

Peritoneal function in clinical practice: the importance of follow-up and its measurement in patients. Recommendations for patient information and measurement of peritoneal function

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Abstract

A review is given on peritoneal function, especially ultrafiltration and ultrafiltration failure followed by recommendations on how to translate pathophysiology into clinical practice. The subsequent consequences for management of peritoneal membrane function and for patient information are also included.

Keywords: long-term PD; peritoneal dialysis; peritoneal function; recommendations; ultrafiltration failure

Introduction

The survival of peritoneal dialysis (PD) patients, especially non-diabetics, is superior to that of haemodialysis (HD) patients during the first years of PD [1,2]. This is probably due to a better preservation of residual renal function [3,4]. The peritoneum is a biological membrane, in which alterations can develop in the long term in some patients. These may influence the initial survival advantage. The major morphological alterations include loss of mesothelial cells, neoangiogenesis and vasculopathy, and also submesothelial and interstitial fibrosis [5–8]. Ultrafiltration failure is the most important functional abnormality. This may lead to hypervolaemia, an important risk factor for cardiovascular death.

The objectives of the present review are to present a compact survey of our current knowledge on peritoneal function, and to give recommendations on how to translate pathophysiology into clinical practice. The following subjects will be discussed: physiology of peritoneal fluid transport, mechanisms of ultrafiltration failure, ultrafiltration failure during peritonitis and in long-term PD, definition and detection of ultrafiltration failure, the measurement

of peritoneal transport and reasons for elective discontinuation of PD. Also recommendations for patient information and management of peritoneal membrane function will be given.

Physiology of peritoneal fluid transport

Fluid transport during PD is determined by hydrostatic and osmotic pressure gradients, and also by uptake from the peritoneal cavity into the lymphatic system. Ultrafiltration in peritoneal capillaries (transcapillary ultrafiltration rate) is dependent on the water permeability (hydraulic permeability) of the peritoneum, the surface area for ultrafiltration and on the hydrostatic, colloid osmotic and crystalloid osmotic pressure gradients. Blood pressure in peritoneal capillaries averages 17 mmHg, but may be variable. The intraperitoneal pressure during CAPD averages 8 mmHg in the supine position [9], but can increase to 20 mmHg during walking [10]. The intraperitoneal pressure is also influenced by the dialysate volume [11]. The colloid osmotic pressure in peritoneal capillaries averages 21 mmHg [12]. The protein concentration in the dialysate is so low that its influence on the pressure gradient can be neglected.

The crystalloid osmotic pressure gradient is especially determined by the glucose concentration in the dialysis solution. The efficacy of glucose as osmotic agent is dependent on the resistance of the peritoneal membrane to its transport. This resistance is expressed as the reflection coefficient (σ). σ can vary between 1 (no passage, ideal semipermeable membrane) and 0 (free passage, so no osmotic effect of glucose). One mosmol/kg H₂O induces an osmotic pressure of 19.3 mmHg when the reflection coefficient equals 1. The peritoneal reflection coefficient of glucose averages 0.03 [13]. The various pressure gradients are summarized in Table 1.

The peritoneum is a heterogeneous dialysis membrane consisting of different structures, that is the mesothelium, interstitial tissue and the endothelial cells of the microvascular wall. The latter is the main barrier for peritoneal fluid transport. Small interendothelial pores are most important

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Table 1. Pressure gradients across the peritoneal membrane during dialysis

	Pressure in peritoneal capillaries	Pressure in the filled peritoneal cavity	Pressure gradient
Hydrostatic pressure (mmHg)	17	8 (recumbent)	9
Colloid osmotic pressure (mmHg)	21	0.1	-21
Osmolarity (mosmol/kg H ₂ O)	305	347 (1.36% glucose) 486 (3.86% glucose)	
Max. crystalloid osmotic pressure gradient (mmHg)		1.36% glucose	$(347 - 305) \times 0.03 \times 19.3 = 24$
		3.86% glucose	$(486 - 305) \times 0.03 \times 19.3 = 105$
Max. net pressure gradient (mmHg)			12 ^a (1.36% glucose) 93 ^a (3.86% glucose)

The reflection coefficient for glucose is 0.03.

^aThese pressure gradients decrease during the dwell due to glucose absorption (61% per 4 h on average).

for the transport of fluid and solutes according to the generally accepted three-pore theory. The number of large interendothelial pores is so small that their contribution to fluid transport can be neglected. Free water transport, that is water transport without solute transport, occurs through endothelial water channels, of which aquaporin-1 is the most important [15]. Free water transport explains the so-called sodium sieving, that is the decrease of the dialysate sodium concentration in the initial phase of dialysis with a strong hypertonic dialysis solution [16,17]. This phenomenon is absent in aquaporin-1 knock-out mice [18].

The peritoneal reflection coefficient of 0.03 consists of two components: one for the small pores (low value) and one for the water channels (1.0). This explains the capability of glucose as osmotic agent despite its small size. The overall efficacy of glucose for osmotic fluid transport can be expressed as the osmotic conductance. This is the product of the peritoneal ultrafiltration coefficient (hydraulic permeability \times surface area) and the reflection coefficient sigma. The contribution of free water transport to total ultrafiltration during the first hour of a 3.86% glucose exchange averages 35–40%, but can vary between 15% and 80% [19,20]. Free water transport decreases to 20% after 4 h due to absorption of glucose [2]. The addition of a macromolecular marker to the dialysis solution makes it possible to estimate lymphatic absorption from the peritoneal cavity and peritoneal tissues by its disappearance rate. The clearance of the marker is indicated as the effective lymphatic absorption rate (ELAR). Although not universally accepted [21], the concept of the ELAR is useful for assessment of causes of ultrafiltration failure. The mean value is 1.5 mL/min [22] and is not dependent on the duration of the dialysis [23]. The ELAR is influenced by the intraperitoneal pressure [9]. A review of the use of the ELAR is given in [24]. The various pathways for fluid transport are illustrated in Figure 1 [25].

Mechanisms of ultrafiltration failure

Ultrafiltration failure may be present at the start of PD. In that situation, it is always associated with fast transport of low molecular weight solutes or with a high ELAR. The

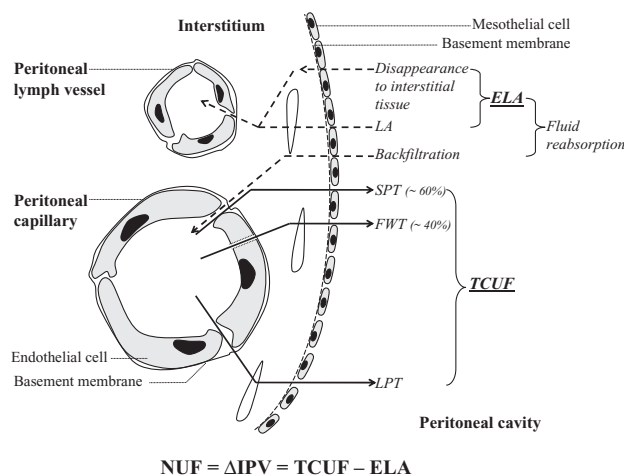


Fig. 1. Transcapillary ultrafiltration (TCUF) is induced by the crystalloid osmotic pressure gradient across the peritoneal membrane. It comprises water transport through small interendothelial pores (SPT) and ultrasmall transendothelial pores, the so-called free water transport (FWT). The amount of transported water across the large pores (LPT) is considered negligible. Changes in intraperitoneal volume (ΔIPV) result from TCUF and fluid reabsorption. Fluid reabsorption includes lymphatic absorption, disappearance to the interstitial tissues (together effective lymphatic absorption, ELA) and backfiltration into the capillaries. Adopted from reference [25] with permission from Oxford University Press.

fast transport of small solutes leads to a higher glucose absorption and thereby to a rapid disappearance of the osmotic gradient. This indicates an enlargement of the effective vascular peritoneal surface area, for instance because more vessels are perfused. A fast transport status is present in $\sim 15\%$ of new patients [26–28], and is probably caused by local release of vasoactive substances by macrophages or mesothelial cells. Cultured mesothelial cells synthesize various chemokines, prostaglandins and growth factors [29]. Some are produced constitutively, like vascular endothelial growth factor (VEGF) [30] and cancer antigen 125 (CA 125) [31]. Others, like interleukin-6 (IL-6) and IL-8, are produced after stimulation with chemokines [32,34]. All these substances can be detected in peritoneal effluent of PD patients. Effluent CA 125 can be considered as a marker for mesothelial cell mass [35]. It follows from these data that the number of mesothelial cells may be involved

indirectly in the regulation of the effective peritoneal vascular surface area.

Clinical judgement and the determination of the above-mentioned mediators make it likely that two types of inherent fast transporters can be distinguished. Both types cause decreased ultrafiltration. One is associated with comorbidity [27,36] and is characterized by high plasma and dialysate concentrations of the inflammatory cytokine IL-6 and of VEGF [37,38]. The other type can be present in patients without marked comorbidity. This type is associated with a high effluent CA 125 concentration suggesting a link with mesothelial cell mass [39–41]. Only effluent VEGF was increased in patients with this type, and it appeared that the relationship between solute transport and CA 125 was probably mediated by VEGF [41]. This type disappears spontaneously [42], because the mesothelial cell mass decreases with the duration of PD, as judged from CA 125 values [43].

Ultrafiltration failure due to an inherent fast transport status or a high ELAR is usually not a clinical problem, because these patients will generally still produce urine. This urine production can be stimulated with high-dose loop diuretics [44,45]. Also the use of icodextrin for the long dwell is especially effective in fast transporters [12].

Ultrafiltration failure during peritonitis

Acute peritonitis causes ultrafiltration failure, which is usually reversible, due to an inflammation-induced enlargement of the effective peritoneal vascular surface area and increased peritoneal blood flow [46,47]. The latter leads to a fast transport status [46,47] causing a rapid disappearance of the osmotic gradient, and consequently ultrafiltration failure. Free water transport is not impaired [48]. The development of the fast transport status is probably mediated by IL-6 and tumour necrosis factor alpha (TNF- α) [49]. The alterations in a transport status are temporary and usually reversible within 1 or 2 weeks after the institution of antibiotic treatment. Similar to other situations with a fast transport status, the use of icodextrin is very effective in increasing ultrafiltration [50,51].

Ultrafiltration failure in long-term PD

Ultrafiltration failure, as defined by the guidelines of the International Society for Peritoneal Dialysis (ISPD), is present in 36% of patients treated with PD for more than 4 years [52]. Age, gender, duration of PD and peritonitis incidence were not different from patients without this complication. The associated fast transport status in this patient group with ultrafiltration failure is reflected in high values of the dialysate/plasma (D/P) ratio of creatinine, the mass transfer area coefficient (MTAC) of creatinine and a high glucose absorption. In addition, free water transport is often impaired (see below).

Table 2 shows a comparison between the causes of ultrafiltration failure in patients treated shorter than 2 years and longer than 4 years [53]. A combination of factors is often present, but impaired free water transport was especially

Table 2. Causes of early and late ultrafiltration failure, expressed as % of the patients in whom one or more causes could be identified [53]

	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*

MTAC: mass transfer area coefficient; ELAR: effective lymphatic absorption rate.

* $P < 0.01$.

The total of the percentages is more than 100% because more than one cause was present in a number of patients.

found in long-term PD. Selective drop out of patients with a high ELAR could explain the lower value in the long-term group. These findings are in line with those of Davies, who reported a qualitative difference in the decrease of ultrafiltration compared to expected values based on D/P creatinine [54]. This underlines that long-term ultrafiltration failure is not only caused by fast solute transport rates. A study in 50 patients with ultrafiltration failure, in whom the effect of the duration of PD on transport could be analysed, showed an increase of the MTAC creatinine, but also a decrease of small-pore fluid transport and of free water transport. Also, the contribution of free water transport decreased, especially after 5 years, as well as the osmotic conductance to glucose [55]. In all time periods, a relationship between free water transport and the osmotic conductance to glucose was present. The development of ultrafiltration failure is associated with vascular abnormalities in the peritoneum. These are often accompanied by increased fibrosis [7]. Up to now, no substance is known that can be determined in peritoneal effluent and that could represent the amount of fibrosis. Loss of mesothelial cells may also occur [7], and is probably reflected in a decrease of effluent CA 125 [56].

In summary, ultrafiltration failure in long-term PD is most often due to a combination of a rapid disappearance of the osmotic gradient, together with a decrease in the osmotic conductance to glucose. The latter leads to a decrease of free water transport. It has not been elucidated whether the decreased osmotic conductance is the consequence of a decrease in aquaporin-1 function, or is due to a lower peritoneal ultrafiltration coefficient.

Ultrafiltration failure in long-term PD patients is a serious problem. It can easily cause overhydration, because those patients will often be anuric. Overhydration can lead to an increased risk for cardiovascular death. A relationship has been found between peritoneal ultrafiltration and death in two studies in anuric patients [57,58].

Figure 2 shows a scheme of the various types of fast transport that can cause ultrafiltration failure.

Definition and detection of ultrafiltration failure

Hypervolaemia or overhydration is a clinical diagnosis that can have a number of causes, like a decreased urine production combined with the usual oral fluid intake. The

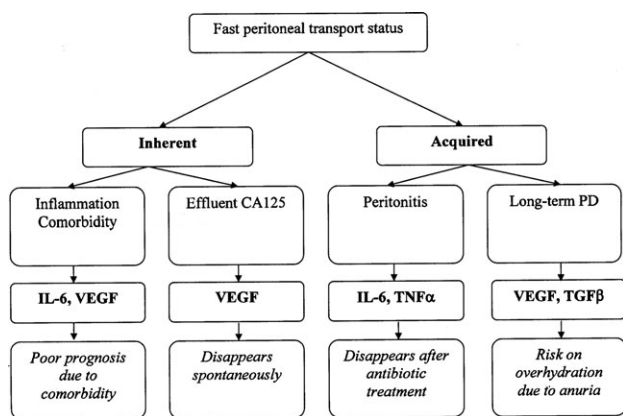


Fig. 2. A schematic representation of the potential pathogenic pathways for different types of fast transport as causes of ultrafiltration failure. Also, the prognosis and the presumed contribution of peritoneal cytokines/growth factors are indicated.

ultrafiltration volume is dependent on the status of the peritoneum. Its function should therefore be investigated during a standardized condition. The world-wide-used peritoneal equilibration test (PET) is useful for this, but only with some modifications [59]. The most important one is the use of a 3.86% glucose solution, instead of the original 2.27%. This allows better assessment of the drained volume. Also, free water transport can be estimated. The use of different glucose concentrations has no effect on D/P creatinine, but influences the D_4/D_0 ratio for dialysate glucose [60]. The higher the glucose concentration, the lower the D_4/D_0 ratio. The transition of a 2.27% PET to a 3.86% PET does not influence longitudinal follow-up of D/P creatinine in individual patients. It also does not matter whether the investigation is done with a conventional or more biocompatible dialysis solution [61].

The definition of ultrafiltration failure by the ISPD can be summarized as the 3×4 rule: (1) less net ultrafiltration than 400 mL, (2) after a dwell of 4 h, (3) of a 4% (3.86%/4.25%) glucose based dialysis solution [62]. The 400 mL limit is based on sparse data from literature [63,64] and clinical data of patients who fulfil this criterion. A cause for ultrafiltration failure could be identified in >95% of these patients [52]. The prevalence of ultrafiltration failure is higher with a limit of 500 mL, but a cause can be defined less often.

The 3.86% glucose PET (modified PET) provides information on net ultrafiltration after 4 h, D/P creatinine (or MTAC creatinine), D_4/D_0 glucose (or glucose absorption, expressed as percentage of the instilled quantity) just like the 2.27% PET, but also information on free water transport. The latter is calculated from the transport of sodium to the peritoneal cavity. Convection is the main mechanism of sodium transport [65] because the concentrations in plasma and dialysate are only slightly different. The importance of diffusion increases, however, in the presence of a relatively large gradient, like in hypernatraemia, or in the presence of a large diffusion area, as present in for instance fast transporters. Free water transport can be underestimated under these conditions when no diffusion correction for sodium is applied (see below).

Determination of D/P Na^+ after 1 h is the simplest way to obtain information on free water transport. D/P Na^+ after 4 h can also be used when a diffusion correction is applied [66]. A precise calculation of free water transport during the first hour of a PET is possible, assuming that the small pores offer no hindrance to sodium transport [67]. This requires the determination of the intraperitoneal volume after 1 h to allow the calculation of the quantity of sodium transported in this period. This amount, divided by the sodium concentration in the small pores (mean of plasma and dialysate sodium), yields the amount of fluid transported through the small pores. Free water transport is the difference between total net fluid transport and the volume transported through the small pores. The percentage-free water transport is the volume of free water transport divided by the total amount of fluid transported [19].

The 3.86% glucose mini-PET, in which the peritoneal cavity is drained after 1 h to determine the volume and dialysate Na^+ , is an elegant method for assessment of free water transport [67]. However, the interpretation of D/P ratios is difficult because MTACs are higher during the first hour of a 4-h dwell than in the period thereafter [13]. It is not possible to use a correction factor to translate to a 4-h dwell [68]. This limits its application for overall assessment of peritoneal function. Determination of the osmotic conductance to glucose is usually done by an estimation of sigma using kinetic modelling and calculation of LpA with a volume marker [54]. A simple alternative has recently been described by La Milia *et al.* using two mini-PETS: one with 1.36% glucose and one with 3.86% (double mini-PET) [69].

The modified PET and the mini-PET can be combined when the peritoneal cavity is drained after 1 h to determine the volume at that time by weighing. After taking a dialysate sample, the drained volume is reinfused and left for another 3 h. With this method, no differences were found for net ultrafiltration and small solute transport compared to those in a modified PET [70].

The personal dialysis capacity test (PDC) is performed by the patients themselves with five exchanges per 24 h [71]. These are different in dwell time and glucose concentration. Kinetic modelling is applied to estimate parameters like surface area available for diffusion, fluid absorption and large-pore flow. Superiority of the PDC over the PET has been claimed [72]. However, the PDC has a number of disadvantages like the risk of inaccuracies, a large number of laboratory investigations, the assumptions used for kinetic modelling and most importantly, the exclusion of sodium kinetics. This makes the PDC less suitable for the analysis of ultrafiltration failure, than the modified PET. A summary of the advantages and limitations of the various peritoneal function tests without the use of a volume marker is given in Table 3.

Assessment of the peritoneum should also include an effluent marker. Most experience has been obtained with CA 125. A single low value is difficult to interpret [73], but a downward trend with time suggests a decrease of mesothelial cell mass. The CA 125 concentration in effluent is dependent on the dwell time. It increases linearly during a dwell of 4 h and is not influenced by the dialysis solution used [55]. A linear increase is also present during

Table 3. Advantages and limitations of the various peritoneal function test without a volume marker

Test ^a	Advantages	Limitations
Original PET	Widely used Gold standard for small solute transport	Limited information on ultrafiltration No Na ⁺ sieving No FWT No OC
Modified PET	Definition for UFF Na ⁺ sieving D/P creatinine similar to original PET	No FWT No OC
Peritoneal dialysis capacity test	Large-pore flow using albumin Peritoneal absorption Area parameter	No Na ⁺ sieving No FWT No OC
Mini-PET	FWT	D/P creatinine difficult to compare with PET values No OC
Double mini-PET	FWT	D/P creatinine difficult to compare with PET values
Modified PET with temporary drainage	OC Definition of UFF Na ⁺ sieving FWT D/P creatinine similar to original PET	Two tests No OC

^aThe value of the test is increased when an effluent CA125 determination is added.

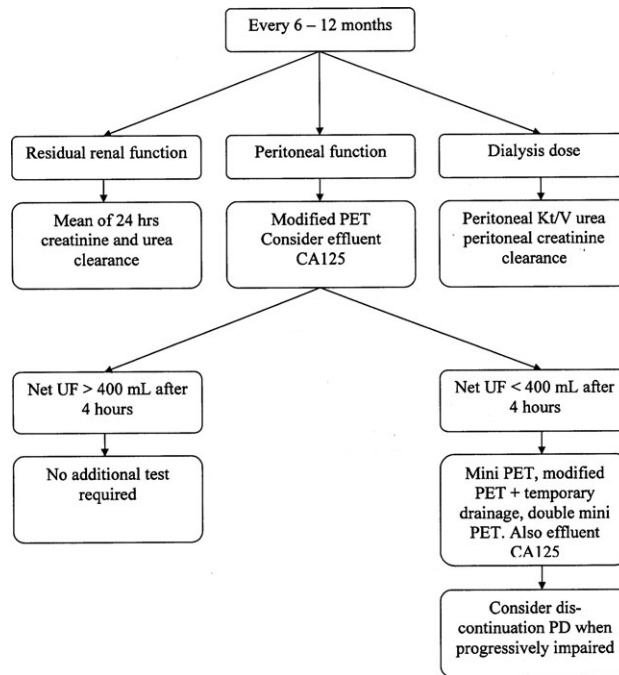
FWT: free water transport; OC: osmotic conductance.

longer dwells [74]. Therefore, it is recommended to express effluent CA 125 as its dialysate appearance rate, that is the product of the concentration and the drained volume, divided by the dwell time. An algorithm for the follow-up of patients is given in Figure 3.

Reasons for elective discontinuation of PD

Both clinical indications and those that are related to the transport function of the peritoneum can be reasons to switch from PD to HD. A $Kt/V_{urea} < 1.7$ /week without clinical manifestations of underdialysis is not a reason for discontinuation of PD [75]. It is evident that untreatable overhydration caused by ultrafiltration failure is an indication to switch to HD. Yet, studies in patients with residual renal function have—with one exception [76]—not been able to show an effect of ultrafiltration on patient survival [77,78]. An effect of peritoneal ultrafiltration on survival is, however, present in patients without urine production [57,58]. Until now, it has been impossible to define a minimum ultrafiltration volume [79], because the occurrence of overhydration is dependent on oral fluid intake and peritoneal ultrafiltration.

At present, it is not possible to give fixed limits of any peritoneal transport parameter below or above which PD

**Fig. 3.** A suggested algorithm for follow-up of patients on peritoneal dialysis.

should be discontinued, because longitudinal investigations on the time course of peritoneal function are only limited. Signs that indicate membrane damage are the development of a fast transport status with ultrafiltration failure, the development of a reduction in free water transport and a decrease of effluent CA 125 during the time course of PD.

Recommendations for patient information and measurement of peritoneal membrane function in PD patients

- The following items should be discussed during the information to predialysis patients:
 - The survival of PD patients is better than that of HD patients during the first years of dialysis, probably because of better preservation of residual renal function.
 - Functional and morphological peritoneal abnormalities may occur in about one-third of patients treated for more than 4 years.
 - An elective switch to HD should be considered when the above-mentioned abnormalities develop to minimize the risk of encapsulating peritoneal sclerosis.
- Measurement of peritoneal membrane function should be incorporated in the follow-up of PD patients. The frequency is at least once a year.
- The measurement should be done with the most hypertonic solution, glucose concentration around 4%,

during a standardized dwell of 4 h. Ultrafiltration failure is defined as net ultrafiltration <400 mL.

- Information should be obtained on the transport of creatinine, glucose and sodium. Net ultrafiltration should be measured and insight into free water transport should be obtained. Determination of effluent CA 125 gives an added value.

Conflict of interest statement. Watske Smit is a part time employee of Baxter, The Netherlands.

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