Adapted APD,

from the « simple » mechanics (varying fill/dwell) of peritoneal dialysis prescription to the peritoneal membrane recruitment (small pores « dialysis ») to improve the volume control

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Peritoneal dialysis « basic needs »

- **Adequacy**: not only small solute control (Kt/V urea) but also volume control (not only UF prescription, but consider the sodium dialytic removal)

- **Tolerance**: session time, fill volume, APD over night and day free (empty abdominal cavity) or day exchange: icodextrine but « cost/pH 5 »

- **Cost**: a reality, « more efficient » for the same cost
ADEMEX STUDY: fill volume increase +30%, impact?

no mortality/morbidity impact of an increased Kt/Vurea (+30%) in adults: Kcreat 60 vs 45 and Kt/V 2.1 vs 1.6

R. Paniagua et al., JASN, 2002
The impact of strict volume control strategy on patient survival and technique failure in peritoneal dialysis patients.


Strict volume control by dietary salt restriction and ultrafiltration was applied over a 10-year period. Mean BP decreased from 138/86 to 114/74 mm Hg. Overall and cardiovascular mortality rates were 48.4 and 29.6 per 1,000 patient-year

Strict volume control (lowered BP) leads to a decrease in mortality of nearly 40%

Euvolemia is probably a more important adequacy parameter than small solute clearance (urea) as fluid status, but not small solute clearance predicts outcome.
Muscle wasting in chronic kidney disease: the role of the ubiquitine proteasome system and its clinical impact


- Malnutrition
- **Volume overload**
- Metabolic acidosis
- Inflammation
- Insuline resistance (PTH)
- GH-IGF1 axis anomalies

Cachexia in uremic patients: loss of protein stores, muscle wasting, growth impairment: *ATP-dependent, ubiquitin-proteasome system*
Fluid status in PD patients: the European body composition monitoring (EuroBCM) study cohort

- 639 PD patients from 28 centers, 6 countries
- Only 40 % normovolemic !!!
- 60 %  7 % underhydrated
  53 % overhydrated
  (25%>15% OH; severe OH)
- **BP and OH were not directly related:**
  importance of both dry weight/UF (« water prescription ») and sodium balance/dialytic removal versus diet
Blood Pressure versus hydration in patients on dialysis: « box plot », importance of the BCM evaluation

**Volume dependent high BP**
- (natural relation) needs an UF prescription in mL (water and/or water and sodium)

**Volume non dependent BP**
- vascular reactivity ?, complex situation: needs more than a «weight loss/water» prescription, importance of sodium balance, nutrition, non osmotic sodium (Tietze)…
Impact of both: the UF amount (mL) and the Na dialytic removal for patients outcome


UF amount in anuric patients

Dialytic sodium removal

Sodium and fluid: the « assassins »

Importance of the UF « quality »: not only free water (AQ1) but also coupled (small pores) sodium and water
Importance of varying dwell time and fill volume to optimize volume control in patients on PD

*UF « water »*: free water (AQ1) and coupled water (small pores)
* sodium removal (small pores)*


**Fischbach Michel**

Pediatric Dialysis Unit
University hospital Strasbourg France
Volume control in PD patients, ultrafiltration and sodium removal

Optimizing PD prescription for volume control: the importance of varying dwell time and dwell volume.
M Fischbach et al. Pediatr Nephrol 2014

Ultrafiltration
(mL; AQ1+Small pores)
1) AQ1, solute free water
2) Small pores, solute coupled water

Pressure gradients
Convective process

Sodium removal
(Small pores)
Coupled water (convective; drag+lag)
Diffusion gradient
Diffusion distance
(ratio area/fill)
1. **Ultrasmall pores, aquaporins**: radius < 3 Å (water selectivity, free water) - the most numerous, transcellular pathway: endothelial cell
   - 50 % UF: **effectiveness of glucose** as an osmotic agent despite its small size (crystalloid osmosis)
   - explains sodium sieving (dip in NaD)

2. **Small pores**: radius 30-50 Å (water + solutes: coupled water)
   - $1/10\,000\,AQ1$, paracellular pathway (interendothelial clefts)
   - 50 % UF: hydrostatic + colloid/oncotic osmotic forces

3. **Large pores**: very rares pores, usually restricted amount of UF, large solutes (number impacted by inflammation status)
Fig. 1. Transcapillary ultrafiltration (TCUF) is induced by the crystalloid osmotic pressure gradient across the peritoneal membrane. It comprises water transport through small interendothelial pores (SPT) and ultrasmall transendothelial pores, the so-called free water transport (FWT). The amount of transported water across the large pores (LPT) is considered negligible. Changes in intraperitoneal volume (∆IPV) result from TCUF and fluid reabsorption. Fluid reabsorption includes lymphatic absorption, disappearance to the interstitial tissues (together effective lymphatic absorption, ELA) and backfiltration into the capillaries. Adopted from reference [25] with permission from Oxford University Press.

from Coester AM et al. NDT plus 2, 2009
Pressure gradients across the peritoneal membrane during dialysis

Capillary hydrostatic perfusion pressure

Colloïd oncotic pressure (albumine)

Back filtration \( \leftarrow \) UF \( \rightarrow \) Filtration

Peritoneal Cavity

UF, BP/vaso activity

UF, Crystalloid osmotic pressure (glucose)

Intraperitoneal pressure (IPP)
UF: pressure gradients across the peritoneal membrane during a dialysis exchange
from Coester AM et al. NDT plus 2, 2009

*Hydrostratic capillary pressure (vascular tonus): inter/intraindividual variability; « pressure wave/vasodilatation » and PDF bio (in)compatibility

Pro
• Hydrostratic capillary pressure* (+17 mmHg)
• Transcapillary osmotic gradient (cristalloid peritoneal osmotic pressure minus plasma osmotic pressure) + 24 mmHg (1.36%) +42 mm Hg (3.86%) disappearance over time

Contra
• Capillary osmotic colloid pressure (-21 mmHg)
• Intraperitoneal pressure (IPP - 9/8 mmHg)

Total (maximum)
pro + 41 to 59
\(\Delta +11 \text{ to } +29\)
contra - 30
Quantification of free water transport during the peritoneal equilibration test

Osmotically induced water transport (osmotic and oncotic « forces ») occurs:
- through small pores (coupled water) and
- through AQ1 (free water)

and is especially marked during the first hour of a dwell (hypertonic) and correlates well with the D/P sodium

\[ UF = (\text{free water}) + (\text{coupled Na water}) \]

with the assumption that lymphatic/tissular absorption and diffusion of sodium are small over the exchange (short dwell), and that coupled Na water = amount of Na transported / plasma Na concentration
Figure 2 | Computer simulation of ultrafiltration pathways across the peritoneal membrane for glucose 3.86%. Once the osmotic gradient has dissipated, at ~240 min, fluid reabsorption will occur through small pores as well as lymphatics. As solute transport equates to the small pore area, high transport membranes will reabsorb more fluid.
Sodium sieving (NaD): early in dwell
« small pores function impact on AQ1 function »
small solute transport rate, glucose conductance

An absent or decreased sodium dip can be due to
1) decreased Aquaporin (AQ1) function but can also be due to
2) a fast diffusive transport (through the small pores).

Evaluation of peritoneal membrane characteristics: a clinical advice for prescription management by the ERBP working group
Importance of the glucose conductance:
fill volume/dwell time, osmotic agent (type/concentration) and exchange permeability (PSA)
« small pores function/transport rate impact on AQ1 function »

Figure 3 | A diagrammatic representation of the change in ultrafiltration profile associated with high transport status seen with glucose and icodextrin.
Threefold peritoneal test of osmotic conductance, ultrafiltration efficiency, and fluid absorption

Osmotic conductance mL/min over mmol/L gradient

UF Efficiency mL/glucose absorption

Glucose conductance or metabolic cost of UF, mL/gr glucose absorbed or delivered
UF failure occurs in 43% of patients (Davies S, Kidney Int 2004) caused by a less effective osmotic gradient that is change in both, in AQ1 and in small pores,

- that is the osmotic conductance (AQ1) to glucose (reflection coefficient=pores capacity, and UF coefficient=numbers of pores), mL/min UF for glucose in mmol/mL as mean concentration/absorption/gradient
- but is also glucose diffusion via the small pores (peritoneal small solute transport rate)
Volume control in PD patients, ultrafiltration and sodium removal

Optimizing PD prescription for volume control: the importance of varying dwell time and dwell volume.
M Fischbach et al. Pediatr Nephrol 2014

Ultrafiltration (mL; AQ1+Small pores)
1) AQ1, solute free water
2) Small pores, solute coupled water
   Pressure gradients
   Convective process

Sodium removal (Small pores)
Coupled water (convective; drag+lag)
   Diffusion gradient
   Diffusion distance (ratio area/fill)
Dialytic (PD) sodium removal: small pores, diffusion and convection

**Small pores recruitment**

- PSA recruited/available (fill volume)
- Fill volume of dialysate \( \text{Cl} = \text{D/PxV} \), that is the volume of diffusion (and membrane recruitment, « full » dialyzer, more small pores)
- Ratio PSA/volume, distance of diffusion: permeability of the exchange

**Diffusive gradient**

- \( \text{(sodium intake/NaD)} = \text{Na}_{\text{plasma}} - \text{NaD} \)

**Convective transport**: coupled with water (drag/lag)

**Diffusion time**: dwell time
Determinants of sodium removal with tidal automated peritoneal dialysis.

- Removal of sodium correlated weakly with UF in tidal APD and showed wide inter-patient variability

- Dialytic sodium removal should be measured rather than roughly estimated from UF (AQ1, only water and small pores, solute diffusion and convective solute coupled water)
Time-dependent associations between total sodium removal (TSR) and mortality in patients on peritoneal dialysis
Dong J et al. Pert Dial Inter 2011, 412-421

- TSR, sodium removal is largely dependent from diet and nutrition parameters +++ (Napl)
- A high TSR remained predictive of low risk of death even after RRF and other covariates were included in the Cox regression model
- Notably, the high TSR observed is the result of higher peritoneal sodium removal: **TSR was doubled** in high TSR group that seen in low TSR group (0.96 versus 1.99 gramme per session), even though **ultrafiltration was only 30% greater, dissociation +++**
Designing a Low Sodium Dialysate: the impact of diffusion Napl-NaD
Rippe et al, PDI 2004;24:10-27

How to improve dialytic sodium removal:
- importance of the diffusive gradient Napl/NaD (« low » NaD)
- small pores recruitment (fill volume optimization)
- dwell time: not too short, 120/240min, diffusion time
How to achieve a low sodium dialysate

- Manufactured PDFs with low sodium (need for "more" osmotic agent: more glucose!), "obligatory low sodium"

- Dilution (with sodium free water/AQ1) of the infused PDF: role of the intraperitoneal residual volume +++ ("adapted" low sodium to patient’s volume overload)

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**Ultrafiltration exchange**
Short/small cycle
AQ1 water, hemoconcentration
Not « fully drained », too low IPP « free water »

**Purification exchange**
Long/large cycle
Small pores water, solute coupled water by diffusion gradient Napl/NaD
Optimizing PD prescription for volume control: the importance of varying dwell time and dwell volume.
M Fischbach et al. Pediatr Nephrol 2014

<table>
<thead>
<tr>
<th><strong>Hemodialysis</strong></th>
<th><strong>Peritoneal Dialysis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrafiltration (mL)</strong></td>
<td>Water removal by filtration (iso-osmotic, isonatric, via a pressure gradient)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sodium (Na) removal</strong></td>
<td>~ 80 % by convection (UF)</td>
</tr>
<tr>
<td></td>
<td>~ 20 % by diffusion (NaPl – NaD gradient)</td>
</tr>
<tr>
<td><strong>Body weight loss: 1kg</strong></td>
<td>1L: 80% Na and water</td>
</tr>
</tbody>
</table>

NaPl: plasma sodium concentration; NaD: dialysate sodium concentration; UF: ultrafiltration
• Which fill volume for which goal?
  – clinical tolerance: « small » fill volume
  – ultrafiltration capacity: « small » fill volume (low IPP)
  – purification capacity: « large » fill volume

• Which dwell time for which goal?
  - ultrafiltration (maintained osmotic gradient): « short » dwells
  - purification (Na/phosphate): « long » dwells

• Ultrafiltration and/or purification:
  « small or large », « short or long »

how to prescribe APD?
adapted APD,
improved efficiency without more costs
The peritoneal surface area involved in the dialysis exchanges is a dynamic dialysis membrane

Peritoneal dialysis prescription in children: bedside principles for optimized practice.
M FISCHBACH, B WARADY. Pediatric Nephrology 2009;24(9):1633-42

the contact surface area, the wetted membrane

\[ \text{MTAC} = \text{MTC} \times A_{\text{wetted}} \]

the recruited contact surface area is dependent from:

- in rats: dwell time, agitation, surfactant (Flessner MF, JASN 2001)
- in humans: fill volume (Fischbach M, Haraldsson B. JASN 2001; Chagnac A, JASN 2002), patient position (Fischbach M, JASN 2001), and dialysate composition (Fischbach M, Haraldsson B. NDT 2004)
Effect of fill volumes on PSA recruitment:

Ao/\Delta x increased significantly, +21 %, from \(19,900 \pm 1,200\) to \(24,000 \pm 1,450\), as the fill volume was raised from 800 to 1400 ml/m² BSA. A further increase to 2,000 ml/m² did not result in any significant change of Ao/\Delta x, \(24,500 \pm 1,700\) (N=8)

_Fischbach M, Haraldsson B, JASN 2001; 1524-29_

+ 21% « more dialyzer », PSA « fully » recruited only at 1400/1500 mL/m²
Effect of posture on PSA recruitment:
Ao/Δx fell significantly when the patients were standing compared to the value obtained in a supine position (N=6) using the same fill volume 1000 ml/m²

Fischbach M, Haraldsson B, JASN 2001; 1524-29
Tolerance of large exchange volumes by peritoneal dialysis patients

• Patient tolerance evaluation of **2, 2.5 and 3 L fill volume**, after 4 hours dwell, scale 0 to 9 converted into four categories: no discomfort (0) mild discomfort (1 to 2) moderate discomfort (7 to 7) or severe discomfort (8 to 9) in 20 patients, BSA 1.8 m² (range 1.3 to 2.4)

• **75 % of the patients were not able to identify the exchange volumes** independently from their corpulence (greater or less than 1.75 m² BSA)

• **False perception of the filled volume is usual**: need for an objective assessment: IPP measurement
Percentage of fill volumes correctly identified by actual instilled volume for total patient group and for patients grouped by: (BSA)<1.66 m² and BSA>1.66 m²

Fukatsu A. PDI 2001

% correctly identified: only around 50%
Measurement of hydrostatic intraperitoneal pressure: a useful tool for the improvement of dialysis dose prescription

Fischbach et al. Pediatr Nephrol 2003; 18; 976-81

- Fill volume should be large enough to achieve optimal exchange dialysis membrane recruitment, but also small enough to avoid the consequences of excessive distension of the peritoneal cavity.

- IPP measurement is easy to perform, and IPP monitoring provides an objective assessment of fill volume prescription.

- In fact it appears that almost all patients cannot accurately tell the difference in fill volume changes.
Fill volume prescription: adjustments individual « need/tolerance »


- How to secure a new prescription
- How to support the patient perception

Measure the intraperitoneal pressure
Normal values of IPP: correlation to the drained volume

Avoid an IPP > 18cm

<table>
<thead>
<tr>
<th></th>
<th>IPP cm H₂O</th>
<th>IPV mL/m² BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults</td>
<td>13.4 ± 3.1</td>
<td>1585 ± 235</td>
</tr>
<tr>
<td>In children over the age of two years</td>
<td>5.2 ± 2.6</td>
<td>600 ± 50</td>
</tr>
<tr>
<td></td>
<td>8.2 ± 3.8</td>
<td>990 ± 160</td>
</tr>
<tr>
<td></td>
<td>14.1 ± 3.6</td>
<td>1400 ± 50</td>
</tr>
</tbody>
</table>

from P.Y.Durand (1992) and M.Fischbach (1994)
Too high an intraperitoneal pressure

- Patient discomfort, poor compliance
- Anorexia, vomiting
- Abdominal wall complications (hernia)
- Reduced UF (pressure gradient) due to « tissue absorption, back filtration, lymphatic flow »
- Enteric peritonitis risk (Dejardin et al. NDT 2007; PIP>13 cm) : ???
Evaluation of peritoneal membrane characteristics: a clinical advice for prescription management by the ERBP working group
Wim van Biesen et al. NDT 2010; 25:2052-2062

• Use larger volumes rather than more dwells (be aware of sodium sieving when using « too » short dwells)

• When negative UF (low UF) is registered, shortening the dwell time rather than increasing glucose concentration is advocated.

*Fill volume can potentially influence the « exchange/membrane permeability »:* using « too low » fill volumes can falsely induce the impression of a fast transporter status (exchange permeability)
Peritoneal anatomic surface area
plane geometry, ex vivo PSA

- The peritoneal surface area is:
  - nearly equal to the body surface area
  - two fold larger in the infants (533 m²/kg) than in the adults (284 m²/kg) if expressed per kg BW, conversely is age independent if expressed per m² BSA

- Therefore, in children to be adequate, fill volume should be prescribed in: mL/ m² BSA, and not in mL/kg BW
Fill volume, membrane recruitment, geometry/distance of diffusion and exchange “permeability”

Plasma

Dialysate

Fill volume: 800 to 1000 ml/m²

Dialysate

Fill volume: 1400 to 1500 ml/m²
Of mice and men, a matter of scale:
area/volume, **diffusion distance**, exchange permeability

<table>
<thead>
<tr>
<th></th>
<th>Mouse</th>
<th>Rat</th>
<th>Man</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>27 gr</td>
<td>300 gr</td>
<td>70 kg</td>
<td>5 kg</td>
</tr>
<tr>
<td>PSA (cm²)</td>
<td>90</td>
<td>500</td>
<td>17 000</td>
<td>2 600</td>
</tr>
<tr>
<td>Fill volume (mL)</td>
<td>2.5</td>
<td>25</td>
<td>2000/3000</td>
<td>100/250</td>
</tr>
<tr>
<td>Area/volume</td>
<td>36</td>
<td>20</td>
<td>8.5/5.6</td>
<td>26/10.6</td>
</tr>
<tr>
<td>Time to D/P = 0.7 (min)</td>
<td>50</td>
<td>70</td>
<td>240/ ? less</td>
<td>60/120</td>
</tr>
<tr>
<td>Exchange permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to $V_{\text{max}}$ (4 % gl) (min)</td>
<td>55</td>
<td>100-110</td>
<td>240/hypo</td>
<td>60/120</td>
</tr>
<tr>
<td>PSA (cm²/kg)</td>
<td>/</td>
<td>/</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>(cm²/m²)</td>
<td>/</td>
<td>/</td>
<td>10 000</td>
<td>10 000</td>
</tr>
</tbody>
</table>

*Modified from Rippe B, PDI 2009,S32-35*
Fill volume: PSA recruitment
more pores (small pores)
more distance of diffusion (preservation from too rapid a glucose loss)

Sodium
Diffusion (Napl > NaD)
Convection (drag + lag)

Glucose
Diffusion gradient
Crystalloid osmotic gradient

Volume and Distance of diffusion

larger fill volume: PSA recruitment and enhanced volume/distance of diffusion
the peritoneal small solute transport rate/permeability and PSA recruitment

- **From blood to dialysate:** more small pores more exchanges, especially enhanced diffusive process for the uremic toxins, small solute transport rate as peritoneal permeability assessment (urea...Na)

- **From the dialysate to the blood:** more small pores more exchanges,
  - diffusive gradient (glucose) and *volume/distance of diffusion (large fill volume)*
  - convective gradient (IPP)
Fill volume and efficiency

- **K = D/P x V**
  - D, P concentrations dialysate, plasma
  - V volume of the exchange/day, drained volume

- Correlation between « V » and urea, until a peak volume (*volume dependency*)

- Bad correlation with the phosphate (and sodium) dialytic removal (*time dependency*)
Dwell times: not an unique choice

• A dwell time that is too long could limit ultrafiltration capacity (loss of cristalloid osmotic over dwell time).

• A dwell time that is too short could induce a positive sodium balance (« more » free water UF)

• Individual prescription of the « dwell times » is essential, with respect of the balance ultrafiltration (not too long) versus purification (not too short)

PET test allows to determine individual permeability parameters (APEX time; Phosphate purification time).
"short" dwell time in PD/APD

- Adapted to maintain adequate UF (but sodium free water, crystallloid osmotic gradient, ultra small pores).

- Allowed acceptable urea purification, despite short dwell.

- Inappropriately for purification of solute which are more time related (creatinine, phosphate, sodium)
«long» dwell time in PD/APD

- Risk of reduced total amount of UF, but less «free water» (time dependent cristalloid osmotic gradient loss), and more coupled water

- achieved acceptable urea purification

- appropriated for purification of solute which are more dwell time related (creatinine; phosphate; sodium) and coupled water
Determination of the APEX time and the PPT (phosphate purification time), D/P = 0.6. Example (2 years): APEX = 36 minutes and PPT = 154 minutes. Normal values: APEX 18 to 71 minutes, PPT 105 to 238 minutes. Fischbach M. PDI 1998
« conventional APD prescription » is since 1980/1985, (Kesaviah P) based on « total dialysate volume per session », with only the possibility of « the repetition » of the same exchanges/cycles:

1) same dwell volume,
2) same dwell time

DPA conventional, limiting prescription, « old fashion »?
Which Fill volume - Which Dwell-time:

*Not a unique choice*

short (and small)  UF favored

large (and long)  Purification favored

interested of sequentially short and longer dwell-time exchanges, and small and larger fill volume exchanges
Adapted APD:

first Ultrafiltration
(low fill, short dwell)
then Purification
(larger fill, longer dwell)


*Determination of individual ultrafiltration time (APEX) and purification phosphate time (PPT) by peritoneal equilibration test (PET). Application to individual peritoneal dialysis (PD) modality prescription in children. FIschbach M, Lahlou A, Eyer D, Desprez P, Geisert J. Perit Dial Int 16, S1 19-22, 1996
Prescription parameters of conventional or adapted (optimized) CCPD (manually performed)

<table>
<thead>
<tr>
<th></th>
<th>Conventional CCPD</th>
<th>Adapted CCPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of exchanges</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Duration of session</td>
<td>5x2 h</td>
<td>2x APEX Time</td>
</tr>
<tr>
<td></td>
<td>= 10 h</td>
<td>(35-45 min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 x Purification Time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(150-120 min)</td>
</tr>
<tr>
<td>Dwell volume</td>
<td>5 x 800 mL/m²</td>
<td>2 x 600 mL/m²</td>
</tr>
<tr>
<td></td>
<td>= 4000 mL/m²</td>
<td>3 x 1000 mL/m²</td>
</tr>
<tr>
<td>Dialysate tonicity</td>
<td>5 x mixed half</td>
<td>2 x hyper (3.86)</td>
</tr>
<tr>
<td>(dextrose %)</td>
<td>Iso (1.36) and</td>
<td>3 x iso (1.36)</td>
</tr>
<tr>
<td></td>
<td>half hyper (3.86)</td>
<td></td>
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</tbody>
</table>

_Fischbach M. Advances in Perit Dial 1994_
Efficiency of adapted CCPD vs. conventional CCPD: lower metabolic cost (UF/ gr of Glucose absorbed) and improved phosphate purification

<table>
<thead>
<tr>
<th></th>
<th>Conventional CCPD</th>
<th>Adapted CCPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF mL</td>
<td>315±120</td>
<td>360±120</td>
</tr>
<tr>
<td>UF/G mL/gr</td>
<td>4.8±1.3*</td>
<td>5.7±0.8*</td>
</tr>
<tr>
<td>D/P phosphate</td>
<td>0.48±0.17*</td>
<td>0.64±0.18*</td>
</tr>
<tr>
<td>$K_p$ mL/min/kg</td>
<td>0.16±0.05*</td>
<td>0.21±0.05*</td>
</tr>
<tr>
<td>Protein intake (g/kg/day)</td>
<td>1.9±0.3</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>Calcium carbonate (mg/kg)</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Phosphate plasma (mmol/L)</td>
<td>2.47±0.35*</td>
<td>2.15±0.21*</td>
</tr>
</tbody>
</table>

* *: p<0.01

Enhanced osmotic conductance

Fischbach M. Advances in Perit Dial 1994
THE BENEFICIAL INFLUENCE ON THE EFFECTIVENESS OF AUTOMATED PERITONEAL DIALYSIS OF VARYING THE DWELL TIME (SHORT/LONG) AND FILL VOLUME (SMALL/LARGE): A RANDOMIZED CONTROLLED TRIAL

Michel Fischbach,1 Belkacem Issad,2 Vincent Dubois,3 and Redouane Taamma3

Nephrology Dialysis Transplantation Children’s Unit,1 University Hospital Hautepierre, Strasbourg; Nephrology,2 Pitié-Salpêtrière, Paris; and Fresenius Medical Care–Nephrocare France,3 Fresnes, France

Determination of the APEX time and the PPT (phosphate purification time), D/P = 0.6
Normal values: APEX 18 to 71 minutes, PPT 105 to 238 minutes
Fischbach M. PDI 1998

![Graph showing APEX and PPT determination](image)
sequential ultrafiltration, adapted APD: *small fill volume, short dwell time* (isotonic dialysate)

- Improved UF related to a low IPP/IPV and a preserved glucose osmotic gradient (isotonic dialysate),
- *More free water than sodium extraction, a risk or a chance*
- Lower metabolic cost (mL of UF/gr of absorbed glucose)?
- Change in diffusion gradient (hemoconcentration/dilution of the following dialysate) with an impact on purification sequence?
Sequential purification, adapted APD: 

*large fill volume, long dwell time* 
(isotonic dialysate)

- More volume, more time, more membrane: diffusion gradient
- PSA recruitment: importance of small pores (coupled water)
- Enhanced diffusion volume (urea, Na)
- Enhanced diffusion time (phosphate)
- Effect of the intraperitoneal residual volume (diffusive gradient?)
Study design:
• same total amount of dialysate balance/lactate: 12000mL, **only isotonic 1.5% glucose**, same costs (economically, metabolic)
• same duration of dialysis session (9 hours)
• dry cavity during the day (a « need » for the study)

**APD-C (conventional)**: 9 hours
6 times same fill (2000mL), same dwell, (cycle 90min)

**APD-A (adapted/profiled)**: 9 hours
2 times low fill (1500mL)-short dwell (45min),
3 times large fill (3000mL)-long dwell (150min)
Automated peritoneal dialysis prescriptions for enhancing sodium and fluid removal: a predictive analysis of optimized, patient-specific dwell times for the day period

<table>
<thead>
<tr>
<th>Therapy</th>
<th>24-hr NaR, mmol</th>
<th>24-hr UF, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>51</td>
<td>621</td>
</tr>
<tr>
<td>Therapy 1</td>
<td>96</td>
<td>1004</td>
</tr>
<tr>
<td>Therapy 2</td>
<td>99</td>
<td>1062</td>
</tr>
<tr>
<td>Therapy 3</td>
<td>148</td>
<td>1327</td>
</tr>
<tr>
<td>Therapy 4</td>
<td>155</td>
<td>1426</td>
</tr>
</tbody>
</table>

Importance of varying dwell time to avoid dialysate reabsorption (back filtration/tissue oedema):
adapted day dwell (and day volume)
Study design:

- same total amount of dialysate balance/lactate: 12000mL, **only isotonic 1.5% glucose**, same costs (economically, metabolic)
- same duration of dialysis session (9 hours)
- dry cavity during the day (a « need » for the study)

**APD-C (conventional)**: 9 hours
6 times same fill (2000mL), same dwell, (cycle 90min)

**APD-A (adapted/profiled)**: 9 hours
2 times low fill(1500mL)-short dwell(45min), 3 times large fill(3000mL)-long dwell(150min)
STUDY DESIGN: cross over/randomized study
Adapted peritoneal dialysis: « tolerance evaluation: results »

Good patient tolerance, but difficulties to convince the doctors to apply large fill volumes

Tolerance is « induced » : « fill...then sleep »++

Catheter alarms : drainage capacity (3 L)
Adapted peritoneal dialysis:
« purification capacities evaluation: methods »

Urea : weekly Kt/V
Creatinine : weekly K creat
Phosphate : removal per day/session
Increased peritoneal weekly $K_t/V_{\text{urea}}$ with APD-A

<table>
<thead>
<tr>
<th></th>
<th>N = 19</th>
<th>APD-C</th>
<th>APD-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>1.44 ± 0.32</td>
<td>1.53 ± 0.37*</td>
</tr>
<tr>
<td>Min / Max (range)</td>
<td></td>
<td>0.83 / 2.33</td>
<td>0.89 / 2.35</td>
</tr>
<tr>
<td>Number of pairs</td>
<td></td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01</td>
<td>(0.0016)</td>
<td></td>
</tr>
</tbody>
</table>
Increased peritoneal weekly K creatinine with APD-A

<table>
<thead>
<tr>
<th></th>
<th>APD-C</th>
<th>APD-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>28.44 ± 13.11</td>
<td>30.74 ± 13.59*</td>
</tr>
<tr>
<td>Min / Max</td>
<td>13.49 / 85.15</td>
<td>12.32 / 77.22</td>
</tr>
<tr>
<td>Number of pairs</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.05 (0.047)</td>
<td></td>
</tr>
</tbody>
</table>

* Significant p<0.05
Enhanced phosphate dialytic removal (mmol/day) with APD-A

<table>
<thead>
<tr>
<th>N = 19</th>
<th>APD-C</th>
<th>APD-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>5.78 ± 3.87</td>
<td>6.31 ± 3.50</td>
</tr>
<tr>
<td>Min / Max</td>
<td>1.52 / 18.84</td>
<td>1.60 / 15.85</td>
</tr>
<tr>
<td>Number of pairs</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.05 (0.03)</td>
<td></td>
</tr>
</tbody>
</table>
puriﬁcation capacities were improved with APD-Adapted, for:

1) **Urea**: weekly $Kt/V$
2) **Creatinine**: weekly $K_{creat}$
3) **Phosphate**: removal per day/session +++
purification capacities were **improved** with APD-Adapted, for:

1) **Urea** : weekly $K_t/V$
2) **Creatinine** : weekly $K_{creat}$
3) **Phosphate** : removal per day/session
4) **Reduced metabolic charge**, « more for less »?
Adapted peritoneal dialysis: ultrafiltration: solute free water, and solute coupled water (sodium)

1) *Ultrafiltration mL/day*  
   *Sodium removal/day*  
   \[ \text{Na/UF : mmoL/mL} \]

2) *Metabolic “cost” or patient glucose charge: normalised to the glucose absorbed or to the glucose delivered*  
   \[ \text{UF achieved per gr of glucose} \]

3) *BP impact, volume overload/protein wasting*
Ultrafiltration (UF; mL/day): increased with APD-A, enhanced osmotic conductance

<table>
<thead>
<tr>
<th></th>
<th>APD-C</th>
<th>APD-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>656 ± 275.3</td>
<td>743 ± 358.3*</td>
</tr>
<tr>
<td>Min – Max</td>
<td>153 - 1199</td>
<td>180 - 1551</td>
</tr>
<tr>
<td>Number of pairs</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.05 (0.023)</td>
<td></td>
</tr>
</tbody>
</table>

+ 100mL/day + 15%

* Significant p<0.05
UF normalised for the glucose (PDFs) delivered or absorbed, osmotic conductance

• The glucose absorbed by the patient, that is a metabolic charge was calculated (in grams) as follows:

\[
glucose\ \text{absorbed}(g) = \{\text{total volume of dialysate collected (L)} - \text{ultrafiltration (L)} \times \text{initial glucose concentration of the dialysate (g)}\} - \{\text{total volume of dialysate collected (L)} \times \text{glucose concentration of total volume of dialysate collected (g)}\}.
\]

• The glucose delivered to the membrane, that is a membrane “toxicity” was calculated (in grams) from the ratio: volume of fluid infused over total volume of dialysate hung.
A-APD: lower metabolic cost, more UF per gr of glucose

\[
\text{Delivered Glucose} = \left( \frac{\text{total volume infused}}{\text{total volume of all solutions hung}} \right) \times (\text{total CHO of all solutions hung})
\]
Dialytic sodium removal (mmol/day): improved with APD-A

*N = 19 APD-C APD-A

<table>
<thead>
<tr>
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<th>APD-C</th>
<th>APD-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>18.35 ± 48.68</td>
<td>32.23 ± 52.00*</td>
</tr>
<tr>
<td>Min / Max</td>
<td>-69.0 / +108.5</td>
<td>-81.7 / +153.2</td>
</tr>
<tr>
<td>Number of pairs</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01 (0.01)</td>
<td></td>
</tr>
</tbody>
</table>

* Significant p<0.01

18 to 32 mmol

+ 90% ! ,?
Arterial blood pressure: lowered BP under APD-A

**Systolic Blood Pressure**

- APD-C: 130 mm Hg
- APD-A: 140 mm Hg

* Significant p<0.05

**Diastolic Blood Pressure**

- APD-C: 70 mm Hg
- APD-A: 75 mm Hg

* Significant p<0.05

**Mean Blood Pressure**

- MA P = PA d + PP/3

- APD-C: 90 mm Hg
- APD-A: 100 mm Hg

* Significant p<0.01
Cachexia in uremic patients: loss of protein stores, muscle wasting, growth impairment: *ATP-dependent, ubiquitin-proteasome system*

- Malnutrition
- **Volume overload**
  - Metabolic acidosis
  - Inflammation
  - Insuline resistance (PTH)
  - GH-IGF1 axis anomalies

Muscle wasting in chronic kidney disease: the role of the ubiquitine proteasome system and its clinical impact
Improved nPCR with APD-A

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</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>1.10 ± 0.21</td>
<td>1.17 ± 0.25*</td>
<td></td>
</tr>
<tr>
<td>Min / Max</td>
<td>0.56 / 1.53</td>
<td>0.76 / 2.04</td>
<td></td>
</tr>
<tr>
<td>Number of pairs</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.05 (0.044)</td>
<td></td>
<td></td>
</tr>
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* Significant p<0.05
Tendency to an increased **Lean Body Mass** (Kg)

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<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>42.03 ± 10.37</td>
<td>43.96 ± 9.94</td>
</tr>
<tr>
<td>Min / Max</td>
<td></td>
<td>23.06 / 74.57</td>
<td>24.18 / 73.20</td>
</tr>
<tr>
<td>Number of pairs</td>
<td></td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>NS (0.067)</td>
<td></td>
</tr>
</tbody>
</table>
The concept of „adapted“ APD prescription

“The beneficial influence on the effectiveness of APD of varying the dwell time (short/long) and fill volume (small/large). A french Study. Michel Fischbach, Belkacem Issad, Vincent Dubois, Redouane Taamma. Perit Dial Inter 2011;31(4):450-8

- Tolerance: first sleep, thereafter “fill large”
- Optimized purification: urea, creatinine, increased dialytic phosphate removal
- Optimized UF and sodium removal: impact on blood pressure
- Reduced metabolic cost to achieve ultrafiltration (and purification)

**Long term outcome for the patient:**

**improvement of both volume overload and nutrition?**
Adapted APD: a new concept of APD prescription: varying dwell time and dwell volume

- **Based on a physiological approach of the exchange permeability**
  - short dwell/small fill favors ultrafiltration (water)
  - long dwell/large fill favors blood purification (sodium and water)

- **Taking into account the pores function**
  - aquaporins over the s/s sequence: solute free water (convection/osmotic crystalloid gradient)
  - small pores over the l/l sequence: solute coupled water (diffusion, concentration gradient and, convection, pressure gradient)
Dialytic sodium removal (mmol/day): improved with APD-A

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<td>47</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01 (0.01)</td>
<td></td>
</tr>
</tbody>
</table>
Volume control with A-APD, impact of the sequences

1) First sequence “Ultrafiltration favored” : AQ1

“sodium free water “ generated through the AQ1 but small IPV, therefore drained or building up an increased residual IPV…a « chance »…

2) Second sequence “Purification favored” : small pores++

increased diffusion volume, more diffusion time, higher gradient plasma 
(hemoconcentration: Napl ▲ ) to dialysate (“low sodium” dialysate by dilution with the “free water” :NaD ▼ ); solute coupled water through the recruited PSA (small pores)+++
**Prove the principle**

Small/short exchange than large/long exchange: an optimized dialytic sequence for better diffusion gradient

Napl hemoconcentration and NaD dilution by free water retention

<table>
<thead>
<tr>
<th>Exchange</th>
<th>Hyper (500 ml/15 min)</th>
<th>Iso (1250 ml/75 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Drained</td>
</tr>
<tr>
<td>Residual volume urea+creat (ml)</td>
<td>127</td>
<td>530</td>
</tr>
<tr>
<td>Drained (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UF drained (ml)</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>UF generated (ml)</td>
<td>(401+530) - (127+500)</td>
<td>304</td>
</tr>
<tr>
<td>NaD (mmol/l)</td>
<td></td>
<td>125</td>
</tr>
<tr>
<td>NaD removal (mmol/exchange)</td>
<td></td>
<td>-1</td>
</tr>
</tbody>
</table>
**Sequence « more » Ultrafiltration**

**Sequence « more » Purification**

**Sodium and Phosphatelimination**

<table>
<thead>
<tr>
<th></th>
<th>First sequence (45min/1500mL)x2 « UF favored »</th>
<th>Second sequence (150min/3000mL)x3 « Purification favored »</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days study</td>
<td>3 days study</td>
<td></td>
</tr>
<tr>
<td><strong>Sodium mmol/Seq</strong></td>
<td>+ 4 +/- 2 « sodium retention »</td>
<td>- 39 +/- 12 « sodium removal »</td>
</tr>
<tr>
<td>mmol/min</td>
<td>0,15</td>
<td>- 0,7375</td>
</tr>
<tr>
<td><strong>Phosphate mmol/Seq</strong></td>
<td>- 0,469</td>
<td>- 17,71</td>
</tr>
<tr>
<td>mmol/min</td>
<td>0,0078</td>
<td>0,059</td>
</tr>
</tbody>
</table>

![Graph showing total time in hours with a peak at around 14:00]
Adapted APD
what have we learned?

• There is an impact of a short/small exchange on the following long/large exchange
• The UF achieved over a short/small exchange, « aquaporins water », is either drained (UF/weight loss) or maintained intraperitoneally (residual volume)
• The long (diffusion time) / large (diffusion surface area; PSA recruitment/small pores) exchange should benefit from an optimized diffusion gradient: higher Napl (hemoconcentration) and lower NaD (PDF dilution)
• Therefore, we believe in the interest of a short/small exchange before each long/large exchange
Adapted APD a « simplified » bedside prescription

Small fill: half the large fill
Long dwell: 3-4 short dwell
Hypopermeable 4x (longer session time?)
Hyperpermeable 2.5/3x (more dialysate volume?)

Largest fill volume « accepted » in supine position
Large fill >>>>1000 mL/m² go up to 1500 mL/m² « full dialyzer »

APEX time (membrane « permeability»)
Short dwell time

for the same cost, more efficient
Fluid overload and sodium balance: an art or A-APD

Intake:
diet, water and sodium

Dialysis removal:
a « water » prescription and a sodium removal

balance, equilibrium
UF favored, sodium free water, a risk or a chance: *alternate cycles*
more volume of diffusion (PSA recruitment)
more diffusion time
more diffusion gradient (alternate cycles)