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The contribution of free water transport and small pore transport to the total fluid removal in peritoneal dialysis

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Background. Water transport in peritoneal dialysis (PD) patients is across the small pores and water channels, the latter allowing free water transport. The objective of the study was to investigate the contribution of each transport route on transcapillary ultrafiltration (TCUF).

Methods. Standard peritoneal permeability analyses of 80 stable PD patients were analyzed. Twenty-nine patients were followed longitudinally. Fluid transport through small pores (SPT) was assessed by the amount of transported sodium. Free water transport (FWT) was calculated by subtracting SPT from TCUF. The contribution of FWT and SPT to the TCUF and water transport rates at any time point was computed.

Results. The ultrafiltered volume due to SPT increased gradually during the dwell, while FWT reached its maximum around 3 hours. The rate of FWT decreased continuously during the dwell. SPT decreased during the initial 2 hours and remained stable thereafter. At 60 minutes, the SPT ($P < 0.05$) and its contribution ($P < 0.05$) were positively related to the $MTAC_{creat}$. The contribution of FWT after 1 hour, but not the absolute amount, showed an inverse relationship. Peritoneal solute transport parameters ($P < 0.01$) and the contribution of SPT ($P = 0.08$), but none of the other fluid parameters showed a U-shape with the lowest values in the second year of PD ($P < 0.01$).

Conclusion. The dwell courses of water transport suggest that the activity of water channels is dependent and limited by the crystalloid osmotic pressure gradient, while other determinants are important in SPT. The time-course of SPT paralleled that of peritoneal solute transport parameters.

Fluid transport during peritoneal dialysis (PD) is induced by a net filtration pressure gradient, which depends on the capillary hydrostatic pressure minus the intraperitoneal hydrostatic pressure, the colloid osmotic pressure gradient caused by plasma proteins, and the crystalloid osmotic pressure gradient created mainly by glucose in the dialysis solution [1, 2]. The latter is known to be one of the major determinants of water transport [3]. Water is transported, according to the 3-pore model, primarily across small pores (radius 40 to 50 Å) and ultrasmall pores (radius <5 Å). A negligible amount is transferred across the large pores [3, 4]. The anatomic equivalents of the small pores are probably interendothelial clefts. The transport of water through the small pores is coupled to the transport of sodium. The ultrasmall pores, of which the morphologic parallel has been identified as aquaporin 1 in peritoneal capillaries and venules, are selective to water [5–7]. The crystalloid osmosis-induced free water transport across these pores is therefore associated with complete sieving of sodium, with a reflection coefficient of 1.0 [3].

It has been shown previously that the contribution of free water transport to the total fluid removal decreases during the dwell simultaneously with the dissipation of the osmotic gradient, caused by dilution and absorption of the osmotic agent [3, 8]. Using a 3.86% glucose solution, Smit et al found that the free water transport comprises approximately 48% of the total fluid flow in the first minute of the exchange, whereas after the first hour this drops to 35% [8]. The possible changes in the quantity of water transported through the small and ultrasmall pores during 4-hour exchanges and during the time course of PD treatment are unknown.

In the present study we investigated the contribution of free water transport and small pore water transport on the total transcapillary ultrafiltration during 4-hour dwell periods and their relation to other transport parameters. In a subgroup of patients in whom 3 peritoneal permeability tests were available the contribution of each path on the total water transport over the time on peritoneal dialysis was analyzed.

Key words: peritoneal dialysis, small pore transport, free water transport.

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METHODS

Eighty standard peritoneal permeability analyses (SPA) were studied in stable PD patients (61% female). The median age was 57 years (range 21–79). The median duration of PD was 15 months (range 1–73); 8% of the patients were on PD for more than 3 years. The SPA was carried out under standardized circumstances.

A subgroup of 29 patients in whom 3 tests were available was analyzed longitudinally. These patients underwent the first test within 6 months after the start of dialysis and thereafter once yearly. The first SPA was performed at 4 (1–6) months after the start of PD. The second SPA was done after 16 (12–19) months, and the third one after 28 (24–50) months. At the third test the last available SPA was taken.

The patients were peritonitis free at and during the 4 weeks preceding the test. All patients used commercially available glucose based dialysate (Dianeal®, Physioneal®, Baxter Healthcare, Ltd., IRL, Dublin, Ireland), 47 of them used 7.5% icodextrin (Extraneal®, Baxter Healthcare Ltd., IRL) for the long dwell. One patient had 1 dwell with an amino-acid based solution (Nutrineal®, Baxter Healthcare Ltd., IRL).

Procedure

The SPAs were performed during 4-hour dwell periods, as described previously [9, 10]. Briefly, after a rinsing procedure a fresh 3.86% glucose based dialysis solution (Dianeal®, Baxter Healthcare Ltd., IRL) was instilled for a test dwell. Dextran 70 (Hyskon®, Pharmacia AB, Emmer-Compascuum, Sweden, or Macrodex, NPBI, Emmer-Compascuum, The Netherlands), 1 g/L was added to calculate peritoneal fluid kinetics [11, 12]. The dialysate samples were taken before and at 10, 20, 30, 60, 120, 180, and 240 minutes after inflow of the test solution. Blood samples were taken at the beginning and at the end of the test. To prevent possible anaphylaxis to dextran 70, 20 mL of dextran 1 (Promiten®, Gynotec, Malden, The Netherlands) was injected intravenously before instillation of the test solution [13].

Measurements

The total dextran concentration in the dialysate was determined by high-performance liquid chromatography [14]. Creatinine and urate in plasma and effluent were measured by means of enzymatic methods (Hitachi, Boehringer Mannheim, Mannheim, Germany). All electrolytes were measured using ion selective electrodes. The glucose concentration was determined by the glucose oxidase-peroxidase assay (SMA II; Technicon, Terrytown, NJ, USA).

Calculations

Peritoneal solute and fluid transport parameters were calculated as described previously [9, 10]. Mass transfer area coefficients of low-molecular-weights solutes (MTAC) were calculated according to the Waniewski model [10, 15]. Solute concentrations are expressed as the solute concentration per volume of plasma water [16]. The osmotic pressure gradient across the peritoneal membrane at 240 minutes was calculated as the difference between the crystalloid osmotic pressure gradient and an estimation of the plasma colloid osmotic pressure. The former was calculated from glucose and urea concentrations in plasma and dialysate, assuming a small solute reflection coefficient of 0.03 [17]. The plasma colloid osmotic pressure was assessed according to Ho-dac-Pannekeet et al [18] using plasma albumin concentration in every patient.

The changes in the in situ intraperitoneal volume arise from transcapillary ultra- and backfiltration and lymphatic absorption. The changes in the in situ intraperitoneal volume during the dwell were calculated by means of dextran dilution after correction for incomplete recovery [11, 19, 20]. Net ultrafiltration is the difference between the in situ intraperitoneal volume and the initial intraperitoneal volume. For the measurement of effective lymphatic absorption (ELA) the disappearance of dextran from the peritoneal cavity is used. It is calculated as the convective loss of dextran during the dwell and expressed as peritoneal dextran clearance [21]. With this methodology, all pathways of uptake into the lymphatic system, both subdiaphragmatic and interstitial are included. The term effective lymphatic absorption is used because a clearance is applied to estimate a flow rate. The transcapillary ultrafiltration (TCUF) during the dwell was calculated by subtracting the initial in situ intraperitoneal volume from the theoretical intraperitoneal volume at any time point when both effective lymphatic absorption and the sampling were neglected [12, 19].

Because of the controversy in literature about peritoneal lymphatic absorption [22], additional calculations of transcapillary ultrafiltration were made in which the theoretical intraperitoneal volume per patient was calculated as the sum of the in situ-intraperitoneal volume in every time point and a lymphatic absorption rate of 0.3 mL/min. The latter was chosen because this is the value used in the 3-pore model [3]. The transcapillary ultrafiltration rate (TCUFR) is calculated by dividing the transcapillary filtrate by the dwell time [12].

For the calculation of water transport, a diffusion correction of sodium sieving was performed using the MTAC of urate [23].

Free water transport was calculated by subtracting transcapillary ultrafiltration coupled to Na^+ transport from the total ultrafiltration [8]. The time point

10 minutes after completion of inflow was taken as the start value. The total ultrafiltration at any time point of the dwell was calculated by subtracting the theoretical intraperitoneal volume at 10 minutes from the theoretical intraperitoneal volume at that moment.

Small pore transport was calculated by multiplying the theoretical intraperitoneal volume at any time point during the dwell by the dialysate sodium concentration corrected for diffusion. By subtracting the amount of sodium at 10 minutes from the amount at every point, the quantity of sodium transported within each period of the dwell was calculated. The fluid transport through the small pores at every time point was computed by dividing the amount of transported sodium with the sodium concentration in the small pores, that is, the average of the plasma and the dialysate sodium concentration.

At each moment, the fluid transport through the small pores was then subtracted from the total ultrafiltered fluid volume, resulting in free water transport within every analyzed period of the dwell. The free water transport and the small pore fluid transport are expressed as absolute values and as their contribution to the total ultrafiltration.

The fluid volume transported in any time interval divided by the number of minutes in this time period resulted in the rate of fluid transport at any time point.

Statistical analyses

Due to asymmetric distribution, results are expressed as medians and ranges. Spearman correlation coefficient was used for the correlations between fluid transport and $MTAC_{creat}$. The Kruskal-Wallis and Mann-Whitney test were applied to compare differences between the different time points during the SPA and between the SPAs in the longitudinal study. The linear mixed model procedure was used to test whether a general model for a time course of the fluid kinetics exists. This analysis examines the average changes in subjects, taking the association between variables into account in every individual, measured at separate time points.

RESULTS

Parameters for solute and fluid transport at the end of the dwell of all patients are listed in Table 1. The correlations with $MTAC_{creat}$ are also given. Five of the patients had a net ultrafiltration less than 400 mL after 4 hours. The osmotic pressure gradient at the end of the dwell had a median value of 2 mm Hg. It was negative in only 24 patients and positive in the other 56, so favoring the fluid transport from the circulation toward the peritoneal cavity, especially because a hydrostatic pressure gradient of 9 mm Hg is also present. $MTAC_{creat}$ was positively related to glucose absorption and effective lymphatic absorption, and negatively to net ultrafiltration. In Table 2 the fluid transport parameters within the first hour and at the end of the dwell and their relation to $MTAC_{creat}$ are shown. The same data of the additional analysis using a lymphatic flow of 0.3 mL/min are given in Table 3.

Regardless of the calculation method, $MTAC_{creat}$ showed a positive correlation with the amount of small pore fluid transport at 60 minutes and its contribution to total ultrafiltration. Likewise, the contribution of free water transport showed a negative correlation with the $MTAC_{creat}$. A negative relationship between the amount of free water transport and the $MTAC_{creat}$ was only

Table 1. The characteristics of peritoneal fluid and solute transport at the end of the dwell in 80 PD patients included in the cross-sectional study

	Median	Range	Correlation coefficient with $MTAC_{creat}$ *mL/min*
$MTAC_{creat}$ *mL/min*	9.1	1.9–30.4	
GA %	64	44–89	0.70[c]
Crystalloid OPG *mm Hg*	21	1–50	−0.24[a]
Colloid OPG *mm Hg*	18	15–27	−0.26[a]
ELA *mL*	308	53–781	0.29[b]
NUF *mL*	635	95–1305	−0.34[c]

Abbreviations are: $MTAC_{creat}$, mass transfer area coefficient of creatinine; GA, glucose absorption; ELA, effective lymphatic absorption; TCUF, transcapillary ultrafiltration; NUF, net ultrafiltration; OPG, osmotic pressure gradient. The correlations between transport parameters and $MTAC_{creat}$ are also given.
[a] $P \leq 0.05$; [b] $P \leq 0.01$; [c] $P \leq 0.005$.

Table 2. The characteristics of peritoneal water transport using the changes in the theoretical intraperitoneal volume, calculated as the sum of the in situ intraperitoneal volume and measured effective lymphatic absorption (see **Methods**) at 60 and 240 minutes in the 80 patients of the cross-sectional study

	Median	Range	Correlation coefficient with $MTAC_{creat}$ *mL/min*
Analysis of fluid transport at 60 minutes			
$TCUF_{0-60}$ *mL*	465	84–1339	0.14
SPT_{0-60} *mL*	273	50–1117	0.25[a]
FWT_{0-60} *mL*	180	48–375	−0.18
$SPTC_{0-60}$ %	60	13–87	0.42[b]
$FWTC_{0-60}$ %	40	13–87	−0.42[b]
Analysis of fluid transport at 240 minutes			
$TCUF_{0-240}$ *mL*	978	377–1941	0.19
SPT_{0-240} *mL*	760	210–1732	0.07
FWT_{0-240} *mL*	222	23–514	−0.46[b]
$SPTC_{0-240}$ %	77	56–98	0.39[b]
$FWTC_{0-240}$ %	23	2–44	−0.39[b]

Abbreviations are: $TCUF_{0-60}$, $TCUF_{0-240}$, transcapillary ultrafiltration within the first hour and after 4 hours; SPT_{0-60}, SPT_{0-240}, small pore fluid transport within the first hour and after 4 hours; FWT_{0-60}, FWT_{0-240}, free water transport within the first hour and after 4 hours; $SPTC_{0-60}$, $SPTC_{0-240}$, contribution of small pore transport to the total transcapillary ultrafiltration within the first hour and after 4 hours; $FWTC_{0-60}$, $FWTC_{0-240}$, contribution of free water transport to the total ultrafiltration in the first hour and after 4 hours; $MTAC_{creat}$, mass transfer area coefficient of creatinine.
[a] $P \leq 0.01$; [b] $P \leq 0.005$.

Table 3. The characteristics of peritoneal water transport using the changes in the theoretical intraperitoneal volume, calculated as the sum of the in situ inraperitoneal volume and the lymphatic absorption set at a lymphatic absorption rate of 0.3 mL/min (see **Methods**) at 60 and 240 minutes in the PD patients of the cross-sectional study

	Median	Range	Correlation coefficient with $MTAC_{creat}$ *mL/min*
Analysis of fluid transport at 60 minutes			
$TCUF_{0-60}$ *mL*	390	96–1276	0.12
SPT_{0-60} *mL*	239	25–1033	0.27[a]
FWT_{0-60} *mL*	154	28–348	−0.31[a]
$SPTC_{0-60}$ %	62	18–92	0.47[b]
$FWTC_{0-60}$ %	38	8–82	−0.47[b]
Analysis of fluid transport at 240 minutes			
$TCUF_{0-240}$ *mL*	645	412–3341	−0.30[a]
SPT_{0-240} *mL*	434	149–2982	0.09
FWT_{0-240} *mL*	208	9–744	−0.62[b]
$SPTC_{0-240}$ %	68	33–99	0.51[b]
$FWTC_{0-240}$ %	32	1–67	−0.51[b]

See Table 2 for abbreviations.
[a] $P \leq 0.01$; [b] $P \leq 0.005$.

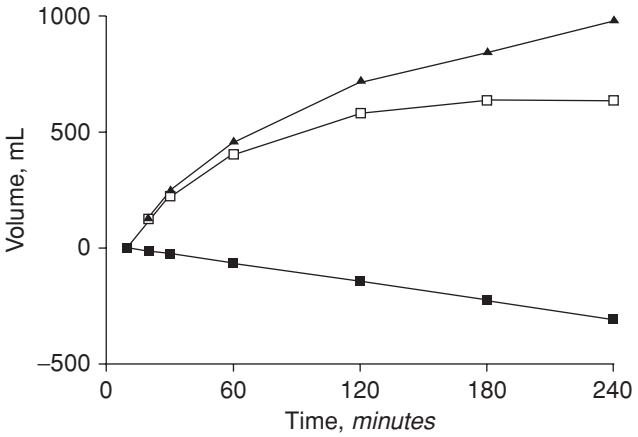

Fig. 1. Fluid profiles of 80 patients included in the cross-sectional part of the study. The total transcapillary ultrafiltration (closed triangles) during the 4-hour dwell, net ultrafiltration (open squares), and effective lymphatic absorption (closed squares).

found in the analysis with a lymphatic absorption rate of 0.3 mL/min.

At 240 minutes, small pore transport was not related to the $MTAC_{creat}$, but its contribution to total ultrafiltration showed a positive correlation. Conversely, negative correlations were present in both models between the amount of free water transport at 240 minutes and its contribution to total ultrafiltration.

In the cross-sectional analysis no relationship was present between the duration of PD and solute transport parameters. Similarly, the transcapillary ultrafiltration ($r = -0.03$) and total net ultrafiltration ($r = -0.06$) at the end of the dwell were not related to the time on PD. Furthermore, no correlation was found between the latter and fluid transport after 1 hour of the dwell. Similar results were found in the analyses using a fixed lymphatic absorption rate of 0.3 mL/min (data not shown).

The time courses of total transcapillary ultrafiltration, net ultrafiltration, and effective lymphatic absorption during the 4-hour dwell are shown in Figure 1. In Figure 2, the curves of total transcapillary ultrafiltration, of small pore fluid transport, and of free water transport are depicted (upper panel). Their rates are also presented (lower panel). Similar results were found in both analyses. The ultrafiltered volume caused by free water transport reached its maximum between 2 and 3 hours. Conversely, the volume due to small pore transport showed a gradual increase during the dwell. All water transport rates decreased during the dwell. The most rapid decrease was found for the free water transport rate. In contrast, the small pore fluid transport rate remained stable during the last 2 hours of the dwell: the values at 120 and 180 minutes were not significantly different from those at 240 minutes.

The peritoneal transport characteristics of the subgroup followed longitudinally are given in Table 4. The time courses of the transport characteristics are shown in Figures 2 and 3. A significant decrease was found for the $MTAC_{creat}$ between the first and second SPA ($P = 0.01$), followed by a significant increase between the second and third test ($P = 0.04$). The same trend was found for glucose absorption ($P = 0.03$ and $P = 0.02$). The effective lymphatic absorption decreased significantly between the first and second SPA ($P = 0.04$), but not between the second and third one. The contribution of free water transport on the total fluid removal within first hour increased significantly ($P = 0.02$) between the first and second measurement. This was associated with a significant decrease of the contribution of small pore transport at 60 minutes ($P = 0.04$). No trend was present between the second and third SPA for the contribution of free water transport within the first hour and that of small pore transport within the first hour. No differences were found for the other parameters between the first and second test or between the second and third one. In the linear mixed model, only the time courses of $MTAC_{creat}$ ($P < 0.01$) and glucose absorption ($P = 0.04$) were significant, in a model in which an initial decrease is followed by a subsequent increase. The model was not significant for the other parameters, although a tendency ($P = 0.08$) was found for the contribution of small pore fluid transport within the first hour.

DISCUSSION

The small pores in the vascular wall and water channels are the major pathways of water transport during peritoneal dialysis [3]. The present study has shown that

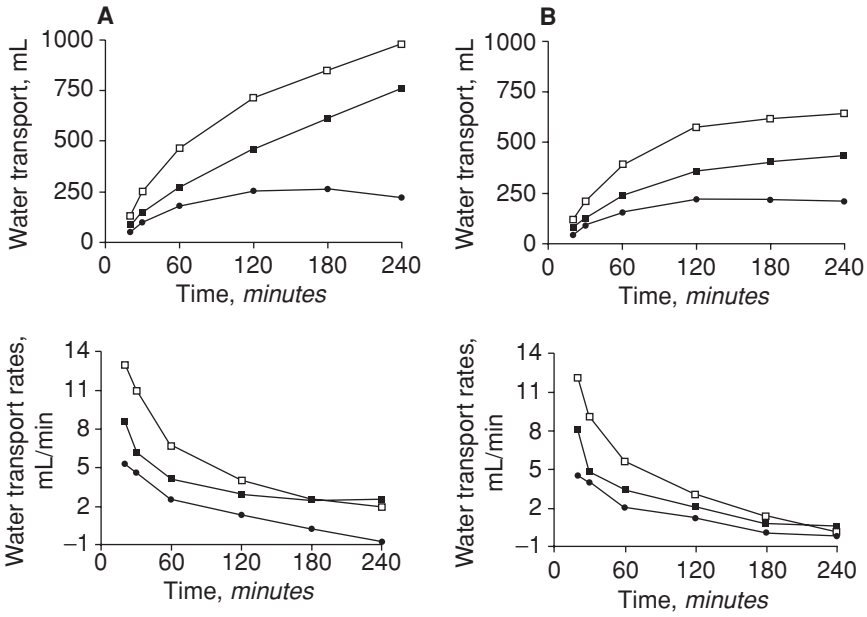

Fig. 2. Peritoneal fluid kinetics for the patients of the cross-sectional study. In panels (*A*) values obtained using the ELAR calculated in every patient are used, and in panels (*B*) the values were calculated according to 3-pore model using a lymphatic absorption rate of 0.3 mL/min. In the upper panels the total transcapillary ultrafiltration during the 4-hour dwell (open squares), the transport through the small pores (closed squares), and the free water transport (closed circles) are shown. The lower panels demonstrate the changes in the rate of the transcapillary ultrafiltration (open squares), of the small pore transport (closed squares), and of the free water transport (closed circles).

Table 4. Medians and ranges of peritoneal fluid and solute transport parameters of 29 PD patients in whom 3 SPAs were available

	1.SPA	2.SPA	3.SPA
Duration of PD *months*	4 (1–7)	16 (12–19)	28 (24–50)
Solute and fluid transport parameters after 4 hours			
$MTAC_{creat}$ *mL/min*	9.8 (4.8–17.5)	7.8 (1.9–13.6)[a]	10.2 (4.4–18.2)[c]
GA%	69 (45–76)	58 (45–80)[b]	67 (44–82)[c]
ELA *mL*	413 (38–1297)	260 (53–751)[b]	321 (133–669)
TCUF *mL*	1015 (638–1611)	1010 (577–1467)	907 (237–1811)
NUF *mL*	651 (300–1228)	670 (333–1287)	589 (95–1295)
Fluid transport at 60 minutes			
$TCUF_{0-60}$ *mL*	506 (287–1103)	468 (127–676)	432 (84–812)
SPT_{0-60} *mL*	301 (146–1006)	285 (61–494)	292 (50–515)
FWT_{0-60} *mL*	178 (94–281)	190 (64–464)	182 (56–427)
$SPTC_{0-60}$%	65 (42–91)	58 (31–73)[b]	62 (35–81)
$FWTC_{0-60}$%	35 (9–58)	42 (27–69)[b]	38 (19–65)

See Table 1 and 2 for abbreviations.
[a] $P = 0.01$ between the first and second test; [b] $P = 0.05$ between the first and second SPA; [c] $P = 0.05$ between the second and third test.

the contribution of free water transport after 60 minutes averaged 40% of the total transcapillary ultrafiltration, a value very similar to the one modeled by Rippe et al [3]. The contribution of small pore fluid transport and the absolute amount of it were strongly correlated with peritoneal solute transport parameters.

Based on the 3 pores model [3, 24] 90% of the peritoneal ultrafiltration coefficient, which is the product of hydraulic permeability (Lp) and peritoneal surface area (S), is dependent on small pores. The water channels contribute approximately 2% to it. Yet, because of the low small pore reflection coefficient of glucose and its high aquaporin reflection coefficient (1.0), 40% to 50% of fluid removal during peritoneal dialysis, with a 3.86% glucose-based dialysis solution, is through water channels. According to the 3-pore model the fractional free water transport rate would remain constant during the first few hours of the dwell [4].

Apart from the lower values of water transport parameters, any other significant discrepancies were not found in the present study using 2 different approaches for calculations of fluid kinetics. The disparity can be explained by the magnitude of the lymphatic flow, which by definition influences the magnitude of the calculated transcapillary ultrafiltration at every time point.

High peritoneal small solute transport parameters ($MTAC_{creat}$,% glucose absorption) reflect the presence of a large vascular peritoneal surface area (ie, a large number of perfused peritoneal vessels [2, 25], so a large number of small pores and water channels). The positive correlations between the $MTAC_{creat}$ and both the absolute amount of small pore fluid transport and its contribution to total transcapillary ultrafiltration support the contention that an important part of small pore fluid transport is caused by nonosmotic pressure gradients. Yet, some decrease in the small-pore transcapillary

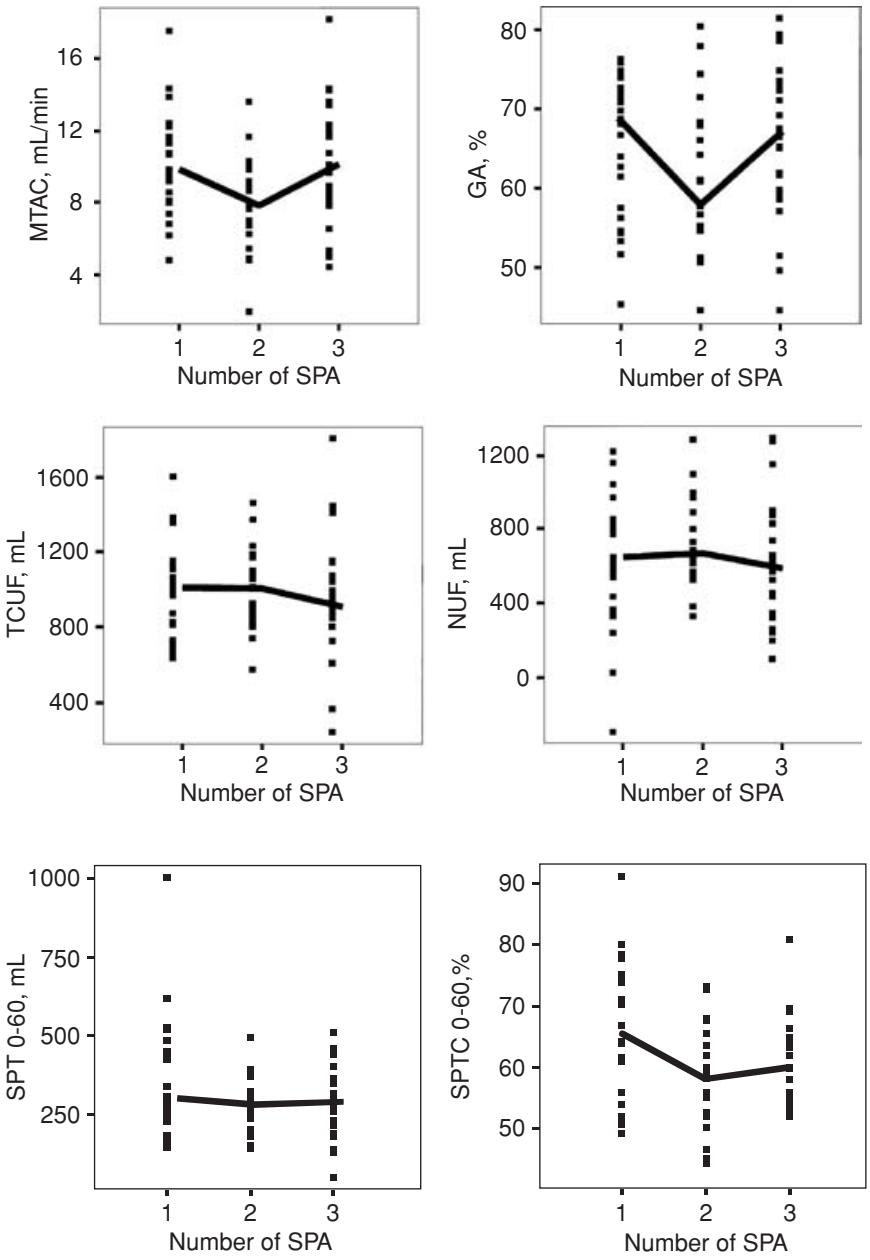

Fig. 3. The overall time trends of fluid and solute parameters depicted in mixed linear models. The lines represent medians. The *P* values indicate the significance of the firmness of the model. MTAC, mass transfer area coefficient of creatinine ($P < 0.01$); GA, glucose absorption ($P = 0.04$); TCUF, transcapillary ultrafiltration ($P = 0.5$); NUF, total net ultrafiltration ($P = 0.4$).

Fig. 4. The time course of small pore transport. The lines represent medians. The *P* value indicates the significance of the time trend in a mixed linear model. SPT_{0-60}, the small pore transport within the first hour ($P = 0.24$); $SPTC_{0-60}$, contribution of small pores transport within the first hour on the total ultrafiltration ($P = 0.08$).

ultrafiltration rate (8.6 mL/min to 3.2 mL/min) was found during the 4-hour dwell. This might have been caused by both a small decrease in the hydrostatic pressure gradient due to an increase in peritoneal volume and by the decrease in the crystalloid osmotic pressure gradient. Nevertheless, the overall osmotic pressure gradient, together with the hydrostatic pressure gradient at the end of the dwell, were still in favor of fluid transport from the circulation to the peritoneal cavity.

According to the computer simulations of the 3-pore model, the decline of the small pore transport and that of free water transport is parallel [4]. In contrast, our results show that the small pore transport levels off in the second half of the dwell, regardless of the methodology used. The discrepancy might have been caused by the assumption in the 3-pore model that the colloid osmotic gradient at the end of the dwell exceeds the crystaloid osmotic gradient, causing backfiltration. The positive value of the osmotic pressure gradient at the end of the dwell as present in the majority of patients in combination with a hydrostatic gradient that is likely to average 9 mm Hg [2] is likely to explain the absence of negative small pore fluid transport during 4-hour exchanges using 3.86% glucose dialysate.

Free water transport is very much dependent on the crystalloid osmotic pressure gradient. The inverse relationship between the $MTAC_{creat}$ and the contribution of free water transport to total transcapillary ultrafiltration can easily be explained: the presence of a large vascular

surface area leads to a high glucose absorption rate and, consequently, a rapid disappearance of the osmotic gradient. This observation underlines the importance of a crystalloid osmotic pressure gradient for free water transport. We did not find a correlation between the $MTAC_{creat}$ and the total amount of free water transport in 1 of the 2 analyses and a negative correlation in the other, though not very strong: the explained variance was 3% in 1 and 9.6% in the other. This can be explained because free water transport is likely to be dependent on 2 opposing mechanisms: a large vascular surface area means that many water channels are available for free water transport, but that their efficiency is decreased by the rapid disappearance of the osmotic gradient. As expected, a marked decrease in the free water transport rate was found during the 4-hour dwell: from a median value of 5.3 mL/min to −0.8 mL/min in 1 of the 2 analyses and from 2.2 mL/min to –0.3 mL/min in the other. The negative values after 4 hours are likely to be an artifact caused by a slight overestimation of sodium diffusion. The $MTAC_{urate}$ is used to predict the concentration gradient of sodium by diffusion [23]. In this model the MTAC is assumed to remain constant during the dwell, and a decrease in the ultrafiltration rate is not taken into account. This might lead to some overestimation of sodium diffusion resulting in lower values of calculated free water transport. Especially during the last part of the dwell, this may lead to slightly negative values for the free water transport rate [26].

The positive relationship between effective lymphatic absorption and small solute transport parameters has already been reported previously [21, 27, 28]. This is also the case for the inverse relationship between the mass transfer area coefficient of creatinine and net ultrafiltration [17, 29].

Similar to the results of other cross-sectional studies [30], no relationship was found between peritoneal transport parameters and the duration of peritoneal dialysis. This may be due to the small amount of patients with ultrafiltration failure [31] and the low number of patients on long-term peritoneal dialysis. Only longitudinal studies with a long follow-up have demonstrated an increase in peritoneal solute transport and a decrease in net ultrafiltration with the duration of peritoneal dialysis [32, 33].

The present longitudinal study showed a U-shaped time course for peritoneal solute transport parameters and a tendency to this for the contribution of small pore fluid transport. We have reported similar results for peritoneal solute transport in another peritoneal dialysis patient population [34]. The observation that higher values are often found in the first year of treatment compared to the second year are also in accordance with the results of Lo et al [35], showing a tendency for the dialysate/plasma ratio of creatinine to decrease, especially in the 'high' and 'high average' transport groups. High initial values for solute transport parameters are likely to be related to the production of cytokines [36] and vascular endothelial growth factor, probably by mesothelial cells [37, 38]. It is speculative whether the lower values after 12 to 19 months of treatment could be caused by a decreased capability of the mesothelium to produce vasoactive substances. The subsequent rise observed after more than 2 years of peritoneal dialysis is in accordance with the results of other longitudinal studies [32, 33], and may be due to the development of peritoneal membrane alterations.

CONCLUSION

It can be concluded that the presence of a large vascular surface area allows high rates of water transport through the small pores. It also leads to a rapid loss of the osmotic gradient, which then becomes insufficient for optimal activity of the water channels. The fast decline in the velocity of the water transport across water channels indicates that free water transport is much more dependent on the osmotic gradient than the small pore water transport, in which nonosmotic pressure gradients are also important determinants. Furthermore, the effective vascular peritoneal surface area is temporarily increased in the initial phase of peritoneal dialysis. The subsequent decrease is followed by an increase in long-term PD patients, suggesting peritoneal angiogenesis, a more permanent morphologic alteration of the peritoneal surface area.

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REFERENCES

1. Gokal R, Khanna R, Krediet RT, *et al*: *Textbook of Peritoneal Dialysis*, 2nd ed, Great Britain, Kluwer Academic Publishers, 2000, pp 153
2. Krediet RT, Lindholm B, Rippe B: Pathophysiology of peritoneal membrane failure. *Perit Dial Int* 20(Suppl 4):S22–S42, 2000
3. Rippe B, Stelin G, Haraldsson B: Computer simulations of peritoneal fluid transport in CAPD. *Kidney Int* 40:315–325, 1991
4. Rippe B, Venturoli D, Simonsen O, de Arteaga J: Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. *Perit Dial Int* 24:10–27, 2004
5. Carlsson O, Nielsen S, Zakaria E, Rippe B: In vivo inhibition of transcellular water channels (aquaporin-1) during acute peritoneal dialysis in rats. *Am J Physiol* 271:H2254–H2262, 1996
6. Devuyst O, Nielsen S, Cosyns JP, *et al*: Aquaporin-1 and endothelial nitric oxide synthase expression in capillary endothelia of human peritoneum. *Am J Physiol* 275:H234–H242, 1998
7. Pannekeet MM, Mulder JB, Weening JJ, *et al*: Demonstration of aquaporin-CHIP in peritoneal tissue of uremic and CAPD patients. *Perit Dial Int* 16(Suppl 1):S54–S57, 1996
8. Smit W, Struijk DG, Ho-Dac-Pannekeet MM, Krediet RT: Quantification of free water transport in peritoneal dialysis. *Kidney Int* 66:849–854, 2004
9. Pannekeet MM, Imholz AL, Struijk DG, *et al*: The standard peritoneal permeability analysis: A tool for the assessment of peritoneal permeability characteristics in CAPD patients. *Kidney Int* 48:866–875, 1995
10. Smit W, van Dijk P, Langedijk MJ, *et al*: Peritoneal function and assessment of reference values using a 3.86% glucose solution. *Perit Dial Int* 23:440–449, 2003

11. Imholz AL, Koomen GC, Struijk DG, *et al*: Residual volume measurements in CAPD patients with exogenous and endogenous solutes. *Adv Perit Dial* 8:33–38, 1992
12. Krediet RT, Struijk DG, Koomen GC, Arisz L: Peritoneal fluid kinetics during CAPD measured with intraperitoneal dextran 70. *ASAIO Trans* 37:662–667, 1991
13. Ljungstrom KG, Renck H, Hedin H, *et al*: Prevention of dextran-induced anaphylactic reactions by hapten inhibition. I. A Scandinavian multicenter study on the effects of 10 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 149:341–348, 1983
14. Koomen GC, Krediet RT, Leegwater AC, *et al*: A fast reliable method for the measurement of intraperitoneal dextran 70, used to calculate lymphatic absorption. *Adv Perit Dial* 7:10–14, 1991
15. Waniewski J, Werynski A, Heimburger O, Lindholm B: Simple membrane models for peritoneal dialysis. Evaluation of diffusive and convective solute transport. *ASAIO J* 38:788–796, 1992
16. Waniewski J, Heimburger O, Werynski A, Lindholm B: Aqueous solute concentrations and evaluation of mass transport coefficients in peritoneal dialysis. *Nephrol Dial Transplant* 7:50–56, 1992
17. Krediet RT, Zemel D, Imholz AL, *et al*: Indices of peritoneal permeability and surface area. *Perit Dial Int* 13(Suppl 2):S31–S34, 1993
18. Ho-Dac-Pannekeet MM, Schouten N, Langendijk MJ, *et al*: Peritoneal transport characteristics with glucose polymer based dialysate. *Kidney Int* 50:979–986, 1996
19. Imholz AL, Koomen GC, Struijk DG, *et al*: Effect of dialysate osmolarity on the transport of low-molecular-weight solutes and proteins during CAPD. *Kidney Int* 43:1339–1346, 1993
20. Struijk DG, Krediet RT, Imholz AL, *et al*: Fluid kinetics in CAPD patients during dialysis with a bicarbonate-based hypoosmolar solution. *Blood Purif* 14:217–226, 1996
21. Struijk DG, Koomen GC, Krediet RT, Arisz L: Indirect measurement of lymphatic absorption in CAPD patients is not influenced by trapping. *Kidney Int* 41:1668–1675, 1992
22. Krediet RT: The effective lymphatic absorption rate is an accurate and useful concept in the physiology of peritoneal dialysis. *Perit Dial Int* 24:309–313, 2004
23. Zweers MM, Imholz AL, Struijk DG, Krediet RT: Correction of sodium sieving for diffusion from the circulation. *Adv Perit Dial* 15:65–72, 1999
24. Rippe B, Stelin G: Simulations of peritoneal solute transport during CAPD. Application of two-pore formalism. *Kidney Int* 35:1234–1244, 1989
25. Numata M, Nakayama M, Nimura S, *et al*: Association between an increased surface area of peritoneal microvessels and a high peritoneal solute transport rate. *Perit Dial Int* 23:116–122, 2003
26. Venturoli D, Rippe B: Validation by computer simulation of two indirect methods for quantification of free water transport in peritoneal dialysis. *Perit Dial Int* 25:77–84, 2005
27. Imholz AL, Koomen GC, Voorn WJ, *et al*: Day-to-day variability of fluid and solute transport in upright and recumbent positions during CAPD. *Nephrol Dial Transplant* 13:146–153, 1998
28. Michels WM, Zweers MM, Smit W, *et al*: Does lymphatic absorption change with the duration of peritoneal dialysis? *Perit Dial Int* 24:347–352, 2004
29. Sobiecka D, Waniewski J, Werynski A, Lindholm B: Peritoneal fluid transport in CAPD patients with different transport rates of small solutes. *Perit Dial Int* 24:240–251, 2004
30. Park MS, Lee J, Lee MS, *et al*: Peritoneal solute clearances after four years of continuous ambulatory peritoneal dialysis (CAPD). *Perit Dial Int* 9:75–78, 1989
31. Mujais S, Nolph K, Gokal R, *et al*: Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. *Perit Dial Int* 20(Suppl 4):S5–21, 2000
32. Davies SJ, Phillips L, Naish PF, Russell GI: Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J Am Soc Nephrol* 12:1046–1051, 2001
33. Selgas R, Fernandez-Reyes MJ, Bosque E, *et al*: Functional longevity of the human peritoneum: How long is continuous peritoneal dialysis possible? Results of a prospective medium long-term study. *Am J Kidney Dis* 23:64–73, 1994
34. Struijk DG, Krediet RT, Koomen GC, *et al*: A prospective study of peritoneal transport in CAPD patients. *Kidney Int* 45:1739–1744, 1994
35. Lo WK, Brendolan A, Prowant BF, *et al*: Changes in the peritoneal equilibration test in selected chronic peritoneal dialysis patients. *J Am Soc Nephrol* 4:1466–1474, 1994
36. Pecoits-Filho R, Araujo MR, Lindholm B, *et al*: Plasma and dialysate IL-6 and VEGF concentrations are associated with high peritoneal solute transport rate. *Nephrol Dial Transplant* 17:1480–1486, 2002
37. Rodrigues A, Martins M, Santos MJ, *et al*: Evaluation of effluent markers cancer antigen 125, vascular endothelial growth factor, and interleukin-6: Relationship with peritoneal transport. *Adv Perit Dial* 20:8–12, 2004
38. van Esch S, Zweers MM, Jansen MA, *et al*: Determinants of peritoneal solute transport rates in newly started nondiabetic peritoneal dialysis patients. *Perit Dial Int* 24:554–561, 2004