Various aspects of peritoneal water transport

Smit, W.

Citation for published version (APA):
Chapter 8

Analysis of the prevalence and causes of ultrafiltration failure during long-term peritoneal dialysis; a cross-sectional study

Watske Smit¹, Natalie Schouten¹, Nicole van den Berg¹, Monique J Langedijk¹, Dirk G Struijk², Raymond T Krediet¹ for the Netherlands Ultrafiltration Failure Study Group³
¹Department of Nephrology, Academic Medical Center, University of Amsterdam
²Dianet Foundation, Amsterdam-Utrechт
³Netherlands UFF Study Group*

* Netherlands UFF Study Group consists of: Dr. RJ Birnie, Amsterdam; Dr FTh de Charro, Rotterdam; Dr GG van Essen, Den Haag; Dr MWJA Fieren, Rotterdam; Dr J van Geelen, Alkmaar; Dr M Koolen, Den Bosch; Dr G Kolsters, Zwolle; Drs PB Leurs, Goes; Dr R van Leusen, Arnhem; Dr AAH Rens, Breda; Dr J Vos, Utrecht; Dr AWL van der Wall Bake, Veldhoven; Prof Dr PM ter Wee, Amsterdam
Abstract

Introduction: Ultrafiltration failure (UFF) is a major complication of PD. It can occur at any stage of PD, but develops in time and is therefore especially important in long-term treatment. To investigate its prevalence and to identify possible causes, we performed a multicenter study in the Netherlands, where patients treated with PD for more than 4 years were studied, using a peritoneal function test (SPA) with 3.86% glucose. UFF was defined as net ultrafiltration of < 400 mL after a 4 hours dwell.

Results: 55 patients, unselected for the presence or absence of UFF were analyzed. Mean age was 48 years (18-74), duration of PD ranged from 48 to 144 months (median 61). UFF was present in 20 patients (36%). Patients with and without UFF did not differ in age, or in duration of PD. Median values for patients with normal UF compared to patients with UFF were: net UF 659 vs. 120 mL, (p < .001), TCUFR 3.8 vs 2.1 mL/min (p < 0.01), effective lymphatic absorption 1.0 vs. 1.6 mL/min (p < 0.05), MTAC creatinine 9.0 vs. 12.9 mL/min (p < 0.01), D/P creatinine 0.71 vs. 0.86 (p < 0.01), glucose absorption 60 vs. 73 % (p < 0.01) and maximum dip in D/P sodium (as a measure of free water transport) 0.109 vs. 0.032 (p < 0.01). As causes for UFF high MTAC creatinine, defined as >12.5 mL/min or a glucose absorption >72%, both reflecting a large vascular surface, a lymphatic absorption rate (LAR) of >2.14 mL/min and a decreased dip in D/P sodium of <0.046 were identified. Most patients had a combination of causes (12 patients), whereas in 3 patients there was only a decreased dip in D/P sodium, in 1 patient only high MTAC creatinine and only high LAR in 2 patients. We could not identify a cause in 2 patients. Both groups had similar clearances of serum proteins and peritoneal restriction coefficients. However, dialysate CA125 concentrations, reflecting mesothelial cell mass, were lower in the UFF patients (2.79 vs. 5.38 U/L).

Conclusion: It can be concluded that the prevalence of UFF is high in long-term PD. It is mainly caused by a large vascular surface area and by impaired channel mediated water-transport. Besides, these patients had also signs of a reduced mesothelial cell mass, indicating damage of the peritoneum on both vascular and mesothelial site.
Introduction

Ultrafiltration failure (UFF) is a serious complication of peritoneal dialysis, that can result in the necessity to prescribe a fluid restriction and use higher dialysate glucose-concentrations, short cycle PD, or incidental ultrafiltration with a hemodialyzer. Sometimes it is the end of PD-treatment. Although UFF can occur in any stage of peritoneal dialysis, it may develop in time [1,2], and is therefore especially important in long-term PD. The exact prevalence of UFF in patients treated with PD for a longer period is not known. Heimburger et al. have reported a prevalence of 31% for patients treated with PD for more than 6 years [3] and in a Japanese long-term study, drop-out because of UFF was as high as 51% after 6 years [4]. Both studies were based on clinical signs of UFF and not on a standardized test.

The definition of UFF has been under discussion over the past years. Some applied a clinical definition: the inability to remain at a certain dry-weight or the use of more than 2 hypertonic bags per day has been considered as ultrafiltration failure [5-7]. Others used a definition based on a standardized exchange and considered UFF to be present, for instance when there was negative net ultrafiltration with a 1.36% glucose dwell [8,9]. The International Society of Peritoneal Dialysis (ISPD) committee on ultrafiltration failure has advised to perform a standardized test with 3.86% glucose, and considered a net ultrafiltration of less than 400 mL after a 4 hours dwell as UFF [10]. A cross sectional study in a small number of PD patients, using the 400 mL/4 hrs on 3.86% glucose definition reported a prevalence of 23% [9].

To elucidate the prevalence of ultrafiltration failure in long-term PD patients, based on the current definition of < 400 mL net ultrafiltration after a 4 hours test with 3.86% glucose, we have performed a study in as many as possible unselected patients on PD in the Netherlands, who had been treated for more than 4 years. The prevalence of UFF in this population was investigated as well as differences in membrane characteristics in patients with and without loss of ultrafiltration capacity. A possible role of chronic inflammation in the development of UFF was studied by measurement of C-reactive protein and albumin. In addition, the causes of ultrafiltration failure were analyzed for each individual patient.

Methods

With the help of the Netherlands Registry on Renal Replacement Therapy (RENINE) the dialysis centers where patients were treated with PD for more than 4 years, could be identified. The nephrologists of these centers were approached to ask the patients to cooperate in this study.
When they gave informed consent a standard peritoneal permeability analysis (SPA), with 3.86% glucose in a 4 hours dwell was performed.

The analyzed SPAs were performed between October 1996 and December 2000. All patients used commercially available, glucose-based dialysis solutions (Dianead®, Baxter BV, the Netherlands or StaySafe®, Fresenius BV, the Netherlands) some of them in combination with a glucose polymer (Extraneal®, Baxter BV, the Netherlands). None of the included patients had peritonitis during the test or in the preceding four weeks. Patients were considered to have ultrafiltration failure when net ultrafiltration after 4 hours was less than 400 mL. The protocol was approved by the committee for medical ethics of the Academic Medical Center of the University of Amsterdam.

**Procedure**

The SPA was performed during a 4-hour dwell period, as described previously [11]. The test was done with 3.86% glucose, using the volume the patient was used to. The test dwell was preceded and followed by a rinsing procedure with 1.36% glucose to avoid the possible effects of the residual volume before the test, and to calculate the residual volume after the test. Dialysate samples were taken before instillation and at multiple time points during the test (10, 20, 30, 60, 120, 180 and 240 minutes). The effect of a dead space volume was avoided by temporarily draining of 100-200 mL before the collection of each sample. Blood samples were taken at the beginning and at the end of the test-period. A volume-marker, dextran 70 1 g/L (Hyskon, Medisan Pharmaceuticals AB, Uppsala, Sweden), was used to calculate fluid kinetics. To prevent a possible anaphylactic reaction to dextran 70, dextran 1 (Promiten, NPBI, Emmercompascuum, the Netherlands) was injected intravenously before instillation of the test bag [12].

**Measurements**

Total dextran was determined by means of high performance liquid chromatography [13]. Creatinine and urate were measured by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). All electrolytes were determined using ion selective electrodes. Glucose was measured by the glucose oxidase-peroxidase method, using an autoanalyzer (SMA-II, Technicon, Terrytown, USA). Beta-2 microglobulin was determined with a microparticle enzyme immuno assay with an Imx system (Abbott Diagnostics, North Chicago, IL, USA). Albumin, IgG and alpha-2-macroglobulin were all measured by nephelometry (BN 100, Behring, Marburg, Germany), with commercial antisera (Dakopatts, Glostrup, Denmark). CRP was measured immunoturbidimetrically.
Dialysate CA125, used as a marker of mesothelial cell mass, was determined by a commercial microparticle enzyme immunoassay (MEIA), using a monoclonal antibody against CA125 (Abbott Laboratories IMx, IL, USA), validated for use in dialysate in our laboratory [14].

Calculations
All calculations were performed as previously described by Pannekeet et al. [11].

Fluid kinetics
Transcapillary ultrafiltration and lymphatic absorption were assessed with the intraperitoneally administered volume marker dextran 70. Transcapillary ultrafiltration (TCUF) was calculated from the dilution of the volume marker, by subtracting the initial intraperitoneal volume (IPV) from the theoretical IPV (when both lymphatic absorption and sampling would not have been present) at any time point. The effective lymphatic absorption rate (ELAR) was calculated as the peritoneal dextran clearance [15]. The residual volume (RV) was determined by the following equation, in which rs is the rinsing solution, ts is the test solution, V is volume, C is concentration [16]:

\[
RV (mL) = \frac{V_{rs} \cdot C_{rs}}{C_{ts} - C_{rs}}
\]

D/P sodium was calculated as the dialysate sodium concentration divided by the plasma sodium concentration. ΔD/P sodium is the difference between the initial D/P sodium and the lowest D/P sodium (usually after 2 hours). A correction for Na⁺ diffusion from the circulation to the dialysate, known to cause blunting of the decrease in D/P Na⁺, was made as described previously [17], using the mass transfer area coefficient of urate. The calculated sodium concentration in the dialysate due to diffusion can then be subtracted from the measured concentration at any time point, resulting in the actual Na⁺ sieving.

Solute transport
Peritoneal handling of low molecular weight solutes was expressed as MTAC and D/P ratios. The MTAC represents the maximal theoretical diffusive clearance of a solute at t=0, before transport has actually started. In this study we used the Waniewski model [18,19] Glucose absorption was calculated as the difference between the amount of glucose instilled and the amount recovered, relative to instilled.
Protein clearances were calculated from the amount of protein in the effluent. The intrinsic permeability to macromolecules can be functionally characterized by the peritoneal restriction coefficient (rc). This is the slope of the power relationship between the clearance of serum proteins and their free diffusion coefficient in water (Dw) [20, 21]:

$$\text{Clearance}(\text{mL/min}) = a \cdot D_w^n$$

in which a is a constant.

All transport parameters were corrected for body surface area and expressed per 1.73 m².

**Analysis of the causes of ultrafiltration failure.**

To analyze the causes of ultrafiltration failure in each individual patient, we used the reference values for peritoneal function tests with 3.86% glucose, obtained in a previous study [22]. When a value was outside the 95% confidence interval, it was considered abnormal. The maximum values for the different causes of UFF were: 12.5 mL/min/1.73 m² for MTAC creatinine, 0.86 for D/P creatinine, 72% for glucose absorption, 2.14 mL/min/1.73 m² for ELAR, 409 mL for residual volume and 0.046 for the maximum dip in D/P sodium (after correction for diffusion).

**Statistical analysis**

Results are expressed as median values and ranges, because most data were distributed asymmetrically. The Mann-Whitney-U test was employed for the comparison of the patients with ultrafiltration failure with those without UFF.

**Results**

**Patients**

RENNINE selected 123 patients who were treated with PD for more than 4 years in the 13 centers cooperating in the study. From this group, 55 patients underwent a SPA. The other 68 patients could not participate because of death (10 patients), transplantation (7 patients), transfer to hemodialysis (8 patients) or refusal to cooperate by the patients (24 patients) or their nephrologists (10 patients) for various reasons (e.g. severe co-morbidity, psychological factors, or participation in other studies). The remainder of the eligible patients was not included because of logistical problems. The patients who did not participate were not different from the investigated group with regard to age, sex and duration of peritoneal dialysis.
The investigated patients had a mean age of 48 years (range 18 to 74 years). The duration of PD therapy ranged from 48 to 144 months, median 61 months. The frequency distribution for the duration of PD is shown in Figure 1. Reasons for renal failure were chronic glomerulonephritis (18 patients), renal vascular disease (9 patients), polycystic kidney disease (4 patients), diabetic nephropathy (3 patients), congenital kidney disease (2 patients), interstitial nephritis, bilateral nephrectomy (cancer), scleroderma (all in 1 patient) and unknown in 16 patients.

Transport characteristics

Among the 55 patients 20 had net UF of < 400 mL after a 4 hours dwell with 3.86% glucose (36%). Patient characteristics for the groups with and without UFF are given in Table 1. The intraperitoneal fluid profiles for both groups are given in Figure 2.

![Figure 1](image)

Figure 1.
Frequency distribution of the number of patients with (black box) and without UF failure (open box) and the duration of PD (months).

### Table 1. Clinical characteristics of the groups with and without ultrafiltration failure. Medians and ranges are given

<table>
<thead>
<tr>
<th></th>
<th>normal ultrafiltration</th>
<th>ultrafiltration failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=35</td>
<td>n=20</td>
</tr>
<tr>
<td>Male/female</td>
<td>17/18</td>
<td>9/11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 (18 - 74)</td>
<td>46 (19 - 73)</td>
</tr>
<tr>
<td>Duration of PD (months)</td>
<td>57 (48 - 144)</td>
<td>72 (48 - 132)</td>
</tr>
<tr>
<td>Peritonitis episodes</td>
<td>1 (0 - 8)</td>
<td>2 (0 - 8)</td>
</tr>
<tr>
<td>Net UF after 4 hours dwell (mL)</td>
<td>659 (412 - 1115)</td>
<td>120 (-659 - 390) *</td>
</tr>
</tbody>
</table>

p < 0.01
Peritoneal transport parameters are given in Table 2. Patients with UFF had a significantly higher MTAC creatinine, D/P creatinine and glucose absorption than those without UFF. In addition they had a higher effective lymphatic absorption rate. The maximum dip in D/P sodium was lower in the patients with UFF than in those without UFF. Neither the residual volume for the both groups, nor the clearances of macromolecules and the restriction coefficient showed significant differences (see also Table 3).

**Table 2.** Peritoneal transport characteristics for the groups with and without UFF: Medians and ranges are given

<table>
<thead>
<tr>
<th></th>
<th>normal ultrafiltration n=35</th>
<th>ultrafiltration failure n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCLT RR (mL/min/1.73 m²)</td>
<td>3.8 (1.6 - 6.7)</td>
<td>2.1 (0.9 - 3.7) *</td>
</tr>
<tr>
<td>ELA RR (mL/min/1.73 m²)</td>
<td>1.0 (0.0 - 2.4)</td>
<td>1.6 (0.5 - 6.3) **</td>
</tr>
<tr>
<td>RV (mL)</td>
<td>218 (11 - 942)</td>
<td>153 (54 - 480)</td>
</tr>
<tr>
<td>max dip D/P Na⁺</td>
<td>0.109 (0.026 - 0.170)</td>
<td>0.032 (0.007 - 0.095) *</td>
</tr>
<tr>
<td>MTAC creat (mL/min/1.73 m²)</td>
<td>9.0 (3.7 - 16.2)</td>
<td>12.9 (7.8 - 18.4) *</td>
</tr>
<tr>
<td>D/P creat</td>
<td>0.71 (0.49 - 0.90)</td>
<td>0.86 (0.67 - 0.96) *</td>
</tr>
<tr>
<td>glucose absorption (%)</td>
<td>60 (41 - 77)</td>
<td>73 (54 - 88) *</td>
</tr>
</tbody>
</table>

* p<0.001, ** p<0.05  
TCUFR is the transcapillary ultrafiltration rate, ELAAR is the effective lymphatic absorption rate, RV is the residual volume, max dip D/P Na⁺ is the maximum dip in D/P sodium during the 4 hrs dwell (after correction for sodium diffusion), MTAC creat is the mass transfer area coefficient for creatinine, D/P creat is the dialysate over plasma ratio for creatinine at t=240 min.

The mean dialysate CA125 concentration in all 55 patients was 4.71 U/L, but it was significantly lower in the patients with UFF compared to those with normal ultrafiltration (2.79 vs. 5.38 U/L, p=0.02).

For the patients with normal UF the median serum value for albumin was 34.3 g/L (21.0-43.3) and C-reactive protein was 4.5 mg/L (<3-68). This was not statistically different from the values for the patients with UFF: 32.8 mg/L (21.0-39.9, p=0.1) for albumin and 7.0 mg/L (<3-
Inflammation parameters, or between net UF and albumin or CRP levels.

Analysis of the causes of ultrafiltration failure

The twenty patients with UFF were analyzed one-by-one for the cause of UFF. Six patients had only one cause of UFF: a decreased dip in D/P sodium (3), a high MTAC creatinine (1) and a high ELAR (2). Nine patients had two causes: a combination of high MTAC creatinine with a decreased dip in D/P sodium (7) or with a high ELAR (2). In two patients 3 causes were found (high MTAC creatinine, high ELAR and a decreased dip), whereas 1 patient also had large residual volume. In 2 patients no cause of UFF could be identified. No relation was found between the cause of UFF and the duration of peritoneal dialysis, as shown in Figure 3.

Discussion

The present study provides evidence for the clinical observation that ultrafiltration failure is an important complication of long-term peritoneal dialysis. Its prevalence was 36% in 55 patients, only selected on the basis of the duration of peritoneal dialysis. This group is probably representative for the whole population of long-term patients, because those who did not participate were not different with regard to age, gender and duration of peritoneal dialysis.

Fluid overload is an important problem in PD patients, especially when residual urine production is absent. It may be caused by a high fluid intake, inappropriate PD prescription, non-
compliance, or by a low drained volume. The latter can be due to mechanical problems, such as catheter dislocation or subcutaneous leakages, or to peritoneal membrane failure. When the diagnosis of ultrafiltration failure is based on a clinical definition, all the above causes of overhydration are included, which might lead to over diagnosis. Under diagnosis is also possible, for instance when a patient with impaired ultrafiltration, due to membrane failure, remains in a good hydration status because of strict adherence to a severe salt and fluid restriction. When a standardized dialysis dwell is used, as in the present study, a low drained volume can either be caused by mechanical problems or by peritoneal membrane failure. Non membrane related causes, such as catheter dislocation or subcutaneous leaks were ruled out in this study. The membrane-related causes of ultrafiltration failure consisted of large vascular surface area, assessed by MTAC creatinine, rapid effective lymphatic absorption and impaired free water transport. A very rare cause like an extremely small vascular surface area, e.g. in case of adhesions, where only
a limited part of the peritoneum is available as a dialysis membrane [23,24] was not detected in our study population. The presence of a large vascular peritoneal surface area leads to a rapid absorption of the dialysis solution and thus to a fast disappearance of the osmotic gradient [25]. A high peritoneal fluid absorption rate [3, 26] leads to a decrease in the drained volume, and also an impaired conductance to glucose (e.g. peritoneal water channel dysfunction or low peritoneal ultrafiltration coefficient) [27-29] results in ultrafiltration failure. A combination of factors may also be present.

In this study, the group of patients with UFF showed higher transport rates for small solutes (65% of the patients), measured as high MTAC creatinine, high D/P creatinine and high glucose absorption. This is in accordance with previous publications were small solute transport parameters were found to be increased in long-term patients, especially when they suffered from UFF [3,30,31]. In addition the UFF patients had higher lymphatic absorption rates (35% of the patients) and a decrease of the maximum dip in D/P sodium (65% of the patients). Most patients had a combination of etiological factors. The combination of a large vascular surface area with an absence in the dip of D/P sodium was the most frequent one. Speculative is whether the absence in dip of D/P sodium in this group is a consequence of the lower net ultrafiltration, caused by the rapid absorption of the osmotic agent due to the large vascular surface area, or an entity by itself. The fact that 3 patients had no other cause of UFF than impaired free water transport, implies that water channel dysfunction is an isolated factor in its etiology. Suggestions about challenging the water channel transport with an even more hypertonic dialysis solution have been made [32], but it is questionable how hypertonic this solution should be and if it would be ethical to use such solutions for investigational purposes.

The relation between the occurrence of UFF in long-term PD and the peritonitis incidence was investigated previously. The results were equivocal. Most publications showed no direct relation [3,5,33], although some authors have found a relation with late peritonitis episodes, recurrent infections or peritonitis clusters [2]. In the present study the peritonitis incidence in the patient groups with and without UFF was similar. This suggests that in long-term PD peritonitis does not play a major role in the development of UFF. An alternative explanation could be that the patients with frequent peritonitis episodes had been transferred to other renal replacement therapies because of UFF before they reached the inclusion criterion of 4 years of PD treatment.

Over the past years, much attention has been given to chronic inflammation as a predictor of outcome in dialysis. An elevated C-reactive protein level at the start of dialysis was found to be correlated to higher mortality [34,35]. The results of previous investigations on possible relationships between peritoneal transport status and serum parameters of inflammation
were equivocal. Chung et al. reported inflammation to be correlated with fast transport status in the first year of peritoneal dialysis [36]. However, Wang and co-workers did not find a correlation between transport rates and states of chronic inflammation [37]. In the present study, the inflammation parameters serum albumin and C-reactive protein were investigated. No difference was found between the groups with and without ultrafiltration failure, nor was there a correlation between transport status and the different inflammation markers. A possible explanation for this may be that effects of chronic inflammation on peritoneal transport are overshadowed by the anatomical changes after years of PD. An alternative explanation could be that the patients with the highest inflammation parameters had already dropped out of PD treatment, because of morbidity and mortality.

CA125 can be used as a marker of mesothelial cell mass or cell turnover in stable, non-infectious PD patients. A negative trend with duration of PD was described previously [38], which is consistent with the reported cell loss that had been observed in peritoneal biopsies [39]. Although mesothelial cells are considered not to be involved in peritoneal transport, loss of the protection of the mesothelial cell layer can probably be of influence in the damage to the endothelial cell layer. The finding in the present study that long-term patients with ultrafiltration failure had lower CA125 levels than those with normal UF, is therefore more likely a sign of damage of the peritoneum than a causative factor of ultrafiltration by itself.

It can be concluded that the prevalence of ultrafiltration failure is high in long-term peritoneal dialysis patients. It is mainly caused by a combination of a large vascular surface area and by impaired free water transport. Besides, long-term patients with ultrafiltration failure had signs of a reduced mesothelial cell mass, indicating damage of the peritoneum, both at the vascular and mesothelial site.

References


