PET applications

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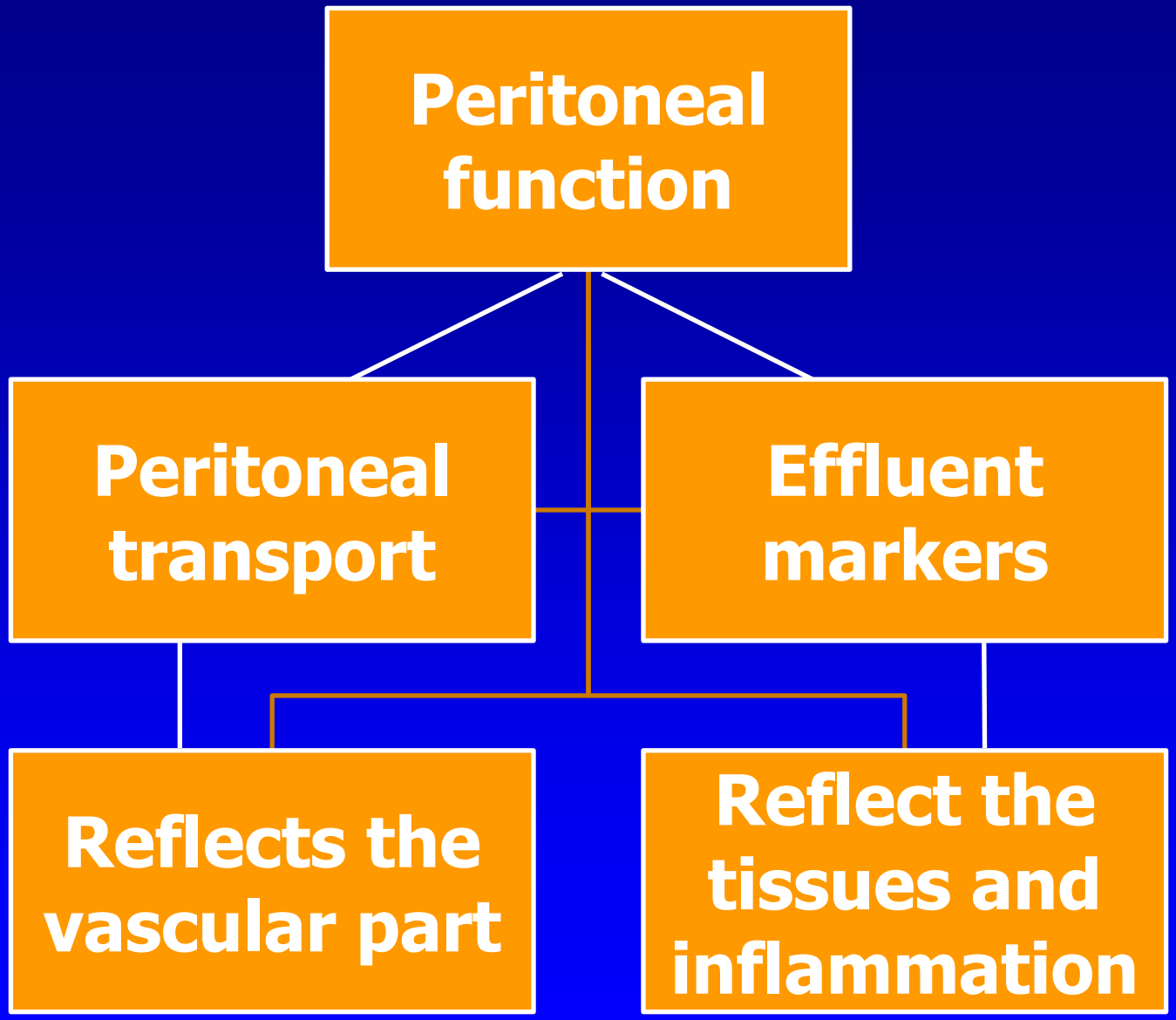
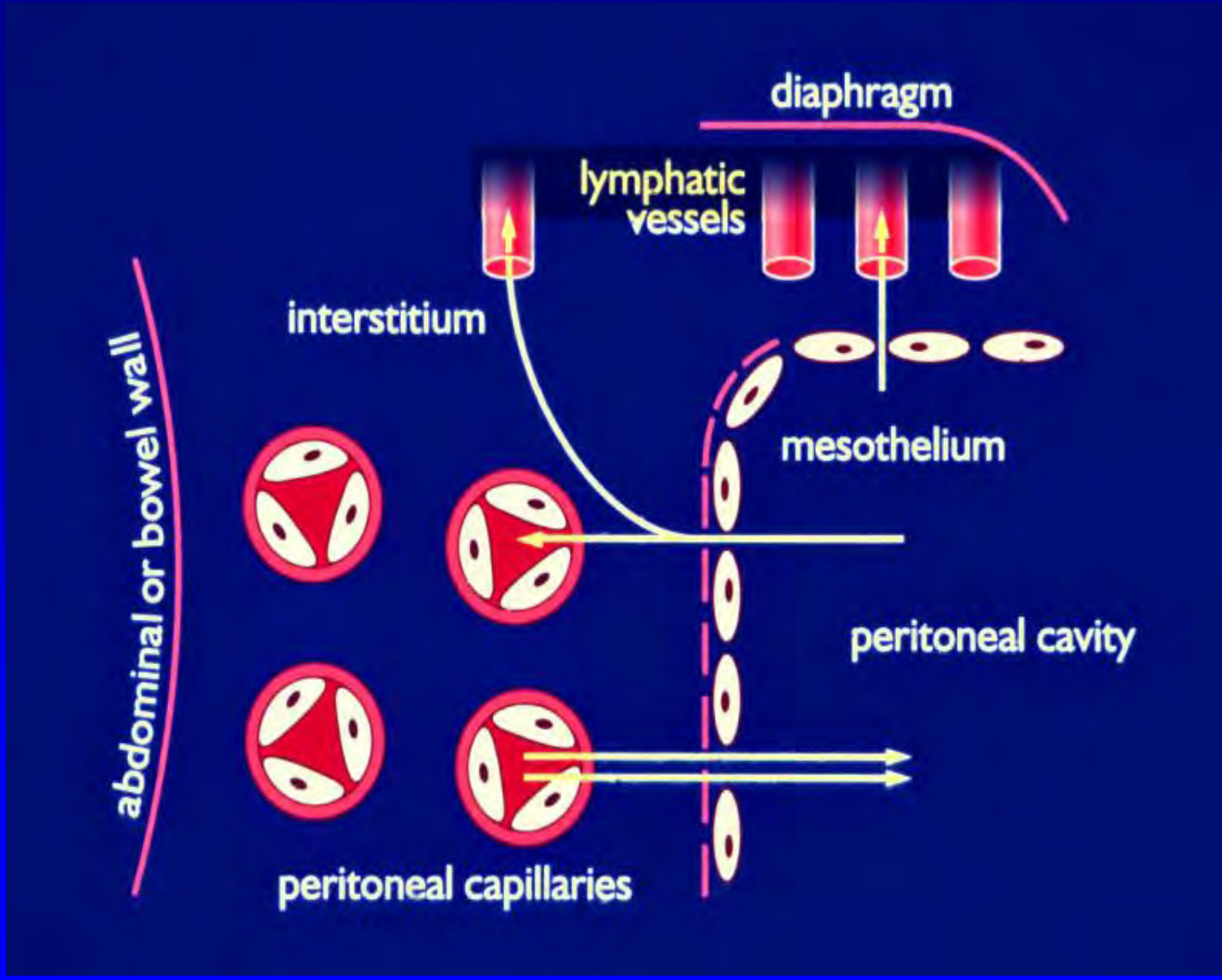
Follow-up of PD patients

- **Measurement of residual renal function**
  - 24 hrs urine collection for residual urea and creatinine clearance
  - MDRD formula cannot be used, because muscle mass is a more important determinant of plasma creatinine, than GFR

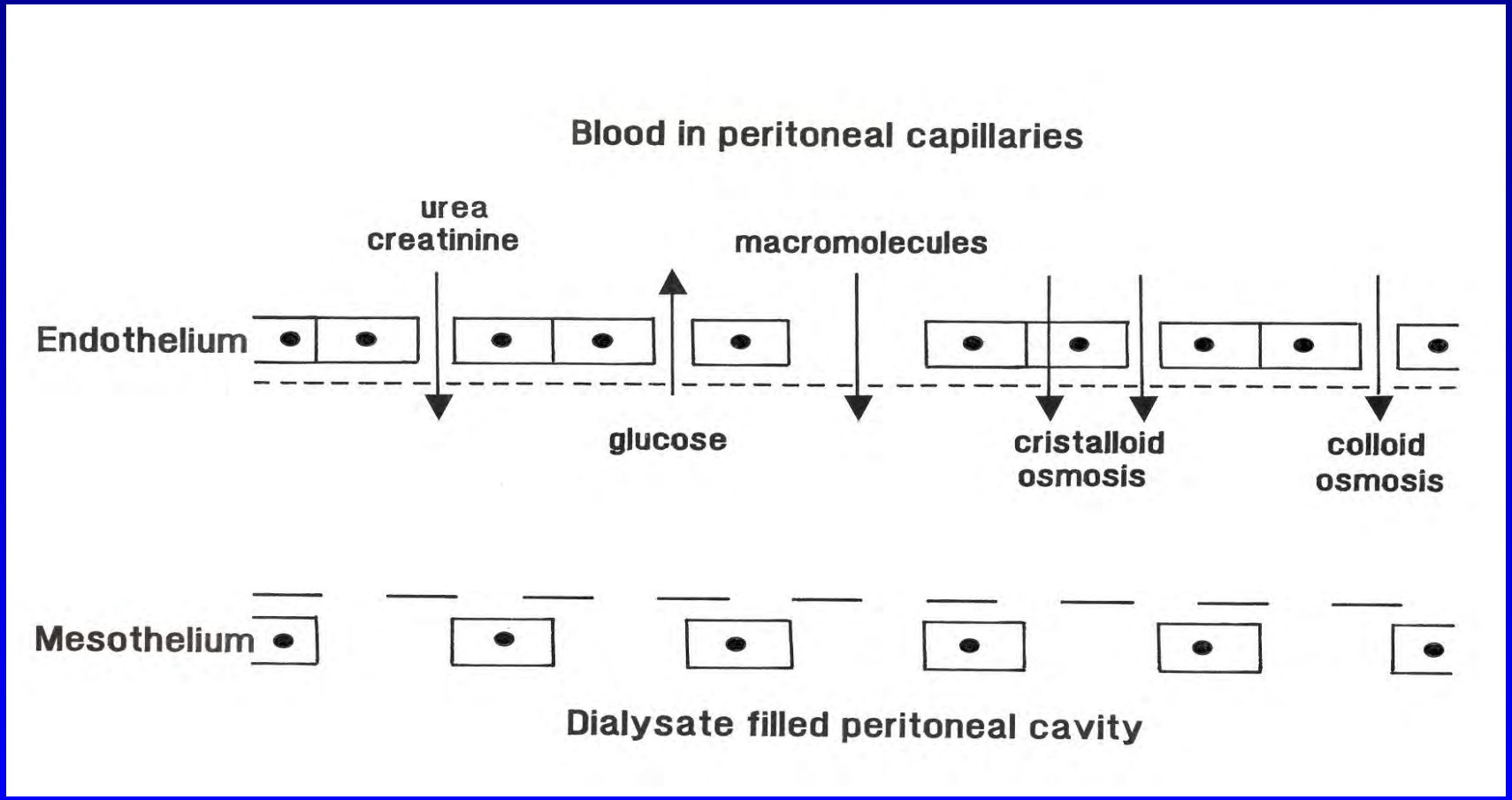
- **Assessment of peritoneal dialysis dose**
  - 24 hrs dialysate collection for small solute clearances

- **Assessment of peritoneal function**


Peritoneal function
Peritoneal transport
Effluent markers
Reflects the vascular part
Reflect the tissues and inflammation

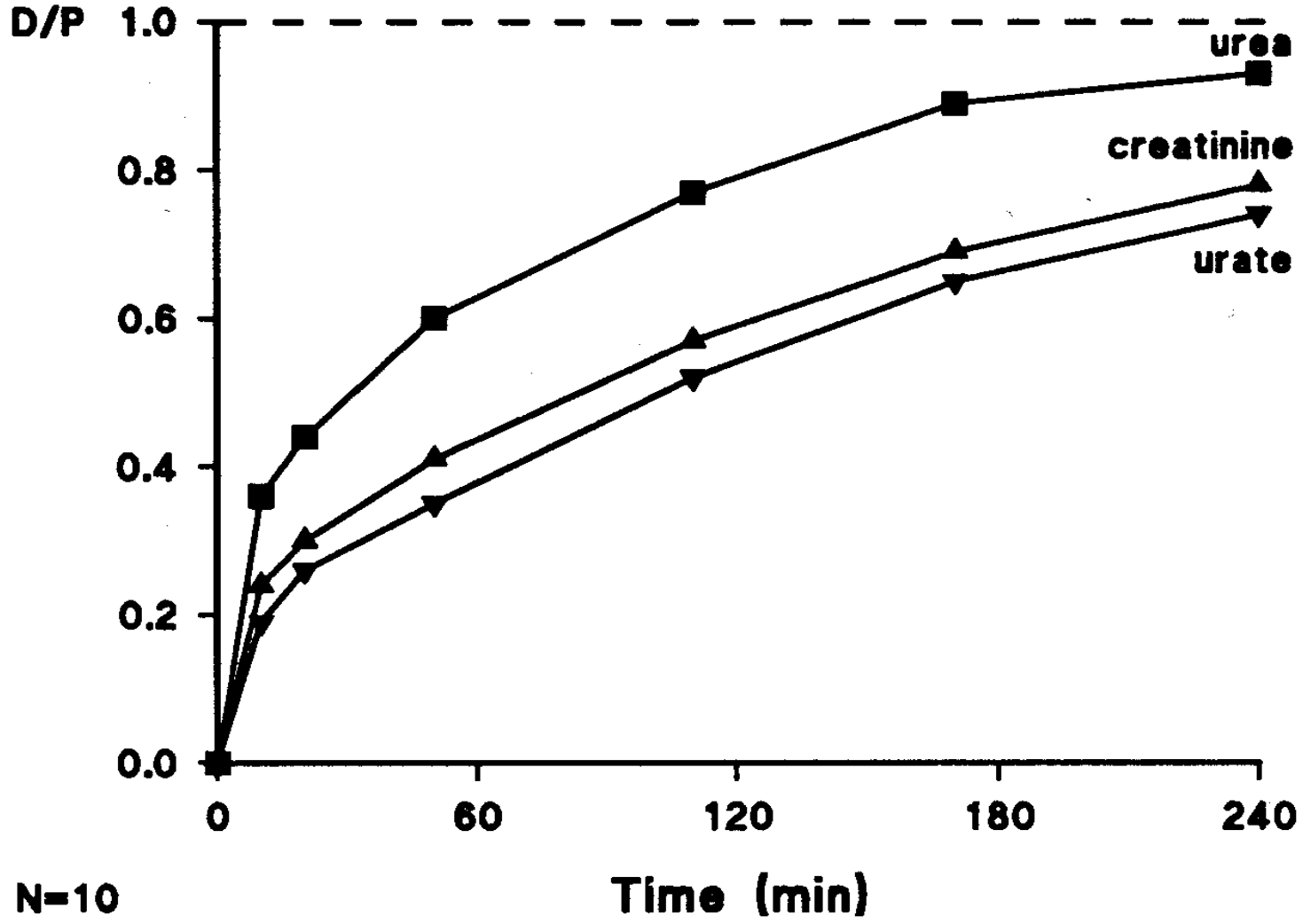

diaphragm
lymphatic vessels
interstitium
abdominal or bowel wall
mesothelium
peritoneal cavity
peritoneal capillaries

Mechanisms for peritoneal transport



Diffusion is important for small solutes

Diffusion


D/P
1.0
0.8
0.6
0.4
0.2
0.0
urea
creatinine
urate
0
60
120
180
240
N=10
Time (min)

Peritoneal equilibration test

- Developed by Twardowski (Perit Dial Bull,1987)
- 4 hours dwell time with 2.27/2.5% glucose-based dialysis solution
- Preceding exchange with 1.36/1.5% glucose
- One blood sample for creatinine and glucose
- Dialysate samples at 2 and 4 hours for creatinine and glucose

Zbylut J. Twardowski

PERITONEAL EQUILIBRATION TEST

Zbylut j. Twardowski Karl O. 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

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

Perit Dial Bull 1987;7:138-147

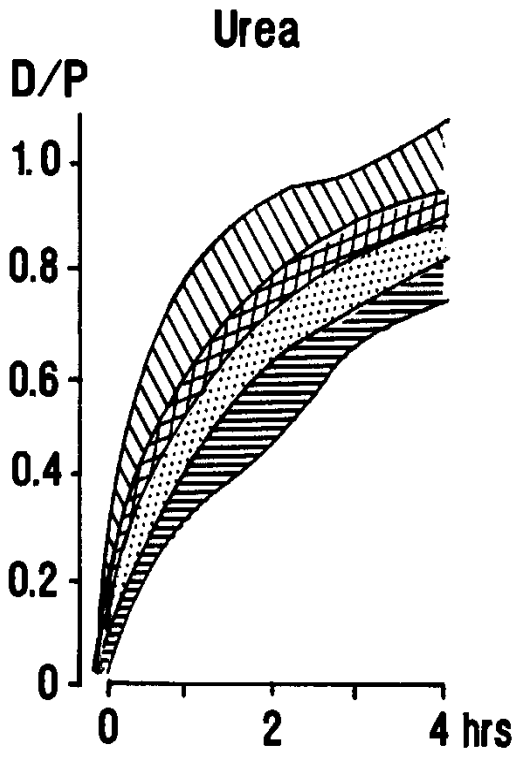
Strong points of the PET

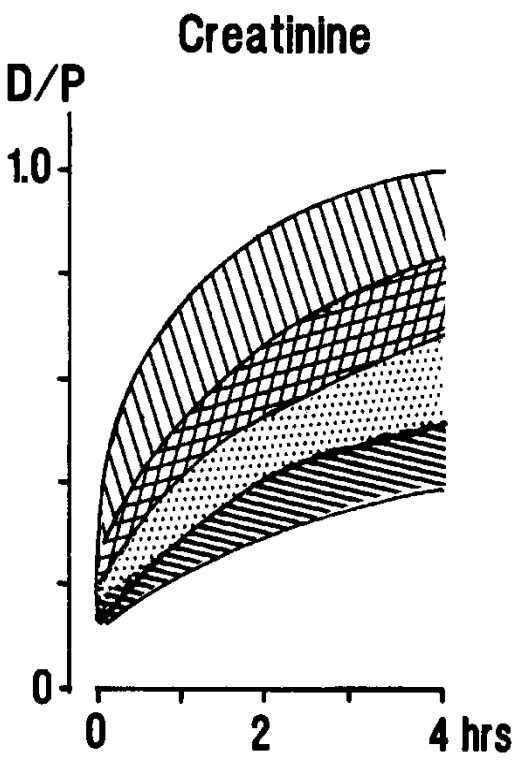
- Simplicity and standardisation
- Dwell time of 4 hours
- No complicated calculations
- No need for computer-based assumptions
- Stable results during short follow-up times
- World-wide promotion and application

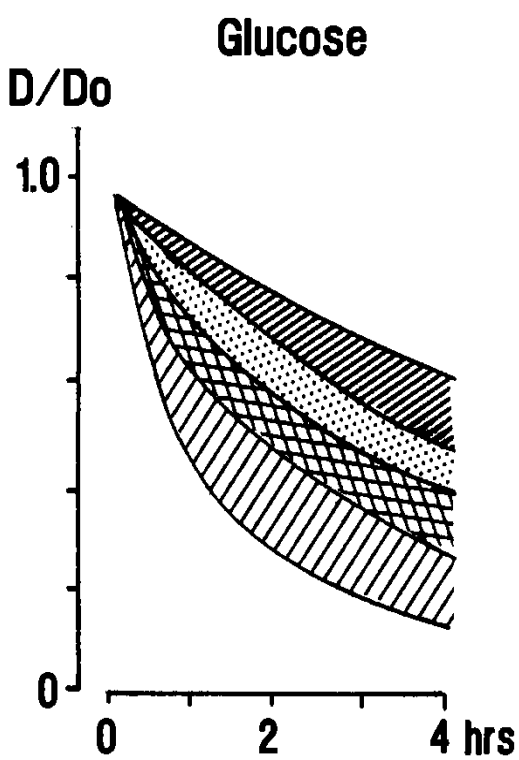
PET applications

- Division of patients into transport types
  - -high
  - -average (high and low)
  - -low
- Used for the determination of the dialysis dose
- Longitudinal follow-up of patients

Types of peritoneal transport



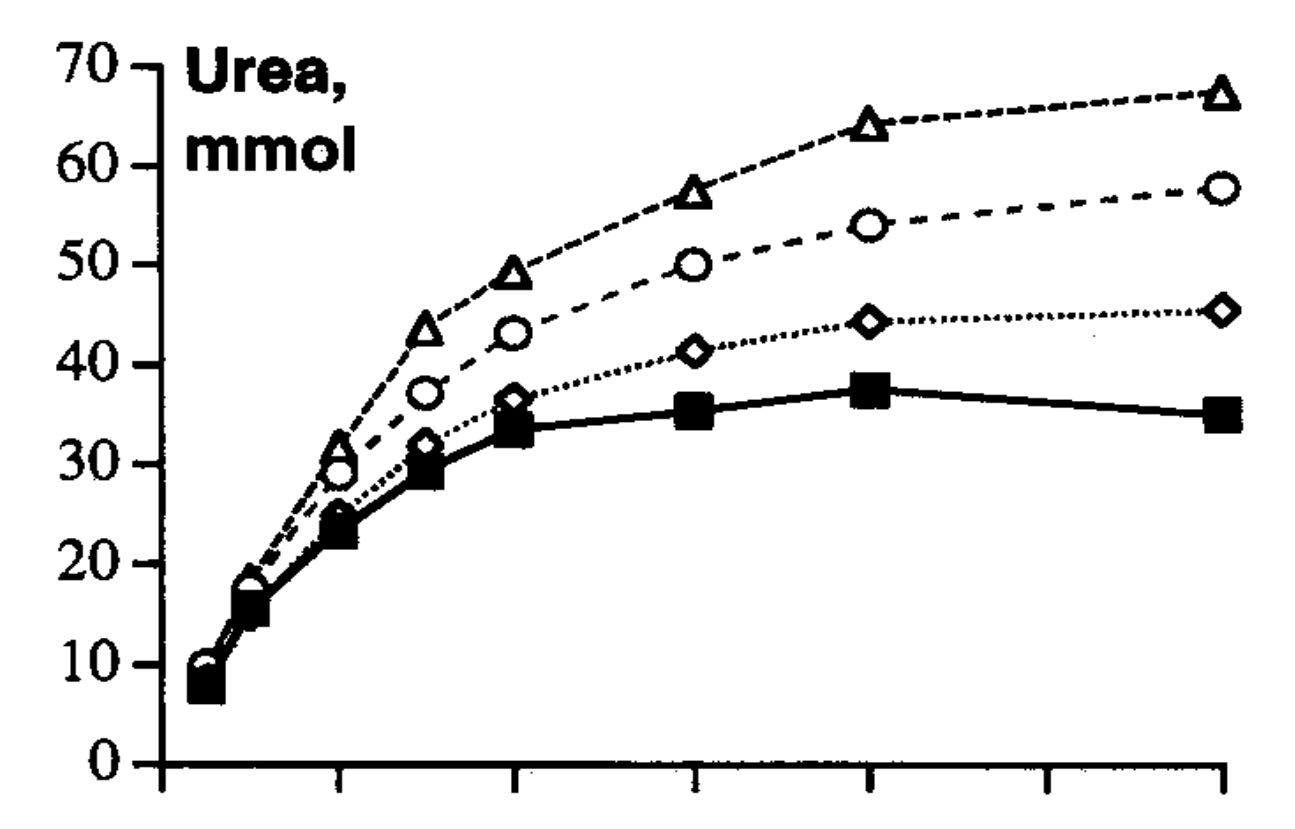




The confusion created by the terminology used in the PET

- Patients with a high D/P ratio are called high transporters.
- They may have low ultrafiltration rates due to rapid absorption of glucose.
- Consequently they may have a low Kt/V_{urea} due to the reduced drained volume.

Peritoneal removal of urea (mmol/6 hours)



"High" transporters

Wang T et al. Nephrol Dial Transplant, 1998

How correct is the term high transport?

	Peritoneal Kt/V_{urea} / week	
	Wang et al. NDT,1998	Churchill et al. JASN, 1998
High	1.48	1.58
Non-high	1.74	1.68

Conclusion: "high transporters" should be renamed "fast transporters"

Fast transport of small solutes

Can lead to ultrafiltration failure, due to rapid absorption of glucose

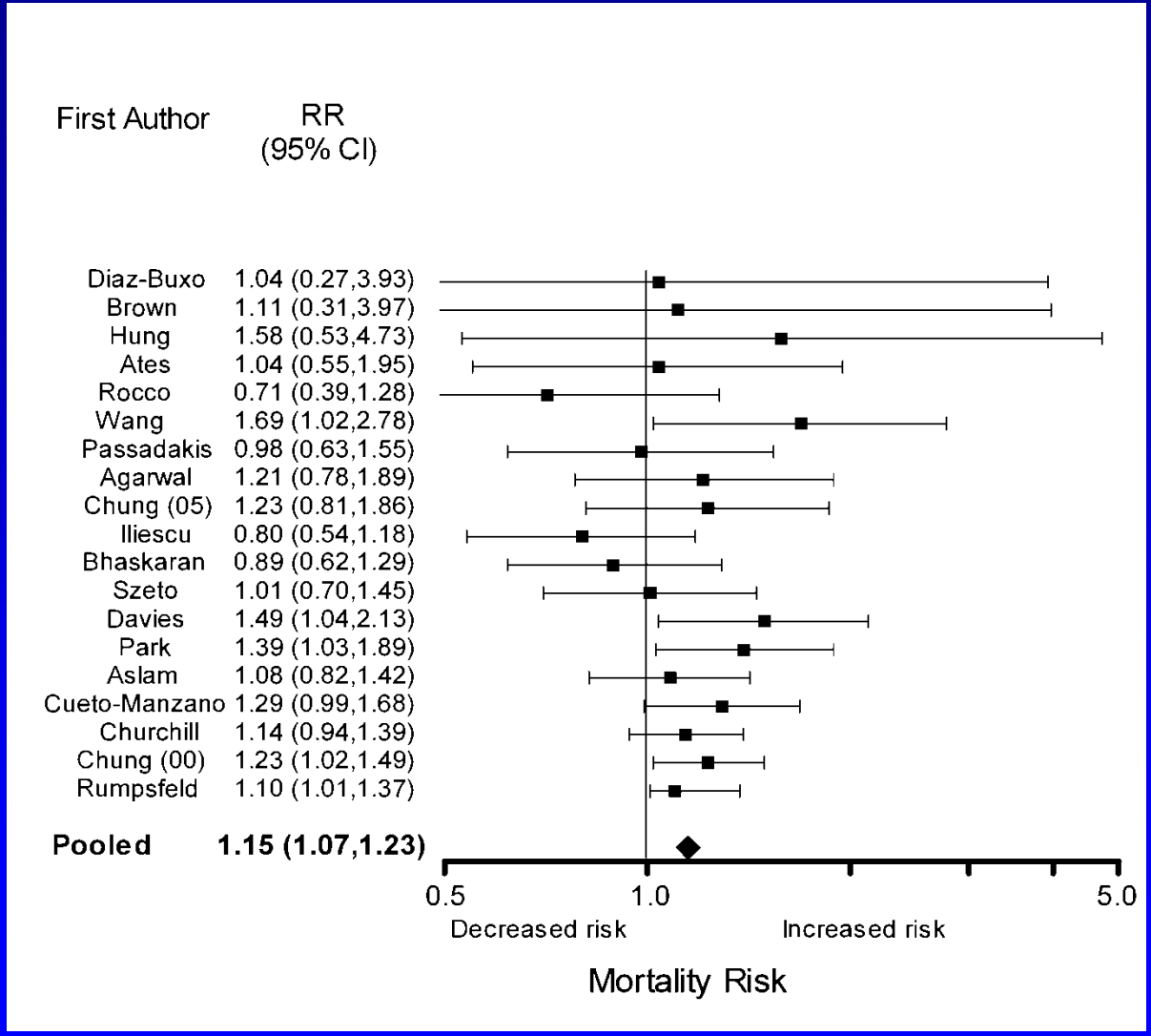
Early UFF, may be due to mesothelial-to-mesechymal transition

Late UFF due to vascular/interstitial damage

Urine production may compensate

When anuria, risk of overhydration

Meta-analysis of mortality in fast transporters



Brimble et al. J Am Soc Nephrol, 2006

Closer look at the meta-analysis

- Only found for CAPD patients
- Relationship with mortality was not present in APD patients
- Icodextrin was not used in any CAPD study included in the meta-analysis

PET applications

- Division of patients into transport types
  - -high (=fast)
  - -average (high and low)
  - -low (=slow)
- Used for the determination of the dialysis dose
- Longitudinal follow-up of patients

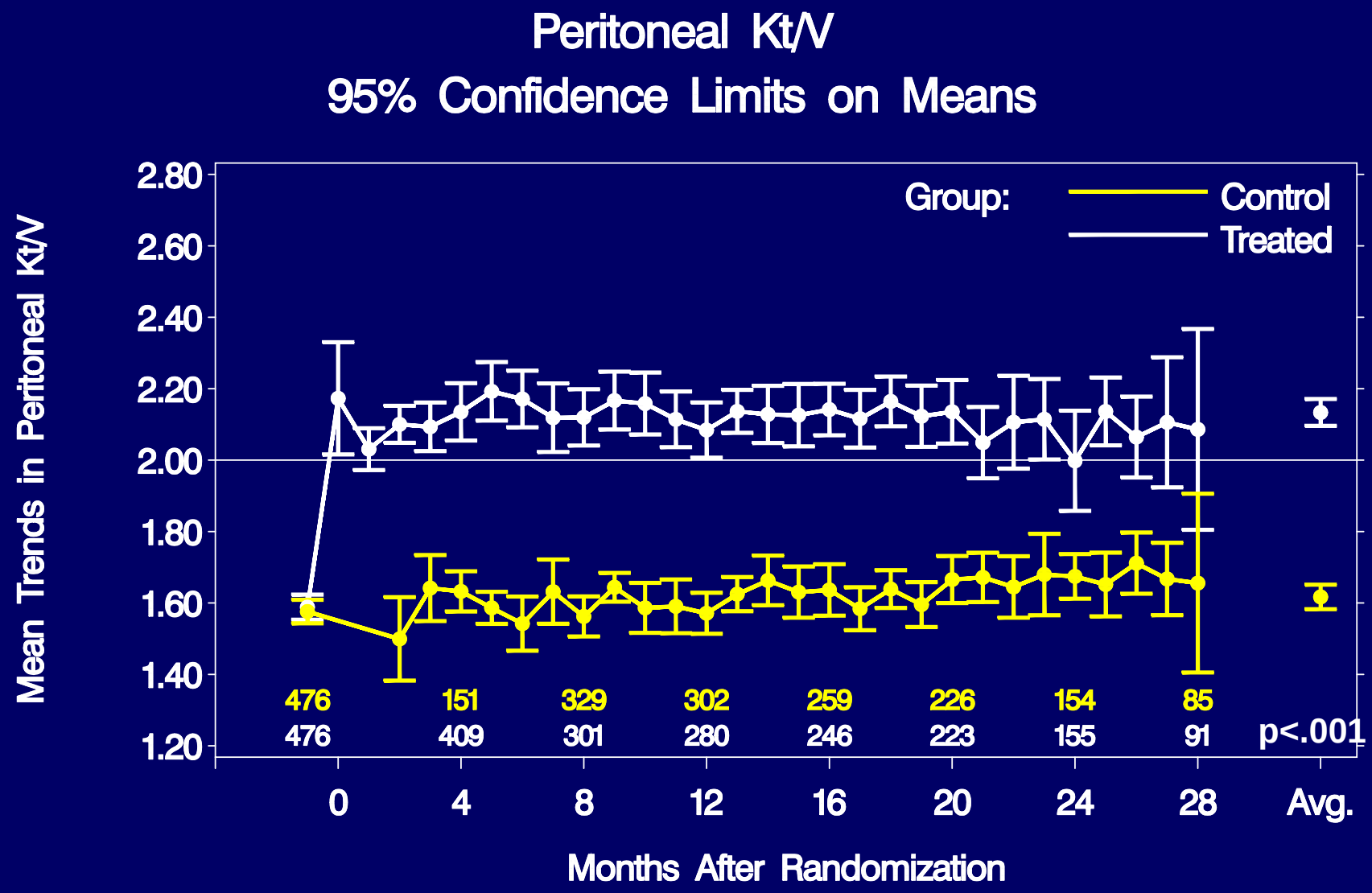
Dialysis dose

- The importance of the DOQI criteria on solute removal is overruled by that of residual kidney function, especially urine production
- The minimum in anuric patients is a Kt/V_{urea} of 1.5/week and creatinine clearance of 40 L/week
- Results of the ADEMEX study on survival
- Not only survival is important, but also quality of life

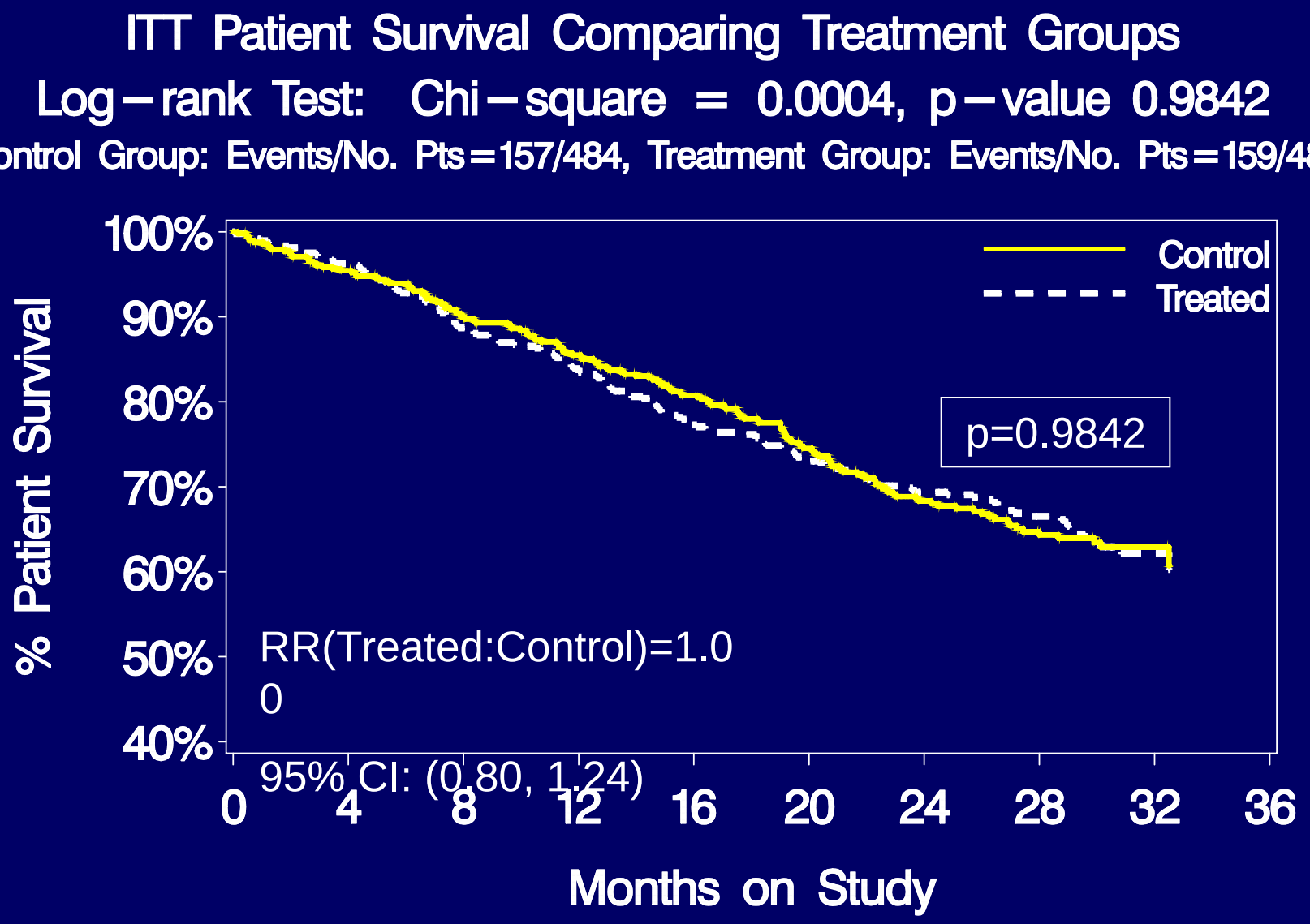
Ademex study
(Paniagua R. et al. J Am Soc Nephrol, 2002)

- 965 Mexican patients with peritoneal creatinine clearance < 60 L/week/1.73 m^2.
- Control: 4 x 2L CAPD
  treated: pCCr $\geq$ 60 L/week/1.73 m^2.
- No differences in baseline characteristics.
- Minimum follow-up: 2 years.

ADEMEX: Treatment Characteristics



ADEMEX: Primary Outcome



Effects of residual renal function and PD dose on quality of life

Quality of life	Residual renal function	Dialysis dose
Physical functioning	↑	=
Social functioning	↑	=
vitality	↑	=
Symptoms of renal failure	↓	↑
Burden of kidney disease	↓	↑

Temorshuizen et al. Am J Kidney Dis, 2003

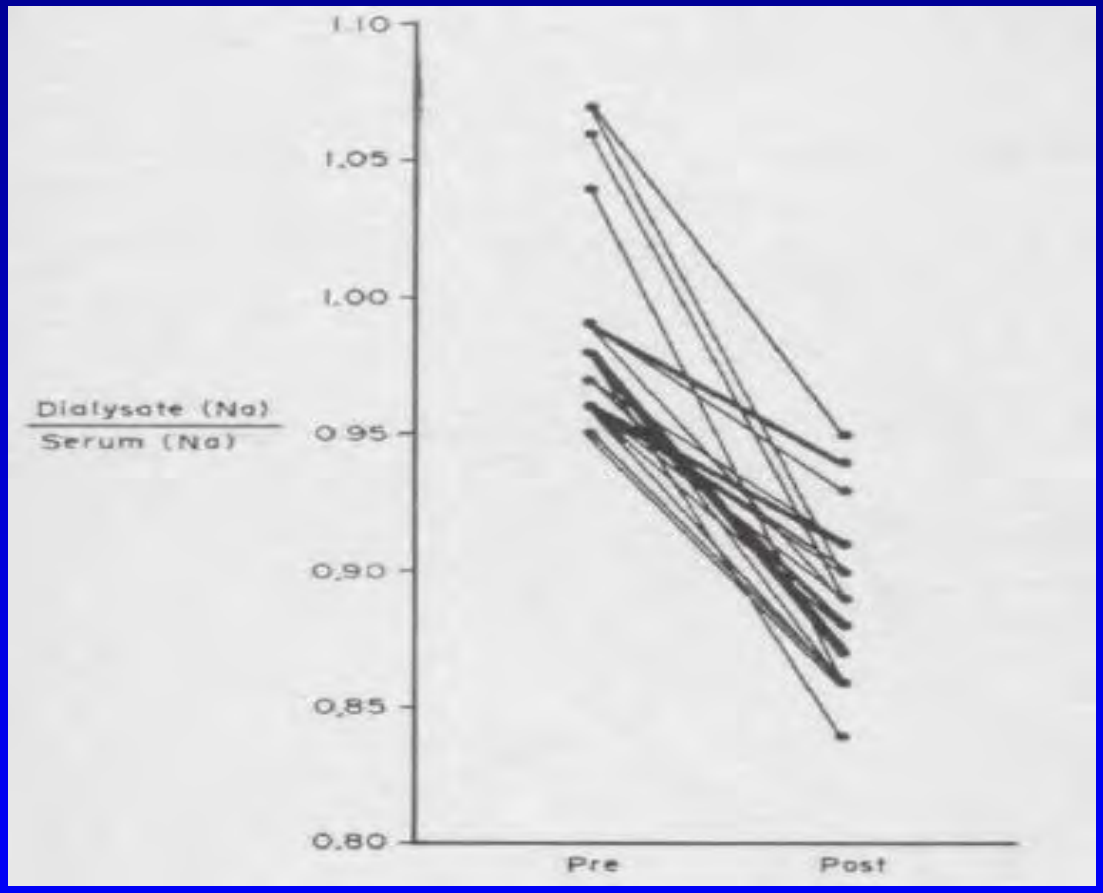
Weak points of the classic PET

- PET is mainly focussed on small solute transport
- The use of 2.27/2.5% glucose gives insufficient information on ultrafiltration, because arousal (incomplete drainage) may be stronger than the signal (ultrafiltered volume)
- Fluid transport is assumed to occur along the same pathways as solute transport
- No information on Na^+ transport

The Godfather of peritoneal function measurements

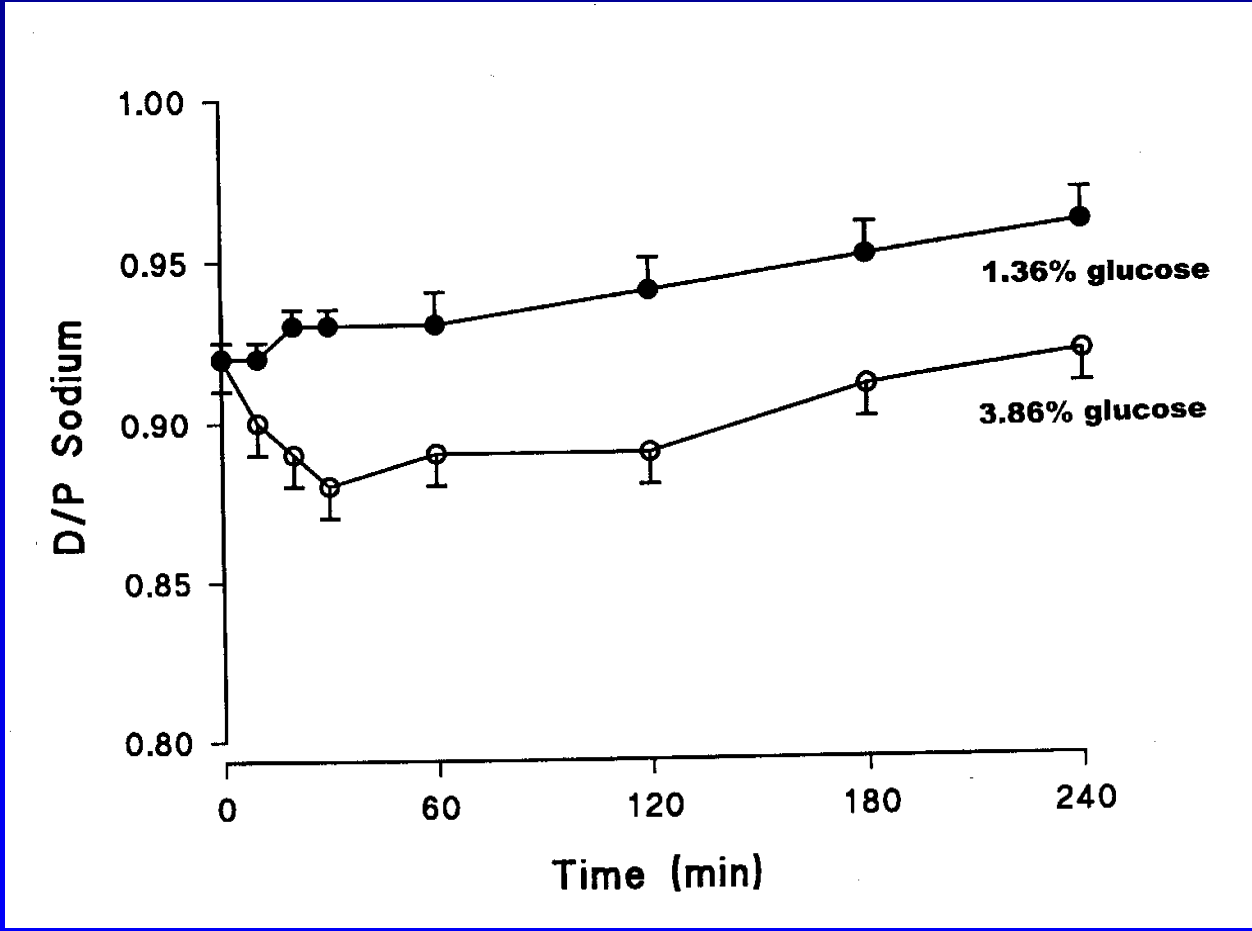
Karl D Nolph

Sodium sieving during acute hypertonic dialysis exchanges



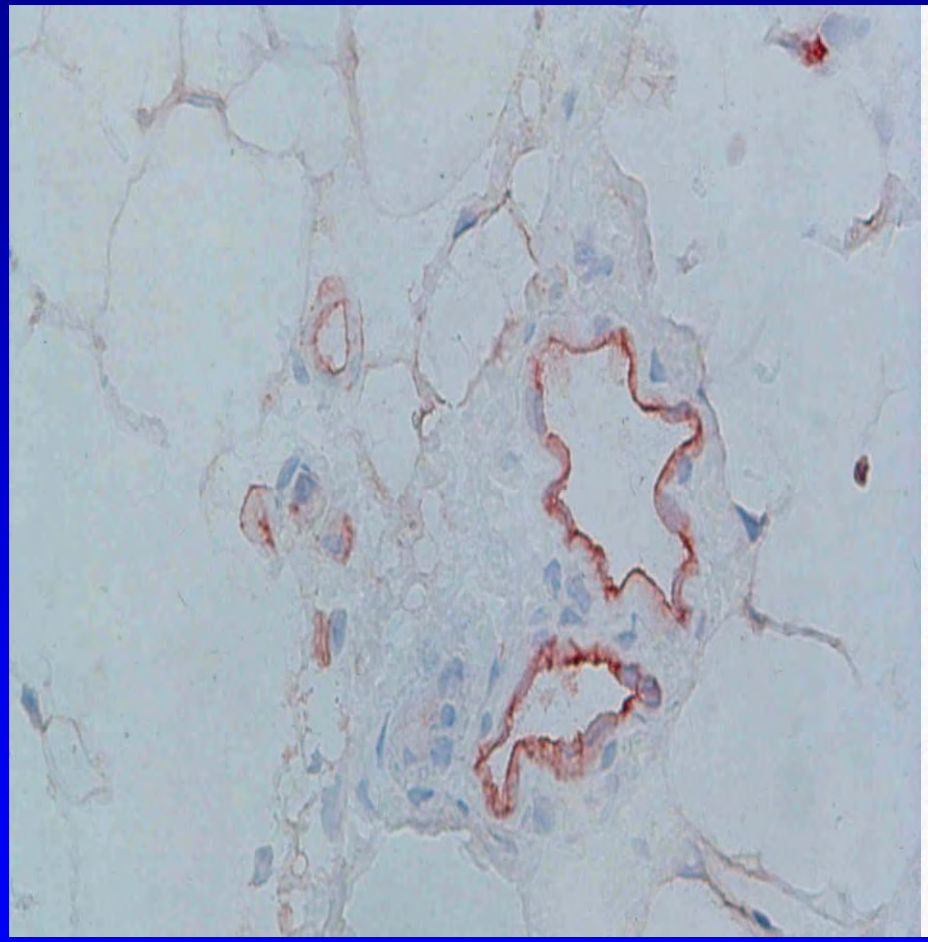
Nolph KD et al. Ann Int Med 1969;70:931-947

Na^+ sieving with high glucose dialysate is by dilution, due to free water transport



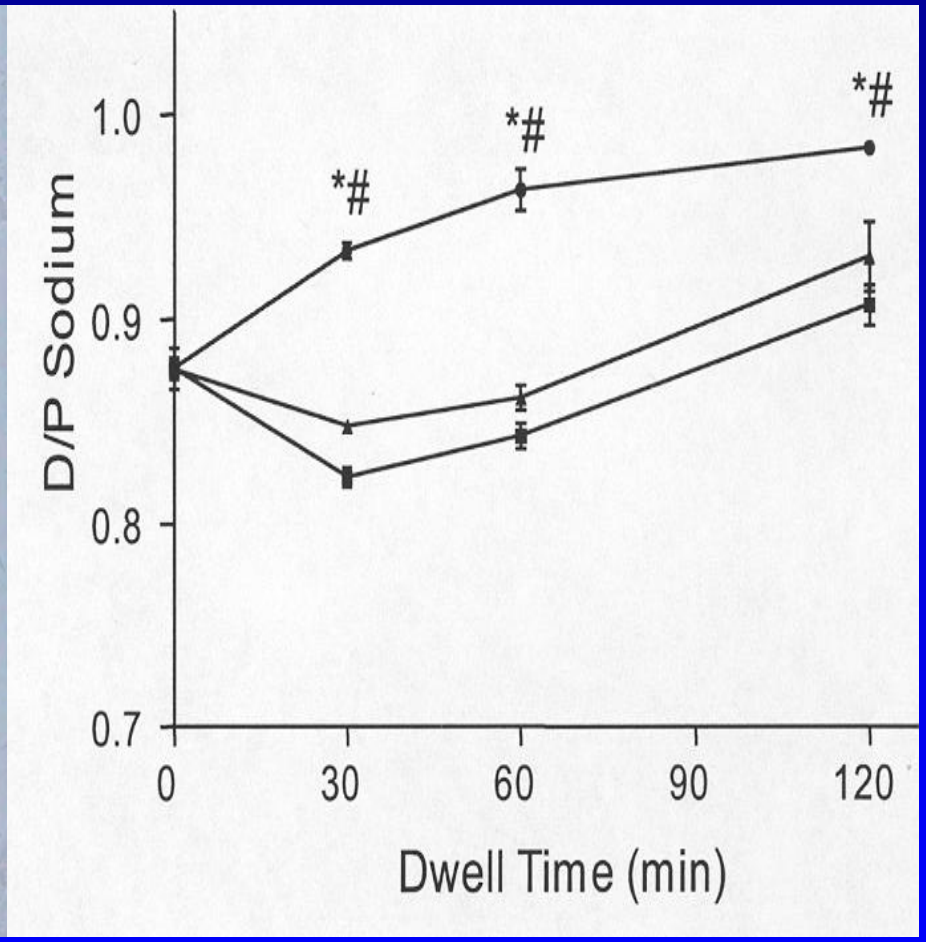
This is especialy important in the 1st hour, when the osmotic gradient is high

Peritoneal AQP-1 is present in human venules and capillaries



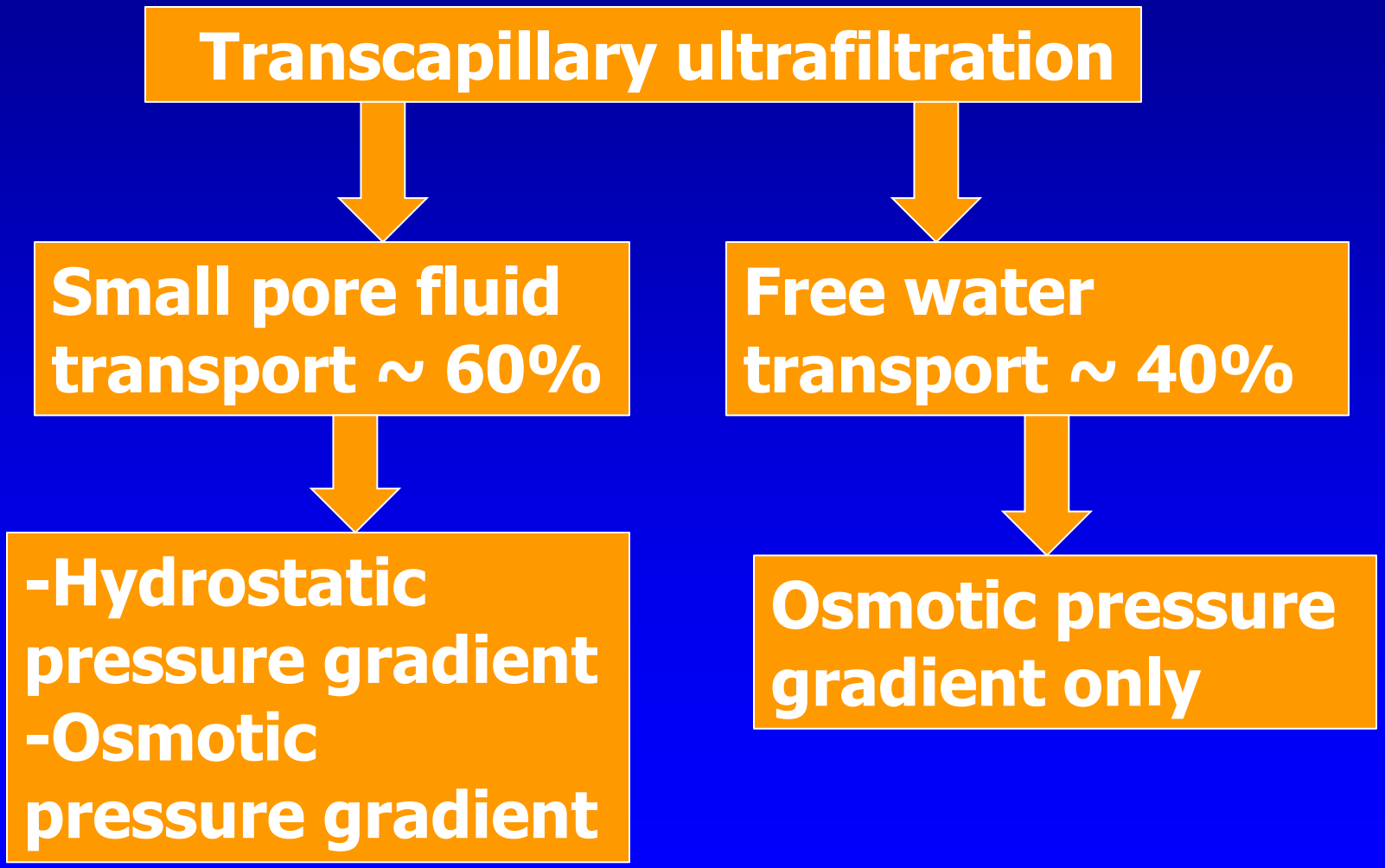
Pannekeet et al. Perit Dial Int, suppl 1,1996

No Na^+ sieving in AQP-1 knock-out mice



Ni et al. Kidney Int,2006

Pathways for ultrafiltration



Quantification of free water transport
(Smit et al.Kidney Int,2004;La Milia et al. Kidney Int, 2005)

- 1 hour PET, 3.86%/4.25% glucose
- Na^+ removal = (drained volume x D_{Na}^+) – (instilled volume x D_{Na}^+)
- UF small pores: Na^+ removal / P_{Na}^+ ~ Na^+ clearance, which occurs through the small pores
- Free water transport: total UF – UF small pores

Modified PET

- Part of the ISPD guidelines on ultrafiltration failure (Perit Dial Int, Suppl 4, 2000)
- 3.86/4.25% glucose and an additional dialysate sample at 60 minutes to assess sodium sieving as a qualitative representation of free water transport
- The 1,4 MoPET uses a temporarily drainage after 1 hr for assessment of the volume by weighing and sampling. This is followed by reinfusion and final drainage after 4 hrs. It has also been called: the two-in-one modified PET

Values after drainage at 4 hours

	PET 3.86%/4.25%	PET 3.86%/4.25% with drainage after 60 minutes
FWT after 60 min (mL)	?	164 mL = 45%
Net UF after 4 hrs (mL)	667	621
D/P creatinine after 4 hrs	0.64	0.64
Dt/Do glucose after 4 hrs	0.42	0.37

None of the differences was significant; paired observations in 10 stable PD patients

From: Cnossen et al. Perit Dial Int, 2009

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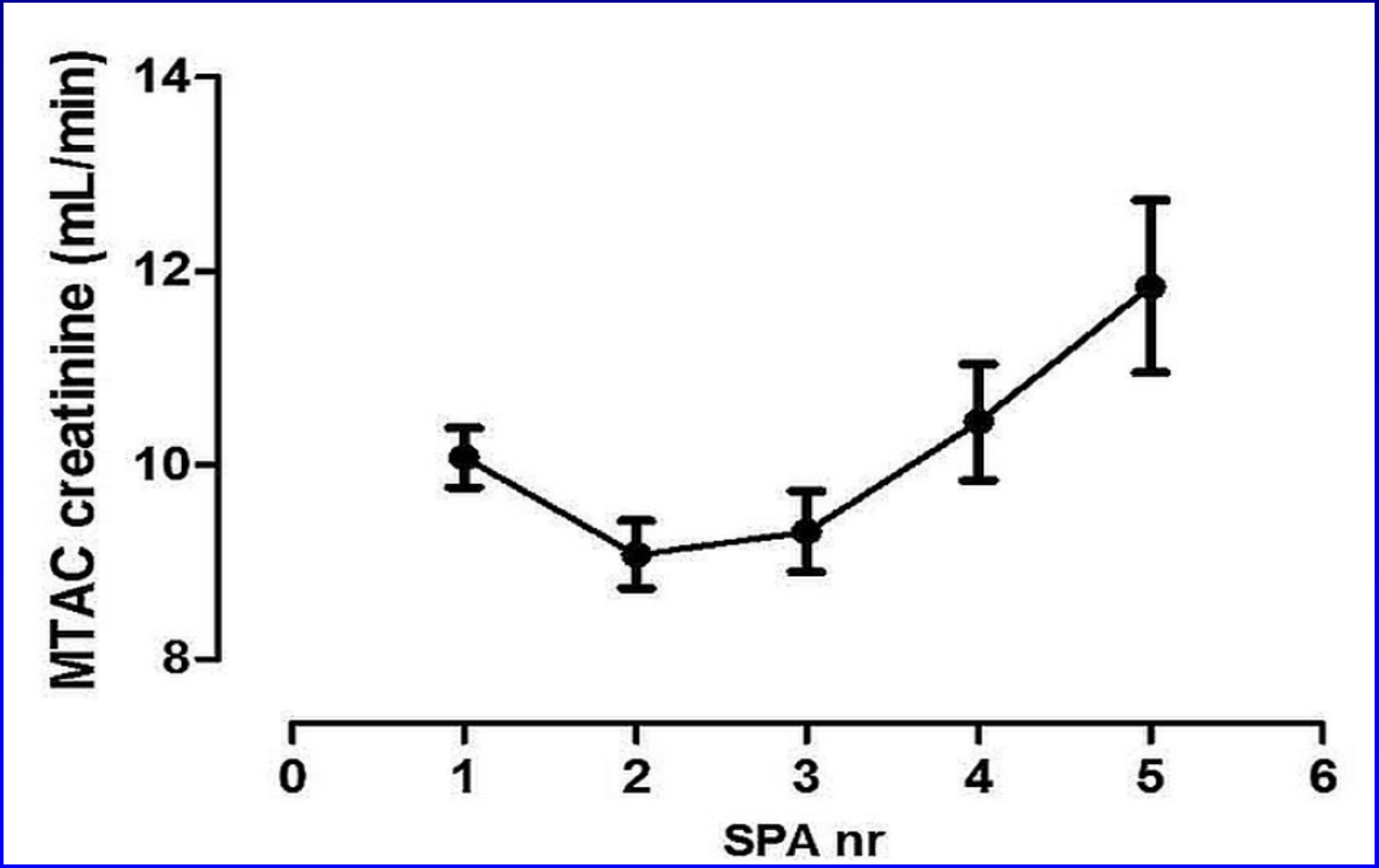
Time-course of MTAC creatinine

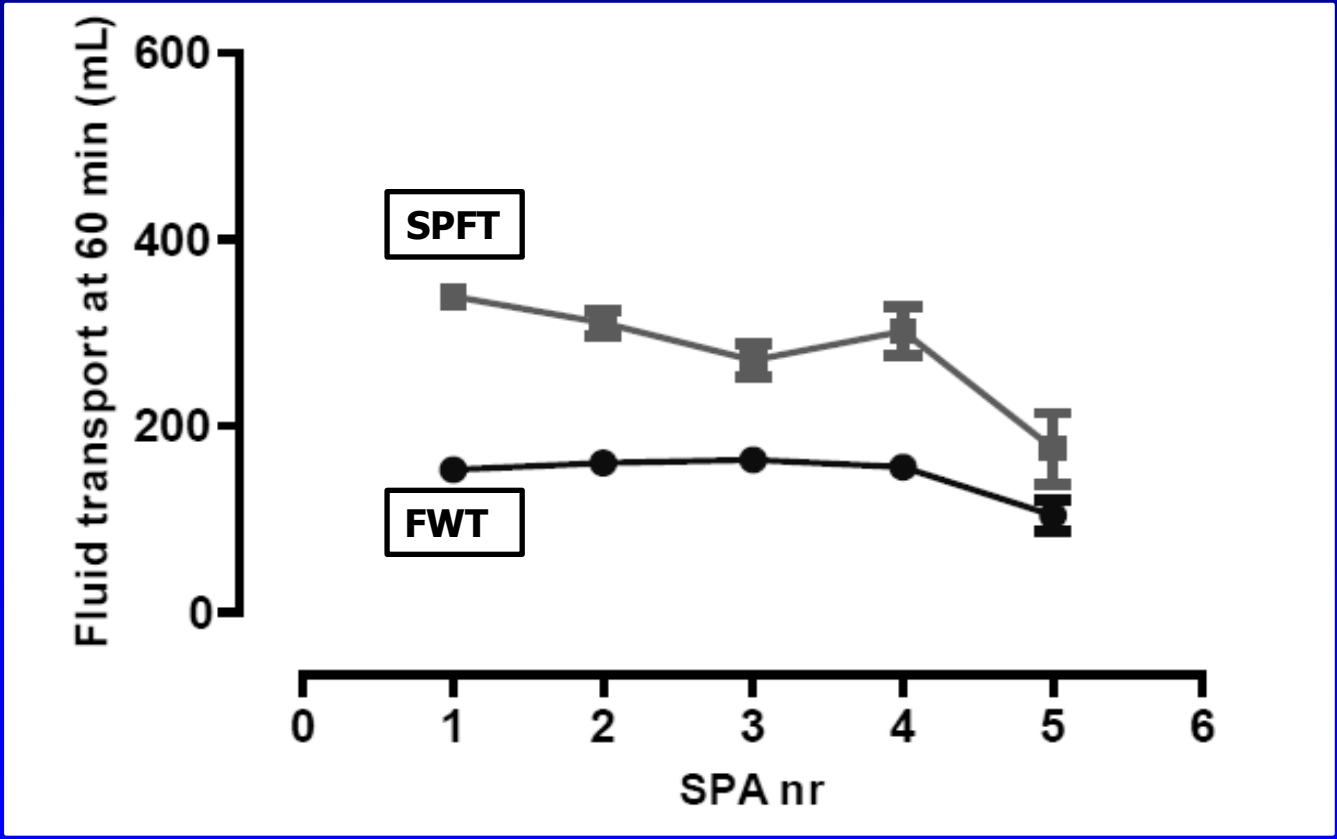


Coester et al. Perit Dial Int, 2014

Ultrafiltration failure

- **ISPD definition : 3x4 rule**
  - **drained volume < 400 mL**
  - **after a dwell-time of 4hrs**
  - **using 4% (3.86/4.25) glucose dialysate**
- **Late UF failure is present in ~ 20% of PD patients treated for >2 years**
- **Both small-pore fluid transport (SPFT) and free water transport (FWT) are affected**
- **SPFT is mainly dependent on hydrostatic pressure, FWT only on osmotic pressure**
- **FWT is severely impaired in encapsulating peritoneal sclerosis**

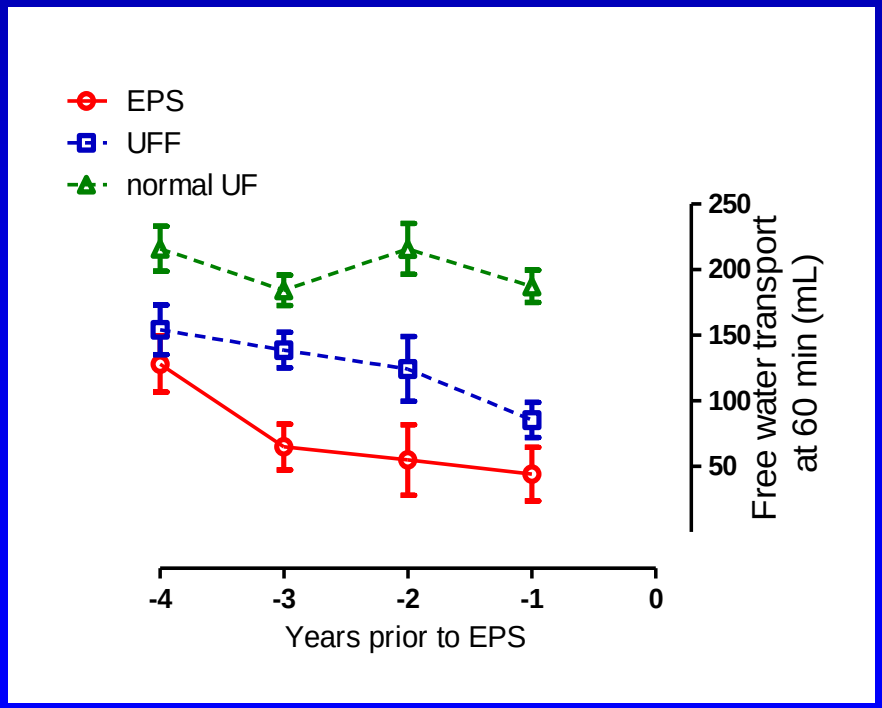
Time course of SPFT and FWT

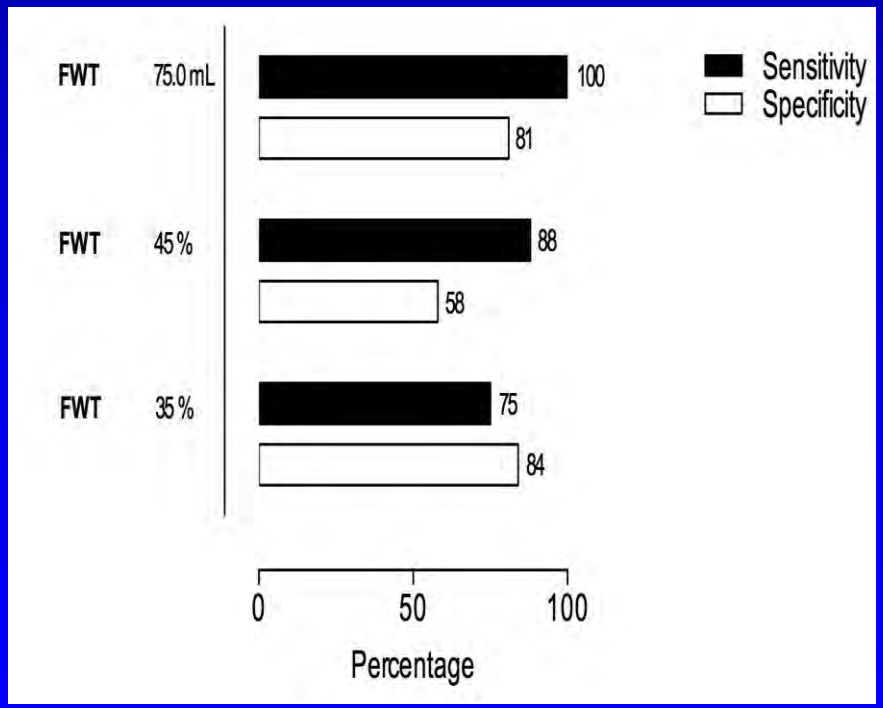


Coester et al. Perit Dial Int, 2014

Severely impaired FWT preceding EPS

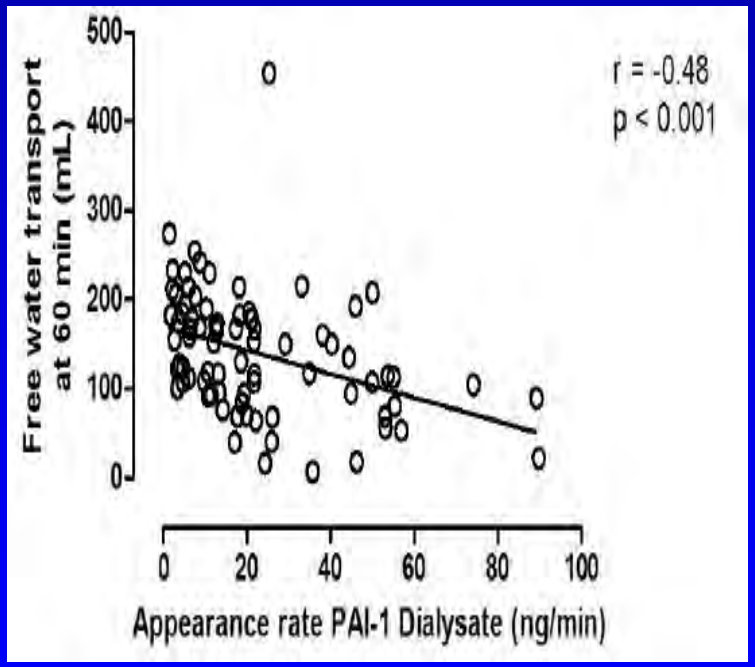
- A total of 19 patients has been described (Sampimon 2011, Morelle 2015)
- All had extremely low FWT rates

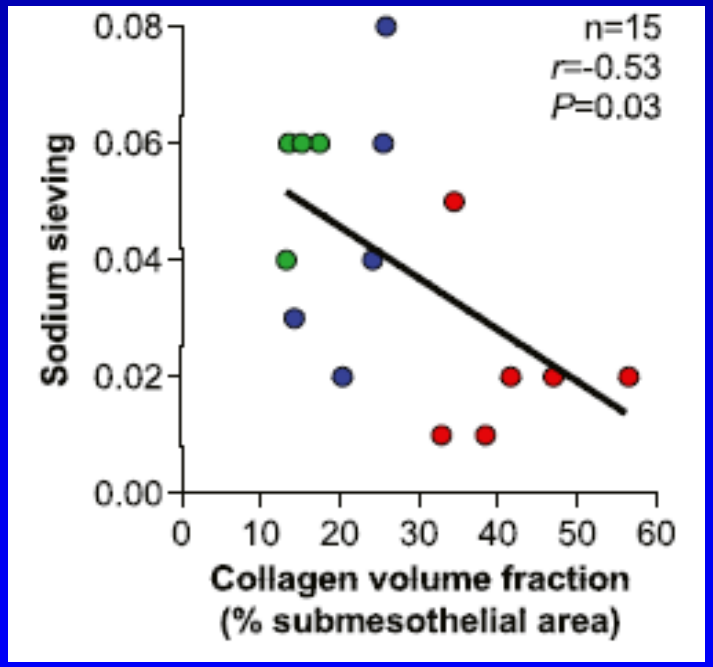




Why is free water transport impaired in peritoneal fibrosis/sclerosis?

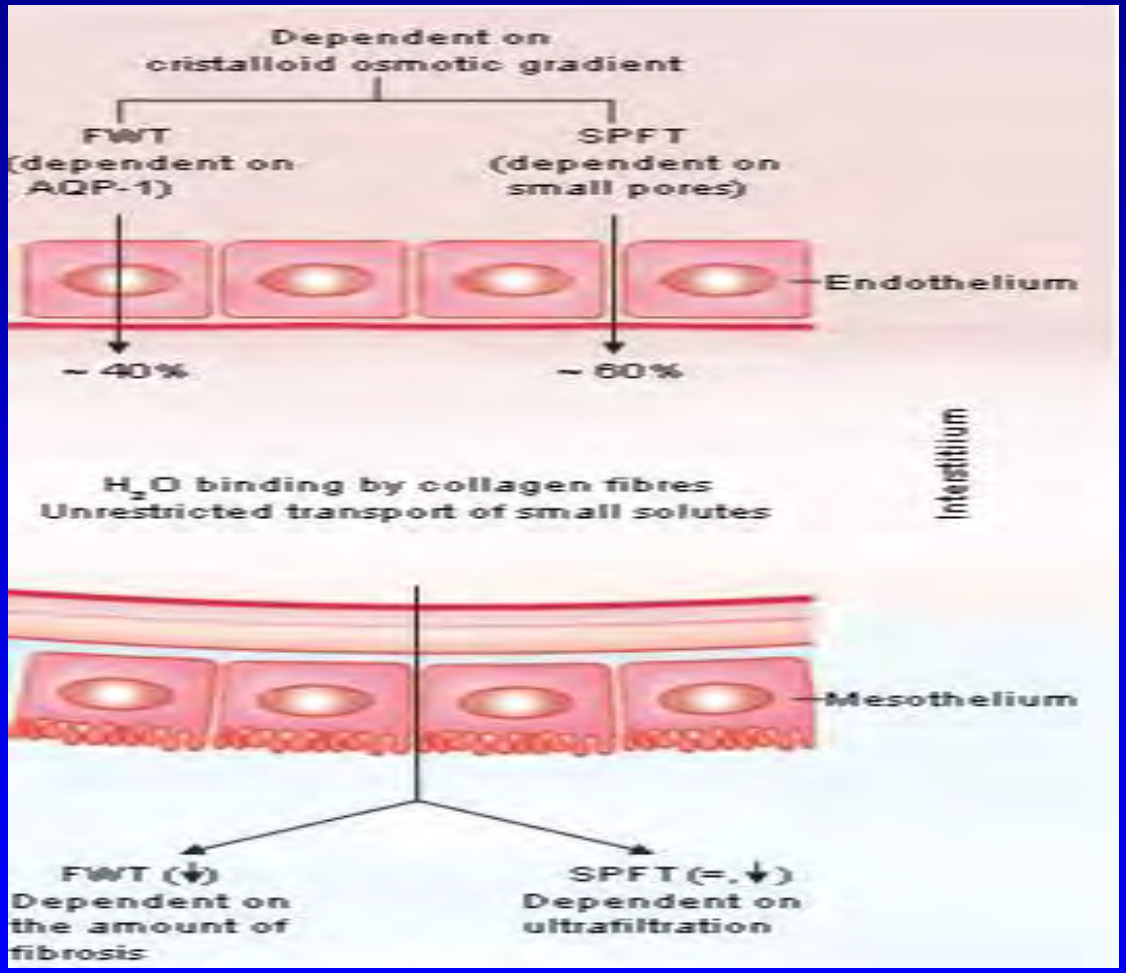
- AQP-1 expression is normal
- Relationships between fibrosis and FWT





- Due to water binding by collagen?

Relationship FWT and fibrosis



Krediet RT, Lopes Barreto D et al. Perit Dial Int, 2016

The state-of- the art PET

- Should always include UF, Na^+ sieving and preferably assessment of FWT and SPFT
- Is done with a 3.86/4.25 % glucose dialysis solution, plasma and dialysate sampling after 60 min for Na^+, creatinine and glucose
- Drainage after 1 hour for volume, followed by reinfusion and final drainage after 4 hrs (1,4MoPET) gives the best information on FWT_{1hr} $SPFT_{1hr}$ $D/P\ creatinine_{4hrs}$ and D_{4hrs}/D_0 glucose