Early Estimation of High Peritoneal Permeability Can Predict Poor Prognosis for Technique Survival in Patients on Peritoneal Dialysis

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At the beginning of continuous ambulatory peritoneal dialysis (CAPD), different patients exhibit large differences in peritoneal permeability. To determine if early estimation of peritoneal permeability can predict the prognosis of CAPD, we used data from a personal dialysis capacity (PDC) study group in Japan to investigate patient and technique survival rates.

Based on the data from a previously reported, prospective multicenter study encompassing eight dialysis centers in Japan (Am J Kidney Dis 2002; 40:1045–54), we recalculated patient and technique survival data. We reviewed the records of 139 patients newly initiated on CAPD from January 1995 to December 1999. Peritoneal permeability was estimated by PDC test within the first year after initiation. We divided the patients into paired groups according to several peritoneal permeability variables as calculated by the PDC test (area, plasma loss, and peritoneal creatinine clearance), and we compared patient and technique survival rate between the groups.

The mean age of the patients was 49.6 years ± 14.9 years (standard deviation). The mean pore area of peritoneum was 19,936 ± 8383 cm²/1.73 m². Estimation of patient survival by the Kaplan–Meier method showed 94.2%, 88.4%, 84.1%, and 79.7% at 1, 2, 3, and 5 years respectively. Estimated technique survival (including death as an endpoint) by the Kaplan–Meier method showed 90.6%, 76.8%, 67.4%, and 54.3% at 1, 2, 3, and 5 years respectively. In the high peritoneal permeability group (high area and high plasma loss), the technique survival at 5 years was significantly lower than in the low peritoneal permeability group area: 55.9% (high) vs. 72.7% (low), p = 0.0459; plasma loss: 43.3% (high) vs. 62.8% (low), p = 0.0197). We observed no significant difference in patient survival between the high and low peritoneal permeability patients. In the high peritoneal creatinine clearance group, patient and technique survival were both significantly lower than in the high peritoneal creatinine clearance group.

Patients with high peritoneal permeability as calculated by the PDC test at the start of PD had a poor prognosis for technique and patient survival on CAPD. We conclude that early estimation of high peritoneal permeability can predict poor outcome for patients on CAPD.

Key words
Technique survival, CAPD, peritoneal permeability, personal dialysis capacity (PDC) test

Introduction
Until recently, evidence concerning the importance of urea clearance and creatinine clearance (CCr) in the prediction of outcome on peritoneal dialysis (PD) has been conflicting. Some previous reports indicated a link between survival and solute clearance (1–3). The CANUSA study, a multicenter prospective cohort study, showed that total weekly urea clearance and total weekly CCr (renal and peritoneal) both were independent and important predictors patient survival (4). The CANUSA study and other studies showed a correlation between small-solute clearance and outcome (4). Recently, the ADEMEX study clearly demonstrated that peritoneal small-solute clearance and clinical outcome are not correlated (5). Those data demonstrated the importance of residual renal
function (RRF) as a predictor of mortality in patients on continuous ambulatory peritoneal dialysis (CAPD), perhaps causing peritoneal CCr to lose its significance.

Hyperpermeability of the peritoneal membrane—defined as fast or high transport as measured by peritoneal equilibration test (6)—develops during long-term peritoneal dialysis (7). However, in some patients, a state of hyperpermeability may also present from the beginning of peritoneal dialysis (8). The meaning of early estimation of a state of high peritoneal permeability is unclear.

At the beginning of CAPD, peritoneal permeability differs widely from patient to patient. To determine whether early estimation of peritoneal permeability can predict prognosis on CAPD, we used data from a personal dialysis capacity (PDC) study group in Japan to investigate patient and technique survival.

Patients and methods

Definition of technique survival
One reason that comparing reported technique survival data is difficult relates to differences in definition. Some reports on technique survival include death and transplantation as endpoints; others do not (9). Blake (9) defines technique failure as any situation in which a patient on peritoneal dialysis (PD) switches to hemodialysis for more than 3 months; he excludes patients who are successfully transplanted or who recover RRF (10). He also excludes patients who die—a decision that may be more controversial.

PDC test
The PDC test was provided by Gambro–Shimizu Pharmaceutical Company (Gambro–Shimizu, Tokyo, Japan) and was used on a version 3.1 system according to the manual by Haraldsson (11). Briefly, during the night before the study day, a 10-hour nighttime dwell was performed. If patients were on home automated peritoneal dialysis (APD), they were converted to a CAPD schedule during the PDC test. The overnight dwell preceding the test was weighed and sampled after mixing (the "zero" sample). The test itself started with a short (2- to 3-hour) PD dwell. That dwell was followed by two 4- to 6-hour intermediate dwells, another short exchange, and finally an overnight dwell (10 hours). Two different glucose concentrations were used in alternation. Well-mixed 10 mL dialysate samples from each dwell and two blood samples taken during the 24-hour period were analyzed. Albumin in dialysate was measured using an assay for micro-albumin or albumin. A 24-hour urine collection was also performed to measure RRF. The exact starting time of dialysate infusion and drainage, the time of blood sampling, the glucose concentration used, and the weight of bags with new and spent dialysate fluid were all carefully documented.

Study protocol
Based on data from a previously reported prospective multicenter study at eight dialysis centers in Japan (12,13), we recalculated survival rates. That study included 139 newly initiated CAPD/APD patients (72 men, 67 women). In those patients, a PDC study was performed within 6 months of CAPD start. We collected the data from the PDC tests between May 1995 and January 1999. Using the Kaplan–Meier method, 5-year follow-up patient and technique survival were calculated for those patients. We then divided the patients into paired groups by pore area (>19936 cm²/1.73 m² (high), <19936 cm²/1.73 m² (low]), plasma losses (>0.10 mL/min/1.73 m² (high), <0.10 mL/min/1.73 m² (low]), peritoneal CCr (>5.43 mL/min/1.73 m² (high), <5.43 mL/min/1.73 m² (low]), and total CCr (>7.30 mL/min/1.73 m² (high), <7.30 mL/min/1.73 m² (low]). We compared patient and technique survival between these four separate high and low groups.

Statistical analysis
All results are expressed as mean ± standard deviation. The analyses were performed using the StatView version 5.0 software (SAS Institute, Cary, NC, U.S.A.) on a Macintosh computer. The analyses of survival and of continuation rate on CAPD used the Kaplan–Meier method, and the log-rank test was used for survival comparisons by PDC test factor and group.

Results

Characterization of the patients
Table I shows the clinical and demographic characteristics of the patients. The mean age of the patients was 49.6 ± 14.9 years. Mean plasma protein level in the patients was 6.3 ± 0.8 g/dL; mean plasma albumin level was 3.5 ± 0.5 g/dL; and mean plasma glucose level was 98.7 ± 20.9 mg/dL.
Table I also shows the results of the PDC study in the 139 patients. The mean pore area was 19,936 ± 8383 cm/1.73 m². The mean absorption rate was 1.48 ± 0.73 mL/min/1.73 m². The mean large-pore flow (plasma loss rate) was 0.10 ± 0.07 mL/min/1.73 m². The mean RRF was 1.88 ± 1.84 mL/min/1.73 m². The mean peritoneal CCr was 5.43 ± 1.09 mL/min/1.73 m². The mean total CCr was 7.30 ± 1.90 mL/min/1.73 m². The mean weekly Kt/V urea was 2.449 ± 0.698. The mean dietary calorie and protein intakes were 1370.8 ± 332.7 kcal daily and 53.3 ± 10.8 g daily respectively. The mean 24-hour protein equivalent of nitrogen appearance/protein catabolic rate was 1.17 ± 0.36 g/kg. The mean urea generation rate was 0.11 ± 0.05 mmol/min. And the mean creatinine generation rate was 5.93 ± 2.24 mmol/24 hr.

Table 1 The clinical and demographic characteristics of the patients undergoing continuous ambulatory peritoneal dialysis

<table>
<thead>
<tr>
<th>Area (cm²/1.73 m²)</th>
<th>19.936 ± 8383</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (mL/min/1.73 m²)</td>
<td>1.48 ± 0.73</td>
</tr>
<tr>
<td>Plasma loss (mL/min/1.73 m²)</td>
<td>0.10 ± 0.07</td>
</tr>
<tr>
<td>Water permeability (mL/min/mmHg/1.73 m²)</td>
<td>0.069 ± 0.030</td>
</tr>
<tr>
<td>Peritoneal UF (mL/24 h)</td>
<td>1422 ± 780</td>
</tr>
<tr>
<td>Urine volume (mL/24 h)</td>
<td>415.1 ± 379.3</td>
</tr>
<tr>
<td>Total UF (mL/24 h)</td>
<td>1835.3 ± 838.7</td>
</tr>
<tr>
<td>Peritoneal CCr (mL/min/1.73 m²)</td>
<td>5.43 ± 1.09</td>
</tr>
<tr>
<td>RRF (mL/min/1.73 m²)</td>
<td>1.88 ± 1.84</td>
</tr>
<tr>
<td>Total CCr (mL/min/1.73 m²)</td>
<td>7.30 ± 1.90</td>
</tr>
<tr>
<td>Kt/V urea</td>
<td>2.449 ± 0.698</td>
</tr>
<tr>
<td>Protein loss from PD (g/24 h)</td>
<td>6.7 ± 3.8</td>
</tr>
<tr>
<td>Dietary protein intake (g/24 h)</td>
<td>53.3 ± 10.8</td>
</tr>
<tr>
<td>Calories from PD (kcal/24 h)</td>
<td>402.8 ± 88.7</td>
</tr>
<tr>
<td>Dietary calorie intake (kcal/24 h)</td>
<td>1370.8 ± 332.7</td>
</tr>
<tr>
<td>Urea generation rate (mmol/min)</td>
<td>0.11 ± 0.05</td>
</tr>
<tr>
<td>Cr generation rate (mmol/24 hr)</td>
<td>5.93 ± 2.24</td>
</tr>
<tr>
<td>Daily PNA/PCR (g/kg)</td>
<td>1.17 ± 0.36</td>
</tr>
</tbody>
</table>

UF = ultrafiltration; CCr = creatinine clearance; RRF = residual renal function; Kt/V = dialysis adequacy; PD = peritoneal dialysis; Cr = creatinine clearance; PNA/PCR = protein equivalent of nitrogen appearance/protein catabolic rate.

**Discussion**

In the present study, we used the PDC test to calculate peritoneal permeability in 139 newly initiated CAPD/APD patients. Our data clearly demonstrate that high peritoneal permeability as assessed by PDC is associated with poor prognosis for patient and technique survival in patients on CAPD. We conclude that early estimation of high peritoneal permeability can predict a poor prognosis for technique survival in patients on CAPD.

In 1992, Rippe (14) introduced the three-pore model of the peritoneal membrane for the transport
A small number of reports regarding the clinical application of PDC testing have appeared thus far (12,13,15). The useful features of the PDC test are the convenience of entering data during routine dialysis (two blood samples in 24 hours), the abundant results regarding peritoneal function and diet, ease in recommending dialysis treatment for each patient, and accurate comparison of digitized data in both the clinical course of individual patients and in large studies (11,16).

FIGURE 1 Effect of peritoneal area on patient and technique survival in 139 newly started continuous ambulatory peritoneal dialysis (CAPD) patients. In the high-area group, the technique survival at 5 years was significantly lower than in the low–area group (55.9% vs. 72.7%, \( p = 0.0459 \)). No significant difference in patient survival was observed between high- and low-area patients [72.7% (high) vs. 83.0% (low), \( p = 0.1228 \)].

FIGURE 2 Effect of plasma loss on patient and technique survival in 139 newly started continuous ambulatory peritoneal dialysis (CAPD) patients. In the high plasma loss group, technique survival at 5 years was significantly lower than in the low plasma loss group [43.3% (high) vs. 62.8% (low), \( p = 0.0197 \)]. No significant difference in patient survival was observed between the high and low plasma loss patients [73.3% (high) vs. 84.6% (low), \( p = 0.1016 \)].

of solutes. Following from that concept, Haraldsson (11) developed a computer program for peritoneal function analysis, calling it the PDC test. The PDC computer program calculates the three physiologic parameters of the peritoneum:

- Pore area (total pore area divided by diffusion distance available for exchange)
- Absorption (final rate of fluid reabsorption from the abdominal cavity when the osmotic gradient has dissipated)
- Plasma loss (rate of protein-rich fluid passing through the large pores from blood to dialysate)

A small number of reports regarding the clinical application of PDC testing have appeared thus far (12,13,15). The useful features of the PDC test are the convenience of entering data during routine dialysis (two blood samples in 24 hours), the abundant results regarding peritoneal function and diet, ease in recommending dialysis treatment for each patient, and accurate comparison of digitized data in both the clinical course of individual patients and in large studies (11,16).

Recently, some clinical applications of the PDC test have been reported. Imai et al. (15) found that the PDC test is useful for evaluating change in peritoneal
function on CAPD. Schaefer et al. (17) reported that the PDC test allowed peritoneal solute and water transport to be modeled with remarkable precision in children of all age groups. More recently, Heaf and colleagues (18) reported that a high peritoneal large-pore fluid flux (JVc) as calculated by PDC test resulted in increased peritoneal protein losses. The JVc is related to hypoalbuminemia and mortality after PD initiation. A high JVc seems to be a marker of pre-existing vascular pathology, which causes hypoalbuminemia after PD initiation. However, no studies have clearly evaluated the association between peritoneal permeability and clinical outcome using this kind of analysis tool.

In the present study, to determine whether early estimation of peritoneal permeability can predict the prognosis of patient and technique survival in patients on CAPD, we reanalyzed data from a multicenter study that used the PDC test. Our study demonstrated that early diagnosis of high peritoneal CCr is associated with higher mortality and lower technique survival in patients on CAPD. This high peritoneal CCr was induced by high peritoneal permeability. On the other hand, high protein losses in dialysate and a high area parameter are associated with lower technique survival, but have no association with patient survival. This discrepancy may be attributable to the small number of patients in the study. However the data demonstrated another possibility: that high small-solute
losses from the peritoneum may be an independent risk factor for patient survival.

High peritoneal permeability had a clearly demonstrated association with poor clinical outcome in patients on CAPD. Previously, CAPD patients with high peritoneal permeability have been shown to have a paradoxically higher morbidity and mortality (10,19). Increased peritoneal transport may be associated with increased removal of uremic solutes, thereby improving patient and technique survival. In the CANUSA study (10), three possible explanations were advanced. First, high peritoneal permeability patients lose ultrafiltration capacity because of rapid equilibration of glucose across the peritoneal membrane, with consequent overhydration and hypertension. Second, high peritoneal permeability patients typically also have large-pore transport, leading to excessive loss of protein with consequent protein malnutrition. Third, high peritoneal permeability patients were noted to already suffer from hypoalbuminemia at the time of their first peritoneal equilibration test, 1 month after the start of dialysis, and hypoalbuminemia is a powerful predictor of mortality. Increased peritoneal permeability induces additional loss of protein from the peritoneum, inducing malnutrition. Rapid absorption of glucose from the dialysate may reduce appetite and contribute to malnutrition. In such patients, repeated use of hypertonic dialysis exchanges may increase the carbohydrate load, possibly suppressing appetite and reducing protein intake. These multiple factors may induce malnutrition and poor clinical outcome. Although protein loss is greater in the high transport group after initiation of PD, high loss of protein cannot explain why some patients have lower baseline serum albumin levels.

Our data demonstrated that total CCr has no effect on patient and technique survival in patients on CAPD. Those data are supported by previous reports (5,20). On the other hand, high peritoneal CCr is a strong predictor of higher mortality and lower technique survival. Considering peritoneal CCr plus CCr from RRF (total CCr), we can speculate that low RRF may be an important predictor of high mortality. In the ADEMEX study, it was reported that peritoneal small-solute clearance is not as critical as RRF for the survival of CAPD patients. In patients starting PD, a low initial RRF and inflammation are both associated with high overall mortality (21). High peritoneal permeability was associated with higher mortality, but only during the initial year on PD (22).

Conclusions
Our data clearly demonstrate that high peritoneal permeability measured early in patients initiated on CAPD was associated with poor prognosis for patient and technique survival. We conclude that an early estimation of high peritoneal permeability can predict poor prognosis for technique survival in patients on CAPD.

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