<20 mo) and very long treatment times (>90 mo).

Methods

Patients provided written consent before the test procedure was initiated. The permeability analysis was performed with 2 L of 1.36% glucose solution (Dianeal; Baxter, Deerfield, IL) according to Krediet *et al.* (25) and Ho-dac-Pannekeet *et al.* (26). In brief, 6% dextran 70 (Longasteril; Fresenius, Bad Hamburg, Germany) in 0.9% NaCl was added to the test bag (final concentration of 8.4 g/L) and mixed thoroughly. During the first rinsing procedure, a blood sample was taken, and 20 ml of low-molecular-weight dextran 1 (Promit; Pharmalink AB) was intravenously administered to prevent possible anaphylactic reaction to dextran. The standardized 4-h dwell with the test bag was preceded and followed by a short rinsing bag (2 L of 1.36% glucose solution). Repetitive dialysate sampling of the test bag (at 0, 15, 60, 120, and 240 min) and from the effluent rinsing bag was performed; blood samples were drawn twice (at 0 and 240 min).

Glucose was determined by the glucose oxidase-peroxidase method and creatinine by the modified Jaffe method. Dextran was measured via high-performance gel-permeation liquid chromatography (28). An LC-250 isocratic pump system (Perkin-Elmer, Rodgau-Jügesheim, Germany), a Bio-Gel TSK 30 XL column (Bio-Rad, Munich, Germany), and a LC-30 refractive index detector (Perkin-Elmer) were used. Dialysate creatinine concentration was corrected for the glucose concentration (27). D/P_{crea} and mass transfer area coefficient of creatinine ($MTAC_{crea}$) were calculated (29). Fluid parameters with TCUF, lymphatic absorption (LAR), effective ultrafiltration, and residual peritoneal volume were calculated according to Krediet *et al.* (25) and Imholz *et al.* (27). The disappearance rate of dextran as a macromolecule correlates to the lymphatic absorption. LAR was determined from the difference between the instilled and the recovered amount of dextran (in the test bag and in the second rinsing bag) divided by the product of mean dialysate concentration and dwell time. TCUF was

Table 1. Anthropometrical and clinical data of 23 patients investigated with an extended transport analysis for fluid kinetics[a]

Parameter	All Patients	CAPD	APD	PD ≥40 mo	PD <40 mo	Peritonitis Episodes >0	Peritonitis Episodes =0
No. of patients	23	9	14	12	11	10	13
Age (yr)	48.4 ± 3.4	50 ± 3.6	47.4 ± 3.1	45.2 ± 3	51.9 ± 3.3	47.9 ± 3.1	48.8 ± 3.5
Gender (F/M)	7/16	4/5	3/11	3/9	4/7	2/8	5/8
Treatment time (mo)	43.4 ± 9	48.2 ± 8.3	40.3 ± 9.2	63.2 ± 7.9	21.7 ± 3.1	62.0 ± 9.1	29.1 ± 5.6
Peritonitis incidence (/yr)	0.25	0.33	0.19	0.3	0.1	0.8	0
BSA (m^2)	1.87 ± 0.2	1.89 ± 0.2	1.86 ± 0.2	1.87 ± 0.2	1.88 ± 0.2	1.87 ± 0.2	1.88 ± 0.2
Weekly CrCl (L/min per 1.73 m^2)	83.9 ± 33.6	96.7 ± 58.6	76.9 ± 29.9	84.7 ± 35.1	83.5 ± 32.8	82.7 ± 32.2	84.9 ± 39.9
Kt/V	2.58 ± 0.4	2.56 ± 0.4	2.61 ± 0.5	2.42 ± 0.4	2.74 ± 0.5	2.49 ± 0.4	2.65 ± 0.5
Residual renal function (GFR, ml/min)	3.25 ± 2.1	5.77 ± 3.6	1.82 ± 0.9	3.39 ± 2.1	3.11 ± 2.5	3.44 ± 2.6	3.1 ± 2.0

[a] CAPD, continuous ambulatory peritoneal dialysis; APD, ambulatory peritoneal dialysis; PD, peritoneal dialysis; BSA, body surface area; CrCl, creatinine clearance; Kt/V, urea removal index; GFR, glomerular filtration rate [(CrCl + urea clearance)/2].

calculated from the relative dilution of dextran corrected for the amount reabsorbed by LAR. Effective ultrafiltration was the difference between TCUF and LAR. Residual peritoneal volume was calculated from the recovery of dextran in the second rinsing bag.

Statistical Analyses

Results are expressed as mean $\pm$ SEM. Distribution was tested to be normal. Paired and unpaired t tests were used for statistical analysis. An alpha error at $P < 0.05$ was judged to be significant. Correlations were calculated by the least-squares method.

Results

The LAR of all patients was 0.72 ± 0.24 ml/min, resulting in an average lymphatic absorption of 172 ± 59 ml during the 4-h dwell. TCUF was 453 ± 61 ml, and average ultrafiltration after 4 h was 281 ± 35 ml. D/P$_{crea}$ was $69.9 \pm 2.5\%$; average MTAC$_{crea}$ was 11.6 ± 0.8 ml/min (Table 2).

Treatment Time

Long-term (>40 mo) PD patients showed a significant increase in D/P$_{crea}$ ($73.5 \pm 2.3\%$ versus $65.9 \pm 2.2\%$, $P = 0.01$) and a trend to increased MTAC$_{crea}$ (12.4 ± 0.8 ml/min versus 10.8 ± 0.6 ml/min, $P = 0.06$). They had a lower effective ultrafiltration after 4 h (242 ± 35 ml/4 h versus 324 ± 30 ml/4 h, $P = 0.04$). Lymphatic absorption was significantly higher in long-term PD patients than in short-term patients (243 ± 69 ml versus 96 ± 31 ml, $P = 0.03$) (Figure 1). Lymphatic absorption was well correlated to treatment time on PD ($r = 0.67$), as was D/P$_{crea}$ ($r = 0.66$) (both $P < 0.05$). According to regression analysis, the D/P$_{crea}$ increased by 2.3% and lymphatic absorption by 52.9 ml/4 h per patient treatment year.

PD Modality

APD and CAPD patients showed no significant difference concerning small solute transport data (D/P$_{crea}$ $69.7 \pm 1.7\%$ versus $70.1 \pm 1.8\%$; MTAC$_{crea}$ 11.8 ± 0.8 ml/min versus 11.3 ± 0.7 ml/min). Lymphatic absorption with 149 ± 58 ml/4 h versus 208 ± 58 ml/4 h and effective ultrafiltration with 291 ± 31 ml/4 h versus 265 ± 40 ml/4 h did not statistically differ between APD and CAPD patients (Figure 2).

Peritonitis

Small solute transport was increased in patients with a history of peritonitis. D/P$_{crea}$ was significantly increased ($73.5 \pm 2.2\%$ versus $67.0 \pm 2.4\%$, $P < 0.03$). MTAC$_{crea}$ did not reach statistical significance (12.2 ± 0.8 ml/min versus 11.2 ± 0.7 ml/min). Lymphatic absorption was also increased in patients with a history of peritonitis (239 ± 69 ml/4 h versus 122 ± 42 ml/4 h, $P = 0.05$). TCUF and effective ultrafiltration did not differ. However, because these data were not adjusted with regard to a longer treatment time in patients with an episode of peritonitis (62.0 ± 9.1 mo versus 29.1 ± 5.6 mo, $P = 0.005$), we corrected for treatment time on the basis of a peritonitis incidence higher or lower than 0.25/yr. Under these conditions, there was no difference in terms of small solute transport, lymphatic absorption, TCUF, and effective ultrafiltration (D/P$_{crea}$ $71.7 \pm 1.4\%$ versus $68.8 \pm 2.4\%$; MTAC$_{crea}$ 11.5 ± 0.5 ml/min versus 11.3 ± 0.9 ml/min; LAR 142 ± 30 ml/4 h versus 162 ± 44 ml/4 h; TCUF 411 ± 57 versus 423 ± 34 ml/4 h; effective ultrafiltration 269 ± 44 versus ml/4 h 261 ± 33 ml/4 h).

Discussion

The risk of developing a clinically relevant ultrafiltration failure increases with time on PD and is assumed to be approximately 35% after 6 yr (30). Four known mechanisms for ultrafiltration failure (10) are known. The most common reason is an increase in peritoneal transport for small solutes (type 1), resulting in a rapid loss of the osmotic gradient (9,10). More recently, the importance of the small pore, transcellular water transport by aquaporine channels (type 2) has been emphasized (14). Data demonstrate impaired aquaporine-mediated water transport in long-term PD patients (14–16). It is speculated that

Table 2. Small solute transport and fluid kinetics in 23 patients investigated with an extended transport analysis using intraperitoneally administered dextran[a]

Parameter	All Patients ($n = 23$)	CAPD ($n = 9$)	APD ($n = 14$)	PD ≥ 40 mo ($n = 12$)	PD <40 mo ($n = 11$)	Peritonitis Episodes >10 ($n = 10$)	Peritonitis Episodes $=0$ ($n = 13$)
D/P ratio$_{crea}$ (%)	69.9 ± 2.5	70.1 ± 1.8	69.7 ± 1.7	73.5 ± 2.3^{b}	65.9 ± 2.2	73.5 ± 2.2^{c}	67.0 ± 2.4
MTAC$_{crea}$ (ml/min)	11.6 ± 0.8	11.3 ± 0.7	11.8 ± 0.8	12.4 ± 0.8	10.8 ± 0.6	12.2 ± 0.8	11.2 ± 0.7
LAR (ml/4 h)	172 ± 59	208 ± 58	149 ± 58	243 ± 69^{d}	96 ± 31	239 ± 69^{c}	122 ± 42
TCUF (ml/4 h)	453 ± 61	472 ± 61	441 ± 61	484 ± 79	419 ± 29	506 ± 81	412 ± 35
UF (ml/4 h)	281 ± 35	265 ± 40	291 ± 31	242 ± 35^{d}	324 ± 30	267 ± 38	219 ± 55

[a] CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; PD, peritoneal dialysis; BSA, body surface area; CrCl creatinine clearance; Kt/V, urea removal index; GFR, glomerular filtration rate [CrCl + urea clearance)/2] D/P ratio, dialysat/plasma ratio of creatinine; MTAC, mass transfer area coefficient; LAR, lymphatic absorption rate; TCUF, transcapillary ultrafiltration; UF, effective ultrafiltration.

[b] $P \leq 0.01$ between long-term and short-term PD patients.

[c] $P \leq 0.05$ between patients with and without a peritonitis episode. After correction for different treatment time (62 ± 9 versus 29 ± 6 mo), no significance was found between patients with or without an episode of peritonitis.
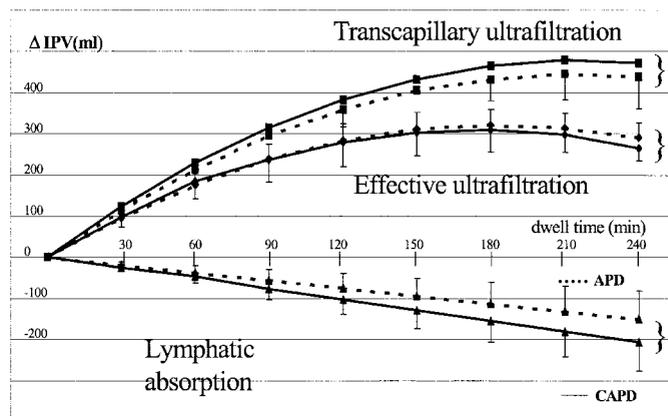
[d] $P \leq 0.05$ between long-term and short-term PD patients.
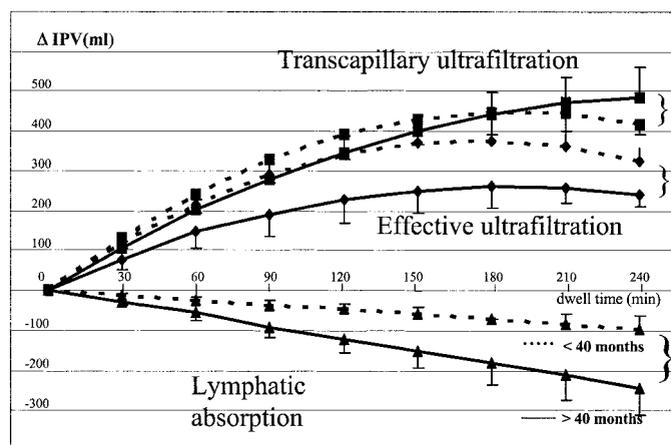
Figure 1. Graph illustrating fluid kinetics after treatment time on PD. Fluid kinetics of transcapillary ultrafiltration, lymphatic absorption, and effective ultrafiltration during the 4-h dwell with a 1.36% glucose solution ($n = 23$) are shown. Kinetics are compared for patients on peritoneal dialysis (PD) for <40 mo (dashed lines) and for >40 mo (solid lines). Significance was reached at a level of $P < 0.05$ for lymphatic absorption and effective ultrafiltration for PD >40 mo *versus* PD <40 mo. Δ IPV, change in intraperitoneal volume.

Figure 2. Graph illustrating fluid kinetics dependent on the mode of dialysis. Fluid kinetics of transcapillary ultrafiltration, lymphatic absorption, and effective ultrafiltration during the 4-h dwell with a 1.36% glucose solution ($n = 23$) are shown. Kinetics are compared for automated peritoneal dialysis patients (dashed lines) and continuous ambulatory peritoneal dialysis patients (solid lines); differences NS. Δ IPV, change in intraperitoneal volume.

this observation is due to the negative influence of glucose, glucose degradation products, and especially advanced glycosylation end products on the peritoneal membrane. Findings of diabetes-like alterations in the peritoneal vessels with increasing numbers of capillaries (20) emphasize the correlation of long-term exposure to PD solution, histologically proven signs of neoangiogenesis, and increased small solute transport due to a higher effective peritoneal surface area. A hypopermeable peritoneum (type 3) with a loss of peritoneal surface area, typically after severe peritonitis with adhesions, or in the case of sclerosing peritonitis, is probably a rare mechanism of effective ultrafiltration failure. A poor effective ultrafiltration due to high lymphatic absorption (type 4) is also considered to be rare.

In this study, however, we were able to show that the ultrafiltration capacity of long-term PD patients is impaired not only as a result of an increase in permeability for small solutes, but also as a result of a higher LAR. Lymphatic absorption was well correlated to treatment time on PD ($r = 0.67$). Because exact intraperitoneal fluid kinetics in chronic PD patients have hardly been investigated in this regard, this is a new result that emphasizes the importance of the lymphatic absorption for the changes of ultrafiltration capacity in general. Although the data presented here are the result of a cross-sectional study, which may weaken the its strength to a certain extent, we believe that the data actually represent the alterations of peritoneal transport over time, rather than being the result of patient selection. The study was performed in a cross-sectional mode within a narrow time interval, and patients were introduced to the study in a nonselected way. It is also unlikely that the patients with increased solute transport and lymphatic absorption had a positive bias concerning treatment time because they are the patients with a higher chance of ultrafiltration failure and

increased mortality on PD (3). This circumstance may therefore strengthen our findings.

In terms of lymphatic absorption, no comparable data are available to date on alterations during long-term PD treatment. In general, LAR was considered to be a stable parameter (10), depending only on the individual morphologic conditions of the lymphatic gaps of a PD patient. Acute changes in LAR have been attributed to other factors, such as the amount of intraperitoneal filling and pressure (31,32). In this regard, the position during PD treatment is also known to play a role: in the upright position, lymphatic absorption is slightly higher as a result of higher intra-abdominal pressure, compared with PD treatment in the recumbent position (33). On the basis of our data, one might speculate that a mechanical effect of long-term PD may be important for the increase of the lymphatic absorption in the long run. A continuously increased intraperitoneal pressure may have a dilating effect on the lymphatic gaps, finally resulting in higher lymphatic absorption after long-term treatment. Whether lower fill volumes or the use of APD with reduced intraperitoneal pressure as a result of the recumbent position during PD have a positive effect on fluid kinetics with regard to lower lymphatic absorption is an open question. The LAR in our study—1.01 ± 0.23 ml/min for long-term and 0.4 ± 0.13 ml/min for short-term PD patients—falls into the lower range of data provided in the literature, in which rates of 0.46 to 1.37 ml/min (14,26,34) are reported. This is most likely due to the high individual variability and the nondefined influence of treatment time reported in the literature.

This study found that APD and CAPD patients with comparable treatment time did not show significant differences concerning small solute transport, lymphatic absorption, TCUF, and effective ultrafiltration. However, although statistical significance was not reached, it was interesting to find that APD patients tended to have a lower lymphatic absorption compared with CAPD patients (149 ± 58 ml/4 h *versus* $208 \pm$

58 ml/4 h). When our findings are extended to a larger data-base, it may turn out that statistical significance is reached. On the basis of the data already discussed, this could support the hypothesis of a potential dilating effect of the higher intraperitoneal pressure in CAPD *versus* APD on the peritoneal lymphatic gaps.

Concerning the influence of peritonitis (Table 2) on peritoneal fluid kinetics, the data show enhanced solute transport and lymphatic absorption in patients with one or more episodes of peritonitis in the past. However, after correction for the longer treatment time of those patients, no significant difference in terms of small solute transport and fluid kinetics were found. These data need to be interpreted with caution because there still might be an effect of peritonitis on transport data that could not be detected as a result of the low overall peritonitis incidence of only 0.25/yr and the low number of events. Other studies reported that recurrences of peritonitis were related to an increase of solute transport (21).

We conclude that ultrafiltration capacity of chronic PD patients decreases with time on PD as a result of an increased permeability to small solutes as well as an increase in lymphatic absorption. PD modality (CAPD *versus* APD) had no statistically significant influence on fluid kinetics, as was found for the peritonitis incidence when corrected for treatment time.

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