The Personal Dialysis Capacity Test Is Superior to the Peritoneal Equilibration Test to Discriminate Inflammation as the Cause of Fast Transport Status in Peritoneal Dialysis Patients

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This study evaluated the potential of the Personal Dialysis Capacity (PDC) test to discriminate fast transport status (FTS) as a consequence of inflammation *versus* FTS because of other causes. This distinction is important because new therapeutic options such as icodextrin and automated peritoneal dialysis can abolish the negative impact on outcome of FTS if fast transport is not caused by inflammation. A PDC test and a Peritoneal Equilibration Test (PET) were performed in 135 incident PD patients. Membrane characteristics were related with baseline biochemical parameters and C-reactive protein. After correction for other covariates, only large pore flux (J_vL) but not surface area over diffusion distance (A0/dX) or dialysate over plasma concentration was related to C-reactive protein. Using the PDC test for detection of inflammation, positive and negative predictive values were 16/36 and 80/99, respectively, whereas with PET, positive predictive value was 5/20 and negative predictive value 92/115 ($\chi^2 = 0.009$). In a Cox regression for patient survival with correction for age, a J_vL higher than expected by the surface area over diffusion distance, predicted outcome ($P = 0.04$). Patients with inflammation had a higher J_vL (0.21 ± 0.12 *versus* 0.17 ± 0.09; $P = 0.06$) and a lower ultrafiltration (89 ± 631 *versus* 386 ± 601 ml/d; $P = 0.06$) and urine output (878.45 ± 533.55 *versus* 1322 ± 822 ml/d; $P = 0.023$) than patients without inflammation. There was no difference for surface area over diffusion distance (A0/dX) or dialysate over plasma concentration. A PDC test yields far more information about the peritoneal membrane characteristics than a PET. A J_vL higher than expected by the A0/dX is an indicator of inflammation and is related to an increased mortality. The PET is not able to discriminate between FTS because of inflammation *versus* because of anatomic reasons, whereas the PDC test does.

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In the CANUSA study (1), a negative relation between fast transport status (FTS) and outcome was notified. This relation was confirmed in some other studies (2,3), but a clear explanation for this observation was not readily available. It was hypothesized that FTS resulted in overhydration, hypoalbuminemia, or less adequate solute removal (4–6). Some later studies pointed to the possibility that the worse outcome found in patients with FTS was related to the underlying inflammation (7,8). Indeed, one can speculate that in case of inflammation, an increase of vascular surface area is found, caused by vasodilation and vascular recruitment, both resulting in an FTS in the peritoneal equilibration test (PET). In case of an anatomic large surface area, the use of icodextrin or automated peritoneal dialysis (APD) can improve fluid balance with the potential to correct the higher mortality related to FTS (9–11). If the underlying cause is inflammation, then outcome will probably not be improved unless the source of inflammation can be cured.

The Personal Dialysis Capacity (PDC) test (Gambro, Lund, Sweden) describes the peritoneal membrane characteristics by means of three parameters that are derived from data obtained from five exchanges with different duration and different glucose strengths (12). The tree parameters are (*1*) the surface area over diffusion distance (A0/dX), which represents the effective surface area available for diffusion and is thought to be roughly comparable with the mass transfer area coefficient and the dialysate over plasma concentration ratio (D/P) value of the PET test; (*2*) the reabsorption parameter, which measures the reabsorption of fluid from the peritoneal cavity after the osmotic gradient has disappeared, representing mainly the lymphatic flow; and (*3*) the large pore flow (J_vL). The test uses a computerized mathematical model based on the three-pore model (13) to describe peritoneal transport characteristics. The PDC test–derived A0/dX is superior to the PET-derived dialysate over plasma concentration (D/Pcrea) to describe the transport of small solutes through the peritoneal membrane (14). The PDC test has been validated to describe membrane characteristics in large patient groups, both in adults and in children (15,16). The PDC test has also been advocated to describe the

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evolution of the functional capacity of the peritoneal membrane over time (17,18). Heaf *et al.* (19) demonstrated that J_vL was related with mortality. As J_vL represents the flow through the large pores, it is related to the "leakiness" of the membrane and thus potentially to inflammation. Until now, no study has evaluated the relation between J_vL and inflammation and between J_vL and fast transport. This might be of importance, as a good understanding of the underlying mechanism of the FTS has therapeutic and prognostic consequences. This study (*1*) evaluated the capacity of PDC to discriminate inflammation from other causes of FTS and (2) identified the relation between inflammation and transport.

Materials and Methods

All new (incident) patients who started PD at the University Hospital Ghent between January 1, 1998, and December 31, 2003, were included in this prospective observational study. In all patients, a standard PDC test was performed during the first 3 mo of their PD treatment. The PDC test was performed as described earlier (15). In brief, patients were visited at home and given the instructions for the PDC regimen (five exchanges) and the collection of the dialysate samples and 24-h urine. A blood sample was drawn. The five exchanges all alternated in glucose concentration and duration (one of 3 h, one of 4 h, one of 5 h, one of 2 h, and one of 10 h) to maximize the effectiveness of the mathematical model. All solutions were low in glucose degradation products at neutral pH. For the 4-h dwell, always a 2.27% glucose solution was used, which allowed calculation of D/P values at 4 h, the key parameter of the PET. The preceding exchange was always 1.36% glucose to avoid carryover effect differences (20,21). The glucose concentrations for the remaining exchanges were at the discretion of the physician in function of the volume status of the patient. Patients noted for each exchange the exact time of start of the drainage, the total drained volume, and the time of start of the inflow on the specifically designed PDC test sheet. The next day, patients brought the collected samples of PD fluid and urine to the hospital, and a second blood sample was drawn. Patients who were on APD were converted to continuous ambulatory peritoneal dialysis (CAPD) for the duration of the PDC test. Data were entered in the PDC program (Gambro, Lund, Sweden), and the PDC-derived parameters were calculated.

Demographic data and biochemical parameters were measured. Inflammation was assessed by the determination of serum C-reactive protein (CRP) levels, using the latex-enhanced immunoturbidimetric method (Tina quant; Roche Diagnostics, Switzerland) on a Modular P analyzer (Hitachi, Tokyo, Japan). Patients with a serum CRP level >10 mg/L were considered to have inflammation.

Residual renal function was determined by collection of a 24-h urine sample, as is usual during the PDC test. Both urea and creatinine clearance were calculated, and GFR was determined as the mean of urea and creatinine clearance. Serum albumin was determined by nephelometry.

Ultrafiltration was defined as the total ultrafiltration obtained during the PDC test day by the PDC test day regimen. Thus, it does not reflect the actual ultrafiltration of the patient on his or her day-to-day CAPD regimen but rather the ultrafiltration capacity in response to a standardized regimen.

Comorbid conditions were noted at baseline (*i.e.*, the moment of PDC test). Diabetes was defined as need for oral antidiabetics or insulin, actual or in the past.

Statistical Analyses

Data were analyzed with SPSS 12.0 (SPSS, Inc., Chicago, IL). The *t* test was used to compare continuous variables between two groups. For univariate correlation analysis, Pearson correlation coefficient calculation was used. Multivariate regression analysis was used to correct for confounding variables when the analyzed parameter was continuous. A linear mixed model was used when parameters were categorical. Cox regression was used to compare survival and outcomes between groups. Patients were only censored for loss to follow-up or at the end of study (intention-to-treat approach). Only baseline parameters were evaluated.

It was hypothesized that a J_vL higher than expected according to the A0/dX was the most sensitive sign of an inflamed peritoneal membrane. Therefore, we divided patients into two groups on the basis of the composite interpretation of J_vL and A0/dX: Those with a J_vL higher than expected on the basis of their A0/dX (hypothesis: This is a sign of inflammation) and patients with a normal J_vL according to their A0/dX (thus the patients without inflammation). Classification was done using quartiles of J_vL and A0/dX. For example, a patient who was in the third quartile for J_vL and in the second quartile for A0/dX was considered to have an inflamed membrane. A patient who was in the third quartile for J_vL and in the third quartile for A0/dX was considered to have a normal, noninflamed membrane.

Results

In total, 135 patients were included in the study. No patient refused to perform the test, and acceptance of the PDC test in this study was good.

Inflammation and Membrane Characteristics

The continuous variables are presented in Table 1, separated for patients with ($n = 25$) and without ($n = 110$) inflammation. Patients with inflammation were older and had a lower serum albumin, a higher J_vL, and a lower peritoneal ultrafiltration rate and residual diuresis. Diabetes was present in 25 patients (20 in the group without inflammation, five in the group with inflammation; NS, Fisher exact). A total of 83 patients were male. On the basis of D/Pcrea at 4 h and according to PET classification, 70 patients were classified as slow or slow average, 46 as fast average, and 19 as fast transporters. There was no difference in the distribution between patients with and inflammation (NS, Fisher exact). Patients who had a higher-than-expected increase in J_vL by their A0/dX were older (65 ± 14 *versus* 56 ± 14 yr; $P = 0.02$), had a higher CRP (13 ± 14 *versus* 7 ± 7 g/L; $P = 0.03$), and had a lower serum albumin (31.8 ± 6.7 *versus* 35.3 ± 5.6 g/L; $P = 0.03$).

Univariate correlations between parameters of interest are represented in Table 2. There was a correlation between J_vL and CRP ($P = 0.04$) but not between D/Pcrea at 4 h and CRP. A multivariate linear regression model for A0/dX is given in Table 3. A0/dX is larger in individuals with diabetes and in men. In a multivariate linear regression model for J_vL (Table 3), a higher J_vL was independently predicted by inflammation ($P = 0.048$) and by A0/dX ($P < 0.001$). This suggests that in patients with comparable A0/dX, a higher J_vL is related with inflammation (Table 3).

Mean A0/dX plus 1 SD was 27,000 cm^2/cm per 1.73 m^2. In parallel with the procedure followed in the PET, this value was used as a cutoff for the definition of FTS. Seventeen patients

Table 1. Univariate comparison of parameters in patients with *versus* without inflammation

	No Inflammation		Inflammation		*P* Value
	Mean	SD	Mean	SD	
Albumin (mg/dl)	36.62	4.73	32.34	7.16	0.001
BMI (kg/m^2)	25.6	4.1	24.1	2.7	0.03
Age, yr	55.17	15.17	62.15	11.49	0.056
GFR (ml/min)	4.9		6.9		0.2
A0/dX (cm^2/cm per 1.73 m^2)	19,336.38	7,447.69	18,182.60	5,532.85	0.51
J_vR (ml/min per 1.73m^2)	1.70	0.89	1.64	0.77	0.78
J_vL (ml/min per 1.73m^2)	0.17	0.09	0.21	0.12	0.06
D/Pcrea (4 h)	0.62	0.12	0.63	0.13	0.74
D/Pcrea (2 h)	0.49	0.10	0.49	0.13	0.99
Ultrafiltration (ml/d)	386.48	601.92	89.47	631.83	0.05
Urine volume (ml/d)	1,322.78	822.72	878.45	533.51	0.03

BMI, body mass index; A0/dX, surface area over diffusion distance; J_vR, reabsorption after dissipation of glucose gradient; J_vL, large pore flux; D/Pcrea, dialysate over plasma concentration.

Table 2. Univariate correlations

	Alb	Ufml	Urine	Age	CRP	A0/dX	J_vR	J_vL	D/Pcrea4
Alb									
ρ	1	0.062	0.158	−0.127	−0.287	−0.268	−0.185	−0.265	−0.267
P value	—	0.483	0.068	0.145	**0.003**	**0.002**	**0.033**	**0.002**	**0.002**
Ufml									
ρ		1	−0.337	−0.183	−0.206	−0.005	−0.122	−0.075	−0.220
P value		—	**0.000**	**0.038**	**0.037**	0.953	0.169	0.400	**0.012**
Urine									
ρ			1	−0.077	−0.185	0.051	0.138	0.191	0.183
P value			—	0.377	**0.058**	0.555	0.110	**0.026**	**0.033**
Age									
ρ				1	0.218	−0.188	0.075	−0.066	−0.112
P value				—	**0.025**	**0.029**	0.390	0.444	0.197
CRP									
ρ					1	−0.047	−0.012	0.197	0.136
P value					—	0.632	0.903	**0.043**	0.164
A0/dX									
ρ						1	0.380	0.502	0.678
P value						—	**0.000**	**0.000**	**0.000**
J_vR									
ρ							1	0.288	0.269
P value							—	**0.001**	**0.002**
J_vL									
ρ								1	0.382
P value								—	**0.000**
D/Pcrea4									
ρ									1
P value									—

Alb, serum albumin value; Ufml, peritoneal ultrafiltration obtained during the Personal Dialysis Capacity (PDC) regimen; CRP, C-reactive protein. Values in bold indicate *P* values <0.05.

had an A0/dX >27,000 cm^2/cm per 1.73 m^2. Ten of those had a normal J_vL, eight of whom also had a normal CRP. In four patients, both CRP and J_vL were elevated. In one patient, CRP was elevated despite a high normal J_vL. In two patients, CRP was normal, despite an elevated J_vL. Nineteen patients had a D/Pcrea at 4 h >0.76; 14 of these had a normal CRP. Only 10 of 19 of these fast transporters on the basis of PET criteria also had an A0/dX >27,000 cm^2/cm per 1.73 m^2. Table 4 represents the distribution of classification according to PDC test–derived (χ^2 $P = 0.009$); Table 5 represents the distribution of classification according PET-derived classification (χ^2: $P = 0.9$) in accordance with inflammation for the complete study population.

Inflammation, Membrane Characteristics, and Outcome

In the univariate analysis, inflammation (relative risk [RR] 1.8 per mg/L CRP; $P = 0.007$), serum albumin (RR 0.92 per g/dl; $P = 0.06$), diabetes (RR 2.2; $P = 0.02$), and age (RR 1.07/yr; $P < 0.001$) were predictive for worse outcome but not A0/dX, or J_vL, or D/Pcrea at 4 h (Table 6). In a multivariate Cox regression analysis with correction for age, diabetes, CRP, and serum

Table 3. Multivariate regression analysis for A0/dX and J_vL[a]

	Standardized Coefficient β	*P* Value
A0/dX		<0.0001
age	−0.212	0.011
GFR	−0.303	<0.000
CRP	−0.099	0.233
diabetes	0.218	0.008
serum albumin	−0.193	0.020
gender	0.151	0.062
J_vR	0.295	0.001
J_vL	0.309	0.001
BMI	−0.094	0.278
J_vL		
age	0.080	0.387
GFR	−0.085	0.381
CRP	0.178	0.048
diabetes	0.036	0.691
serum albumin	−0.126	0.171
gender	−0.044	0.624
J_vR	0.221	0.022
A0/dX	0.366	0.001
BMI	−0.027	0.775

[a]Model: $P < 0.0001$ (constant).

albumin, patients who had a J_vL higher than expected by their A0/dX had a higher mortality than those who had a normal J_vL according to their A0/dX (Figure 1). D/Pcrea at 4 h was not related to mortality in any of the multivariate analyses.

Discussion

The relation between inflammation and high transport status is probably the most important explanation for the increased mortality risk found in PD patients with an FTS. This analysis demonstrates that the use of D/Pcrea based on the PET leads to an incorrect perception of the mortality risk of PD patients with FTS, as with PET-based information alone, the different causes of FTS cannot be discriminated. In contrast, with the PDC test, the combined interpretation of the J_vL and the unrestricted area for diffusion corrected for diffusion distance (A0/dX) allows much better discrimination of inflammation from anatomic constitution as a cause of an FTS. When age is taken into account, a higher-than-expected J_vL by A0/dX and CRP level are equipotent predictors of outcome, whereas D/Pcrea is not. Analysis of the peritoneal membrane characteristics with PDC test thus is more informative than a simple PET. This discrimination has important prognostic and therapeutic consequences, because for patients with a large surface area but without inflammation, outcome can be improved by increasing the fill volume or by the use of icodextrin, whereas for patients with inflammation, the underlying cause of the inflammation should be identified and eventually cured. If no evident cause of the inflammation is found, then use of more biocompatible PD solutions (22,23) or a transfer to hemodialysis to rest the peritoneal membrane should be considered. In patients with inflammation, use of icodextrin and of short cycles is also warranted to avoid overhydration, which might be an important additional cause of the inflammation and the increased mortality in these patients (5,6,9,24,25).

The PET (26) is the most widespread tool used to analyze peritoneal membrane characteristics (18). The test, however, has several drawbacks (27,28). First, the categorization into four groups has only limited value, as it has been validated only in a (limited) North American population. For other populations, epidemiologic adaptations should be made, especially when patient physiognomy is strongly different from the "average" American patient, *e.g.*, in Asian patients (29–31). Using the D/Pcrea ratio at 4 h gives already a more objective and continuous representation of the transport status of the membrane. For CAPD patients, this in addition gives the advantage that peritoneal clearances can easily be estimated (32), although still then, caution must be taken to extrapolate PET data to clearances in individual patients (28), whereas PDC allows calculation of the effect on clearance and ultrafiltration of different alternative regimens. Second, the use of a standard instillation volume in the PET leads to bias. In PDC, the fill volume of the different dwells can be adapted to the clinical needs of the patient. In addition, in a slow transporter, the D/Pcrea is further falsely decreased by the dilution created by the additional convective flow. Third, newer evaluation methods of the peritoneal membrane, such as PDC or Peritoneal Function Test (Fresenius Medical Care, Bad Homburg, Germany) can be performed by the patient at home, even for the blood sample, which can be drawn when the patient collects his or her material or during a home visit. For the PET, although always advocated as a more simple and more patient-friendly method, the patients have to come to the clinic and stay for at least 4 h. In our institution, where PDC is performed routinely, no patient has ever objected to this procedure, and most prefer it over staying 4 h in the outpatient clinic to perform a PET.

Our study highlights another important advantage of PDC

Table 4. Classification of patients as having inflammation or not by PDC test[a]

	Inflammation	No Inflammation	Total	
CRP >10	16	19	35	TP 16/35; FN 19/35
CRP <10	20	80	100	TN 80/100; FP 20/100
Total	36	99		
	PPV 16/36	NPV 80/99		$\chi^2 = 0.009$

[a]In the PDC test, the criterion for being determined as having inflammation is that the J_vL is higher than expected by the A0/dX (see Materials and Methods). TP, true positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

Table 5. Classification of patients as having inflammation or not by PET-derived D/Pcrea[a]

	Fast transporter	Nonfast transporter	Total	
CRP >10	5	23	28	TP 5/28; FN 23/28
CRP <10	15	92	107	TN 92/107; FP 15/107
Total	20	115		
	PPV 5/20	NPV 92/115		$\chi^2 = 0.9$

[a]In the PDC test, the criterion for being determined as having inflammation is that the J_vL is higher than expected by the A0/dX (see Materials and Methods). PET, Peritoneal Equilibration Test.

Table 6. Cox regression analysis for mortality: Univariate analysis

	P Value	Relative risk
Age (yr)	0.009	1.048
CRP (mg/L)	0.001	2.3
Diabetes (present)	0.06	2.0
Serum albumin (mg/dl)	0.003	0.98

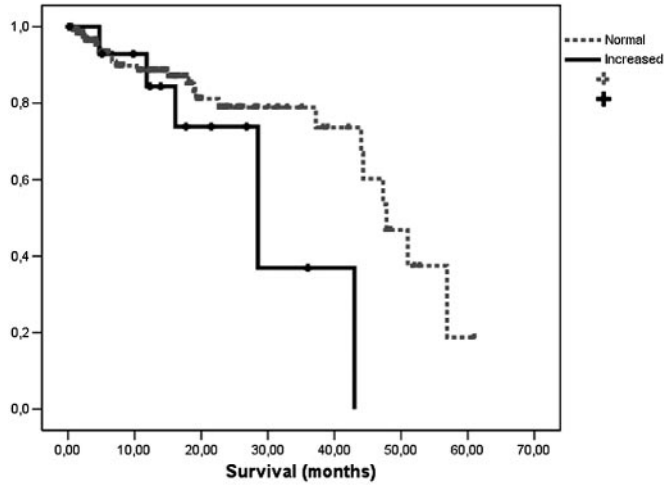

Figure 1. Survival of patients with or without increased larger pore flux (J_vL; corrected for age, diabetes, C-reactive protein and serum albumin, and potential interaction terms). Patients are divided into those with a J_vL higher than expected by their surface area over diffusion distance (A0/dX; "increased," solid line) and those with a normal J_vL as related to their A0/dX (normal, dotted line). $P = 0.04$.

over PET: It gives more essential information on the peritoneal membrane characteristics. With a PET, it is impossible to discriminate inflammation, which leads to changes in membrane quality and vascular recruitment and thus an increased area for diffusion on the one hand and anatomic large surface area with normal distribution of the vessels on the other hand by a PET. In this study, we found a substantial misclassification of "inflammation" when only D/P was taken into account. In contrast, by using a composite marker of PDC data, *i.e.*, J_vL that is higher than expected on the basis of the A0/dX, we were able to discriminate inflammation from other causes of FTS. This finding also suggests that during inflammation, not only recruitment of vessels takes place but also a change in pore and membrane quality, as large pore flow increases more rapidly than the perfused area. It gives an explanation for the observed differences in transport of water and large solutes and small uremic toxins: In inflammation, there is not only vascular recruitment but also alterations in membrane porosity.

Serial measurement of the PDC data also allows timely detection of changes in peritoneal membrane characteristics (17). An increase in J_vL without a correlated increase in A0/dX might be a warning sign that the peritoneal membrane is wearing off and that a (temporary?) transfer to hemodialysis might be indicated.

Another important finding in this study is the independent impact of J_vL, when corrected for A0/dX, on mortality. An in-depth analysis of the PDC-derived parameters thus yields a powerful prognostic marker.

In a previous study, Johnson *et al.* (14) demonstrated that the PDC-derived A0/dX was superior to PET-derived D/Pcrea at 4 h in describing the transperitoneal membrane transport of small solutes. This study adds another argument in favor of the PDC test as compared with the PET: A better discrimination of inflammation *versus* anatomic constitution as the cause of an FTS. In view of the prognostic difference between these two conditions, this is a relevant finding.

Conclusion

This article demonstrates that PDC delivers more information on peritoneal membrane status than a classic PET. This information has both prognostic and therapeutic importance. J_vL, when corrected for A0/dX is a marker of inflammation and is related to outcome.

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See related editorial, "Peritoneal Inflammation and High Transport Status," on pages 167–169.