

Quantifying Ultrafiltration in Peritoneal Dialysis Using the Sodium Dip

Jakob Helman ¹, Hedda Wahlgren,¹ Linn Andersson,¹ Johann Morelle ^{2,3} and Carl M. Öberg ¹

Key Points

- Ultrafiltration (UF) is a key component of clinical peritoneal dialysis prescription, but the traditional method to assess UF is hampered by large inaccuracies.
- Here we propose a novel method, based on a computational model and on a single dialysate sodium measurement, to accurately estimate UF and osmotic conductance to glucose in patients on peritoneal dialysis.

Abstract

Background Volume overload is highly prevalent among patients treated with peritoneal dialysis (PD), contributes to hypertension, and is associated with an increased risk of cardiovascular events and death in this population. As a result, optimizing peritoneal ultrafiltration (UF) is a key component of high-quality dialysis prescription. Osmotic conductance to glucose (OCG) reflects the water transport properties of the peritoneum, but measuring it requires an accurate quantification of UF, which is often difficult to obtain because of variability in catheter patency and peritoneal residual volume.

Methods In this study, we derived a new mathematical model for estimating UF during PD, on the basis of sodium sieving, using a single measure of dialysate sodium concentration. The model was validated experimentally in a rat model of PD, using dialysis fluid with two different sodium concentrations (125 and 134 mmol/L) and three glucose strengths (1.5%, 2.3%, and 4.25%). Then, the same model was tested in a cohort of PD patients to predict UF.

Results In experimental and clinical conditions, the sodium-based estimation of UF rate correlated with UF rate measurements on the basis of volumetry and albumin dilution, with a $R^2=0.35$ and $R^2=0.76$, respectively. UF on the basis of sodium sieving was also successfully used to calculate OCG in the clinical cohort, with a Pearson r of 0.77.

Conclusions Using the novel mathematical models in this study, the sodium dip can be used to accurately estimate OCG, and therefore, it is a promising measurement method for future clinical use.

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Introduction

Fluid management is a key component of high-quality peritoneal dialysis (PD) prescription. Fluid overload contributes to detrimental consequences, such as hypertension and left ventricular hypertrophy, and has been associated with a higher risk of death and other complications, independently from comorbidities.^{1–3} In addition, inadequate sodium removal during PD leads to sodium retention, extracellular volume expansion, and fluid overload.^{4,5} Initial dialysate sodium kinetics closely reflect the osmotic transport of water. Because current computational models do not account

for changes in dialysate sodium transport kinetics over time,⁶ it has been difficult to draw clinical conclusions about the total amount of ultrafiltration (UF) from sodium measurements alone. The difference between drained and instilled dialysis fluid volume is the commonly used method to estimate UF in clinical settings. This is sufficient for managing a PD prescription, but not precise enough for more detailed assessments of peritoneal membrane function. Variation in catheter patency and peritoneal residual volume contribute to the inaccuracy of UF measurements.^{7,8} Determining osmotic conductance

¹Department of Clinical Sciences Lund, Skåne University Hospital, Lund, Sweden

²Division of Nephrology, Cliniques universitaires Saint-Luc, Brussels, Belgium

³UCLouvain School of Medicine, Université catholique de Louvain, Brussels, Belgium

Correspondence: Prof. Carl M. Öberg, Department of Clinical Sciences Lund, Skane University Hospital, Njurmottagningen, Barngratan 2a, Lund 221 85, Sweden. Email: carl.oberg@med.lu.se

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to glucose (OCG), which is a measure that reflects the capacity of the peritoneum to transport water, is heavily dependent on a precise estimation of UF.⁹ Although several methods for estimating OCG have been developed,^{8,10,11} the requirement of accurate UF determination introduces complexity, limiting the clinical utility of present methods.

The sodium dip corresponds to the initial decrease of dialysate sodium concentration, typically during the first hour, and arises because of the presence of free-water transport and the fact that plasma sodium concentrations are close to those in the dialysate. Because a fixed percentage (40%–50%) of UF in patients is free water transport,^{12,13} the sodium dip is proportional to the UF rate. The sodium dip is also affected by diffusive influx of sodium from the circulation, and earlier studies have corrected the sodium dip for this influx.^{14,15} Performing this correction, and knowing the fractional free water transport, enables estimation of UF from the magnitude of the sodium dip. Transperitoneal sodium transfer is also affected by the Gibbs–Donnan effect, which is an electric potential that arises from negatively charged proteins that cannot pass the capillary wall. Finally, the fact that only 93%–95% of plasma consists of water means that equilibrium dialysate concentrations (*e.g.*, after a very long dwell) will be approximately 5%–7% higher than plasma concentrations¹⁶—the so called plasma water effect. If precise enough, estimations of UF from the sodium dip that consider these factors could then be used when estimating OCG.

In this study, we show that the sodium dip can be used to estimate UF in PD using novel mathematical models, considering the Gibbs–Donnan effect and the proportion of plasma water, in addition to free water transport and sodium influx. These models were developed and validated in rat models of experimental dialysis, then applied to a cohort of PD patients to estimate UF rate and OCG.

Methods Overview

Initially, a theoretical model for UF estimation from sodium transport was created, taking into account that a fraction of water transport is solute-free, and the Gibbs–Donnan and plasma water effects. The Gibbs–Donnan effect arises because of the presence of large anionic plasma proteins which are nearly impermeable across capillary walls, which causes an electric potential to arise, retaining cationic charges in plasma to preserve electroneutrality. To validate the model, experimental PD was performed in anesthetized Sprague–Dawley rats, using fluids of three glucose strengths (1.5%, 2.3%, and 4.25%) and two different sodium concentrations (125 and 134 mmol/L). Literature values for plasma water and Gibbs–Donnan effects were analyzed with a three-pore model analysis to validate them for present data, which is described in detail in the [Supplemental Material](#) and [Supplemental Figure S1](#).¹⁷ The plasma water effect arises because large molecular species, such as proteins, take up a considerable amount of volume in blood plasma, such that the fraction of water is approximately 93%–95% of the plasma volume, which means that the concentration of a solute in plasma water

is 5%–8% higher than the plasma concentration. Finally, the model was applied to PD patients in a clinical cohort where sodium concentrations, glucose, and UF had been precisely measured. On the basis of estimated UF, the OCG was calculated in the cohort and compared with established methods.

Theoretical Modeling

The change of sodium mass in the dialysate is the sum of diffusive and convective flux of sodium ($j_{diffusion}$ and $j_{convection}$) into the peritoneal cavity, modeled using the continuity equation

$$\partial_t(vc) = j_{diffusion} + j_{convection}$$

where v is the intraperitoneal volume and c is the concentration of sodium. Boundary values are intraperitoneal volume v and sodium concentration c at time 0 and at time T (40 or 60 minutes). $v(0)$, $c(0)$, and $c(T)$ are known.

Sodium mainly resides in the extracellular space. Sodium diffusion capacity (PS_{Na}) across the peritoneal membrane should therefore be proportional to that of other extracellular solutes, such as ^{51}Cr -EDTA (PS_{EDTA}). Under this assumption of a common paracellular pathway of transport, PS_{Na} can be obtained by multiplying with the ratio of their respective diffusion coefficients ($PS_{Na} \approx 2.18 \cdot PS_{EDTA}$). Plasma sodium was adjusted for Gibbs–Donnan and plasma water effects by multiplication with the quotient q between the respective effects ($q = 0.96^z / 0.93$, where z is the valence). The change in sodium concentration c as a function of time was modeled by an isocratic¹⁸ transport equation as follows

$$\frac{dc}{dt} = \frac{1}{J_v t + V_0} \left(\left(\frac{J_v t + V_0}{V_0} \right)^{2/3} PS_{Na} (c_p - c) + J_v (1 - fFWT) \frac{c_p + c}{2} - J_v c \right) \quad (7)$$

The fractional amount of free water transport (fFWT) was assumed to be 50%. The UF rate (J_v) is here unknown, and to find it, the above differential equation was solved using a root-finding algorithm (uniroot) to find the root of $F(c) = c(T) - \text{dialysate sodium at } T \text{ min}$ (the time of the sodium measurement). The isocratic transport equation assumes the UF rate to be constant, which has been shown to be a valid approximation of solute transport in PD for short timespans (herein the initial 40–60 minutes of the PD dwell), equivalent to the three-pore model.¹⁸

In experiments, ^{125}I -albumin (radioiodinated serum albumin [RISA]) was used to calculate the intraperitoneal volume. To do this accurately, the dialysate-to-plasma clearance of RISA was calculated. The clearance of albumin from the dialysate to plasma, that is, the first-order dissipation of the total intravascular mass of ^{125}I -albumin, was described by a boundary value problem and solved using a shooting algorithm. Derivation of equations can be found in the [Supplemental Material](#).

Calculation of OCG

OCG was calculated using a single dwell equation according to Martus *et al.*⁸

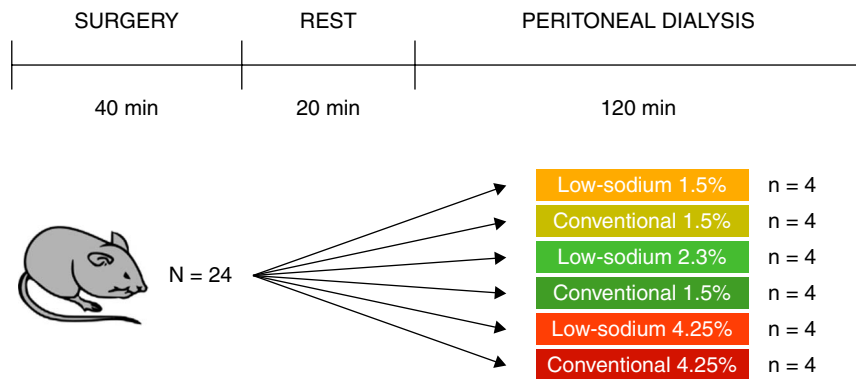


Figure 1. Schematic diagram of the experimental setup. Peritoneal dialysis was performed in anesthetized Sprague–Dawley rats using a fill volume of 20 ml with 1.5%, 2.3%, or 4.25% glucose fluid using conventional ($n=12$) or low-sodium ($n=12$) fluids. Blood samples were obtained before and after dialysis. Samples of the dialysate were taken at baseline and at 1, 40, and 120 minutes of dwell time.

$$OCG = \frac{UF}{19.3 T \left(\bar{G}_{4.25} - C_r \right)} \times 1000$$

Where $\bar{G}_{4.25} = (C_0 - C_T) / \ln \left(\frac{C_0}{C_T} \right)$, T is the dwell time, C_r is the net average concentration gradient opposing the glucose gradient, estimated to be 40 mmol/L, and UF is the ultrafiltrate volume.

Experiments in Rats

Twenty-four, male, 9-week-old Sprague–Dawley rats were divided into six groups of four animals and treated with low-sodium PD fluid with a sodium concentration of 125 mmol/L ($n=12$) (noncommercial fluid provided by Fresenius Medical Care, Bad Homburg, Germany) or with conventional fluid with a sodium concentration of 134 mmol/L ($n=12$) (Balance, Fresenius Medical Care, Bad Homburg, Germany) for all three glucose strengths 1.5%, 2.3%, and 4.25%, using a fill volume of 20 ml and a 120-minute dwell time (Figure 1). Samples were obtained from the dialysate before infusion and from the dialysate at 1, 10, 20, 30, 40, 60, 90, and 120 minutes and blood serum at 5, 15, 35, 65, 95, and 120 minutes and analyzed on a gamma counter (Wizard 1480; Wallac Oy, Turku, Finland). Dialysate samples for analysis of sodium, potassium, urea, creatinine, calcium ion, total carbon dioxide, and glucose (CHEM8, Abbott) were obtained directly after instillation, at 40 minutes and after 120 minutes of dwell time. A detailed description of validation and correction for matrix effects in dialysate concentration measurements can be found in the [Supplemental Material](#).

The experiments were approved by the Lund University Ethics Committee for Animal Research (Dnr 5.8.18-08386/2022), and all animals were handled in accordance with the National Institutes of Health's standards for the Care and Use of Laboratory Animals. Induction of anesthesia was initiated by gently placing the rat into a covered glass cylinder, with a continuous flow of 5% isoflurane in air (Isoban, Abbot Stockholm, Sweden). Once fully anesthetized, the rat was removed from the container, and anesthesia was maintained using 1.6%–1.8% isoflurane in air delivered through a small mask. After tracheostomy, the rat

was connected to a volume-controlled ventilator (Ugo Basile; Biological Research Apparatus, Comerio, Italy), with a positive end-expiratory pressure of 4 cm H₂O. End-tidal pCO₂ was maintained between 4.8 and 5.5 kPa (Capstar-100, CWE, Ardmore, PA). Body temperature was regulated between 37.1°C and 37.3°C, using a feedback-controlled heating pad. The right femoral artery was cannulated for continuous monitoring of mean arterial pressure and heart rate. It was also used for obtaining blood samples (95 μl) for measuring glucose, urea, electrolytes, hemoglobin, and hematocrit (I-STAT, Abbott, Abbott Park, IL), as well as blood 51Cr-EDTA activity. The right femoral vein was cannulated and connected to the dialyzer using plastic tubing. In addition, the right femoral artery was cannulated and connected to a pressure transducer for continuous monitoring of arterial line pressure. The right internal jugular vein was cannulated for the infusion of maintenance fluid at a rate of 3 ml/h. Hematocrit was determined by centrifuging thin capillary glass tubes. Postexperiment, animals were euthanized through an intravenous bolus injection of potassium chloride.

Clinical Cohort

After validation of the above model in the experiments, equations were applied to a cohort of 21 PD patients treated at the Skåne University Hospital in Lund between 2015 and 2017, by Martus *et al.*⁸ The dataset contained data on samples taken on dialysate during two 1-hour dwells, the first being performed with 1.5% glucose and the second with 4.25% glucose, with sodium, glucose, and albumin samples collected at the start and end of dialysis. In this study, UF estimations from sodium dip were compared with UF estimation on the basis of volumetry and albumin dilution. Sodium concentrations were analyzed at the Department of Clinical Chemistry at Lund University Hospital, using indirect potentiometry (Cobas 8000/6000; Roche Diagnostics, Basel, Switzerland). Statistical power analysis was conducted on the basis of the largest acceptable difference in estimated UF between the two methods, which was set to 100 ml. Power was 95.7%, for a measurement error of 20%. OCG was calculated on the basis of the UF values estimated using the two methods. Bland–Altman

Table 1. Effects on sodium, chloride and water transport, and clearances of ^{125}I -albumin during experimental PD using conventional (134 mmol/L) and low-sodium (125 mmol/L) fluids

Group	Dialysate Sodium Clearance ^a , $\mu\text{l min}^{-1}$	Sodium Removal per Liter UF, mmol L^{-1}	Dialysate-To-Plasma Clearance of ^{125}I -Albumin, $\mu\text{l min}^{-1}$	Dialysate Clearance of ^{125}I -Albumin, $\mu\text{l min}^{-1}$	D/P Creatinine	UF Rate for 120 Minutes ^a , $\mu\text{l min}^{-1}$
1.5% glucose						
Conventional	22 (21–23)	120 (117–123)	14 (10–20)	49 (36–62)	0.20 (0.15–0.23)	26 (24–27)
Low sodium	0 (–9 to 10)	144 (75–227)	16 (11–21)	90 (75–104)	0.21 (0.15–0.25)	–7 (–19 to 5)
2.3% glucose						
Conventional	32 (29–35)	123 (117–125)	15 (13–18)	64 (60–69)	0.16 (0.13–0.18)	40 (36–41)
Low sodium	48 (40–55)	138 (137–148)	13 (10–19)	51 (43–59)	0.14 (0.11–0.16)	45 (34–56)
4.25% glucose						
Conventional	51 (46–58)	92 (90–99)	12 (10–16)	75 (74–81)	0.14 (0.09–0.17)	71 (69–75)
Low sodium	66 (62–71)	118 (113–123)	17 (15–20)	65 (62–74)	0.11 (0.10–0.13)	77 (72–79)
2×2 ANOVA						
Sodium <i>P</i> value	0.69	0.009	0.80	0.33	0.54	0.33
Glucose strength <i>P</i> value	<0.001	0.03	0.99	0.08	0.20	<0.001
Interaction <i>P</i> value	<0.01	0.76	0.73	0.007	0.82	<0.01
95% CI for sodium effect ^b	(–5 to 8)	(2 to 13)	(–1 to 11)	(–10 to 3)	(–8.7 to 4.7)	(–10 to 3)

CI, confidence interval; PD, peritoneal dialysis; UF, ultrafiltration.
^aOn the basis of ^{125}I -albumin dilution corrected for dialysate sampling.
^bAveraged over all glucose strengths.

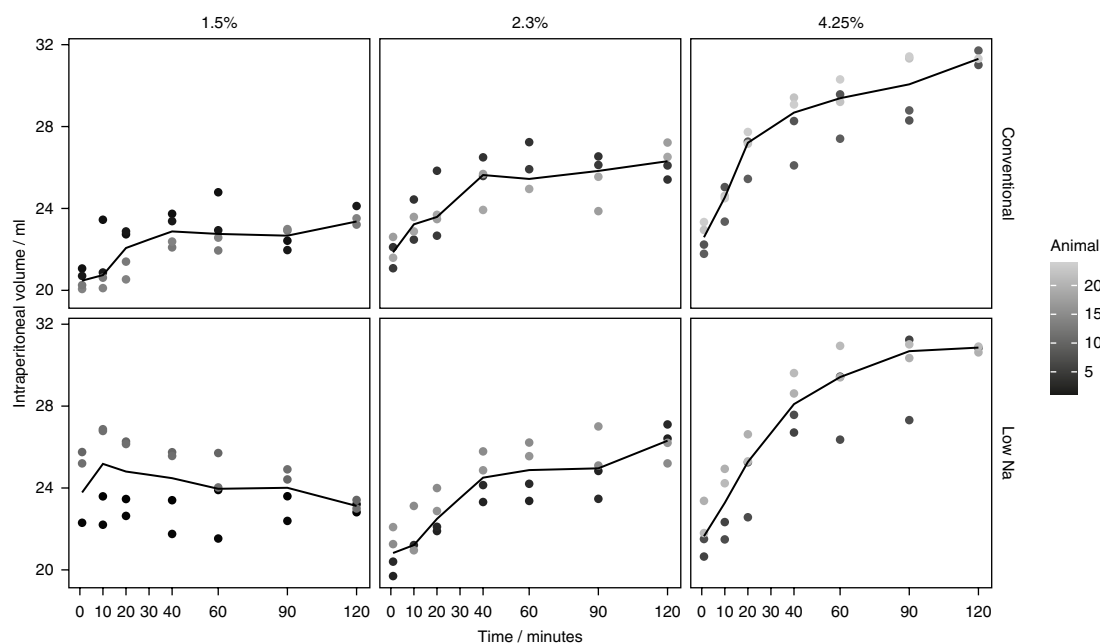


Figure 2. Intraperitoneal volume over time in rats ($n=24$) during experimental peritoneal dialysis with fluids of two different sodium concentrations (125 and 134 mmol/L) and three different glucose strengths (1.5%, 2.3%, and 4.25%). Volumes are presented in ml, and the time is in minutes after the start of dialysis. The lines are drawn between median volumes for each time point.

diagrams and linear regression were used to compare methods regarding UF and OCG.

Analysis of the clinical cohort had ethical approval from the Swedish Ethical Review Authority (Dnr: 2022-07325-02), as an extension of the earlier approved study where the data were collected (Dnr: 2012/327). All patients had given informed consent before collection of data.

Statistical Analysis

Data are displayed as median (interquartile range [IQR]) unless otherwise stated. Comparisons between groups were assessed using a nonparametric 2×2 ANOVA (ARTool), followed by *post hoc* contrasts when significant. Adjustment for multiple comparisons was performed using the Benjamini–Hochberg procedure when applicable. Data were imputed for one data point in the dataset (volume out) in animal 24 (4.25% glucose, conventional solution) by using the median (30.3, 30.6 and 31.0 ml) of the other three animals in the same treatment group (30.3, 30.6 and 31.0 ml). Activities for ^{51}Cr -EDTA and ^{125}I -albumin at 1 minute were more than one order of magnitude lower than that at 10 minutes and were replaced by estimating their value using an exponential model. Estimation methods for UF and OCG were compared with Bland–Altman analysis and linear regression in both experimental data and in the clinical cohort. t tests were used for hypothesis testing in Bland–Altman analyses. P values below 5% were considered significant. Calculations were performed using R for mac version 4.1.1.

Results

We constructed a new mathematical model to explain the kinetics of intraperitoneal sodium, which considers the Gibbs–Donnan effect and the proportion of plasma water,

while also compensating for free water transport and sodium sieving. The model describes the change in concentration in the intraperitoneal dialysate on basis of the dynamics of sodium in the dialysate.

Transport Parameters in Experimental PD

Electrolyte and water transport were analyzed in an established rat model of PD, which is summarized in Table 1 and Supplemental Tables S1 and S2. Dialysate sodium clearance was higher for low-sodium fluids than for conventional fluids, with an effect that was dependent on glucose strength ($P < 0.001$). At the same time, no association with dialysate sodium strength was found ($P = 0.69$). Sodium clearance for conventional fluids was around 80% of the UF rate for conventional fluids, but for low-sodium fluids, the sodium clearance closely matched the UF rate. Sodium removal per liter UF was higher for low-sodium fluids than conventional fluids ($P = 0.009$) and was lower for fluids with high glucose strength ($P = 0.03$). Dialysate clearance of ^{125}I -albumin was around five times higher than dialysate-to-plasma clearance. Dialysate-to-plasma clearances of ^{125}I -albumin had no association with glucose strength or dialysate sodium content, as opposed to most of the other parameters in Table 1. No association could be observed for D/P creatinine with either dialysate glucose strength ($P = 0.54$) or sodium concentration ($P = 0.20$). Intraperitoneal volume (IPV) curves are presented in Figure 2. UF is higher, and IPV increases more quickly with higher dialysate glucose content.

UF Is Accurately Predicted by the Corrected Sodium Dip in Experimental PD

UF was estimated in the rat model using the sodium dip and compared with RISA-based estimations of UF.

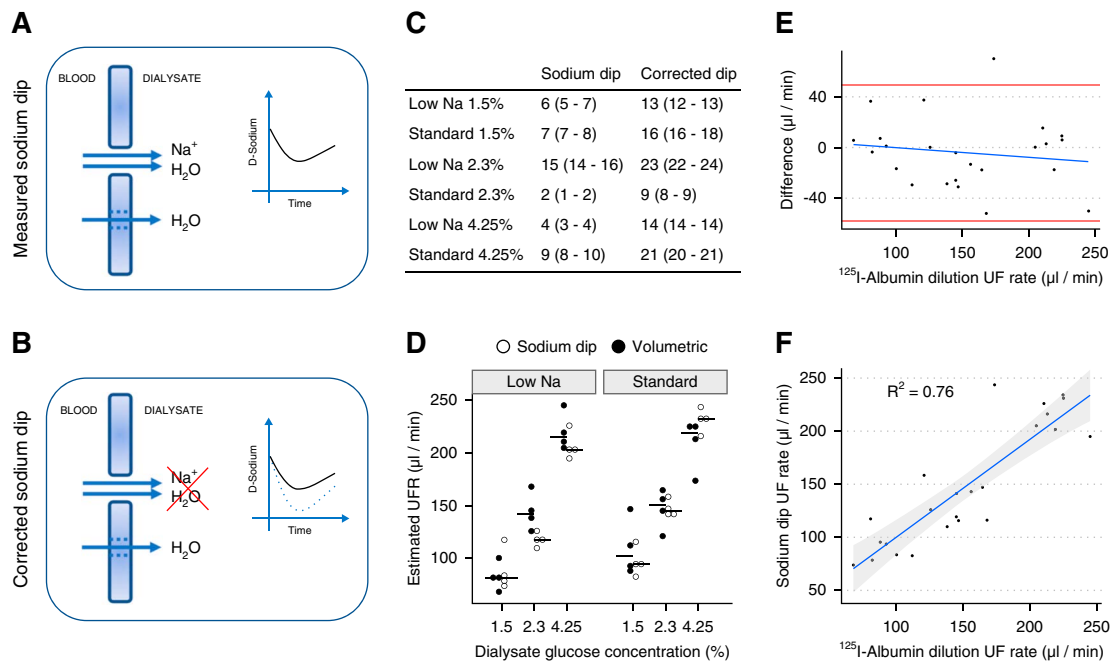


Figure 3. The fully corrected sodium dip and its use for estimating ultrafiltration rates in experimental PD. (A–B) Illustration of the theory behind sodium dip and corrected sodium dip. Sodium dip arises due to dilution because of solute free water transport across the peritoneum, due to water-specific channels (A). To properly assess water flux from intraperitoneal sodium dilution, a correction must be made with respect to influx of sodium bearing water into the peritoneum (B). (C) Measured sodium dip next to corrected sodium dip in experimental peritoneal dialysis in rats, $n=4$ in each group. (D) Ultrafiltration rate estimated from sodium dip alongside ultrafiltration estimated from corrected sodium dip. (E) Bland–Altman diagram depicting the mean of ultrafiltration rate measured using volumetry and dilution of ¹²⁵I-albumin and ultrafiltration rate estimated using sodium dip in each animal on the x axis and the difference between same measurements on the y axis. (F) Linear regression between ultrafiltration rate measured using volumetry and dilution of ¹²⁵I-albumin (x axis) and ultrafiltration rate estimated using sodium dip on (y axis) R^2 is 0.76. The gray area demarks the 95% confidence interval. The equation of the regression line is $y=7.4+0.92x$. UF, ultrafiltration.

During PD, dialysate sodium is diluted because of free water transport, giving rise to the sodium sieving phenomenon (Figure 3A). If there is no free water transport, there is no sodium dip. The corrected sodium dip is the sodium dip that would have occurred if there was no sodium influx into the peritoneal cavity from the circulation (Figure 3B). Because about half of UF is free-water transport, the relationship between the corrected (40 minutes) sodium dip ($Na_0 - Na_{corr}$) (Figure 3C) and UF can be approximated from the dilution of the IPV as follows.

$$UF \approx 2 \cdot IPV \frac{Na_0 - Na_{corr}}{Na_{corr}}$$

In an experimental setting, UF predicted using the corrected sodium dip closely matched the UF rate assessed from the dilution of ¹²⁵I-albumin at 40 minutes (Figure 3, D–F) for both sodium strengths (125 and 134 mmol/L) and for all three glucose strengths (1.5%, 2.3%, and 4.25%), with a mean difference of $-1.7 \mu\text{l/min}$ between methods in Bland–Altman analysis and R^2 of 0.76 in the linear regression. UF rate was much higher during the first 40 minutes of dialysis, than during the whole dwell (Table 1). The impact of our assumption of 50% free water transport was assessed by reanalyzing results assuming 40% and 60% instead, resulting in $R^2=0.76$

and median difference of $35 \mu\text{l/min}$ and $R^2=0.75$ and $-40 \mu\text{l/min}$, respectively.

Prediction of Osmotic Water Transport in Patients

The clinical cohort consisted of 21 PD patients (see Table 2 for baseline characteristics). Mean age in the clinical cohort was 72 years (SD: 12 years), and 38% were women ($n=8$), whereas 62% were men ($n=13$). Mean PD vintage was 13 months (range, 2–72 months). The median sodium dip was 9 mmol/L (IQR: 8–9 mmol/L). There was no significant difference between UF estimated from sodium dip which was 518 ml (IQR: 465–629) and UF estimated from volumetric measurements and albumin dilution which was 571 ml (IQR: 410–662). Linear regression shows a modest correlation between UF rates estimated using the two methods with an R^2 of 0.35 (Figure 4A). Bland–Altman analysis (Figure 4B) revealed a mean difference of 2 ml (95% confidence interval, -401 to 405), with a t test P value of 0.96. Data points seem spread symmetrically above and below the mean difference line, and there is no observable trend between x and y values. UF values from both volumetric and sodium-based measurements were then used to estimate OCG in the same clinical data according to Equation 2. Median sodium dip estimated OCG was $3.7 \mu\text{l/min per mm Hg}$ (IQR 3.1–4.7) compared with $3.5 \mu\text{l/min per mm Hg}$ (IQR 1.5–4.2) for the La Milia double mini-positron emission tomography method and $3.9 \mu\text{l/min/mm Hg}$

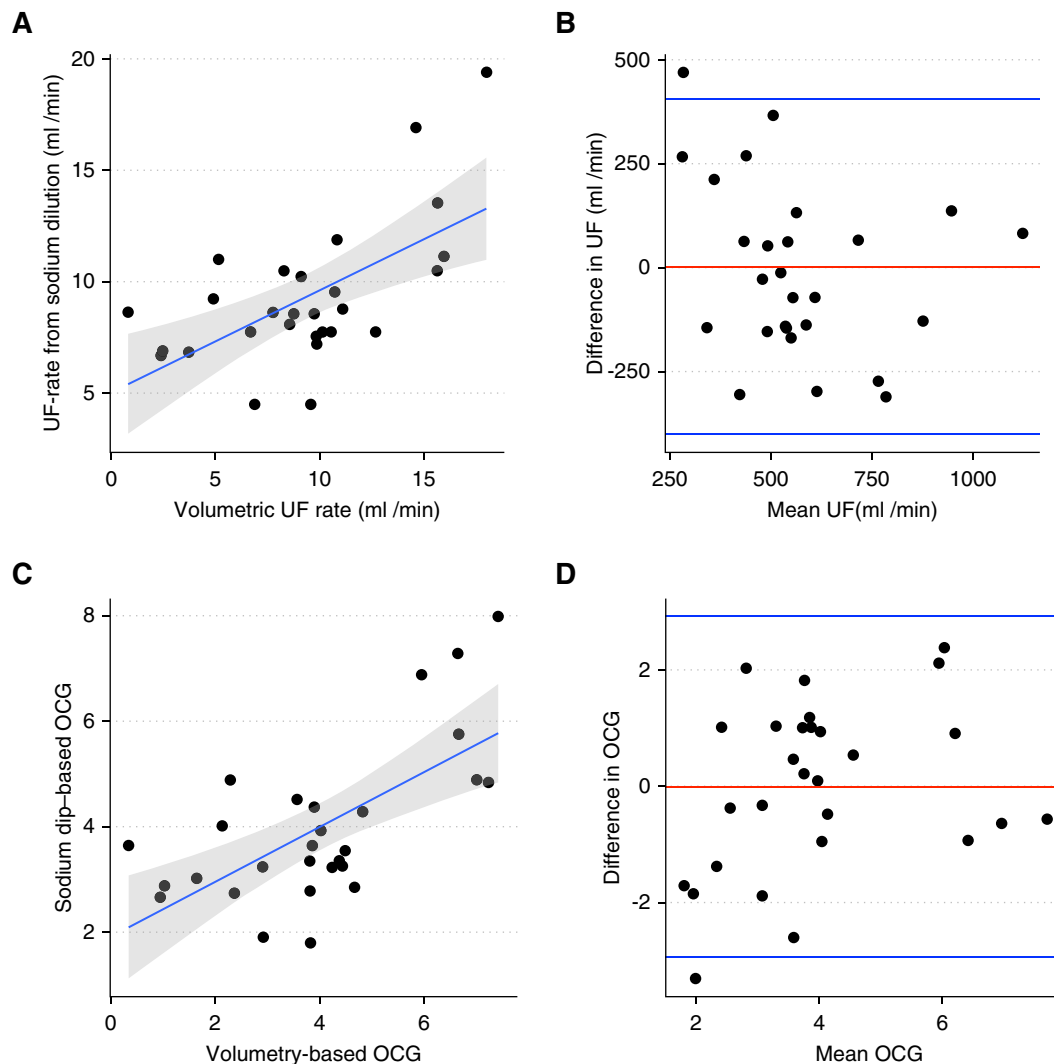


Figure 4. Analysis of ultrafiltration and osmotic conductance to glucose estimated from sodium dip versus ultrafiltration and osmotic conductance to glucose estimated from volumetry (corrected for residual volumes on the basis of albumin dilution, see also 8) in a cohort of 21 patients, with a total of 28 measurements. For estimations of ultrafiltration, the Bland–Altman diagram depicts the mean difference, which was 2 ml, with a *t* test *P* value of 0.96. The regression line is described by the function, $y = 5 + 0.46x$ and R^2 is 0.35. For estimations of osmotic conductance to glucose (bottom row), the Bland–Altman diagram depicts the mean difference of $-0.0076 \text{ nl min}^{-1} \text{ mm Hg}^{-1}$, with a *t* test *P* value of 0.98. The linear regression curve is described by the equation, $y = 1.92 + 0.52x$, with a Pearson *R* of 0.77. The gray areas depict the 95% confidence interval. OCG, osmotic conductance to glucose.

(IQR 2.8–4.7) for the single dwell method. Linear regression analysis showed a strong, positive correlation between sodium dip estimated OCG and single-dwell OCG (Pearson $r = 0.77$, $P < 0.001$) (Figure 4C). Similar to results for UF, points were symmetrically spread above and below mean difference. The mean difference between estimated OCG between the two methods of estimation was only $-0.008 \text{ L min}^{-1} \text{ mm Hg}^{-1}$ (95% confidence interval, -2.94 to 2.92), with a *t* test *P* value of 0.98 (Figure 4D).

Discussion

The fully corrected sodium dip, which takes into account both diffusive and convective processes, can be used to closely predict osmotic water transport across all glucose strengths both for standard and low-sodium fluids in an

experimental setting. Applied to clinical data, the same model for sodium dip can be used to predict UF in patients undergoing a 1-hour PD dwell with 4.25% glucose dialysis fluid. This is in line with findings in earlier studies¹⁵—but the concept is here extended to correct also for convective transport. Given the large variation in clinical UF data, the much smaller error of measurement in dialysate sodium concentrations implies that the corrected sodium dip will provide a much more accurate estimation of the UF rate in patients. However, to confirm this, clinical studies must be performed using a much more accurate marker than albumin to measure residual volumes. The sodium dip based UF rate was also used to accurately estimate OCG in patients. Martus *et al.*⁸ describe a method for estimating OCG, which builds on the double mini-positron emission tomography by La Milia *et al.* One of the key challenges in OCG estimation is

Table 2. Patient characteristics

Characteristics	Value
General characteristics	Mean (SD)
Age, yr	72 (12)
BMI, kg m ⁻²	25.2 (2.5)
PD vintage, mo (min-max)	13 (2-72)
Sex	n (%)
Men	8 (38)
Women	13 (62)
Primary kidney disease	n (%)
Glomerular disease	5 (24)
Diabetes kidney disease	3 (14)
Polycystic kidney disease	3 (14)
Chronic interstitial nephritis	2 (10)
Amyloidosis	1 (5)
Other	7 (33)
Comorbidities	n (%)
Hypertension	21 (100)
Diabetes mellitus	5 (24)
Congestive heart failure	7 (33)
Coronary heart disease	7 (33)
Blood chemistry	Mean (SD)
P-sodium, mmol/L	139 (2)
P-glucose, mmol/L	6.8 (1.2)
P-creatinine, μ mol/L ^a	611 (175)
P-urea, mmol/L ^b	15.3 (4.7)
S-albumin, g/L	33.4 (3.2)
Peritoneal dialysis parameters	Median (IQR)
Dialysate sodium dip, mmol/L	9 (8-10)

BMI, body mass index; IQR, interquartile range; PD, peritoneal dialysis.

^aTo convert a creatinine result in μ mol/L to mg/dl, divide the μ mol/L result by 88.5 (or multiply by 0.0113).

^bTo convert a urea result in mmol/L to a mg/dl, multiply the mmol/L result by 6.

the accurate estimation of UF, where the simple clinical measurement of drained minus instilled volume was shown to be inaccurate,⁹ forcing clinicians to resort to methods for estimating UF that are more time-consuming and expensive because the residual volume before and after the dwell must be quantified. By contrast, if used in clinical practice, the sodium-based method for UF and OCG estimation would only require a single dialysate sample for the measurement of glucose and sodium concentrations after the dwell. UF measurements on the basis of sodium dip can also be used to estimate OCG in available data on PD, where sodium and glucose concentrations are measured, but no precise UF measurement was made, thus enabling *post hoc* analysis of larger datasets with respect to OCG. Such an approach could be used to assess the correlation between sodium dip-estimated OCG and important clinical outcomes.

Our analyses of patient data, the large, symmetrical spread of data points on both sides of the mean difference indicates that there could be a large discrepancy between the two methods of UF and OCG estimation in individual cases. At the same time, conclusions regarding the consistency of measurements are difficult to draw because of the small number of repeated measurements in the same test patient. Therefore, performing an experiment with

repeated measurements would be the natural next step. At this stage, we can see that both OCG and UF are accurately estimated at group level, but at the given moment, conclusions cannot be drawn as to the precision of the method in individual patients.

The study of sodium transport in PD is complicated by several factors. The measurement itself of Na⁺ in fresh dialysis fluid or dialysate has several pitfalls, such as matrix effects (mainly glucose),¹¹ inappropriate correction for plasma water,¹⁹ and, for some instruments, large measurement errors. In addition, the plasma concentration of sodium cannot be used directly in calculations without taking into account the plasma water effect¹⁶ and the Gibbs-Donnan effect.¹⁷ In this study, earlier determined values for Gibbs-Donnan and plasma water effects work well in the three-pore model, predicting intraperitoneal sodium values accurately over time.

The present results also have some interesting findings related to the sodium removal per liter UF, which was very similar to plasma sodium for the 1.5% and 2.3% low-sodium fluid, but not 4.25% glucose low-sodium fluids. It is well known that dialytic sodium removal per liter water removed is low in PD.^{20,21} In hemodialysis, sodium removal is usually isonatric, with sodium clearance approximately equal to the UF rate, because of the lower concentration gradient between plasma and dialysate. This implies that sodium clearances in PD can be improved by using low-sodium fluids. Indeed, Nakamaya *et al.* obtained a hypernatric sodium removal of 348 mmol per L water removed using an ultra-low-sodium (98 mmol/L) 2.48% glucose dialysis fluid.²² Leyboldt *et al.* obtained very comparable results using a similar ultra-low-sodium solution (105 mmol/L).²³

The potential clinical advantages of increased sodium removal are relatively well studied. Davies and colleagues found that blood pressure, thirst, and volume status improved in patients treated with low-sodium fluids.²⁴ More recently, a randomized trial showed improved sodium removal in patients treated with a low-sodium solution (125 mmol/L) compared with a conventional sodium concentration (134 mmol/L).²⁵ However, despite improved blood pressure and sodium removal, patients treated with the low-sodium solution had approximately 25% lower residual kidney function at the end of the study period (25 weeks). In a very recent randomized trial, Davies *et al.* found that a once daily treatment using a low-sodium solution (112 mmol/L) resulted in more hypotensive episodes.²⁶ Taken together, several studies have been conducted on low-sodium fluids in PD, but no clear-cut clinical benefits have been delineated. Is overhydration the price to pay for hemodynamic stability and preserved residual renal function? Probably not, but sodium removal likely needs to be individualized to each patient.

There are several limitations in this study. In the experimental part, the number of animals per group was low meaning that the ability to detect anything but large effect sizes is limited. Furthermore, only a single acute treatment was studied which means that long-term effects are not detected. While sufficient in statistical power, the clinical cohort was also small, and some of the measurements had been conducted twice in the same patient, potentially skewing results. Finally, only male rats were included in the

experimental part of the study which may affect the generalizability of the findings. However, the retrospective analysis showed that experimental results could be extended to clinical data which included both male and female patients.

In summary, the sodium dip, compensated for free water transport and taking into account Gibbs–Donnan and plasma water effects, was successfully used to assess UF and OCG in both experimental dialysis in rats and in a patient cohort. Values for Gibbs–Donnan and plasma water effects are verified using three-pore model analysis. Sodium dip–based estimations have very good agreement with estimations on the basis of volumetry and albumin dilution on group level. Further study of intra-individual and interindividual variation in estimations are warranted.

Disclosures

J. Morelle reports the following—Consultancy: Alexion Pharmaceuticals, AstraZeneca, Bayer, GlaxoSmithKline, Sanofi-Genzyme; Research Funding: Alexion Pharmaceuticals, AstraZeneca, and Baxter Healthcare; Advisory or Leadership Role: Alexion Pharmaceuticals, AstraZeneca, Bayer, Sanofi-Genzyme, Versantis; Speakers Bureau: AstraZeneca, Baxter Healthcare, and Fresenius Medical Care; and Other Interests or Relationships: Funding from the National Fund for Scientific Research (FRS-FNRS, Brussels, Belgium), the Saint-Luc Foundation (Brussels, Belgium), and the Association pour l'Information et la Recherche sur les Maladies Rénales Génétiques (AIRG, Brussels, Belgium); travel grant from Sanofi-Genzyme. C.M. Oberg is one of the inventors of two pending patents filed by Gambro Lundia AB (Baxter; unrelated to this work). C.M. Oberg reports research grants (unrelated to this work) from Baxter Healthcare and Fresenius Medical Care and speaker's honoraria from Baxter Healthcare and Boehringer Ingelheim. C.M. Oberg reports a consultancy agreement with Baxter Healthcare and an advisory or leadership role with the Peritoneal Dialysis International editorial board. All remaining authors have nothing to disclose.

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Author Contributions

Conceptualization: Jakob Helman, Johann Morelle, Carl M. Öberg.

Formal analysis: Linn Andersson, Jakob Helman, Carl M. Öberg, Hedda Wahlgren.

Funding acquisition: Carl M. Öberg.

Investigation: Linn Andersson, Jakob Helman, Johann Morelle, Carl M. Öberg, Hedda Wahlgren.

Methodology: Carl M. Öberg.

Project administration: Carl M. Öberg.

Software: Jakob Helman, Carl M. Öberg.

Supervision: Carl M. Öberg.

Writing – original draft: Linn Andersson, Jakob Helman, Johann Morelle, Carl M. Öberg, Hedda Wahlgren.

Writing – review & editing: Linn Andersson, Jakob Helman, Johann Morelle, Carl M. Öberg, Hedda Wahlgren.

Data Sharing Statement

Original data created for the study are available in a Dryad persistent repository, see <https://doi.org/10.5061/dryad.gmsbcc2v0>.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/KN9/A426>.

[Dialysate to plasma clearance boundary value problem.](#)

[ISTAT-1 Calibration.](#)

[Three-pore model validation.](#)

Supplemental Figure 1. Three-pore model validation of Gibbs–Donnan effect and plasma water fraction. (A) Illustration of Gibbs–Donnan and plasma water effects. Large, negatively charged complexes, such as proteins, are abundant in blood plasma and scarce in intraperitoneal fluid, decreasing the fraction of plasma water to approximately 93%, and at the same time having a unilateral effect on the membrane potential across the peritoneal capillary walls, while having very low permeability across the peritoneum. (B) Table of diffusion capacities of sodium and chloride, calculated using the modified pore model, adjusting for Gibbs–Donnan and plasma water effects, alongside a more classic version of the pore model. (C) Na concentration on the y axis and time since the start of peritoneal dialysis on the x axis. Each diagram is based on data from experimental data for a specific dialysate ($n=4$ in each group). The black dots represent Na concentration modeled using the modified pore model and the red triangles represent measured concentrations in dialysate at time points 1 min, 40 mins, and 120 mins after start of dialysis.

Supplemental Table 1. Differences in sodium, chloride, total CO_2 , and erythrocyte volume fraction (before–after dialysis) during peritoneal dialysis in rats.

Supplemental Table 2. Diffusion capacities, chloride clearance, and UF rates during experimental peritoneal dialysis in rats.

[STROBE statement.](#)

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