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Fluid loss from the peritoneal cavity by back-filtration through the small pores of the three-pore model

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The partitioning of fluid flows among small and ultrasmall pores of the three-pore model in peritoneal dialysis has been traditionally assessed using 4-hour dwells with 3.86% glucose solutions. Under these conditions, however, back-filtration through small pores has been hard to demonstrate. As nicely shown by Asghar and Davies, however, the use of low-concentration (1.36%) glucose-based solutions allows accurate studies of the partitioning of fluid flows from the peritoneal cavity under conditions of fluid loss.

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As they report in this issue of *Kidney International*, Asghar and Davies[1] have studied the mechanisms of fluid reabsorption across the peritoneal membrane under conditions of a so-called 'standardized peritoneal permeability analysis' in patients on peritoneal dialysis. Paired glucose 3.86% and 1.36% dwell studies were performed using ^{125}I-albumin as an intraperitoneal volume marker. Changes in intraperitoneal sodium concentration and in volume were assessed to determine the transperitoneal clearance of sodium, which, at least during the first hour of the dwell, can be used as an indicator of the ultrafiltration (UF) occurring across the small pores of the three-pore model. This approach, though in an ingeniously simple form, was first described by La Milia *et al.*[2] and is here referred to as the La Milia technique. For dwells longer than 1 hour, a correction for the diffusion of Na^+ through the small pores is required to correctly assess small-pore UF from the transperitoneal clearance of Na^+.[3]

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The major difference between the analysis of Asghar and Davies[1] and previous analyses of this kind[3–5] is that the present study includes a 1.36% glucose exchange, permitting the analysis of fluid reabsorption occurring when the osmotic gradient has more or less dissipated, and when net fluid reabsorption from the peritoneal cavity to plasma has started. In previous standardized peritoneal permeability analyses, 3.86% glucose exchanges have been used, and the separation of fluid flows among the various fluid conductive pathways (mainly small pores and ultrasmall pores) was carried out in relatively short dwells (4 hours), in which net reabsorption had barely started at the end of the dwell. This is problematic, because it is quite difficult to partition small-pore UF from ultrasmall-pore UF, without error, when total net UF is very small. Therefore, not surprisingly, previous analyses using 3.86% glucose standardized peritoneal permeability dwells have failed to show peritoneal fluid loss occurring via small-pore back-filtration.[3–5] Indeed, in order to study the fluid loss from the peritoneal cavity in hypertonic glucose dwells, dwell time has to be increased markedly beyond 4 hours.

Alternatively, it is possible to analyze the mechanisms of fluid loss from the peritoneal cavity in relatively short dwells (4 hours) using peritoneal dialysis solutions with low glucose concentration. This is one of the approaches taken in the study by Asghar and Davies.[1] In 1.36% glucose dwells, fluid reabsorption through small pores starts at around 60 minutes, not at 240 minutes as in 3.86% glucose dwells. Another major advantage in the study of Asghar and Davies[1] is the use of radio-iodinated serum albumin instead of dextran 70 (molecular weight 70,000) as an intraperitoneal volume marker. Dextran 70 is a rather polydisperse dextran mixture, which is relatively rapidly disappearing from the peritoneal cavity during the early phase of the dwell, leading to a tendency to overestimate the apparent initial UF.

One ambiguity in all studies using an intraperitoneal macromolecular volume marker is that the disappearance of such a marker from the peritoneal cavity is very complex. For more than 20 years it has been debated to what extent peritoneal marker clearance, K_E, represents just local clearance of marker into peritoneal tissues, or lymphatic clearance (lymphatic reabsorption). K_E is a complex parameter that includes convection of macromolecules and fluid into the peritoneal tissues. Fluid is drained from the tissues by three mechanisms: (1) small-pore reabsorption, that is, back-filtration of fluid, but not of marker, to the blood capillaries; (2) lymphatic reabsorption (a minor portion); and (3) 'volume recirculation' of fluid, but not of marker, back into the peritoneal cavity again. Such a volume recirculation, described at some length in another article,[6] will make K_E exceed the sum of lymphatic and capillary (small-pore) fluid reabsorption, usually by 0.7–1.0 ml/min. However, only the fluid that effectively leaves the peritoneal cavity by capillary and lymphatic reabsorption will affect the net fluid kinetic parameters. Hence, according to the three-pore model, only the lymphatic reabsorption term (~0.2–0.3 ml/min) should be added to the net UF curve to establish the (total) transcapillary ultrafiltered volume curve.

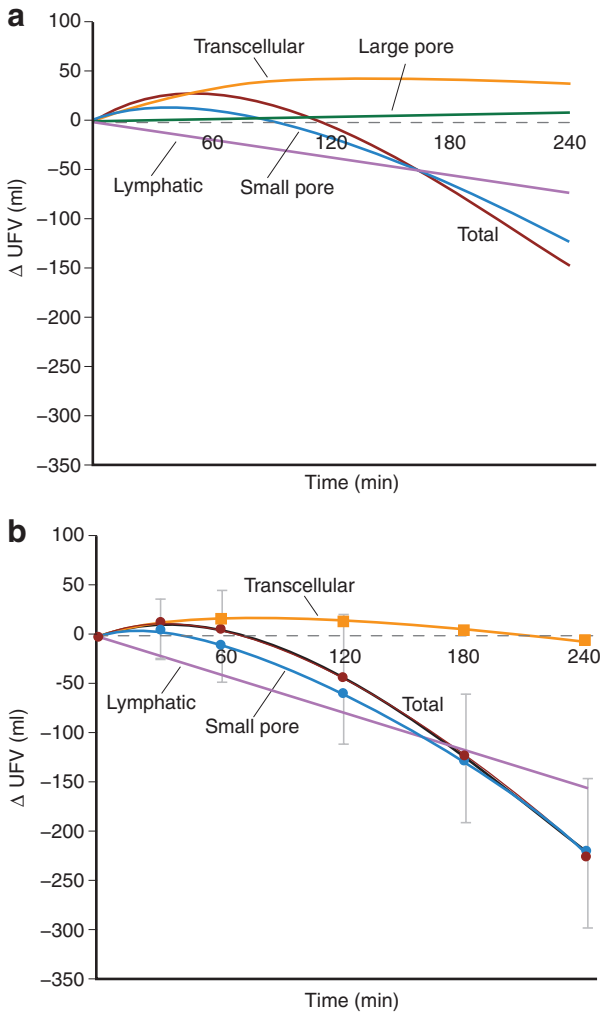

Figure 1 | Partitioning of changes in ultrafiltered volumes (ΔUFV) among the different fluid conductive pathways of the three-pore model for 1.36% glucose. (**a**) ΔUFV partitioned among the various fluid conductive pathways according to computer simulations using the three-pore model of peritoneal transport for 1.36% glucose and standard patient parameters, but having increased the plasma colloid osmotic pressure from 22 to 27 mm Hg, to create a more reabsorptive state than in the standard patient of the three-pore model. Ultrafiltration rates are denoted 'Total,' "Transcellular," 'Small pore,' and 'Large pore,' and the rate of lymphatic reabsorption is denoted 'Lymphatic.' Note that back-filtration across the small pores accounts for most of the net fluid loss from the peritoneal cavity in the late phase of the 1.36% glucose dwell. UFV, ultrafiltered volume. (**b**) The achieved partial fluid flows occurring through the different fluid conductive pathways of the three-pore model measured by Asghar and Davies.[1] Measured data seem to conform well with the computer-simulated data generated by the three-pore model.

Despite the use of indicator dilution-assessed volume as a function of dwell time and its complication by the K_E term, Asghar and Davies[1] have done a very scrupulous evaluation of peritoneal fluid reabsorption and how it is partitioned among the different fluid conductive pathways for 1.36% glucose dwells. Figure 1a shows the computer-simulated partitioning of the partial UF flows through the different pores of the three-pore model for 1.36% glucose, using standard model parameters for an average patient,[7] after a moderate increase of the plasma colloid osmotic pressure from 22 to 27 mm Hg. This was done to match the high reabsorption found in the patient cohort of Asghar and Davies.[1] The modeling of volumes shows that the transcellular ('water-only') UF for 1.36% glucose is rather small during 240 minutes, whereas the small-pore back-filtration is considerable. Furthermore, there is a 'crossover' of the net ultrafiltered volume curve and the small-pore ultrafiltered curve at about 180 minutes. Figure 1b demonstrates that this pattern is more or less exactly mimicked by measured data.[1] Indeed, it is striking how well the measured data correspond to the computer simulation, given the fact that the three-pore model was originally created based on volumetric, not on tracer dilution-assessed, ultrafiltered volumes.

The article by Asghar and Davies[1] points to the difficulty of using the La Milia technique for partitioning small-pore ultrafiltered volume from aquaporin-mediated (ultrasmall-pore) ultrafiltered volume when dwells are exceeding 2 hours and net reabsorption of fluid has not yet started in hypertonic dwells. Studies aiming to analyze the pathways of reabsorption of fluid from the peritoneal cavity to plasma should use solutions based on a low glucose concentration (1.36%), or, alternatively, they should substantially extend the dwell times (to 6–8 hours) if hypertonic glucose solutions are used. Under all circumstances, the article by Asghar and Davies[1] represents a nice experimental confirmation of the prediction by the three-pore model that small-pore back-filtration accounts for the bulk of net fluid loss from the peritoneal cavity under conditions of fluid reabsorption from peritoneum to plasma.

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