Inherent high peritoneal transport and ultrafiltration deficiency: their mid-term clinical relevance

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Abstract

Background. High peritoneal transport has been associated with poorer outcome in peritoneal dialysis (PD) patients, but not necessarily because of PD-dependent conditions. Our primary objective was to analyse the influences of baseline peritoneal small solute transport and ultrafiltration (UF) capacity on patient and technique survival, after adjusting for comorbid conditions. A secondary objective was to determine whether high transport was associated with basal comorbidity.

Methods. In this prospective observational patient/technique survival study, we followed 410 patients who started PD. At the baseline, we collected data to define comorbidities, tally the Charlson index, determine the baseline mass transfer area coefficients (MTAC) of urea and creatinine, net UF, plasma albumin and residual renal function (RRF). No data other than the information on patient and technique survival were recorded after baseline.

Results. The mean follow-up was 33 ± 28 months. Dropouts during the study were due to renal transplantation in 140 cases, death in 142 cases and transfer to haemodialysis (HD) in 77 cases. Patients with inherent UF deficiency, high transport rate or both were not significantly different in the survival analysis from the rest. In the Cox hazards analysis, only age, Charlson index and a lower RRF were the significant mortality risk factors. None of the baseline parameters studied was a predictor of technique failure. High transporter patients had lower plasma albumin and UF capacity, comorbidity and more frequent liver diseases than the rest. Moderate to severe liver disease (n = 14) was significantly associated with the inherent high transport status, but was never accompanied by UF failure (UFF). UFF patients showed higher RRF, creatinine-MTAC and age.

Conclusions. Neither the high transport nor the inherent UFF status has any influence on patient and technique survival. The inherent high small solute transport status is associated with hypoalbuminaemia and a greater comorbidity index. The Charlson index, age and lower RRF are the only independent predictors of mortality. Technique dropout is not predicted by any of the variables studied at the baseline.

Keywords: fast peritoneal transport; PD outcomes; ultrafiltration

Introduction

The revision by our group [1] and others [2] of the existence of great variability in peritoneal membrane transport characteristics leads to a challenge for the interpretation of its causes, involved mechanisms and later repercussions. High transporter peritoneal dialysis (PD) patients have poorer outcomes than lower transporter PD patients [3–5]. At the same time, there is no question that a higher transport status develops over time on PD [6–11]. To distinguish the two situations from a pathogenetic point of view we have proposed the terms ‘inherent’ and ‘acquired’ high transport. While the acquired status has been related to the composition of the dialysate (GDP, glucose, acid pH and lactate) [11] and to the infectious complications linked to PD [7], there are no apparent features that might explain the inherent status.

Probably due to the confusion regarding the reasons behind differing peritoneal transport characteristics in patients commencing PD, some authors have reported that a high transport status is associated with a poorer outcome [3–5], while others have either failed to demonstrate any association at all between...
transport status and outcome [12–14], or have found that concomitant peritoneum-dependent comorbid conditions actually are the causes of such poor prognosis [15,16].

Our objective was to identify the influences that baseline peritoneal small solute transport and ultrafiltration (UF) capacity may have on patient and technique survival, after adjusting for comorbid conditions. A secondary objective was to determine if the high transport situation is, in fact, a marker of comorbidity.

**Patients and methods**

All patients (410) who started PD in two hospitals during the period 1980–2001 and were followed for at least 3 months were included in this prospective study. The collection of their data was finished in April 2004. All patients were on continuous ambulatory peritoneal dialysis (CAPD) with glucose-based peritoneal dialysate at the beginning of treatment. After 1995, some patients were transferred to automated peritoneal dialysis (APD) and after 1998, some of them used icodextrin. Patients with abdominal pathology diagnosed prior to starting PD were excluded. There was no other selection criterion.

**Clinical and laboratory data**

Data at baseline were collected and used to define comorbidity and tally the Charlson index as modified by Beddhu [17]. Patient age was not used in tallying the Charlson index so that the influence of true comorbidities and/or age on peritoneal function parameters and outcomes could be separately probed. The presence of liver disease was specifically studied. Moderate to severe liver disease was defined as the presence of portal hypertension, cirrhosis or both. Plasma albumin levels were measured during the peritoneal kinetics study. Residual renal function (RRF) was estimated based on the average of the renal urea and creatinine clearances. A patient with an RRF less than 1 ml/min was considered anuric.

We performed the peritoneal transport kinetic study on each patient 1 month after the initiation of CAPD. This study consisted of a glucose exchange with a 4-h dwell time and taking six peritoneal effluent samples (at 0, 30, 60, 120, 180 and 240 min) and one blood sample to calculate the peritoneal mass transfer area coefficient (MTAC) of urea (ml/min) and creatinine (ml/min) using a previously described mathematical model [7]. This coefficient represents the isolated diffusive capacity of the membrane under theoretically infinite dialysate flow [18]. Patients fasted during each functional study, and they received no drugs—except low doses of subcutaneous insulin, if necessary. All studies were performed in the absence of apparent peritoneal inflammation (<100 white blood cells/μl with <50% polymorphonuclear cells). The net UF (ml) was estimated based on the net negative balance (weighing the bag after drainage), after a 2 L 3.86% glucose exchange with 4 h of dwell time. This value represents mostly the convective transport capacity of the peritoneum. A negative balance lower than 400 ml was taken as an indicator of UF failure (UFF) [19].

**Statistical analysis**

For statistical analysis, we used the SPSS-11 program. Values are expressed as percentages and means (±SD). A P < 0.05 was considered statistically significant. Proportions were compared by the chi-square test and means by the Student’s t-test for non-paired data. The Pearson or Spearman (the latter in the cases of non-normal distribution) tests were used for the regression analysis. The patient/technique survival analysis employed the Kaplan–Meier method with survival curves compared using the log-rank test. Cox’s proportional analysis was used to ascertain the simultaneous effect of several variables on patient mortality and on the probability of patients being transferred to haemodialysis (HD).

**Results**

The clinical and peritoneal characteristics of patients, separated according to the evolution of their condition are presented in Table 1. The mean time on follow-up was 33 ± 28 months; 142 patients died, 140 were transplanted, 78 were transferred to HD and 50 continued on PD. The causes of deaths were as follows: 42 cardiac, 43 infectious, 29 vascular, 15 general deterioration, 4 neoplastic and 9 due to other reasons. Some patients were transferred to HD for the following reasons: 20 for UFF, 19 for peritonitis, 5 for abdominal wall problems, 20 following patient decision, and 13 for other reasons.

The patients who died were older and had more severe comorbidities at baseline than the patients who received kidney transplantations or were switched to HD (Table 1; Student’s t-test). However, we found no significant differences in peritoneal small solute transport or UF capacity between the patients who died and those who survived (transplanted, on HD or alive on PD).

The high transporter patients were more frequently males, and they had lower baseline plasma albumin levels, UF capacities, more severe comorbidities and more frequently moderate–severe liver diseases (Table 2) than the low transporter patients (creatinine-MTAC <6.8 ml/min). Age and the incidences of diabetes were similar in both groups. The differences observed between those two groups were the same as those observed between high transporter patients and non-high transporter patients (data not shown).

To explore the influence of high peritoneal transport on patient and technique survival, we established five transport categories according to the following quintiles of creatinine-MTAC: 1st quintile: creatinine-MTAC ≤6.8 (n = 82); 2nd quintile: creatinine-MTAC 6.8–8.7 (n = 83); 3rd quintile: creatinine-MTAC 8.71–11 (n = 88); 4th quintile: creatinine-MTAC 11.1–13.8 (n = 76) and 5th quintile: creatinine-MTAC >13.8 (n = 81). True high transporters are defined as patients with creatinine-MTAC values above 13.8 ml/min. These patients were compared with the rest (MTAC ≤13.8 ml/min) in terms of patient and technique survival, and no significant differences

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were detected. Comparing the high transporters with patients in the lowest quintile did not reveal significant differences, either.

The characteristics of the patients are shown in Table 3, separated according to their basal UF results: UFF, no UFF and high UF (P75: UF >1100 ml). Patients with UFF were older and had higher creatinine-MTAC and RRF than patients with high UF capacity. We found no differences in comorbidity and plasma albumin levels between these groups.

Patients with a UF capacity <400 ml/4 h (n = 27), which is considered an inherent UFF, did not show significant differences in the patient/technique survival analysis when compared with either all other patients or with the patients in the highest UF quartile.

Both inherent UFF and high transport status were present in 12 patients. We compared these patients with the rest in terms of patient and technique survival, and found no significant differences.

We analysed 72 anuric patients separately. Neither patient and technique survival nor HD transfer rate were influenced by peritoneal transport characteristics (i.e. transport status and UF capacity).

To evaluate the influence of RRF, we divided the whole group around its median value of 2.28 ml/min. Technique survival did not differ, but patient survival was significantly lower in patients with RRFs <2.28 ml/min (Figure 1).

Fourteen patients with moderate or severe liver disease had significantly higher creatinine-MTACs (19.9 ± 8.5 vs 10.2 ± 4.6, P < 0.001) than patients without liver disease, with no significant differences in UF (957 ± 629 vs 880 ± 337 NS).

To explore the factors influencing patient survival, we performed a Cox hazards analysis that included the variables detected as significant in the first analysis (Table 1) as well as the states of high transport and inherent UFF. Table 4 shows the results of this analysis. Only age, Charlson index and a lower RRF were significant risk factors for mortality. Neither high transport status nor inherent UFF were risk factors for mortality. Plasma albumin level, which is a significant isolated predictor of mortality (RR 0.57, 95% IC 0.47–0.77), lost its significance when the Charlson index was introduced in the analysis. Plasma albumin was significantly correlated with the Charlson index of comorbidity (Spearman test R = 0.31, P < 0.0001). None of the studied parameters was a predictor of technique failure.

**Discussion**

The main findings of this study are the following:

(i) Neither baseline high transport status nor inherent UFF is associated with patient and technique survival.

(ii) The inherent high small solute transport status is associated with hypoalbuminaemia and a greater comorbidity index.
Comorbidities, age and lower RRF are all independent predictors of mortality.

Technique dropout is not predicted by any of the variables measured at baseline.

Moderate to severe liver disease is significantly associated with the inherent high transport status, but it is not accompanied by UFF.

Despite the great variability of the parameters of peritoneal transport at baseline, our data do not show a significant relationship between the basal functional parameters of small solutes or water, or both, and patient or technique survival of PD. Moreover, patients in extreme conditions at baseline (either anurics or with high transport rate plus inherent UFF) did not have poorer outcomes. Other authors have found a higher mortality among high transporter patients [3–5], although in some cases this relationship could be only established for those with higher comorbidity indices [15,16].

The hypoalbuminaemic state is associated with morbidity and mortality in HD [20] and PD [21–23] patients. Like us, other authors have found a significant inverse relationship between plasma albumin and peritoneal transport of small solutes [3–5,24]. In fact, greater peritoneal protein losses have been demonstrated among high transporters [3,23]; our data, however, do not cover this point. Hypoalbuminaemia could also be the result of haemodilution secondary to UFF and extracellular volume expansion, but in this study, we did not find a significant correlation between UF capacity and plasma albumin levels, even among anuric patients. Finally, some authors have shown that hypoalbuminaemia is a marker of inflammation and comorbidity [25–27]. Due to the early initiation of this prospective study (1980), it did not include data on parameters of inflammation; however, our cohort with inherent high transport status had lower plasma albumin levels and higher comorbidity indices than the patients without that condition. This observation and the significant association between plasma albumin and comorbidity index (\(R = 0.31\)) suggest that hypoalbuminaemia in high transport status could be caused, at least partially, by other comorbid conditions. Other authors have shown that a low level of plasma albumin may be present before, or just after the very beginning of PD, as a result of processes that might also simultaneously be responsible for hypoalbuminaemia, peritoneal high transport and greater mortality—processes, like atherosclerosis, inflammation, malnutrition and other comorbid conditions [4,5,16,28]. Nevertheless, in most cases, a causal relationship between inflammation and peritoneal transport characteristics has not been demonstrated [14,29,30]. In fact, in our study, age, comorbidity and basal RRF were the only variables predicting mortality in the Cox hazards model.

Regarding technique survival, we have not found that it has been influenced by peritoneal transport of small solutes and water or by RRF. Our study is remarkable for its long-term follow-up of patients and its low haemodialysis transfer rates, when compared with other reported studies. This may be due to the fact that patients underwent one, or several, peritoneal resting periods once the acquired UFF appeared [31]. If done early, this practice is extremely efficient in restoring the normal peritoneal function.

**Table 3.** Characteristics of patients with or without ultrafiltration failure (UFF) and patients with high UF (\(P_{75}: UF > 1100\) ml/4 h); most data obtained at baseline

|                     | UFF  
|---------------------|---
| \((n = 27)\)        | No UFF  
| \((n = 383)\)       | High UF  
| \((n = 90)\)        |                     |
|---------------------|---------------------|----------------------|----------------------|
| Gender, male (%)    | 59                  | 51                   | 44                   |
| Age (years)         | 57.5 ± 14.8         | 52.19 ± 15           | 48.4 ± 16.6**        |
| Diabetics (%)       | 15                  | 26                   | 28                   |
| Follow-up (months)  | 33.4 ± 26.2         | 33.8 ± 28.3          | 38.8 ± 37.8          |
| Plasma albumin (g/dl) | 3.7 ± 0.5       | 3.7 ± 0.5            | 3.6 ± 0.6            |
| Residual renal function (ml/min) | 4.8 ± 2.5 | 4 ± 3               | 3.4 ± 2.8**          |
| Exitus (%)          | 33                  | 35                   | 41                   |
| Creatinine- MTAC (ml/min) | 13.8 ± 4.7   | 10.4 ± 5*            | 8.9 ± 5.5**          |
| BMI (kg/m²)         | 24.5 ± 4.2          | 24 ± 4.1             | 23.2 ± 4.7           |
| Charlson index (without age) | 4.3 ± 2.6 | 3.6 ± 1.6            | 3.6 ± 1.6            |
| Liver disease (%)   | 11.1                | 2.8                  | 3.5                  |

*\(P < 0.05\) between patients with or without UFF.

**\(P < 0.05\) between patients with UFF and patients with high UF.

**Fig. 1.** Patient survival stratified according to RRF values higher (continuous line) and lower (dashes) than 2.28 ml/min.
It is universally recognized that acquired type I UFF limits the use of long intraperitoneal dwell times, because it induces a high glucose absorption, which impedes the establishment of the appropriate negative salt and water balance. The consequent extracellular volume overload causes difficulties in blood pressure control and left ventricular hypertrophy, both of which are recognized cardiovascular risk factors. A recently published paper highlights that lower negative balances of water and salt are independent risk factors for mortality on PD [32]. In that report, the high transport condition was associated with patient survival only in the univariate analysis, and its predictive power disappeared once daily elimination of water and salt and the comorbidity index were introduced into a Cox multivariate hazards analysis.

Many earlier papers have coincided on the frequent presence of overhydration in PD patients, although its clinical signs may be absent [33,34]. As previously mentioned, on commencing PD, the inverse relationship between peritoneal transport of small solutes and UF is not as tight as seen in later stages; in fact, it is possible to observe an inherent UFF without high solute transport and vice versa [1]. Therefore, to determine which factors predict patient and technique survival, patients with inherent high solute transport should be separated from those with inherent UFF. The present study demonstrates that this last condition, whether associated with high transport status or not, is not associated with greater mortality or dropout. We also have data [35] demonstrating that many patients with inherent UFF show decreased solute transport and increased UF capacity, as long as they do not suffer peritonitis during the first year on PD, remaining on PD treatment for a medium-term. All these data lead us to regard these adverse situations as potentially transitory conditions and, therefore, not as contraindications for PD in these patients. The lack of association between initial parameters of peritoneal function and patient or technique survival reinforces this opinion.

Another interesting feature of our present study, and one that confirms the findings of previous studies with fewer patients [16,36], is the association between moderate or severe liver disease and high transport status at the inception of PD. Portal hypertension and other abnormalities of splenic blood flow may lead to high peritoneal post-capillary pressure and vasodilatation and, thereby, favour high UF and small solute transport. Patients with liver disease show high transport status with high UF capacity. It is possible to observe an inherent UFF without high solute transport and vice versa [1]. Therefore, to determine which factors predict patient and technique survival, patients with inherent high solute transport should be separated from those with inherent UFF. The present study demonstrates that this last condition, whether associated with high transport status or not, is not associated with greater mortality or dropout. We also have data [35] demonstrating that many patients with inherent UFF show decreased solute transport and increased UF capacity, as long as they do not suffer peritonitis during the first year on PD, remaining on PD treatment for a medium-term. All these data lead us to regard these adverse situations as potentially transitory conditions and, therefore, not as contraindications for PD in these patients. The lack of association between initial parameters of peritoneal function and patient or technique survival reinforces this opinion.

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One of the limitations of this study is the use of an old mathematical model, albeit with recent adjustments, to study peritoneal transport kinetics; however, the advantage of this model is that it calculates MTAC exactly. Another limitation is that the collection of data began so long ago that we have no data on inflammation or daily peritoneal losses—such data might have helped to interpret the findings related to hypoalbuminaemia in high transporters. Finally, for the same reason, data on sodium transport are also lacking. They might have completed the information about daily water/salt elimination and might have shed light on its relationship with volume expansion as cardiovascular risk factor. The main strengths of this study are the high number of patients, the relatively long follow-up and the diversity represented by patients treated in two different PD units using the same methods and criteria.

In summary, the functional characteristics of the peritoneal membrane at the beginning of PD do not contraindicate its long-term use, since they appear to have no influence on patient and technique survival. For us, there is a substantial conceptual difference between acquired high transport status, which usually represents a peritoneal response to inflammation, and inherent high transport status, which in some cases is just a marker of comorbidity (as in the case of patients with liver disease) and in others it is simply due to slow peritoneal adaptation to the infused fluids. Therefore, we defend the idea that inherent high transport status or UFF, or both, are not conditions limiting for PD, but situations to be observed and evaluated at 6 months and 1 year looking for inflammation and checking for associated comorbidities as well as for checking negative peritoneal, renal salt and water balances. Probably, after some time on PD (we usually wait for 1 year), with stable peritoneal characteristics and significant diminution of RRF, the inherent high transport status actually acquires an independent negative prognostic value.

**Conflict of interest statement.** None declared.

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**Table 4. Cox hazards analysis for mortality**

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Inferior 95% IC</th>
<th>Superior 95% IC</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.052</td>
<td>1.037</td>
<td>1.067</td>
</tr>
<tr>
<td>Charlson index (without age)</td>
<td>1.287</td>
<td>1.192</td>
<td>1.390</td>
</tr>
<tr>
<td>Residual renal function (per ml/min)</td>
<td>0.941</td>
<td>0.887</td>
<td>0.999</td>
</tr>
<tr>
<td>Creatinine-MTC (per ml/min)</td>
<td>0.992</td>
<td>0.960</td>
<td>1.024</td>
</tr>
<tr>
<td>Ultrafiltration; glucose 3.86%/4 hour dwell time (ml)</td>
<td>1.000</td>
<td>1.000</td>
<td>1.001</td>
</tr>
</tbody>
</table>

NS, no significance.
References


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