

Mechanisms in ultrafiltration failure of long-term peritoneal dialysis patients

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■ INTRODUCTION

Patients treated with peritoneal dialysis have good survival during the first year of treatment¹. Impaired net ultrafiltration may be present already at the beginning of peritoneal dialysis, for instance, due to malposition of the catheter, herniations and other mechanical reasons, and also to a high lymphatic absorption from the peritoneal cavity². In addition, a fast solute transport status, leading to a rapid disappearance of the osmotic gradient due to a fast absorption of glucose, is present in about 15% of new peritoneal dialysis patients³⁻⁵. This fast transport status is related to vasoactive substances that can be measured in peritoneal effluent, such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF). Both can lead to local vasodilation, thereby increasing the peritoneal vascular surface area. The resulting fast transport status can be caused by inflammation^{4,6-8}, or by the presence of a large mesothelial cell mass⁹⁻¹¹. These types have been reviewed recently¹². Impaired ultrafiltration in incident PD patients is only rarely an important clinical problem, because the majority of these patients will have urine production. This can be stimulated by high dose loop diuretics^{13,14}. Accordingly, most studies found no effect of peritoneal ultrafiltration on mortality in patients with residual renal function¹⁵⁻¹⁷. In contrast, peritoneal ultrafiltration was related to death in patients that had become anuric^{18,19}.

This review will focus on the mechanisms that are involved in the development of ultrafiltration failure in long-term peritoneal dialysis patients.

■ PHYSIOLOGY OF PERITONEAL FLUID TRANSPORT

Fluid transport during peritoneal dialysis is dependent on the hydraulic permeability of the membrane, the transcapillary pressure gradients, and uptake into the lymphatic system. The pressure gradient is the sum of the hydrostatic, colloid osmotic and crystalloid osmotic gradients. The latter is especially determined by the glucose concentration of the dialysis solution. The resistance of the peritoneal membrane to transperitoneal transport of glucose is expressed as the reflection coefficient (σ). Sigma can vary between 1 (no passage, ideal semipermeable membrane) to 0 (free transport, no osmotic effect). In peritoneal dialysis sigma equals 0.03²⁰. The determinants of the transcapillary ultrafiltration rate (TCUFR) can be expressed in Starlings' equation:

$$TCUFR = LpA \times (\Delta P - \Delta\pi + \sigma\Delta O)$$
in which Lp is the hydraulic permeability of the membrane, A is its surface area, ΔP is the hydrostatic pressure gradient, $\Delta\pi$ is the colloid osmotic pressure gradient, σ is the reflection coefficient and ΔO is the crystalloid osmotic pressure gradient. LpA is also called the ultrafiltration coefficient. The efficiency of glucose as an osmotic agent is expressed as osmotic conductance, which is the product of the ultrafiltration coefficient and the reflection coefficient: $LpA \times \sigma$.

The peritoneum is a biological membrane consisting of mesothelium, endothelial cells of the microvascular

wall and interstitial tissue. The vessel wall is the most important structure for transport in the 3 pore theory. In this theory it is assumed that small interendothelial pores are especially involved in fluid and solute transport. The number of large interendothelial pores is so small that their contribution to fluid transport can be ignored. Intraendothelial aquaporin-1 allows transport of water, but not of solutes: free water transport. The reflection coefficient sigma equals 1.0 for the water channels, so the over-all value of sigma is very much dependent on aquaporin-1 function²¹. Free water transport leads to the well-known phenomenon of “sodium sieving”, that is the decrease in dialysate sodium in the initial phase of a dwell with a strong hypertonic dialysis solution^{22,23}. The maximal dip in D/P sodium provides an estimation of the amount of free water transport. Free water transport and small pore fluid transport can be quantified using sodium kinetics as described recently^{24,25}. The principle is that the amount of sodium transported during the first hour of a 3.86% glucose dwell divided by plasma sodium results in the volume transported through small pores. Free water transport is the difference between total ultrafiltration and small pore fluid transport. It averages 35-40% of the ultrafiltered volume, but has a very wide variability²⁴.

■ ULTRAFILTRATION FAILURE IN LONG-TERM PERITONEAL DIALYSIS

A diagnosis of ultrafiltration failure should not be made on clinical grounds, but should be based on the 3 x 4 definition of the International Society for Peritoneal Dialysis (ISPD)²⁶: less than 400 mL ultrafiltration after a 4 hours dwell with a 4% (3.86%-4.25%) glucose based dialysis solution. Using this definition it appeared that ultrafiltration failure was present in 36% of patients treated with peritoneal dialysis for more than 4 years²⁷. Clinical characteristics including age, gender, peritonitis incidence and duration of dialysis, were no different from those in patients without ultrafiltration failure. The most striking difference was the markedly reduced sieving of sodium. Also when long-term ultrafiltration failure was compared with ultrafiltration failure in short term patients, sodium sieving appeared to be reduced²⁸ in comparison to reference values²⁹. Peritoneal transport characteristics in short- and long-term patients with and without ultrafiltration failure are summarised in

Table I. A comparison of the causes of early and late ultrafiltration failure is given in Table II. A combination of factors was often found, but impaired free water transport was especially present in long-term patients. Lymphatic absorption is not influenced by the duration of peritoneal dialysis². Therefore, the lower value for the ELAR in the long-term group can possibly be explained by selective drop out of patients with a high value.

It appears from our studies that a decrease in free water transport is an important contributing factor in the pathogenesis of ultrafiltration failure in long-term PD. This is in accordance with the observation of Davies, who reported a lower net ultrafiltration compared to expected values based on D/P creatinine³⁰. These findings make it likely that an impaired osmotic conductance of glucose, leading to reduced free water transport, develops in some long-term patients. The hypothesis was investigated further in 50 patients with ultrafiltration failure. In all of them a relationship between the osmotic conductance obtained by mathematical modelling, and free water

Table I

Peritoneal transport characteristics in short- and long-term patients with and without ultrafiltration failure. Median values are given. Data were obtained during standard peritoneal permeability analyses.

	Short-term		Long term	
	Normal UF	UFF	Normal UF	UFF
D/P creatinine	0.70	0.83	0.71	0.86
Glucose absorption (%)	58	72	60	73
ELAR (mL/min)	1.3	2.4	1.0	1.6
Max dip D/P Na+	0.111	0.08	0.109	0.032

Glucose absorption: % of the instilled quantity

ELAR: effective lymphatic absorption rate

Based on reference [27-29]

Table II

Causes of early and late ultrafiltration failure, expressed as % of the patients in whom one or more causes could be identified. Based on reference 28.

	Early UF failure (< 2 years)	Late UF failure (> 4 years)
High MTAC creatinine	44	61
High ELAR	68	30*
Low Δ D/P Na+	8	43*

* $p < 0.01$ The total of the percentages is more than 100% as more than one cause was present in a number of patients

transport was present³¹. Both parameters were lowest in the long-term patients with ultrafiltration failure. Interestingly, in patients treated for more than 5 years, the osmotic conductance decreased further with the duration of dialysis. Small pore fluid transport also declined with the duration of peritoneal dialysis. It is currently unsolved whether the reduced osmotic conductance is caused by a lower L_pA ³¹ or by a decrease in the reflection coefficient²⁷. The first points to a reduced fluid permeability and the latter to impaired aquaporin-1 function. Longitudinal studies are required to solve this point.

■ DETECTION OF ULTRAFILTRATION FAILURE

The peritoneal equilibration test, as originally described³² is not very suitable for detecting the presence and causes of ultrafiltration failure. This is also the case for the peritoneal dialysis capacity test (PDC)³³. However, the PET can easily be adapted for analysis of ultrafiltration failure. The refinements that will be discussed are the modified PET, the mini PET and the modified PET with temporary drainage.

■ Modified PET

This test has been advocated by the International Society for Peritoneal Dialysis²⁶. The original 2.2.7%/2.5% glucose solution is replaced by a 3.86%/4.25% one and an additional dialysate sample is taken at one hour for the determination of sodium. The test gives more accurate information on net ultrafiltration, because the drained volume is larger than in the original PET. The D/P sodium at one hour gives information on free water transport. Increasing the dialysate glucose concentration to 3.86%/4.25% has no effect on D/P creatinine³⁴. The modified PET is feasible in routine clinical practice³⁵ and can be used for patient follow-up¹⁰.

■ Mini PET

The mini PET is performed with a 3.86%/4.25% glucose based solution, but the dwell time is only one hour²⁵. It allows the calculation of free water transport from the transport of sodium (see section on physiology

of peritoneal fluid transport). However, the interpretation of D/P ratios is difficult, because mass transfer area coefficients are higher during the first hour of a 4 hours dwell than in the period thereafter³⁶. More recently D/P creatinine at 1 hour showed a relationship with D/P creatinine at 4 hours that was dependent on the actual value; that is an overestimation is present especially for high values³⁵. Therefore the mini PET cannot replace the modified PET completely.

■ Modified PET with temporary drainage

The modified PET and the mini PET can be combined when the peritoneal cavity is drained after one hour to determine the volume at that time by weighing. After taking a dialysate sample, the drained volume is reinfused and left for another 3 hours. With this method, no differences were found for net ultrafiltration and small solute transport compared to those in a modified PET³⁷. The contribution of free water transport after one hour averaged 44% of net ultrafiltration.

■ CONCLUSION

Ultrafiltration failure occurs in about one third of long-term peritoneal dialysis patients. It is characterised not only by the development of fast solute transport rates, indicating an increase in the vascular surface area, but also by a reduced osmotic conductance to glucose, which leads to a reduction of free water transport. Both a decrease in the ultrafiltration coefficient and in the reflection coefficient may be involved, but more studies are needed on this issue. An assessment of free water transport should be part of peritoneal function tests. The modified PET with temporary drainage provides good information on solute transport, ultrafiltration and free water transport. This test is likely to be feasible in clinical practice.

Conflict of interest statement. None declared.

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