Experimental and clinical studies on peritoneal physiology and morphology during chronic peritoneal dialysis
Zweers, M.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
The standard peritoneal permeability analysis in the rabbit: a longitudinal model for peritoneal dialysis

MM Zweers¹, CE Douma¹, DR de Waart², AB van der Wardt³, MM Ho-dac-Pannekeet¹, RT Krediet¹, DG Struijk¹,4

¹Departments of Nephrology and ²Clinical Chemistry, Academic Medical Center Amsterdam, ³Communal Animal Institute Amsterdam and ⁴Foundation for Home-dialysis Midden-West Nederland, Utrecht, The Netherlands

Perit Dial Int 1999;19:56-64
Abstract
An experimental peritoneal dialysis model in rabbits was developed to investigate peritoneal transport characteristics during a longitudinal follow-up and to assess normal values of these peritoneal transport parameters.

Peritoneal transport parameters were determined in conscious, unrestrained rabbits by standard peritoneal permeability analysis adjusted for rabbits (SPAR). In this test a 1-hour dwell with 3.86% glucose dialysate was used. Dextran 70 (1 g/L) was added to the dialysate, to allow calculation of fluid kinetics. Dialysate samples were taken before, 10 and 40 minutes after instillation and at the end of the dwell. Blood was drawn at the end of the dwell. Eighteen female New Zealand White rabbits (2565 g) were included for catheter implantation. SPARs were performed in fifteen animals, the other three were excluded due to complications. The mass transfer area coefficients (MTAC) of the low molecular weight solute urea and creatinine (MTACu,cr) were calculated. The clearances of albumin (Clalb) and IgG (ClIgG), glucose absorption and fluid transport were computed. Coefficients of intra individual variation (Vc) were calculated for these parameters.

The main complications were catheter obstruction and/or dislocation, 5 rabbits underwent uncomplicated PD during a 4 week period. Fifteen SPARs in 15 stable rabbits were performed and analyzed to obtain normal values. Means and standard deviations of the transport parameters were: MTACu 2.24 ± 0.57 mL/min, MTACcr 1.61 ± 0.30 mL/min, Clalb 52.9 ± 17.2 μL/min, ClIgG 44.5 ± 22.9 μL/min. The transcapillary ultrafiltration rate (TCUFR) was 0.66 ± 0.13 mL/min and the lymphatic absorption rate 0.47 ± 0.26 mL/min. The parameters of solute transport were upscaled to those in humans using two different methods. MTACs of low molecular weight solutes in rabbits and patients were in the same order of magnitude, but the clearance of albumin was approximately four times higher in rabbits than in patients, and that of IgG eight times. In all rabbits sieving of sodium was observed. The D/P of sodium decreased to a minimum at 40 minutes (p<0.003 versus the initial value), followed by a rise to 60 minutes. The minimal value was 0.884 ± 0.002. The coefficients of variation calculated on 7 rabbits that underwent 2 or more SPARs, were similar to those assessed from the patient data. This indicates stability of the model and reproducibility of the SPAR.

The conscious rabbit model for peritoneal dialysis can be used for repeated studies on peritoneal transport.

Introduction
Most models of peritoneal dialysis in rabbits have focussed on interventions in peritoneal transport through experiments during short-term peritoneal dialysis in anesthetized animals [1-4]. In the limited number of longitudinal rabbit models, emphasis was mainly on clinical parameters and histopathological changes [5-9]. A uremic model obtained by partial nephrectomy has been reported [10], but mortality and morbidity were substantial in these uremic animals. The aim of this study was to develop a longitudinal, non-omentectomized, non-nephrectomized model in an conscious and unrestrained rabbit. A model in which fluid and
solute transport across the peritoneal membrane could be investigated by applying a standardized analysis, as in CAPD patients.

The model was evaluated using conventional glucose-based dialysis solutions and, subsequent to the appropriate scaling, the results were compared with clinical investigations of peritoneal membrane transport parameters in CAPD patients [11].

Materials and methods

Rabbits
Specified pathogen free female New Zealand White rabbits (n=18), obtained from Broekman Institute (Zomeren, The Netherlands) were included in this study. The rabbits were housed solitarily in regular cages under controlled conditions (temperature 19° ± 1°C, relative humidity 50 ± 5%, 12/12 hour light/dark cycle) and fed standard chow (Hope-Farms, Woerden, The Netherlands), radiated hay (BMI, Helmond, The Netherlands) and water ad libitum. These controlled conditions were maintained throughout the period of investigation. All rabbits acclimatized for at least one week after catheter implantation. Body weight and temperature were measured every day during the experimental interval. Mean body weight at the day of the catheter implantation was 2565 ± 107 g (mean ± SD) and mean temperature during the trial 39.6° ± 0.2°C. Two out of the three following events were reason to suspect peritonitis and to terminate the experiment: weight loss over 5% in 5 days, body temperature exceeding 40.2°C, a turbid effluent with or without a positive Gram's stain. Peritonitis was not treated. Occlusion of the catheter or chronic subcutaneous leakage were also reason to sacrifice the rabbit.

Catheter implantation
The rabbits were anesthetized with 5 mg/kg body weight xylazine i.m. and 35 mg/kg body weight ketamine i.m. The abdominal and neck fur was clipped and subsequently iodined. A coiled silastic catheter with two loose dacron cuffs (Coil-Cath™, Accurate Surgical Instruments Corporation, Toronto Canada) was inserted via a small medio-lateral incision in the left flank, just below the first rib, using a stylet. The coil was positioned in Douglas pouch. The first cuff was attached to the catheter (Medical adhesive, Fa. Biotronik, Veenendaal, The Netherlands) just outside the peritoneal cavity. The external part of the catheter was tunneled subcutaneously to the neck, exteriorized between the ears and sealed with a titanium adaptor and a plastic cap (Baxter Healthcare Co., Deerfield IL, USA). The second cuff was secured to the catheter approximately 1.5 cm below the exit-site. Catheter length was adjusted for each rabbit. The implantation procedure was performed under strict aseptic conditions.

Dialysis
The catheter was flushed daily with 2.5 mL 5 IU/mL heparin in 0.9% NaCl for 7 days, following the operation, to prevent obstruction during recovery. Thereafter peritoneal dialysis was performed once a day with commercially available dialysis solution (Dianea®*, Baxter Healthcare S.A., Ireland), containing 1.36% glucose. The dialysis procedure consisted of a rapid exchange of 40 mL/kg body
weight with 1.36% glucose containing dialysate, preheated to 37°C. The drainage was followed by instillation of 40 mL/kg body weight dialysate minus the residual volume, i.e. the previously instilled volume minus the drained volume. The catheter was then filled with 5 mL 5 IU/mL heparin in 0.9% NaCl to avoid overnight fibrin formation in the catheter coil. The instilled dialysate was left to be absorbed overnight. In- and outflow were accomplished by gravity. In some cases, the onset of outflow had to be initiated by gentle massage of the abdomen of the rabbit.

**Standard peritoneal permeability analysis in the rabbit**
The standard peritoneal permeability analysis in the rabbit (SPAR) is a modification of the human standard peritoneal permeability analysis (SPA) described by Pannekeet et al. [11]. The SPAR was performed during a 1-hour dwell with 40 mL per kilogram body weight of 3.86% glucose containing dialysate. Dextran 70, 1 g/L dialysate, (Macrodex, NPBI, Emmer-Compascuum, The Netherlands or Hyskon®, Medisan Pharmaceuticals AB, Uppsala, Sweden), was added to each test bag as a volume marker, to allow calculation of fluid kinetics [12]. The procedure included rinsing of the peritoneal cavity with 50 mL of the test solution prior and subsequent to the test to avoid possible effects of a residual volume preceding the test, and to calculate the residual volume after the experiment. Dialysate samples were taken before instillation of the test solution and 10, 40 and 60 minutes after completion of inflow. Blood was drawn at the end of the dwell from the ear vein under light sedation with etomidate (0.25 mL/kg body weight i.m.). The first SPAR was performed after one week of stable peritoneal dialysis. The protocol was approved by the Committee of Animal Ethics of the University of Amsterdam.

**Assays**
Total dextran was determined by high performance liquid chromatography [13]. Sodium concentrations were measured by an ion selective electrode on a automated analyzer (Hitachi H747, Boehringer Mannheim, Germany). Urea and creatinine were determined with enzymatic methods. Urea was measured on the before mentioned automated analyzer and creatinine was determined with the enzymatic PAP method on a Hitachi H911 automated analyzer (Boehringer, Mannheim, Germany). The glucose concentration was assessed by glucose oxidase-peroxidase assay (SMA II, Technicon, Terrytown, NJ, USA). Enzymatic methods for the measurement of creatinine are influenced by high glucose concentrations [14,15]. For the method used in our laboratory, the following correction factor (cF) was determined: $cF = -3.10^{-4} [\text{gluc}]^2 + 0.11 [\text{gluc}] + 105$, in which [gluc] is the glucose concentration of the dialysate. Albumin was measured with the bromocresol green (BCG) method. In 13 experiments performed in 3 different rabbits, the results of this method were compared to albumin measurements using bromocresol purple (BCP). IgG was measured with a peroxidase sandwich enzyme-linked immuno assay. ELISA plates (Maxisorp immunoplate, NUNC, Roskilde, Denmark) were coated with IgG goat anti-rabbit/7S antibody (Nordic Immunology, Tilburg, The Netherlands). Horseradish peroxidase labeled goat anti-rabbit IgG (H+L) was used as conjugate (Nordic Immunology, Tilburg, The Netherlands) and o-phenylenediamine dihydro-
chloride (Sigma, St Louis, MO, USA) as substrate. The reaction was stopped by the addition of 2M H$_2$SO$_4$ to each well. Absorbance was read at 490 nm against a buffer blank and chromatographically purified rabbit IgG (Nordic Immunology, Tilburg, The Netherlands) was applied as standard.

**Calculations**
Peritoneal fluid kinetics and solute transport parameters were calculated as described previously [11,12]. In brief, transcapillary ultrafiltration increases the intraperitoneal volume. Fluid loss from the peritoneal cavity is assumed to occur by backfiltration and uptake in the lymphatic system. The resultant of these is the net ultrafiltration. The transcapillary ultrafiltration was calculated as the dilution of dextran 70. The transcapillary ultrafiltration rate was determined by dividing the transcapillary ultrafiltration by the dwell time. The convective disappearance of the volume marker from the peritoneal cavity can be used as an indirect method to quantify the contribution of the peritoneal lymphatics in the absorption of fluid from the peritoneal cavity [16]. These calculations include all pathways of uptake into the lymphatic system, both interstitial and subdiaphragmatic. The change in intraperitoneal volume during the dwell can be calculated from the dilution of the volume marker after correction for incomplete recovery. The net ultrafiltration rate is defined as the change in intraperitoneal volume divided by the dwell time.

The mass transfer area coefficient (MTAC) represents the maximal theoretical diffusive clearance of a solute at $t=0$, before transport has actually started. It depends on the effective vascular peritoneal surface area. The MTAC of the low molecular weight solutes urea and creatinine were calculated according to Waniek et al. [17,18] with a modification for the 60 minute dwell used for our rabbit model. The solute concentration in plasma ($P$) was expressed per volume of plasma water ($18$). The following equation was used:

$$\text{MTAC (mL/min)} = \frac{V_{10}}{t} \ln \frac{V_{10}^{0.5}(P-D_{10})}{V_{t}^{0.5}(P-D_{t})}$$

in which $V_{10}$ is the intraperitoneal volume at time $t=10$, $D_{10}$ the dialysate concentration at time $t=10$ min, $V_t$ and $D_t$ are these parameters at time $t=60$ min. $V$ represents the mean intraperitoneal volume, calculated as the area under the intraperitoneal volume versus time curve, divided by the dwell time. The application of the correction factor 0.5 as the exponent of the intraperitoneal volume at time $t=10$ min and time $t=60$ min corrects for convective transport [17]. The glucose absorption was estimated as the difference between the instilled and the recovered amount of glucose, relative to the amount of glucose instilled. The clearances of albumin and IgG were calculated according to the equation: $\text{Cl (mL/min)} = \frac{(D.V)}{(P.t)}$, in which $\text{Cl}$ is the clearance, $D$ is the dialysate concentration, $V$ is the dialysate volume at the end of the dwell, $P$ represents the plasma concentration and $t$ is the dwell time. The results were compared with those obtained in CAPD patients. Therefore, the MTACs of urea and creatinine and the clearances of albumin and IgG were also expressed per
Table 1. Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>0-2 weeks</th>
<th>2-4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>obstruction/dislocation</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>sc leakage</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>peritonitis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>exit-site/tunnel infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>diarrhea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>paralysis lower legs</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Early complications, 0-2 weeks after catheter implantation, and late complications, 2-4 weeks after catheter implantation. *: complications considered to be caused by inexperience.

1.73 m² body surface area and per 70 kg body weight. Upscaling to 1.73 m² was done by dividing the calculated values by 0.23, which is the mean body surface area of rabbits with a mean body weight of 2.6 kg [19,20] and subsequent multiplication with 1.73, method 1. The other approach is scaling to body weight by dividing 70 kg, mean body weight of a patient, by the rabbit body weight taken to the power 0.667 [20], method 2.

Statistical analysis
The data are expressed as mean values and standard deviations (SD) of the measurements and calculations. Student's t-test for paired data was applied to assess the differences in the rabbit D/PNa. The agreement of the solute and fluid transport parameters between rabbits and CAPD patients were investigated by Student's t-test for unpaired data. Bland and Altman analysis was used to compare the methods for the determination of creatinine and albumin. Correlations were calculated using the method of least squares [21]. The intra-individual coefficients of variation (Vc) of all rabbits as a group were determined as the over-all standard deviation divided by the mean of the total number of experiments (m) and multiplied by 100. The over-all standard deviation was defined as the square root of the mean of the squares of the standard deviations of each experiment. The following equation was applied, in which n represents the total number of experiments:

\[
Vc = \frac{\sqrt{\frac{SD_1^2 + SD_2^2 + \ldots + SD_n^2}{n}}}{m} \times 100
\]

Results
Model
Peritoneal catheters were implanted in 18 rabbits. Three rabbits were excluded for peritoneal permeability analysis and sacrificed within 2 weeks after catheter implantation. Two of them had peritonitis in combination with a tunnel infection and the other had catheter dysfunction. Early complications were defined as the complications encountered during the first two weeks after catheter implantation. These were exit-site infection (n=2), peritonitis (n=2),
Chapter 1.1

Table 2. Peritoneal transport parameters in 15 rabbits and 40 stable CAPD patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rabbits</th>
<th>CAPD pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>dwell time (min)</td>
<td>60</td>
<td>240</td>
</tr>
<tr>
<td>glucose concentration (%)</td>
<td>3.86</td>
<td>1.36</td>
</tr>
<tr>
<td>instilled volume</td>
<td>40 mL/kg</td>
<td>2 L</td>
</tr>
</tbody>
</table>

**Solute transport**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method 1</th>
<th>Method 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTAC&lt;sub&gt;urea&lt;/sub&gt; (mL/min)</td>
<td>16.8 (4.3)</td>
<td>20.3 (5.4)</td>
</tr>
<tr>
<td>MTAC&lt;sub&gt;cr&lt;/sub&gt; (mL/min)</td>
<td>12.2 (2.2)</td>
<td>14.7 (3.0)</td>
</tr>
<tr>
<td>glucose absorption (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59 (8)</td>
<td>61 (9)</td>
</tr>
<tr>
<td>clearance albumin (µL/min)</td>
<td>398 (129)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>482 (170)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>clearance IgG (µL/min)</td>
<td>335 (173)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>408 (226)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Fluid transport**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method 1</th>
<th>Method 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELAR (mL/min)</td>
<td>3.40 (1.98)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4.60 (2.22)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>TCUFR (mL/min)</td>
<td>4.95 (1.00)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5.98 (1.26)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>residual volume (%)&lt;sup&gt;c&lt;/sup&gt;&lt;sup&gt;g&lt;/sup&gt;</td>
<td>6.3 (4.5)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 (4.2)</td>
</tr>
</tbody>
</table>

Parameters, mean (SD), were obtained by standardized peritoneal permeability analyses in rabbits and stable CAPD patients (pts). 

- Method 1: upscaled to 1.73 m².
- Method 2: upscaled to 70 kg body weight, MTAC<sub>cr</sub>: mass transfer area coefficient of creatinine, ELAR: effective lymphatic absorption rate, TCUFR: transcapillary ultrafiltration rate, 
  - <sup>c</sup>: p<0.005, <sup>d</sup>: p<0.0003 significantly different from the values in patients, 
  - <sup>f</sup>: no upscaling applied, <sup>g</sup>: percentage of the instilled volume.

Subcutaneous leakage (n=1) and catheter dysfunction caused by dislocation (n=1). Late complications are those occurring during the dialysis period. They consisted mainly of catheter obstruction, or dysfunction of the catheter caused by dislocation of the coil (n=8) (Table 1). In a pilot experiment the instilled volume was increased to 45 mL/kg body weight. This however caused distress and subcutaneous leakage at the position of the extraperitoneal cuff. The setup of the model was to perform 3 standard peritoneal permeability analyses per week in each rabbit with a maximum of 10, subsequent to one week of stable peritoneal dialysis. At least one of the 3 SPARs was an experiment without drug intervention, a control SPAR. The SPARs with drug interventions will be reported in separate papers. A total of 67 peritoneal permeability analyses were performed in 15 rabbits, 30 of which were control experiments. Five out of 15 rabbits underwent 7 or more SPARs during at least four weeks of uncomplicated peritoneal dialysis.

**Solute transport**

The 15 first SPARs without drug intervention, performed in 15 rabbits, were analyzed to obtain baseline values. The mean value of the MTAC of urea was 2.24 ± 0.57 mL/min, the MTAC of creatinine with correction for overestimation by high glucose concentrations was 1.61 ± 0.30 mL/min and 1.87 ± 0.36 mL/min without this correction. The mean glucose absorption was 59 ± 8.1%, the albumin clearance 52.9 ± 17.3 µL/min and the clearance of IgG 44.5 ± 22.9 µL/min. Analysis of agreement between the MTAC of creatinine determined with and without correction for overestimation by high glucose concentrations
Figure 1 left panel. Analysis of agreement between the MTAC of creatinine (MTACc) with and without correction for overestimation caused by high glucose concentrations in the dialysate determined by a Bland and Altman analysis. Data from 15 first SPARs in 15 rabbits. A strong correlation was present between the mean and the difference of the uncorrected and corrected MTACc. Figure 1 right panel. Comparison of the BCG and BCP method showed no indication of a systemic error relative to the magnitude of the albumin concentration. Data were obtained from 13 SPARs performed in 3 rabbits. Mean of the differences (•), and mean ± 2SD (—) are shown.

showed a mean overestimation of the MTAC of creatinine of 0.26 mL/min when no glucose correction was made (Figure 1, left panel). Moreover, a correlation was present between the MTAC differences and means (r = 0.83, p<0.0001). This implies that systematic errors were present relative to the magnitude of the MTACs: the overestimation was more pronounced the greater the MTAC. A similar comparison of the BCG and BCP method for the measurement of albumin showed no overestimation, and the differences were randomly distributed when plotted against their means (Figure 1, right panel).

Table 2 depicts the transport data after upsampling with the 2 different scaling methods, compared to the data obtained in adult CAPD patients. With exception of the macromolecules, the transport values of the low molecular weight solutes were in the same order of magnitude as the human adult data. The corrected albumin clearance was 398 ± 129 μL/min/1.73 m², approximately four times greater than the albumin clearance in PD patients. The clearance of IgG was approximately eight times greater.

The time course of the transcapillary ultrafiltration, the lymphatic absorption and the change in intraperitoneal volume are shown in Figure 2. The effective lymphatic absorption rate was 0.47 ± 0.26 mL/min and the transcapillary ultrafiltration rate 0.66 ± 0.13 mL/min without correction for body surface area. The residual volume, calculated as a percentage of the instilled volume, was significantly lower (p<0.003) in rabbits compared to the residual volume calculated for CAPD patients. A dissociation between the transport of water and sodium was observed in each rabbit in the initial phase of the dwell. The initial D/PNa of 0.903 ± 0.013 decreased to 0.884 ± 0.011 (p<0.003) within 40 minutes after installation, followed by an increase to 0.899 ± 0.021 at 60 minutes.
In 7 of the 15 rabbits, 2 to 5 SPARs without drug intervention were performed. The total number of control SPARs in these animals was 21. The intra individual coefficients of variation of the transport parameters were calculated on the basis of these 21 observations. The results were compared to those obtained from 92 SPAs done in 40 CAPD patients (Table 3), in whom at least 2 investigations had been performed with 1.36% glucose containing dialysate during a 4-hour dwell. Figure 3 shows small variations in the time course of the transcapillary ultrafiltration in 3 rabbits, in whom 4 or more control SPARs were performed. The results of the intra individual coefficients of variation are presented in Table 3. The values for the transport of low molecular weight solutes were similar in rabbits, but those for fluid transport were lower than in CAPD patients. The coefficient of variation of albumin determined with the BCP method was marginally smaller (15%) than that of the BCG method (16%). A comparison with the coefficients of variation in CAPD patients is inappropriate because here albumin was measured with nephelometry. Serum concentrations of total protein, albumin and IgG did not change significantly during the observation period in these 7 rabbits. The intra individual coefficients of variation of the plasma macromolecules were 3% for total protein, 4% for albumin and 20% for IgG.

Discussion

Our study showed that daily dialysis for four weeks was possible in this rabbit model. Furthermore, frequent measurement of peritoneal permeability characteristics during this period, yielded reproducible results and emphasized the stability of the model. Part of the early complications encountered during the development of the model could be explained by inexperience and were therefore potentially avoidable. Catheter occlusion caused by omentum wrapping during the intervention period of dialysis, two to four weeks after catheter implantation was the main complication. Omentectomy was not performed, because this procedure has been reported to cause substantial proteinloss [5,10]. This would interfere with the longitudinal setup of the model.
Table 3. Coefficients of intra individual variation of peritoneal solute and fluid transport in rabbits and stable CAPD patients.

<table>
<thead>
<tr>
<th>parameter</th>
<th>rabbit Vc (%)</th>
<th>CAPD pts Vc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>solute transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTACurea</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>MTACr</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>glucose absorption</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>clearance albumin</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>clearance IgG</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>fluid transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELAR</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>TCUFR</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>residual volume</td>
<td>17</td>
<td>34</td>
</tr>
</tbody>
</table>

Vc: intra individual coefficients of variation calculated in 7 rabbits with a total of 21 SPARs without interventions and compared to the those of 40 CAPD patients with a total of 92 SPAs.

The peritoneal transport characteristics were assessed by a standard peritoneal permeability analysis for rabbits, SPAR, during a 1-hour dwell with 3.86% containing dialysate. This duration was chosen because pilot experiments had shown that near equilibrium between plasma and dialysate concentrations of low molecular weight solutes was present after a 2-hour dwell. The high glucose concentration was necessary because otherwise net fluid absorption would have occurred in all rabbits, and to assess the time course of the dialysate concentration of sodium. Similar to the situation in humans, the D/P Na⁺ ratio can be used to assess aquaporin-mediated water transport [22]. The rabbit data were scaled to body surface area and body weight and compared with those of stable PD patients. The human values were obtained by a standardized analysis (SPA) during a 4-hour dwell using 1.36% glucose dialysate as osmotic agent [11].

The MTACs of urea and creatinine in rabbits were not essentially different from the values obtained in CAPD patients after correction for body surface area. Since these MTACs mainly reflect the vascular peritoneal surface area [23], it is likely that the relationship between body surface area and peritoneal surface area in rabbits is similar to that in adult CAPD patients. This is in accordance with anatomic data: it can be calculated from the paper of Esperança and Collins [24] that the ratio between peritoneal surface area and body surface area in adults averages 0.60. A similar ratio of 0.58 could be calculated from their data for infants assuming a length of 50 cm. Although the instilled volume in rabbits was 40 mL/kg body weight, and 30 mL/kg body weight in humans, the instilled volume per body surface area in rabbits was only 40 % of that used in adult CAPD patients. This may explain the rapid equilibration found in rabbits, necessitating the use of 1-hour dwells.

The MTAC values of creatinine calculated on uncorrected measurements of this solute were rather close to those obtained for urea, despite the difference in molecular weight between the substances. This was caused by glucose interference. Although it is generally known that glucose interferes with the
Jaffé method for measurement of creatinine [25], interference can also occur with enzymatic methods in the presence of extremely high glucose concentrations, as is the case with 3.86% glucose dialysate [14,15]. Especially in models with normal renal function the absolute difference between dialysate and plasma concentrations is so small that even limited glucose interference can substantially influence the results of the MTAC of creatinine.

The transcapillary ultrafiltration rate was greater in rabbits investigated with 3.86% glucose dialysate than in humans investigated with 1.36% glucose. However, the values were not essentially different from those obtained with 3.86% glucose dialysate in 10 stable CAPD patients [26]. The effective lymphatic absorption rate was, however, four times higher in rabbits than in CAPD patients. This may explain the negative net ultrafiltration found with 1.36% glucose dialysate in our pilot study. Furthermore, it may explain the finding that the glucose absorption after one hour in the rabbit was similar to that after a 4-hour dwell in CAPD patients. The values we found for the effective lymphatic absorption rates were in accordance with those obtained by Fox et al. in conscious and anesthetized rabbits [27]. It is likely that the greater fill volumes per kg body weight used in the rabbits compared to adult PD patients, caused a rise in intraperitoneal pressure, leading to an increased dextran absorption rate [28-30]. In rats a relationship has also been found between instilled volume and the peritoneal fluid absorption rate [31].

The clearance of albumin and other macromolecules [28,31,32] is unaffected by either high fill volumes or dialysate glucose concentrations. However, a fourfold greater albumin clearance and an approximately eight times greater IgG clearance were observed after a 1-hour 3.86% glucose dwell in our rabbits. This was not likely to be caused by the methods of measurement. For albumin both the BCG and the BCP method yielded similar results. Although no comparison could be made with the nephelometric method used for CAPD patients, a method difference is not likely to cause a difference of this magnitude [33] in the albumin clearance. IgG was measured, both in rabbits and in patients, by immuno-assays, but different ones. Again it is not likely that determination of IgG by either nephelometry or ELISA would cause a difference of this magnitude. Possible explanations could be local production of IgG by the milky-spot like structures in the greater omentum of rabbits [34] in combination with a species specific greater number of large pores relative to the number of small pores in rabbits, or the absence of uremia in the model. However, the scarce data on this subject suggest that uremia may be associated with increased peritoneal permeability [35]. An artifact caused by upscaling is not conceivable, as peritoneal albumin clearances in children were not different when compared with transport of low molecular weight solutes [unpublished]. The protein loss during the SPARs did not lead to a decreased serum concentrations of total protein, albumin and IgG as the concentrations of these macromolecules did not change during the observation period. It can be concluded that the chronic conscious rabbit model for peritoneal dialysis can be used for repeated investigations on peritoneal transport. The results are similar to those in CAPD patients regarding to the transport of low molecular weight solutes, the sieving of Na+ and transcapillary ultrafiltration. However, the clearances of albumin and IgG, and the effective lymphatic absorption rate are higher.
Figure 3. The time course of the transcapillary ultrafiltration of repeated control SPARs in 3 different rabbits.
References


18. Waniewski J, Heimbürger O, Werynski A, Lindholm B. Aqueous solute
Peritoneal transport in experimental PD


