

Peritoneal transport: The problem of fast transport status

Anabela Rodrigues

Serviço de Nefrologia. Hospital Geral de Santo António. Porto, Portugal.

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INTRODUCTION

Peritoneal dialysis (PD) is a successful end stage renal disease treatment which has been used increasingly over the last 20 years^{1,2}.

The peritoneal transport rate of solutes and the ultrafiltration capacity are the main characteristics of the peritoneal membrane in patients treated by peritoneal dialysis, conditioning treatment prescription and clinical outcomes³⁻⁵.

Much is already known about the physiology and structure of peritoneal transport but many questions still remain open to research⁶. Patients with small solute fast transport rate deserve a special focus because they represent a clinical challenge in peritoneal dialysis treatment⁷. Its determinants and prognosis are not fully known and appropriate therapeutic strategies are also under debate⁸.

This review will address the main aspects of peritoneal physiology and the determinants of peritoneal fast transport status, with a focus on the most recent concepts and doubts about the characteristics and management of fast transporters.

THE STRUCTURE AND FUNCTION OF PERITONEAL MEMBRANE

The peritoneum is a continuous serous membrane consisting of a monolayer of mesothelium, the submesothelium interstitium, the lymphatics and the capillary bed⁹. Within the interstitium reside

the capillaries, the main barrier to peritoneal transport.

The peritoneum acts as a complex biological membrane with a semipermeable heteroporous structure, involving simultaneous mechanisms of diffusion, convection, ultrafiltration, sieving and absorption.

Peritoneal transport is assumed to be size selective. The transport of small solutes is mainly diffusive while higher molecular weight solutes depend more on convection. Only the perfused peritoneal membrane in contact with the dialysis solution participates in the solute and fluid transport. This means the effective capillary surface depends not only on the anatomic number of capillaries but also on the vessels which are perfused and in some instances recruited or dilated, variably distributed in the interstitium. This conditions the intrinsic permeability of the membrane.

Different and progressively improved mathematical models¹⁰⁻¹³ have been developed to allow prediction of solute and fluid transport through this dialyser. After considerable refinements the three pore model¹⁴ is currently the accepted design of peritoneal membrane.

The three pore theory predicts that small solute transport occurs without much restriction, mainly through the small pores (40-50 Å in diameter), the most abundant, and likely represented by intercellular gaps between capillary endothelial cells. An increase of the number of perfused capillaries will be reflected in an increase of small pores available for the transport. On the other hand, macromolecules

pass through larger pores (150 Å), though the corresponding anatomic clef is less clear, with this passage being probably also conditioned by the interstitial structure.

The ultra small pore (<5 Å) is a specific endothelial water channel known to be represented by aquaporin-1. Evidence for the functional role of aquaporin-1 and peritoneal localization of this transcellular pore has been consistently presented¹⁵⁻¹⁹. Studies with aquaporin-1 knockout mice confirmed that this channel provides a major route for osmotically driven water transport²⁰.

Water is removed due to an osmotic pressure gradient, provided by the instilled dialysis solution. The osmotic agent is usually glucose, which due to its small size of 2.9 Å shows a reflection coefficient of only 0.02-0.05 through the small pores, meaning it is only able to exert its crystalloid effect through the ultra small pores, permeable only to water.

The function of these ultra small pores can be estimated with sodium sieving²¹: the decrease of dialysate sodium concentration due aquaporin-1 mediated water transport during the early phase of the exchange with an hypertonic dwell, when osmotic pressure gradient is maximum.

Absorption of macromolecules from the peritoneal cavity to the circulation through the lymphatic system occurs linearly in time, independently of size or concentration. Fluid lymphatic absorption counteracts transcapillary ultrafiltration, making net ultrafiltration the result of these opposite fluid processes²².

The role of the interstitium in the peritoneal transport characteristics is still not completely known²³, but it looks increasingly relevant²⁴. Hyaluronan is a matrix component involved in the restriction of proteins. An increase in the restriction coefficient to macromolecules²⁵ has been documented with time in PD, probably induced by alterations such as sub-mesothelial fibrosis. A decrease in osmotic conductance may depend not only on capillary but also interstitial changes known to occur with long-term PD²³.

On the other hand, the mesothelium is not an active transport barrier²⁶ although its indirect role

in transport alterations is a matter of current investigation²⁷. Recent studies have progressively shown that mesothelial cells are not bystander cells but constitutively produce a number of vasoactive and growth factors, with an active role in peritoneal defence, repair and transport.

Effective peritoneal surface area, intrinsic peritoneal permeability and selective transcellular water transport are the main properties in this updated concept of peritoneal membrane²⁸.

METHODS OF PERITONEAL MEMBRANE TRANSPORT EVALUATION

The capacity of the membrane for the transport of a given solute is the product of the permeability of the membrane to that solute and its effective surface area, called the mass transfer area coefficient (MTAC). This measures the theoretical maximal diffusive transport rate at time zero, in the beginning of the dwell before diffusion and ultrafiltration has actually begun^{12,13}.

Simplified models for MTAC calculation, such as the Garred and Krediet formulas, have been developed to be accessible in clinical practice^{10,29}. Values of MTAC for low molecular weight solutes can be more easily calculated. The introduction of the peritoneal equilibration test (PET)³⁰, later, the standard permeability analysis (SPA)³¹, and recently the personal dialysis capacity (PDC) test³² have offered the clinician simplified methods to monitor membrane function.

PET is the most widely used standardized form of peritoneal transport assessment also useful for longitudinal evaluation of patients³³. Dialysate:plasma ratio of creatinine (D/P creatinine) at the end of 4 hours standardized dwell closely correlates with MTAC creatinine. The small differences related to the use of a more complex method are smaller than the differences induced by clinical collection and laboratory measurements errors. In addition, inter and intraindividual changes also occur when more rigorous calculation methods are used³⁴⁻³⁶. A PET limitation is that it does not allow the diagnosis of ultrafiltration failure (UFF) due to lymphatic absorption. Although increased lymphatic absorption is one of the causes of ultrafiltration

capacity failure, lymphatic³⁷ absorption does not seem to change with the duration of peritoneal dialysis³⁸. Another method for more accurate peritoneal transport assessment is the SPA^{37,39,40}, which includes the evaluation of an intraperitoneal marker, dextran, disappearance rate as an index of peritoneal membrane absorption. This, however, remains a research domain test, with sophisticated calculations.

Therefore the modified PET test with 3.86% solution is the recommended tool⁴¹ for peritoneal transport categorization and ultrafiltration failure (UFF) investigation because it gives similar information about small solute transport but is more sensitive for the definition and investigation of UFF causes, allowing the calculation of sodium sieving at 60 min as an estimate of free water transport.

Very recent research has been carried out to propose correction of sodium sieving for sodium diffusion⁴², because a fast transport rate with rapid sodium diffusion may mask the initial decrease of intraperitoneal sodium due to ultrafiltration. This correction is also applicable to the PET⁴³. In addition, new clinically accessible formulas have been proposed to more directly measure free water transport capacity at 60 min dwell, during a fast-fast PET⁴⁴. These efforts come from the definitive clinical relevance of fluid and sodium removals in the management of PD patients⁴⁵.

■ RELATIONSHIP BETWEEN SOLUTE TRANSPORT AND UF

There is a large variability in membrane transport categories at the start of PD^{28,46-50}. It is not fully known why this occurs. Differences in effective capillary surface area probably account for such large inter-patient variability. Ultrafiltration (UF) profile also presents enormous variability. While we would expect a strong and significant negative correlation between small solute transport rate and ultrafiltration, differences in solute transport only account for 5-10% of the variability of UF capacity⁵¹, meaning categorization of peritoneal small solute transport based on ultrafiltration capacity is unreliable. UF has a high error in reproducibility of measurement, typically 20-25%^{28,52}. It depends on

the intrinsic membrane function, such as hydraulic conductance and glucose reflection coefficient, and also results from the sum of fluid absorption, instilled volume and intraperitoneal pressure effect. As such, it is not proportional to small solute transport.

Additionally, the relative importance of water transport through the transcellular and intercellular pathways is a matter of current investigation^{52,53}. Simple methods of water transport evaluation for population studies are under scrutiny⁴⁴.

■ THE CLINICAL PROBLEM: FAST TRANSPORT RATE

From a clinical point of view, fast peritoneal transport rate (as expressed by D/P creatinine levels higher than 0.81 or currently by D/P creatinine higher than the average plus standard deviation levels of the studied population³⁰) would be expected to permit higher dialysis clearances. However, more rapid dissipation of the osmotic gradient due to glucose absorption induces reduction of ultrafiltration capacity with less fluid removal. This is a high risk condition for metabolic consequences of glucose absorption and fluid overload. This means that a fast transport rate is an immediate relevant problem, to be managed in day to day clinical practice^{8,47}.

This status may present either from the beginning or be acquired during long-term PD treatment. Technical failure, comorbidity and higher mortality have previously been associated to acquired fast transport^{4,5,54-56}. It is controversial if intrinsic baseline fast transport status brings uniformly similar threats^{50,57,58}. Whichever the case, timely detection, characterization and adequate therapeutic strategies are fundamentally important for the outcome of these patients. In the absence of sufficient residual renal function, this status usually implies individualization of prescription⁵⁹⁻⁶¹ with shorter dwell times, increased use of hypertonic glucose solutions or an alternative agent with colloid-osmotic properties, such as icodextrin. Acquired fast transport state is also a risk factor and an early marker of encapsulating peritoneal sclerosis^{62,63}, a rare although serious and life threatening PD complication⁶⁴.

■ DETERMINANTS OF FAST TRANSPORT STATE

■ Baseline fast transport status

Link with systemic inflammation

Effective peritoneal surface area is determined by the number of perfused peritoneal capillaries that are in contact with the dialysate. Therefore peritoneal transport rate is only weak and inconsistently correlated to patient body surface area. Splanchnic blood flow through the peritoneum averages 70-100 ml/min^{65,66} but this is influenced by conventional peritoneal solutions which cause generalized microvascular dilation⁶⁷. Studies demonstrating that nitric oxide mediated vascular tone and permeability changes are involved in the loss of ultrafiltration and transient fast transport state during peritonitis⁶⁸ suggest that an inflammatory acute situation induces a fast transport state through variations in splanchnic blood flow and volume. The effect of inhibition of nitric oxide (NO) synthesis on peritoneal transport during peritonitis also confirms this pathophysiological process: the NO inhibitor N-nitro-L-arginine methyl ester (L-NAME), given intraperitoneally, prevented the expected fall in ultrafiltration and increase in small solute transport⁶⁹. A number of many other vasoactive and growth factors, among them prostaglandins, cytokines, hialuronic acid, are released from resident and infiltrating cells during peritonitis, modulating the peritoneal membrane transport and response to the insult.

Acute episodes of systemic infection also temporarily induce a state of fast transport⁷⁰.

Taking these examples of acute transient increase in peritoneal transport rate into account, extrapolation was done to baseline PD patients and the most recent appealing theory points to a causal link between systemic chronic inflammation and peritoneal fast transport rate. It is hypothesized though not yet confirmed that systemic inflammation, such as in uraemia or diabetes⁷¹⁻⁷³ mellitus, could also induce increased effective capillary surface at start of PD. The peritoneal Biopsy Study Group has reported vascular changes and submesothelial fibrosis in the peritoneal membrane of uraemic patients even before PD treatment⁷⁴. There are also studies supporting the higher prevalence of diabetes⁷⁵, comor-

bidity^{76,77} or serum markers of systemic inflammation such as IL-6⁷⁸ in baseline fast transporters. Others, however, refute such associations^{50,57,79-81}.

Controversies from epidemiological studies

There are very few large clinical studies researching into and explaining the variability in solute transport at the start of PD and its impact on patient outcomes. The multicentre study, Canada-USA (CANUSA) Peritoneal Dialysis Study Group⁴ concluded that peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis (CAPD) patients. Australian registry data⁸² also showed similar worse outcomes in Australian and New Zealand peritoneal dialysis fast transporters. No details of dialysis prescription in these patients were given. In analyzing predictors of baseline fast transport in this population⁷⁹, high transport status was associated with older age but was not independently predicted by gender, diabetes, other comorbid diseases, smoking, previous haemodialysis therapy or transplantation or residual renal function. Similar results were found when peritoneal permeability was modeled as a continuous variable (D/P creatinine). In the STOKE PD study⁵² independent demographic factors associated with higher solute transport at baseline were male gender and higher residual urine volume with comorbidity or serum albumin not independently predictive. In a cohort of Spanish patients⁵⁰ no relationship between baseline transport parameters and gender, age, patient size, or diabetes was observed. As pointed out by Davies SJ²⁸ these epidemiological variables account for very little of the between patient variability in solute transport and there is very little that we identify that explains the variability in solute transport in patients commencing PD.

Therefore controversy still remains concerning the causes and clinical characteristics of intrinsic peritoneal fast transport status in the beginning of PD.

Link with mesothelial cells

Selgas' group concluded recently that the peritoneal transport parameters tended toward normalization during the first year on PD, mainly with a decrease of small solute transport and an increase of ultrafiltration capacity⁵⁰. This evolution was independent of age, gender, diabetes and higher exposure to glucose in PD solutions. This profile of D/P creatinine was also

documented in our Unit (data not published) and in a recent study which reported a U-shape curve of peritoneal solute transport parameters, with the lowest values in the second year of PD⁵³. A candidate determinant of such early period evolution could be the indirect role of mesothelial cells as important sources of vasoactive mediators such as vascular endothelial growth factor (VEGF), a potent angiogenic factor^{27,80,81}. Local intraperitoneal processes mediated by mesothelial cells could be determinants of fast transport status at PD start⁸⁰, indirectly influencing baseline peritoneal transport through the recruitment and vasodilatation of peritoneal vessels, therefore causing a state of temporary functional hyperpermeability. Our investigation supported this hypothesis⁸¹. This would explain that not all fast transporters will progress to worse outcomes⁵⁷ and some will tend to normalize D/P creatinine in short-time PD, as we usually see.

■ Acquired long-term peritoneal fast transport status

More consistent studies were able to shed some light on the determinants of longitudinal acquired changes of peritoneal function. These are known to be mainly expressed as an increase in low-molecular weight solute transport and coincident decrease in ultrafiltration⁸³. The onset of UFF with fast transport usually occurs after three or four years on PD with variable prevalence rates of 23%³¹ and 30.9%⁸⁴, possibly higher in long-term PD patients.

Peritonitis

Severe and recurrent peritonitis episodes are important causes of peritoneal damage^{50,63}. Peritonitis induces an acute inflammatory situation and although the relationship between long-term changes such as fibrosis and peritonitis is not clear, profibrotic interleukines are up-regulated in peritonitis.

Bio-incompatible solutions: up-regulation of neoangiogenic and fibrotic agents

Acquired fast transport status may occur in the absence of infectious insults. Patients with earlier loss in residual renal function exposed to significantly more hypertonic glucose during the first 2 years of treatment showed an increased transport rate later⁸⁵. Selgas' group also verified that diabetic state and a high-

er glucose requirement to obtain adequate UF are risk factors for developing early UFF with fast transport, meaning the use of hypertonic glucose PD solutions is associated with increase in solute transport⁸⁶.

Ex vivo studies⁸⁷⁻⁸⁹ and animal models also demonstrated the effects of bio-incompatible solutions on mesothelial cells, showing the detrimental effect of glucose, glucose degradation products, lactate buffer or acidic pH on peritoneal membrane cells viability and function, but glucose degradation products (GDP) seem to be the main vectors of lesion⁹⁰.

Glucose degradation products are reactive carbonyl compounds produced in peritoneal dialysate during heat sterilization and are more potent inducers of advanced glycation end-products (AGEs) than glucose itself⁹¹. Interaction of AGEs and RAGE (receptor for AGE) leads to secretion of inflammatory cytokines and growth factors such as VEGF and transforming growth factor (TGF)- β .

There is evidence of accumulation of AGEs in the peritoneal membrane in uraemia, exposure to high glucose concentrations and exposure to glucose degradation products⁹¹. These AGEs correlate with peritoneal membrane fibrosis⁹² and also with solute transport and ultrafiltration dysfunction⁹³, just as they co-localize with VEGF in peritoneal vessels⁹⁴.

Local peritoneal production of VEGF was found to increase with glucose PD solution and decrease with glucose free PD solutions⁸⁶. Reduction of the number of vessels with anti-angiogenic therapy also induced improvement in net ultrafiltration in an animal model⁹⁵.

On the other hand, high glucose upregulates TGF- β ¹⁹⁶ and fibronectin⁹⁷ expression by human peritoneal mesothelial cells. These cells also secrete more VEGF and procollagen III N-terminal⁹⁸ after exposition to dialysis solutions.

Neoangiogenesis is also associated with the nitric oxide⁹⁴ system: this is upregulated in animal models of peritonitis⁶⁸ and uraemia¹⁶ but inversely regulates TGF- β , preventing fibrosis.

Other cytokines such as platelet derived growth factor (PDGF) connective tissue growth factor (CTGF), fibroblast growth factor (FGF) and plasminogen acti-

vator inhibitor (PAI)-1 are involved on fibrogenic processes^{99,100}.

The use of low-GDP two chambered solutions is expected to reduce these effects⁶¹. However it is not known whether the use of alternative solutions will translate into better peritoneal function preservation.

■ Peritoneal sclerosis: Correlation with increased solute transport

Biopsy studies revealed important data⁷: average submesothelial thickness was 50 μm in control non uraemic patients; uraemia alone was associated to 140 μm , but increase to 700 μm submesothelial thickness was observed in patients on PD for more than 8 years. Angiogenesis and vasculopathy was also observed, mainly in UFF patients. Therefore progressive thickening of the submesothelial compact collagenous zone occurs with time on dialysis^{95,100-102}. Interstitial collagen deposition and vascularization correlate with α -smooth muscle actin (α SMA) positive myofibroblasts.

Peritoneal fibrosis occurs as a normal response to a variety of insults including bioincompatible dialysate solutions, peritonitis, uraemia, and chronic local inflammation. Increased submesothelial thickness also correlates with increased solute transport, as measured by the D/P creatinine¹⁰³ and loss of mesothelial cells⁷⁴.

A role for peritoneal mesothelial cells: Epithelial-mesenchymal transdifferentiation

TGF-beta plays a central role in fibrogenesis^{95,10}. It induces fibroblast activation, collagen deposition, inhibition of fibrinolysis through PAI-1, maintenance of fibrosis and inhibition of matrix metalloproteinase (MMP), and angiogenesis. TGF-beta also mediates conversion of epithelial cells into myofibroblasts; this means epithelial-to-mesenchymal transition^{105,106}. A recent study demonstrated that peritoneal mesothelial cells suffer this transdifferentiation with expression of mesothelial markers in stromal α SMA positive myofibroblasts. Mesothelial cells migrate toward the interstitium and acquire a myofibroblast phenotype. This myofibroblastic conversion of mesothelial cells was confirmed *in vivo* by injection of an adenovirus vector that transferred active TGF β 1 in rat peritoneum^[101]. Inhibition of RAGE induces less TGF- β

production and less submesothelial and interstitial fibrotic tissues, as expressed by less α SMA and cytokeratin staining¹⁰⁷. It is not clear that measurement of TGF, in peritoneal fluid, which is found mostly in an inactive state, bound to latency associated protein, reflects tissue levels of active TGF β .

In parallel to fibrosis, an increase in capillary number also occurs. Angiogenesis may be induced as part of the fibrotic response, as many key fibrogenic cytokines are also strongly angiogenic. Fibrotic tissue may support and preserve angiogenesis¹⁰⁰. VEGF is a main vector of neoangiogenesis, with mesothelial cells being its important source. It seems that mesothelial cells that have undergone epithelial-to-mesenchymal transition produce more VEGF than epithelioid mesothelial cells^{27,50}, suggesting a link between mesothelial cell transdifferentiation, fibrosis and acquired fast transport⁹⁵.

This can progress to encapsulating peritoneal sclerosis after a “second hit” triggering event such as a late peritonitis or serious staph. aureus, pseudomonas or fungal peritonitis, abdominal bleeding or abdominal surgery. These could possibly enhance collagenous tissue proliferation and TGF β expression. Inflammatory cytokines and growth factors secreted by mesothelium, endothelial and interstitial cells up-regulate fibrogenic processes with increase of TGF β . Increased VEGF is also able to increase neoangiogenesis and plasma exsudation with fibrin formation. Reduced fibrinolytic activity of the peritoneal membrane adds to these pro-sclerosis steps.

Mesothelial cell denudation with a decrease in effluent CA125 occurs with time on PD and it has been monitored in patients before transfer to haemodialysis due to UF failure¹⁰⁸⁻¹¹. It has been concluded that CA125 was very low in patients who developed peritoneal sclerosis and a lack of response to a peritoneal rest also predicted peritoneal encapsulating sclerosis after PD discontinuation¹¹¹.

■ CONCLUSIONS AND FUTURE PERSPECTIVES

It can be concluded that evaluation of peritoneal transport is an obligatory clinical task for characterising our baseline patients, tailoring the PD pres-

cription, understanding their natural history on PD and detecting signs of peritoneal membrane deterioration.

Some knowledge has been gathered on long-term peritoneal membrane changes, since both molecular biology and histological studies point to neoangiogenic and fibrogenic processes as the key factors of acquired fast transport with ultrafiltration failure. The clinical expression of these alterations is an increase in D/P creatinine with long-term PD, although others report a relatively stable membrane function, at least in the first 2-3 years on PD¹¹². Less is known about the characteristics of baseline fast transporters and the explanations for early peritoneal membrane function profiles. This is a field worth investigating.

■ A role for genetics

In the search for baseline peritoneal fast transport determinants, genetic factors were also presumed to explain why some patients are intrinsically fast transporters at the beginning of PD or develop this status with time on PD. Vascular endothelial growth factor polymorphisms have been associated with susceptibility to diabetic microvascular complications¹¹³ and retinopathy¹¹⁴. In peritoneal dialysis it was found that there was no relation between VEGF genotype and baseline peritoneal transport group but AA genotype of VEGF promoter at -2578 position was associated with progressive increase in peritoneal transport^{115,116}. It was also suggested that systemic and local peritoneal VEGF production may be differentially regulated. Another recent study on genetic polymorphisms pointed to a possible pathologic involvement of receptor for advanced glycation end products (RAGE) for development of encapsulating peritoneal sclerosis in Japanese CAPD patients¹¹⁷.

■ Role for effluent markers

The Biopsy Registry^{74,118} allowed important investigation of vascular and fibrotic changes but only cross-sectional results of PD patient membrane were obtained. Repeated biopsies are also not feasible. There is a need for real markers of peritoneal pathological processes, accessible and informative of more

subtle and earlier abnormalities. Locally produced factors may be associated with structural alterations mirroring functional changes.

A number of effluent markers have been used¹¹⁹. However, *in vitro* and *in vivo* studies are not really equivalent, because the rate of production *in vitro* is 10-30 times higher. Uraemic milieu and dialysis solutions may modulate this secretion. In spite of these limitations those have been measured in many *in vitro* biocompatibility studies.

Among many investigated cytokines and growth factors, cancer antigen-125 (CA125) seems to be the most useful^{109,110}. Its measurement has been found both *in vitro* and *in vivo* studies^{120,121} to support a role for CA125 as an useful marker of membrane status, related to mesothelial cell mass. Its longitudinal measurement during PET evaluation has been recommended⁴¹.

Exposition to more biocompatible solutions was also associated with mesothelial repair and increase of CA125⁸⁹. Although some authors report limitations of CA125 as an index of peritoneal mesothelial cell mass¹²², they demonstrated a reduction of CA125 secretion and expression with chronic exposition to glucose solutions

It is usually measured in biocompatibility studies and recommended as a tool for longitudinal membrane status evaluation, but controversy still exists about the definite meaning of this marker, because neither its regulation or its biological significance is yet known¹²³.

Apart from these doubts, investigators underline the need for patient longitudinal studies, also investigating the information that can be brought from other biomarkers¹¹⁹ such as VEGF, IL-6, or TGF- β .

Measurable markers would be useful if they showed prognostic value, predicting membrane failure.

■ Alternative PD solutions: expectation on hard clinical outcomes

Considerable efforts were developed to understand the effect of dialysis solutions on the peritoneal membrane. *In vitro* and *ex vivo* models of investigation

were used to further document the alterations of mesothelial and fibroblast cells exposed to glucose, glucose degradation products and other components of dialysis solutions. However, the doubt still remains that these test systems do not mimic the *in vivo* equilibration of dialysis solutions and may overestimate the clinical relevance of some *in vitro* effects¹²⁴. In addition to this they lack the natural humoral mediators and cellular components resident in the peritoneal cavity.

Animal models also present limitations¹²⁵: consensus is still needed to elect a standardized and valid long-term exposure animal model to more accurately reproduce the *in vivo* human membrane alterations¹²⁴. Uraemia and other comorbid conditions such as diabetes have not been simulated in the present animal models. Also the degree of exposition with 10-30 week period of exposition to 3.86% glucose may overestimate the normal pathophysiology of peritoneal membrane. The human situation is certainly more complex and still unclear.

While alternative solutions promise less angiogenic, inflammatory and fibrogenic peritoneal membrane changes, presumably avoiding acquired fast transport status and peritoneal sclerosis, cost issues limit their wider use. But hard clinical end points from the use of these alternative solutions will need to be investigated, although long-term PD is necessary to definitively prove patient and technique survival advantages. Research into the effect of alternative solutions on peritonitis rate and residual renal function is needed.

■ Rescue therapies

Apart from some research-based pharmacological essays and genetic modulation to avoid or treat peritoneal sclerosis⁶⁴, peritoneal rest demonstrated that peritoneal lesions may be reversible, at least if it is offered soon after membrane functional changes are documented. Clinical experience with peritoneal rest showed that this strategy may successfully recover ultrafiltration failure associated with acquired fast transport during PD^{126,127}. Temporary transfer to haemodialysis for at least 28 days is able to give time for peritoneal remesothelization and reduction of D/P creatinine in some patients¹²⁸. Interruption of PD may determine progression of fibrin and sclero-

sis but periodical lavages with intraperitoneal heparin is an adjuvant therapy to avoid such a complication¹²⁹⁻¹³¹. Although there is a scarcity of published reports, recent investigation focused again on this strategy: animal models¹³² and cultured human peritoneal mesothelial cell model¹³³ reproduced the clinical data demonstrating that peritoneal membrane lesions may be reversible, with a potential benefit of peritoneal rest. Wider clinical experience is needed to clearly support its recommendation but our personal experience suggests it should be timely essayed before definite transfer to haemodialysis.

Conflict of interest statement. None declared.

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Correspondence to:

Dr Anabela Rodrigues
Serviço de Nefrologia
Hospital Geral de Santo António
Porto, Portugal
ar.cbs@mail.telepac.pt