Practical application of peritoneal dialysis adequacy

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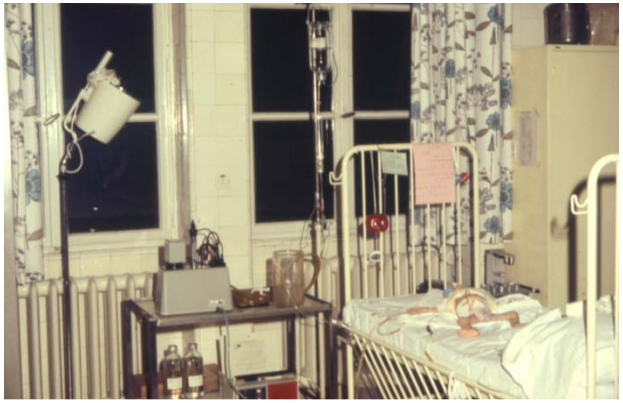
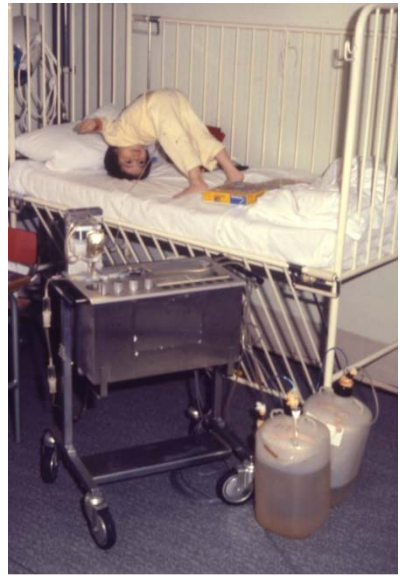
Peritoneal Dialysis

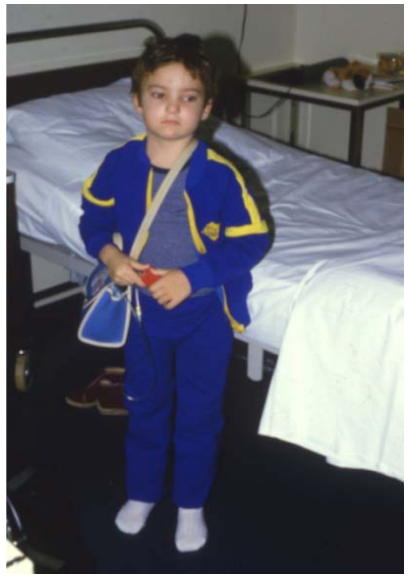
Michel Fischbach and the « dialysis team». Strasbourg



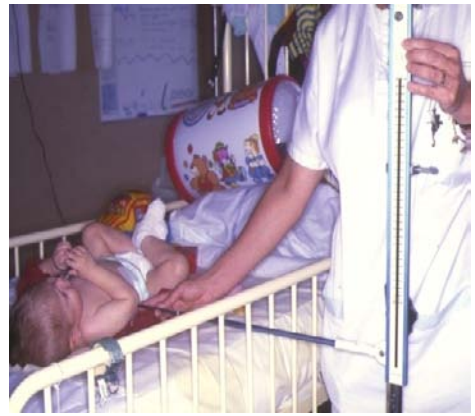
PD « bottles», 1972



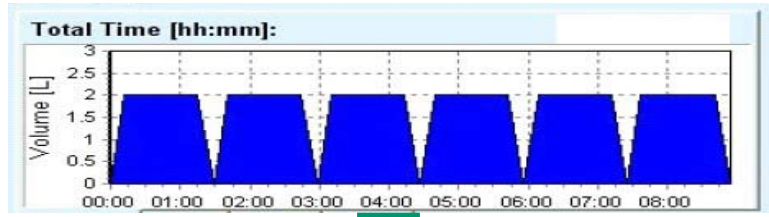
IPD, with « LKB »,1976



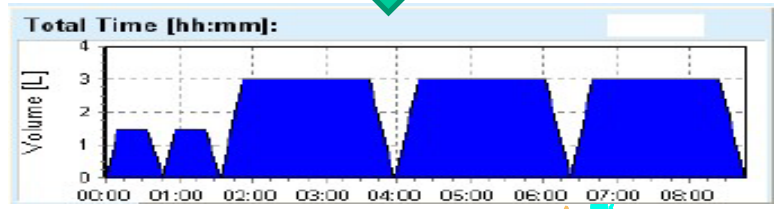
CAPD , « bags »,1979



IPP 1994



Same cost
« more » efficient



APD-adapted, 1994/2011

Practical application of dialysis adequacy

- Limited value of urea kinetic parameters (Kt/V>1,7)
- Importance for outcome (in adult patients) of volume control, that is diet, nutrition and UF (consider water, and sodium dialytic removal) (optimizing PD prescription for volume control: the importance of varying dwell time and dwell volume. Fischbach M et al. Pediatr Nephrol 2013)
- Bedside principles for optimal practice
  (Fischbach M, Warady BA. Pediatr Nephrol 2009;24:1633-42)
  (Fischbach M, Stefanidis CJ, Watson AR for the European Paediatric Dialysis Working Group .Nephrol Dial Transpl 2002;17:380-5)

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Kt/V urea : simple but accurate?

- Only a urea parameter (surrogate), impacted by metabolic state, nutrition, hydration, renal residual function…and dialysis removal
- « V » the urea « sea », the total body water (Morgenstern formula calculation; multiimpedancemetry measurement by BCM®)
- « K/day »: urea dialytic removal (urea concentration x total volume of dialysate)
- « t »: duration of the dialysis (CAPD/APD)

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Dialysis dose : Kt/Vurea (Kcreatinine) today recommandations

- **KT/V_{urea} per week (Kt/V x 7) (>1,7-2 ?)**
- **$K_{creatinine}$ per week (Liters/week/1,73 m²) (>45L/week/1,73 m²)**
- Renal residual function is of importance :

  1) GFR = K_{creat} or more accurate (K_{creat} + K_{urea} /2) and

  2) volume of diuresis (CAKUT+++)

- « oftently » there are practical difficulties to achieve K_{creat}

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KT/Vurea and Kcreatinine : often (too often?)discrepancies

- Small fill volume and short dwell time will more reduce dialytic creatinine clearance than urea clearance : APD versus CAPD
- Renal residual function contributes more to creatinine clearance (proximal tubular excretion) than to urea clearance
- Therefore, anuric young children, using small fill volume, and short dwell times (APD) may have an adequate (preserved) KT/V_{urea} despite a tendency of a « too » low K_{creat} : is this an inadequate dialysis prescription ?

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The Mid European Pediatric Peritoneal Study Group : peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis.

Schaefer F et al. JASN 1999; 1786-92

- Growth outcome was :
  - Negatively impacted by peritoneal transport capacity (high transporter) and total dialysate volume (increased urea clearance)
  - Positively impacted by dialytic K_{creat} +++
- Mean fill volume prescribed for these APD children was (too?) small IPV 824±125mL/m², conducting to a restricted peritoneal membrane recruitment *« less peritoneal membrane, less dialyzer »*
- Speculation : *discrepancy between urea (high range) and creatinine (low range) adequacy parameters could be a risk factor for clinical outcome, especially a factor of bad statural growth*

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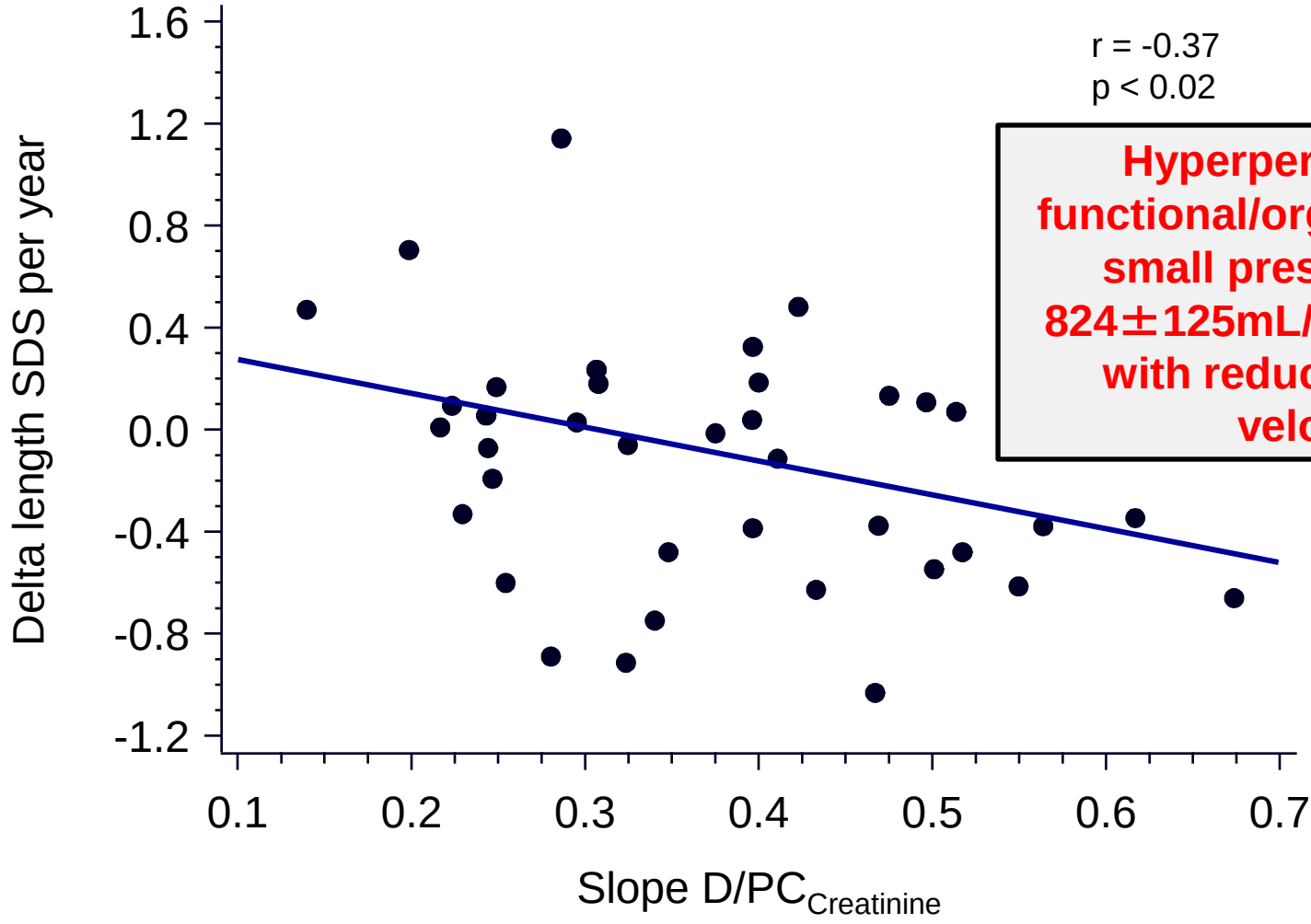
PD transport characteristics and length gain: importance of the wetted membrane



Hyperpermeability, functional/organic : « too » small prescribed IPV 824±125mL/m² correlated with reduced growth velocity

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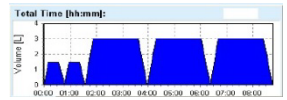
Schaefer F et al. JASN 1999; 1786-92

How to assess adequate dialysis: not a unique marker/surrogate

- Repeated **dietary** counselling (water, salts, protein, acidosis…)
- Achieve sufficient **ultrafiltration** (glucose exposure/metabolic cost)
- Optimize solute clearance to achieve acceptable/normal plasma values and body content (“not only urea”, creatinine, phosphate,sodium,pH, albumine…)
- **Individually adapted prescription** of dwell volume to BSA and IPP, of dwell numbers and dwell time according to PET; concept of adapted Peritoneal Prescription (A-APD) 
- Perform PET initially, at least yearly and if major problems with PD occur
- Measure residual renal function +++ (e.g. every 6 months)
- Follow growth rate and cardiovascular (BP, LVH…)outcome: volume control

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PD Adequacy parameters

- Kt/Vurea and Creatinine clearance, Phosphate, β2microglobuline : « not only urea » ?

- Adult targets (historically) are considered the lower limit of adequacy for children (factor 30/creat versus urea):

  CAPD: CCR > 60 l/1,73 m²/week and Kt/V > 1.7-2/week

  APD: CCR > 63 l/1,73 m/week and Kt/V: > 1.7-2.1/week

- *No pediatric reference values! and today guidelines suggest hydration status assessment of major importance* (volume control: BP, LVH, water and sodium ; BCM®: body composition monitoring) : *patient outcome is "better" correlated to volume control than to the achieved Kt/Vurea*

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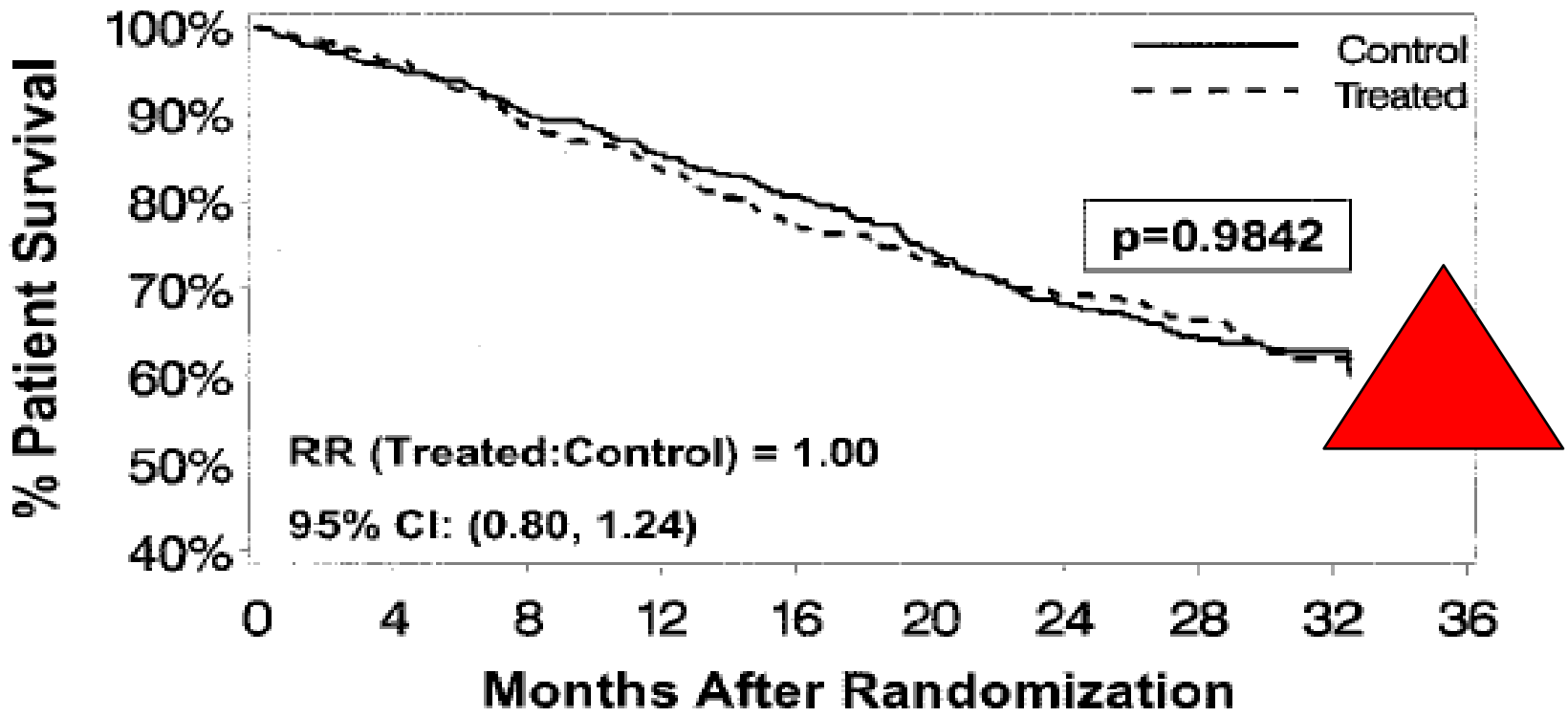
ADEMEX STUDY : Kt/Vurea (+30%) impact ?

no mortality/morbidity impact of an increased Kt/Vurea (+30%) in adults : CCR 60 vs 45 et Kt/V 2.1 vs 1.6 *R. Paniagua et al., JASN, 2002*



R. Paniagua et al., JASN, 2002

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The impact of **strict volume control** strategy on patient survival and technique failure in peritoneal dialysis patients.

Kircelli F et al. Blood Purif. 2011; 32: 30-7

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

Euvolemia is probably a more important adequacy parameter than small solute clearance (urea) as fluid status, but not small solute clearance predicts outcome

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

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Fluid status in PD patients: the European body composition monitoring (EuroBCM) study cohort

W. Van Biesen et al PLOS ONE 2011; 6(2): E17148; 2011

- 639 PD patients from 28 centers, 6 countries
- **Only 40 % normovolemia !!!**
- 60 %
  - 7 % underhydrated
  - 53 % overhydrated
  - 25%>15% OH; severe OH
- **BP and OH were not directly related (discrepancy)**
- **OH was correlated to the permeability** (more OH if highly permeable), not correlated to RRF

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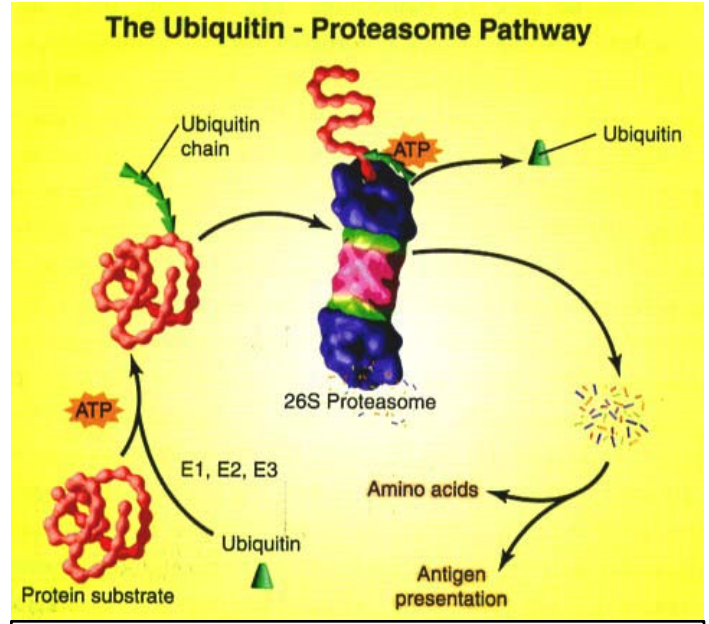
volume overload, a factor of inflammation and cachexia in CKD

Cheung WW, Paik KH, Mak RH. Pediatr Nephrol 2010; 25:711-24

The nutritional importance of the « volume control » :

Brink M. Price SR, Chrast J. Bailey JL, Anwar A, Mitch WE, Delafontaine P (2001) *Angiotensin II induces skeletal muscle wasting* through enhanced protein degradation and down-regulates autocrine insulin-like growth factor I. Endocrinology 142:1489-1496

Zhang L, Du J, Hu Z, Han G, Delafontaine P, Garcia G, Mitch WE (2009) IL-6 and serum amyloid A synergy mediates *angiotensin II induced muscle wasting*. J Am Soc Nephrol 20:604-612



from WE Mitch, Nobel Price

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protein wasting/cachexia in chronic kidney disease

Fouque D et al (2008) Kidney Int 73:391-398

- Inflammation, a multifactorial event : ***volume overload, dialysis biocompatibility***
- Nutrition, malnutrition (restricted and limited, anorexia, food intake), body weight, body composition (fat tissue, lean tissue) : importance of the adipocytes, glucose metabolic cost in PD ?

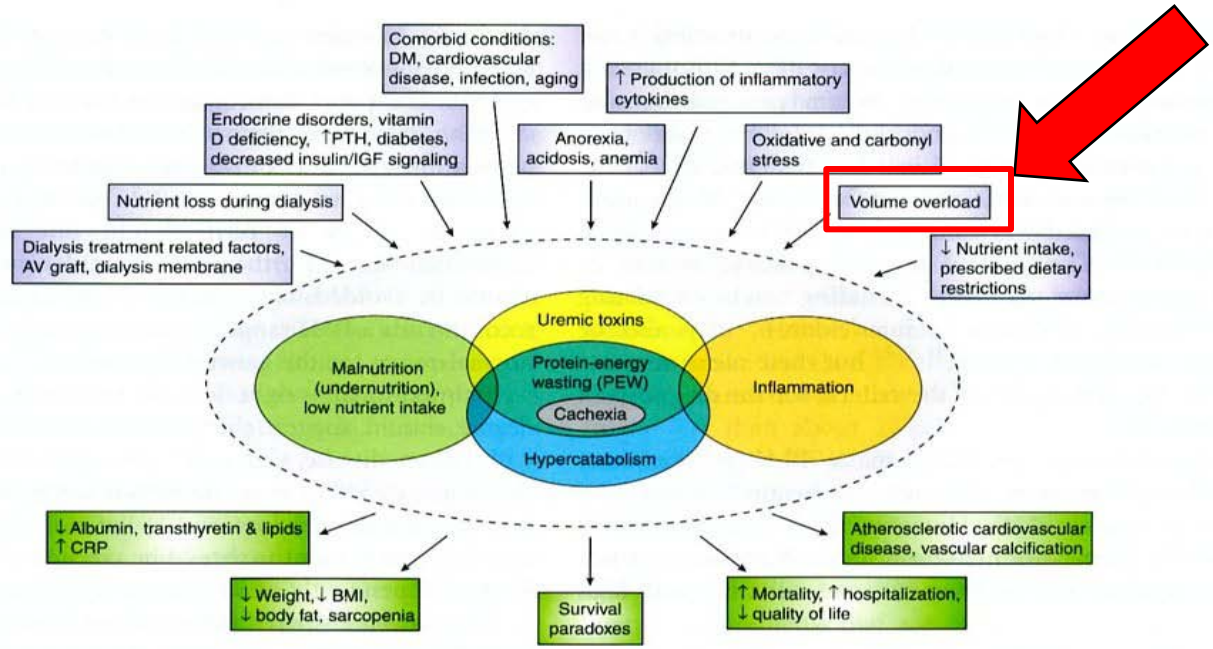

Figure 1 | Schematic representation of the causes and manifestations of the protein–energy wasting syndrome in kidney disease.

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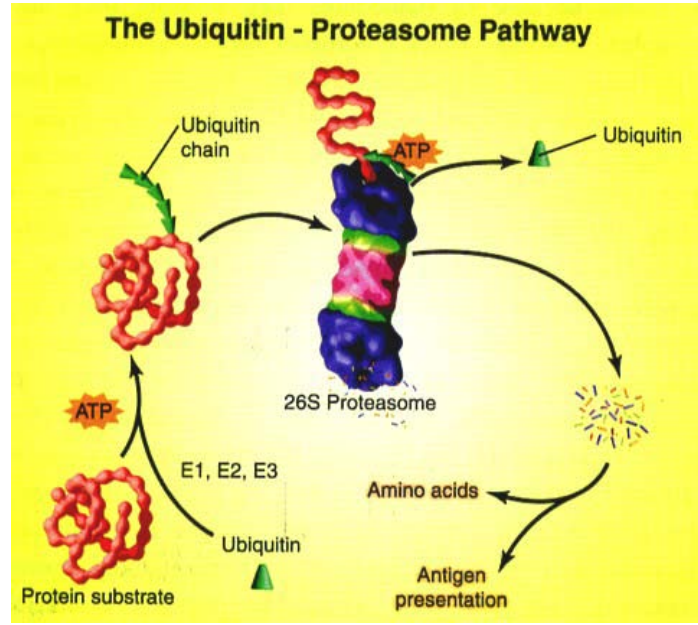
Cachexia in uremic patients : loss of protein stores, muscle wasting, growth impairment :

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
VR Royan, WE Mitch. Pediatr Nephrol 2008; 23:527-35

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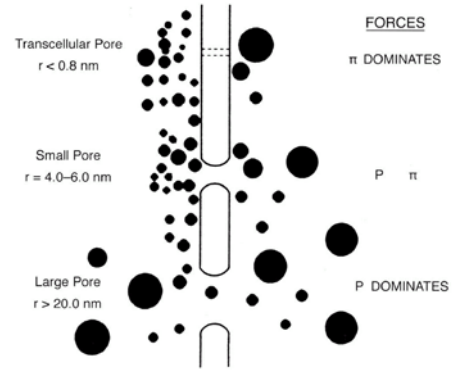
The personal Dialysis Capacity test is superior to PET to discriminate **inflammation** as the cause of fast transport status in peritoneal dialysis patients

W.Van Biesen et al. Clin Am Soc Nephrol 1:269-274, 2006

- **Inflammation** (CRP>10 mg/l) is corraleted to an increment in large pores recruitment (J_VL)
- The increment in large pores recruitment (not correlated to a proportional enhancement of a vascular surface area ; Ao/dX) is a **mortality risk factor**
- If only Ao/dX increase (peritoneal surface area, PSA) (without inflammation, without J_VL increase) the outcome can be improved by increasing the fill volume or by the use of icodextrin, whereas in case of inflammation this will not change the overhydratation/mortality risk



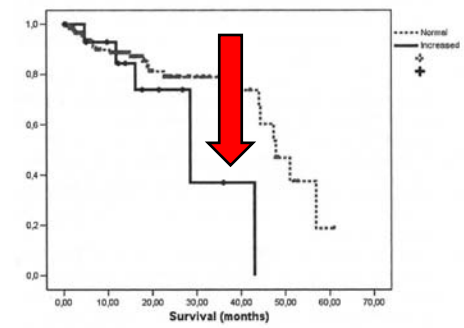


Figure 1. Survival of patients with or without increased larger pore flux (J_vL; corrected for age, diabetes, C-reactive protein and serum albumin, and potential interaction terms). Patients are divided into those with a J_vL higher than expected by their surface area over diffusion distance (A0/dX; "increased," solid line) and those with a normal J_vL as related to their A0/dX (normal, dotted line). $P = 0.04$.

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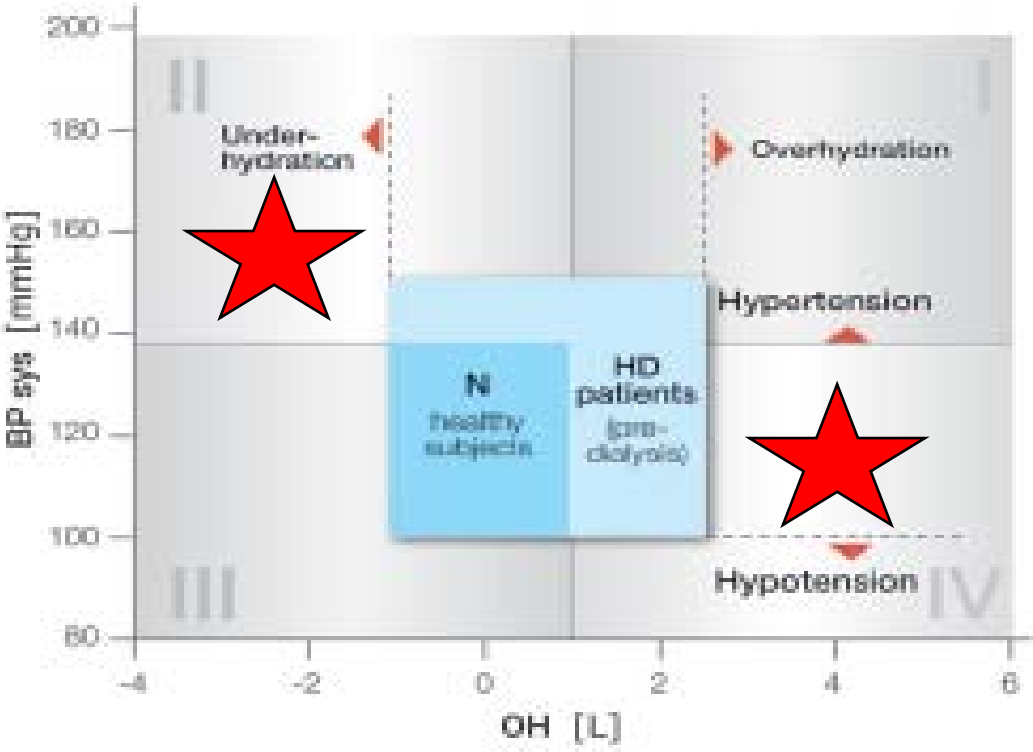
Blood Pressure versus hydration in patients on dialysis : « box plot », importance of the BCM evaluation



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)…

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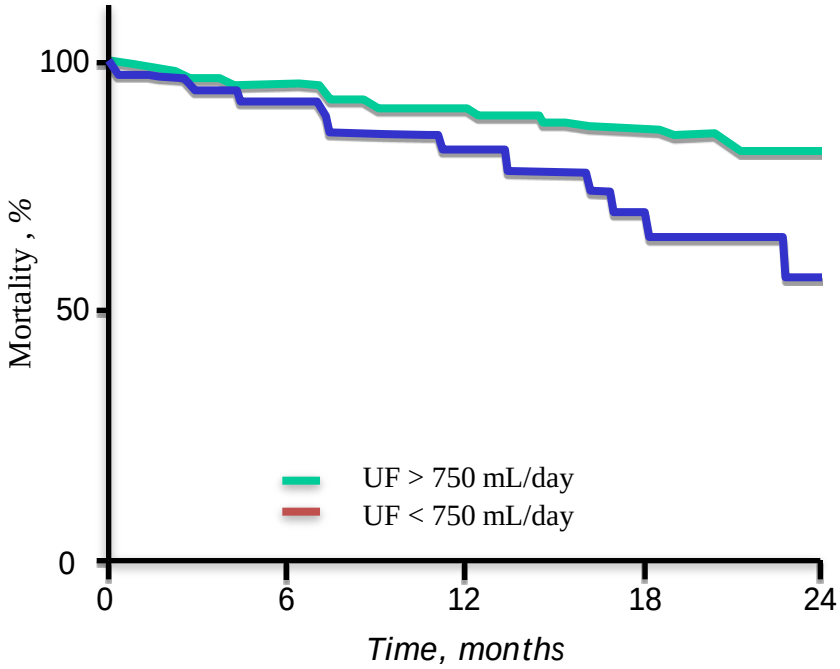
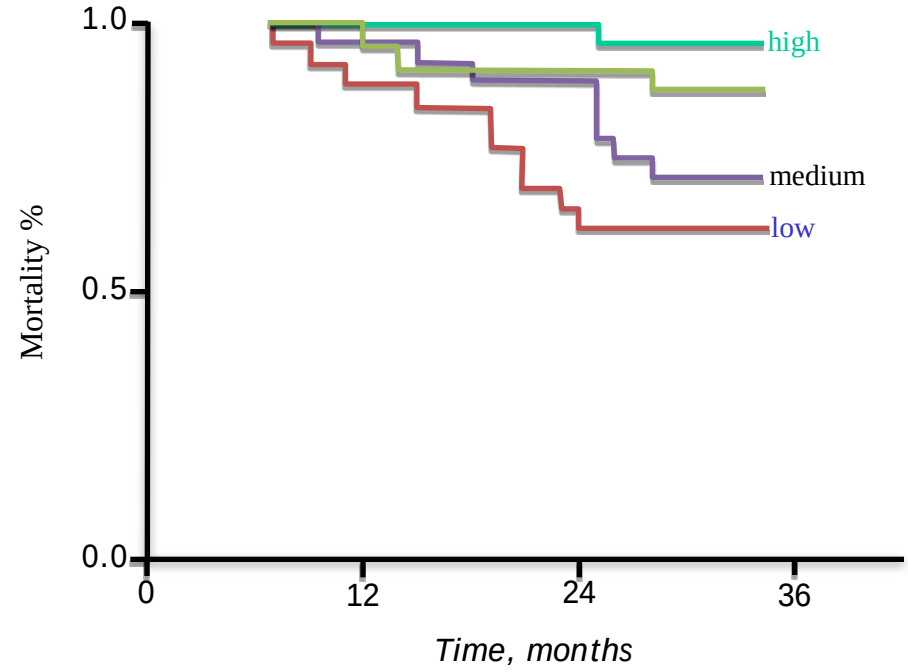
impact of both: the UF amount (mL) and the Na dialytic removal for patients outcome

From Brown EA et al. J Am Soc Nephrol 2003 and Ates et al. Kidney Int 2001

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

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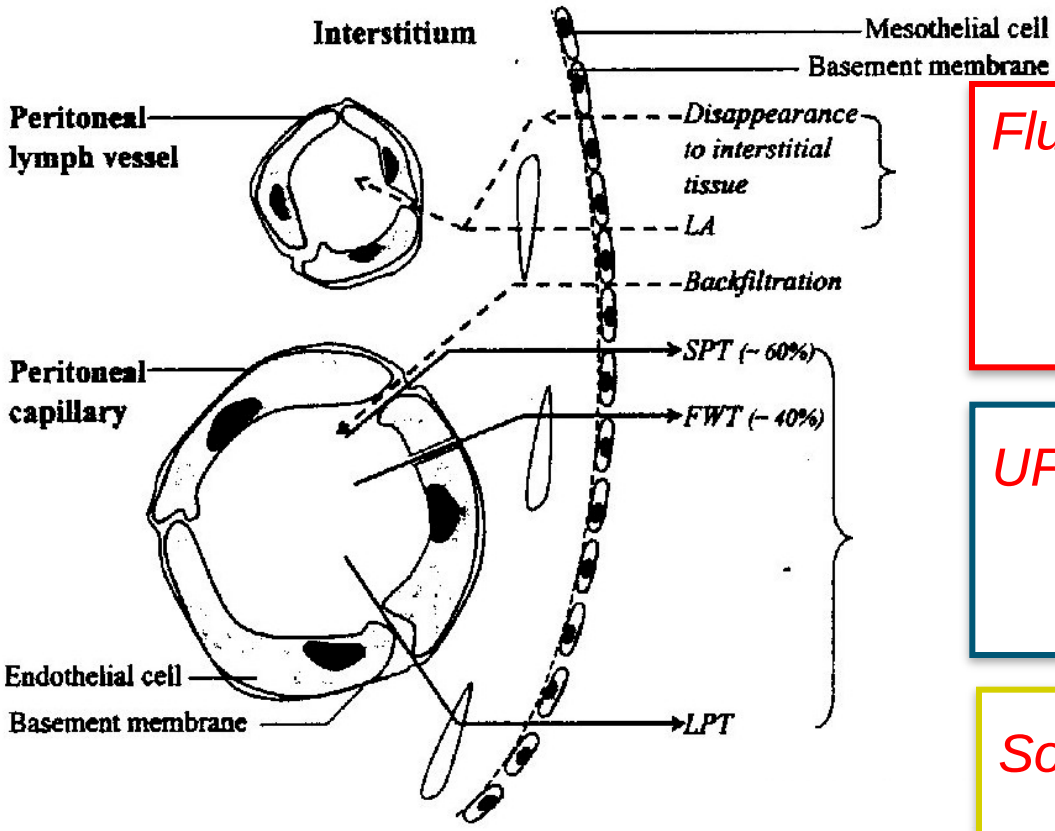
The three pores theory. B Rippe 1991



$$NUF = \Delta IPV = TCUF - ELA$$

Fluid Reabsorption :

- Interstitial Space (tissular oedema)
- Capillaries (0.9ml/min)
- Lymphatics (0.2-0.3ml/min)

UF:

- AQP1 (40-50%)
- Small pores (50-60%)
- Large pores (insignificant))

Solute removal: urea, creatinine, sodium

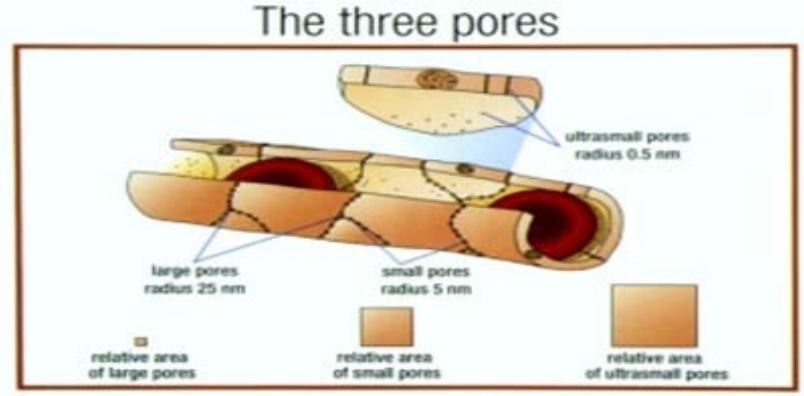
- 99% via small pores
- Large pores (proteins)

Modifiers of the "three pores theory":

⇒Individual (genetic / PD related) membrane function : AQ1, mesothelial cells

⇒IPP, pressure gradient, vascular perfusion

⇒Peritoneal contact surface area, the "wetted" membrane ("50% recruitment")



Transport across the Peritoneum

Rippe B et al. Kidney Int 40, 1991

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)

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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

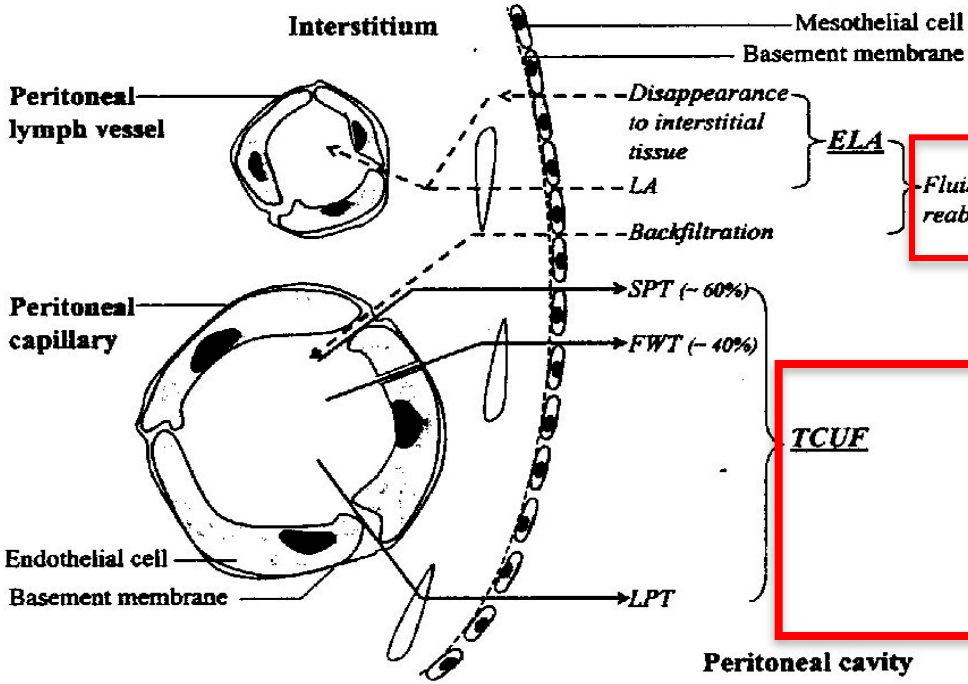
(Small pores)

Coupled water (convective; drag+lag)

Diffusion gradient

Diffusion distance

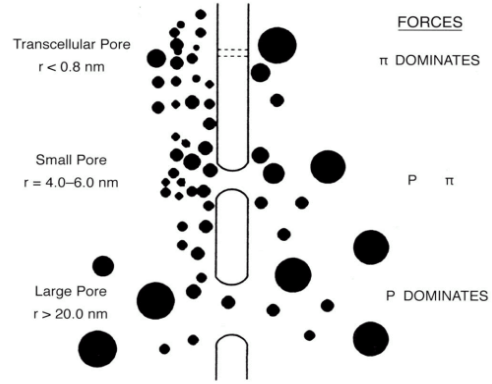
(ratio area/fill)



$$NUF = \Delta IPV = TCUF - ELA$$

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 (ΔIPV) 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.

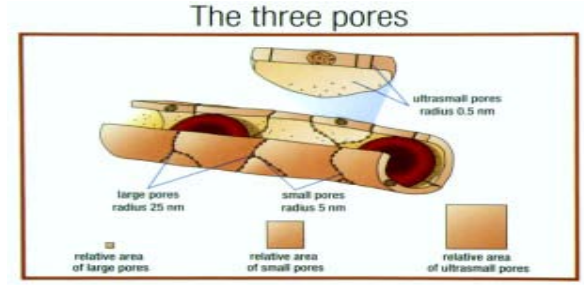
from Coester AM et al. NDT plus 2, 2009



and tissu oedema

UF : AQ1 (40/50%) +
small pores (60/50%)
large pores (negligible)

Rippe B et al. Kidney Int 40, 1991



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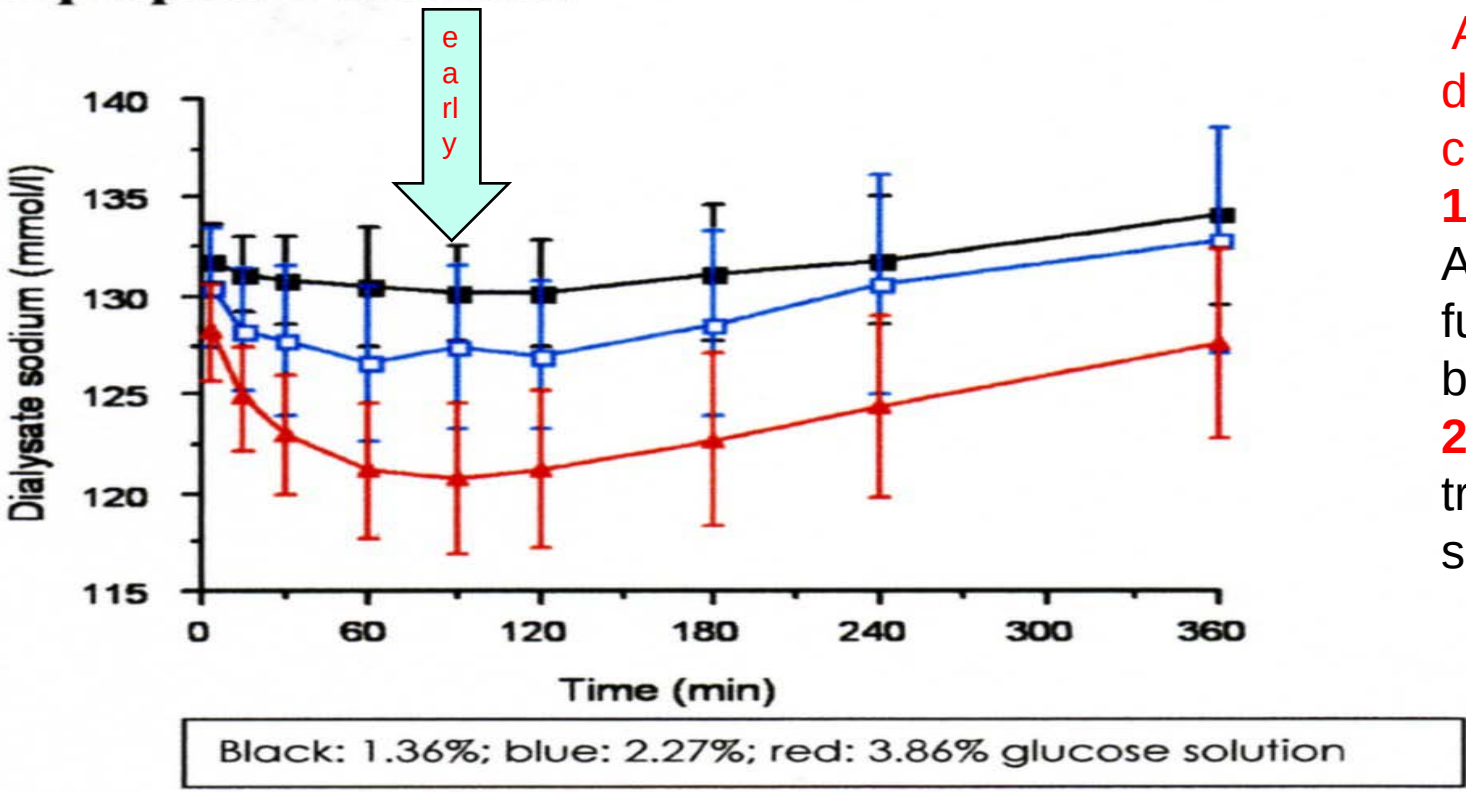
Sodium sieving (NaD): early in dwell

« small pores function impact on AQ1function »

small solute transport rate, glucose conductance

Appendix 3: the concept of sodium sieving and aquaporin function



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).

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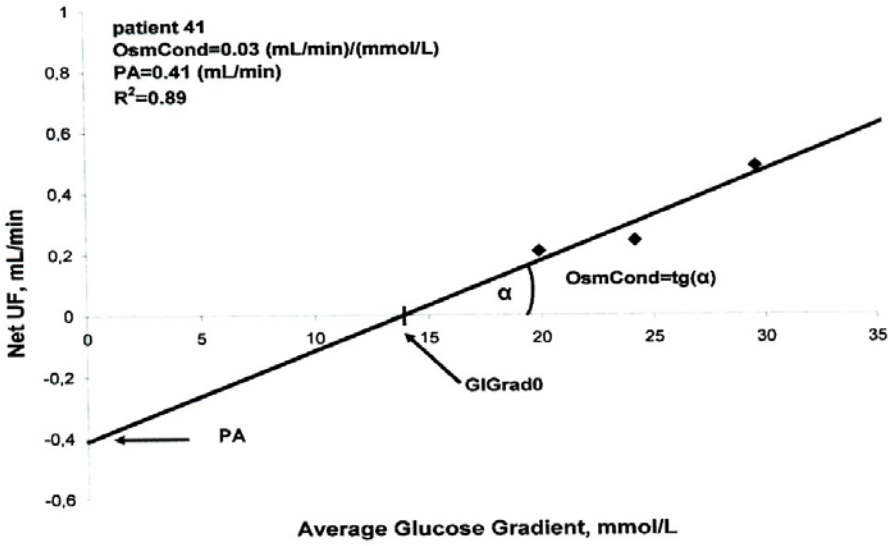
Evaluation of peritoneal membrane characteristics: a clinical advice for prescription management by the ERBP working group
Wim van Biesen et al Nephrol Dial Transplant (2010) 25: 2052–2062

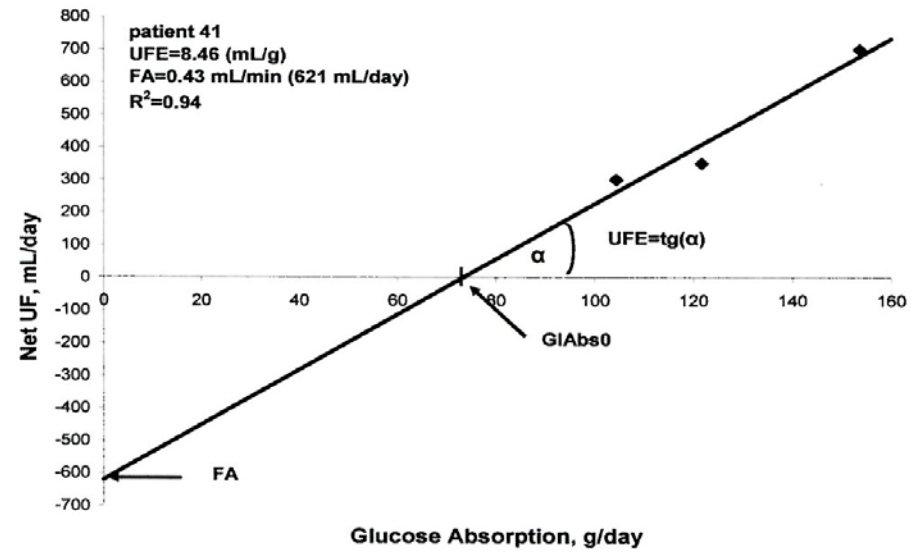
Threefold peritoneal test of osmotic conductance, ultrafiltration efficiency, and fluid absorption

Waniewski J, Paniagua R et al. Perit Dial Int 2013; 4(vol 33):419-425

Osmotic conductance mL/min over mmol/L gradient



UF Efficiency mL/glucose absorption



glucose conductance or metabolic cost of UF (*Fischbach M et al. Advances in Peritoneal Dialysis 10, 307-309, 1994*) mL/gr glucose absorbed or delivered

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Volume control in PD patients , ultrafiltration and sodium removal

Optimizing PD prescription for volume control:
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(mL; AQ1+Small pores)

1) AQ1, solute free water

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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 gradient/time (and convection)

Small pores recruitment (wetted membrane)

- PSA recruited/available (fill volume)
- Fill volume of dialysate (Cl=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 : Na_{plasma} – NaD (sodium intake/NaD)

Diffusion time: dwell time

Convective transport : coupled with water (drag/lag)

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Optimizing PD prescription for volume control: the importance of varying dwell time and dwell volume

M Fischbach et al. Pediatr Nephrol 2014

	Hemodialysis	Peritoneal Dialysis
Ultrafiltration (mL)	Water removal by filtration (iso-osmotic, isonatric, via a pressure gradient)	~ **50 % via aquaporin 1** (osmotic gradient): sodium-free UF , early in dwell ~ **50 % via small pores,** transport of water and solutes (concentration and pressure gradient), coupled UF, later in dwell
Sodium (Na) removal	~ 80 % by convection (UF) ~ 20 % by diffusion (NaPl – NaD gradient)	**Mainly via small pores, coupled and by diffusion** (NaPl-NaD gradient)
Body weight loss: 1kg	**1L: 80% Na and water**	**1L : only 50% Na and water**

NaPl: plasma sodium concentration ; NaD: dialysate sodium concentration ; UF: ultrafiltration

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Mechanics of peritoneal dialysis

- Peritoneal surface area recruitment, the wetted membrane : a dynamic dialysis membrane
- Fill volume prescription in mL/m^2
- Intraperitoneal pressure measurement an objective parameter of tolerance, to secure the prescription
- Diffusion time , from the PET to the dwell time
- Adapted peritoneal dialysis :
  - Ultrafiltration favored (small fill/short dwell)
  - Purification favored (large fill/long dwell)
- Aquaporines function (biocompatibility of the PDF's)

Fill volume prescription :

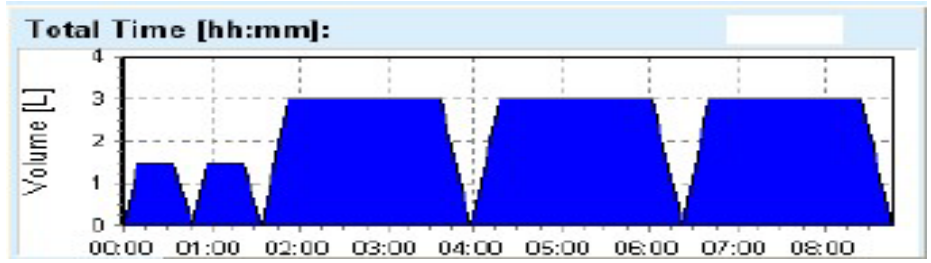
small or large, not a unique choice +++

Can the patient tell the difference ?

A dilemna solved by intraperitoneal pressure measurement.

Prof. Dr. M. Fischbach

University Hospital of Strasbourg,France



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Fill volume

1) Tolerance, Intra peritoneal pressure (IPP)
2) Impact on peritoneal surface area : the dialyzer recruitment, the wetted membrane
3) Impact on dialysis efficiency

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Fill volume and tolerance(1)

- ***Patient perception of the filled cavity*** *: limited value of such a too subjective parameter*
- *Too large a fill volume (too high the IPP):*
  - Pain
    - Supine/upright
    - Filling process, draining process (empty perception)
    - Diaysate (pH)
  - Hernia (inguinal)
    - Boys/girls
    - Age dependency
  - Vomiting, anorexia, appetite

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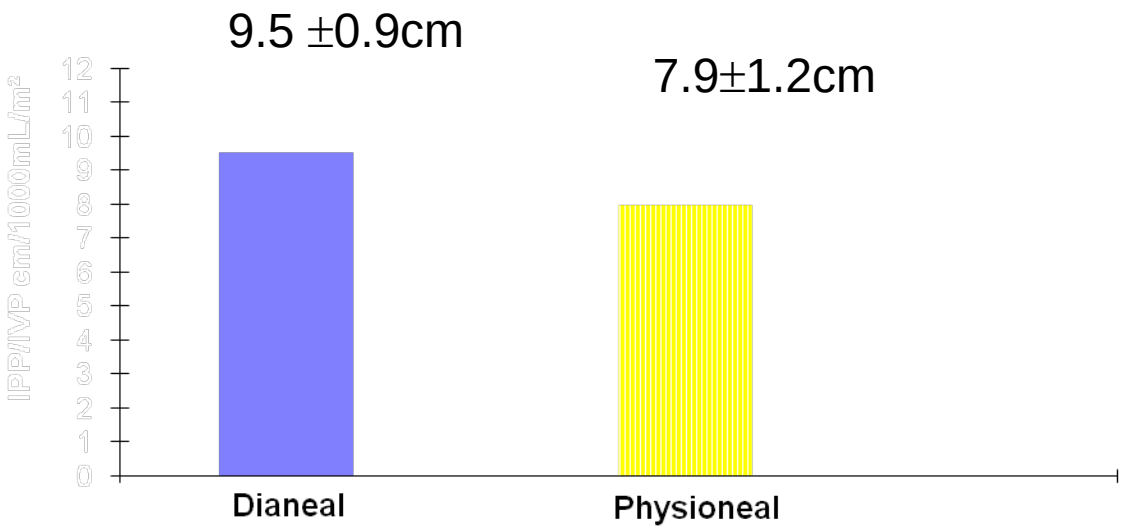
Intraperitoneal pressure (IPP cm) normalized for fill volume (IPV; 1000mL/m²) in children (N=6) :

an objective parameter of tolerance/pain,

less pressure with the new more physiological solutions, pH neutral



n = 24 data paired ; p<0.01

- less IPP less pain?
- less IPP could allow IVP optimization/increase

M.Fischbach , B.Haraldsson Nephrol Dial Transplant 2004

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Too high an intraperitoneal pressure

- Patient discomfort, poor compliance
- Anorexia, vomiting
- Abdominal wall complications (hernia)
- **Reduced UF** (pressure gradient) due to « tissue absorption/oedema (change in permeability ?) more than simple back filtration (lymphe/vessel)
- **Enteric peritonitis risk** (Dejardin et al. NDT 2007; PIP>13 cm) : ???
- **Avoid an IPP> 18cm (in practice « security » of 15 cm, supine, at rest)**

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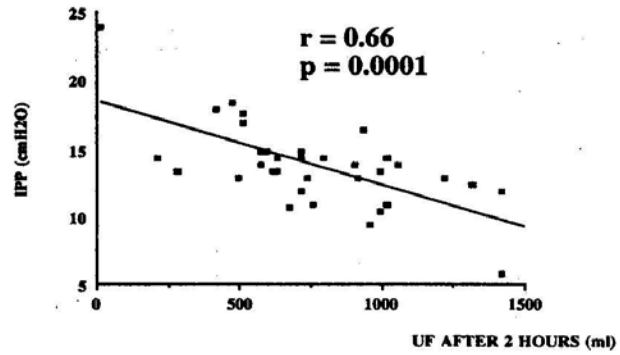
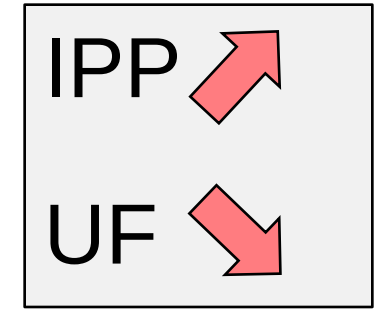
Intraperitoneal hydrostatic pressure and ultrafiltration volume in CAPD

Durand PY et al. Adv Perit Dial 1993 ; 46-8

- **The linear regression test showed that any increase of 1 cm H_2O in the IPP mean reduced the overall UF volume by 70 ml in 2 hours dwell (Dianeal® 3.86 %)**





- **IPV 2820 ± 319 mL ; IPP 13 ± 3.5 cm**
- **UF 744 ± 323 mL after 2 hours dwell**
- **Mean IPP correlated to UF volume : r=0.66 ; p=0.001**

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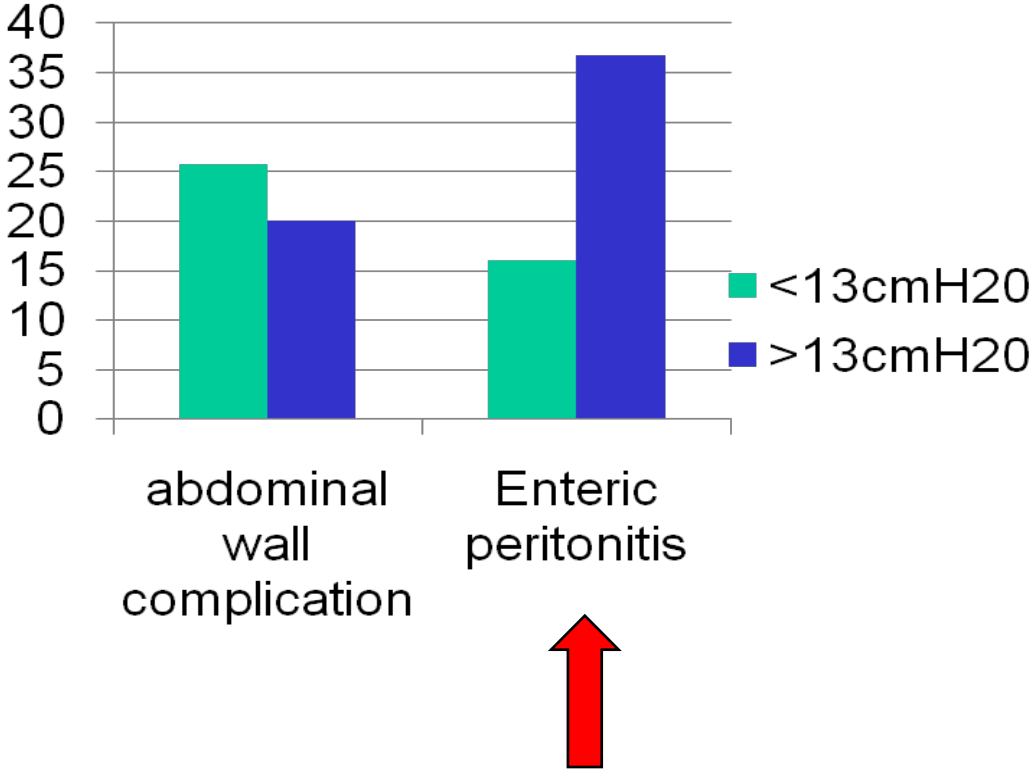
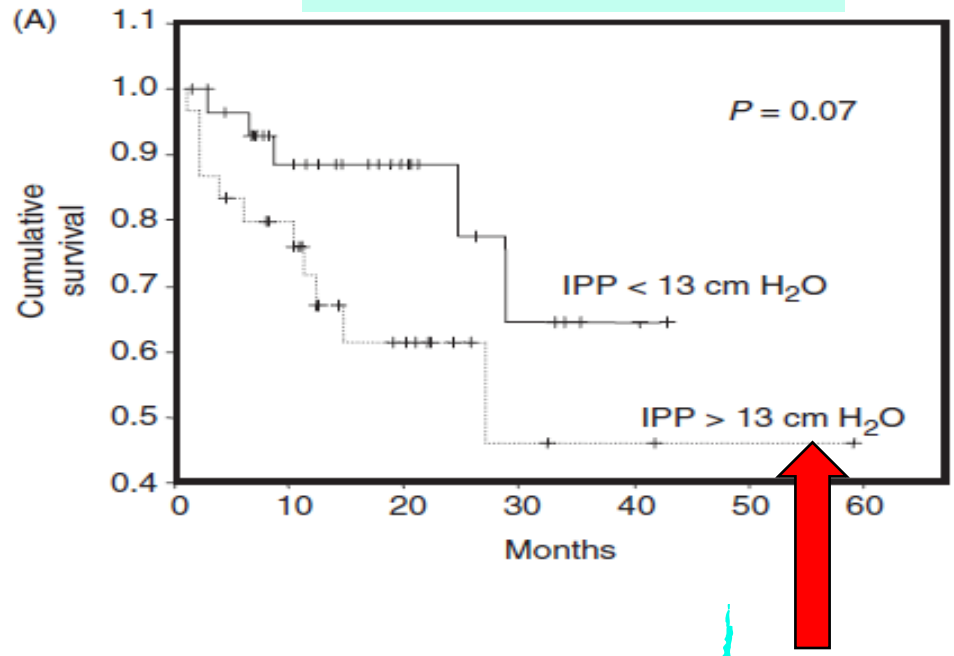
Intraperitoneal pressure in PD patients: relationship to intraperitoneal volume, body size and PD-related complications. *Dejardin A, Robert A, Goffin E.*

Nephrol Dial Transplant 2007;22(5):1437-44.



Peritonitis free survival



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Tolerance of large exchange volumes by peritoneal dialysis patients

Sarkar S et al. Am J Kidney Dis 1999; 33:1136-41

- 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 m^2 (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 m^2 BSA)
- ***False perception of the filled volume is usual : need for an objective assessment : IPP measurement***

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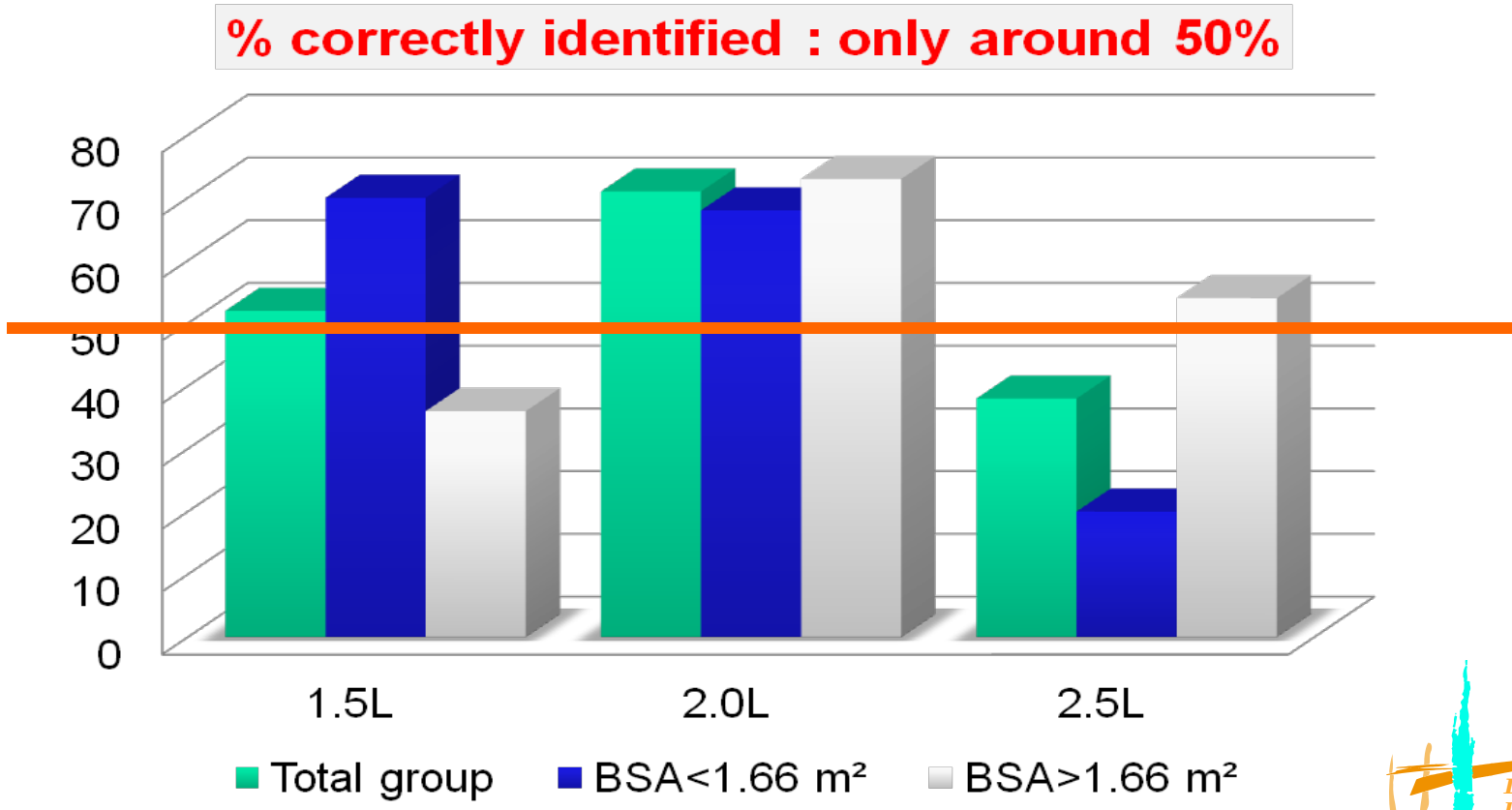
Percentage of fill volumes correctly identified by actual instilled volume for total patient group and for patients grouped by : (BSA)<1.66 m² and BSA>1.66 m²

Fukatsu A. PDI 2001



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Fill volume prescription : adjustements

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

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

Measure the intraperitoneal pressure

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The pressure measurement :

How to procede?

How to measure ?

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

« Baxter video »

- Patient conditions
- Supplies
- Procedure
- Results : IPP in cm H_2o

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Thank you to:

Djehina and Louise

Secretary assistance: Evelyne Jung

Video assistance: Sophie Flambard (Baxter)

Nurse assistance: Carine, Claudine, Agnes

Supported by BAXTER SAS Maurepas, France (2003)

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Normal hydrostatic intraperitoneal pressure: correlation to the intraperitoneal drained volume

Avoid an IPP > 18cm

	IPP cm H_2O	IPV mL/m² BSA
In adults	13.4 ± 3.1	1585 ± 235
In children over the age of two years	5.2 ± 2.6	600 ± 50
	8.2 ± 3.8	990 ± 160
	14.1 ± 3.6	1400 ± 50

from P.Y.Durand(1992) and M.Fischbach (1994)

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Fill volume and intraperitoneal pressure

- IPP, objective parameter of tolerance
- IPP and ultrafiltration capacity
- IPP related to fill volume
- IPP at the best correlated to BMI

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Fill volume

1) Tolerance, Intra peritoneal pressure (IPP)
2) Impact on peritoneal surface area : the dialyzer recruitment, the wetted membrane
3) Impact on dialysis efficiency

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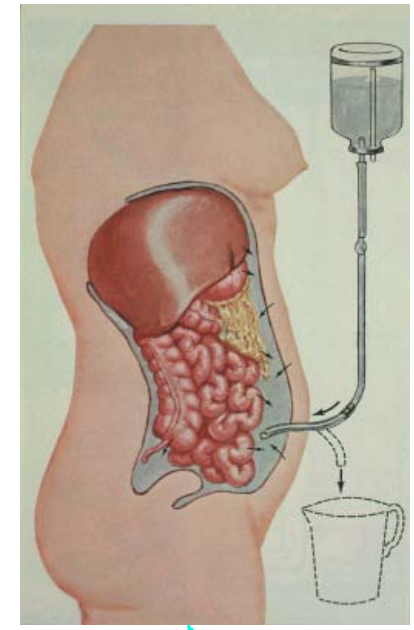
Fill volume and in vivo peritoneal surface area recruitment (2)

- A dynamic dialysis membrane : recruitment capacity (wetted membrane), until a peak volume, impact on MTAC (MTC x Area)
- Fill volume and patient position +++



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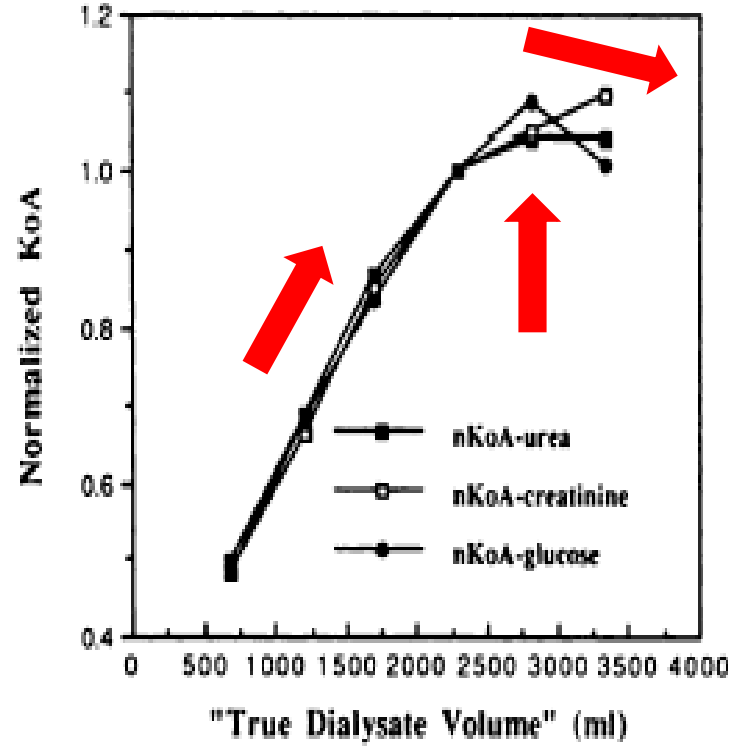
Impact of a large fill volume on small solute transfer, on PSA recruitment (coupled water/small pores)

- positive relation between fill volume and clearance : K_{urea}= D/PxV, more valid for urea (volume dependency) than for phosphate (time dependency)
- Peak volume : high IPP

  « retrofiltration »/tissu oedema ;)
- **Fill volume and dialytic efficiency (MTAC) :**

  PSA recruitement; « wetted » membrane; more « pores » (small pores: coupled solute and water removal) +++



Relationship between body size, fill volume, and mass transfer area coefficient in peritoneal dialysis.

***Kesaviah P**, Emerson PF, Vonesh EF, Brandes JC. JASN* **1994**,4(10):1820-6.

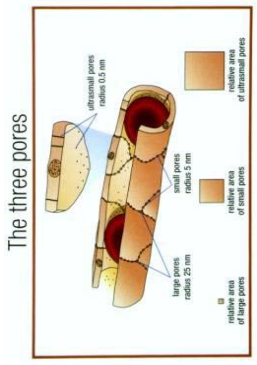
Effect of fill volumes on PSA recruitment :

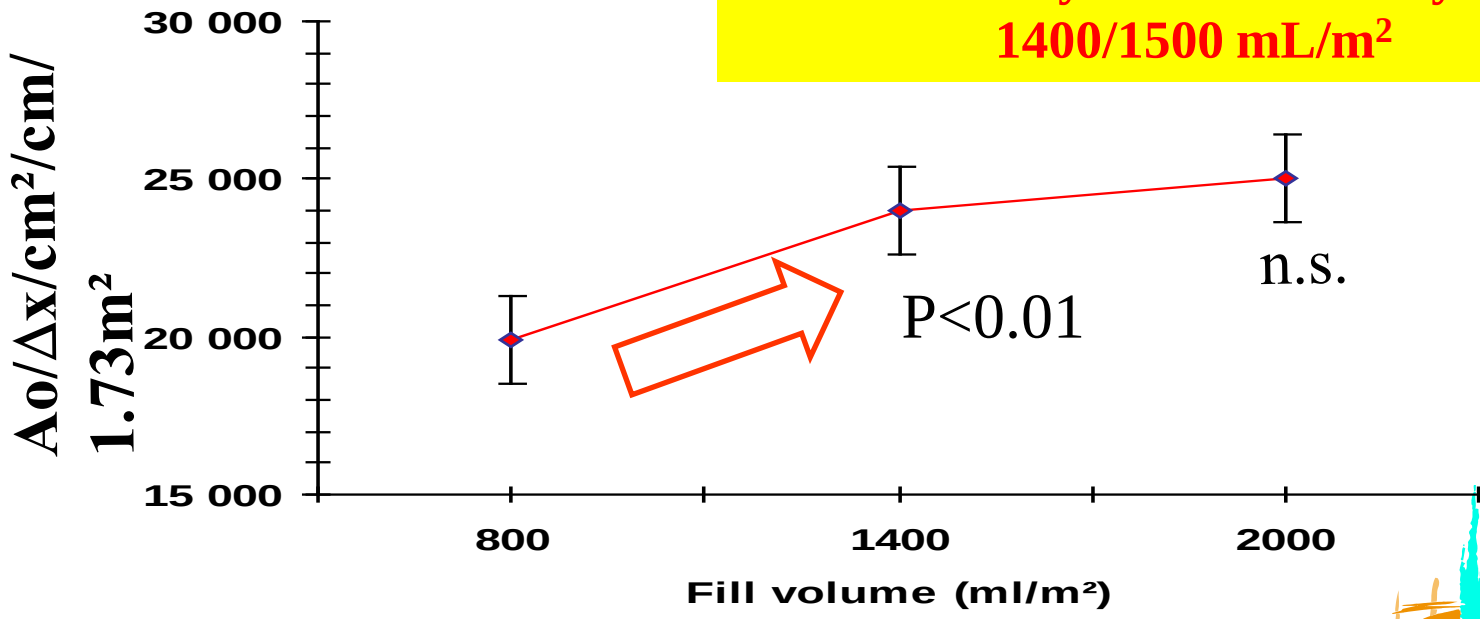
Ao/Δx increased significantly, +21 %, from19900±1200 to 24 000±1.450, as the fill volume was raised from 800 to 1400 ml/m² BSA.

A further increase to 2.000 ml/m² did not result in any significant change of Ao/Δx, 24 500±1.700 (N=8)

Fischbach M, Haraldsson B, JASN 2001; 1524-29

+ 21% « more dialyzer »,
PSA « fully » recruited only at 1400/1500 mL/m²





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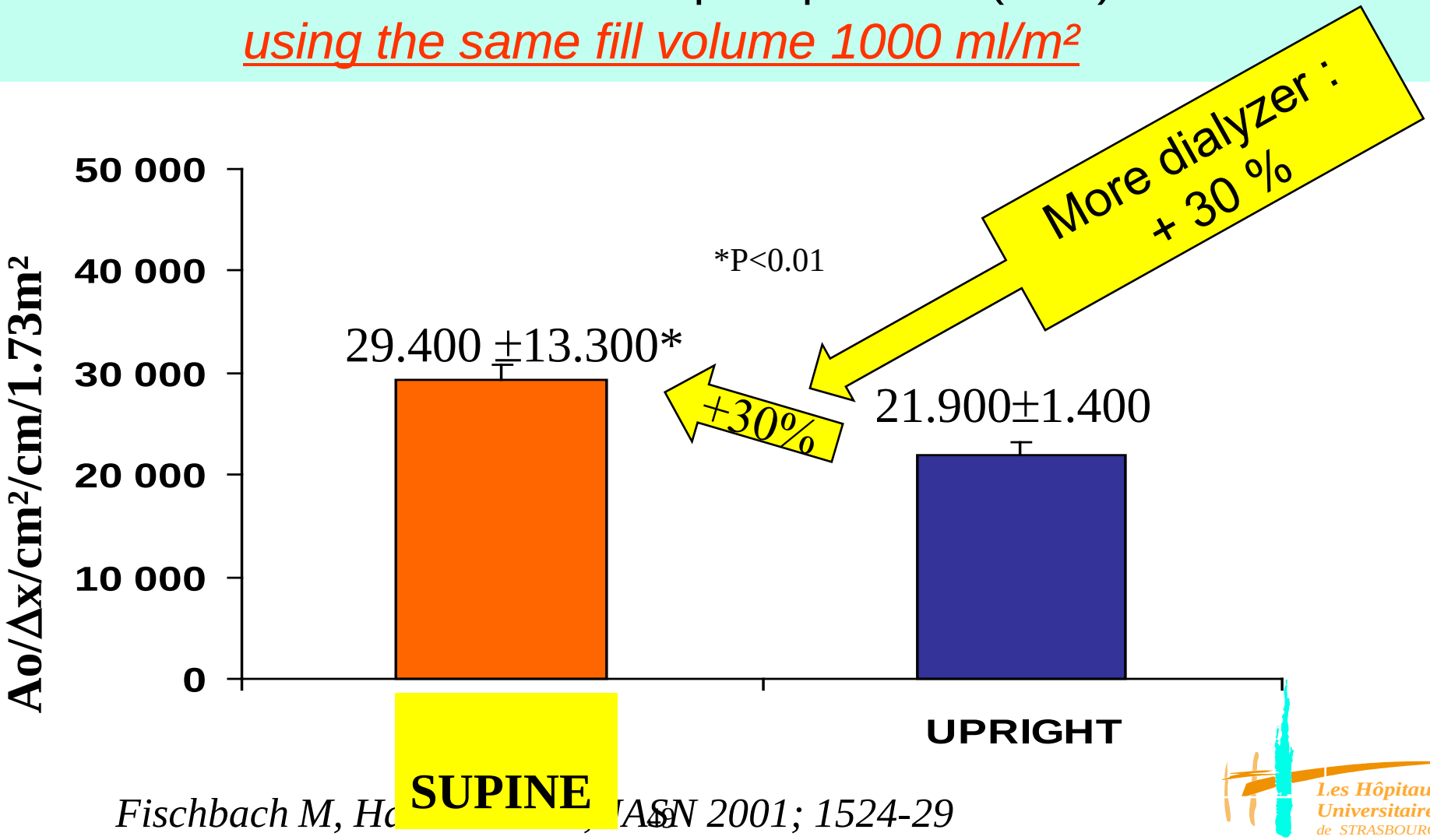
Effect of posture on PSA recruitment :

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, Ho… JASN 2001; 1524-29

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Fill volume

1) Tolerance, Intra peritoneal pressure (IPP)
2) Impact on peritoneal surface area : the dialyzer recruitment, the wetted membrane
3) Impact on dialysis efficiency

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Fill volume and efficiency(3)

- Dialytic purification capacity:

  clearance/drained volume (urea)

  peritoneal surface area recruitment

  exchange permeability (IPV/PSA)

- Ultrafiltration capacity:

  exchange permeability, (IPP/retrofiltration)

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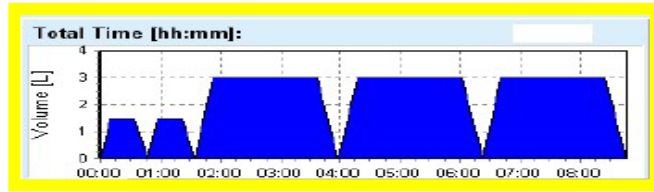
The optimal fill volume?
adapted, individually



- ✓ Which fill volume? mL/m^2
- ✓ Not a unique choice :
  - small (tolerance; patient comfort; low IPP = UF favored)
  - large (« membrane recruitment = small pores; diffusion volume »)
- ✓ Impact on both ultrafiltration capacity (small/short : AQ1 water) and purification process (diffusion volume/smallpores dialysis, more than urea : « volume control »): **exchange permeability**

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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)

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A low fill volume, even prescribed by mL/m² impact on peritoneal permeability: *« hyperpermeable exchange »*

*D/P urea ratio, peritoneal exchange hyperpermeability, « favors urea purification »

* D/D0 glucose ratio, peritoneal exchange hyperpermeability, « reduced » UF

	IVP mL/m²	*Urea*		
		D/P	K0A mL/min/m²	D_{120}/D_o glucose
Hyper	800	0.55+0.04	10.6+1.2	0.4+0.15
Normo	1400	0.48+0.07	15.3+1.6	0.6+0.10
	2000	0.40+0.06	17.1+1.9	0.65+0.08

M. Fischbach, Perit Dial Int 2000 :503-6

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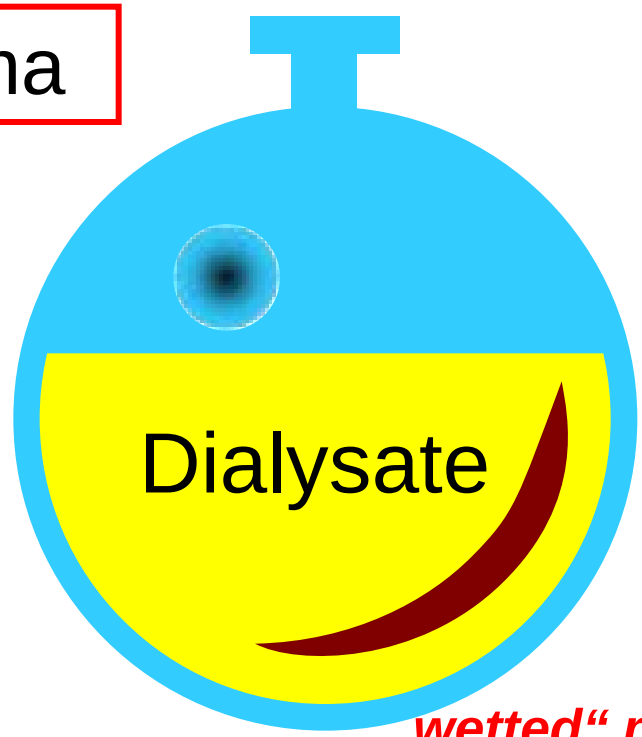
Fill volume, membrane recruitment, geometry/distance of diffusion and exchange “permeability”(small pores capacity)

Plasma



Plasma

„wetted“ membrane

Fill volume:

800 to 1000 ml/m^2

Fill volume:

1400 to 1500 ml/m^2

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Of mice and men, a matter of scale : PET/solute transfer rate

area/volume, **diffusion distance**, exchange permeability

	Mouse	Rat	Man	Infant
Weight	27 gr	300 gr	**70 kg**	5 kg
PSA (cm^2)	90	500	**17 000**	2 600
Fill volume (mL)	2.5	25	**2000/3000**	100/250
Area/volume	36	20	**8.5/5.6**	26/10.6
Time to D/P = 0.7 (min) **Exchange permeability**	50	70	240/ ? less	60/120
Time to V_{max} (4 % gl) (min)	55	100-110	240/hypo	60/120
PSA (cm^2/kg)	/	/	250	500
(cm^2/m^2)	/	/	10 000	10 000

Modified from *Rippe B, PDI 2009,S32-35*

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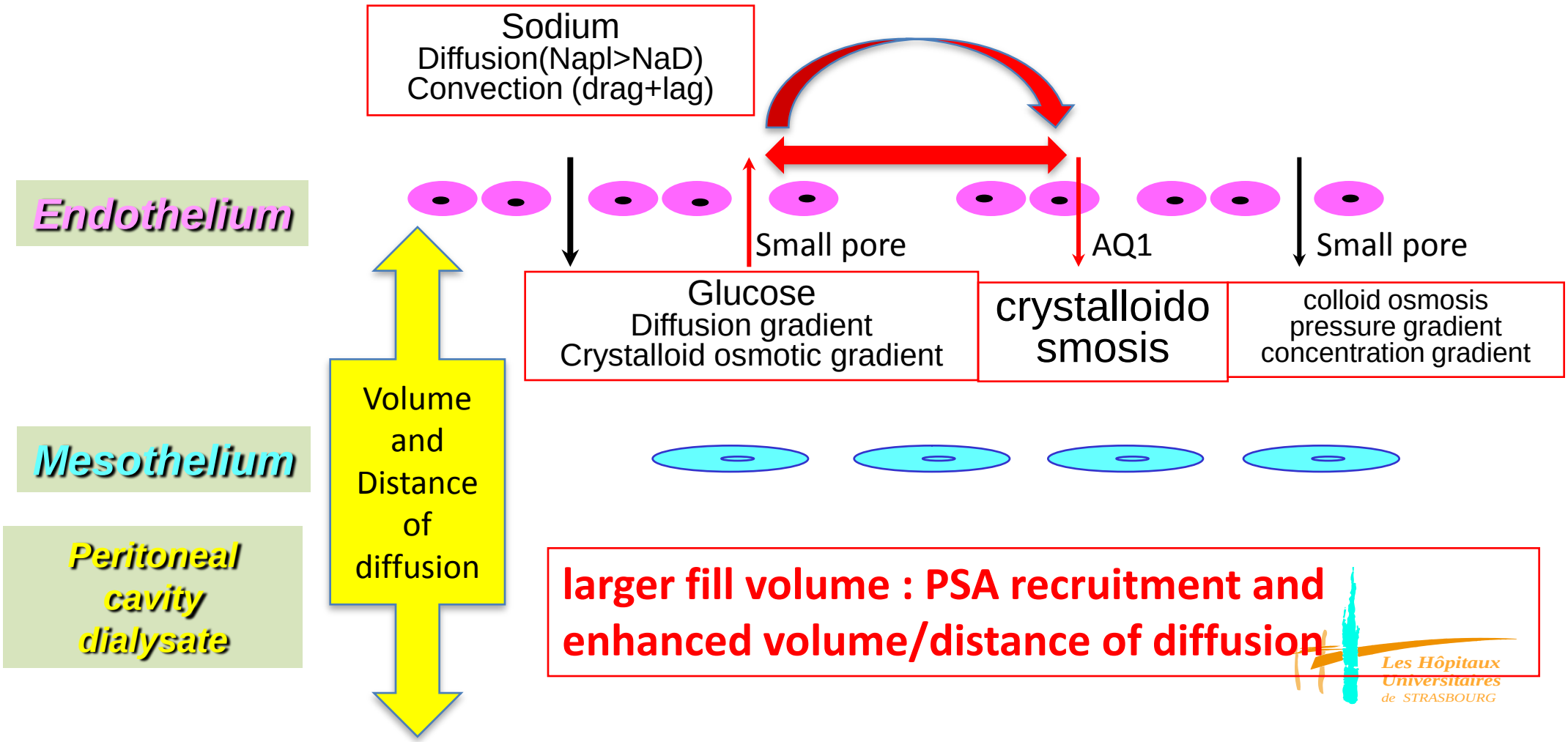
Fill volume : PSA recruitment, solute transfer rate, more pores (small pores),more distance of diffusion (preservation from too rapid a glucose loss)



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the wetted peritoneal membrane :

the exchange permeability, ivPSA/fill volume, the number of recruited pores (small pores) due to larger fill volumes

- More ivPSA, that is more pores, also the «solute coupled pores», the small pores implicated in both diffusion process and convective mass transport
- More small pores due to a larger fill volume, that is also an increased diffusion distance, which should impact on exchange permeability, on the osmotic conductance, maintained glucose osmotic cristalloid gradient, finally more UF (through the AQ1, free water)
- More small pores, that is an increased diffusive/convective mass transport capacity, more solute coupled water (sodium or others uremic toxins; drag/lags)

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Fill volume

1) *First choice in children (more than 2 years): 800 -1000mL/m^2*
2) *Increase step wise under tolerance control (maximum 1500mL/m^2)(infants 600/800mL/m^2)*
3) Intra peritoneal pressure (IPP)
4) Optimize to the patient needs : small, large

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Evaluation of peritoneal membrane characteristics: a clinical advice for prescription management by the ERBP working group, adapt individually your prescription

Wim van Biesen et al. NDT 2010; 25:2052-2062

- When negative UF (low UF) is registered, ***shortening the dwell time rather than increasing glucose concentration*** is advocated
- *Fill volume can potentially influence the « permeability »:* using « too low » fill volumes can falsely induce the impression of a fast transporter status (exchange permeability)
- *Use larger volumes* rather than more dwells (be aware of sodium sieving when using « too » short dwells)

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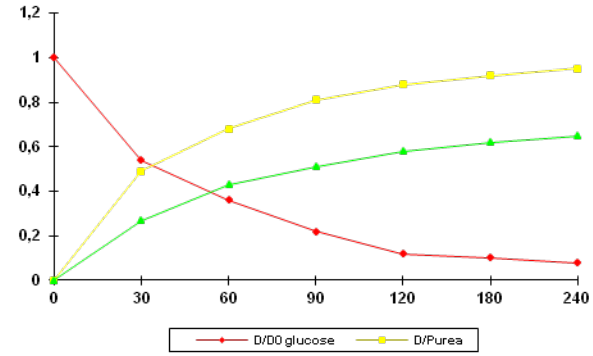
Fill volume and efficiency

- 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 peack volume (*volume dependency*)
- Bad correlation with the phosphate (and sodium) dialytic removal (*time dependency*)



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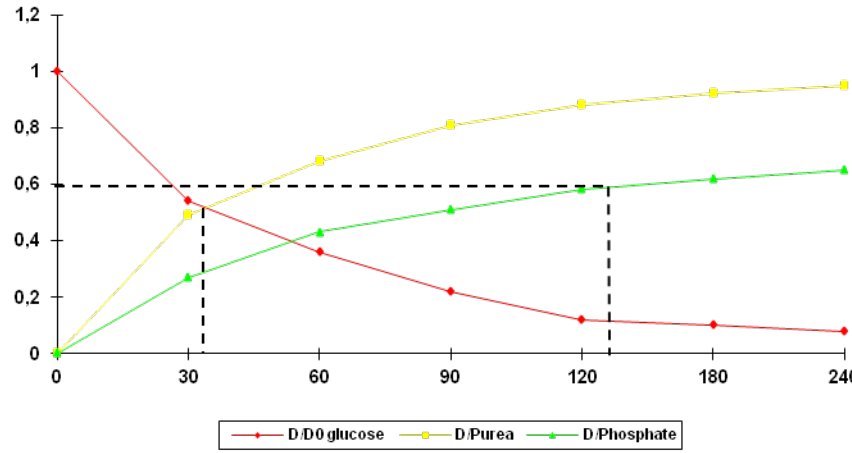
Intraperitoneal contact time: dwell time, diffusion time

- Which dwell time ?
- Not a unique choice : short/long
- Impact on both ultrafiltration capacity(maintained osmotic gradient) and purification process (diffusion time)



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Intraperitoneal contact time (Tip)

- Has a direct impact on the rate of dialysate solute saturation (D/P)
- Influences more phosphate clearance (time dependency), conversely for urea clearance (volume dependency)
- A peritoneal equilibration test for a given IPV can be used as an « index » for the prescription of the dwell time: which goal, UF or purification (urea/phosphate) ?

Fischbach M. PDI 1998

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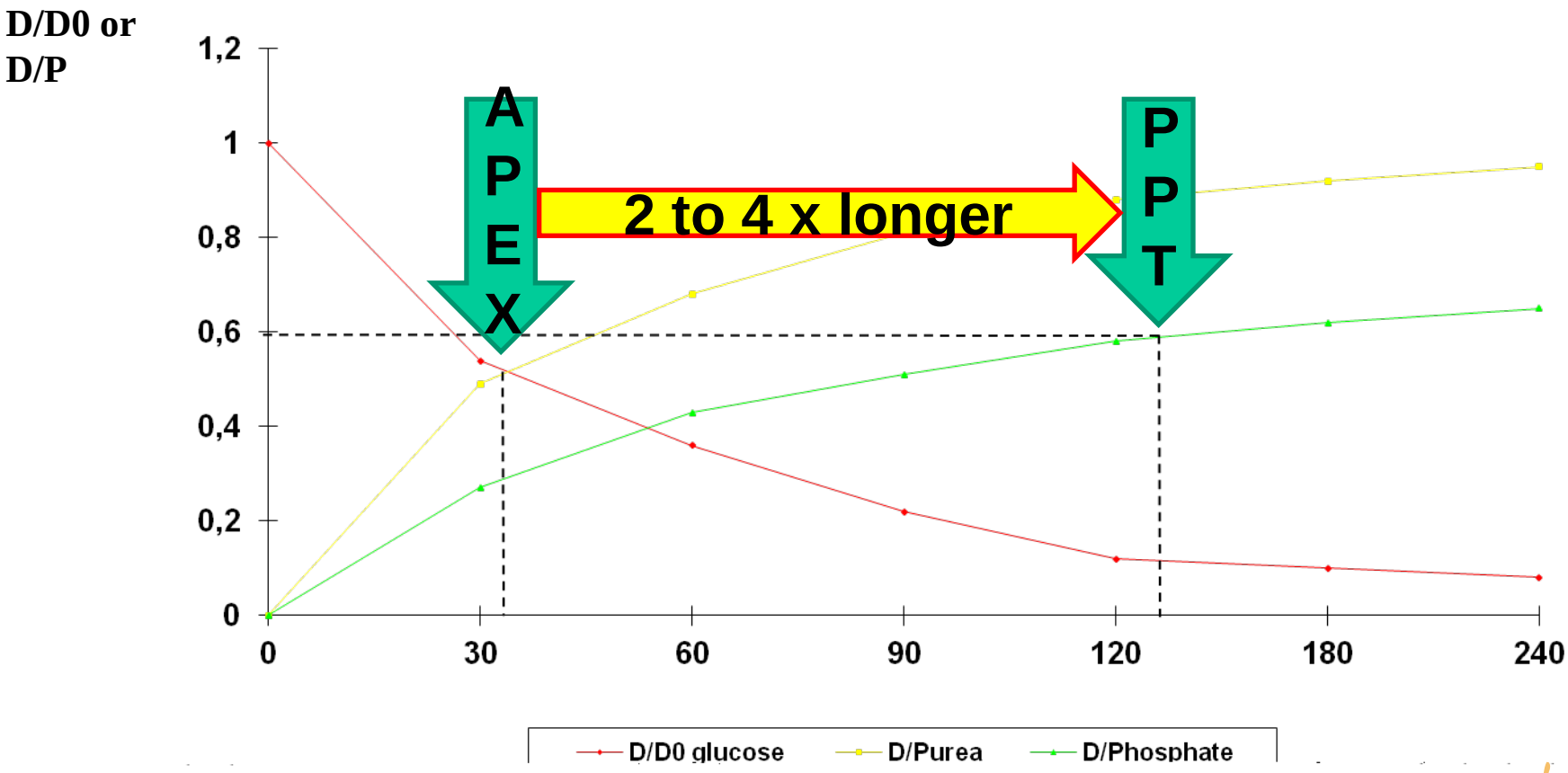
Determination of the APEX time and the PPT (phosphate purification time), D/P = 0.6.

Exemple (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



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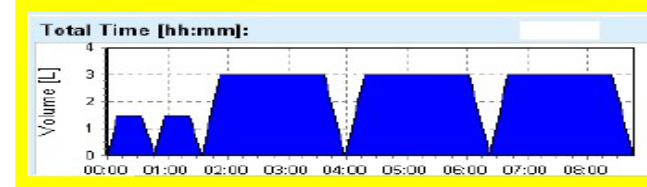
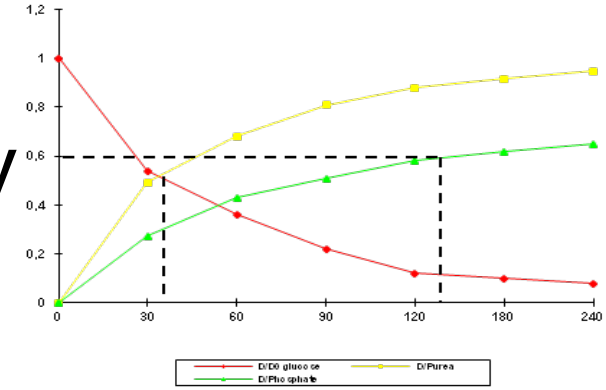
The optimal dwell time ?
adapted, individually

- Which dwell time ?
- ***Not a unique choice*** :

- short (« aquaporins » time)
- long (« small pores » time)

- Impact on both ultrafiltration capacity (maintained osmotic gradient) and purification process (diffusion time and uremic toxins, more than urea)





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Conflicting goals of a peritoneal dialysis prescription.

Fischbach M et al, PDI 2000; 20:603-6

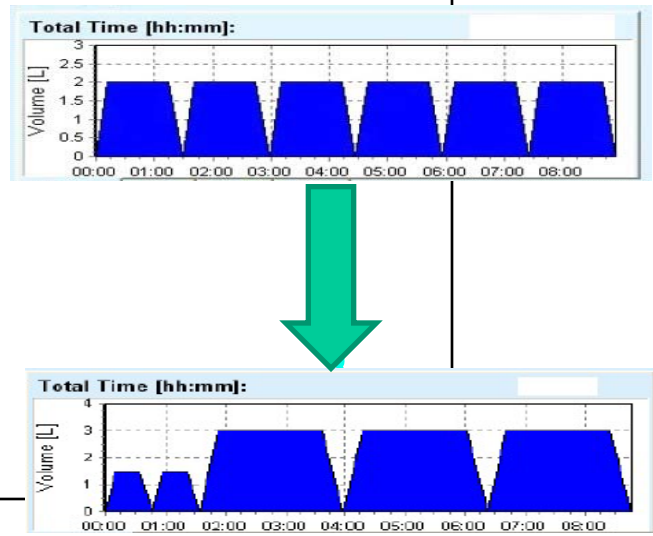
- Which fill volume for which goal ?
  - clinical tolerance : « *small* » fill volume
  - ultrafiltration capacity : « *small* » fill volume (low IPP)
  - purification capacity : « *large* » fill volume
- Which dwell time for which goal ?
  - ultrafiltration (maintained osmotic gradient) : « *short* » dwells
  - purification (Na/phosphate) : « *long* » dwells
- Ultrafiltration and/or purification :

« small or large », « short or long »

how to prescribe APD ? :

adapted APD,

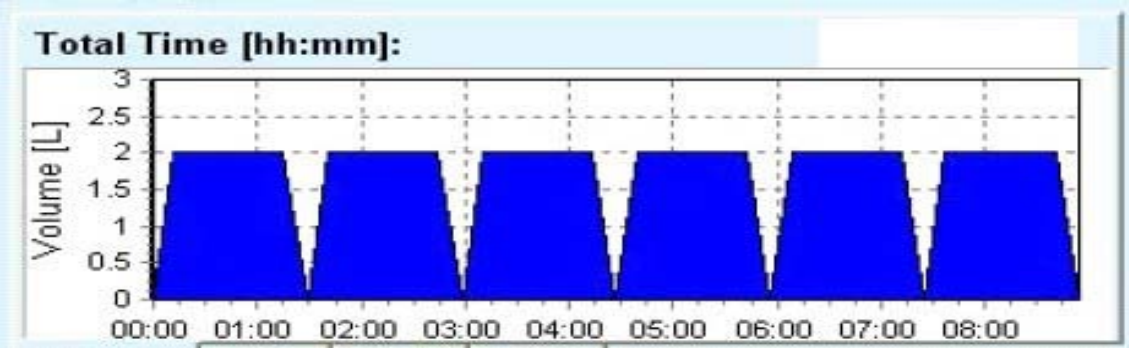
improved efficiency without more costs



« **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,

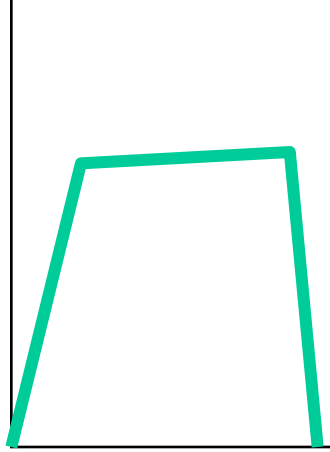
2) same dwell time



Can we do better for the same cost ?

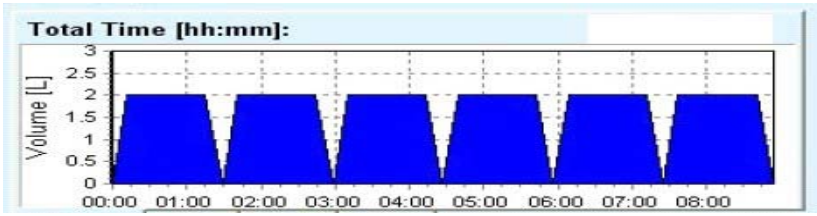
Which Fill volume - Which Dwell-time :
Not a unique choice

short (and small) UF favored



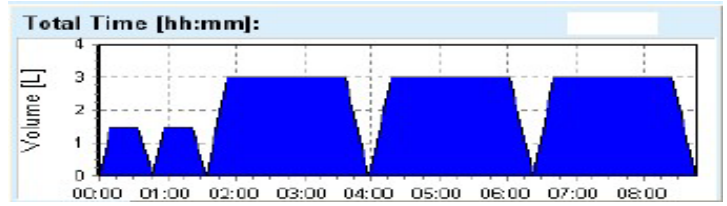
large (and long) Purification favored

APD « conventional »



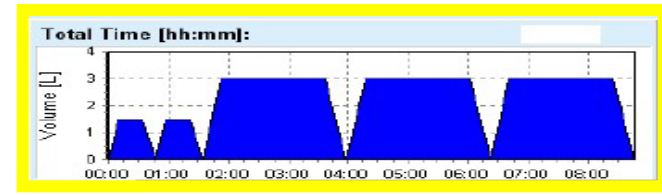
adapted

APD « adapted »



interest of sequentially short and longer dwell-time exchanges, and small and larger fill volume exchanges

The principles of Adapted APD



- Peritoneal dialysis mechanics : patient individually dialysis prescription, importance of varying dwell volumes (small/large) and of varying dwell times (short/long)
- Peritoneal exchange permeability
  - surface area recruitment (wetted membrane)
  - pores recruitment (small pores = 1/10000AQ1)
  - application to the volume control : UF (AQ1+small pores) and sodium dialytic removal (small pores)

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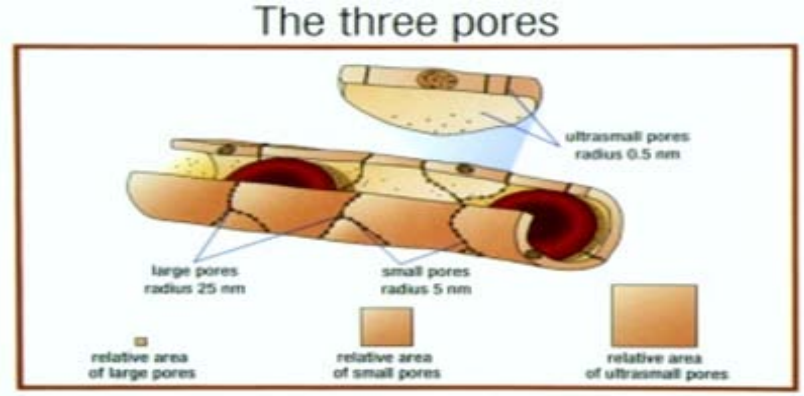

Transport across the Peritoneum

Rippe B et al. Kidney Int 40, 1991

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)

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What is expected with adapted APD

- *Improved dialysis efficacy without more cost :* the same total volume of dialysate is delivered sequentially, short/small thereafter long/large and not as a repetition of the same exchanges (same dwell time, same dwell volume)
- *More UF that is an improved osmotic conductance* (mL/min/gr of glucose)
- *More blood purification* as assessed by Kt/V, Kcreat, Phosphate dialytic removal, Sodium dialytic removal
- *Impact on volume control*, lowered BP with the hope of reduced uremic protein wasting

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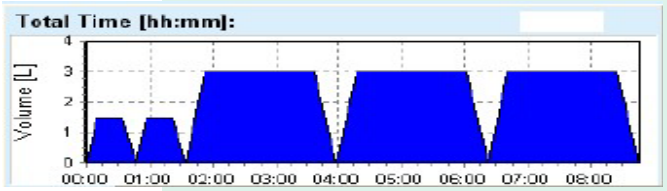
Adapted APD:

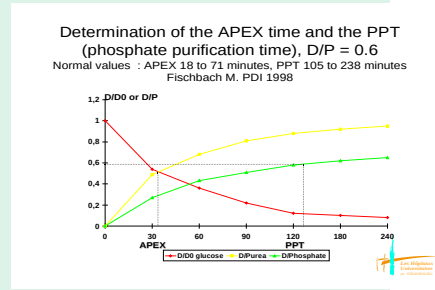
first Ultrafiltration

(*low fill,short dwell*)

then Purification

(*larger fill, longer dwell*)





**Optimization of CCPD prescription in children using peritoneal equilibration test. Fischbach M et al. Advances in Peritoneal Dialysis 10, 307-309, 1994*

**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*

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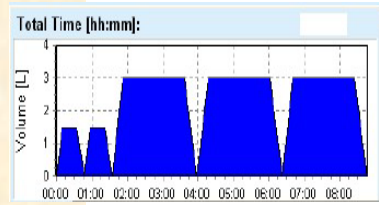
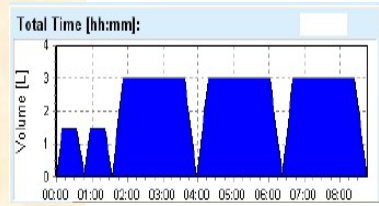
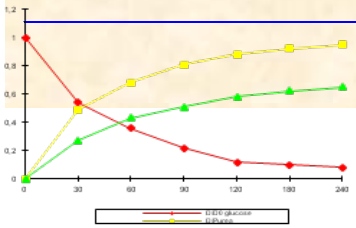
Prescription parameters of conventional or adapted (optimized) CCPD (manually performed)

	Conventional CCPD	**Adapted CCPD**
Number of exchanges	5	5
Duration of session	**5x2 h** = 10 h	**2x APEX Time** (35-45 min) **3 x Purification Time** (150-120 min) = 10 h 20 min (9 h 45 – 10 h 55)
Dwell volume	**5 x 800 mL/m²** = 4000 mL/m²	**2 x 600 mL/m²** **3 x 1000 mL/m²** = 4200 mL/m² = 4200 mL/m²
Dialysate tonicity (dextrose %)	5 x mixed half Iso (1.36) and half hyper (3.86)	2 x hyper (3.86) 3 x iso (1.36)







Fischbach M. Advances in Perit Dial ***1994***

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Efficiency of adapted CCPD vs. conventional CCPD: lower metabolic cost (UF/ gr of Glucose absorbed) and improved phosphate purification

	Conventional CCPD	Adapted CCPD
UF mL	315±120	360±120
UF/G mL/gr	**4.8±1.3***	**5.7±0.8***
D/P phosphate	0.48±0.17*	0.64±0.18*
K_P mL/min/kg	**0.16±0.05***	**0.21±0.05***
Protein intake (g/kg/day)	1.9±0.3	2.0±0.3
Calcium carbonate (mg/kg)	40	40
Phosphate plasma (mmolL)	2.47±0.35*	2.15±0.21*

Enhanced osmotic conductance

Fischbach M. Advances in Perit Dial ***1994***

*: p<0.01

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What is expected with adapted APD

- *Improved dialysis efficacy without more cost :* the same total volume of dialysate is delivered sequentially, short/small thereafter long/large and not as a repetition of the same exchanges (same dwell time, same dwell volume)
- *More UF that is an improved osmotic conductance* (mL/min/gr of glucose)
- *More blood purification* as assessed by Kt/V, Kcreat, Phosphate dialytic removal, Sodium dialytic removal
- *Impact on volume control*, lowered BP with the hope of reduced uremic protein wasting

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Peritoneal Dialysis International

Peritoneal Dialysis International, Vol. 31, pp.
doi: 10.3747/pdi.2010.00146

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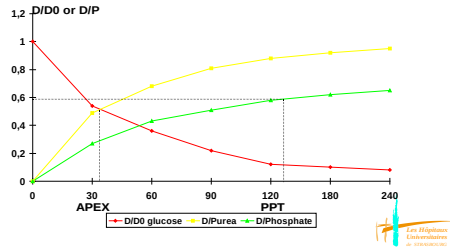
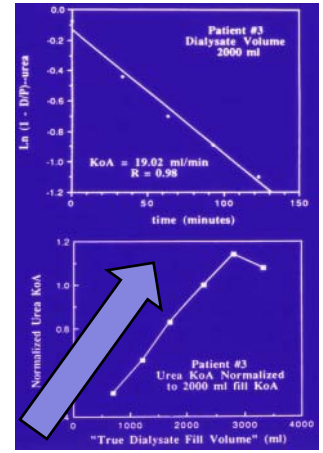
THE BENEFICIAL INFLUENCE ON THE EFFECTIVENESS OF AUTOMATED PERITONEAL DIALYSIS OF VARYING THE DWELL TIME (SHORT/LONG) AND FILL VOLUME (SMALL/LARGE): A RANDOMIZED CONTROLLED TRIAL

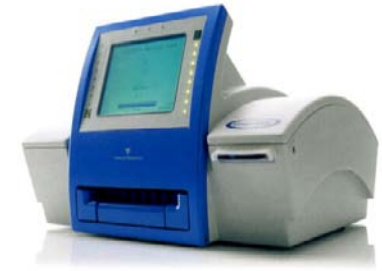
Michel Fischbach,[1] Belkacem Issad,[2] Vincent Dubois,[3] and Redouane Taamma[3]

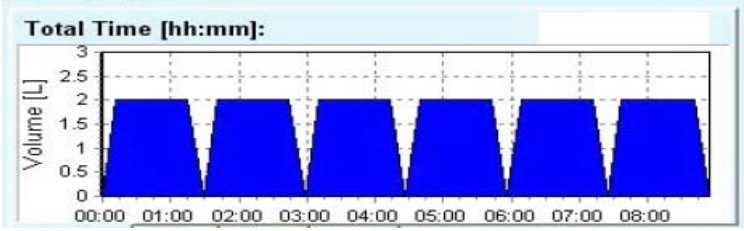
Nephrology Dialysis Transplantation Children's Unit,[1] University Hospital Hautepierre, Strasbourg; Nephrology,[2] Pitié-Salpétrière, Paris; and Fresenius Medical Care–Nephrocare France,[3] Fresnes, France

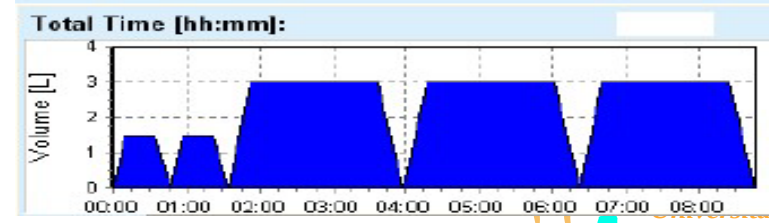
Determination of the APEX time and the PPT
(phosphate purification time), D/P = 0.6
Normal values : APEX 18 to 71 minutes, PPT 105 to 238 minutes
Fischbach M. PDI 1998











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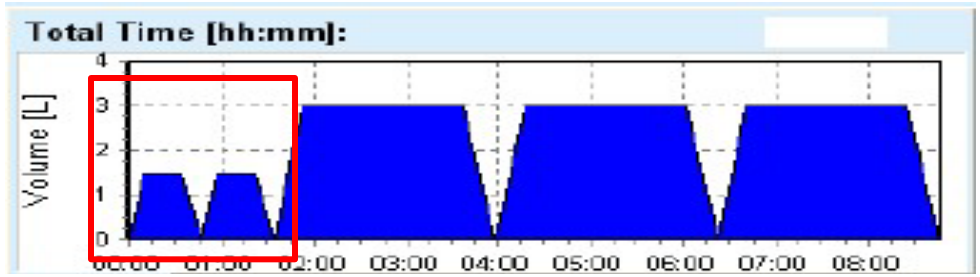
sequential ultrafiltration, adapted APD : ***small fill volume, short dwell time*** (isotonic dialysate)

- 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?



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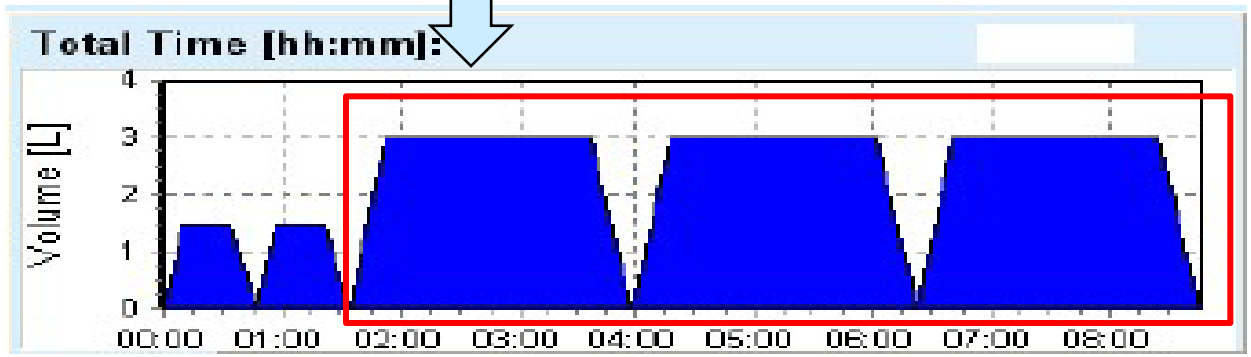
Sequential purification, adapted APD : *large fill volume, long dwell time* (isotonic dialysate)

- 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?)



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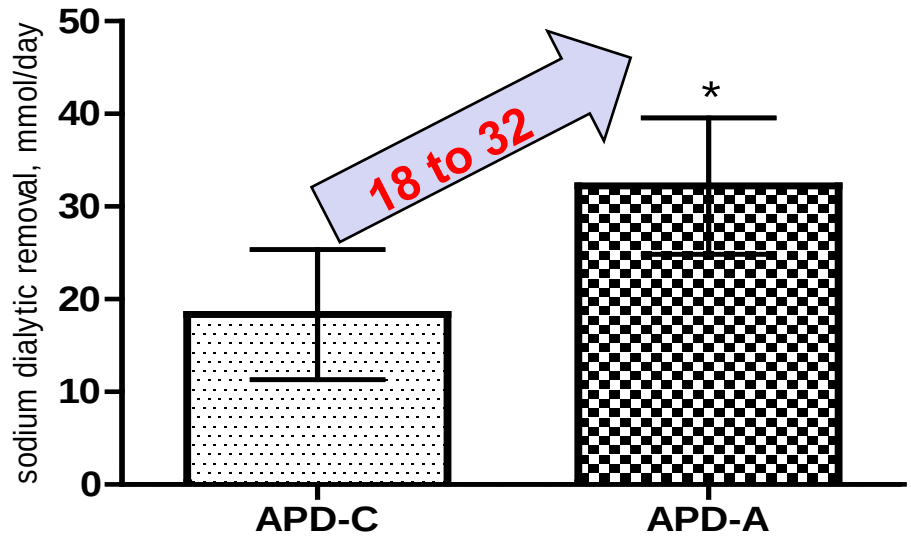
Dialytic sodium removal (mmol/day): improved with APD-A



* Significant p<0.01

N = 19	APD-C	APD-A
Mean ± SD	18.35 ± 48.68	32.23 ± 52.00*
Min / Max	-69.0 / +108.5	-81.7 / +153.2
Number of pairs	47	
p value	< 0.01 (0.01)	

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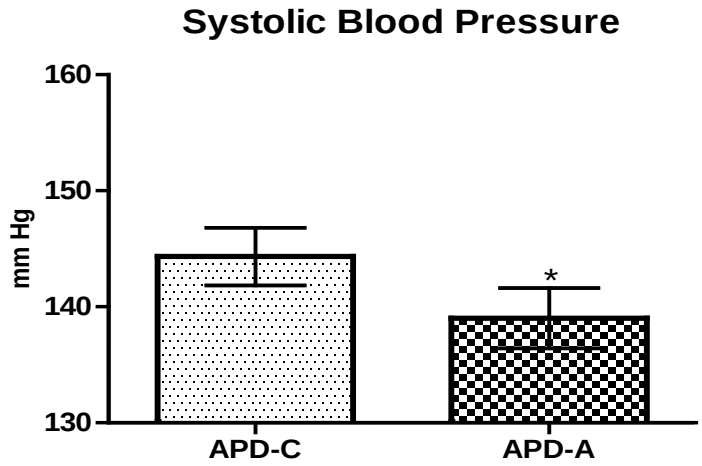
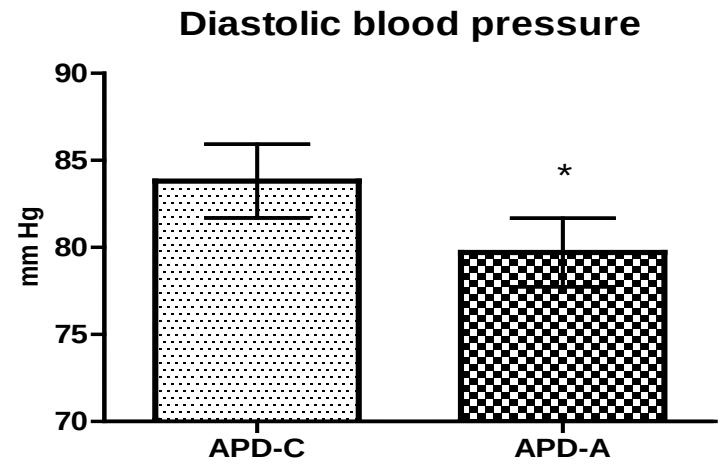
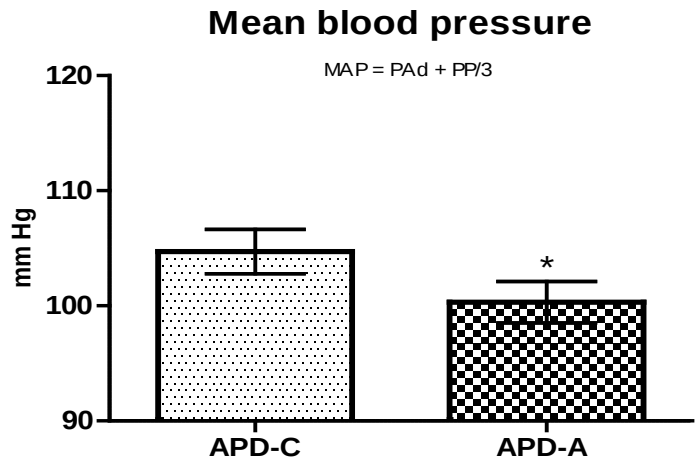
Arterial blood pressure: lowered BP under APD-A



* Significant p<0,05



* significant p<0.05



* Significant p<0,01

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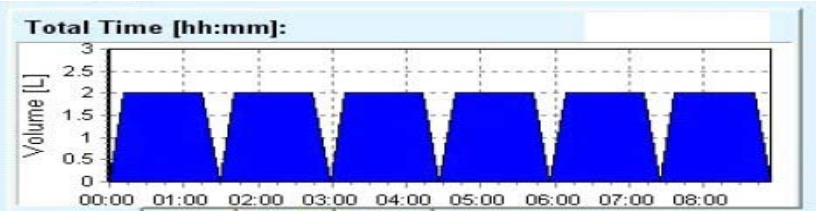
The concept of „adapted“ APD prescription

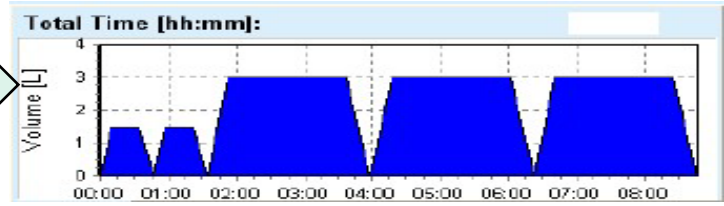
“The beneficial influence on the effectiveness of APD of varying the dwell time (short/long) and fill volume (small/large). A french Study.

Michel Fischbach, Belkacem Issad, Vincent Dubois, Redouane Taamma.

Perit Dial Inter 2011;31(4):450-8



same costs, *more efficient*



- Tolerance: first sleep, thereafter “fill large”

- Optimized purification : urea, creatinine, increased dialytic phosphate removal

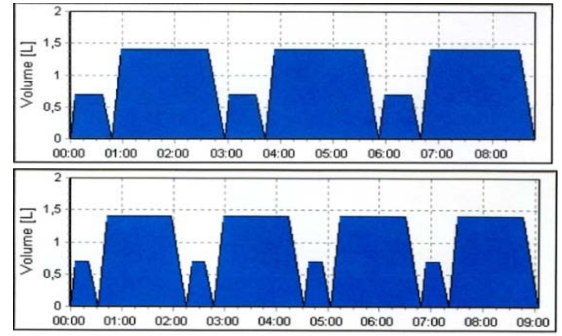
- Optimized UF and sodium removal: impact on blood pressure

- Reduced metabolic cost to achieve ultrafiltration (and purification)

Long term outcome for the patient:

improvement of both volume overload and nutrition?

Adapted APD
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

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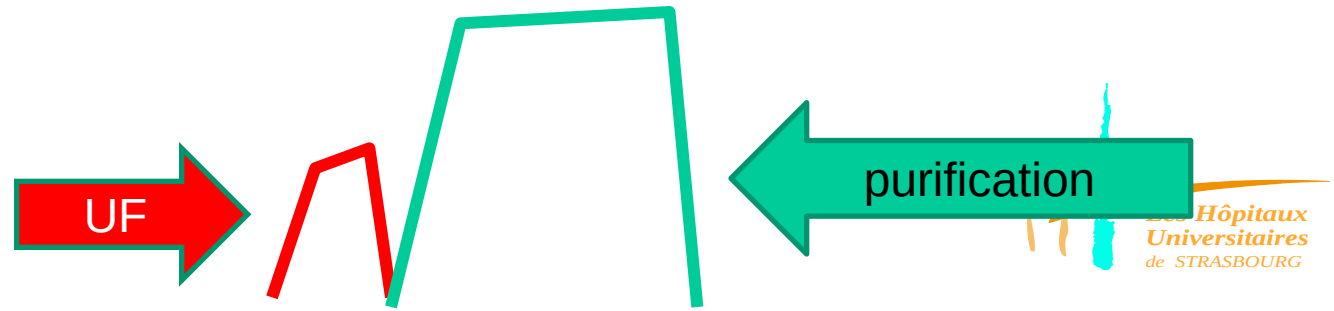
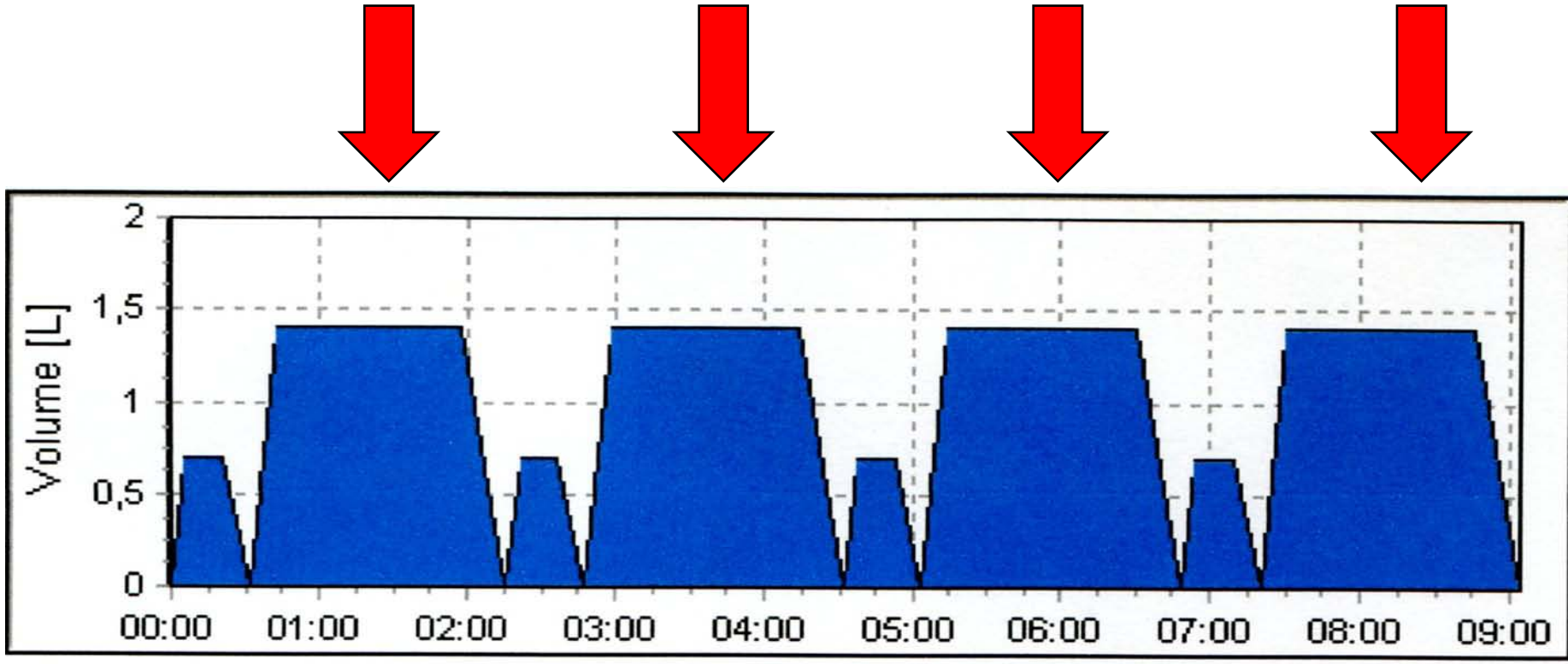
A-APD : impact of the sequences UF/purification on the sodium removal

1) First sequence "Ultrafiltration favored" : *"sodium free water "generated through the AQP but small volume, therefore drained or bulding up a residual intraperitoneal volume*

2) Second sequence "Purification favored": *increased diffusion volume/PSA recrutment, more diffusion time, higher gradient plasma (hemoconcentration) to dialysate ("low sodium " dialysate by dilution with the "free water")*



more volume of diffusion (PSA recruitment)
more diffusion time
more diffusion gradient (alternate cycles)



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Mechanics of peritoneal dialysis

- Peritoneal surface area recruitment, the wetted membrane : a dynamic dialysis membrane
- Fill volume prescription in mL/m^2
- Intraperitoneal pressure measurement an objective parameter of tolerance, to secure the prescription
- Diffusion time , from the PET to the dwell time
- Adapted peritoneal dialysis :
  - Ultrafiltration favored (small fill/short dwell)
  - Purification favored (large fill/long dwell)
- Biocompatibility of the PDF's: Bicavera, AQ1function

Standardized Peritoneal Equilibration Test in Japanese children and the influence of long-term peritoneal dialysis

Kaku Y. and Honda M. PDI 2008; vol 28 (Suppl 3) S150-3

Induced hyperpermeability

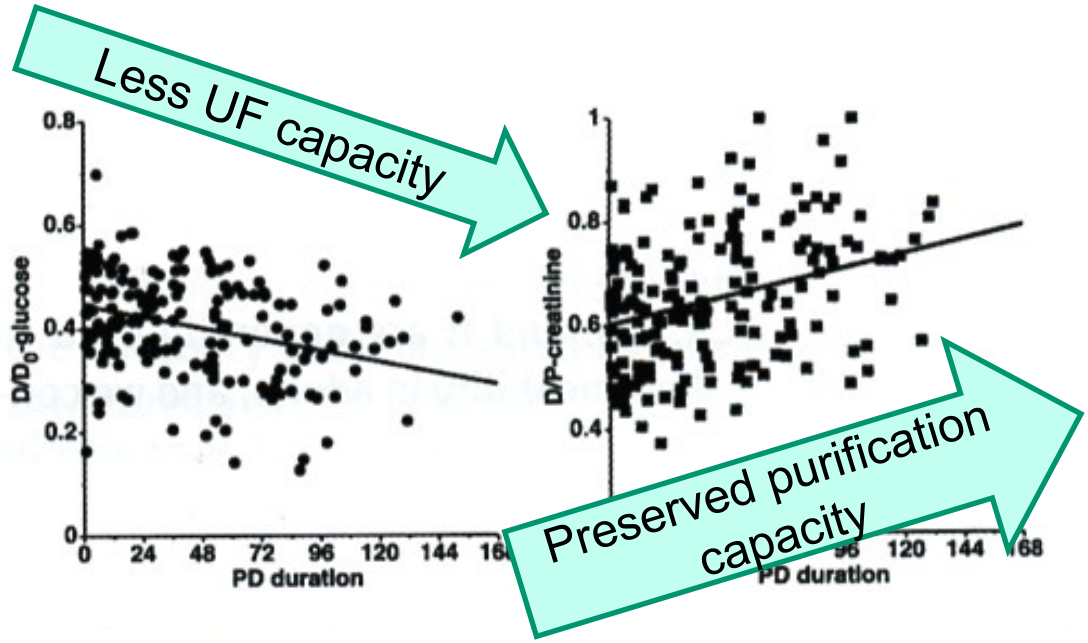

Figure 2 — Correlation between peritoneal permeability and duration of peritoneal dialysis (PD). Ratios of end dialysate–to–initial dialysate (D/D_0) glucose and dialysate-to-plasma (D/P) creatinine correlated significantly with PD duration ($r = 0.324$ and $r = 0.313$ respectively; $p < 0.0001$).

Too rapid loss of the crystalloid glucose osmotic gradient: osmotic conductance decreased (UF)

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Biocompatible PDF's

- Biocompatibility : neutral pH, low/very low GDPs (heterogenicity)
- Pure bicarbonate (BICAVERA®) versus mixed buffer bicarbonate/lactate (PHYSIONEAL®25/15)
- Place/importance of the buffer
  - Lactate (Lactate Balance®): highly biocompatible but not « the » physiological buffer, needs hepatic metabolism, toxicity (?) of hyperlactatemia (>4 mmol/L)
  - Pure bicarbonate : the « physiological » buffer, importance in case of hepatopathy, metabolic disease, dialysis post cardiac surgery, and « babies »…

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GDP's concentrations in commercially available PD fluids (Lact or mixed or pure Bicarbonate)

FLUID	Glucose compartment Glucose (%)	pH	Ready-to-use fluid Glucose (%)	pH	3-DG	3,4-DGE	5-HMF	FoA	AcA	GDP total
Gambrosol	2.5	5.3	2.5	5.3	175±3.9	13±1.1	5.4±0.0	6.4±0.5	292±17	492
Dianeal	2.27	5.0	2.27	5.0	213±0.6	19±0.6	15±1.0	6.0±0.4	173±12	426
StaySafe	2.3	5.4	2.3	5.4	185±7.5	12±0.5	2.9±0.3	5.3±0.3	359±1	564
GambrosolTrio (L)	50	3.1	2.5	6.5	29±0.7	0.5±0.0	19±0.6	2.3±0.7	<1.1	52
Physioneal (L+B)	5.82	4.2	2.27	7.3	178±3.4	11±0.8	30±4.7	3.4±0.7	5.5±0.6	228
Balance (L)	4.6	3.1	2.3	6.8	10±0.2	0.4±0.0	10±0.3	<1.7	1.5±0.5	24
Bicavera (B)	4.6	2.8	2.3	7.1	17±0.5	0.2±0.0	18±1.0	1.9±0.3	2.4±0.3	40
Extraneal[a]	7.5	5.0	7.5	5.0	11±0.1	3.0±0.3	2.1±0.1	9.3±1.5	37±0.6	62

3-DG = 3-deoxyglucosone; 3,4-DGE = 3,4-dideoxyglucosone-3-ene; 5-HMF = 5-hydroxymethyl furaldehyde; FoA = formaldehyde; AcA = acetaldehyde.

[a] Contains polyglucose.

Adapted from: Erixon M. et al., *PDI* 2006; 26: 490-7

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The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function:

the balANZ trial. Johnson DW et al. On behalf of the balANZ Trial investigators. NDT 2012; 27:4445-4453

Administration of a neutral pH, lactate buffered, low GDPs fluid (Balance) to incident PD patients was associated with :

- Less frequent and severe peritonitis
- Preservation of membrane function (long time follow up)
- Higher peritoneal solute transport rates at 1 month (CpCr↗, D/D_0 ↘) (CA125 and inflamation) which then remained stable over the 2 years follow up period (improved small pores function ?)
- Lower UF initially, but increased (maintained) significantly over time (AQ1 preservation?).

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Effect of the dialysis fluid buffer on peritoneal membrane function in children

Schmitt CP et al. Clin J Am Soc Nephrol 2013 S108-115

Improved long term preservation of peritoneal membrane function may be achieved with bicarbonate based peritoneal dialysis fluids: UF preservation, not glucose (coupled water) related, AQ1 impact ?

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Effect of the dialysis fluid buffer on peritoneal membrane function in children

Schmitt CP et al. Clin J Am Soc Nephrol 2013 S108-115

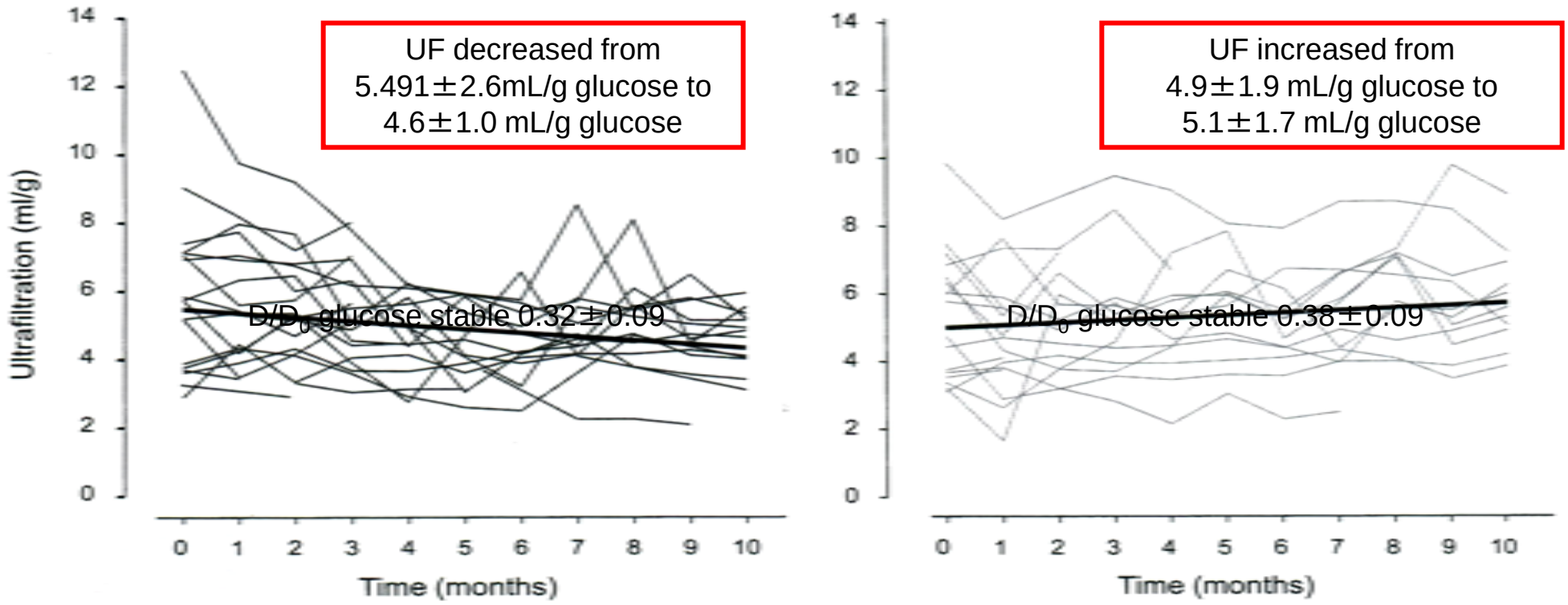
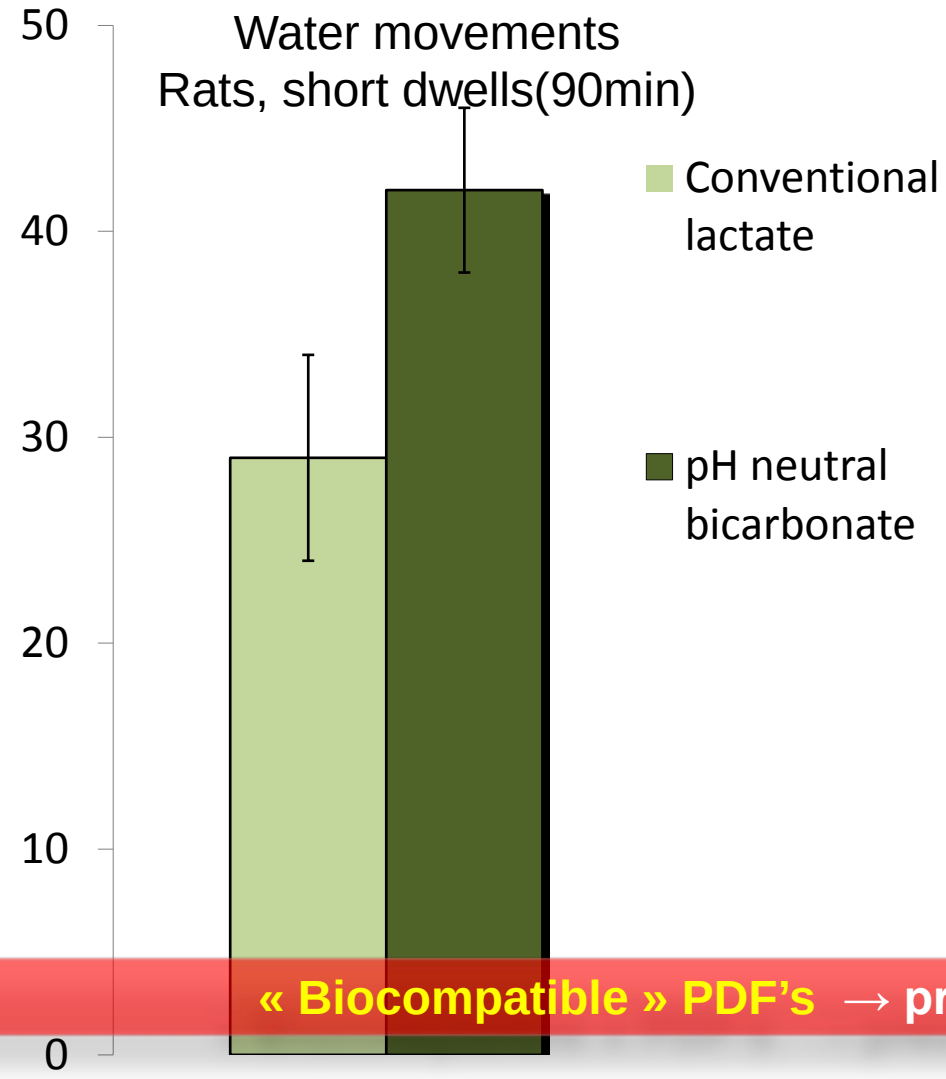
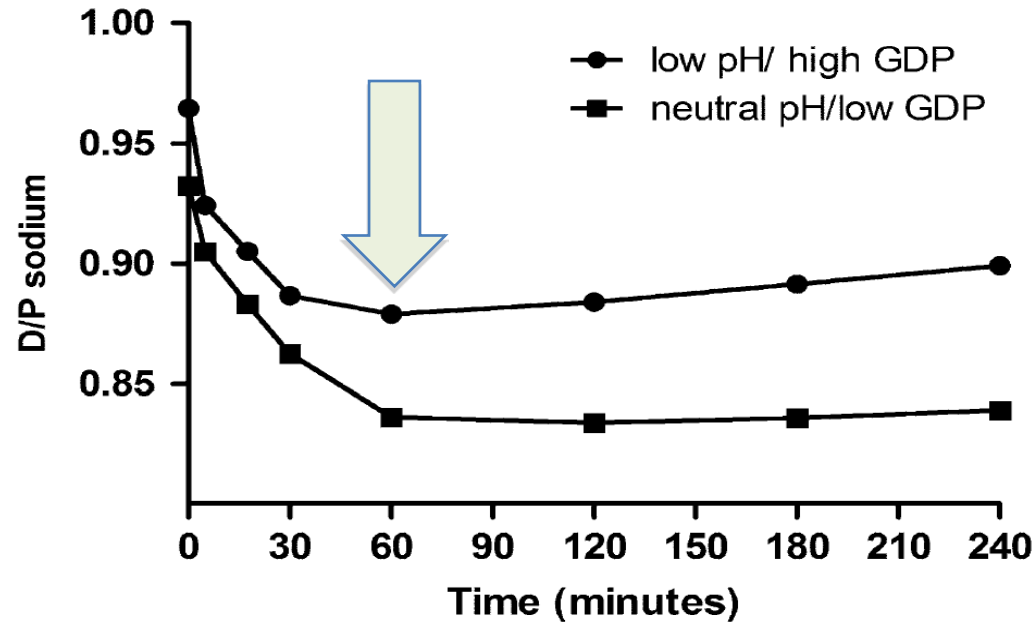


Figure 3. | **Peritoneal ultrafiltration capacity over time.** Ultrafiltration per 1 g glucose administered in patients on L-PDF (left) and B-PDF (right). Based on the daily ultrafiltration rates documented by the parents, monthly averages are given from each patient (P=0.006 for interaction).

Biocompatibility of the PDF's : impact on the free water transport



D/P sodium over a PET after 12 months
n = 65 patients (mean age 12 years)



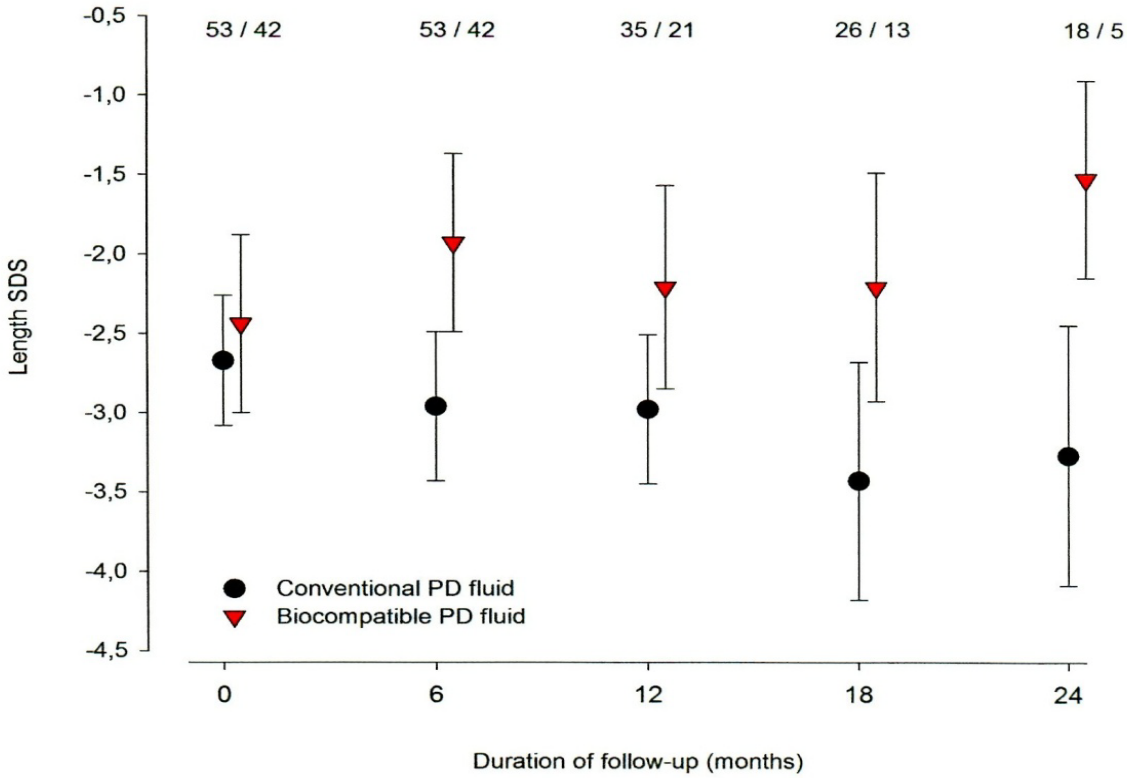
« Biocompatible » PDF's → preservation of AQP1 function?

Aubertin, Pediatr Nephrol 2012

Raaijmakers, Nephrol Dial Transplant 2012

Growth in very young children undergoing chronic peritoneal dialysis

Rees L et al. for the international Pediatric Peritoneal Dialysis Network (IPPN) registry. J Am Soc Nephrol 2011; 22:2303-2312.



Among the children followed prospectively for at least 6 months, lenght SDS did not change in children on conventional solutions (-0.06±1.96 SDS/year, NS), whereas significant catch-up growth was observed in those dialyzed with biocompatible PD fluid (+0.52±1.82 SDS/year) (supplemental Fig.2)

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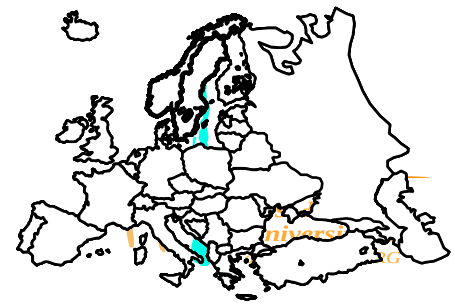
Dialysis prescription in children should be

- Individualized , not a unique choice adapted to the aim(purification,ultrafiltration)
  - fill volume prescribed in mL/ $m^{2,}$
  - dwell/contact time adapted to the aim(purification,ultrafiltration)
- Importance of biocompatibility (ph neutral, lowGDP's, buffer ?)
- Adapted to RRF (preservation, dose adjustment) but not only guided by numerical targets (KT/V_{urea}, K_{creat}), in an integrated care therapy (nutrition, , growth development), before transplantation
- IPP measurement is a key factor of good clinical practice (« wetted » membrane)

and we should consider the ability for peritoneal membrane recruitment, in fact we can choose the dialyzer even for PD (concept of adapted APD)



Fischbach M, Stefanidis CJ, Watson AR for the European Paediatric Dialysis Working Group .Nephrol Dial Transpl 2002 ; 17:380-5