

Water transport across the peritoneal membrane

Olivier Devuyst^{1,2} and Bengt Rippe³

¹Institute of Physiology, Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland; ²Division of Nephrology, Université catholique de Louvain Medical School, Brussels, Belgium and ³Department of Nephrology, Lund University, Lund, Sweden

Peritoneal dialysis involves diffusive and convective transports and osmosis through the highly vascularized peritoneal membrane. The capillary endothelium offers the rate-limiting hindrance for solute and water transport. It can be functionally described in terms of a three-pore model including transcellular, ultrasmall pores responsible for free-water transport during crystalloid osmosis. Several lines of evidence have demonstrated that the water channel aquaporin-1 (AQP1) corresponds to the ultrasmall pore located in endothelial cells. Studies in *Aqp1* mice have shown that deletion of AQP1 is reflected by a 50% decrease in ultrafiltration and a disappearance of the sodium sieving. Haploinsufficiency in AQP1 is also reflected by a significant attenuation of water transport. Conversely, studies in a rat model and in PD patients have shown that the induction of AQP1 in peritoneal capillaries by corticosteroids is reflected by increased water transport and ultrafiltration, without affecting the osmotic gradient and small-solute transport. Recent data have demonstrated that a novel agonist of AQP1, predicted to stabilize the open-state conformation of the channel, modulates water transport and improves ultrafiltration. Whether increasing the expression of AQP1 or gating the already existing channels would be clinically useful in PD patients remains to be investigated.

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The development of peritoneal dialysis (PD) as a successful therapy for patients with end-stage renal disease has been paralleled by the need to understand the transport mechanisms operating in the peritoneal membrane. Functional alterations in the dialysis capacity of the membrane, leading to ultrafiltration (UF) failure, are associated with increased morbidity and mortality and represent a major obstacle to successful long-term PD therapy.¹ Over the past three decades, investigations based on human and animal models provided significant insights into the physiology of transport pathways for water and solutes across the peritoneal membrane. Subsequent development of genetically modified mouse models yielded further insights and, in particular, molecular counterparts involved in peritoneal water transport.² The purpose of this brief review is to discuss the current understanding of water transport mechanisms operating in the peritoneal membrane, and to delineate potential strategies to improve water transport and UF in patients on PD.

STRUCTURE OF THE PERITONEAL MEMBRANE

The peritoneal cavity is lined by a thin, translucent membrane covering the inner surface of the abdominal wall and the majority of visceral organs, and also forming omenta. The peritoneal membrane (Figure 1a) has a relatively large surface area ($\sim 1 \text{ m}^2$),³ a high degree of capillarization, and a relatively high blood flow (100–150 ml/min) in adults.^{4–6} The compact zone of the visceral peritoneum (that forms most of the peritoneal surface area) is $\sim 20 \mu\text{m}$ thick in PD patients, whereas the parietal peritoneum can be thickened up to $500 \mu\text{m}$ in long-term PD patients, compared with $50 \mu\text{m}$ in controls.⁷

The blood capillaries are distributed in a thin interstitium where their density is relatively high: for 1 m^2 of peritoneal surface area and $200 \mu\text{m}$ tissue depth, the total available capillary surface area is $\sim 2 \text{ m}^2$.⁸ The surface of the peritoneal membrane is lined by a continuous layer of flattened epithelial cells, the mesothelium ($0.5\text{--}2 \mu\text{m}$ thickness), covered with numerous microvilli. The mesothelium reduces the friction between visceral organs through the continuous production of lubricants, anticoagulants, and surface tension-lowering substances.⁸

The pathways available for solute and water exchange between the plasma in the peritoneal capillaries and the fluid

Correspondence: Olivier Devuyst, Institute of Physiology, ZIHP, University of Zurich, Winterthurerstrasse 190, Zurich, CH-8057, Switzerland.
E-mail: olivier.devuyst@uzh.ch

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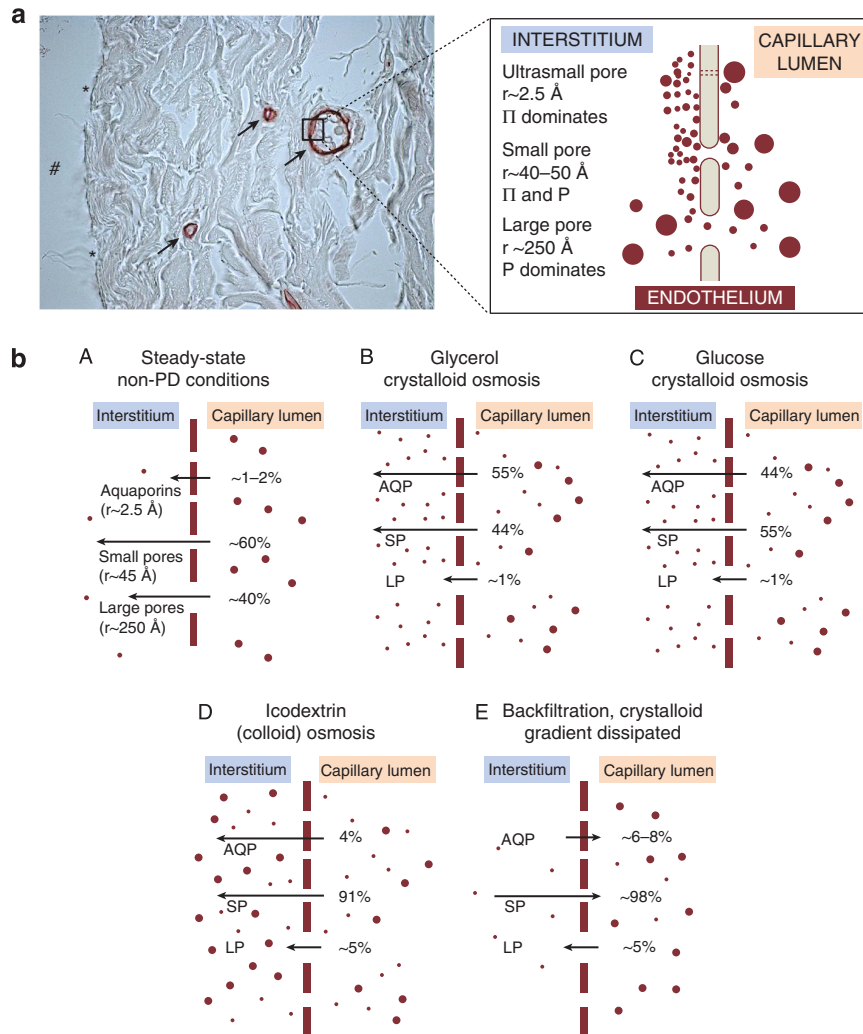


Figure 1 | Structure of the peritoneal membrane and the three-pore model (TPM). (a) Cross-section of the human parietal peritoneum stained for the water channel aquaporin-1 (AQP1). The peritoneal membrane contains three components: a layer of ciliated mesothelial cells (*), with microvilli and apical protrusions into the peritoneal cavity (#); the interstitial tissue containing bundles of collagen and mucopolysaccharides; and a dense network of capillaries, blood vessels, and lymphatics. During peritoneal dialysis (PD), the microvascular endothelium (arrows, stained in red) represents the functional barrier for the transport of solutes and water from the blood of the patient to the dialysate that has been instilled in the peritoneal cavity. (a, inset) The continuous endothelium lining the peritoneal capillaries can be functionally described as the TPM. The small pores (radius ~40–50 Å), located between the endothelial cells, account for ~90% of the peritoneal ultrafiltration (UF) coefficient (L_pS , or hydraulic conductance) and 99.5% of the total pore area available for solute transport. The large pores (radius ~250 Å), thought to correspond to interendothelial gaps, account for 5–8% of the L_pS , occupying <0.5% of the total pore area. The ultrasmall pores (radius ~2.5 Å), which account for only 2% of the L_pS , are the only ones to be located in the endothelial cells. The Starling forces (P, hydrostatic pressure; Π , oncotic pressure) operating across each type of pore are indicated. Å, angström (10^{-10} m); r, functional radius. (b) Transcapillary UF in the TPM. (A) Fractional fluid flows across the peritoneum under normal conditions with no dialysis. In the absence of an osmotic agent, ~60% of the transcapillary fluid flow occurs through small pores, where the Starling forces are close to equilibrium. Approximately 40% of the capillary UF occurs across large pores where there is hardly any colloid osmotic pressure counteracting the transcapillary hydrostatic pressure gradient. (B) With glycerol (Stokes–Einstein (SE)-radius ~3 Å) as the osmotic agent, ~55% of the transperitoneal water flow will occur through water-only, ultrasmall pores and 45% through small pores. This is due to the relative inefficiency of glycerol as an osmotic agent across the small-pore pathway ($\sigma \sim 0.02$). LP, large pore; SP, small pore. (C) With glucose (SE-radius ~3.7 Å) as the osmotic agent, ~45% of the transperitoneal water flow will occur through water-only pores and 55% through small pores. Although glucose is a relatively inefficient osmotic agent in the small pore pathway ($\sigma \sim 0.03$), it is 50% more efficient than glycerol. (D) In a conventional icodextrin PD solution, ~25–30% of the molecules (~3 mM) act as a colloid, implying a reflection coefficient close to unity. It should be noted that 3 mM of high-molecular-weight (MW) icodextrin will produce a colloid osmotic pressure of ~58 mm Hg (3×19.3 mm Hg), which is sufficient to counteract the plasma colloid osmotic pressure (22–26 mm Hg) exerted by ~1 mM of negatively charged plasma proteins. Note that the partitioning of fluid flows among the different porous pathways in the TPM is now almost identical to that in the peritoneum occurring during high net UF conditions in the absence of crystalloid osmotic forces. (E) Reabsorption of fluid across the small pores occurs when the crystalloid (glucose) osmotic gradient has totally dissipated (usually after 4 h). The net Starling fluid balance is biased toward reabsorption across the small pores in PD. Some fluid reabsorption will also occur across AQP1. Minute UF still occurs across the large pores.

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