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# COMPUTER SIMULATIONS OF CONTINUOUS FLOW PERITONEAL DIALYSIS USING THE 3-PORE MODEL—A FIRST EXPERIENCE

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♦ ***Background:*** **Continuous flow peritoneal dialysis (CFPD) is performed using a continuous flux of dialysis fluid via double or dual-lumen PD catheters, allowing a higher dialysate flow rate (DFR) than conventional treatments. While small clinical studies have revealed greatly improved clearances using CFPD, the inability to predict ultrafiltration (UF) may confer a risk of potentially harmful overfill. Here we performed physiological studies of CFPD *in silico* using the extended 3-pore model.**

♦ ***Method:*** **A 9-h CFPD session was simulated for: slow (dialysate to plasma creatinine [D/P crea] < 0.6), fast (D/P crea > 0.8) and average (0.6 ≤ D/P crea ≤ 0.8) transporters using 1.36%, 2.27%, or 3.86% glucose solutions. To avoid overfill, we applied a practical equation, based on the principle of mass-balance, to predict the UF rate during CFPD treatment.**

♦ ***Results:*** **Increasing DFR > 100 mL/min evoked substantial increments in small- and middle-molecule clearances, being 2 – 5 times higher compared with a 4-h continuous ambulatory PD (CAPD) exchange, with improvements typically being smaller for average and slow transporters. Improved UF rates, exceeding 10 mL/min, were achieved for all transport types. The $\beta_2$-microglobulin clearance was strongly dependent on the UF rate and increased between 60% and 130% as a function of DFR. Lastly, we tested novel *intermittent-continuous* regimes as an alternative strategy to prevent overfill, being effective for 1.36% and 2.27%, but not for 3.86% glucose.**

♦ ***Conclusion:*** **While we find substantial increments in solute and water clearance with CFPD, previous studies have shown similar improvements using high-volume tidal automated PD (APD). Lastly, the current *in silico* results need confirmation by studies *in vivo*.**

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Ever since its introduction, peritoneal dialysis (PD) has struggled to achieve adequate clearance in patients with low residual renal function (RRF) and, typically, once RRF is lost, the patient is transferred to hemodilysis (HD). In general, the solute clearance and ultrafiltration (UF) rate are dependent on the dialysate flow rate (DFR) (1). For a standard nightly 6 × 2-L 9-h automated PD (APD) session, the DFR, defined as the total treatment volume divided by treatment time, is only about 1.3 L/h (~22 mL/min) compared with about 4 – 500 mL/min for a typical HD session. In this regard, APD offers an advantage, since larger volumes of dialysis fluid can be used which would otherwise be unpractical or impossible to manage using manual exchanges. Technically, APD can be performed using 3 different exchange techniques: intermittent PD (IPD), tidal PD (TPD), and continuous flow PD (CFPD). In IPD, the peritoneal cavity is completely drained before fresh dialysis fluid is instilled, while in TPD, only a portion of the initial fill volume is drained and replaced by fresh dialysis fluid during each cycle. In CFPD, a continuous flow of dialysis fluid is instilled and, at the same time, spent dialysate is drained via a separate catheter or lumen. Due to the fact that CFPD requires the use of double or dual-lumen catheters, it has only rarely been used (2). In addition, the UF rate varies over time, especially at lower DFRs, and is difficult to predict in individual patients. There is thus a risk for either over- or under-filling the peritoneal cavity, especially during longer treatments.

In a recent study (3), Nourse and colleagues compared conventional (intermittent) PD and CFPD in infants and found creatinine and urea clearances as well as UF rates to be nearly 3 times higher with CFPD, despite quite a small fill volume. In their study, the drain rate was set slightly higher (102.5 mL/min) than the inflow rate (100 mL/min) to account for the UF rate and to prevent overfill. In a case report, Amerling *et al.* used a dual-lumen catheter to achieve urea clearances exceeding 30 mL/min with DFRs > 200 mL/min in an adult patient (4). Similar improvements have been reported in small clinical and experimental studies (2).

In this study, we present the first 3-pore model simulations of CFPD and explore 2 novel strategies to prevent overfill: intermittent CFPD regimes with regular drains and a mass-balance based method to predict the average UF rate. We show that CFPD can induce substantial improvements in small- and middle-molecular clearance as well as marked increments in the UF rate. These enhancements are similar to those recently obtained in tidal APD at higher DFRs (1).

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## METHOD

The difference between the classic 3-pore model and the extended version used herein is that the change in intraperitoneal volume ($V_D$) as a function of time $t$ is dependent not only on transport processes occurring over the membrane, but also the fill flow rate ($J_{fill}$) and the drain flow rate ($J_{drain}$), as follows:

$$\frac{dV_D}{dt} = J_{v,C} + J_{v,S} + J_{v,L} - L + J_{fill} - J_{drain} \quad (1)$$

In intermittent or tidal APD, $J_{fill}$ and $J_{drain}$ are set to 0 except during filling or draining (1), whereas during CFPD they will be continuous. The drain flow rate may optionally be set higher than the fill flow rate to account for UF (Figure 1). The lymph flow (L) was set to 0.3 mL/min (5). $J_{v,C}$, $J_{v,S}$ and $J_{v,L}$ are the volumetric flows (mL/min) across the ultra-small, small, and large pores, respectively, which are calculated by simple application of Ohm's law, Flow = Hydraulic Conductance × Pressure, in the form of Starling equilibriums, as follows:

$$J_{vC} = af \cdot \alpha_C L_p S(\Delta P - RT\sum_{i=1}^{N} \varphi_i(C_{P,i} - C_{D,i})) \quad (2)$$

$$J_{vS} = af \cdot \alpha_S L_p S(\Delta P - RT\sum_{i=1}^{N} \varphi_i \sigma_{S,i}(C_{P,i} - C_{D,i})) \quad (3)$$

$$J_{vL} = af \cdot \alpha_L L_p S(\Delta P - RT\sum_{i=1}^{N} \varphi_i \sigma_{L,i}(C_{P,i} - C_{D,i})) \quad (4)$$

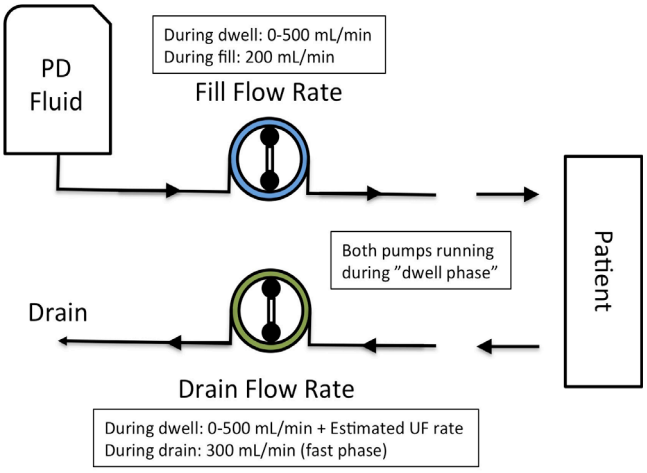


Figure 1 — Schematic representation of continuous flow peritoneal dialysis performed using 2 pumps. The fill flow is driven by a pump which maintains a steady flow of 0–500 mL/min during the "dwell phase" and 200 mL/min during the fill phase and 0 mL/min during draining. The drain flow is maintained at the same flow rate as the fill flow + the expected average UF rate during the dwell phase, 0 mL/min during filling and 300 mL/min during the fast drain phase (see also (1)). A practical application would also include a heater on the fill line and pressure transducers (see, e.g., (2)). PD = peritoneal dialysis; UF = ultrafiltration.

Here $\alpha_C$, $\alpha_S$, and $\alpha_L$ represent the fractional hydraulic conductance for the different pathways (see for example (6)), RT ≈ 19.3 mmHg per mmol/L of concentration difference. $\varphi_i$ is the osmotic coefficient of solute $i$ (unity for most non-electrolytes and 0.93 for sodium chloride); The fractional peritoneal surface area in contact with the dialysate ($af$) as a function of intraperitoneal volume (IPV) was estimated using the estimate (6):

$$af = 16.18(1 - e^{-0.00077 \cdot IPV})/13.3187 \quad (5)$$

Interestingly, this experimentally derived equation will vary much in the same way as the surface of a sphere changes as a function to its volume (i.e., $af = \sqrt[3]{(IPV/2{,}250)}$, see Supplemental Figure 1).

### EQUATIONS FOR DIALYSATE SOLUTE CONCENTRATION

The change in dialysate solute concentration for each solute $i$ was calculated as follows:

$$\frac{dC_{D,i}}{dt} = \frac{J_{s,S,i} + J_{s,L,i}}{V_D} - C_{D,i}\frac{J_{v,C} + J_{v,S} + J_{v,L} + J_{fill}}{V_D} + \frac{C_{B,i}J_{fill}}{V_D} \quad (6)$$

Here, a positive solvent or solute flow is directed into the peritoneal cavity, increasing IPV and solute concentration. The differential equation for the concentration in the drain reservoir for each solute $i$ is given by:

$$\frac{dC_{B,i}}{dt} = J_{drain}\frac{C_{D,i} - C_{B,i}}{V_B} \quad (7)$$

The initial conditions for the above system of differential equations are:

$$V_D(0) = V_r \quad (8)$$

$$C_{D,i}(0) = C_{D,i,0} \quad (9)$$

$$C_{B,i}(0) = C_{I,i} \quad (10)$$

$$V_B(0) = V_I \quad (11)$$

Here, $V_r$ denotes the peritoneal residual volume (set to 250 mL), $V_I$ the fill volume (or set to 0 at the beginning of the drain phase), $C_{I,i}$ is the solute concentration in the dialysis fluid and $C_{D,i,0}$ is the initial dialysate concentration of solute $i$. It was assumed that a rinse had been performed before simulations had been started, and thus the initial concentrations were set to (Sodium+anion: 132 mmol/L, Urea: 0 mmol/L, Creatinine 0 mmol/L, Albumin: 0 mmol/L, $\beta_2$-microglobulin (for mass transfer area coefficient [MTAC] see(7)): 0 mmol/L, Phosphate: 0 mmol/L, Glucose: 75 mmol/L). The above system of ordinary differential equations was solved with a Runge-Kutta scheme (as described at some length in (1)) in order to obtain the functions $V_D(t)$, $C_{D,i}(t)$, $V_B(i)$, and $C_{B,i}(t)$.

### CALCULATION OF SOLUTE FLOW

The solute flow (in mmol/min) over each porous pathway was calculated using the Patlak equation (8), as follows:

$$J_{s,S,i} = J_{v,S}(1-\sigma_{s,i})\frac{C_{P,i}-C_{D,i}e^{-Pe_{S,i}}}{1-e^{-Pe_{S,i}}} \quad (12)$$

$$J_{s,L,i} = J_{v,L}(1-\sigma_{L,i})\frac{C_{P,i}-C_{D,i}e^{-Pe_{L,i}}}{1-e^{-Pe_{L,i}}} \quad (13)$$

Here the Péclet numbers are given by $PeS,i=JvS(1-\sigma_{S,i})/(af\cdot PS_{S,i})$ and $Pe_{L,i}=J_{vL}(1-\sigma_{L,i})/(af\cdot PS_{L,i})$ for the small and large pores, respectively. The diffusion capacities, $PS_{S,i}$ and $PS_{L,i}$ (mL/min), are either set according to (1) or calculated according to $PS=H\cdot D\cdot A_0/\Delta x$, where H is the diffusive restriction factor (see (8)), D is the free diffusion coefficient ($cm^2$/min) and $A_0/\Delta x$ (cm) is the unrestricted pore area $A_0$ over diffusion length $\Delta x$. The reflection coefficients were calculated according to theory based on the pore sizes as in (1). Water and solute transport were simulated for 3 different transport types: slow (dialysate to plasma creatinine [D/P crea] < 0.6), fast (D/P crea > 0.8), and average (0.6 ≤ D/P crea ≤ 0.8) and glucose concentrations: 1.36% (75.5 mM), 2.27% (126.1 mM), and 3.86% (214.4 mM) as explained in (1). Thus, solute diffusion capacities were all scaled in proportion to the area parameter $A_0/\Delta x$ (see Table 1).

## RESULTS

### SIMULATION OF A 4-H CFPD SESSION—EFFECTS ON TRANS-PERITONEAL WATER AND SOLUTE TRANSPORT

We first assessed the impact of varying the fill flow rate (Q) in a 540-min CFPD session between 0 mL/min and 500 mL/min (similar to the dialysate flow in HD). The drain flow rate was either set slightly higher than Q (according to equation 14, below) to account for the expected UF rate or set equal to Q (leading to overfill). Knowing the clearance K of the osmotic gradient (here estimated as $1.5\times MTAC_{crea}$) and the maximal UF rate ($U_{max}$), the expected UF rate was estimated from:

$$UF\ rate = \frac{1}{2}\sqrt{(K+Q)^2+4QU_{max}} - \frac{1}{2}(K+Q) \quad (14)$$

(for a derivation of this equation, see the Supplemental material). As Q increases, the UF rate will tend to $U_{max}$, the maximal UF rate, which was estimated from the osmotic conductance and the glucose concentration ($C_g$) used: $U_{max}\approx 19.3\cdot OCG\cdot C_g - 3.1$ (see Supplemental material). To illustrate the ability of equation 14 to predict the average UF rate, the intra-peritoneal volume as a function of dwell time in hours was plotted in Figure 2 for a fill flow rate Q of 100 mL/min. The results for the other flow rates were very similar. As can be seen, there was a tendency for the above equation to slightly overestimate UF. Overfill was, however, effectively prevented.

TABLE 1
Extended 3-Pore Model Parameters

| Parameters used for the computer simulations according to an extended 3-pore model. | |
|---|---|
| Small pore radius ($r_s$) (Å) | 43 |
| Large pore radius ($r_L$) (Å) | 250 |
| Fractional small pore UF-coeff. ($\alpha_s$) | 0.900 |
| Fractional transcellular UF-coeff. ($\alpha_c$) | 0.020 |
| Fractional large pore UF-coeff. ($\alpha_L$) | 0.080 |
| Ultrafiltration coefficient ($L_pS$) (mL/min/mmHg) | 0.074 |
| Osmotic conductance to glucose ($L_pS\,\sigma_g$) (µL/min/mmHg) | 3.6 |
| "Unrestricted" pore area over unit diffusion distance for small pores ($A_0/\Delta x$) (cm) | 25,000[a] |
| Transperitoneal oncotic pressure gradient (Πpprot) (mmHg) | 22 |
| MTAC[b] for glucose (mL/min) | 15.4[c] |
| MTAC[b] for urea (mL/min) | 26.0 |
| MTAC[b] for $Na^+$ and anions (mL/min) | 4.5 |
| MTAC[b] for phosphate (mL/min) | 10.2 |
| MTAC[b] for $\beta_2$-microglobulin (mL/min) | 0.95[d] |
| Peritoneal residual volume ($V_r$) (mL) | 250 |
| Serum urea conc. (mmol/L) | 20 |
| Serum creatinine conc. (µmol/L) | 660 |
| Serum $\beta_2$-microglobulin conc. (µmol/L) | 2.0 |
| Dialysis fluid sodium conc. (mmol/L) | 132 |
| Serum sodium (and sodium associated "anion" conc.) (mmol/L) | 140 |
| Serum glucose conc. (mmol/L) | 6.5 |
| Dissociation factor for "$Na^+$" and "anions" | 0.93 |

MTAC = diffusion capacity (PS) or mass transfer area coefficient.
[a] 25,000 cm for an average peritoneal transport type, 40,000 cm for high transporters, and 15,000 cm for low transporters.
[b] For average transporters, otherwise scaled according to $A_0/\Delta x$.
[c] 9.3 mL/min for the disappearance of glucose from the dialysate (see ref. 6).
[d] See ref. 7.

### SMALL SOLUTE TRANSPORT

As can be seen in Figure 3a – c, the clearance of urea, creatinine, and phosphate depend strongly on the DFR (= Total treatment volume/Total treatment time); for fast transporters, the small solute clearance can increase by almost 300%, while the effect is less prominent for average and slow transporters. Apparently, increasing the DFR to above 200 mL/min will not lead to any significant improvements in clearance, while the increase up to 100 mL/min (6 L/h) leads to marked improvements. The improvements are similar, albeit somewhat smaller, to those obtained in previous simulations of tidal APD (1). The estimated weekly Kt/V urea for a nightly 9-h CFPD session can reach values close to that achieved in HD (Figure 3d). To facilitate comparison with other simulated APD regimens (1), we present the transport rates as functions of DFR rather than fill flow rate (Q); thus, in Figure 2, DFR varies between ~8 mL/min (Q: 0 mL/min) and ~490 mL/min (Q: 500 mL/min).

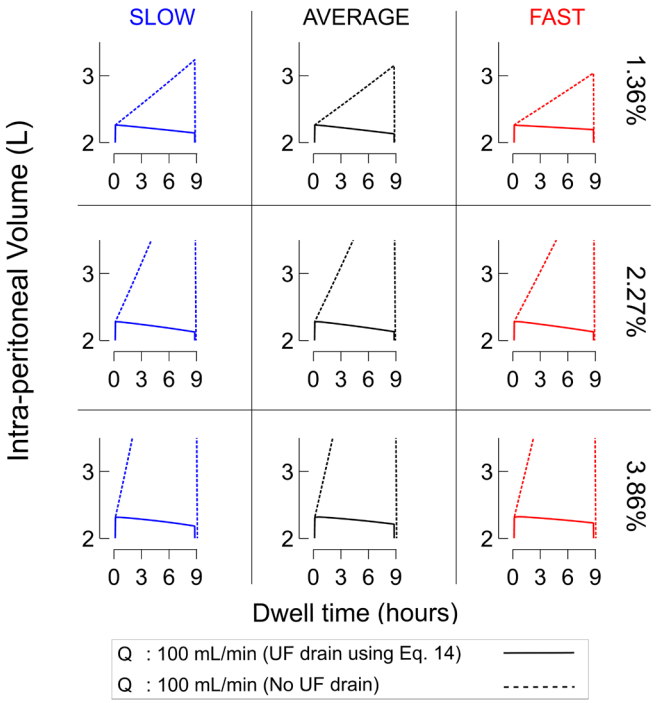


Figure 2 — Intraperitoneal volume during a 9-h CFPD session. The fill flow rate (Q) was set to 100 mL/min and the drain flow rate was either set slightly higher than Q (solid line) to account for the expected UF rate (according to Eq. 14) or set equal to Q (dotted line) leading to overfill. The results for the other flow rates were very similar. Simulations were performed for 3 different transport types: slow (D/P crea < 0.6, blue line), average (0.6 ≤ D/P crea ≤ 0.8, black line), and fast (D/P crea > 0.8, red line) and glucose concentrations: 1.36%, 2.27%, and 3.86%, as indicated. CFPD = continuous flow peritoneal dialysis; UF = ultrafiltration; D/P crea = ratio of dialysate to plasma creatinine.

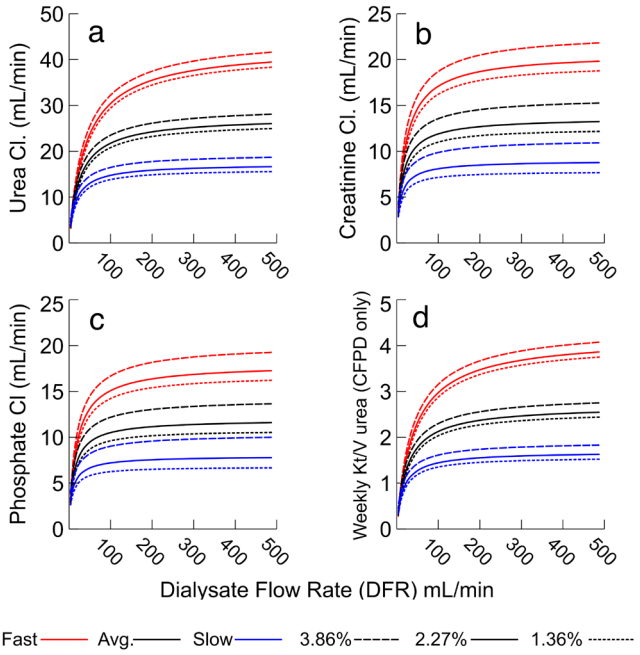


Figure 3 — Solute clearances plotted as a function of dialysate flow rate for a 9-h CFPD session for slow (blue line), average (black line) and fast (red line) transporters for 1.36% glucose (dotted line), 2.27% glucose (solid line), and 3.86% glucose (dashed line). a) Urea; b) Creatinine; c) Phosphate; d) Estimated weekly Kt/V urea for a nightly 9-h treatment vs DFR. CFPD = continuous flow peritoneal dialysis; DFR = dialysate filtration rate; Cl = clearance.

## MIDDLE- AND MACRO-MOLECULAR SOLUTE TRANSPORT

The clearance of $\beta_2$-microglobulin ($\beta_2\mu$) is critically dependent on convective transport, with clearances being higher for the high glucose concentration (Figure 4a). However, as seen, there is also a diffusive component of $\beta_2\mu$ transport, where high transporters exhibit a higher overall clearance for a given glucose concentration. As is shown in Figure 4b, the clearance of albumin is strongly dependent on convection, and thus the reverse pattern is present compared with $\beta_2\mu$, and fast transporters actually lose less albumin. In fact, as indicated by the 1.36% glucose simulations (Figure 4b), albumin losses will actually increase very little as a function of DFR *per se* and are in fact mainly a function of the UF rate.

## ULTRAFILTRATION RATE AND SODIUM TRANSPORT

The UF rate increased approximately 5-fold across the different DFRs tested (Figure 4c). The differences in UF between the different transport types are diminished at higher DFRs, when glucose dissipation becomes negligible, and the remaining differences are due to differences in the water permeability (UF coefficient) of the peritoneal membrane. The sodium removal in mmol per dL of UF was decreased at higher DFRs (Figure 4d). Thus, the increment in UF rate (water clearance) is higher in relation to sodium clearance, and water removal becomes progressively hyponatric in relation to blood plasma water (14 – 15 mmol/dL), with the sodium removal reaching a lower plateau at about 10 mmol/dL UF. The transient behavior of the curve for 1.36% glucose and fast transport is due to a very small amount of overall UF being attained at small DFRs, which inflated the ratio. Higher flow rates also resulted in marked increments in the amount of UF per g glucose absorbed (Figure 4e) being inflated by a factor of ~2 when increasing DFR to 100 mL/min. Similar to the other small solutes, the clearance of sodium rises sharply as DFR is increased (Figure 4f).

## A NIGHTLY 9-H INTERMITTENT CFPD SESSION VS STANDARD 9-H 2 × 6-L 1.36% APD SESSION

The above strategy, using an equation, avoids overfill by estimating the UF rate and compensating for the generated UF by increasing the drain flow rate slightly. Another option is to perform full drains at regular intervals to ensure that overfill does not occur. Here, we simulated such *intermittent* CFPD regimes having the same fill volume and number of "exchanges" as a standard nightly 9-h (6 × 2-L) APD regime, but with continuous flow rates acting only during the "dwell phase." The drain flow rate here was set equal to the fill flow rate, letting the IPV increase just as in a non-continuous APD

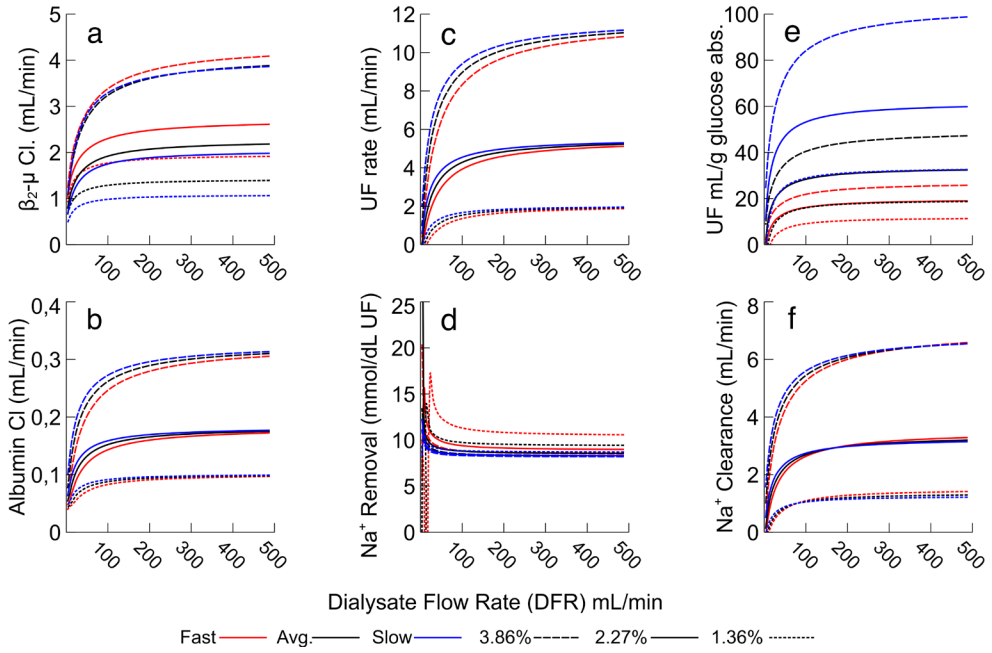


Figure 4 — Clearance of $\beta_2$-microglobulin (a) and albumin (b) plotted as a function of DFR during a 9-h CFPD session. Ultrafiltration rate (c), sodium removal per deciliter UF (d), UF in mL per g glucose absorbed (e), and sodium clearance (plotted as a function of DFR) for a 9-h CFPD session for slow (blue line), average (black line), and fast (red line) transporters for 1.36% glucose (dotted line), 2.27% glucose (solid line), and 3.86% glucose (dashed line). DFR = dialysate filtration rate; CFPD = continuous flow peritoneal dialysis; UF = ultrafiltration.

regime, but with a continuous flow during the "dwell phase." As seen in Figure 5, intermittent CFPD regimes prevented overfill for 1.36% and 2.27% glucose where the IPV was safely below 2.8 L at all times. However, for the hypothetical 3.86% glucose regimes, a certain amount of extra drain flow may be needed since the IPV was up to 3.4 L to the end of the cycle. The intermittent CFPD regimens exhibited very similar clearances and UF rates (in relation to DFR) as those in the above CFPD simulations since the drain and fill phases are short in relation to the total duration of the treatment (Supplemental Figure 2).

## DISCUSSION

We herein provide the first simulations of CFPD using an extended version of the 3-pore model of PD. It is demonstrated that increments in the fill flow rate of up to 200 mL/min lead to parallel improvements in both UF and small- and middle-molecule clearance. The improvements are, however, somewhat smaller than those found in early clinical studies (2), which warrants further discussion. Is there a "stirring effect" associated with higher DFRs? Conceivably, the formation of stagnant layers close to the peritoneal membrane may be counteracted by more frequent filling and draining of the peritoneal cavity. Indeed, in a recent study it was suggested (1) that the extended 3-pore model underestimated urea clearances at higher DFRs both for IPD and TPD. Another possibility is that the stimulus from filling the peritoneal cavity with, usually hypertonic, dialysis fluid may induce vasodilation and/or vascular recruitment, increasing the diffusion capacity of the peritoneal membrane, and thus more frequent exchanges would increase small solute clearance more than what would be expected simply from adding fresh dialysis fluid. Indeed, if present, such effects could double the apparent diffusive area of the peritoneal membrane (9). However, in many experimental and clinical studies on CFPD, the actual IPV was not measured and it cannot be excluded that part of the observed increments in MTACs are due to an increased IPV. As is demonstrated in the current simulations, inflating the IPV is unavoidable if the UF rate is underestimated. Although our use of equation 14 effectively predicted UF rate, preventing overfill, it requires the measurement of the osmotic conductance to glucose, a parameter that is not routinely assessed in many clinics.

The increments in small solute clearances may not be the most interesting aspect of CFPD or, indeed, in PD as a whole. Urea Kt/V as an adequacy marker has been questioned both in PD (10) and in HD (11). By contrast, $\beta_2\mu$ is a well-established uremic retention solute and the HEMO study showed that it was the plasma $\beta_2\mu$ concentrations—not Kt/V urea—that predicted mortality in HD patients (12). Our current data suggest that increasing the DFR can enhance the clearance of $\beta_2\mu$ up to a factor of ~2. Middle molecular removal is, however, lower in CAPD compared with high-flux HD (13). For example, a high-flux dialyzer can achieve a $\beta_2\mu$ clearance of about 20 – 40 mL/min (14), which results in a weekly clearance of about 15 – 30 L for a typical 4-h thrice-weekly HD treatment. In contrast, the $\beta_2\mu$ clearance is only about 0.5 – 1 mL/min in CAPD, resulting in about 5 – 10 L in weekly clearance, i.e., ~3 times less than HD. On the other hand, it has been demonstrated that the initial mortality appears to be lower in PD patients than in HD patients (15). It has been suggested that part of this effect

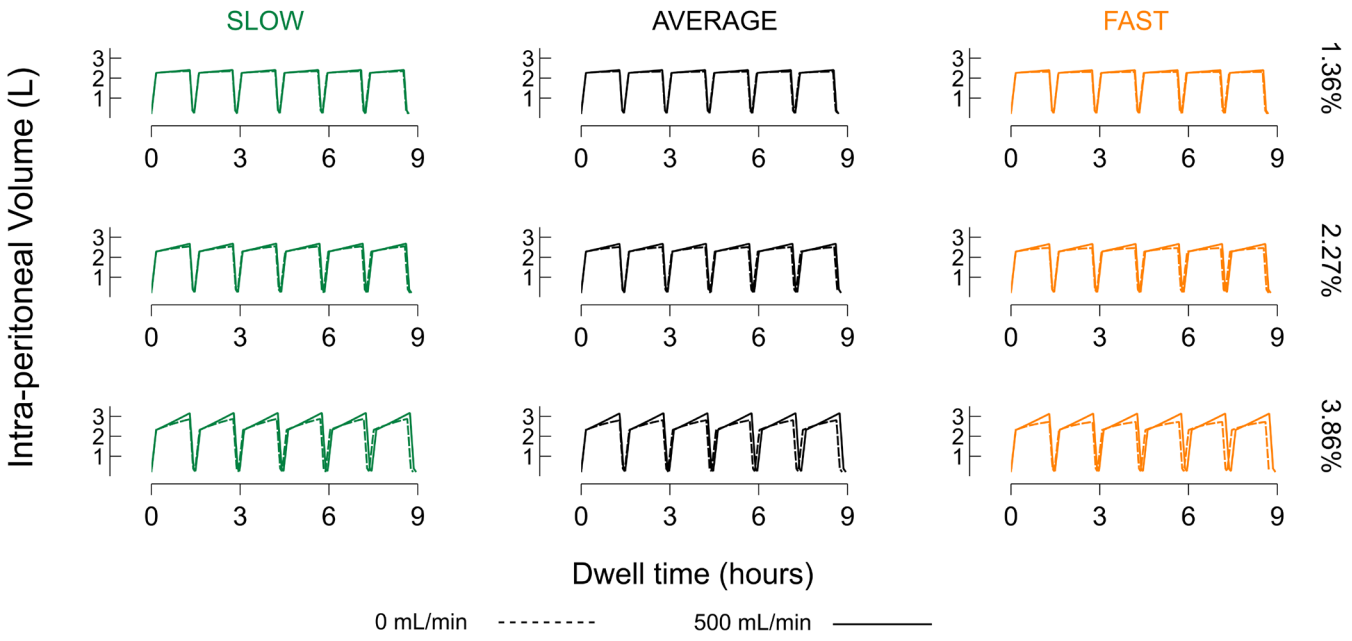


Figure 5 — Intraperitoneal volume as a function of treatment time for intermittent high-flow CFPD regimes (solid lines) vs standard 6 × 2-L intermittent APD regimes (dashed lines). The dwell time was kept constant at 71 min to accomplish a total treatment time of ~9 h. CFPD = continuous flow peritoneal dialysis; APD = automated peritoneal dialysis.

may be explained by differences in RRF (15,16). Indeed, RRF is strongly associated with better survival in studies of both HD and PD (17). In addition, it can, from calculations similar to those above, be realized that RRF is an important determinant of middle molecular clearance since the glomerular $\beta_2\mu$ clearance represents about 90% of the glomerular filtration rate (GFR) (18) and thus as little as 3 mL/min of RRF will provide a similar weekly clearance as that of high-flux HD. Thus, RRF will, in many cases, be the main determinant of the serum concentration of many uremic toxins, rather than dialysis dose. This may be a conceivable explanation for the apparent lack of correlation between solute clearance and hard outcomes in PD and, perhaps, also in HD. In line with this, in a recent study, Kalim *et al.* showed that, out of 164 metabolites, only 8 decreased a year after conversion from a thrice-weekly regime to nocturnal dialysis, whereas several established uremic retention solutes did not change with extended dialysis, despite a much higher dialysis dose (19).

During PD, typically about 80% of sodium transport occurs via convection (1,6). Water removal using glucose-based PD fluids is, however, typically hyponatric, meaning that the amount of sodium per deciliter (dL) of water removed (typically 8 – 10 mmol/dL) is lower than the amount of sodium per dL of plasma water, leading to a relative sodium retention, which, via osmoregulation, may contribute to vasopressin-mediated renal water retention and thirst. Our current findings imply that lower DFRs confer overall higher sodium removal than APD (20). Indeed, in Figure 4d, the leftmost points represent dialysate flow rates similar to a single 4-h CAPD dwell, while the leftmost point in Supplemental Figure 2g represents a 9-h 6 × 2-L APD regimen. Possible strategies to improve sodium removal comprise lowering the dialysate sodium concentration and/or using colloidal osmotic agents such as icodextrin (21). In a recent study, Morelle *et al.* demonstrated that combined fluids, having both glucose and icodextrin, had superior sodium removal and lower "metabolic cost" than glucose-based fluids (22).

Continuous flow PD would, if implemented, be one of the most exciting innovations in the field of PD. However, to perform CFPD, 2-way access to the peritoneal cavity must be achieved, most likely in the form of a dual-lumen catheter (23). A dual-lumen catheter may, however, result in a certain degree of recirculation, which was not taken into account in our modelization. Importantly, similar improvements in solute transport have been obtained for tidal APD in previous modeling studies (1), and thus our current results imply that the clinical benefit of CFPD over tidal APD may be limited. Moreover, online production of PD fluid would be necessary, as using the solutions currently available in sufficient volumes would be both costly and impractical unless a recirculation system is applied (24). Lastly, we conclude that the reasons for the discrepancy between the lower small solute clearances simulated herein and those measured in previous experimental studies remain obscure. Surely, in many patients, the residual volume may significantly contribute to the net IPV and, if not taken into account, a large residual volume may make impossible any modeling approach based on a small or constant IPV (25). Thus, further experimental research, taking the IPV into account, is clearly needed to cast light on this issue. While the 3-pore model has been robustly validated in several clinical studies on CAPD, there are no such studies on CFPD, and thus, the current findings must be verified in clinical and experimental studies.

## ACKNOWLEDGMENTS

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## DISCLOSURES

CÖ has worked as a consultant for Baxter Healthcare and has also received speakers' honoraria from Baxter Healthcare. GM has no conflicts of interest to declare.

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