Come valutare la permeabilità peritoneale: istruzioni per l'uso! Cosa sono i test di permeabilità peritoneale e come si possono utilizzare nella pratica quotidiana.

Vincenzo La Milia

Nefrologia e Dialisi

Ospedale A. Manzoni, Lecco

Valutazione della funzione e follow-up della membrana peritoneale

I test di equilibrazione peritoneale (PET)

Summary of my talk

Peritoneal functional tests

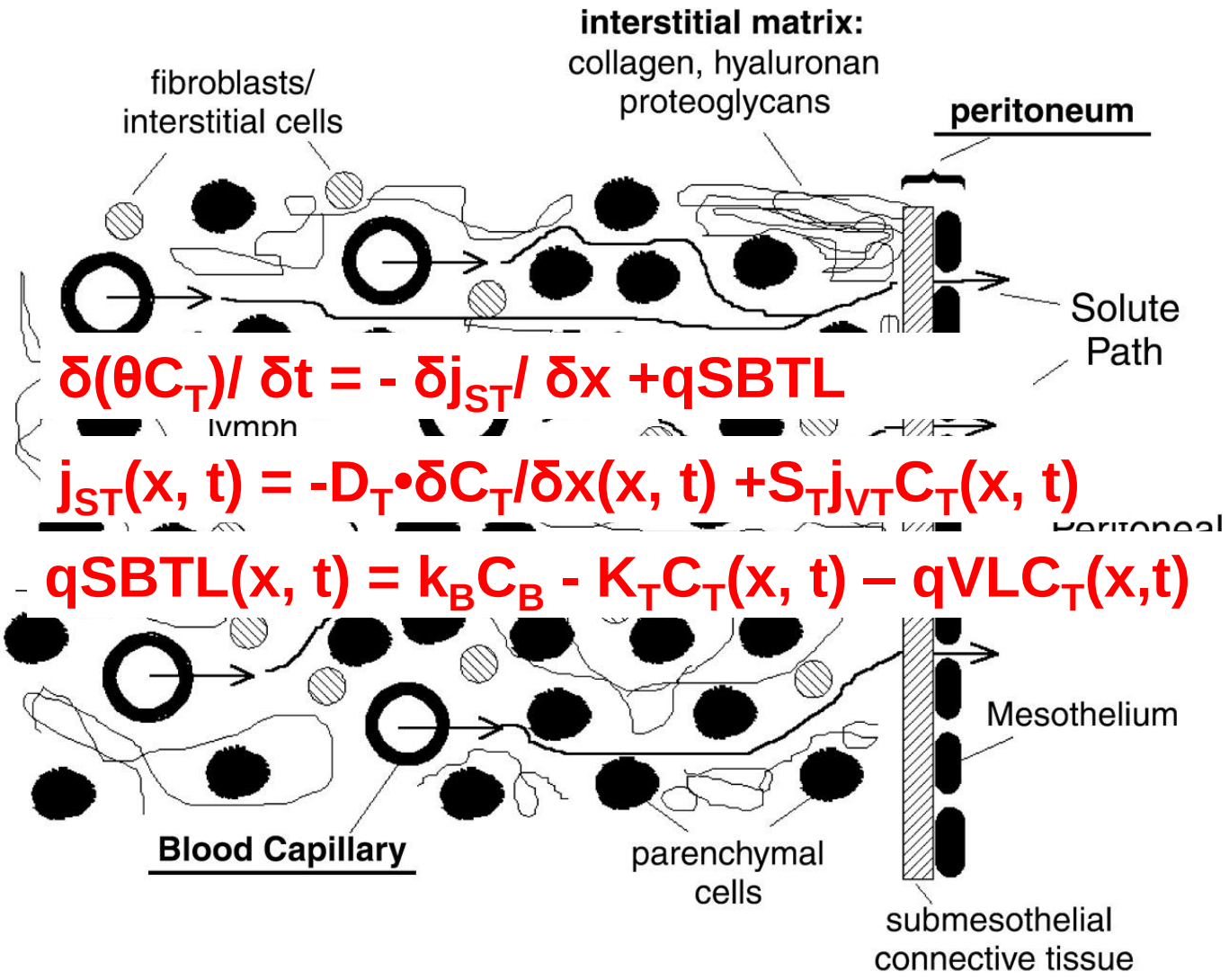
- **Why we need of peritoneal tests?**
- **What kind of peritoneal tests we have?**
- **Are the peritoneal tests useful in clinical practice?**

The three-pore model of peritoneal membrane

Parameters Employed for Computer Simulations of V(t) Curves According to a Three-Pore Model of Membrane Selectivity

ΔP (mmHg)	8
$\Delta\pi_{prot}$ (mmHg)	22
Dialysis volume instilled (mL)	2050
Peritoneal residual volume (mL)	300
Serum urea (mmol/L)	20
Serum sodium (& sodium-associated "anion") (mmol/L)	140
Ionized serum calcium (mmol/L)	1.25
Serum glucose (mmol/L)	6
Calcium in residual volume (mmol/L)	1.25
PS for Na^+ and Ca^{2+} (mL/min)	6
PS for glucose (mL/min)	15.3
L_pS (mL/min/mmHg)	0.074
$L_pS \cdot \sigma_g$ (mL/min/mmHg)	0.0036
Peritoneal lymph flow (mL/min)	0.3
$A_0/\Delta X$ (cm)	25 000
Fractional L_pS accounted for by aquaporins, α_c	0.02
Fractional L_pS accounted for by small pores, α_s	0.90
Fractional L_pS accounted for by large pores, α_L	0.08

Distributed model



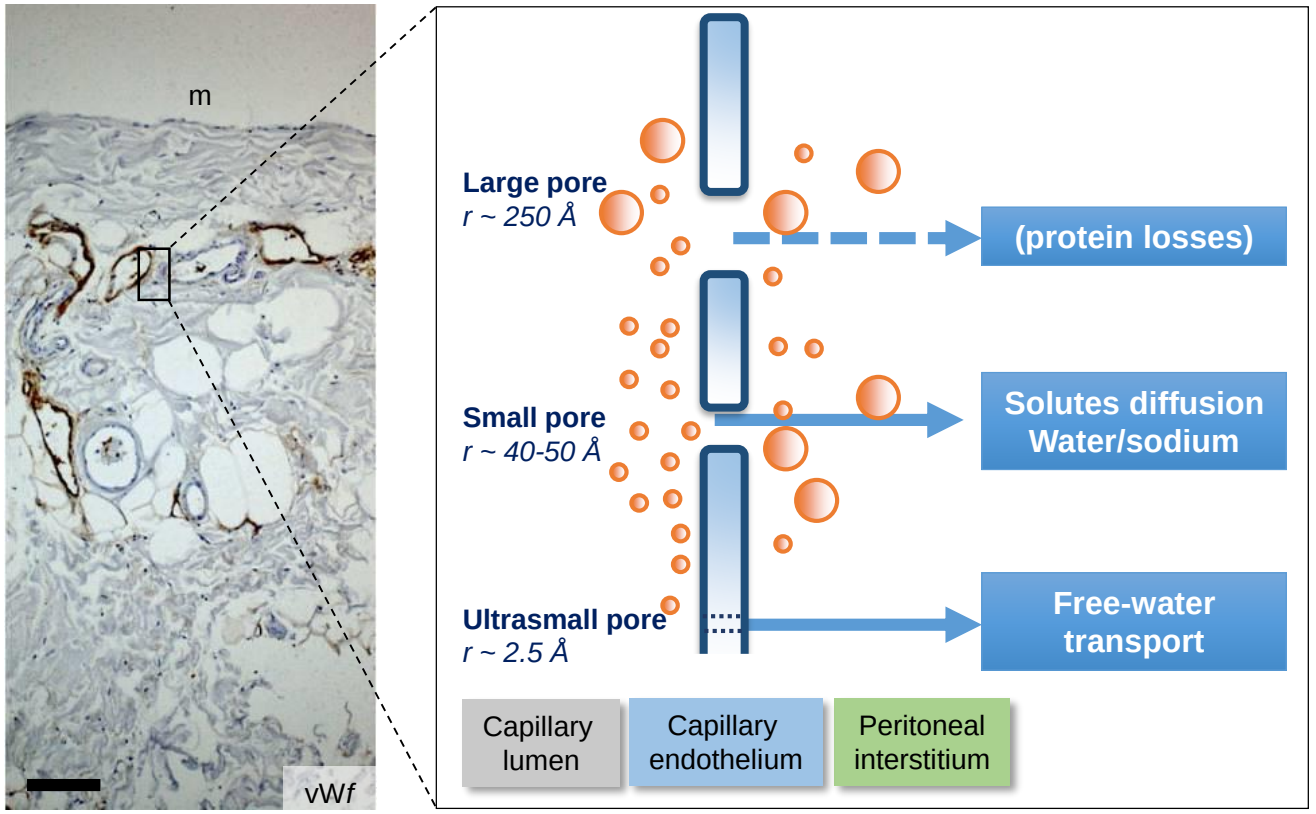
$$\delta(\theta C_T)/\delta t = -\delta j_{ST}/\delta x + qSBTL$$

$$j_{ST}(x, t) = -D_T \bullet \delta C_T/\delta x(x, t) + S_T j_{VT} C_T(x, t)$$

$$qSBTL(x, t) = k_B C_B - K_T C_T(x, t) - qVLC_T(x,t)$$

Flessner MF et al . Am J Physiol 1984; 246:R597-R607
Flessner MF. Contrib Nephrol 2006; 150:28-36

The peritoneal membrane and the 3-pore model



Rippe et al, *Kidney Int* 1991

Peritoneal Dialysis
INTERNATIONAL

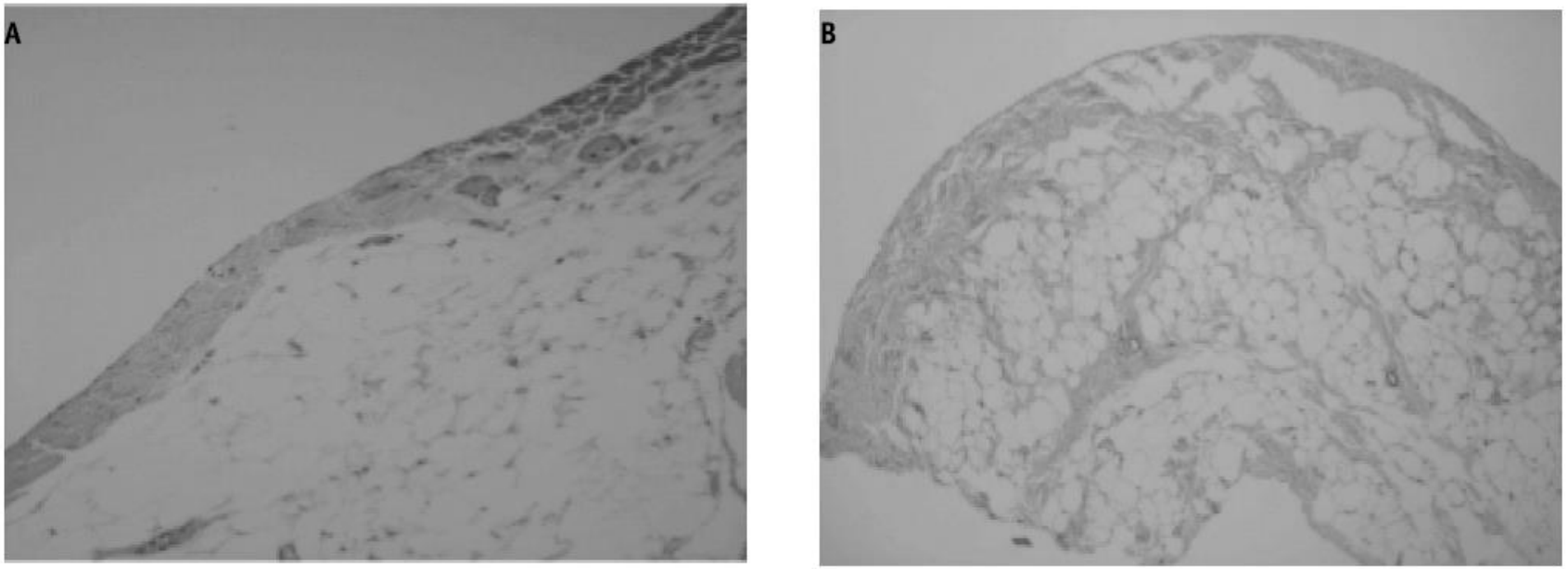
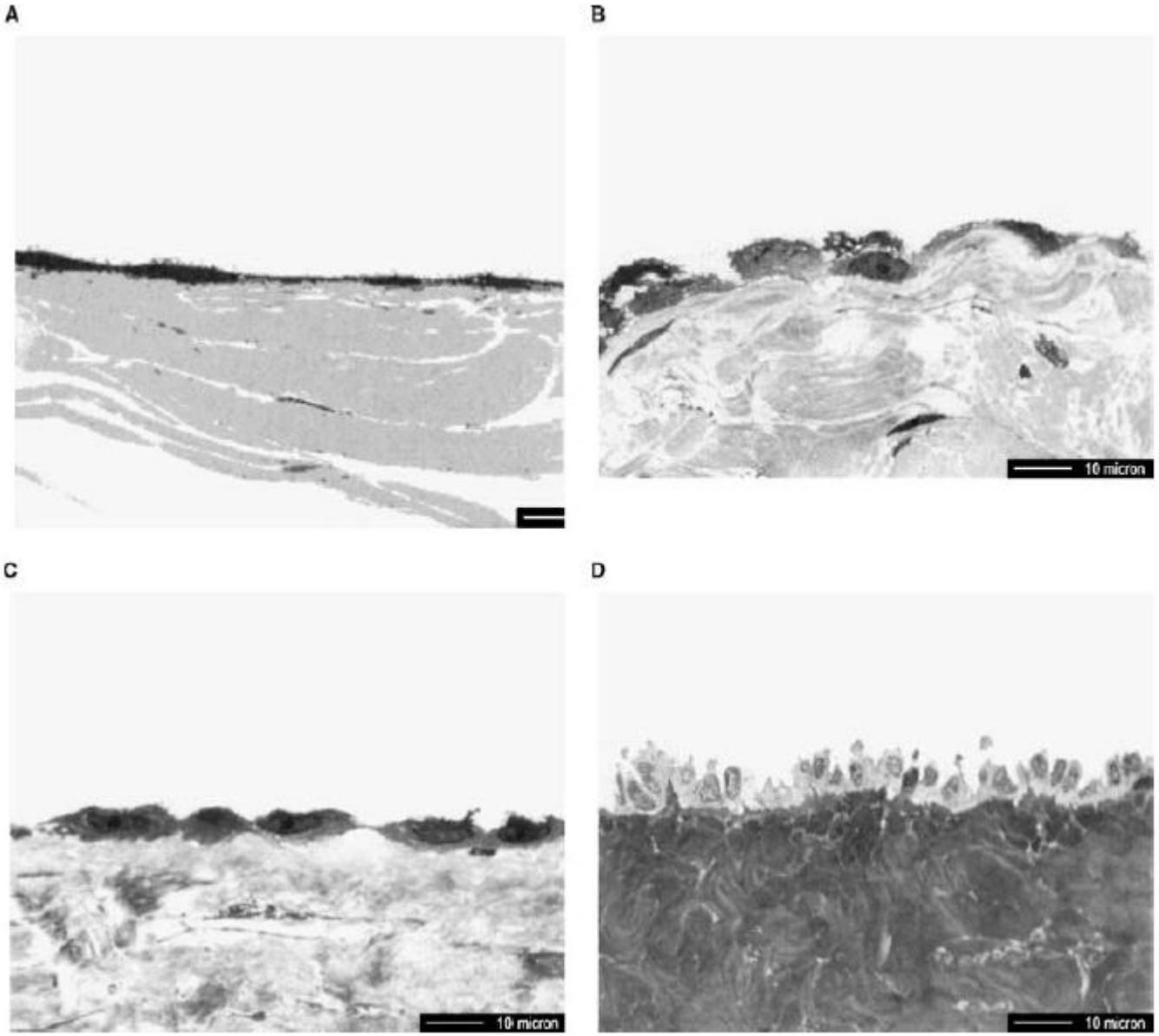


Figure 1 — Peritoneal histology at the time of catheter insertion (A) and catheter removal (B). Both specimens showed peritoneal mesothelial cells (PMCs) lining in a single layer, thin interstitial tissues, and normal capillaries. Degeneration of PMCs, thickening of interstitial tissue, and occlusion of capillaries were not observed on catheter removal (B).

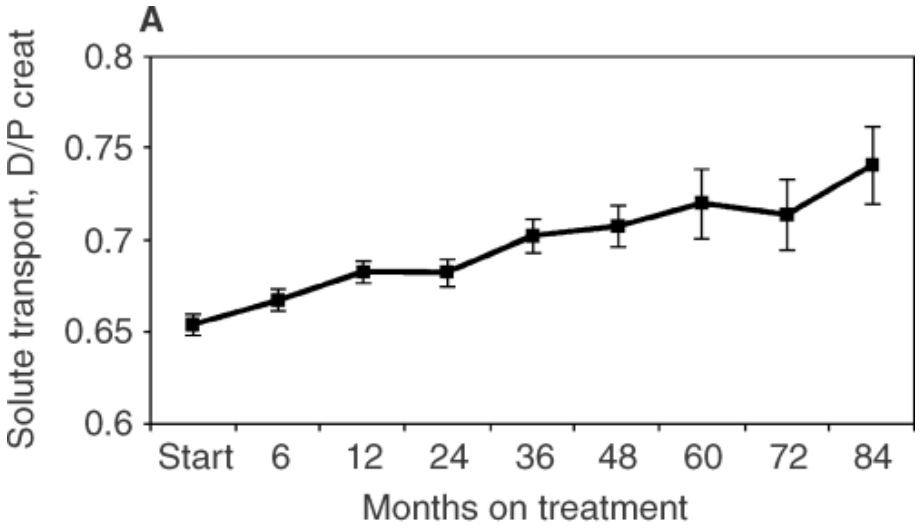
Shimizu H et al PDI 2007

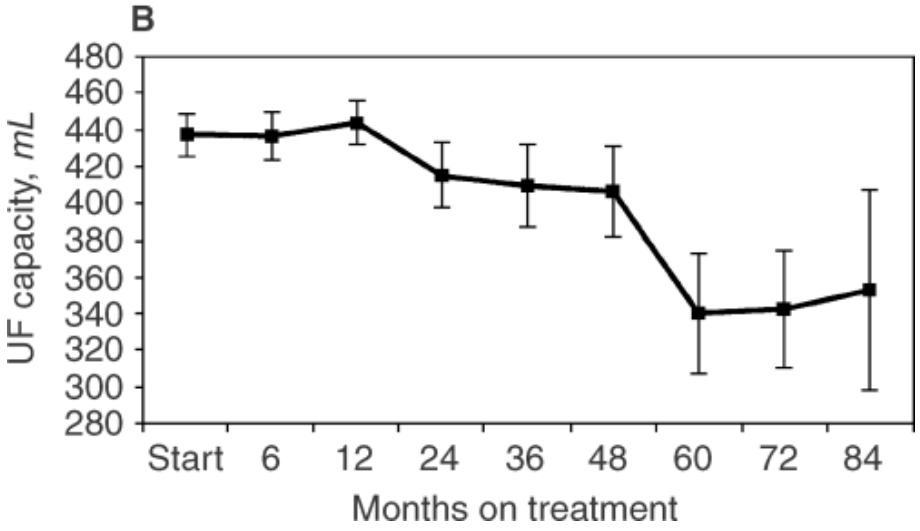
Natural course of peritoneal membrane biology during PD



Williams JD et al Kidney Int 2004

Longitudinal relationship between solute transport and UF capacity in PD patients



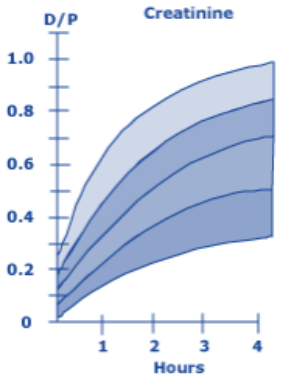


Davies SJ Kidney Int 2004

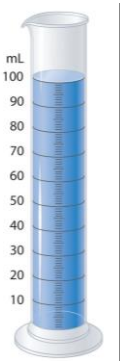
- **Il follow-up della funzionalità della membrana peritoneale può essere effettuata con dei test di funzionalità peritoneale**
- **Molto più difficile è effettuare delle biopsie seriate della membrana peritoneale per valutare il danno anatomico**

Back to the patient: peritoneal transport testing and expectations from clinicans

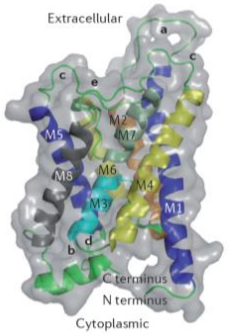
Diffusion rate of small solutes



Water transport ('ultrafiltration')



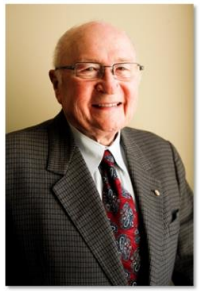
AQP-mediated water transport



→ Individual transport characteristics of the peritoneal membrane

Morelle et al, *Perit Dial Int* 2021

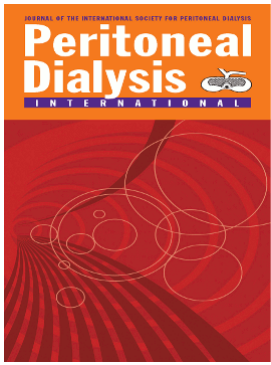
Il PET standard (2.27% glucosio)



Prof. dr. Zbylut Twardowski
University of Missouri

Zbylut J. Twardowski

PERITONEAL EQUILIBRATION TEST



Zbylut J. Twardowski
Karl D. Nolph
Ramesh Khanna
Barbara F. Prowant
Leonor P. Ryan
Harold L. Moore
and
Marc P. Nielsen

obtaining and processing samples and laboratory assays. Diabetics did not have lower peritoneal solute transfers than nondiabetics. Wide variations were found in the study population.

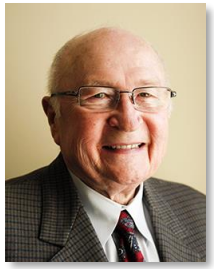
Measurements of creatinine, glucose and sodium transfer were particularly useful in predicting the transport rates were likely to develop symptoms and signs of inadequate dialysis as their residual renal function became negligible, particularly in individuals with high body surface area.

Repeated tests were helpful in evaluating causes of insufficient ultrafiltration and/or inadequate

Twardowski ZJ, et al. Peritoneal equilibration test. Perit Dial Bull 1987; 7:138-47

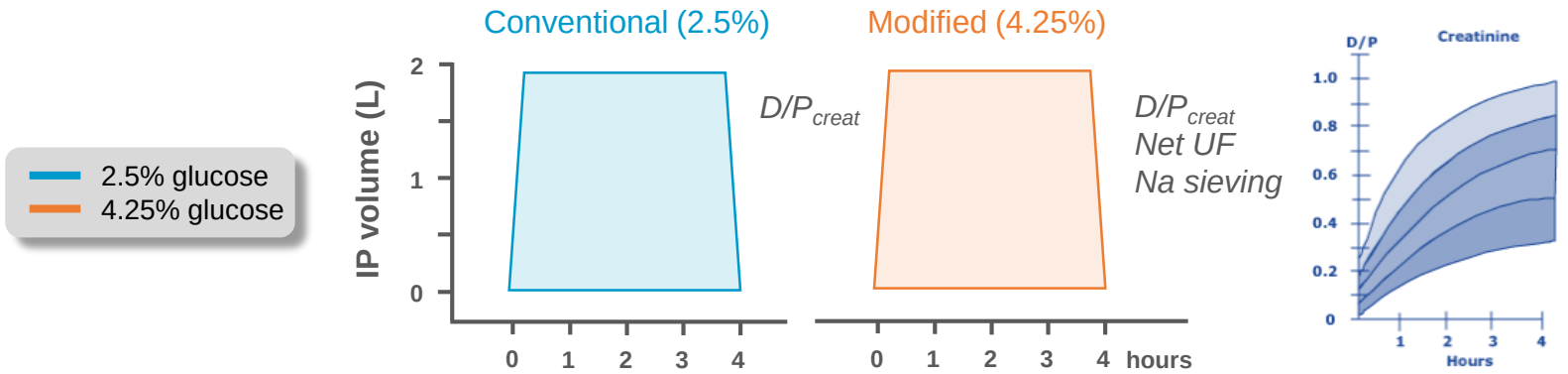
Peritoneal equilibration test (PET)

Dr. Verger
France



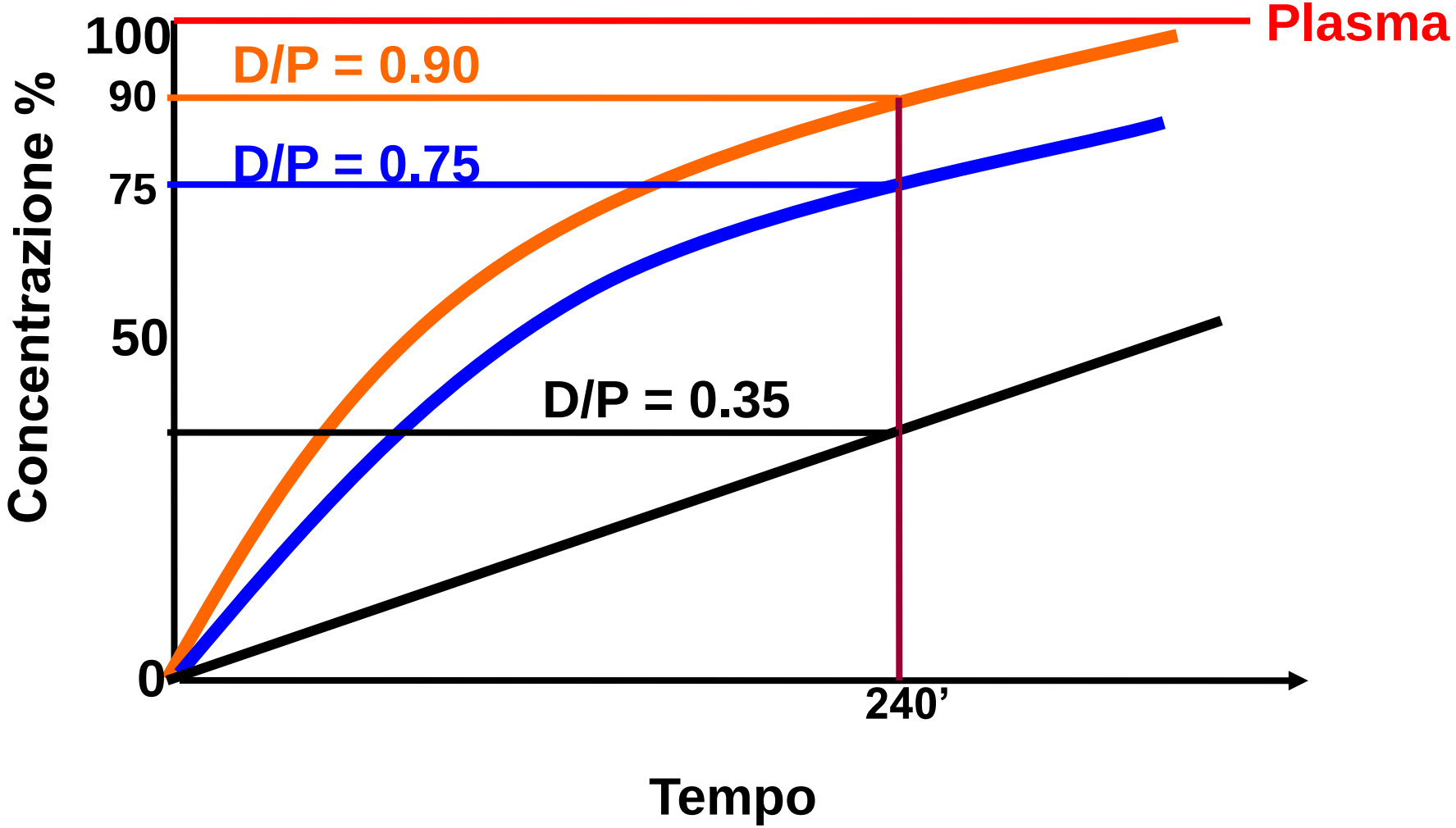
Dr. Twardowski
USA

- Standardized 4-h dwell, using 2.5% or 4.25% glucose
- Quantification of the equilibration rate of small solutes across the membrane (D/P_{creat} 4h)
  + net UF and sodium sieving (using hypertonic glucose)
- Safe, easy, accurate, highly reproducible

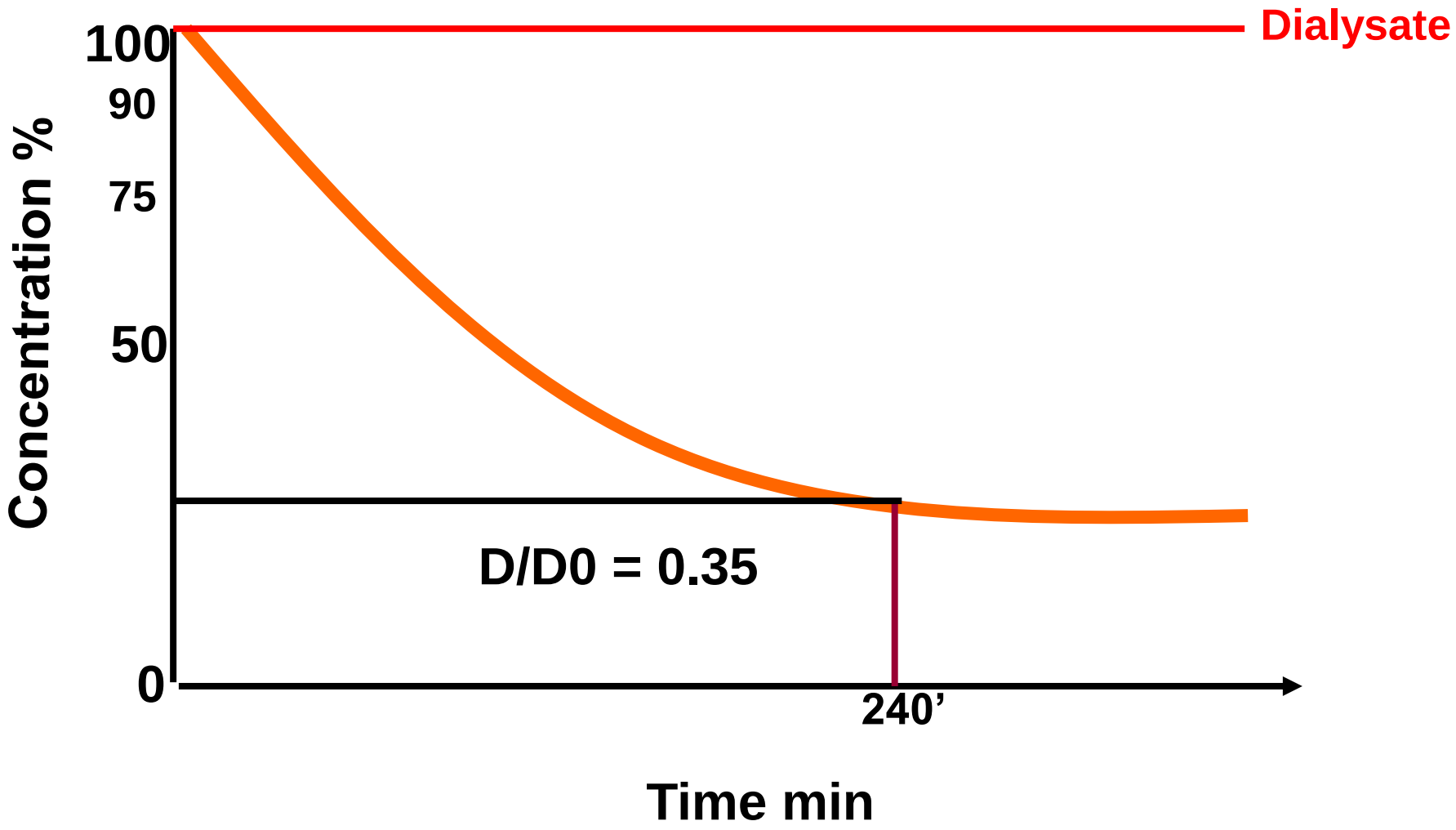


Verger et al, et al, *Front Perit Dial* 1986; Twardowski et al, *Perit Dial Bull*, 1987

Trasporto Diffusivo Peritoneale

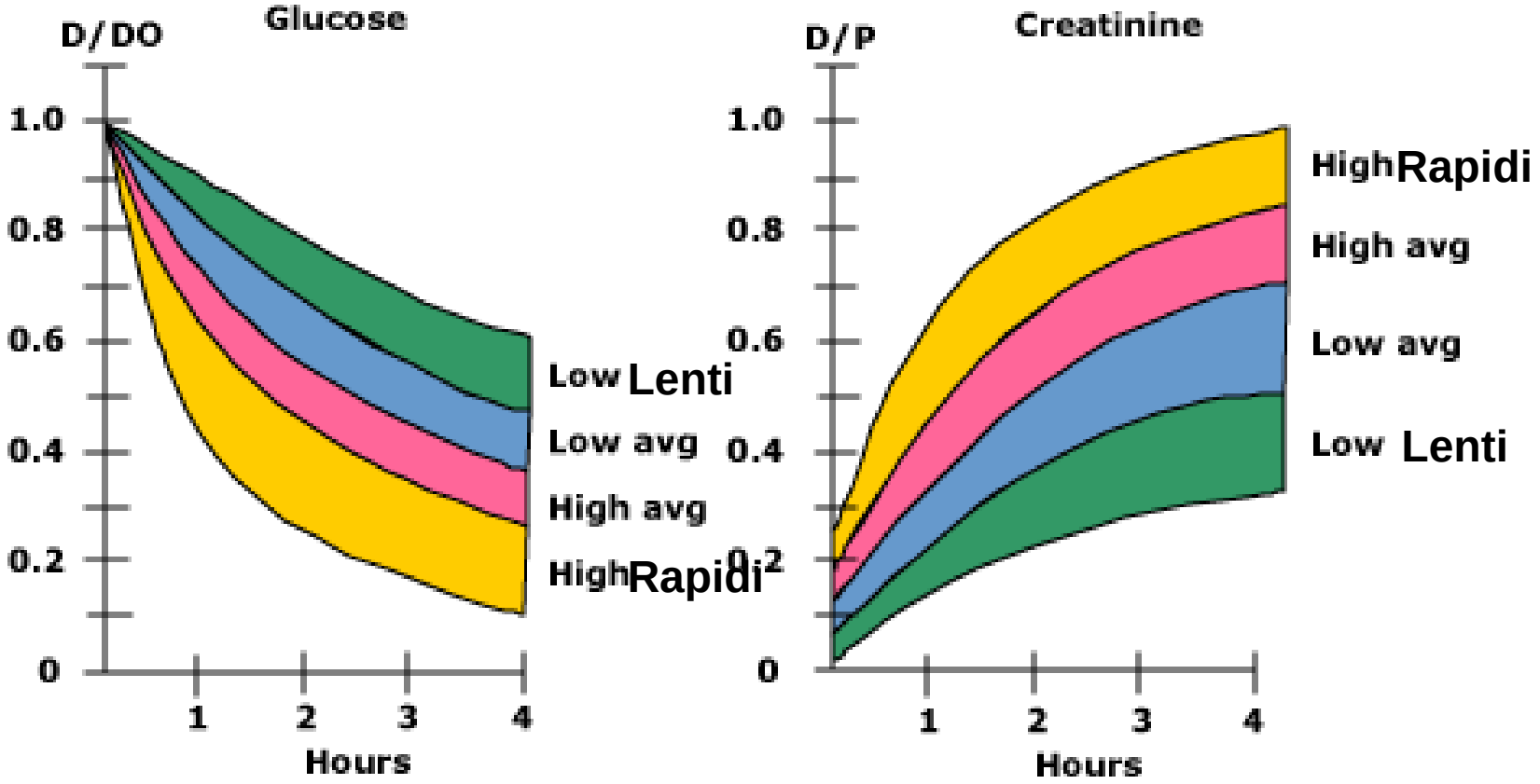


Peritoneal transport



Il PET standard

Classificazione del tipo di trasporto



(Twardowski ZJ, et al Blood Purif 1989)

Test di Equilibrazione Peritoneale
Categorie nelle varie casistiche

	Twardowski [1]	USA [2]	Messico [3]	UK [4]	NZ-Australia [5]	Netherland [6]	Italy [7]
H	>0.81	>0.79	>0.80	>0.78	>0.81	>0.82	>0.80
HA	0.65-0.81	0.67-0.79	0.68-0-80	0.65-0.78	0.69-0.81	0.72-0.82	0.71-0.80
Media	0.65	0.67	0.68	0.65	0.69	0.72	0.71
LA	0.50-0.61	0.55-0.66	0.56-0.67	0.52-0.64	0.57-0.68	0.62-0.71	0.62-0.70
L	<0.50	<0.55	<0.56	<0.52	<0.57	<0.62	<0.62

1. Twardowski ZJ, et al. Perit Dial Bull 1987.
2. Mujais S, et al. Kidney Int 2002.
3. Cueto-Manzano AM, et al. Perit Dial Int 1999.
4. Davies SJ. Kidney Int 2004.
5. Rumpsfeld M, et al. J Am Soc Nephrol 2006.
6. Smit W, et al. Perit Dial Int 2003.
7. La Milia V, et al. Kidney Int 2006.

Da: La Milia V. Test di equilibrazione peritoneale: attualità e prospettive future. GIN 2007; 6: 510-525.

- **What kind of peritoneal tests we have?**

1. Tests based on the PET principle

2. Tests not based on the PET principle

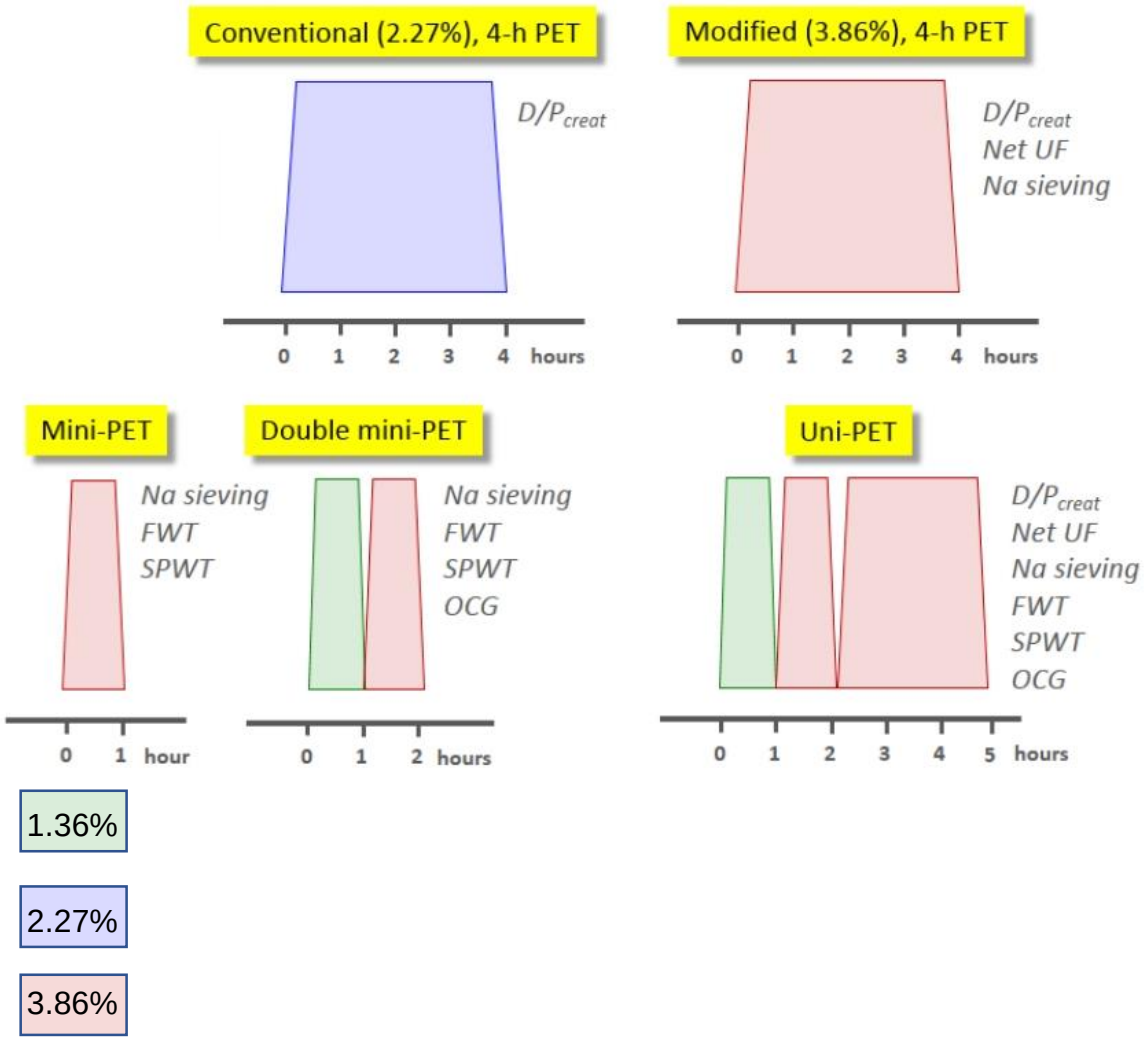
Tests not based on the PET principle

- **Personal Dialysis Capacity (PDC)**
- **PT 50 (time required to reach 50% solute equilibrium)**
- **APEX (Accelerated Peritoneal Examination) test**

Test basati sui principi del PET

- **PET Modificato (3.86%-PET)**
- **Standard Peritoneal Permeability Analysis (SPA)**
- **Mini-PET e Doppio Mini-PET**
- **PET Modificato con un drenaggio temporaneo**
- **PET-Unico (Uni-PET) (Doppio Mini-PET integrato con il 3.86%-PET)**
- **Altri test (es. Dialysis Adequacy and Transport Test or DATT; APEX)**

Tests based on the PET principle



Guidelines

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SAGE

ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

Table 4. Comparison of the use of middle and high strength glucose when undertaking a 4-h Peritoneal Equilibration Test.

		2.27% glucose/2.5% dextrose	3.86% glucose/4.25% dextrose
Clinical measurement	Solute transfer rate	Equivalent	Equivalent
	UF capacity	Potentially less discriminatory	Potentially more discriminatory
	Free water transport	Cannot estimate	Estimated from the sodium dip at 1 h
	Catheter flow dysfunction	Equivalent	Equivalent
Clinical use	PROS	Estimates suggest that over 90% units worldwide use this concentration routinely. Provides sufficient information to guide the majority of prescription decisions. Reflects everyday practice	Allows better diagnosis of membrane dysfunction in combination with a 1 h sodium dip.
	CONS	Lacks diagnostic value for membrane dysfunction	Requires availability of solution with this tonicity (some countries this is an issue) Does not reflect everyday practice
Clinical validation (Survival, technique failure and hospitalization)	Solute transfer rate	Very high – given that most studies reporting clinical associations use this strength. Faster solute transfer rate indicates higher mortality and hospitalization risk	Likely high – no reason to think this is different to 2.27/2.5%, but no supporting evidence.
	UF capacity	Data on survival and technique failure shows no clear relationship. More frequent hospitalizations when UFC < 200 mL	No data on survival, technique failure or hospitalization
	Free water transport	Cannot estimate	No data on survival, technique failure or hospitalization
Clinical validation (Ultrafiltration insufficiency)	Solute transfer	Identifies poor ultrafiltration that should respond to prescription interventions	Identifies poor ultrafiltration that should respond to prescription interventions
	UF capacity	Cut-off <100 mL based on small and large data sets	Cut-off of <400 mL based on small data sets
	Free water transport	Cannot estimate	Identifies ultrafiltration failure that will not respond to prescription interventions and membrane injury that is a risk for EPS

UF: ultrafiltration; EPS: encapsulating peritoneal sclerosis.

Table 3. Summary of different peritoneal function tests and the membrane characteristics they measure.

	Membrane test				
	Classic PET[46]	Modified PET[a] (SPA)[93]	Mini-PET[b]	Double mini-PET[43]	Personal dialysis capacity test (PDC)[94]
	2.27%	3.86%	3.86%	1.36% and 3.86%	Multiple
Membrane characteristic	4 h	4 h	1 h	2 × 1 h	24 h
Solute transfer	Yes	Yes	Yes (at 1 h)	Yes (at 1 h)	Yes (expresses this as diffusion distance ($A_0/\Delta x$))
Ultrafiltration capacity	Yes	Yes		Yes (at 1 h)	
Sodium dip (free water transport)		Yes	Yes	Yes (Also calculates the proportion of UF via AQP and small pores)	
Osmotic conductance				Yes	Yes (Calculates the UF capacity for glucose, LpS)
Net fluid reabsorption					Yes (This is possible because it includes a long exchange)
Effective lymphatic reabsorption		Yes (Calculated from instilled macromolecule)			
Protein Clearance		Yes (Uses proteins of different molecular weights)			Yes (Measures large pore flux ($J_V L$))

PET: peritoneal equilibration test; UF: ultrafiltration; AQP: aquaporins.

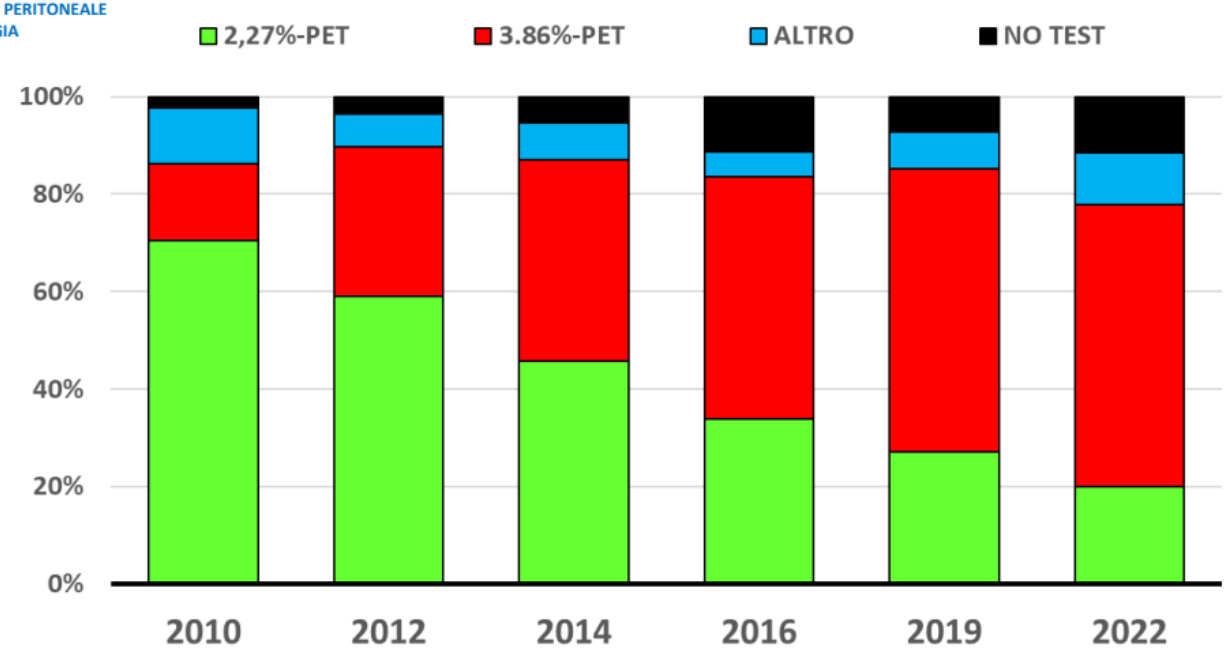
[a]The modified PET, also known as the Standard Permeability Analysis (SPA)[93] when measurement of peritoneal proteins and large-molecular weight markers are included, can be combined with the mini-PET by doing a temporary drain at 1 h.

[b]The modified PET with a temporary drain at 1 h can be combined with the first part of the double mini-PET, as can the mini-PET be combined with the classic PET, referred to the sPET,[95,96] to get a complete data set (these combinations will take 5 h in total). The PDC requires specific software and a complex regime to gain all the information, so is rarely used.[94]

GRUPPO di PROGETTO di DIALISI PERITONEALE
SOCIETA' ITALIANA di NEFROLOGIA

CENSIMENTO GPDP 2022

PET – QUALE ? 225 CENTRI



ALTRO = MINIPET, DOPPIO MINIPET, PDC (Personal Dialysis Capacity), **NON SPECIFICATO**
227 CENTRI DI CUI 2 NON HANNO RISPOSTO

Tests based on the PET principle

3.86% Glucose PET

More information on peritoneal UF and sodium sieving phenomenon (Free-water transport)

ISPD Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis Perit Dial Int 2000; Monquil M et al Perit Dial Int 1995

Mini-PET

More information on free-water transport La Milia V et al Kidney Int 2005

Tests based on the PET principle

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Mini-PET

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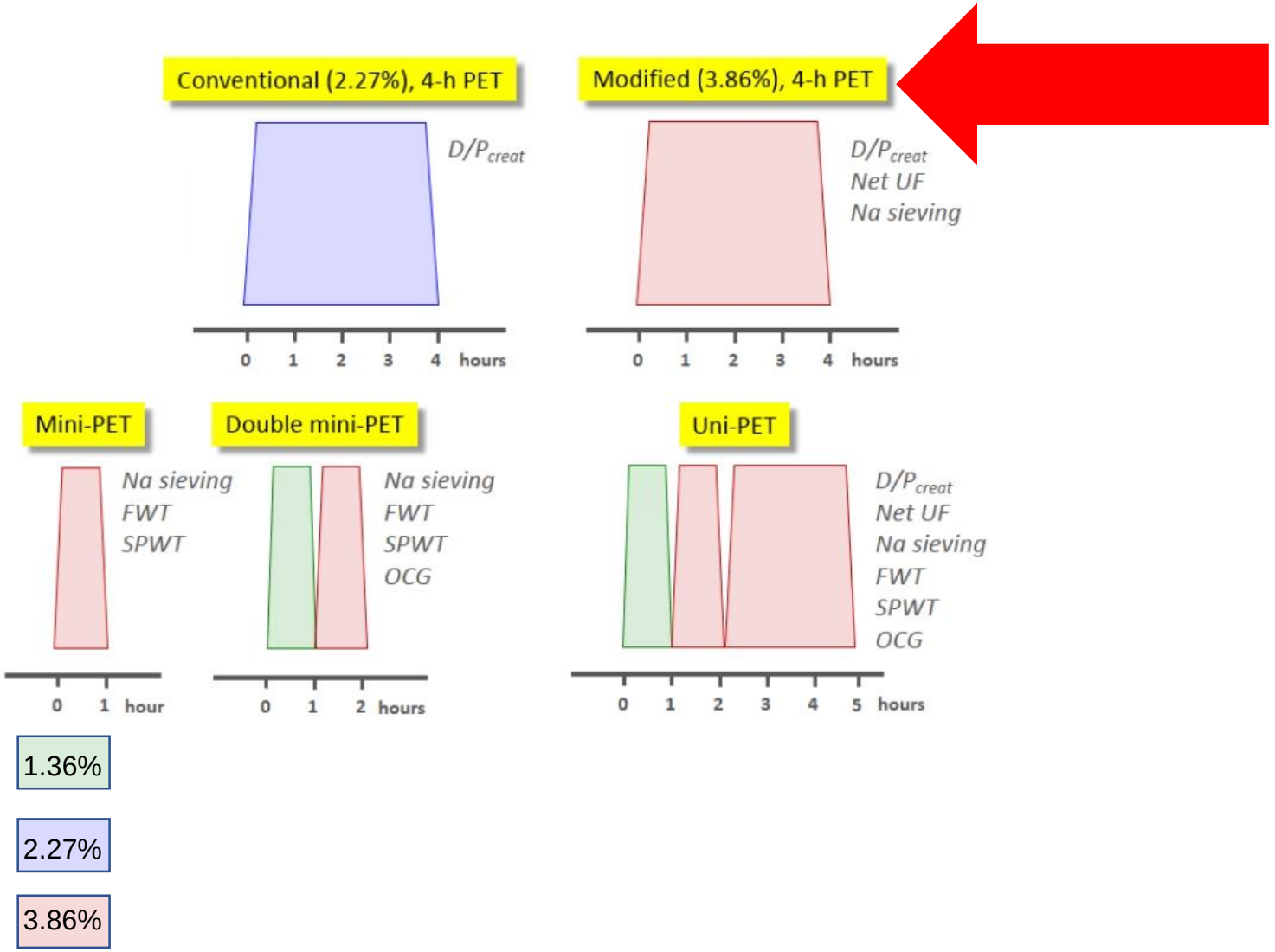
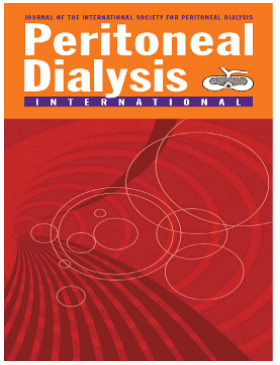
Tests based on the PET principle



3.86% PET vs 2.27% PET



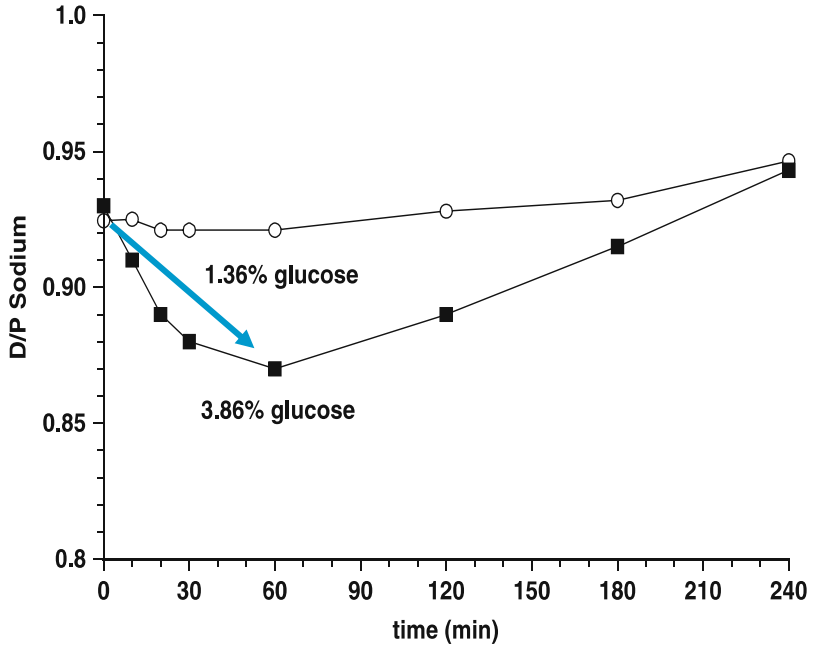
ISPD Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis Perit Dial Int 2000

- **Risultati simili sul trasporto dei soluti di piccolo peso molecolare** (Smit W et al Perit Dial Int 2000; Pride ET et al Perit Dial Int 2002)

- **Migliori informazioni sulla UF peritoneale per il maggiore gradiente osmotico (coefficiente di variazione: 10% vs 25%** (Davies SJ Kidney Int 2006;La Milia V et al. Kidney Int 2006)

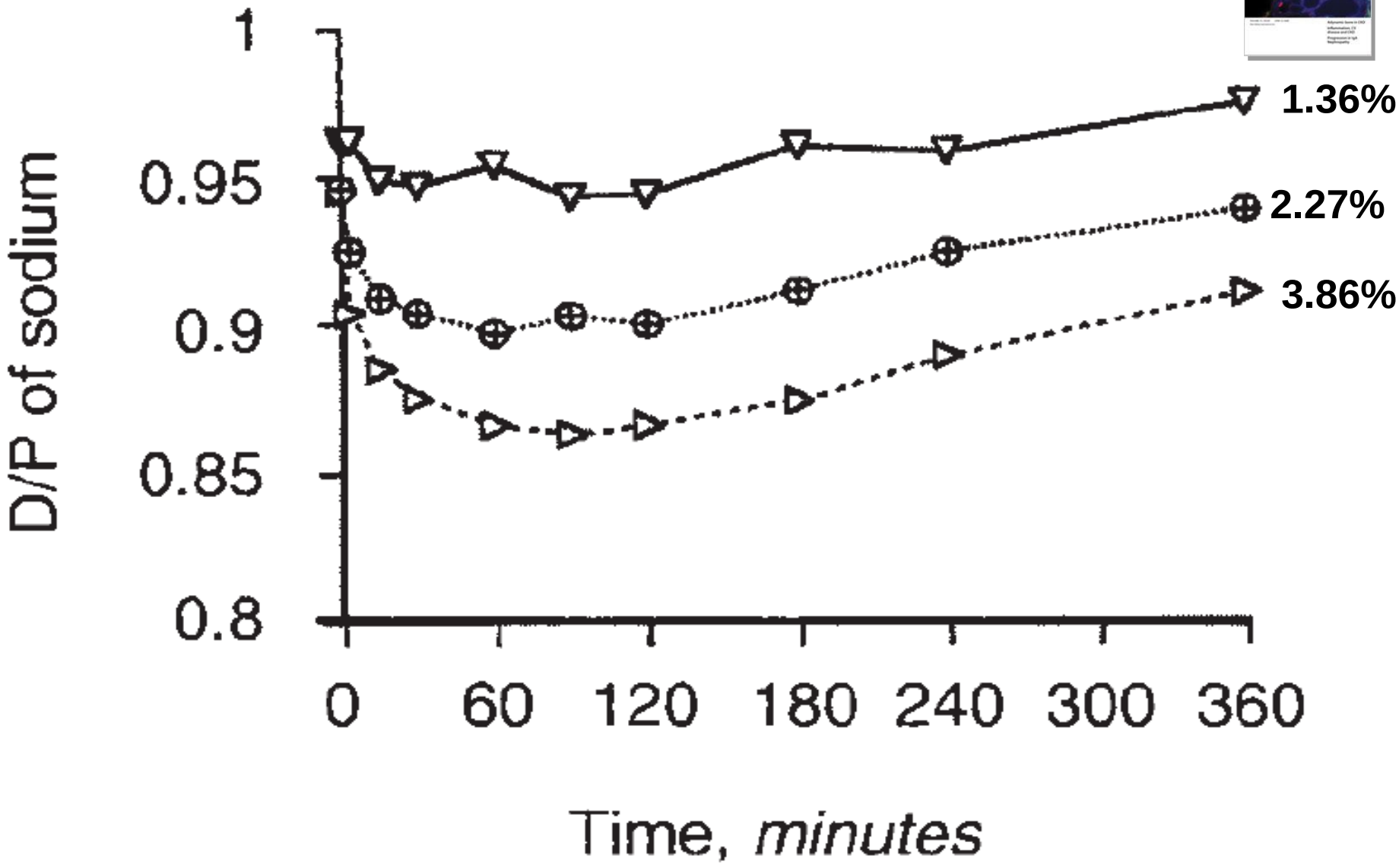
- **Fenomeno del sieving del sodio (D/P_{Na}) e valutazione indiretta del trasporto di acqua libera** (Monquil M et al Perit Dial Int 1995)

Free-water transport across the ultrasmall pores explains the sodium sieving or sodium dip



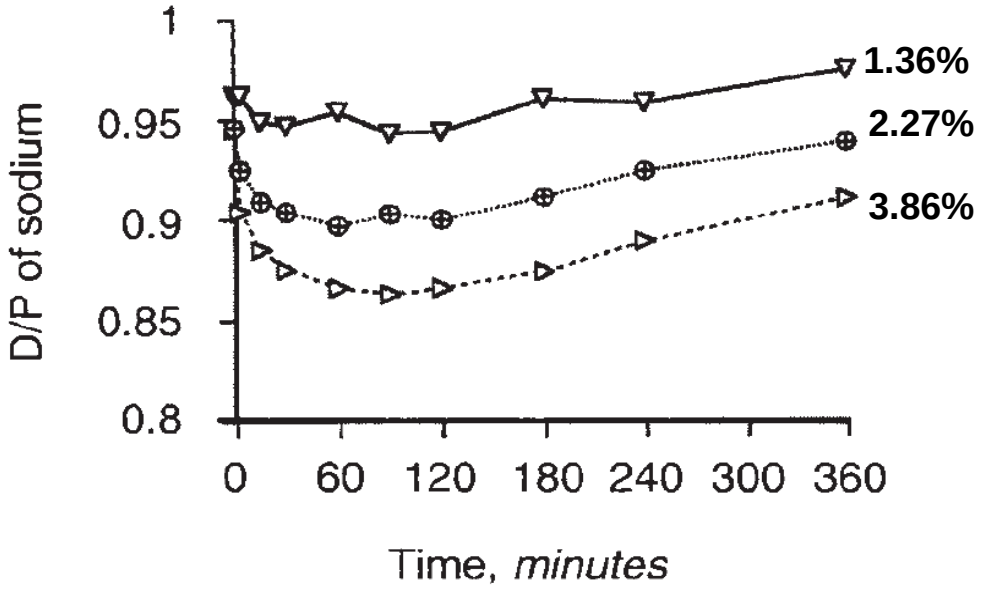
- Rapid decrease in dialysate sodium concentration
  - during the first part (60 min)
  - of a dwell with hypertonic glucose
- Dilution of sodium in the peritoneal fluid by free-water transport across
  - the ultrasmall pores and
  - the ‘whole’ peritoneal membrane

Sodium sieving during peritoneal dwell with different glucose concentration

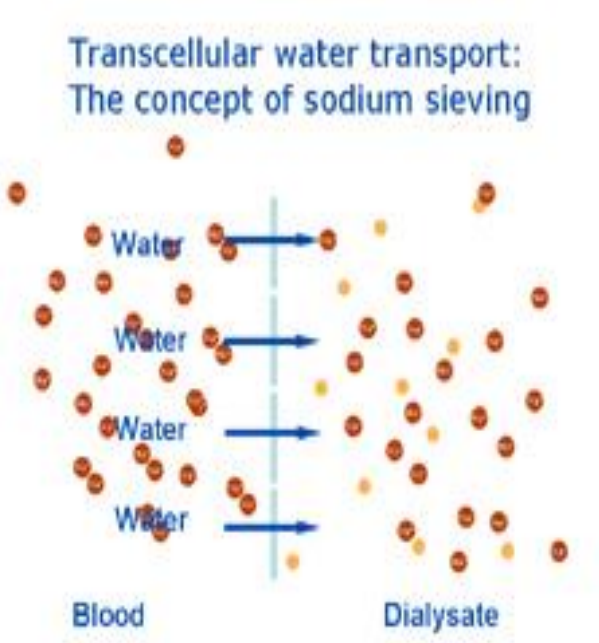


Wang T et al Kidney Int 1997

Sodium sieving during peritoneal dwell with different glucose concentration



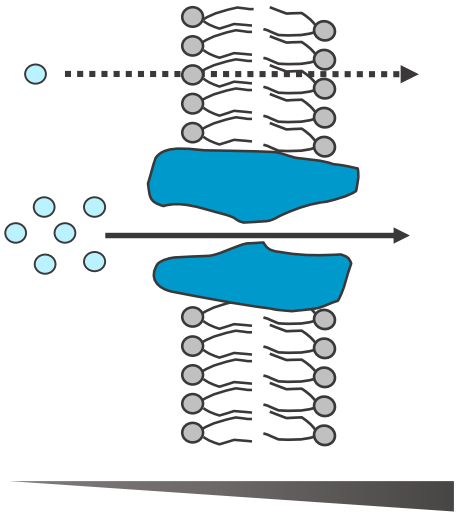
Wang T et al Kidney Int 1997

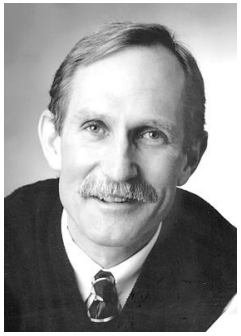


Identity of ‘water-specific channels’

Appearance of Water Channels in *Xenopus* Oocytes Expressing Red Cell CHIP28 Protein

Gregory M. Preston, Tiziana Piazza Carroll, William B. Guggino, Peter Agre*





Peter Agre
Nobel Prize in Chemistry, 2003

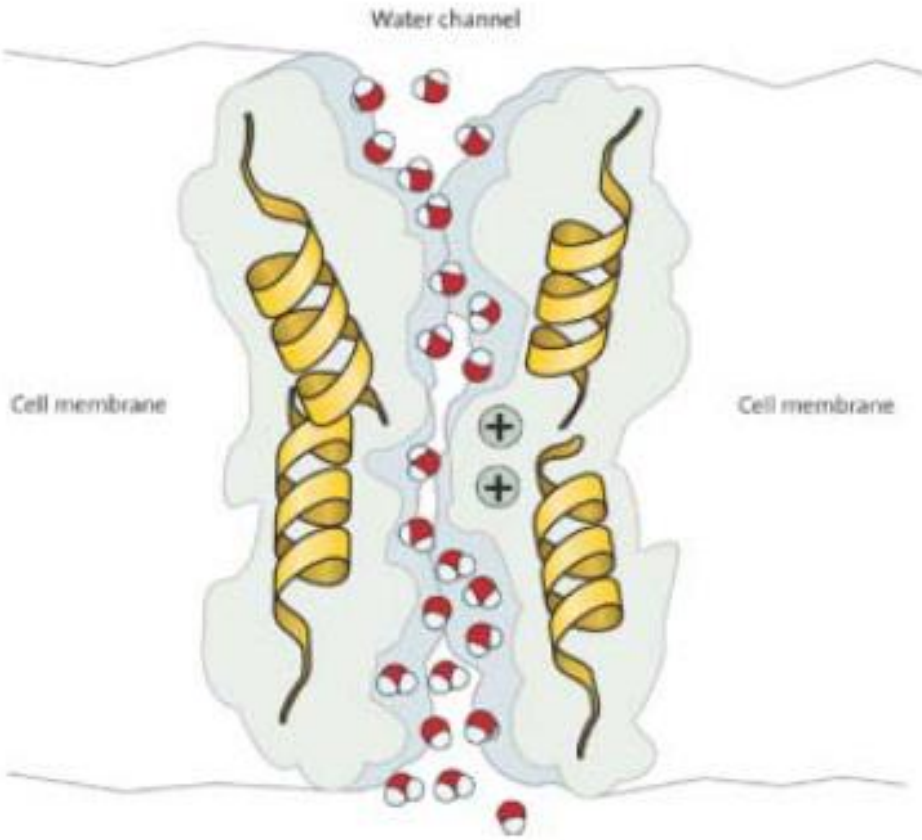
- Small proteins with properties of water channels
- Facilitate the diffusion of water molecules across biological membranes - called *aquaporins*
- Expressed in RBC and in kidney tubules

SCIENCE • VOL. 256 • 17 APRIL 1992

Aquaporin-1 (AQP1)

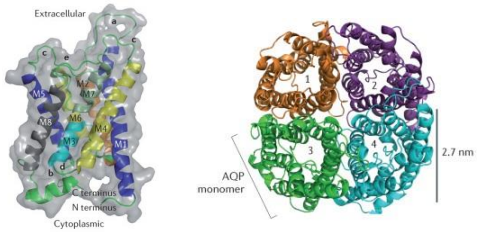
Structural information obtained by electron cryomicroscopy shows that the pore formed by AQP1, with its narrow diameter of only 2.8 Å, allows the accommodation of a single water molecule and perfectly fits the postulated size of the ultrasmall pore (by B. Rippe) of the peritoneal membrane.

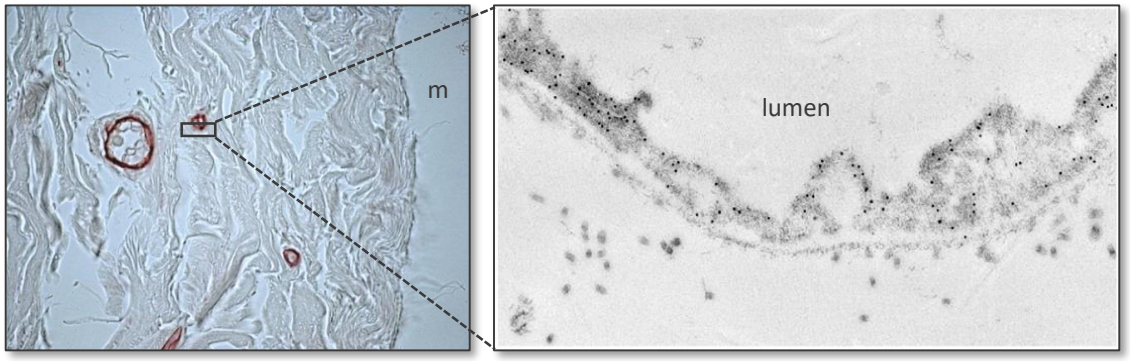
Aquaporin-1 : The ultrasmall pore

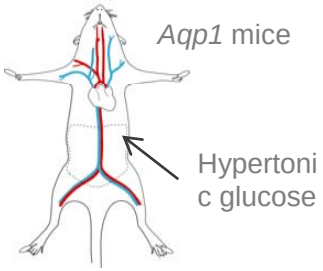


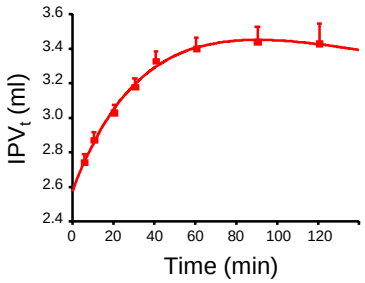
Aquaporin-1 Water Channels in PD

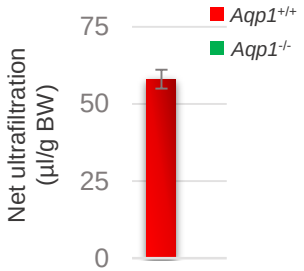
Aquaporin water channels

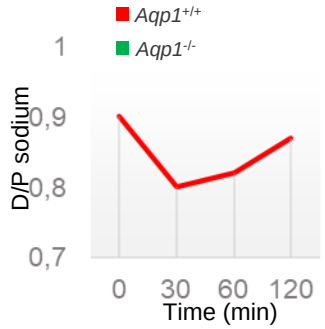








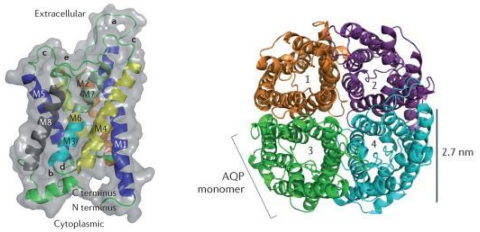


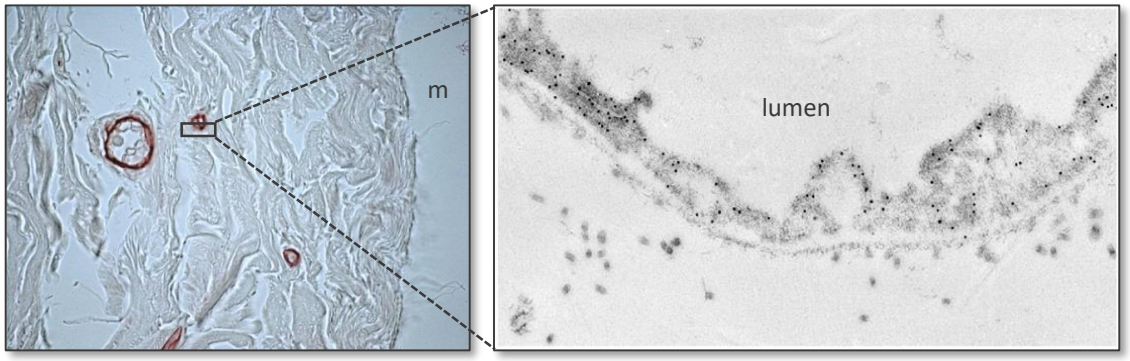


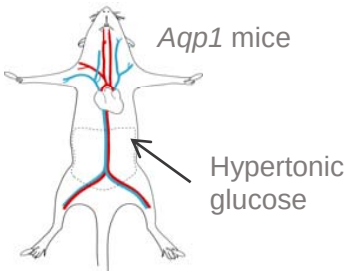
Devuyst et al, *Am J Physiol* 1998 ; Ni et al, *Kidney Int* 2006; Morelle et al, *Am J Physiol Renal Physiol* 2014

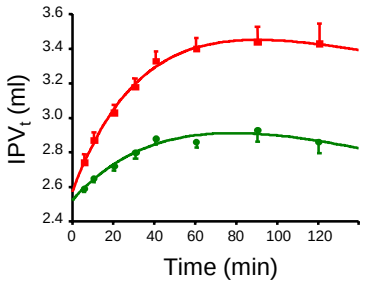
Aquaporin-1 Water Channels in PD

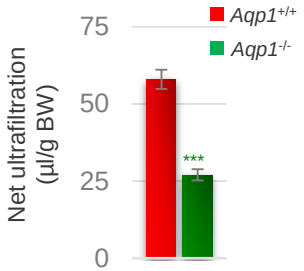
Aquaporin water channels

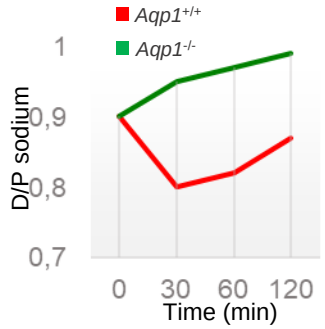










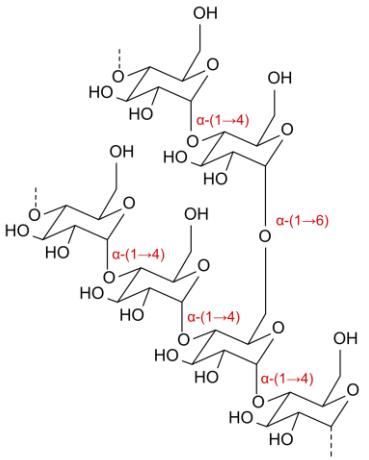


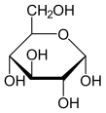
Endothelial AQP1 → 40-50% UF and sodium sieving (glucose)

Devuyst et al, *Am J Physiol* 1998 ; Ni et al, *Kidney Int* 2006; Morelle et al, *Am J Physiol Renal Physiol* 2014

BASIC RESEARCH www.jasn.org

Mechanisms of Crystalloid versus Colloid Osmosis across the Peritoneal Membrane





Glucose

- **Critical role for AQP1**
- Small molecule (MW 180 Da, R_H 0.37 nm)
- Diffuses rapidly across membranes, transient effect on UF

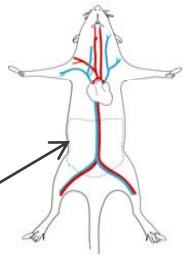
Icodextrin

- Mixture of glucose polymers
- Variable size, incl. large (colloidal) molecules
- Slowly absorbed, long-dwells
- **Role of AQP1?**

Morelle et al, *J Am Soc Nephrol* 2018

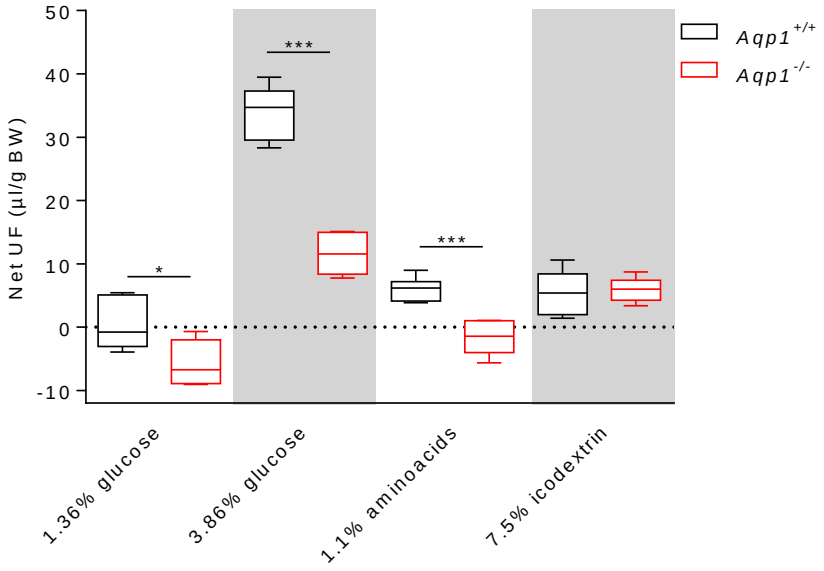
Pathways and mechanisms of icodextrin-induced water flow?

Mouse model of PD



Icodextrin vs. glucose or aminoacids

Aqp1 mice
2-h dwells



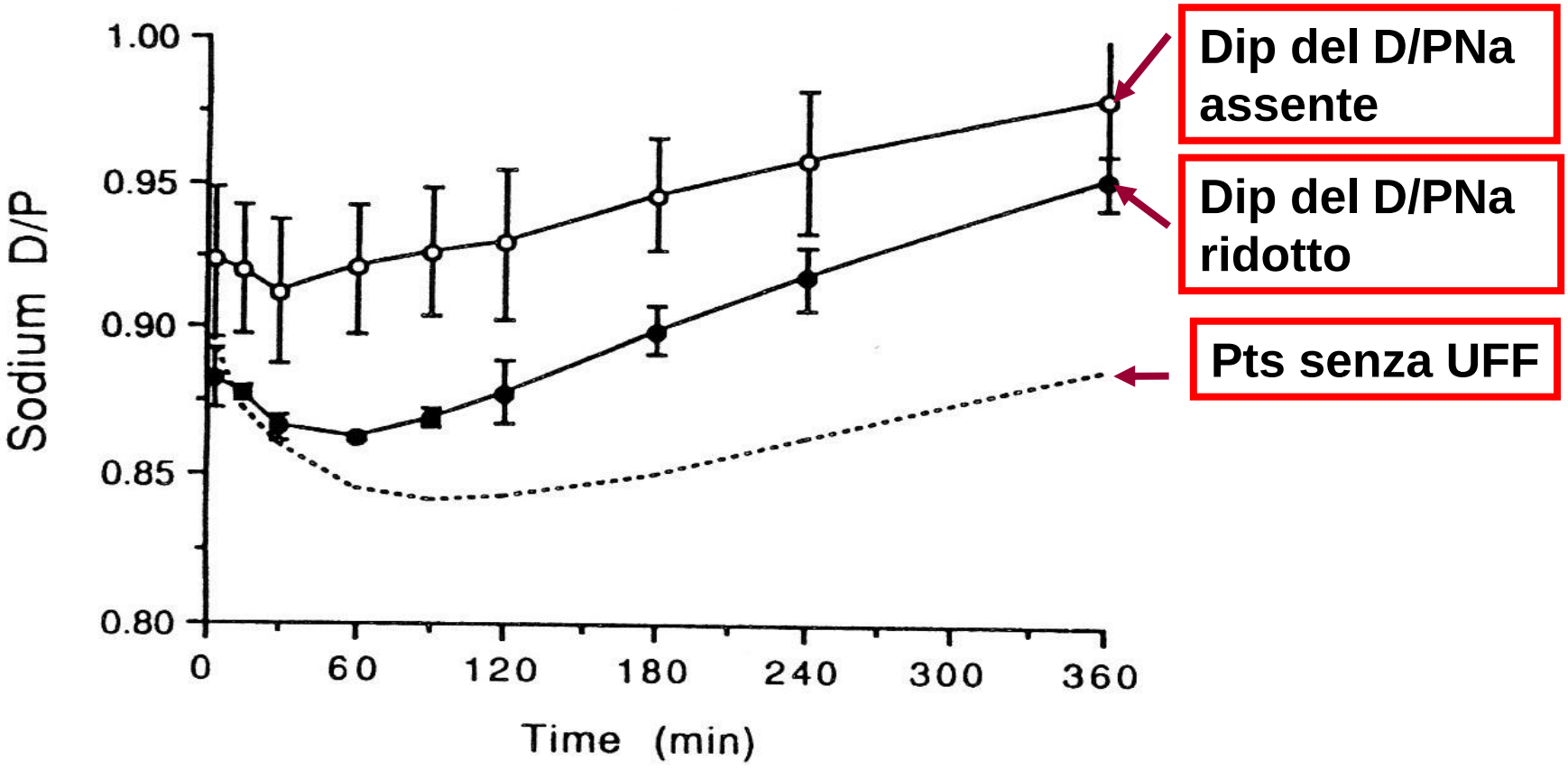
Icodextrin induces water transport independently of water channels, exclusively across small pores (enhanced water and sodium removal)

Morelle et al, *J Am Soc Nephrol* 2018

Critical Role of Water Channels in PD

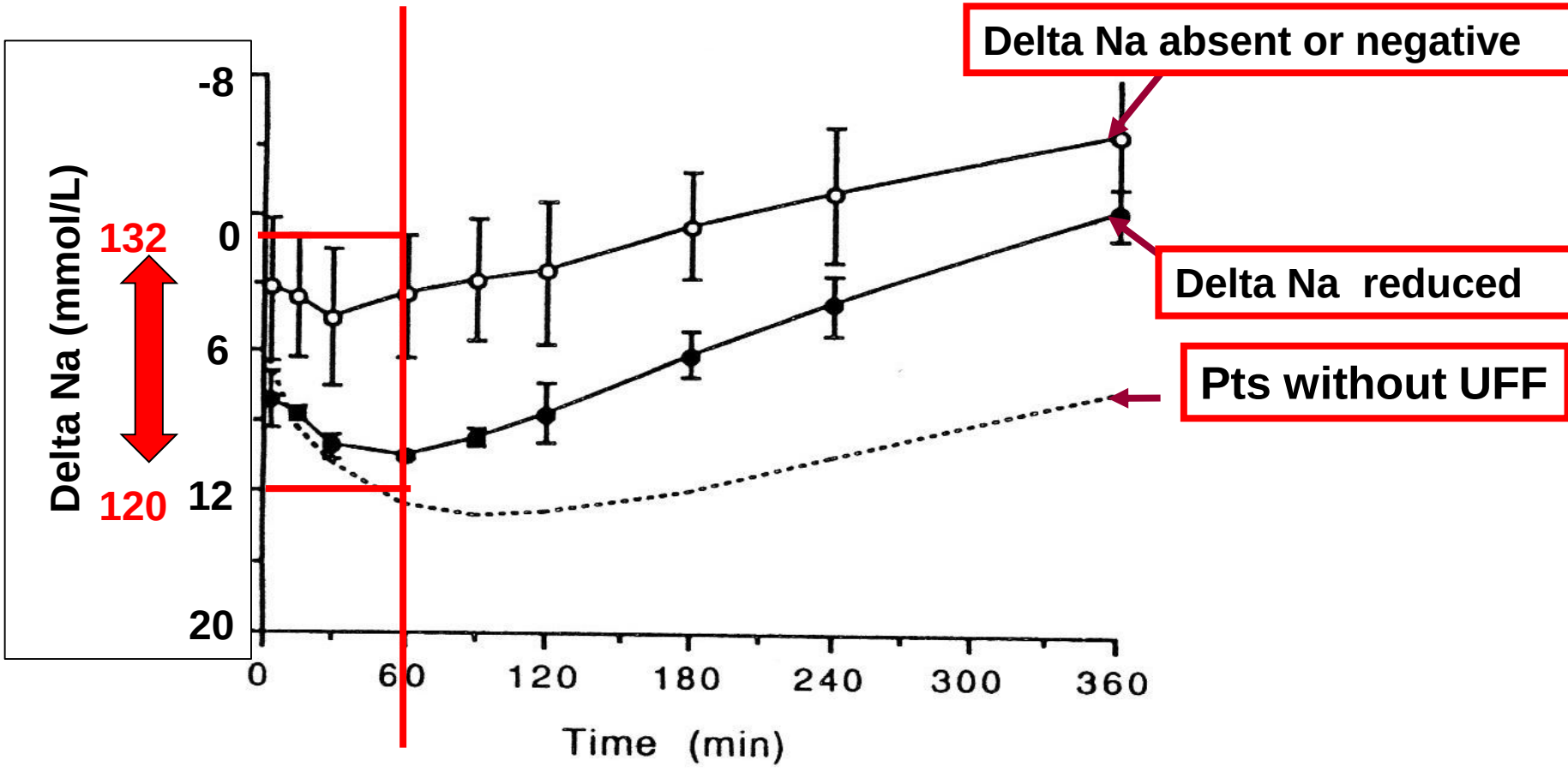
- AQP1 water channels expressed in the microvascular endothelium of the peritoneal membrane
- Facilitate osmotic water transport across the peritoneal membrane (40-50% of net ultrafiltration using hypertonic glucose)
- Pharmacological modulation of water channels (expression or function) influences glucose-driven UF
- Icodextrin generates water transport independently from water channels (colloidal osmosis)

D/P Na in pazienti con deficit di ultrafiltrazione

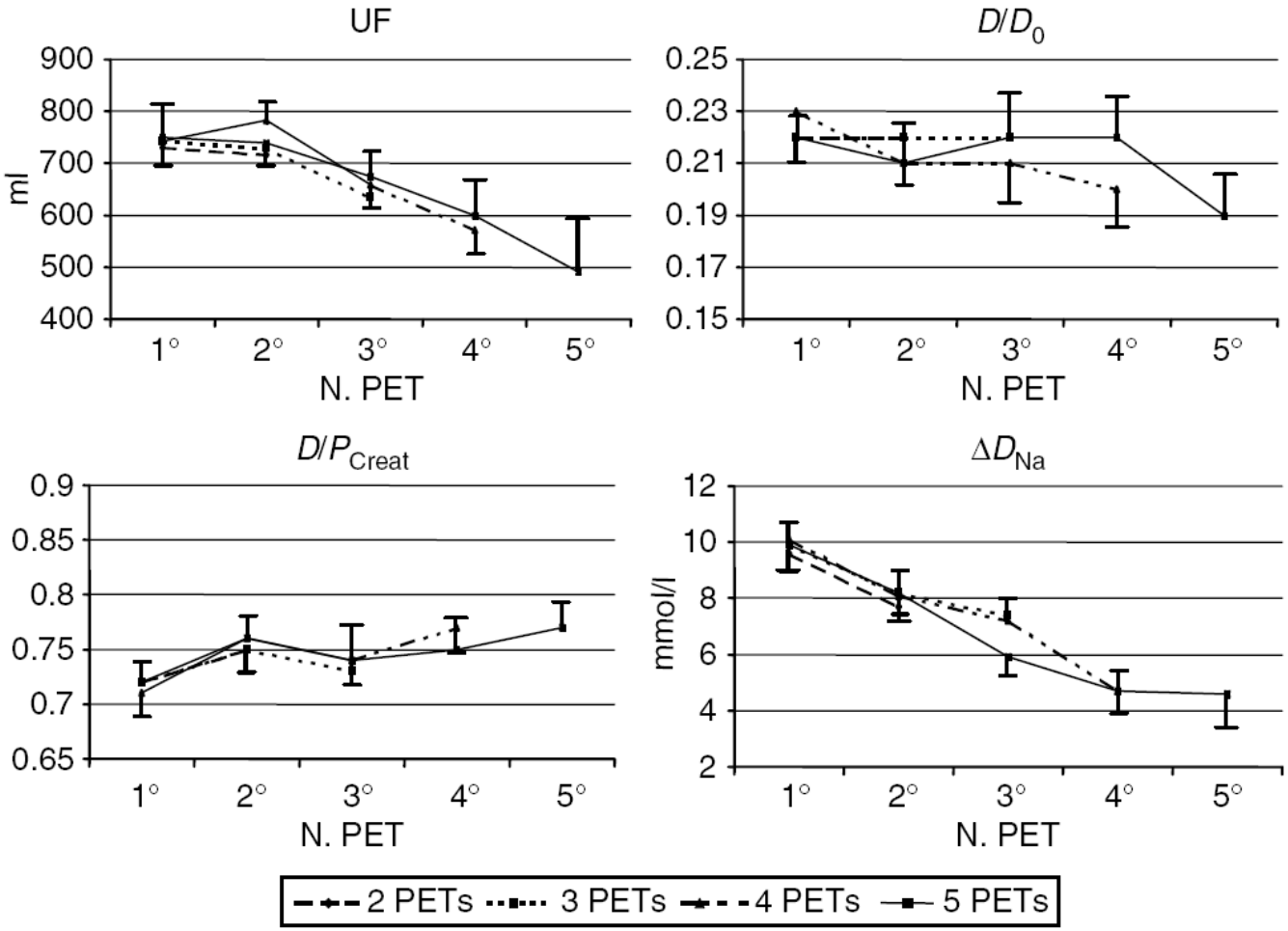


Heimbürger O et al Nephrol Dial Transplant 1994

Delta Sodium in patients with ultrafiltration failure

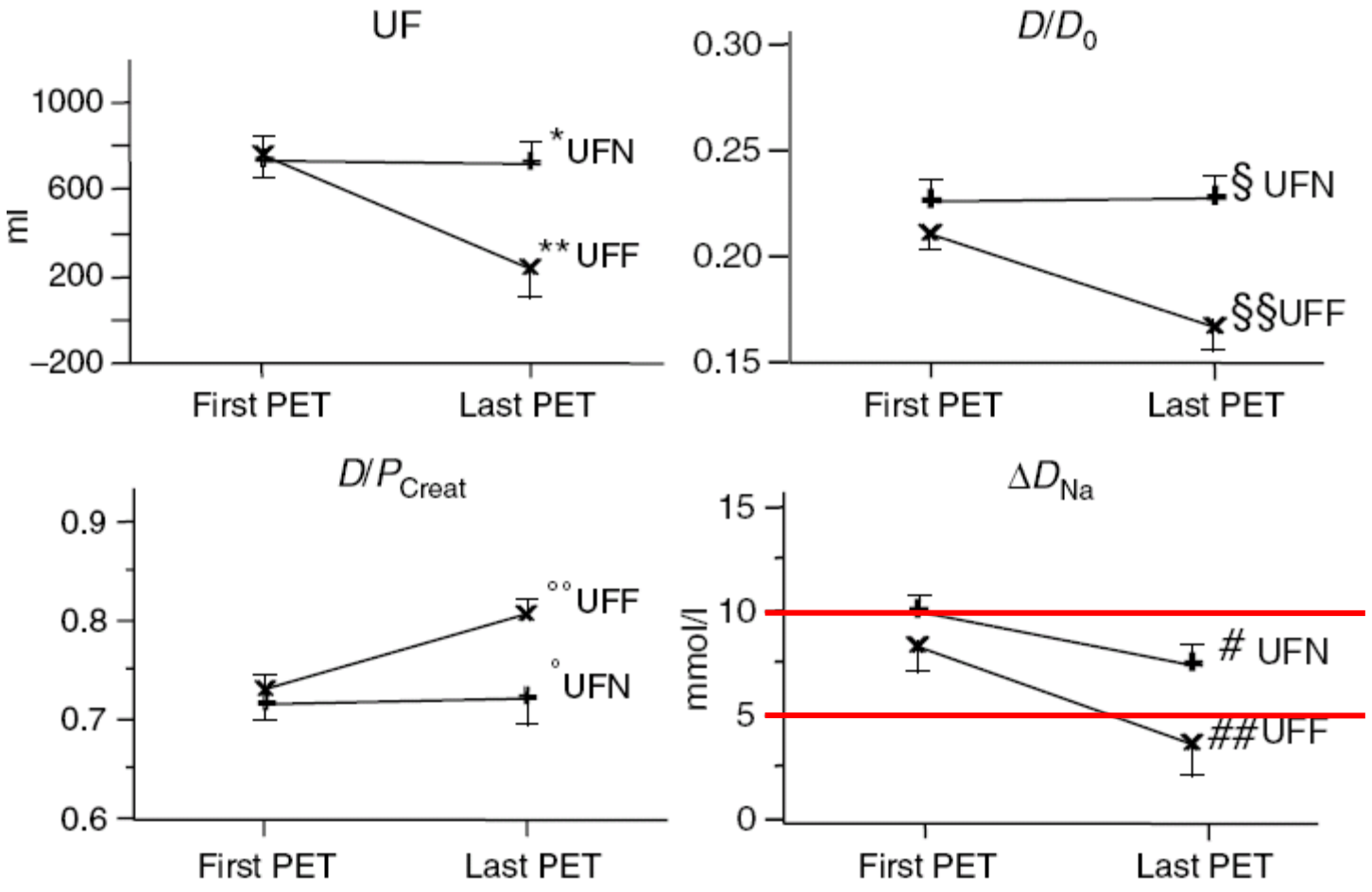


Δ Dialisato Na nei pazienti in dialisi peritoneale



La Milia V et al Kidney Int 2006

Δ Dialisato Na nei pazienti in dialisi peritoneale



La Milia V et al Kidney Int 2006

Tests based on the PET principle

3.86% Glucose PET

More information on peritoneal UF and sodium sieving phenomenon (Free-water transport)

ISPD Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis Perit Dial Int 2000; Monquil M et al Perit Dial Int 1995

The sodium sieving is a semi-quantitative measure of FWT

With the 3.86%-PET we can not measure the FWT

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3.86% Glucose PET

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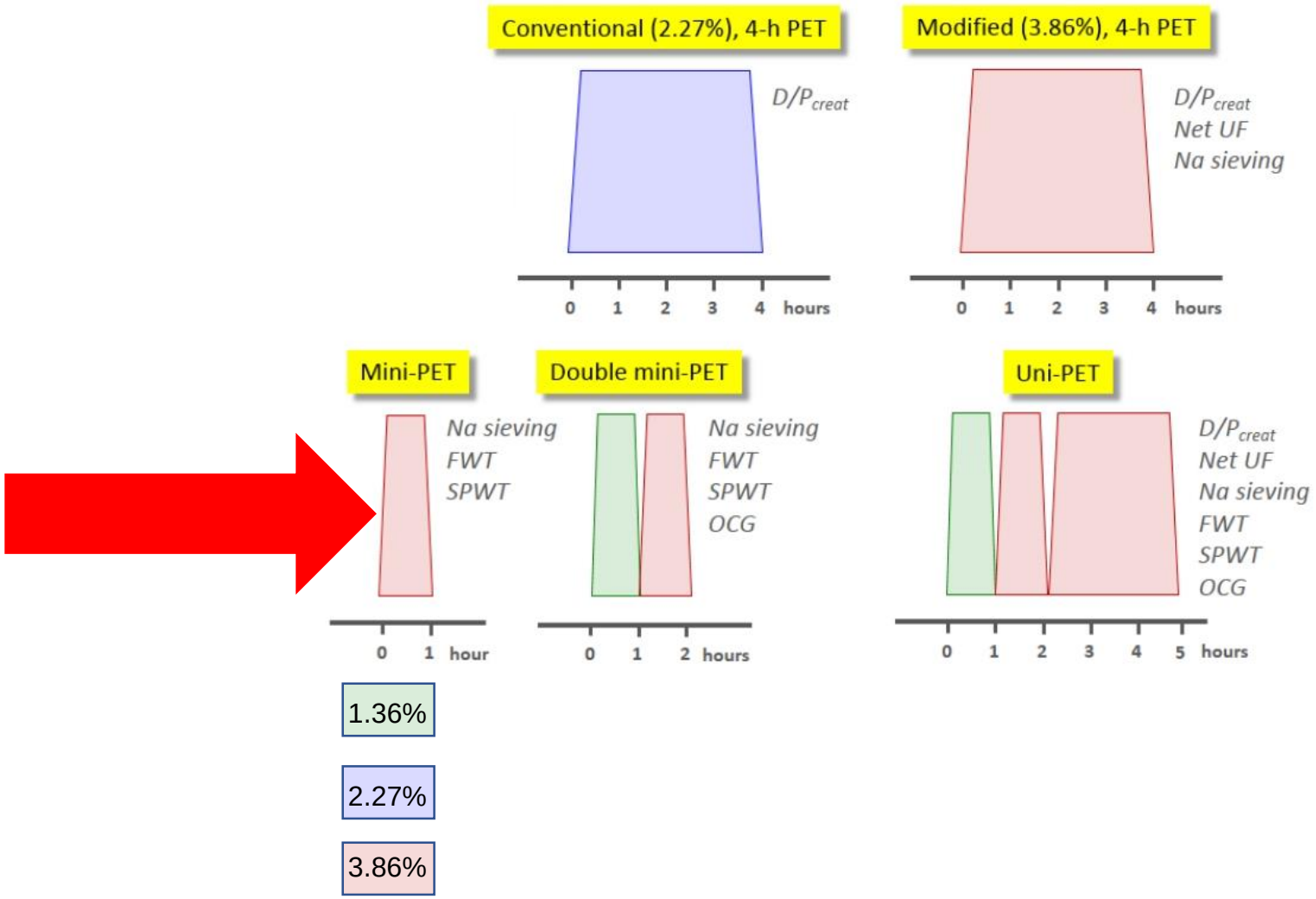
Mini-PET

More information on free-water transport La Milia V et al Kidney Int 2005

Tests based on the PET principle



3.86% Mini-PET

Kidney International, Vol. 68 (2005), pp. 840–846

Mini-peritoneal equilibration test: A simple and fast method to assess free water and small solute transport across the peritoneal membrane

VINCENZO LA MILIA, SALVATORE DI FILIPPO, MONICA CREPALDI, LUCIA DEL VECCHIO, CESARE DELL'ORO, SIMEONE ANDRULLI, and FRANCESCO LOCATELLI

Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy

UFSP = NaR/Nap

Free-H_2O = UF totale - UFSP

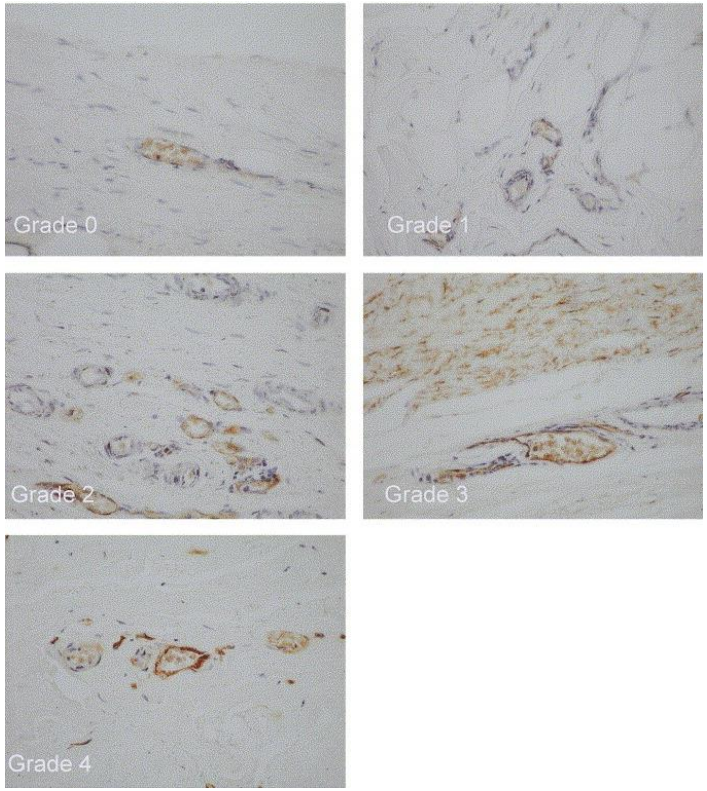
La Milia *et al.* Kidney Int 2005

Peritoneal transport characteristics of 52 patients in PD therapy assessed during the 3.86%-PET and the 3.86%-Mini-PET

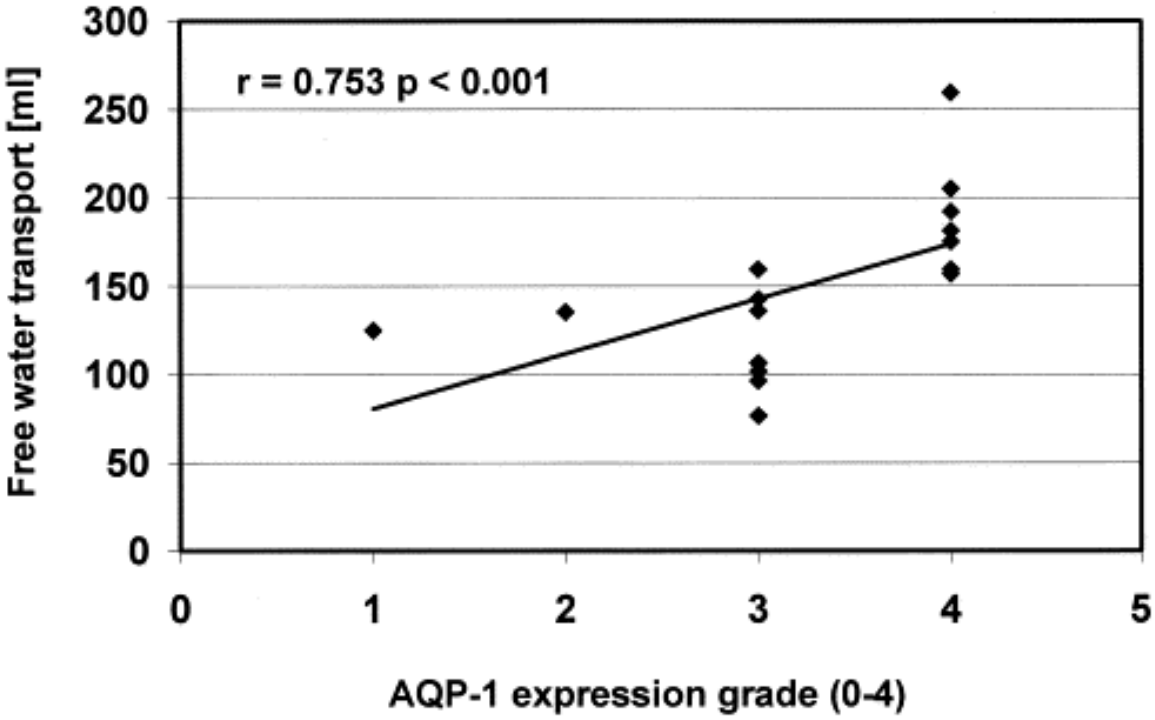
	3.86%-PET	3.86%-Mini-PET
UF (mL)	749 ± 224 (686-749)	493 ± 170 (446-541)
UFSP (mL)	-	279 ± 142 (239-318)
Free water transport (mL)	46 ± 18%	215 ± 86 (191-239)
D/D_0	0.28 ± 0.08 (0.25-0.30)	0.58 ± 0.09 (0.56-0.61)
D/P_{Creat}	0.69 ± 0.10 (0.66-0.72)	0.43± 0.09 (0.41-0.46)
Na_p (mmol/L)	141.8 ± 2.1 (141.2-142.4)	142.2± 2.7 (141.5-143.0)
$Na_{DialysateIn}$ (mmol/L)	133.4 (132.2-134.7)	133.2 (132.2-134.8)
$Na_{DialysateOut}$ (mmol/L)	127.5 ± 5.2 (126.1-129.0)	123.3 ± 3.9 (122.2-124.4)
DipNa (mmol/L)	-6.2± 5.1 (-7.6, -4.7)	-10.0 ± 4.2 (-11.1, -8.8)
D/P_{Na} 60’	0.89 ± 0.03 (0.88-0.90)	0.89 ± 0.03 (0.88-0.89)
NaR (mmol)	82 ± 26 (75-89)	40 ± 20 (34-45)

La Milia V et al Kidney Int 2005

Peritoneal biopsy specimens testing AQP-1 expression for endothelial cells in blood vessels



Free water transported through AQP after 1 hour in the PET and AQP-1 expression

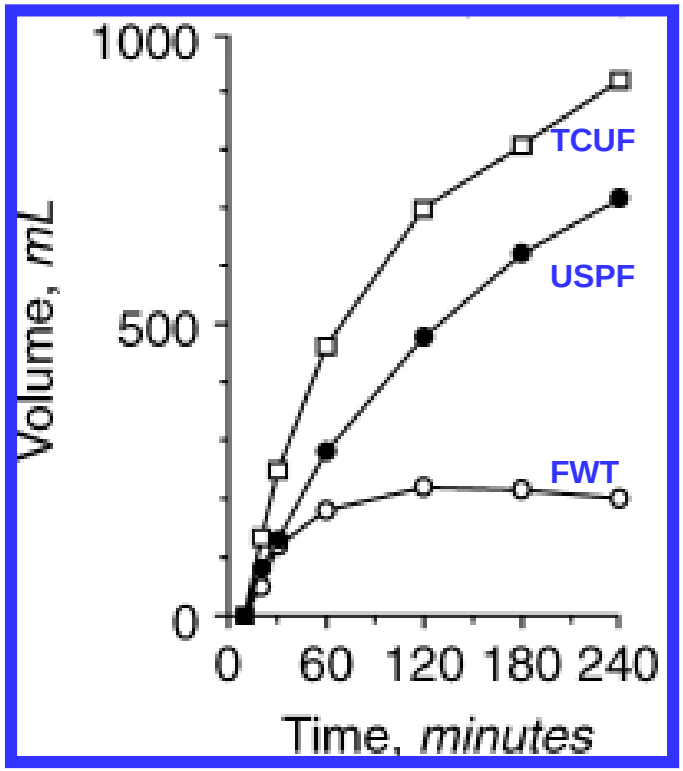


N = 57

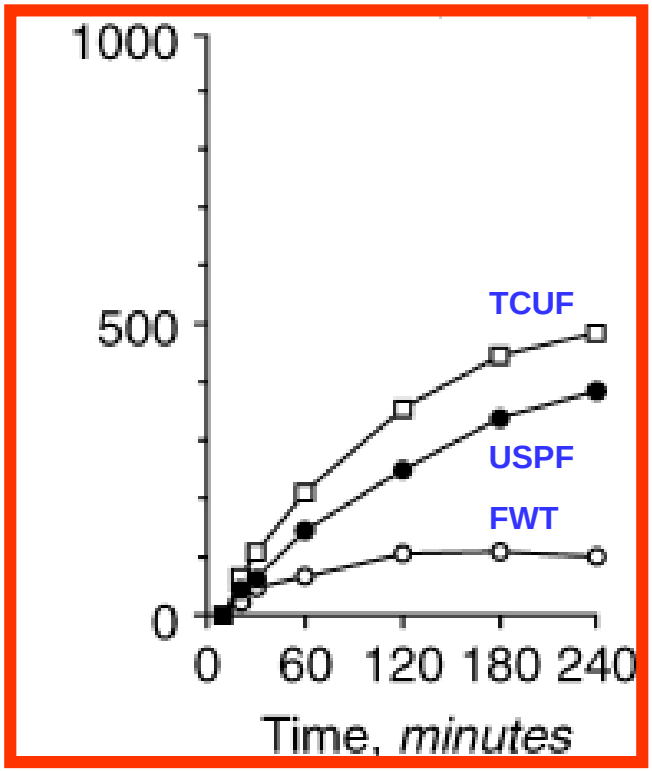
Schoenicke G et al Am J Kidney Dis 2004

Fluid profiles for patients with normal ultrafiltration or with ultrafiltration failure (SPA with dextran 70)

Normal UF (n = 29)



UF failure (n = 11)



Corrected for Na diffusion

Smit W et al Kidney Int 2004

Tests based on the principle of PET

3.86% Glucose PET

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Mini-PET

More information on free-water transport La Milia V et al Kidney Int 2005

Double Mini-PET

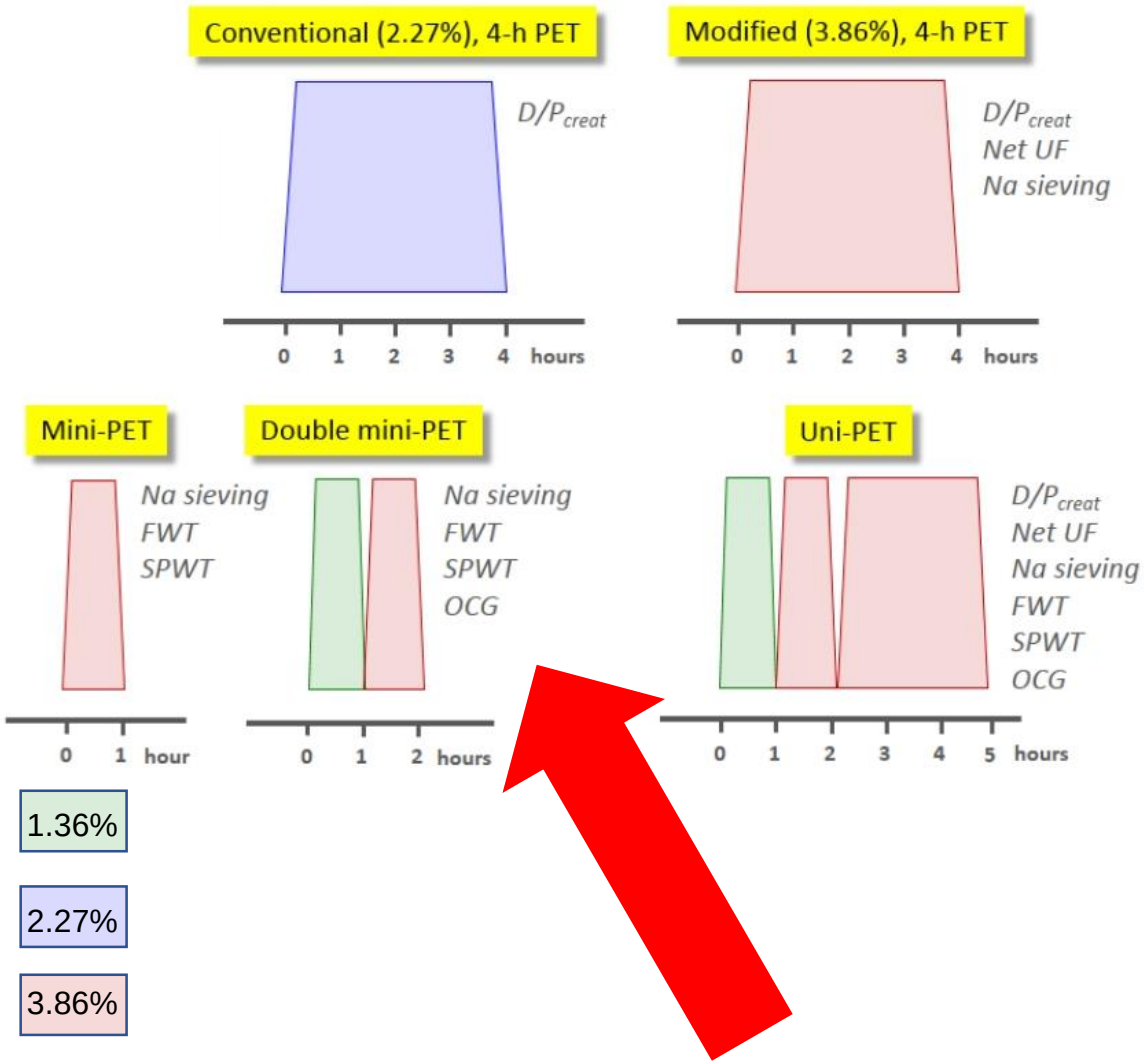
More information on osmotic conductance to glucose La Milia V et al Kidney Int 2007

Doppio Mini-PET

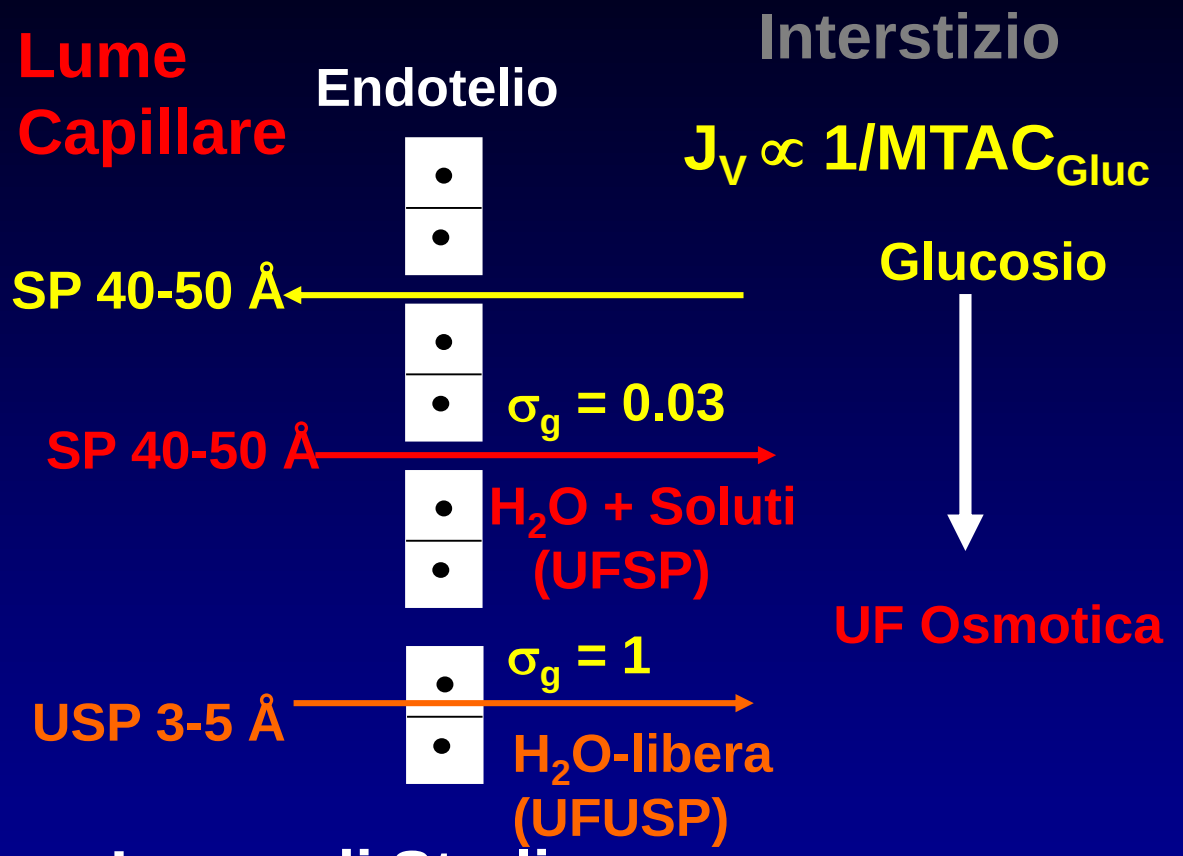
- **Due mini-PET sequenziali di 60 minuti**

- **Il primo mini-PET effettuato con una soluzione di glucosio al 1.36%, il secondo effettuato con una soluzione di glucosio al 3.86%**

Tests based on the PET principle



Conduttanza Osmotica al glucosio



Legge di Starling

$$d_V/d_t = J_V = L_p \cdot S \cdot (\Delta P - \sigma_{prot}\Delta\pi_{prot} + \sigma_g\Delta\pi_g - \sum_{i=1}^{n} -\sigma_i\Delta\pi_i) - L$$

$L_p \cdot S \cdot \sigma_g$ = Conduttanza Osmotica al glucosio

Osmotic conductance to glucose and peritoneal UF

	UF Normal (N=35)	UF Failure (N=20)
TCUFR (mL/min/1.73m^2)	3.8 (1.6-6.7)	2.1 (0.9-3.7)*
ELAR (mL/min/1.73m^2)	1.0 (0.0-2.4)	1.5 (0.5-6.3)**
Max dip D/PNa	0.109 (0.026-0.170)	0.032 (0.007-0.095)*
$L_P S \bullet \sigma_g$ (μL/min/mmHg)	3.0 (0.8-7.1)	2.1 (0.4-4.3)**
$MTAC_{Creat}$ (mL/min/1.73m^2)	9.0 (3.7-16.2)	12.9 (7.8-18.4)*
Assorbimento Gluc. (%)	60 (41-77)	73 (54-88)*

*P<0.001; **P<0.05

Smit W et al Perit Dial Int 2004

Table 1 | A comparison between peritoneal solute transport, fluid kinetics, and determinants of TCUF between Group I (PD duration <24 months), Group II (PD duration 24–60 months), and Group III (PD duration >60 months)

	Group I (UFF)	Group II	Group III	
Number of patients	22	14	14	
PD duration	8 (1–23)	43 (32–59)	96 (61–154)	Overall *P*-value
Solute and fluid transport parameters after 4 h				
$MTAC_{creat}$ (ml/min)	12.2 (5.7–18.6)	13.3 (9.5–26.6)[a]	15.0 (7.5–25.3)	0.06
GA (%)	71 (45–81)	73 (64–90)	73 (50–84)	0.28
ELAR (ml/min)	2.2 (0.4–5.0)	2.4 (1.0–6.6)	1.7 (0.3–5.0)[b]	0.05
TCUF (ml)	734 (21–1303)	742 (523–1310)	625 (265–1386)[c,d]	0.01
Water transport during the first hour				
$TCUF_{0-60}$ (ml)	393 (114–883)	365 (256–850)	273 (129–431)[c,d]	0.01
SPT_{0-60} (ml)	267 (77–666)	247 (75–683)	199 (61–345)[c,d]	0.01
FWT_{0-60} (ml)	127 (36–217)	119 (40–285)	73 (55–149)[c,d]	0.02
$FWTC_{0-60}$ (%)	32 (14–62)	32 (2–65)	27 (13–45)[c,d]	0.01
$SPTC_{0-60}$ (%)	68 (38–83)	68 (33–98)	73 (55–87)	0.11
Determinants of TCUF				
LpA (ml/min/mmHg)	0.10 (0.01–0.16)	0.11 (0.05–0.21)	0.08 (0.03–0.19)[b]	0.05
σ	0.045 (0.033–0.054)	0.042 (0.032–0.051)	0.042 (0.036–0.053)	0.31
OC (μl/min/mmHg)	4.7 (2.1–7.1)	4.6 (2.0–10.6)	3.2 (1.3–7.9)[b]	0.05

Parikova A et al Kidney Int 2006

D PET
Condutta a al glucosio
(CG)

raperitoneale (mL)

3000
2750
2500
2250

http://www.kidney-international.org

Simultaneous measurement of peritoneal glucose and free water osmotic conductances

V La Milia[1], M Limardo[1], G Virga[2], M Crepaldi[1] and F Locatelli[1]

[1]Department of Nephrology and Dialysis, A Manzoni Hospital, Lecco, Italy and [2]Nephrology and Dialysis Unit, Camposampiero, Padova, Italy

Tempo (min)

Stelin G, Rippe B Kidney Int 1990

Rippe B et al Perit Dial Int 2004

Uni-PET: 3.86%-PET integrato con il Doppio Mini-PET (PET-Unico)

- **Sosta con 1.36%, di 1 ora, seguita da:**
- **3.86%-PET, di 4 ore**
- **Drenaggio temporaneo dopo 1 ora:**

-valutazione del volume intra-peritoneale (pesatura)

-campionatura dell'effluente per misurare il Na

-reinfusione dell'effluente

- **Drenaggio finale dopo 4 ore**

La Milia V J Nephrol 2010; 23:633-647

- **Are the peritoneal tests useful in the clinical contest?**

1. PET data provide information for the PD prescription

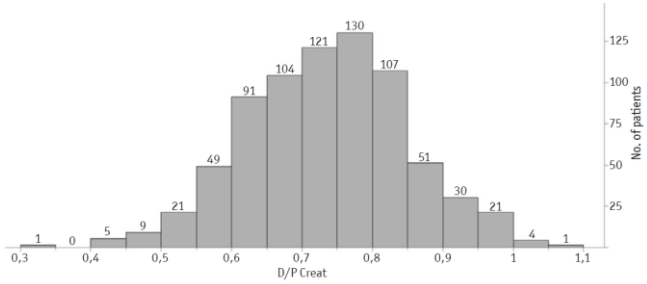
2. Peritoneal transport changes over time

3. PET data are important for the diagnosis and prognosis of PD patients

Why evaluation of membrane function matters

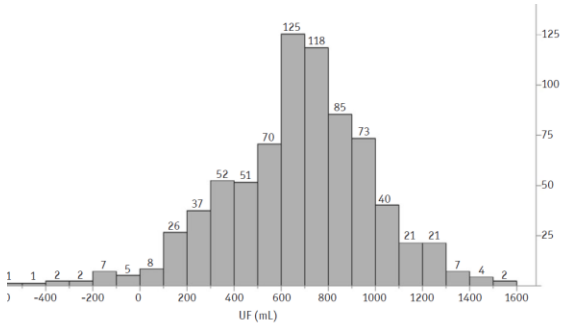
758 incident PD patients with 4.25% dextrose-based 4-h PET at PD start, Italy

PSTR



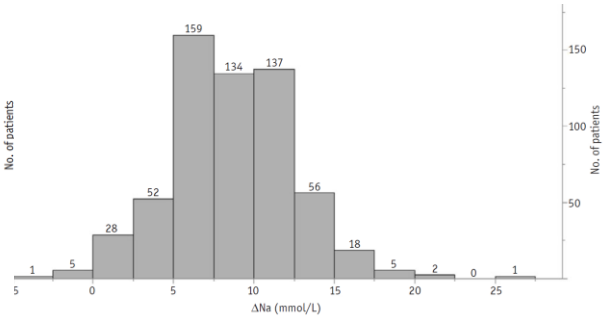
0.3 to >0.9

Net UF



-600 to +1500 ml

Dip Na

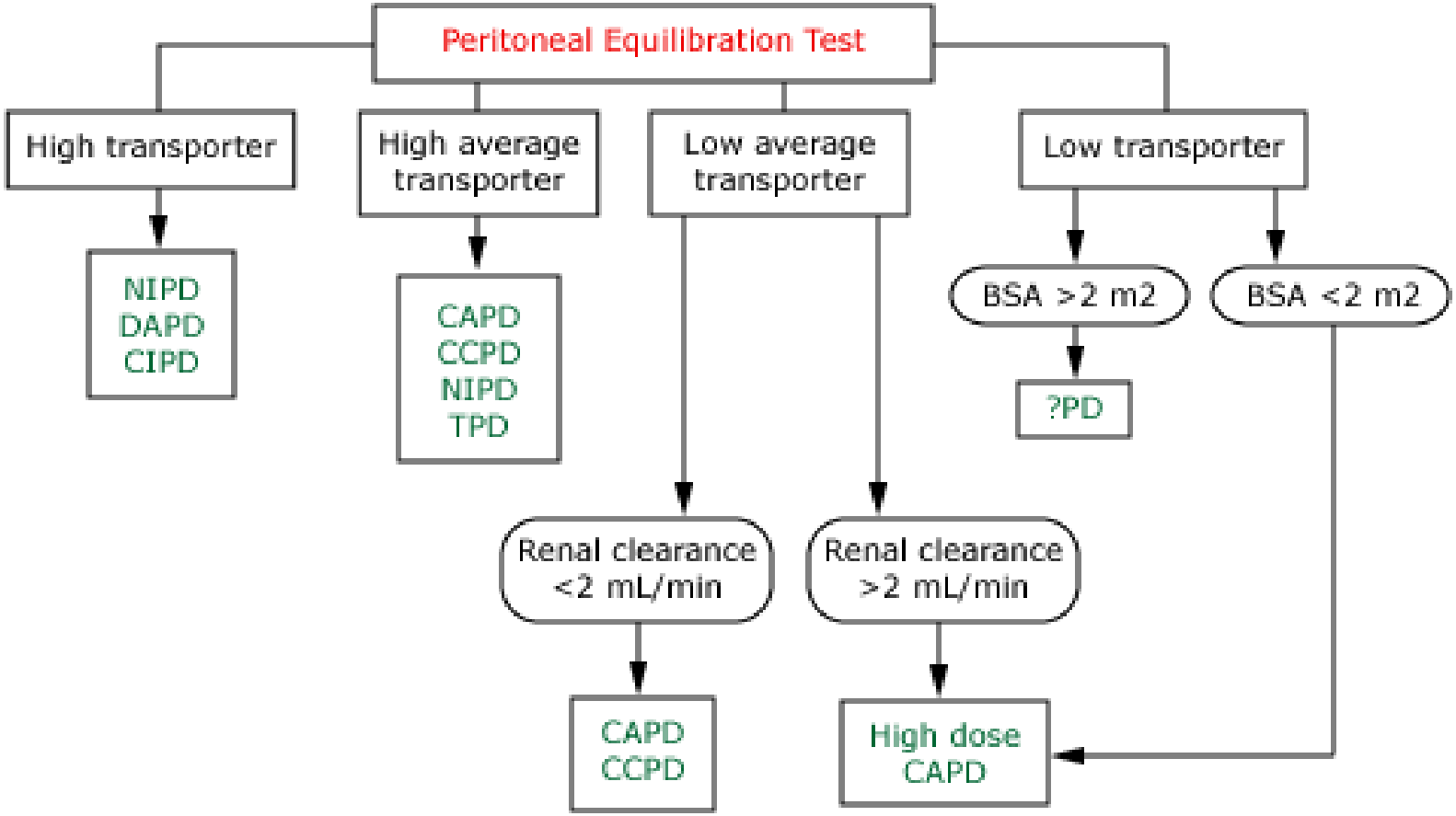


-3 to +20 mEq/l

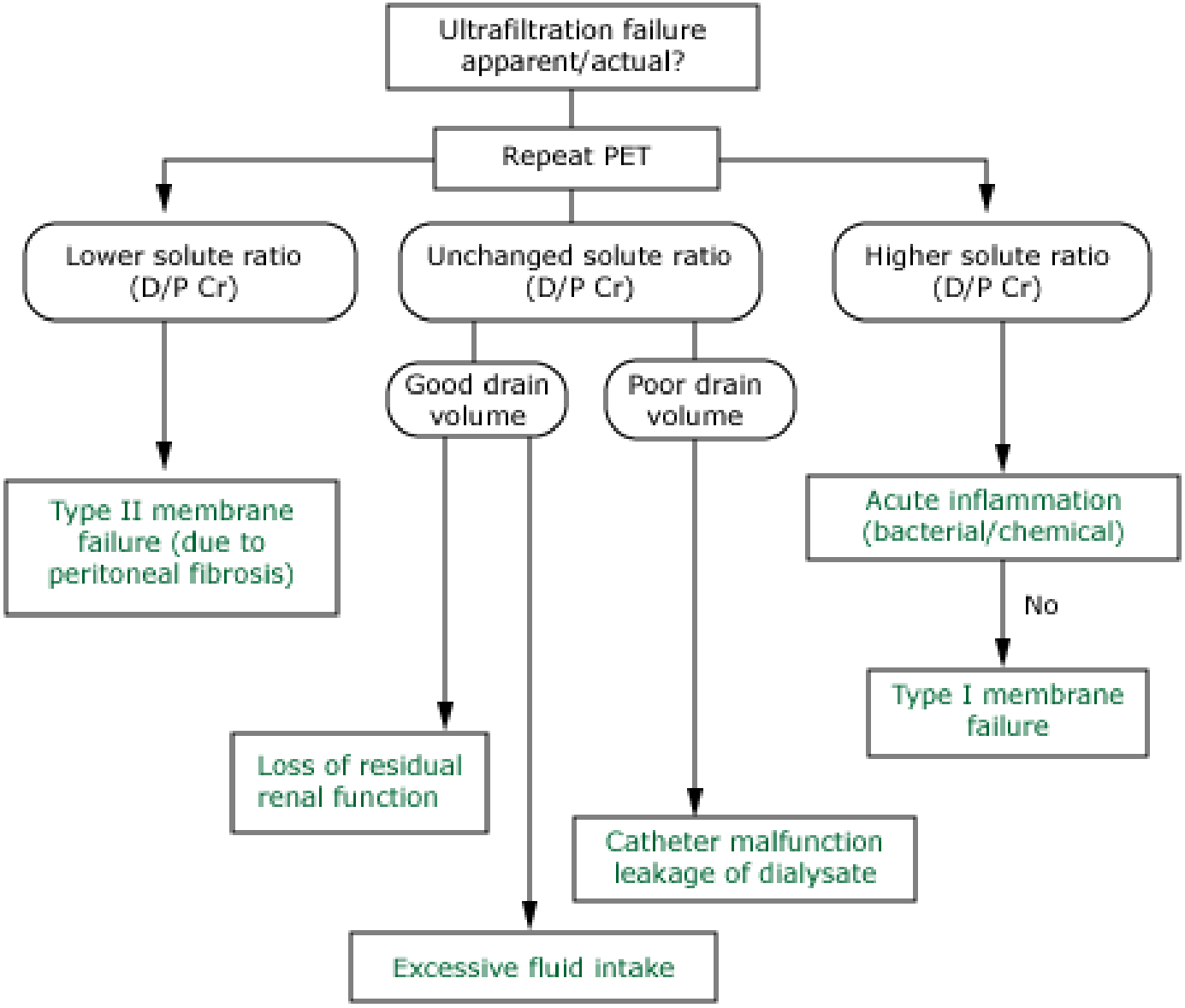
Significant variability in membrane characteristics between individuals, already at PD initiation

- Associated with outcome
- Clinical impact on fluid removal and dialysis prescription

La Milia et al, *Perit Dial Int* 2017



(Twardowski ZJ, et al ASAIO Trans 1990)



(Twardowski ZJ, et al ASAIO Trans 1990)

Prescrizione della tecnica in base al PET

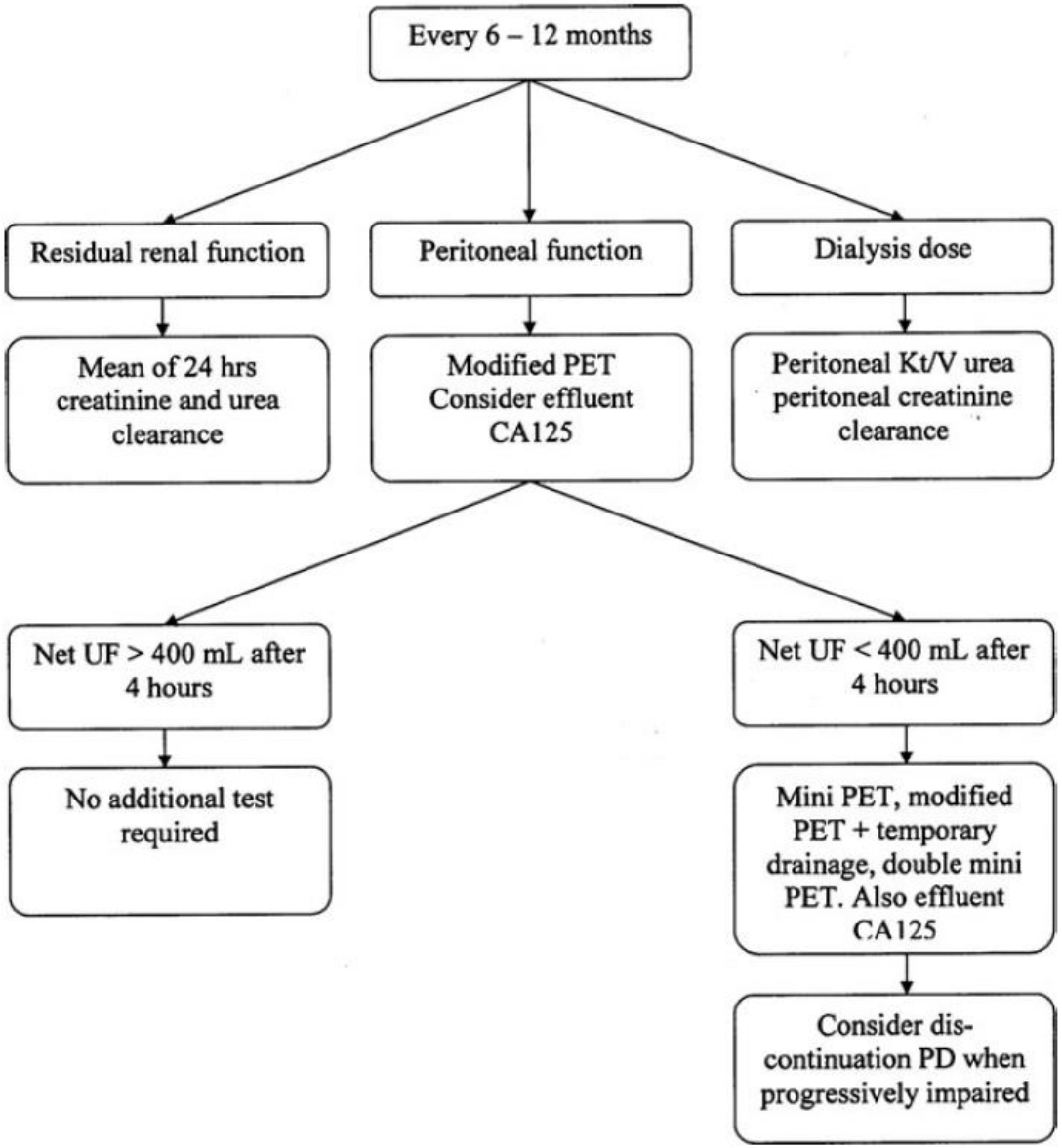
Rapidi (H) Trasportatori → APD

Medio Rapidi Trasportatori (H-A) → CAPD o CCPD1

Medio Lenti (L-A) Trasportatori → CAPD o CCPD2

Lenti (L) Trasporatori → high-dose CAPD (HD)

Un algoritmo per il follow-up dei pazienti in dialisi peritoneale



Coester AM et al NDT Plus 2009

Guidelines

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
1–21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SAGE

ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

Table 1. Classification of membrane dysfunction, including definition, underlying pathophysiology and clinical implications.

Classification	Definition	Pathophysiology	Clinical implications and actions
Fast PSTR	D/P creatinine ratio above the population mean value at the end of a 4-h PET using either 2.27/2.5% or 3.86/4.25% glucose/dextrose-based solution. While most studies report that PSTR is normally distributed, with a typical average value of 0.65, multicentre studies show a significant centre effect. It can be present at the start of PD and/or develop or resolve over time	• Membrane inflammation causing a large effective vascular surface area • Neovascularization • Both the above may potentially be, in part, genetically determined	• Reduces net ultrafiltration with glucose-based dialysate due to early loss of the osmotic gradient and more rapid fluid reabsorption • In patients with significant residual kidney function, 'dry' nights when treated with CAPD or partial or complete 'dry' days when treated with APD. If long dwells required use icodextrin (daytime for APD, overnight for CAPD) • Shorten glucose-based overnight dwells (e.g. 90–180 min) when using APD coupled with icodextrin during the day long dwell. • If neither APD nor icodextrin available increase glucose strength to prevent reabsorption.
Poor intrinsic ultrafiltration (low OCG at start of PD	Sodium dip at 60 min $\leq$5 mmol/l or sodium sieving ratio <0.07 with a 3.86% glucose/4.25% dextrose PET	• Explanations largely not understood • Potential influence of genetic determinants (e.g. aquaporin expression) • Note: a low ΔD_{Na} 0–60 min can also be observed in patients with very fast PSTR due to early dissipation of the osmotic gradient	• Low OCG at baseline: careful evaluation and monitoring of fluid volume. • May be associated with fast PSTR • Earlier indicator of ultrafiltration insufficiency than fast PSTR
Acquired intrinsic ultrafiltration insufficiency (low OCG) developing over time (years) on PD	Sodium dip at 60 min $\leq$5 mmol/L or sodium sieving ratio <0.07 with a 3.86% glucose /4.25% dextrose PET	• Structural alterations in the peritoneal interstitium in keeping with progressive fibrosis • Usually associated with fast PSTR	• Discussion about the potential risks of continuing PD, including EPS, vs. transition to another modality, and shared decision-making with the patient and the PD team

PSTR: peritoneal solute transfer rate; D/P: dialysate to plasma; PET: peritoneal equilibration test; PD: peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; APD: automated peritoneal dialysis; OCG: osmotic conductance to glucose; EPS: encapsulating peritoneal sclerosis.

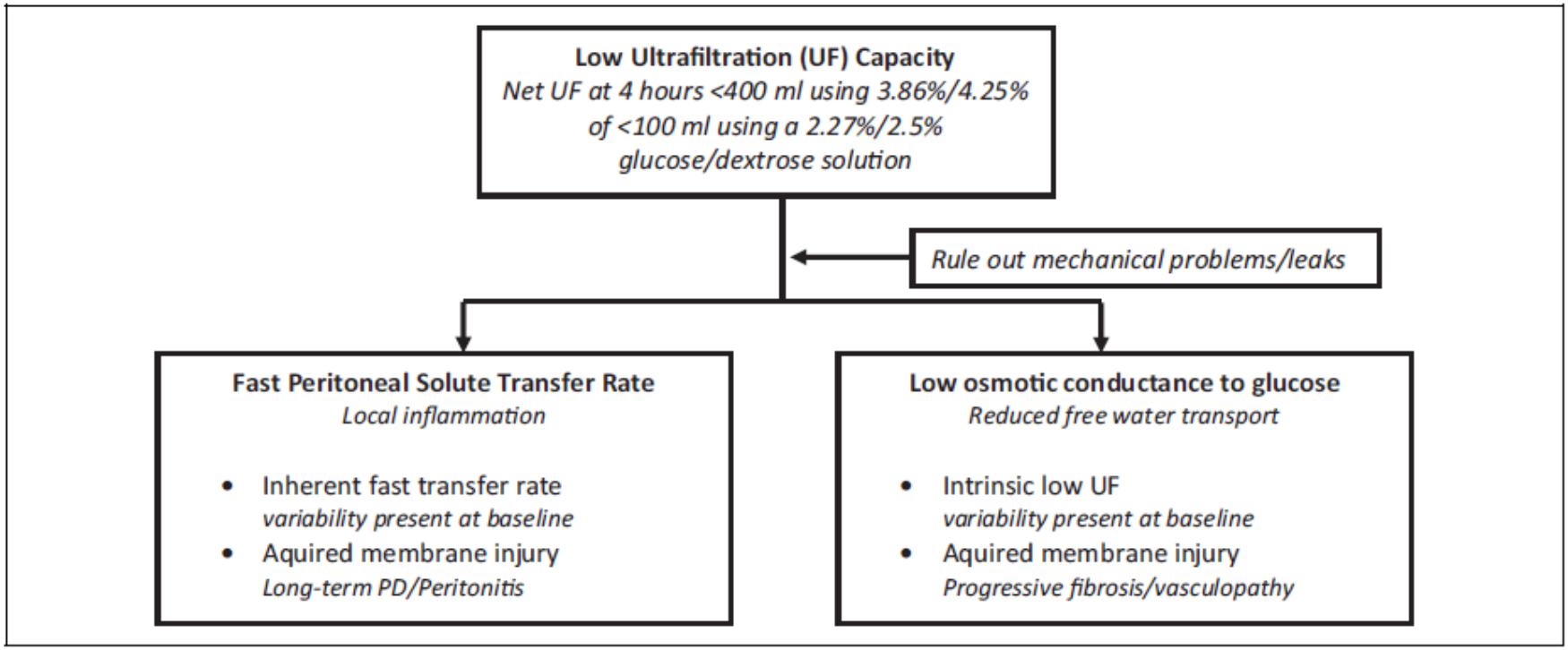


Figure 3. Classification of the causes of membrane dysfunction.

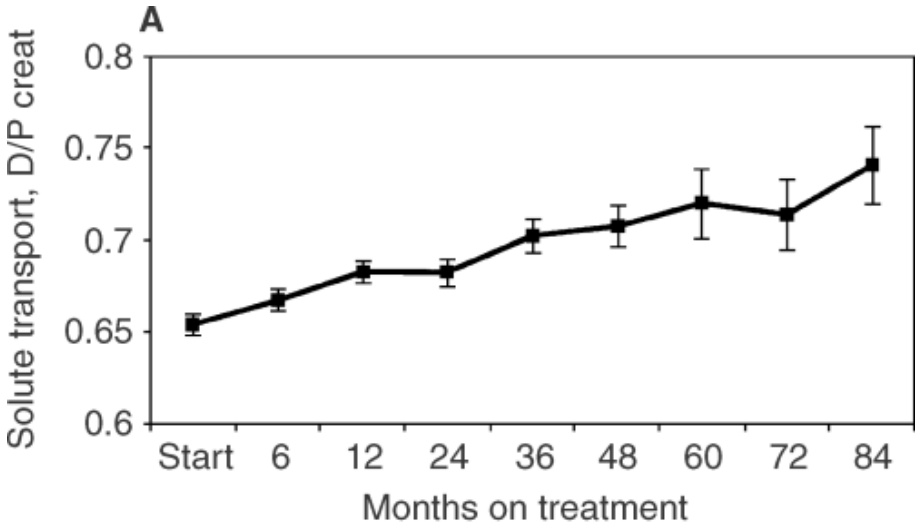
- **Are the peritoneal tests useful in the clinical contest?**

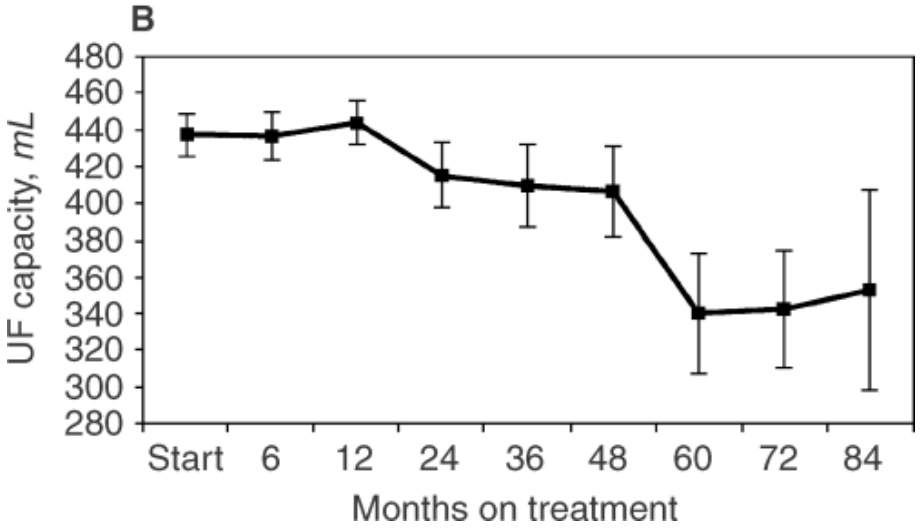
1. PET data provide information for the PD prescription

2. Peritoneal transport changes over time

3. PET data are important for the diagnosis and prognosis of PD patients

Longitudinal relationship between solute transport and UF capacity in PD patients





Davies SJ Kidney Int 2004

- **The follow-up of the peritoneal membrane functionality can be performed with the peritoneal functional test**
- **Much more difficult is to perform the serial biopsies of the peritoneal membrane to evaluate the anatomical damage**

- **Are the peritoneal tests useful in the clinical contest?**

1. PET data provide information for the PD prescription

2. Peritoneal transport changes over time

3. PET data are important for the diagnosis and prognosis of PD patients

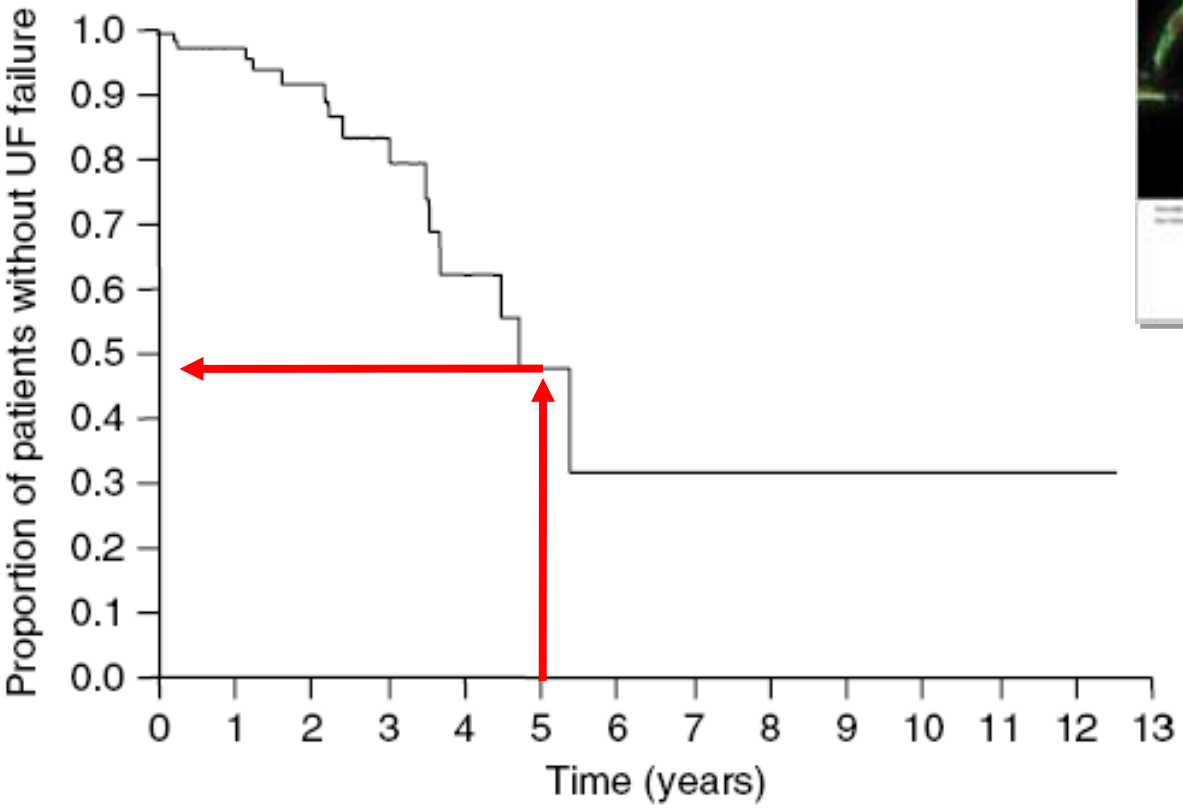
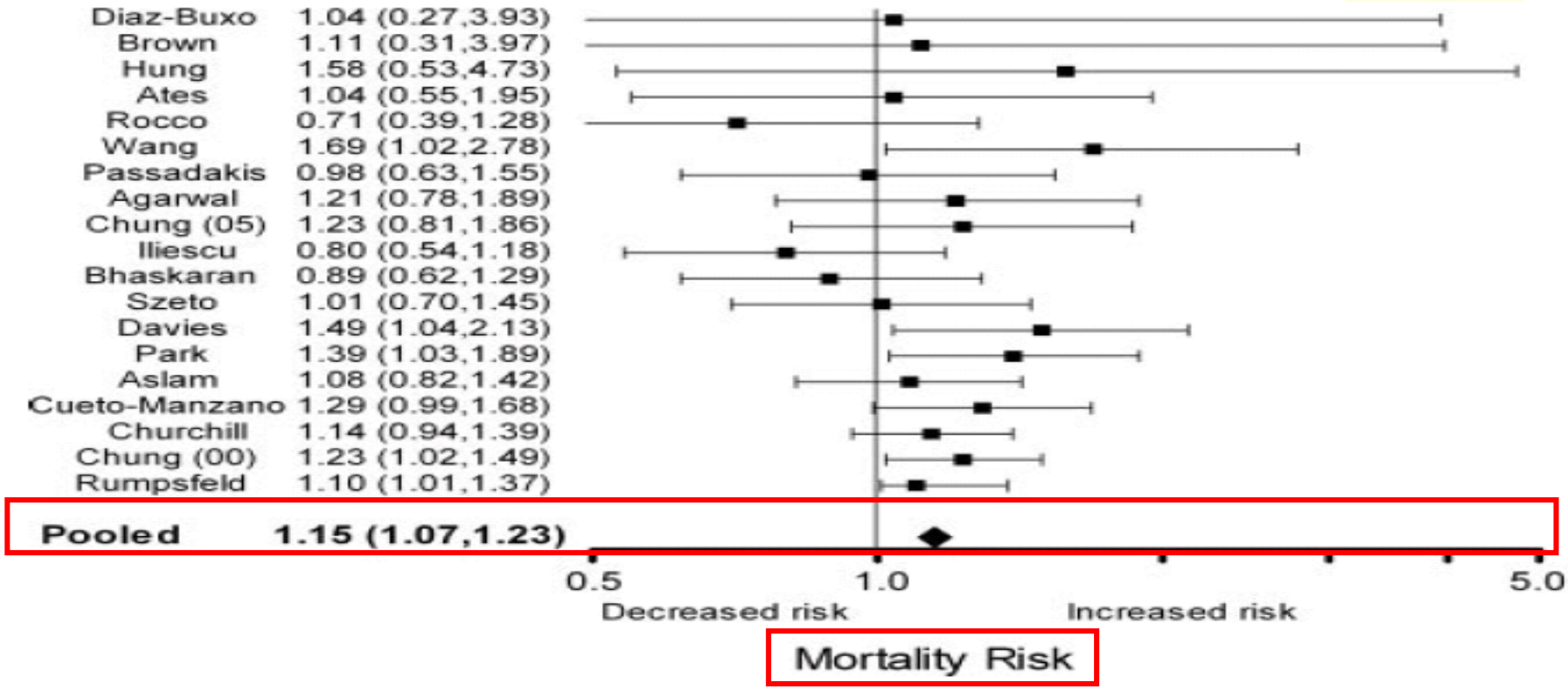


Figure 3 | Kaplan–Meier curve of proportion of patients with and without UF failure during the follow-up ($n = 95$).

La Milia V, et al. Kidney Int 2006; 69: 927-33.

The ratio of creatinine in the dialysate and in the plasma after a 4-h dwell (D/P_C; per 0.1 increment) and mortality in PD patients



Brimble KS et al JASN 2006; 17:2591-8

Table 5. Adverse outcomes associated with faster PSTR.

Outcomes	Source	Number of patients	Adjusted relative risk (95% CI) per 0.1 increase in D/P creatinine
All-cause mortality	Brimble meta-analysis 2006[103] 19 studies, includes CANUSA study, Stoke Study,[104] EAPOS and ANZDATA Registry.	6648	1.15 (1.07–1.23)
	Global Fluid Study 2013 (10 centres from UK, Korea and Canada)42		
	Incident cohort	499	1.12 (0.98–1.23)
	Prevalent cohort	307	1.18 (1.003–1.41)
	Davita database 2015 (764 US centres)45	10,142	1.07 (1.02–1.13)
Technique Failure (death censored)	Brimble KS meta-analysis 2006 6 studies	5104	1.18 (0.96–1.46)
	Davita database	10,142	1.01 (0.98–1.05)
Hospitalization	Davita database 2015	10,142	1.05 (1.03–1.06)

CANUSA: Canada–USA Study[105]; ANZDATA: Australia New Zealand Registry[50]; EAPOS: European Automated Peritoneal Dialysis Outcomes Study (Anuric Patients)[12]; PSTR: peritoneal solute transfer rate; CI: confidence interval; D/P: dialysate to plasma.

Peritoneal Equilibration Test and Patient Outcomes

Mehrotra, Rajnish; Ravel, Vanessa; Streja, Elani; Kuttykrishnan, Sooraj; Adams, Scott V.; Katz, Ronit; Molnar, Miklos Z.; Kalantar-Zadeh, Kamyar

Clinical Journal of the American Society of Nephrology10(11):1990-2001, November 2015.

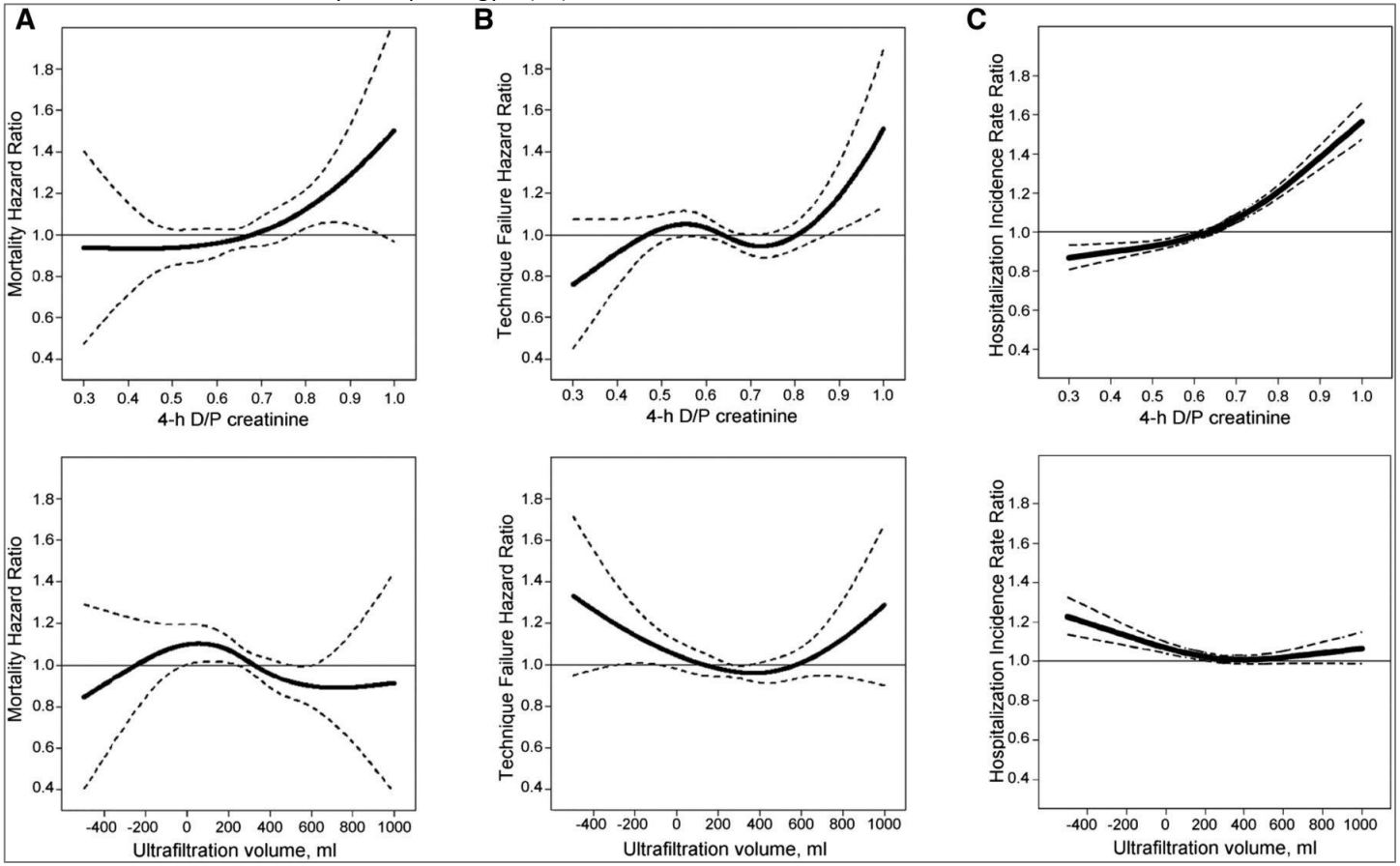


Table 3. Association of different peritoneal equilibration test parameters with clinical outcomes

Outcome	4-h D/P Creatinine per 0.1 Unit Higher		4-h Ultrafiltration Volume per 250 ml Lower	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
All-cause mortality HR (95% CI)	1.13 (1.07 to 1.18)	1.07 (1.02 to 1.13)	1.14 (1.08 to 1.21)	1.05 (0.99 to 1.11)
Technique failure HR (95% CI)	1.02 (0.98 to 1.06)	1.01 (0.98 to 1.05)	1.03 (0.99 to 1.07)	1.02 (0.98 to 1.07)
Hospitalization IRR (95% CI)	1.09 (1.08 to 1.11)	1.05 (1.03 to 1.06)	1.02 (1.01 to 1.04)	1.02 (1.00 to 1.04)

D/P creatinine, dialysate to plasma ratio of creatinine; HR, hazard ratio; 95% CI, 95% confidence interval; IRR, incidence rate ratio; h/o, history of; APD, automated peritoneal dialysis.

a Adjusted for demographics (age, sex, race, health insurance, geographic region, and year of incidence), case mix (cause of ESRD, h/o previous transplant, h/o previous treatment with hemodialysis, comorbidities, and residual kidney function), peritoneal dialysis–related variables (peritoneal Kt/V_{urea} and treatment with APD), and selected laboratory variables (hemoglobin, serum calcium, phosphorus, parathyroid hormone, creatinine, and potassium).

http://www.kidney-international.org

Mitigating peritoneal membrane characteristics in modern peritoneal dialysis therapy

SJ Davies[1,2]

[1]Institute for Science and Technology in Medicine, Keele University, Keele, UK and [2]Department of Nephrology, University Hospital of North Staffordshire, Stoke-on-Trent, UK

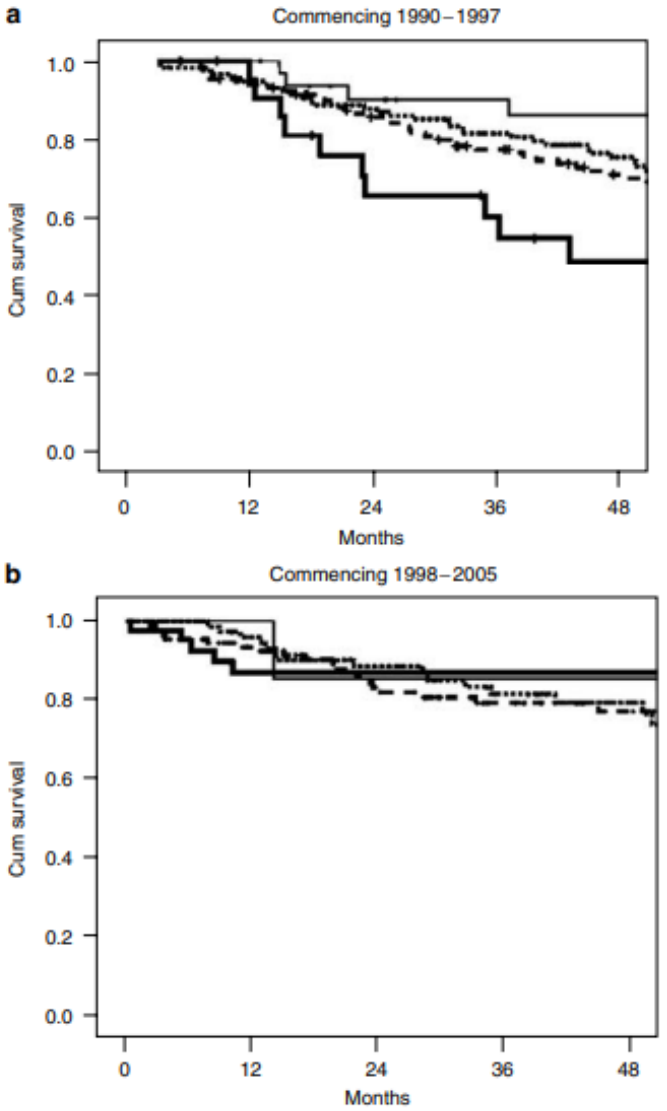


Figure 4 | Survival on PD (patients censored at transplant or transfer to hemodialysis), according to transport category at the start of treatment in two cohorts commencing between (a) 1990–1997, $n = 320$ and (b) 1998-2005, $n = 300$. Low (—), Low average (· · · ·), High average (– –) and High (▬). In the first cohort, transport category was significantly ($P = 0.009$) associated with survival, whereas in the second this was not the case due to an improvement in the survival of high transport patients.

High and Low transporters
APD vs CAPD

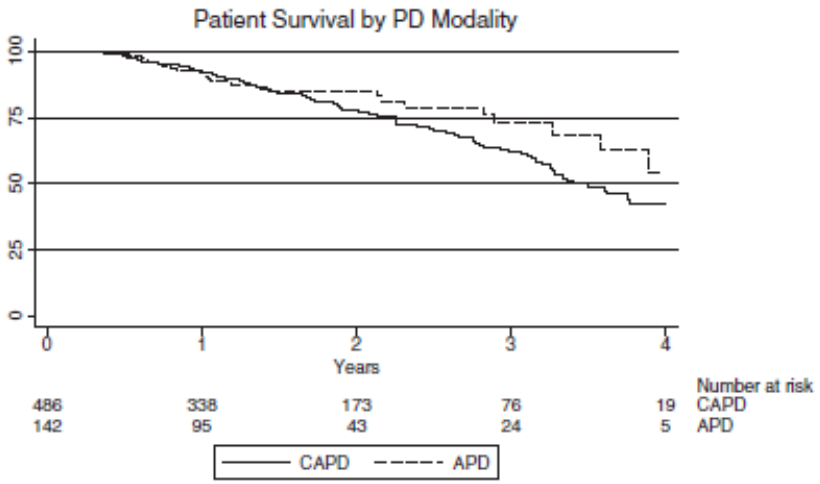


Fig. 1. Kaplan–Meier graph showing patient survival in 628 high transporters treated with APD or CAPD. The difference between the two groups was statistically significant (log rank 6.16, $P = 0.01$).

Table 2. Results of intention-to-treat Cox proportional hazards model analyses of the relative hazard of APD *versus* CAPD for patient survival, according to peritoneal transport group

	Univariate analysis			Multivariate analysis		
Transport group	HR	95% CI	*P*	HR	95% CI	*P*
High ($n = 628$)	0.57	0.35–0.94	0.03	0.56	0.35–0.87	0.01
High-average ($n = 1936$)	0.98	0.72–1.34	0.9	1.08	0.81–1.45	0.6
Low-average ($n = 1146$)	0.70	0.46–1.07	0.1	0.98	0.66–1.45	0.9
Low ($n = 196$)	2.21	1.24–3.93	0.007	2.19	1.02–4.70	0.04

Johnson DW, et al. Superior survival of high transporters treated with automated versus continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2010.

- **I test di funzionalità peritoneale sono utili nella pratica clinica?**

1. I dati del PET forniscono informazioni per la prescrizione della DP

2. Il trasporto Peritoneale varia con il tempo

3. I dati del PET sono importanti per la diagnosi e la prognosi dei pazienti in DP

- **Are the peritoneal tests useful for the diagnosis of EPS?**

1. The classical PET is not discriminative for the diagnosis of EPS and do not confirm the presence or the absence of EPS

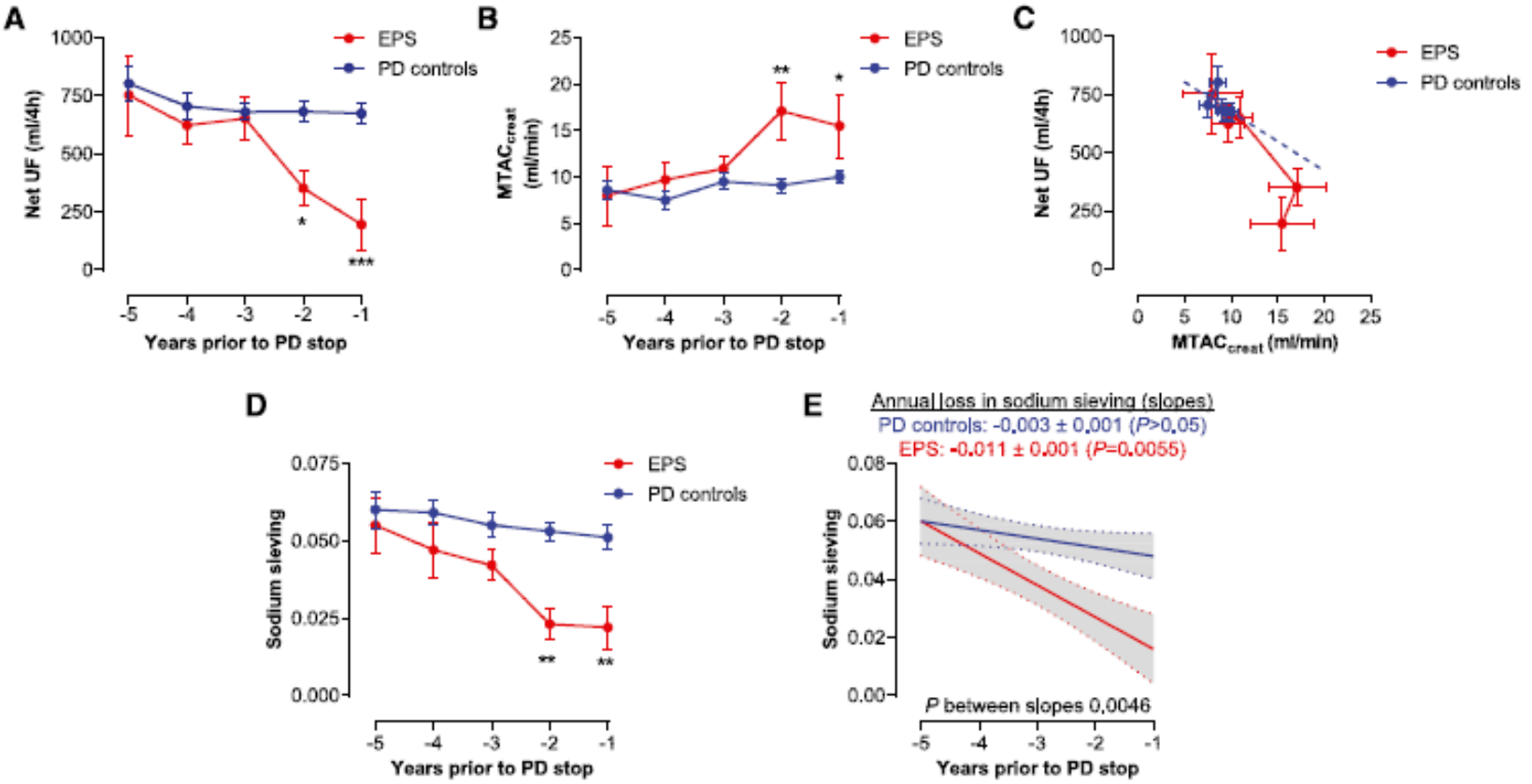
2. The new tests could be more useful for the diagnosis of EPS?

Interstitial Fibrosis Restricts Osmotic Water Transport in Encapsulating Peritoneal Sclerosis

Johann Morelle,* Amadou Sow,* Nicolas Hautem,* Caroline Bouzin,† Ralph Crott,‡ Olivier Devuyst,*§ and Eric Goffin*

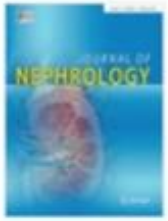
*Division and Laboratory of Nephrology, Cliniques Universitaires Saint-Luc, Institute of Experimental and Clinical Research, Université Catholique de Louvain Medical School †Imaging Platform, Institute of Experimental and Clinical Research, and ‡School of Public Health, Université Catholique de Louvain Medical School, Brussels, Belgium; and §Institute of Physiology, Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

J Am Soc Nephrol October 2015 26: 2521–2533 www.jasn.org CLINICAL RESEARCH



The Value of Osmotic Conductance and Free Water Transport in the Prediction of Encapsulating Peritoneal Sclerosis

Denise E. Sampimon,* Deirisa Lopes Barreto,* Annemieke M. Coester, Dirk G. Struijk, Raymond T. Krediet



Journal of Nephrology
February 2018, Volume 31, Issue 1, pp 137–145 | Cite as

The peritoneal sieving of sodium: a simple and powerful test to rule out the onset of encapsulating peritoneal sclerosis in patients undergoing peritoneal dialysis

Authors Authors and affiliations

Vincenzo La Milia, Selena Longhi, Elisabetta Sironi, Giuseppe Pontoriero

Peritoneal Dialysis International
Volume 37, Issue 4, July/August, Pages 362-374

https://doi.org/10.3747/pdi.2017.00018

SAGE journals

ISPD Guidelines/Recommendations

Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis — Position Paper for ISPD: 2017 Update

Edwina A. Brown, Joanne Bargman, Wim van Biesen, Ming-Yang Chang, Frederic O. Finkelstein, Helen Hurst, David W. Johnson, Hideki Kawanishi, Mark Lambie, Thyago Proença de Moraes, Johann Morelle, and Graham Woodrow

ISPD statement

Peritoneal Dialysis International

6. There are no specific predictors for the development of EPS:
   a. Although many patients with EPS have high PSTR, this is not true for all patients and this is a common finding in patients on long-term PD.
   b. There is no evidence that CT scanning has any value in predicting EPS.
   c. Progressive loss of osmotic conductance to glucose (uncoupling between water and solute transport, altered sodium sieving, decreased free-water transport) may reflect the development of peritoneal interstitial fibrosis and may help identifying patients at risk of EPS. However, this needs to be confirmed in prospective studies.

Current recommandations about peritoneal transport testing

National Kidney Foundation®

NF/KDOQI
Baseline peritoneal membrane transport characteristics should be established after initiating a daily PD therapy

ERBP

European Renal Best Practice – ERA-EDTA
An evaluation of peritoneal membrane characteristics should be used to guide prescription of PD therapy

Kidney Health Australia

CARI (Caring for Australians with Renal Impairment)
Patient's membrane transport status should be evaluated by the standard peritoneal equilibration test (PET)

INTERNATIONAL SOCIETY FOR PERITONEAL DIALYSIS

International Society for Peritoneal Dialysis
Evaluation of peritoneal membrane-related causes of fluid overload
→ modified PET utilizing 4.25%/3.86% glucose
→ 1. UF response? 2. Small solute transport profile?

Guidelines

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
1–21

DOI: 10.1177/0896860820982218
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ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

JNEPHROL 2013; 26(Suppl 21): S120-S139

DOI: 10.5301/JN.2013.11637

Functional assessment of the peritoneal membrane

Vincenzo La Milia[1]

Reviewers: Giovambattista Virga[2], **Giampaolo Amici**[3], **Silvio Bertoli**[4], **Giovanni Cancarini**[5]

[1]Nephrology and Dialysis Unit, A. Manzoni Hospital, Lecco - Italy
[2]Nephrology and Dialysis Unit, Camposampiero Hospital, Camposampiero, Padua - Italy
[3]Department of Nephrology and Dialysis, S. Maria dei Battuti Regional Hospital, Treviso - Italy
[4]Nephrology and Dialysis Unit, IRCCS Multimedica, Sesto S. Giovanni, Milano - Italy
[5]Nephrology and Dialysis Unit, A.O. Spedali Civili di Brescia, Brescia - Italy

Key words: *Pet, Ultrafiltration failure, Peritoneal transport, Classes of peritoneal transport, Sodium sieving, mini-pet*

2. When should the PET be performed?

A peritoneal membrane functional assessment test should be performed at the start of dialysis treatment (after 4-8 weeks and within 3 months from the start of PD and repeated at least once a year and whenever a clinical issue (inadequate depuration or ultrafiltration [UF]) arises whose interpretation may benefit from the performance of the test. The test should not be performed during episodes of peritonitis (it increases the small solute transport rate and reduces UF), and it is recommended to wait at least 1 month after the complete resolution of the peritonitis before performing it (4-7).

JNEPHROL 2013; 26(Suppl 21): S120-S139

3.86%-PET provides more information than the classic PET performed using a 2.27% glucose solution.

Significant emphasis is placed on the hydration status of patients in PD and on peritoneal UF capacity. This is due both to the demonstration that an increase in the already adequate total purification (Kt/V = 1.9, creatinine clearance [CrCl] = 60 L) of 20%-30% is not associated with a corresponding result in terms of better survival (12), and to the increasingly consistent evidence that the removal of fluids

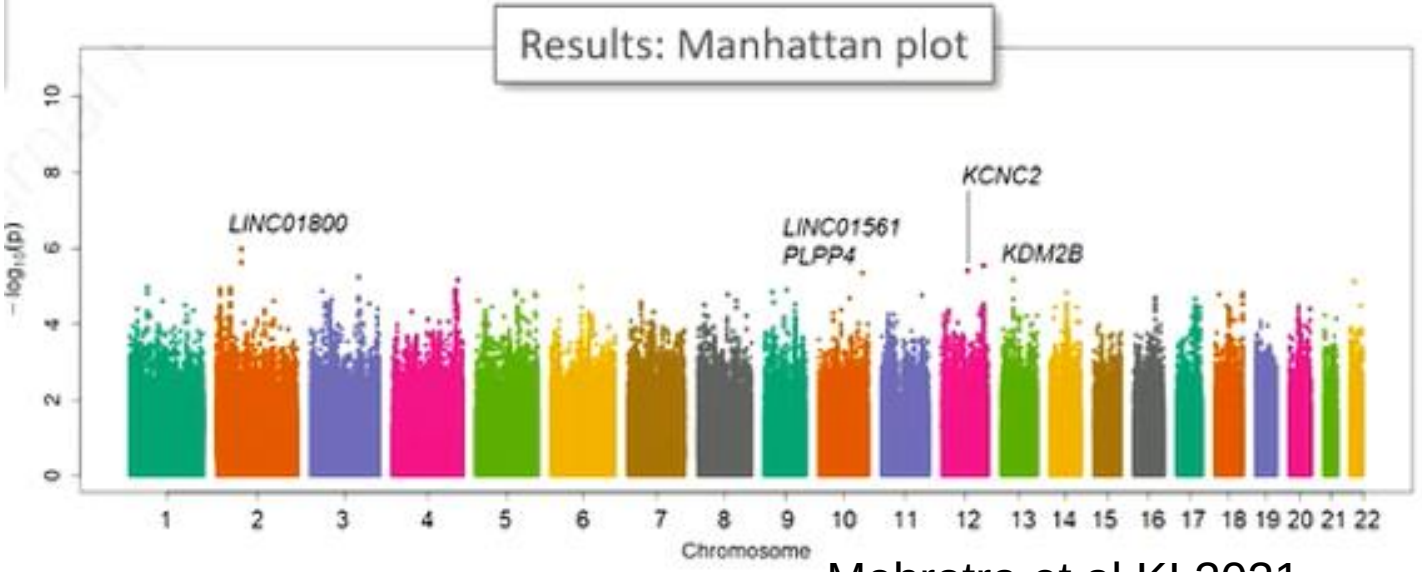
- **What is the next future?**

A genome-wide association study suggests correlations of common genetic variants with peritoneal solute transfer rates in patients with kidney failure receiving peritoneal dialysis

Rajnish Mehrotra[1], Ian B. Stanaway[1], Gail P. Jarvik[2,3], Mark Lambie[4], Johann Morelle[5,6], Jeffrey Perl[7], Jonathan Himmelfarb[1], Olof Heimburger[8], David W. Johnson[9], Talha H. Imam[10], Bruce Robinson[11], Peter Stenvinkel[8], Olivier Devuyst[5,6] and Simon J. Davies[4]; on behalf of the Bio-PD Consortium[12]

[1]Kidney Research Institute, Division of Nephrology, Department of Medicine, University of Washington, Seattle, Washington, USA; [2]Department of Medicine (Medical Genetics), University of Washington, Seattle, Washington, USA; [3]Department of Genome Sciences, University of Washington, Seattle, Washington, USA; [4]School of Medicine, Faculty of Medicine and Health Sciences, Keele University, Keele, UK; [5]Division of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [6]Institut de Recherche Experimentale et Clinique, UClouvain, Brussels, Belgium; [7]Division of Nephrology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [8]Division of Renal Medicine, Department of Clinical Science, Intervention, and Technology, Karolinska Institute, Stockholm, Sweden; [9]Australasian Trials Network, University of Queensland, Brisbane, Australia; [10]Department of Nephrology, Kaiser Permanente, Fontana, California, USA;

- Heritability of PSTR ~20%
- Polygenic risk score associates with PSTR
- 4 loci with suggestive associations with PSTR



Mehrotra et al KI 2021

The NEW ENGLAND JOURNAL of MEDICINE

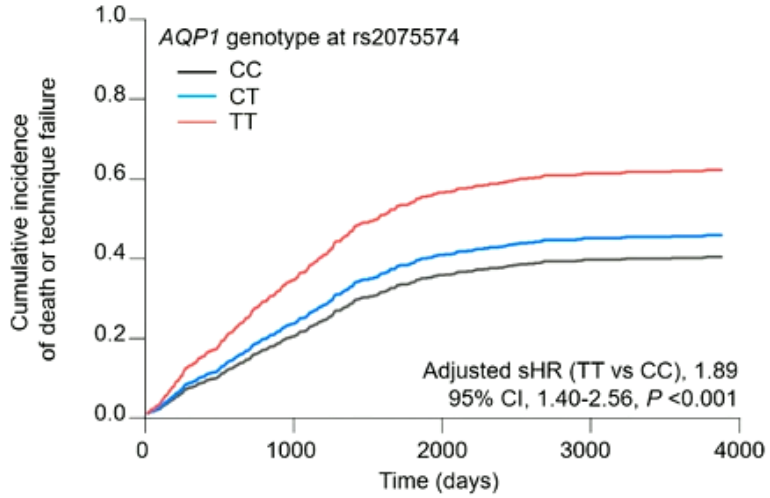
ORIGINAL ARTICLE

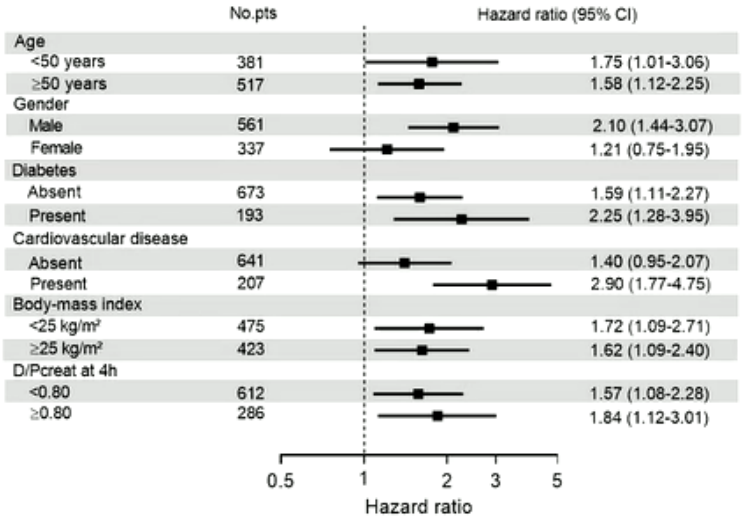
AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis

Johann Morelle, M.D., Ph.D., Céline Marechal, Ph.D., Zanzhe Yu, M.D., Ph.D., Huguette Debaix, M.Sc., Tanguy Corre, Ph.D., Mark Lambie, M.D., Ph.D., Marion Verduijn, Ph.D., Friedo Dekker, Ph.D., Philippe Bovy, M.D., Pieter Evenepoel, M.D., Ph.D., Bert Bammens, M.D., Ph.D., Rafael Selgas, M.D., Ph.D., Maria A. Bajo, M.D., Ph.D., Annemieke M. Coester, M.D., Ph.D., Amadou Sow, M.D., Ph.D., Nicolas Hautem, Ph.D., Dirk G. Struijk, M.D., Ph.D., Raymond T. Krediet, M.D., Ph.D., Jean-Luc Balligand, M.D., Ph.D., Eric Goffin, M.D., Ralph Crott, Ph.D., Pierre Ripoche, Ph.D., Simon Davies, M.D., and Olivier Devuyst, M.D., Ph.D.

N ENGL J MED 385;17 NEJM.ORG OCTOBER 21, 2021

AQP1 promoter risk variant and outcome in PD patients





Outcome	Overall n=898	CC n=384	CT n=400	TT n=114	*P*
Composite – no. (%)	419 (47)	162 (42)	191 (48)	66 (58)	0.01
Technique failure – no. (%)	280 (31)	105 (27)	136 (34)	39 (34)	0.10
All-cause death – no. (%)	139 (15)	57 (15)	55 (14)	27 (24)	0.03

Morelle...Davies, Devuyst, *N Engl J Med* 2021

Conclusioni

- **Oggi abbiamo numerosi test sulla funzione della membrana peritoneale, più sofisticati rispetto al classico 2.27%-PET di Twardowski**

- **Con questi test è possibile un'esplorazione "completa" delle funzioni della membrana peritoneale**

- **Un uso estensivo di questi nuovi test potrebbe essere utile nel prossimo futuro sia per migliorare la diagnosi che la prognosi dei pazienti in dialisi peritoneale**