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Distributed Modeling of Osmotic Fluid Flow during Single Exchange with Hypertonic Glucose Solution

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The aim of the study was to model fluid and solute peritoneal transport inside the tissue together with the kinetics in peritoneal cavity during single exchange with hypertonic glucose 3.86% solution. The distributed model of osmotic flow and glucose transport was formulated and applied for computer simulations assuming 1 cm width of tissue layer. The simulated kinetics of intraperitoneal volume and glucose concentration were in good agreement with clinical data. The predicted intratissue profiles of glucose concentration and hydrostatic pressure of the interstitial fluid demonstrated a restricted penetration of glucose (0.1 cm) and water (0.25 cm) into the interstitium at the end of dwell time, in agreement with animal data. The proposed model was able to describe correctly the basic kinetics of peritoneal dialysis as investigated in clinical studies and intratissue profiles known from animal studies.

K e y w o r d s: peritoneal dialysis, distributed model, osmotic flow

1. Introduction

The analysis of osmotic water flow from blood into the peritoneal cavity induced by high concentration of glucose (or another osmotic agent) is currently carried out using two methods: 1) a membrane model applied for the estimation of osmotic conductance of the barrier for peritoneal transport, or 2) a three pore model that allows for separation of the reflection coefficient from the hydraulic conductance [1–3]. These

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two methods proved to be useful in providing information about transport characteristics of various groups of patients on peritoneal dialysis. However, any realistic description of the anatomy of the peritoneal transport system should include the capillaries, which are the source of water flow to the cavity and are distributed within the tissue with the distance from the peritoneal surface [4]. Distributed modeling of solute transport yielded important insights into the solute transport mechanisms in the tissue [4–10], whereas distributed modeling of fluid flow has not been so successful yet. The first attempt to include distributed modeling of ultrafiltration flow yielded a prediction of negative hydrostatic pressure inside the tissue [11]. This prediction was later disproved in experimental peritoneal dialysis in rats [11, 12]. Another aspect of peritoneal fluid transport – absorption of dialysis fluid to the tissue – was also studied theoretically using distributed model [13, 14]. Many experimental studies provided information about solute concentration and hydrostatic pressure distribution during acute peritoneal transport studies in animals [12, 15–24]. However, in clinical practise it is impossible to asses the conditions in the subperitoneal tissue. The only available clinical data on patient transport status are gained via measurements of changes of intraperitoneal volume and solutes amount in the peritoneal cavity [2].

Recently a new distributed model of osmotic flow in the tissue was proposed and discussed theoretically [25–27]. Moreover, the simplified version of the model has been tested using experimental and clinical data [26]. The model predicted a high rate of fluid flow, as observed in clinical studies at the beginning of the dwell period with hypertonic glucose solution, and a non-negative hydrostatic pressure within the tissue [25, 26]. The obtained intratissue profiles were in agreement with results from experiments performed on rats; however, a more precise verification of this version of the model using clinical data was not performed yet. The boundary conditions for the model were kept constant at the peritoneal surface, i.e. the changes that occur in the peritoneal cavity during peritoneal dialysis were not taken into account. In the present study we extended the previous model by taking into account the changes in dialysate, while applying the same description of the transport in the tissue as previously [26]. The impact of water ultrafiltered into the cavity on the changes in the volume of dialysis fluid and intraperitoneal hydrostatic pressure has been analysed for single exchange with hypertonic glucose solution. Moreover, we took into account the decrease in intraperitoneal glucose concentration due to water dilution and its absorption from the peritoneal cavity, as observed clinically.

2. Mathematical Model

Infusion of hypertonic solution into the peritoneal cavity induces fluid and solutes exchange between the peritoneal cavity and the tissue layer that surrounds the peritoneal cavity. High concentration of glucose used as an osmotic agent causes water flow from blood through the tissue to the peritoneal cavity. This flow decreases with

the time due to diffusion of glucose to the tissue and blood. Moreover, water is also absorbed directly from the peritoneal cavity partly due to peripheral lymphatics and partly due to absorption to the tissue (because of the increased intraperitoneal hydrostatic pressure). According to experimental data there are two main transport barriers for the fluid and solutes transport in the tissue: interstitium and blood capillary wall. Those barriers as well as local lymphatic absorption of fluid and solute from the tissue have been taken into account, Fig. 1.

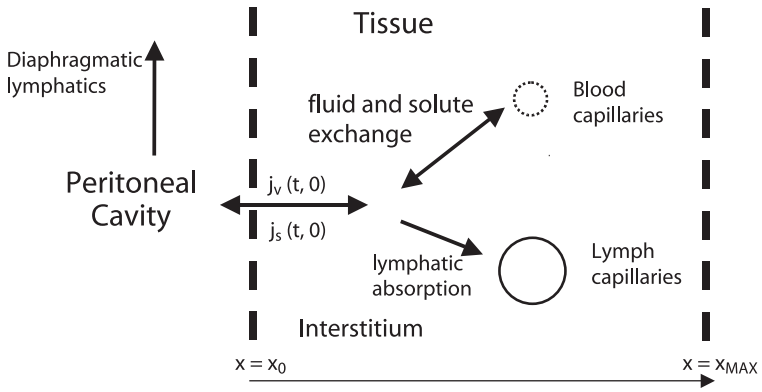

Fig. 1. Fluid and glucose transport pathways during peritoneal dialysis

The changes in fractional interstitial fluid void volume (fluid void volume, θ), are caused by the local volumetric flux across the tissue and the local exchange between the tissue, blood capillaries and lymphatics. This can be described as follows:

$$\frac{\partial \theta}{\partial t} = -\frac{\partial}{\partial x}\left(j_V\right) + q_V \tag{1}$$

where j_V – volumetric flux across the tissue, q_V – rate of the net local fluid flow to the tissue due to the fluid exchange between the blood, tissue and lymphatics, x – distance from the peritoneal surface through the tissue to the external tissue surface measured from x_0 to x_{MAX}, and t – dwell time [14, 28]. The volumetric flux across the tissue is generated by the hydrostatic and osmotic pressure gradient and is described by the following formula (the extended Darcy's law):

$$j_V = \theta K\left(-\frac{\partial P}{\partial x} + \sigma_{TG} RT \frac{\partial C_G}{\partial x}\right) \tag{2}$$

where $P = P(t, x)$ – local tissue pressure, $C_G = C_G(t, x)$ – local tissue glucose concentration, K – hydraulic permeability of the tissue, R – gas constant, T – temperature,

and σ_{TG} – Staverman reflection coefficient for glucose in the tissue [14, 25, 26]. Rate of the net fluid inflow to the tissue, q_V, depends on the local exchange between the blood and the tissue through the blood capillary wall and by the local tissue lymphatic absorption as follows [26–28]:

$$q_V = q_V(P) = L_p a\left(P_B - P - \sigma_{CG} RT\left(C_{GB} - C_G\right)\right) - q_L \tag{3}$$

where $L_p a$ – capillary wall hydraulic conductivity, P_B – hydrostatic blood capillary pressure, C_{GB} – glucose concentration in blood, σ_{CG} – Staverman reflection coefficient for glucose in the capillary wall, q_L – lymphatic absorption from the tissue. On the basis of experimental data, we assume also that the lymph flow is a function of interstitial pressure given by $q_L = q_{L0} + q_{L1}(P - P_0)$, where P_0 is the initial interstitial fluid hydrostatic pressure [13, 14]. Finally, according to the animal data, fluid void volume θ can be described as the following function of P [14, 28], see also Fig. 2:

$$\theta = \theta_{\min} + \frac{\theta_{\max} - \theta_{\min}}{1 + \left(\dfrac{\theta_{\max} - \theta_{\min}}{\theta_0 - \theta_{\min}} - 1\right) e^{-\beta(P - P_0)}} \tag{4}$$

where θ_{max} and θ_{min} are the maximal and minimal value of fluid void volume ratio, respectively, θ_0 is the interstitial fluid void volume for P_0, and β is the sensitivity of fluid volume ratio to increase in P. Therefore, combining equation (4) and equation (1) one can get the following equation for the changes in time of interstitial pressure as a function of t and x:

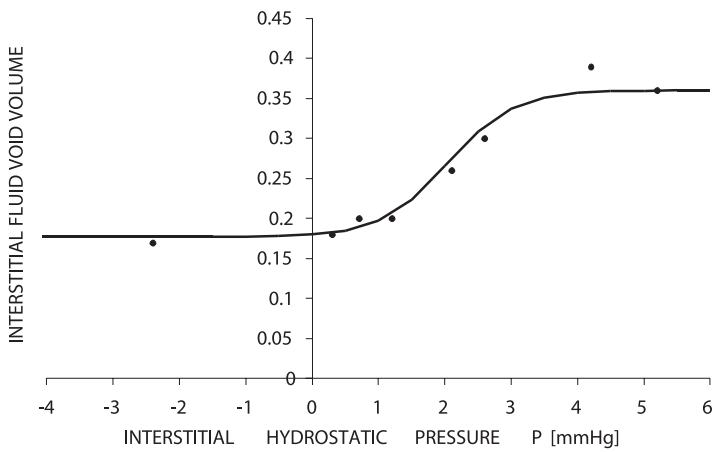

Fig. 2. Fractional interstitial fluid void volume, θ, as a function of interstitial pressure: dots – experimental data form [22], solid line – fitted function used in simulation given by equation (4)

$$\frac{\partial P}{\partial t}\cdot\frac{\partial \theta}{\partial P}=-\frac{\partial}{\partial x}\left(j_V\right)+q_V. \tag{5}$$

The local change in the glucose amount in the tissue depends on the local glucose flux across the tissue, j_G, and the rate of net glucose exchange between the tissue, blood and lymphatics, q_G, and is given by the following equation:

$$\frac{\partial\left(\theta C_G\right)}{\partial t}=-\frac{\partial}{\partial x}\left(j_G\right)+q_G \tag{6}$$

assuming that the glucose void volume is the same as the fluid void volume i.e. $\theta_G = \theta$ [8, 26, 28]. The glucose flux across the tissue is composed of a diffusive component (proportional to the glucose concentration gradient in the tissue) and a convective component (proportional to glucose concentration and volumetric flux):

$$j_G=-\theta D_G\frac{\partial C_G}{\partial x}+s_{TG}j_V C_G \tag{7}$$

where D_G – diffusivity of glucose in the interstitium and $S_{TG} = 1 - \sigma_{TG}$ – sieving coefficient of glucose in the tissue [8, 26, 28]. The density of glucose flux from blood to the tissue has a diffusive component (proportional to the difference between glucose concentration in blood and in the tissue) and a convective component (proportional to the density of the volumetric flux from blood to the tissue). Therefore, the rate of the net glucose flow to the tissue is equal to the density of glucose flux from blood to the tissue decreased by the lymphatic absorption of glucose from the tissue:

$$q_G=p_G a\left(C_{GB}-C_G\right)+s_{CG}q_V\left[\left(1-F_G\right)C_{GB}+C_G F_G\right]-q_L C_G \tag{8}$$

where $p_G a$ – diffusive permeability of total capillary surface area per unit tissue volume, $S_{CG} = 1 - \sigma_{CG}$ – sieving coefficient for glucose in the capillary wall, F_G – weighing factor [8, 26, 28]. A more detailed description of this model can be found elsewhere [8, 14, 26].

The ultrafiltration fluid flux to the peritoneal cavity, q_U, was defined as $q_U(t) = -j_V(t,0)$, i.e. the flux to the peritoneal cavity across the tissue surface ($x = 0$). The ultrafiltration flow, Q_U, was calculated as the ultrafiltration flux multiplied by the surface area of the contact between dialysis fluid and the tissue, A, $Q_U(t) = q_U(t)\cdot A$.

It is assumed that initially the interstitial hydrostatic pressure is zero, and glucose concentration in the tissue remains in equilibrium with its concentration in blood. Thus, $P(0,x) = P_0 = 0$ and $C_G(0,x) = C_{G0} = C_{GB}$ at $t = 0$. Moreover, it is assumed that at the peritoneal surface both, hydrostatic pressure and glucose concentration in the interstitial fluid are in equilibrium with dialysis fluid. It is also assumed

that there is no water and solute outflow through the other surface opposite to the peritoneal one, as in the abdominal wall muscle [14, 26, 28]. Therefore, boundary conditions are: $P(t,0) = P_D$ and $C_G(t,0) = C_{GD}$ at $x_0 = 0$, and $(\partial P/\partial x)\ (t, x_{MAX}) = 0$ and $(\partial C_G/\partial x)\ (t, x_{MAX}) = 0$ at $x_{MAX} = L$, for all t, where P_D and C_{GD} are hydrostatic pressure and glucose concentration in the peritoneal cavity, respectively, and L is the width of the tissue layer. It is assumed that blood parameters such as hydrostatic pressure, P_B, and plasma glucose concentration, C_{GB}, are constant during the simulated dwell time. On the contrary in the peritoneal cavity, both hydrostatic pressure P_D and glucose concentration, C_{GD}, are changing mainly due to changes in the intraperitoneal volume by the inflow of ultrafiltered water to the peritoneal cavity and due to glucose absorption to the tissue. The intraperitoneal volume, V_D, increases because of osmotic flow from the tissue through the peritoneal surface and decreases by the fluid absorption from the peritoneal cavity. The changes in the glucose amount in dialysate occur due to its absorption from the peritoneal cavity. The changes in the peritoneal dialysis fluid volume and glucose concentration can be described by a system of ordinary differential equations as follows:

$$\frac{dV_D}{dt} = -A \cdot j_V(t,0) - K_E \tag{9}$$

$$\frac{d(V_D C_{GD})}{dt} = -A \cdot j_G(t,0) - K_E C_{GD}(t) \tag{10}$$

where $j_G(t,0)$ and $j_V(t,0)$ are glucose flux and fluid flux through the peritoneal surface to the tissue, respectively, and K_E is the fluid absorption from the peritoneal cavity. The intraperitoneal pressure can be calculated from the intraperitoneal volume according to formula

$$P_D(t) = P_{D0} + \left(V_D(t) - V_{D0}\right)/490 \tag{11}$$

where P_{D0} and V_{D0} are pressure and volume values in the peritoneal cavity at $t = 0$ [29, 30].

Equations (5), (6), (9), and (10) for a system of two partial differential equations ((5) and (6)) for fluid and solute transport inside the tissue and two ordinary differential equations ((9) and (10)) for fluid and solute kinetic in the peritoneal dialysate. The transport equations in the tissue and kinetic equations for the peritoneal dialysate are coupled as follows: 1) the fluid and the solute flows into the peritoneal dialysate (see equations (9) and (10)) are determined by the transport inside the tissue, equations (2) and (7), and 2) the boundary values of P and C_G at the peritoneal surface for equation inside the tissue (equations (5) and (6)) change with the dwell time according to the equations for peritoneal dialysate, equations (9) – (11).

3. Computer Simulations

The system of (2)–(11) equations was solved numerically using Matlab 7.9 software for the following values of parameters: $K = 5.14 \cdot 10^{-5}$ [cm^{2}min^{-1}mmHg^{-1}], $D_G = 11.7 \cdot 10^{-5}$ [cm^{2}min^{-1}], $L_p a = 14.8 \cdot 10^{-5}$ [mLmin^{-1}mmHg^{-1}g^{-1}], $p_G a = 7.14 \cdot 10^{-2}$ [mL$\cdot$min^{-1}g^{-1}], $\sigma_{CG} = 0.61$, $C_G = 6$ [mmol$\cdot$L^{-1}], $F_G = 0.5$, $P_0 = 0$ [mmHg], $P_B = 22.88$ [mmHg], $L = 1$ [cm] (e.g. human abdominal wall muscle), $RT = 18 \cdot 10^3$ [mmHg$\cdot$mmol^{-1}mL], $A = 5000$ [cm^2], $q_{L0} = 0.0034$ [1/min], $q_{L1} = 0.00204$ [1/(min mmHg)] [25, 31]. The parameter σ_{TG} was 0.0048 to obtain values of P close to zero (between –0.5 and 0.5 [mmHg]) deep inside the tissue [25]. The parameters that describe function θ, equation (4), were given in [14]. The initial values of variables in the peritoneal cavity were: $C_{GD} = 180$ [mmol$\cdot$L^{-1}] (representing glucose 3.86% in dialysis fluid), $P_{D0} = 9$ [mmHg], $V_{D0} = 2050$ [mL], and $K_E = 1.5$ [mL/min] [3, 25, 29]. The simulations were carried out for a typical single six-hour peritoneal dwell time.

Infusion of hypertonic solution into the peritoneal cavity causes, during the initial minutes of fluid exchange, slight transient dehydration of tissue (represented in Figures 3 and 4, left panel, by the negative hydrostatic pressure and on the right

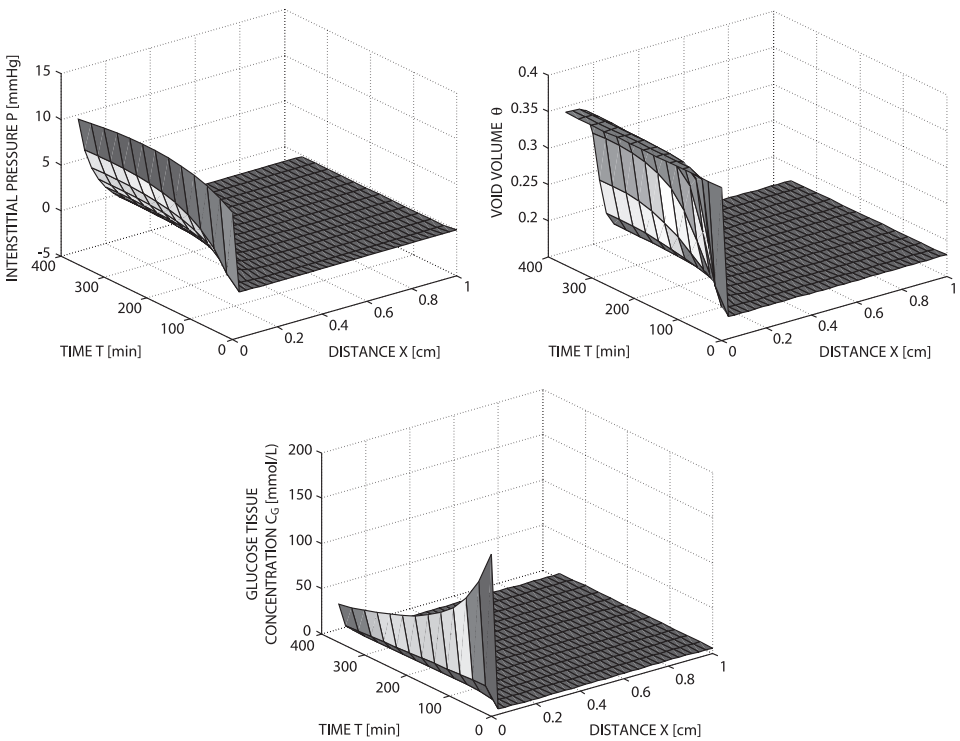

Fig. 3. Hydrostatic pressure of interstitial fluid, P, eq. (5) (left upper panel), interstitial fluid void volume, θ, eq. (4) (right upper panel), and glucose concentration in interstitial fluid, C_G, eq. (6) (bottom panel), as functions of distance from the peritoneal cavity, x, and dwell time, t

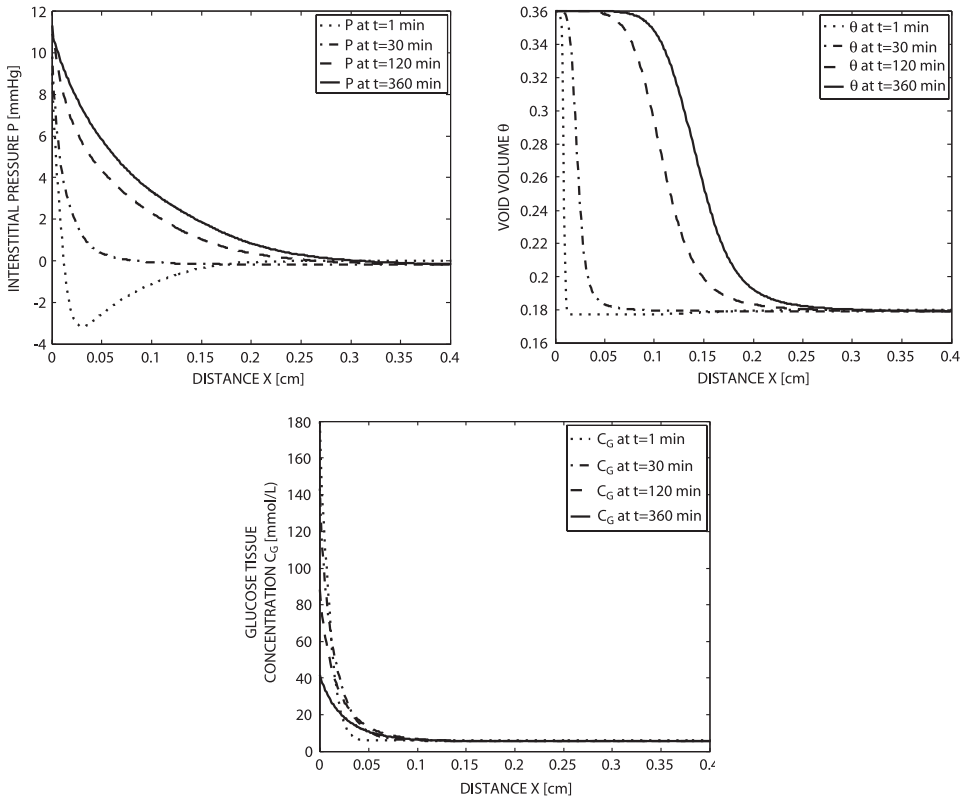

Fig. 4. Hydrostatic pressure of interstitial fluid, P, eq. (5) (left upper panel), interstitial fluid void volume, θ, eq. (4) (right upper panel), and glucose concentration in interstitial fluid, C_G, eq. (6) (bottom panel) at t = 1, 60, 120, and 360 min. as a function of distance from the peritoneal cavity, x

panel, by the lower than physiological ($\theta < 0.18$) values of the void volume), when water is suddenly pulled out of the tissue by high osmotic pressure at the peritoneal surface. The increase in interstitial hydrostatic pressure and tissue hydration can be observed in the tissue layer close to the peritoneal cavity (about 2.5 [mm] from the peritoneal surface, Figures 3 and 4) during next minutes and hours whereas the hydration of deeper tissue layers remains unchanged. The water flow into the peritoneal cavity decreases during the dwell time from 17 to –2.5 [mL/min]. Thus, at the end of the peritoneal exchange the reabsorption of water from the peritoneal cavity occurs at rate of 2.5 [mL/min]. Inflow of water into the peritoneal cavity increases dialysis fluid volume and interstitial pressure (Fig. 3). Glucose diffuses from the peritoneal cavity into the tissue causing increase of glucose concentration in a thin layer of the tissue close to the peritoneal cavity of the width less than 0.5 [mm] (Figures 3 and 4). Glucose concentration in peritoneal dialysate decreases from 180 [mmol/L] to about 40 [mmol/L] because of its fast diffusion to the tissue and blood (Fig. 5).

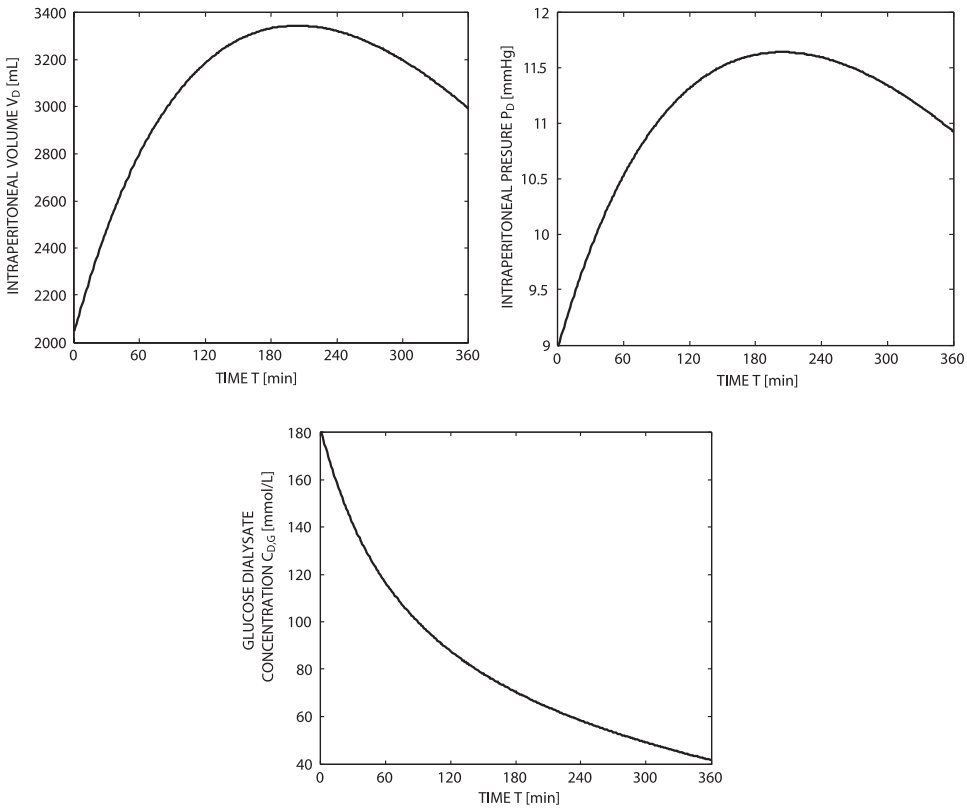

Fig. 5. Intraperitoneal volume, V_D, (left, upper panel), intraperitoneal hydrostatic pressure, P_D, (right, upper panel), and glucose concentration in dialysis fluid, C_{DG}, (bottom panel) as function of dwell time t

4. Discussion

Despite its relative simplicity, the presented here model of osmotic fluid transport and diffusive – convective glucose transport, can correctly describe a single six-hour exchange with hypertonic glucose solution. The only study which addressed clinical peritoneal dialysis, published previously by Seames et al., failed to predict correctly the intratissue hydrostatic profiles [11, 12]. The basic difference between that and our approach consists in the assumed characteristic of the tissue osmotic barrier. Seames et al. assumed that the osmotic barrier in the tissue is the mesothelial layer on the tissue surface with characteristics similar to those for endothelium [11]. In contrast, a distributed osmotic barrier in the interstitium with a rather low osmotic reflection coefficient is attributed in our model. Other studies that dealt with the description of both peritoneal dialysis kinetics and intratissue profiles did not addressed the problem of osmotic flow and were applied only for the analysis of animal experiments [5, 6].

Positive, decreasing interstitial pressure profiles, the tissue hydration, and the glucose concentration profiles in the tissue are in agreement with experimental data. Similar profiles were observed previously in computer simulations and animal experiments [12, 25, 26]. Transient negative hydrostatic pressure in the interstitial fluid was found in our computer simulations only during initial minutes of the peritoneal dwell (Figures 3 and 4). It was caused by a sudden change in the conditions at the tissue surface during the initiation of computer simulations; it's not likely that such fast change occurs also in real conditions. The initial value of ultrafiltration (around 17 [mL/min]) remains in agreement with clinical investigations [3]. The initial increase of intraperitoneal volume from 2050 [mL] to about 3350 [mL] with the peak between third and fourth hour of peritoneal exchange as well as its later decrease to 3000 [mL] is accompanied by the changes in the interstitial pressure from the 9 [mmHg] through 11.5 to 11 [mmHg] after six-hour exchange. Similar changes in dialysate volume with maximal value 3200 [mL] obtained at 197 minute and final volume around 3 [L] were observed clinically [3, 32]. According to our simulation, glucose concentration in dialysate decreases during 6 hour exchange with hypertonic glucose solution from 180 [mmol/L] to 40 [mmol/L]. Similar decrease to about 30% of the initial value, was previously observed in patients using hypertonic glucose solution [3].

The obtained results are promising. The presented model, despite its simplicity, is able to describe clinical data but at the cost of inflated level of lymphatic absorption at the steady state. The assumed level of q_{L0} is 0.0034 [1/min], whereas the reported values of lymphatic absorption from the tissue are of order magnitude lower and remain close to 0.0003 [1/min] assuming total lymph flow around 2 [mL/min] and average man weight 70 [kg]. Further improvements of the presented model such as taking into account the oncotic pressure difference across the capillary wall as well as the transport of other small solutes of clinical interest, as urea, creatinine and sodium, may result in more realistic values of tissue lymphatic absorption. Another possible approximation is to assume that the Starling forces, which include both hydrostatic and osmotic pressure differences across the capillary wall, and lymphatic absorption are wrongly balanced (as in the physiological steady state), and take into account only glucose osmotic pressure difference across the capillary wall; this approach was explored for the analysis of the initial peritoneal ultrafiltration rate in [26].

In summary, the extended version of the distributed model that combines modeling of the intratissue transport phenomena with kinetics of changes in the peritoneal cavity provided a good qualitative description of both processes. It demonstrated the usefulness of the distributed model for the description of clinical peritoneal dialysis.

Acknowledgment

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