ERBP position statement on membrane evaluation in PD

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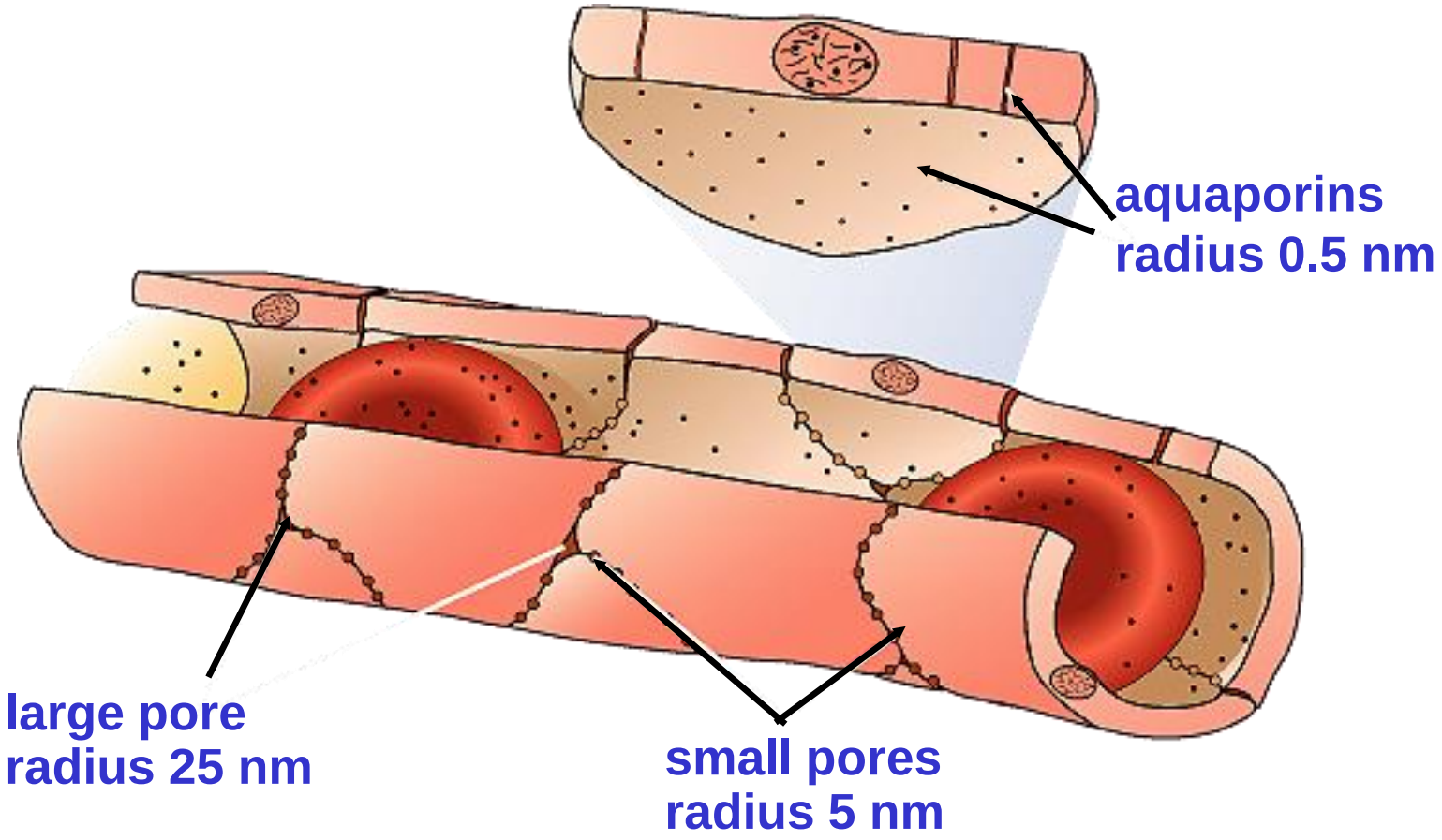
NDT
Nephrology Dialysis Transplantation

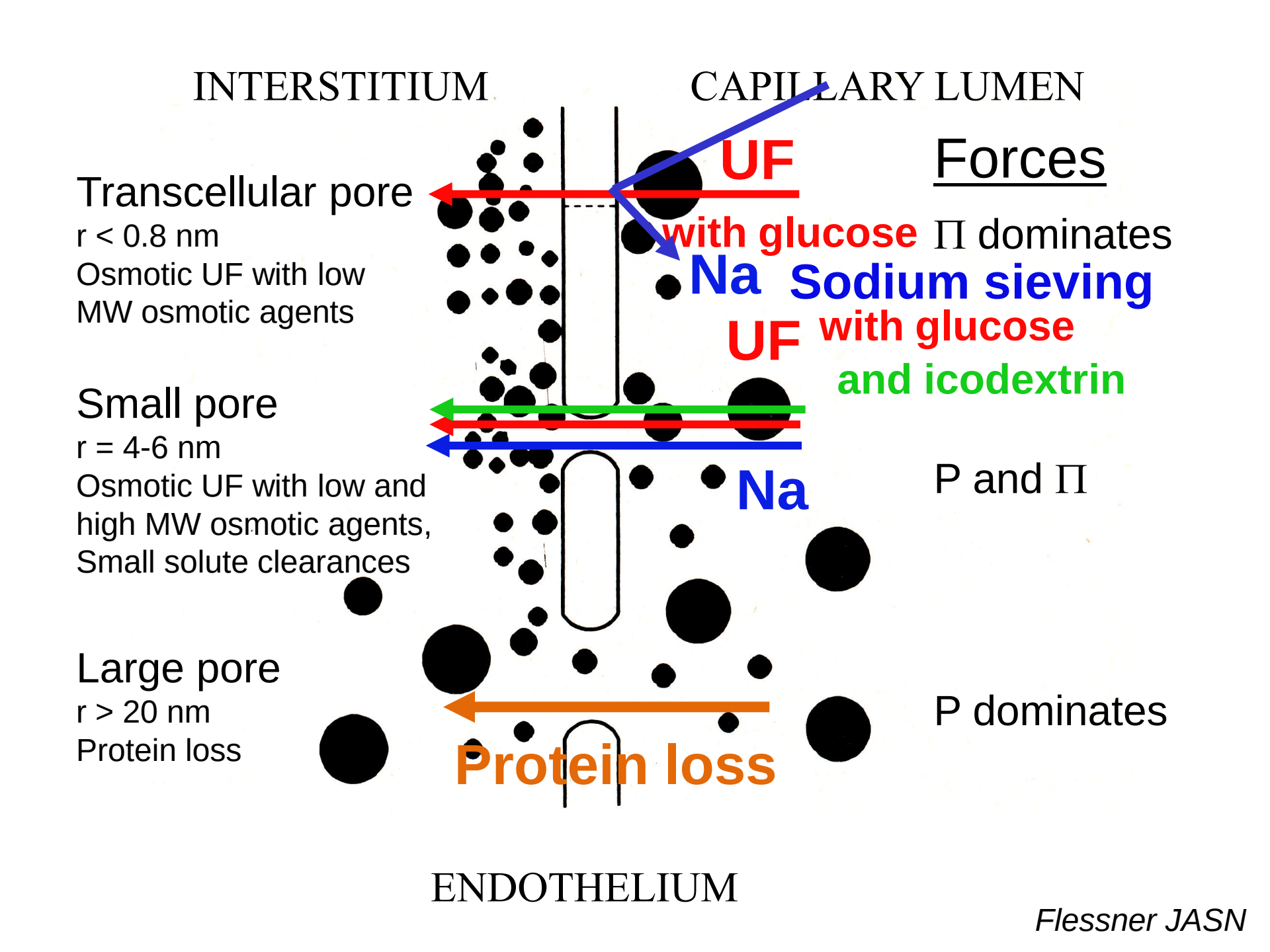
Editorial Comment

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

Wim van Biesen[1], Olof Heimburger[2], Raymond Krediet[3], Bengt Rippe[4], Vicenzo Lamilia[5], Adrian Covic[6], Raymond Vanholder[1] and for the ERBP working group on peritoneal dialysis

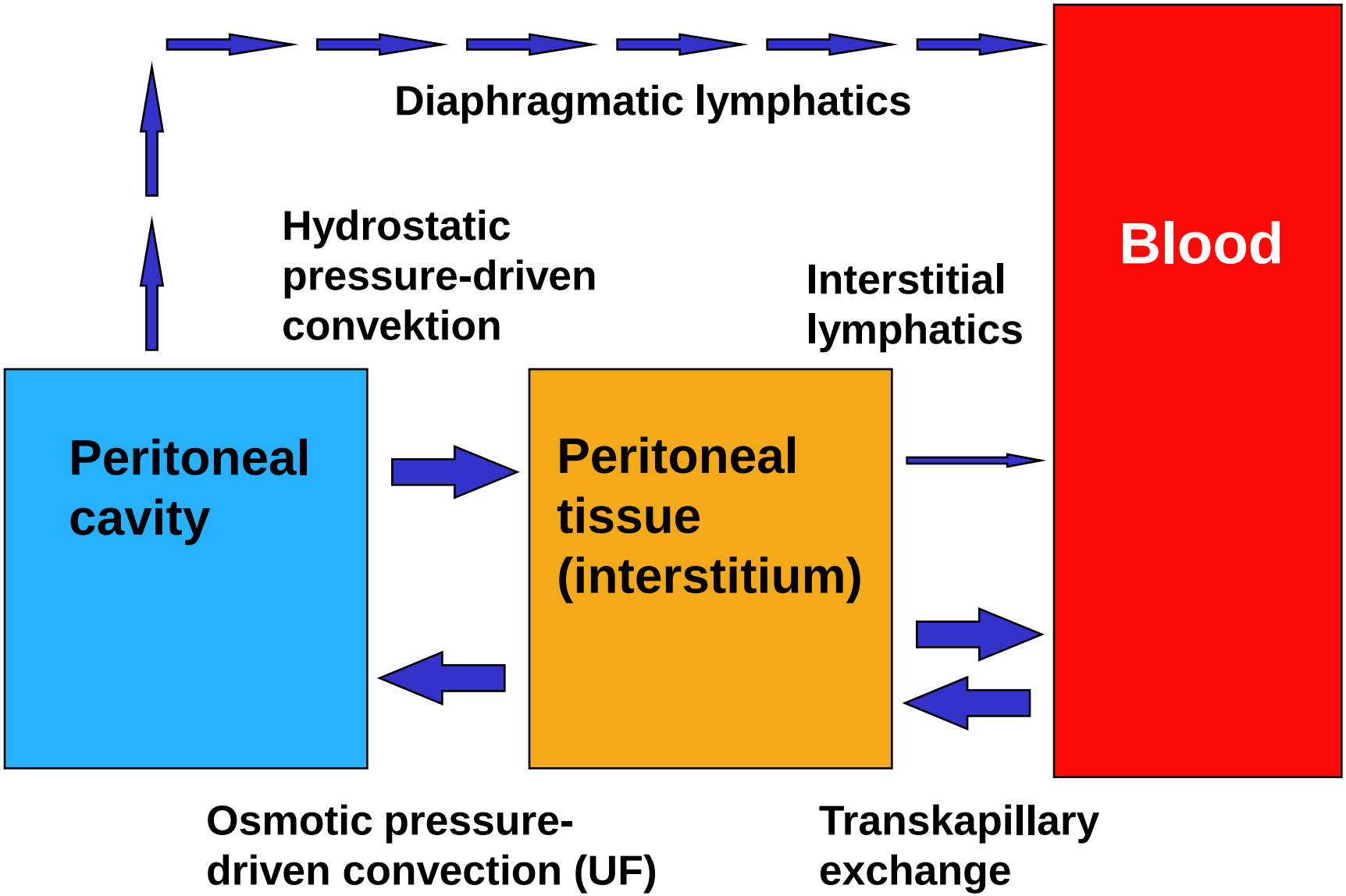
3 -pore model


aquaporins
radius 0.5 nm
large pore
radius 25 nm
small pores
radius 5 nm



Flessner JASN

Fluid transport



Why is peritoneal transport important?

- **Related to outcome**
  - **Rapid solute transport (impotant for prescription)**
  - **High albumin losses (endothelial dysfunction)**
- **Important for the dialysis prescription:**
  - **Solute clearance (Kt/V, Creatinine cl.)**
  - **Fluid removal**
- **Changes in transport with time**
  - **Affects the dialysis prescription**
  - **Related to structural membrane changes**

Peritoneal membrane assessment

ERBP advisory board opinion statement, (Van Biesen et al, NDT 2010)

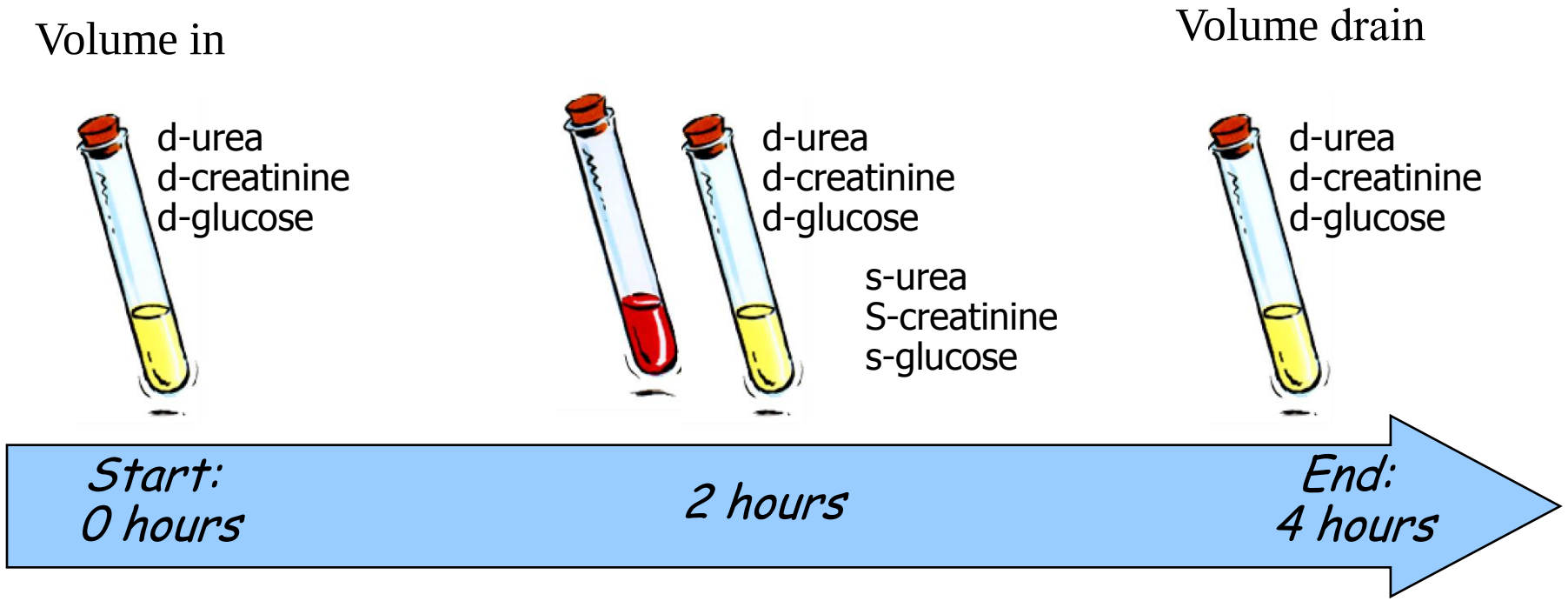
1.1 Tests of peritoneal membrane characteristics should be used to guide prescription of PD therapy and follow evolution of peritoneal membrane function over time.

The aims of evaluating peritoneal membrane function are:

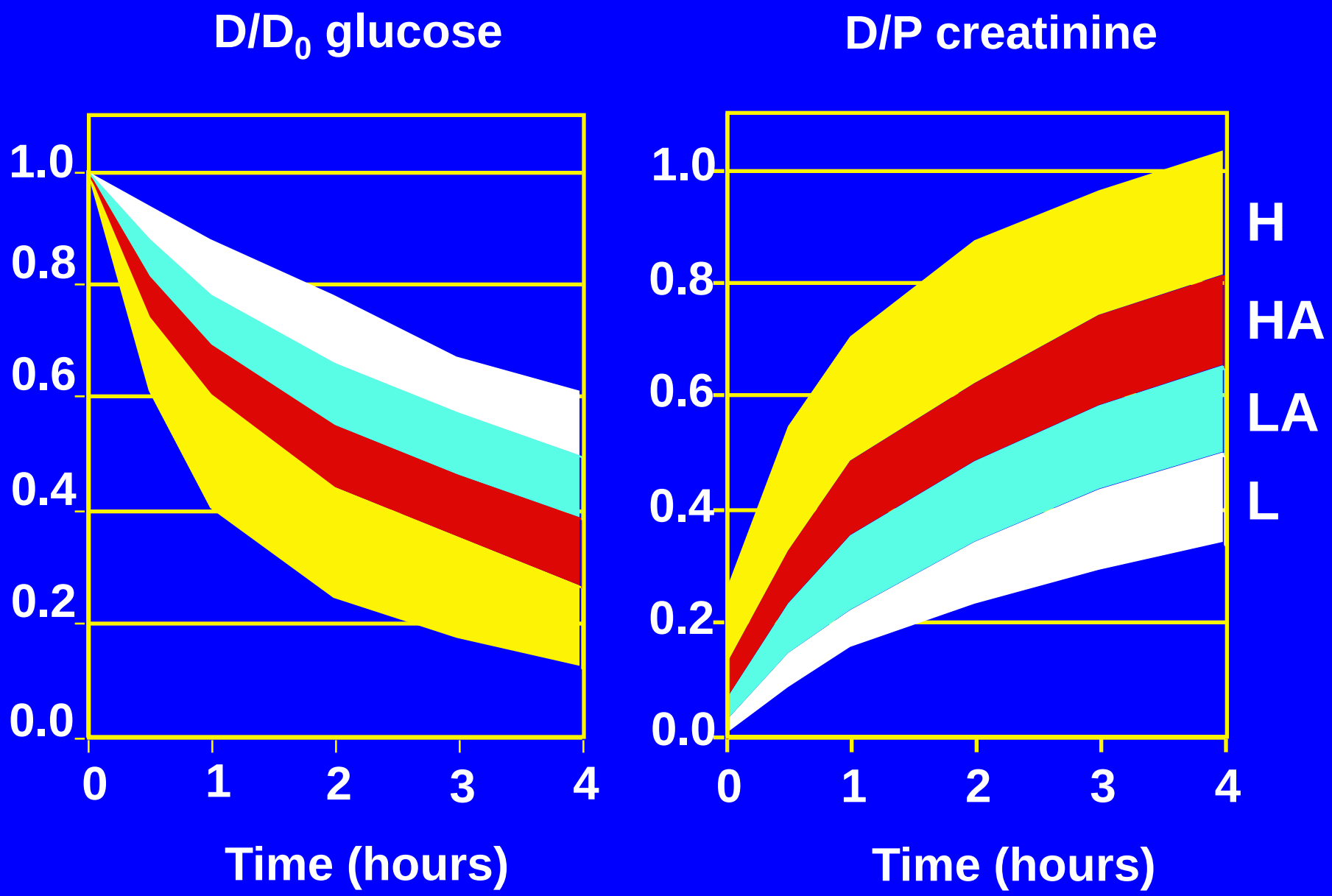
- **To optimize treatment prescription with regard to small-solute clearance, volume regulation and reduction of uraemic toxicity.**
- **To assess membrane characteristics not related to small solutes: osmotic conductance of glucose, aquaporins, hydraulic conductance, large-solute flow, lymphatic reabsorption.**
- **To evaluate the evolution of peritoneal function over time.**

PET- Peritoneal Equilibration Test

Standard PET: 2.000 ml, 2,27 % glucose, 4 hours



Twardowski et.al 1988

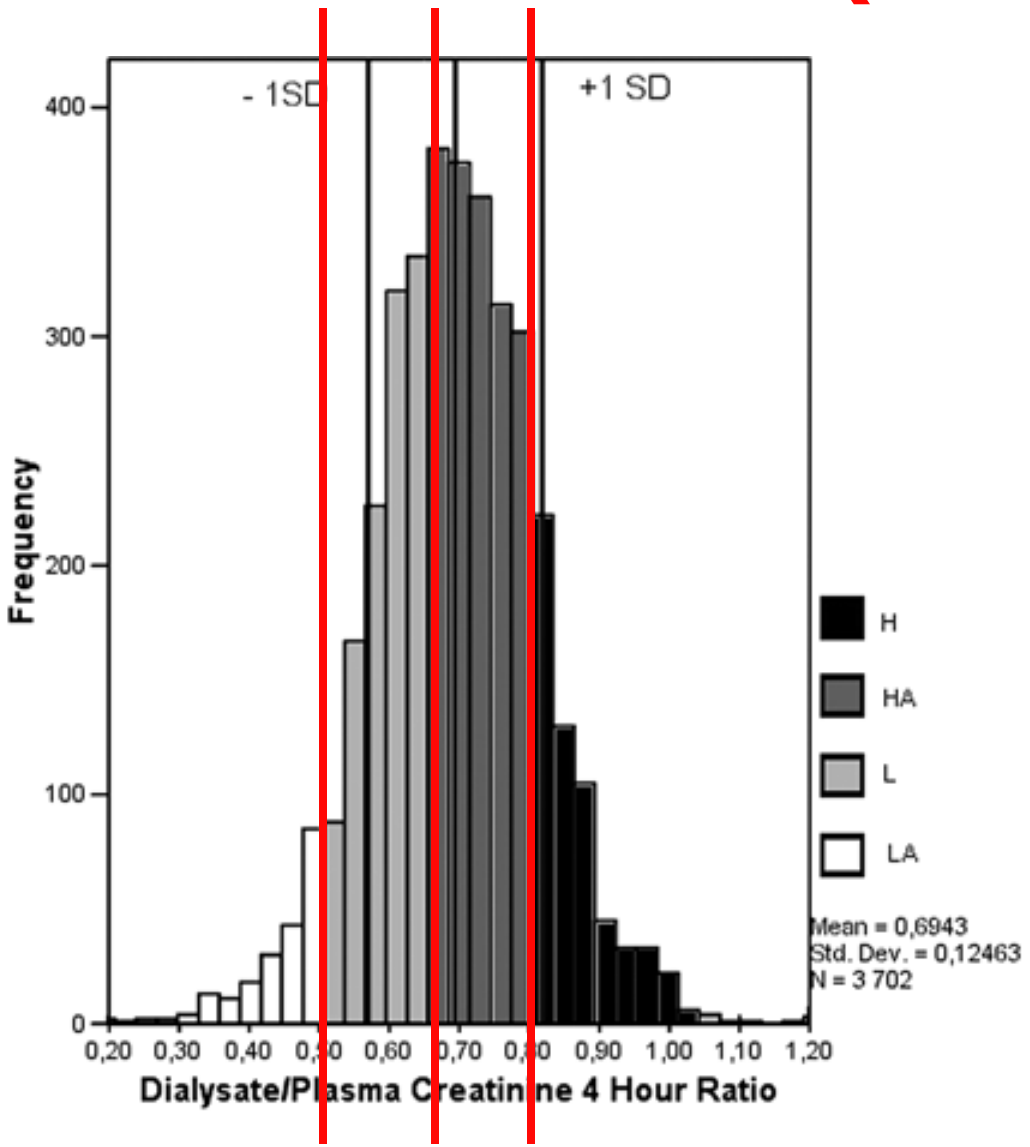


Twardowski et al: PDI 7: 138-147, 1987

2.27% or 3.86% glucose?

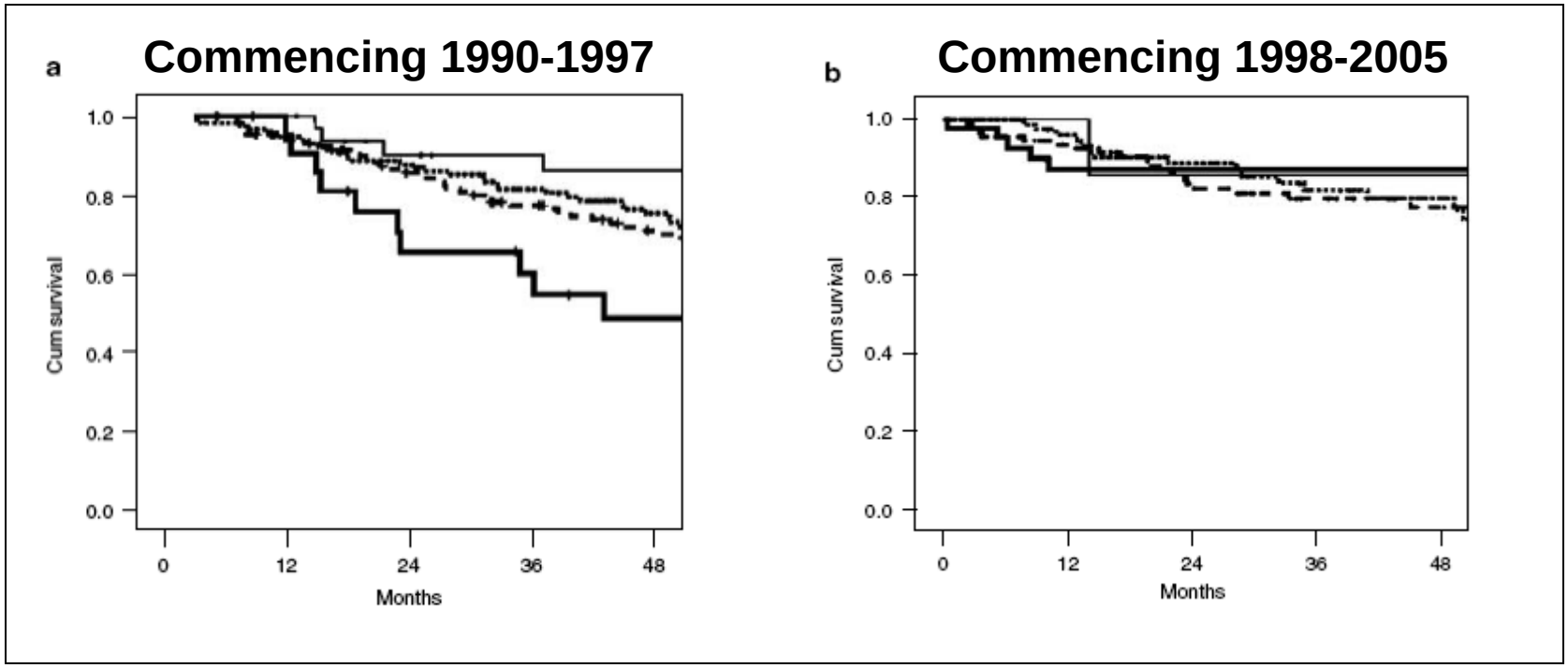
- **2.27% glucose**
  - Normal values better established
  - Less impact of convective transport than with 3.86% solution
- **3.86% glucose**
  - Higher UF-rate gives better estimation of fluid transport
  - Dialysate sodium can be used as an additional parameter (transcellular water transport)
  - Therefore preferred for analysis of UF capacity failure, defined as a UF <400 ml/4 hours

PET data (n=3702)



Rumpsfeld et al, JASN 17:271-278, 2006

Outcome in fast transporters is improved during recent years

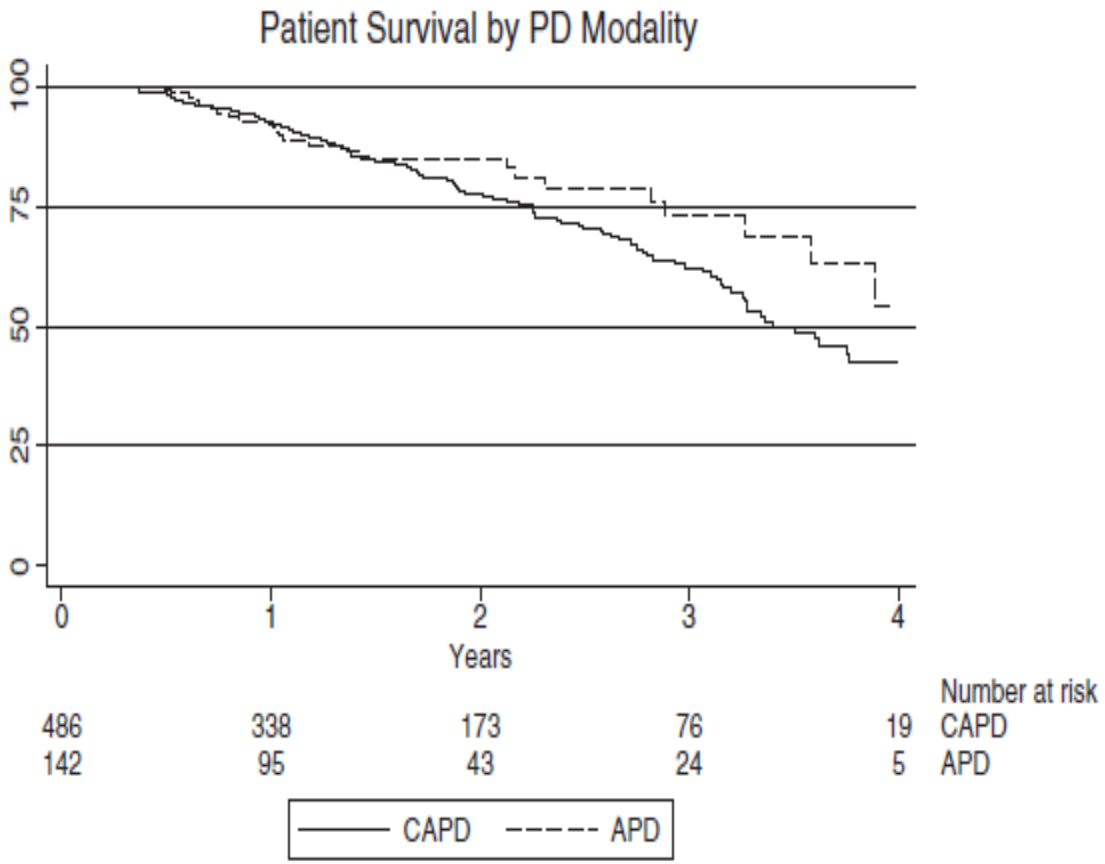


Davies SJ, Kidney Int 70: S76-S83, 2006

Survival fast transporters APD vs CAPD

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

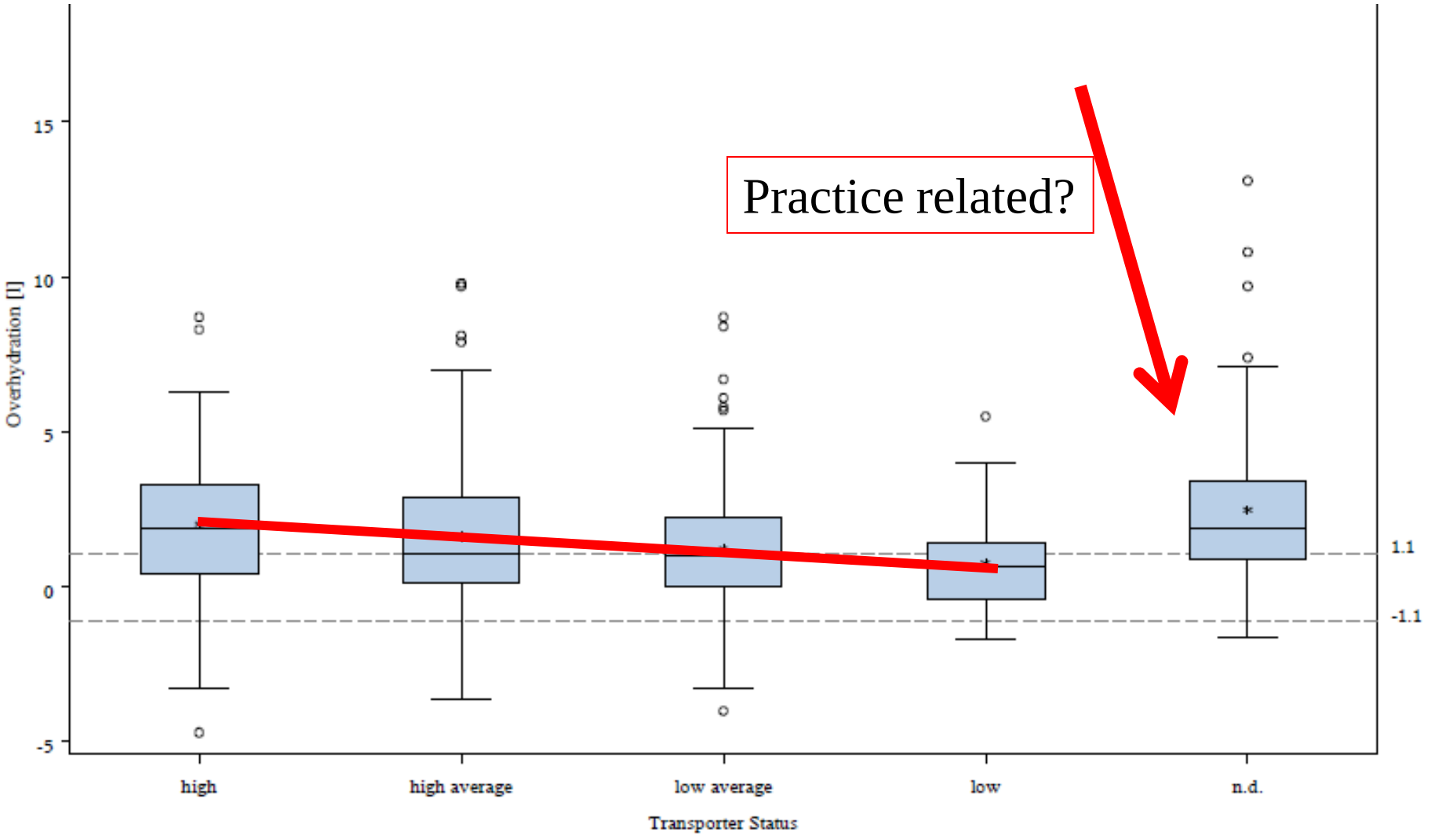
	Univariate analysis			Multivariate analysis		
Transport group	HR	95% CI	*P*	HR	95% CI	*P*
High (n = 628)	0.57	0.35–0.94	0.03	0.56	0.35–0.87	0.01
High-average (n = 1936)	0.98	0.72–1.34	0.9	1.08	0.81–1.45	0.6
Low-average (n = 1146)	0.70	0.46–1.07	0.1	0.98	0.66–1.45	0.9
Low (n = 196)	2.21	1.24–3.93	0.007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



APD survival superior in fast transporters, but CAPD better in slow transporters

Johnson et al, NDT, 2010

Relation transport status and overhydration



Van Biesen et al for the EuroBCM study group, Plos One, 2011

1.2 An evaluation of peritoneal membrane characteristics should routinely be repeated at least once per year or when new clinical problems (overhydration, malnutrition, metabolic disturbances) are noticed.

1.3 PD prescriptions should be optimized according to Table 1 in function of the results of the peritoneal membrane characteristics.

Van Biesen et al for ERBP workgroup

Table 1. Peritoneal membrane transport types and their consequences for clinical management

Transport type	Properties	Recommendations
Fast transporter	Fast, hyperbolic, equilibration of creatinine, typically with a D/P_{creat} >0.80 after 4 h	Short dwells, preferably shorter than 180 min
	Fast dissipation of glucose from the peritoneal cavity, with negative ultrafiltration in dwells with 1.36% glucose longer than 180 min	Icodextrin to be considered for longest dwell, unless sufficient residual diuresis
	Limited sodium sieving, with 3.86% PET and small (<5 mmol/l) delta D_{sodium} (difference between the D_{sodium} at start and after 1 h)	Check inflammatory status (peritoneal protein loss). When negative, check transport status using larger fill volumes
Average transporter	Moderately fast equilibration of creatinine, with a steeper slope in the beginning than at the end of the dwell	Too short (<120 min) and too long dwells (>300 min) should be avoided, except for one exchange/day (the 'long dwell')
	Moderately fast disappearance of osmotic agent. Negative ultrafiltration only in too long dwells (>240 min)	
Slow transporter	Slow, semi-linear equilibration of creatinine, typically with a D/P_{creat} <0.55–0.60 after 4 h	Long dwells, preferably longer than 240 min
	Sustained ultrafiltration even in dwells longer than 240 min	Use larger volumes rather than more dwells
	Important sodium sieving, with 3.86%-PET and substantial delta D_{sodium} (>5 mmol/l) after 1 h (the peak of delta D_{sodium} could occur later in the dwell)	Icodextrin probably not necessary for longest dwell Be aware of sodium sieving when using dwells shorter than 180 min

- **2.1 There is insufficient evidence to prefer one test of peritoneal membrane characteristics over another for clinical prescription. However, some tests may render specific information not provided by the classical peritoneal equilibration test (PET) test. The type of test to be used is thus dependent on the type of information one wants to obtain and the question one wishes to be answered.**
- **2.2 As evidence is scarce, ERBP strongly recommends and supports epidemiological follow-up of the relation between peritoneal membrane characteristics, patient characteristics, treatment parameters and outcome.**

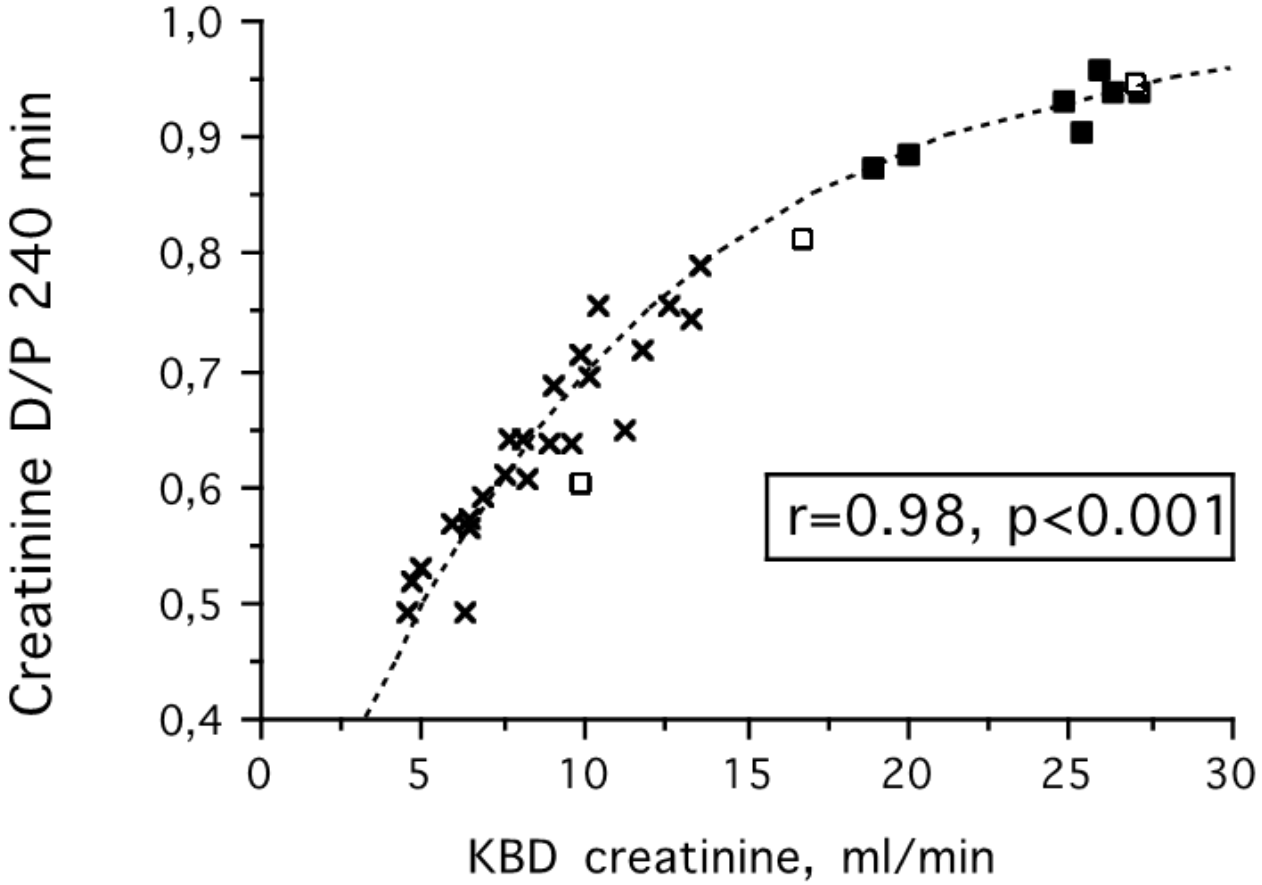
Diffusive transport

- Driven by the concentration difference, and is proportional to the diffusive mass transport coefficient (K_{BD}) for the particular solute:

  $M = K_{BD}(C_B - C_D)$
- D/P is strongly related to K_{BD}
- K_{BD} is often called ”mass transfer coefficient”

  K_{BD} = MTC = MTAC = pMTAC = KoA = PS
- K_{BD} is directly related to a particular solutes diffusion constant and A_0/Δ_x (the urestricted pore area over unit diffusion distance)

D/P vs. K_{BD}



Heimbürger et al, Nephrol Dial Transplant 9: 47-59, 1994

There are many similar tests

- Accelerated peritoneal examination (APEX)
- Peritoneal equilibration test (PET)
- Mini-PET (Fast-fast PET)
- Standard permeability assessment (SPA)
- Peritoneal function test (PFT)
- Personal dialysis capacity test (PDC)
- Which one to use depends on what you want to assess

2.3 In scientific publications, one should avoid reporting the results of PET only as transport categories.

Expression of data as exact figures of D/P (dialysate over plasma) ratios is recommended.

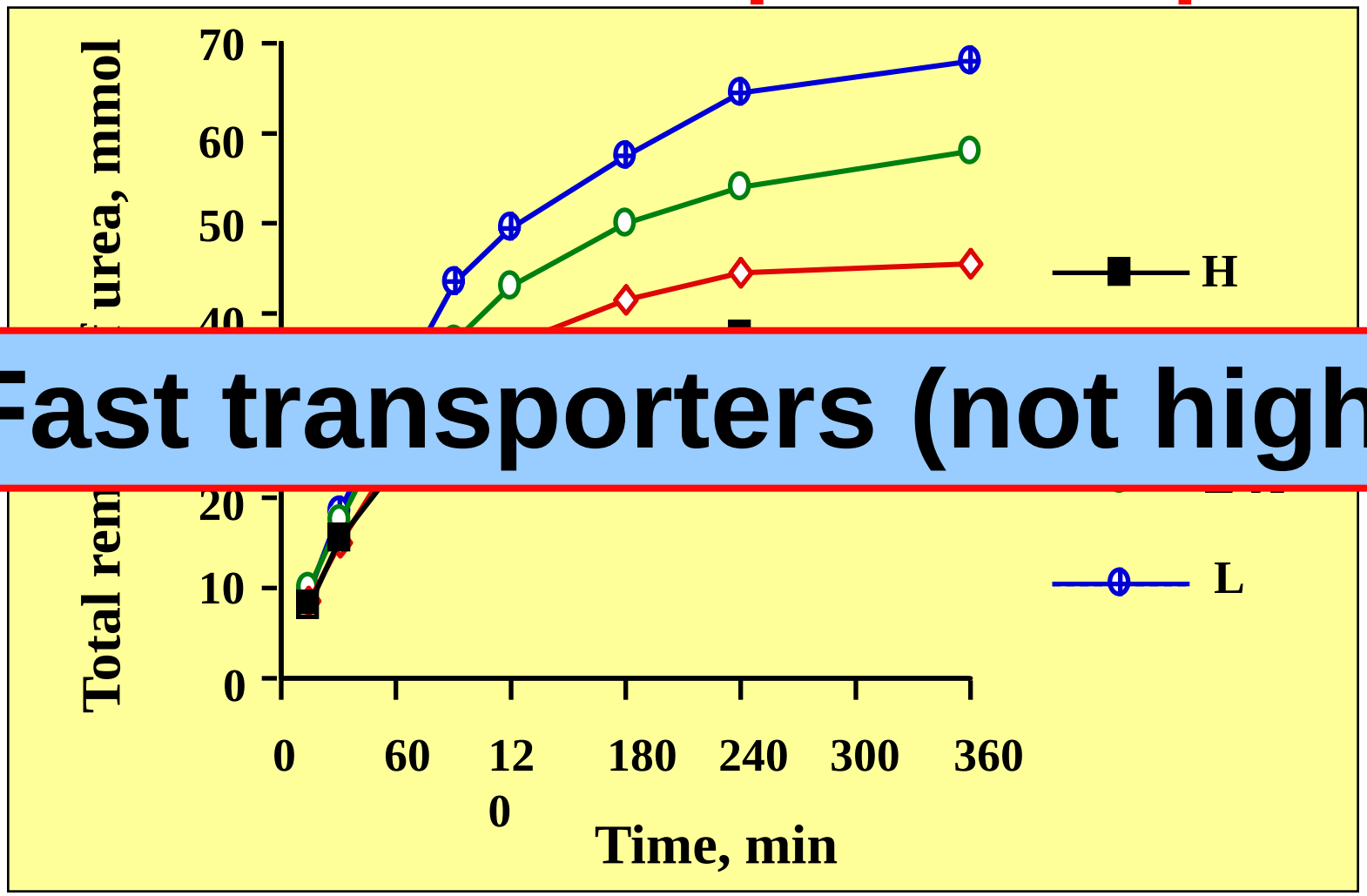
For clinical use and prescription management, the current terminology should be replaced by the more relevant descriptions ‘fast’, ‘average’ and ‘slow’, as these terms more intuitively relate to the optimal dwell length.

Van Biesen et al for ERBP workgroup

Fast transporters

- Fast transport of small solutes due to increased surface area (not a test of permeability permeability)
- Low ultrafiltration due to rapid glucose absorption
- Lower urea removal due to low ultrafiltration (if PD prescription not modified)
- Likely different types of fast transporter:
  - Early inherent (large surface area, comorbidity)
  - Late acquired (with time on PD)
  - Peritonitis

Total Removal of Urea in Different Transport Groups



Fast transporters (not high)

Wang et al. Nephrol Dial Transplant 1998: 13: 1242-49

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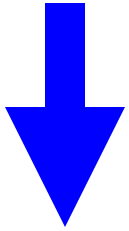
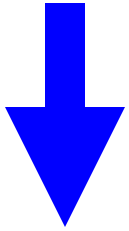
Peritoneal Equilibration Test

Peritoneal Equilibration Test



Advanced Kinetic
- Simulations



Regimen
Optimization

Peritoneal Equilibration Test

Peritoneal Equilibration Test

Advanced Kinetic - Simulations

Regimen Optimization

Transport parameters:

(MM=membrane model)

(3pM= three pore model)

MTAC – diffusive mass transport parameter (MM)

A0/dx – pore area over pore length parameter (3pM)

LpA – hydraulic permeability (3pM)

σ – reflection coefficient (3pM)

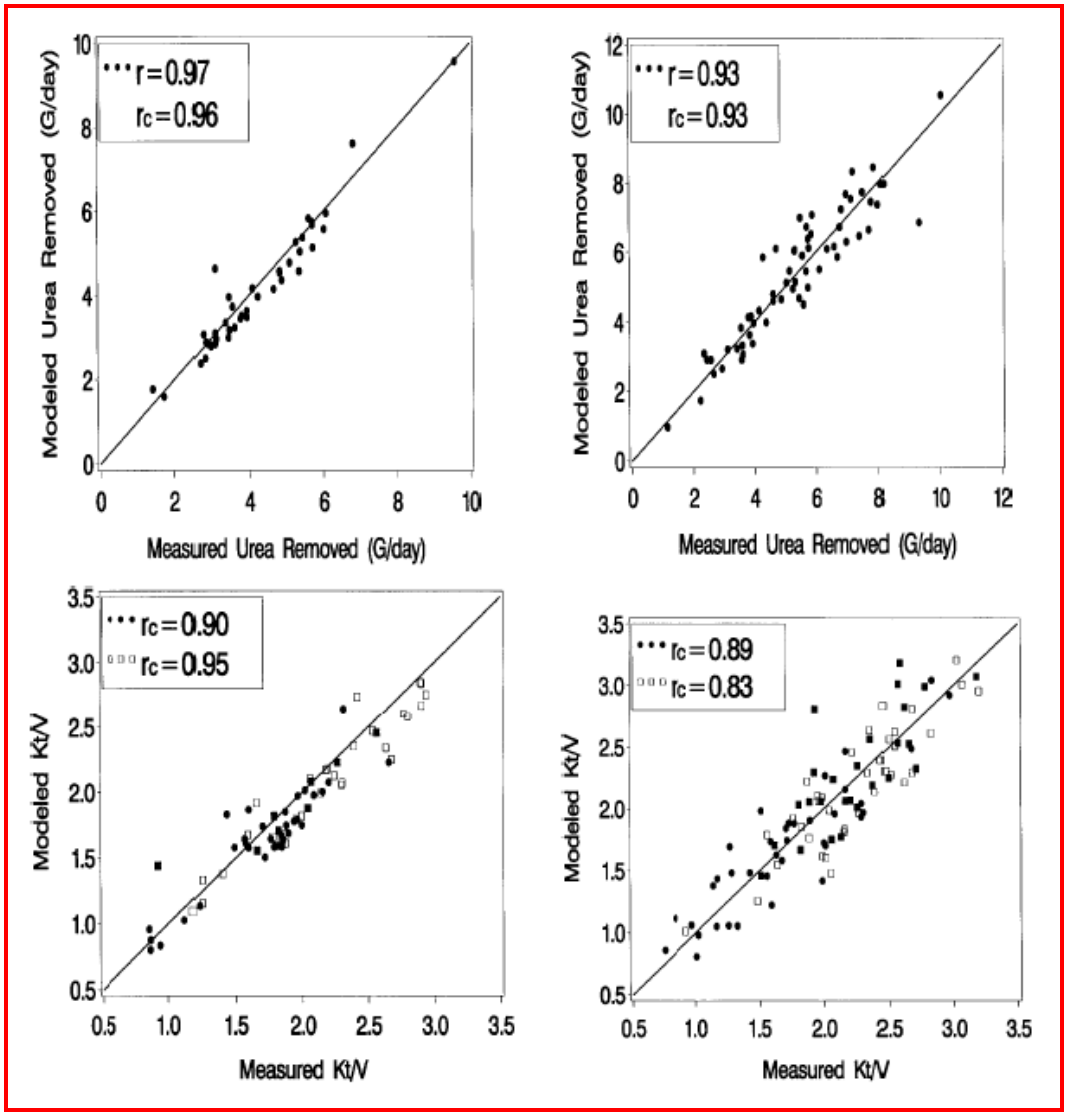
QL – fluid absorption (MM+3pM)

S – sieving coefficient (MM)

CAPD APD

Urea removal

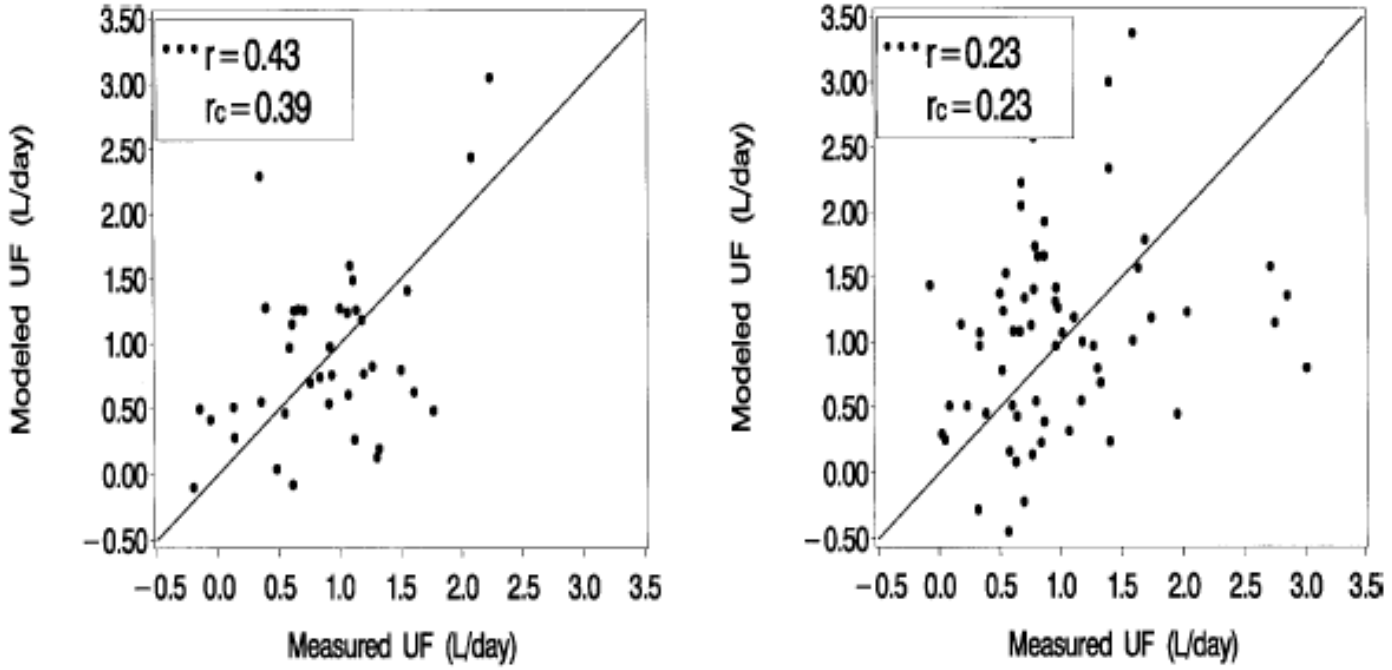
Kt/V urea



Vonesh et al PDI 19:556-571, 1999

CAPD APD

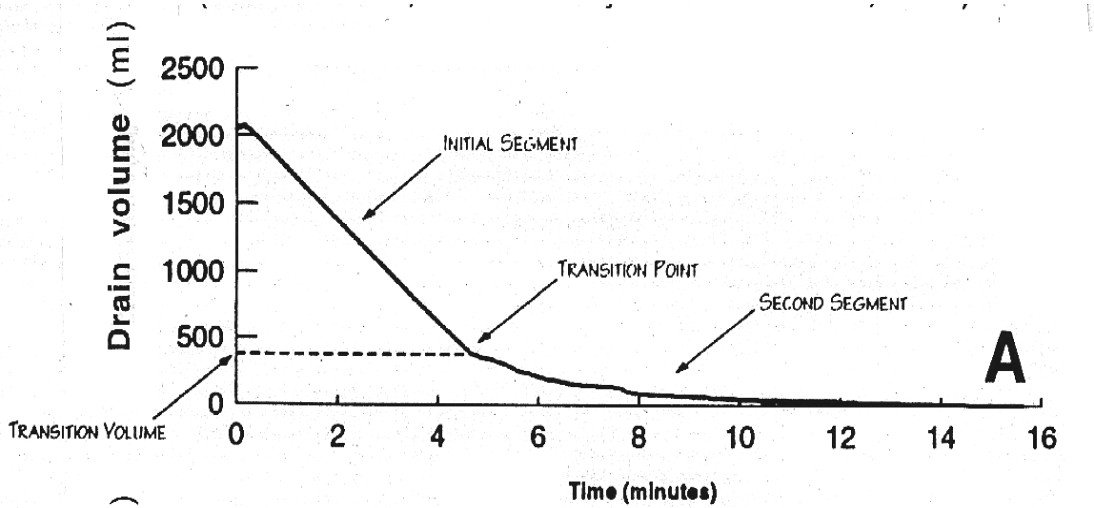
UF

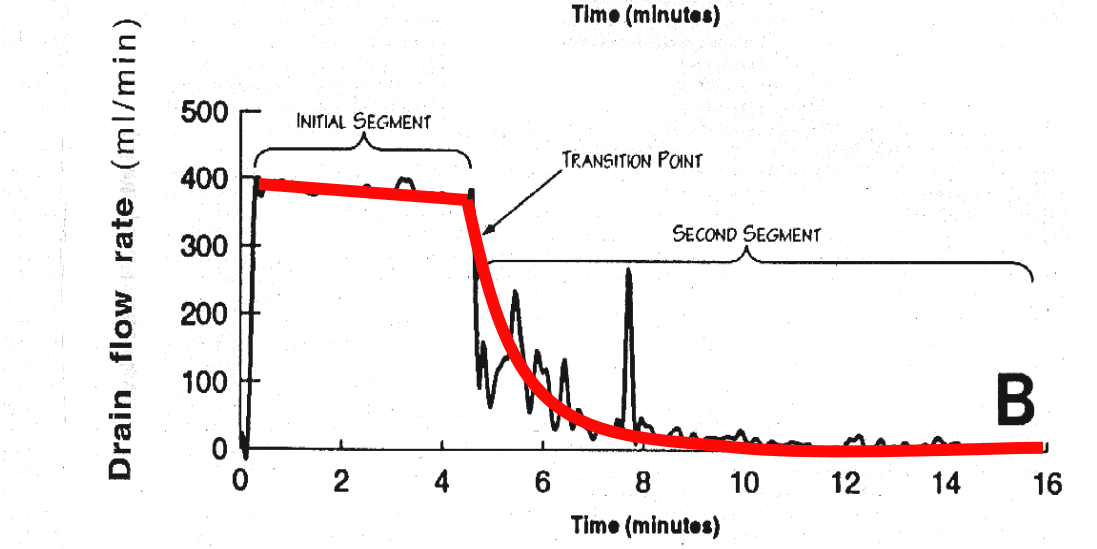


Problem: Few volume data points (only 4h and overnight) makes the calculations sensitive to variations in the intraperitoneal residual volume.

Vonesh et al PDI 19:556-571, 1999

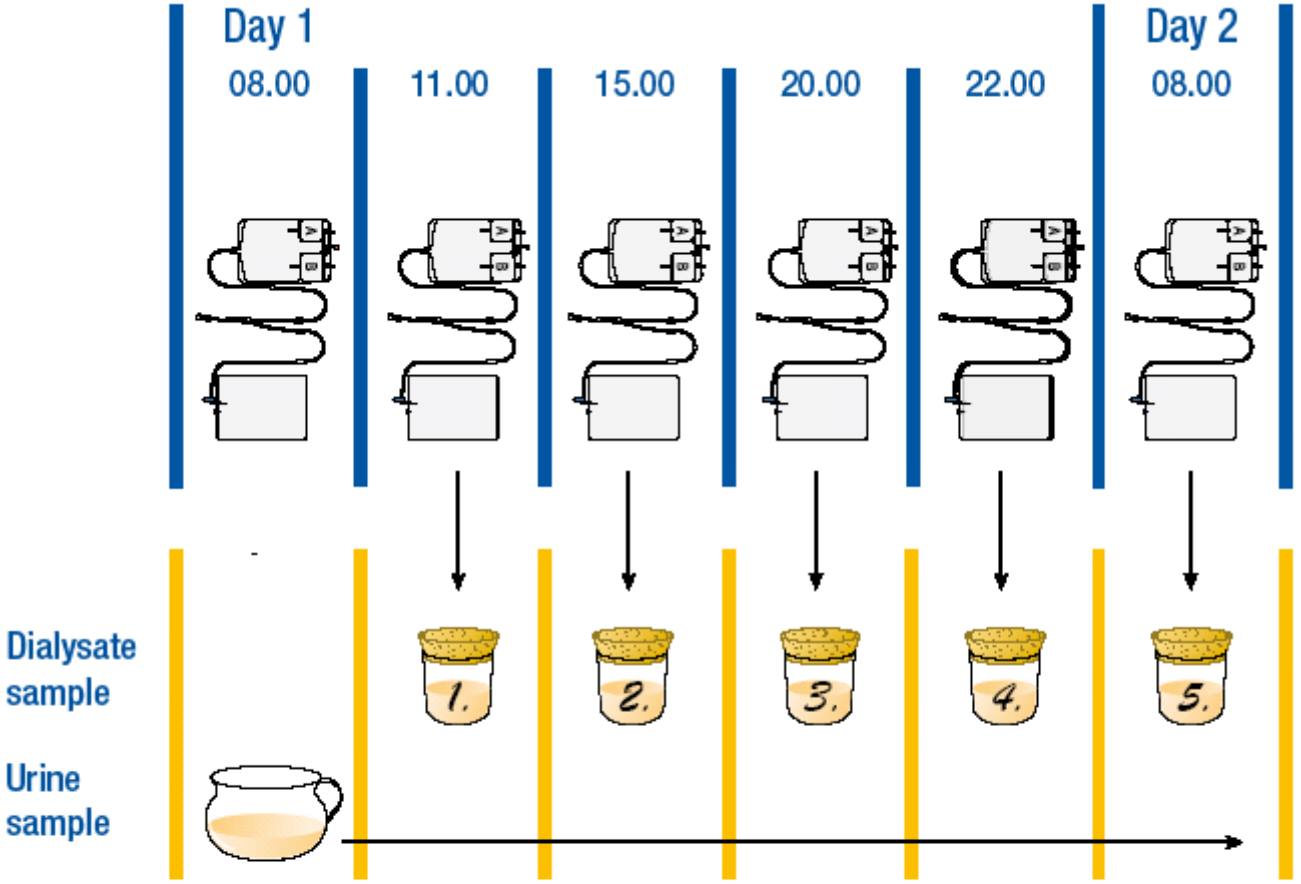
Catheter flow rate





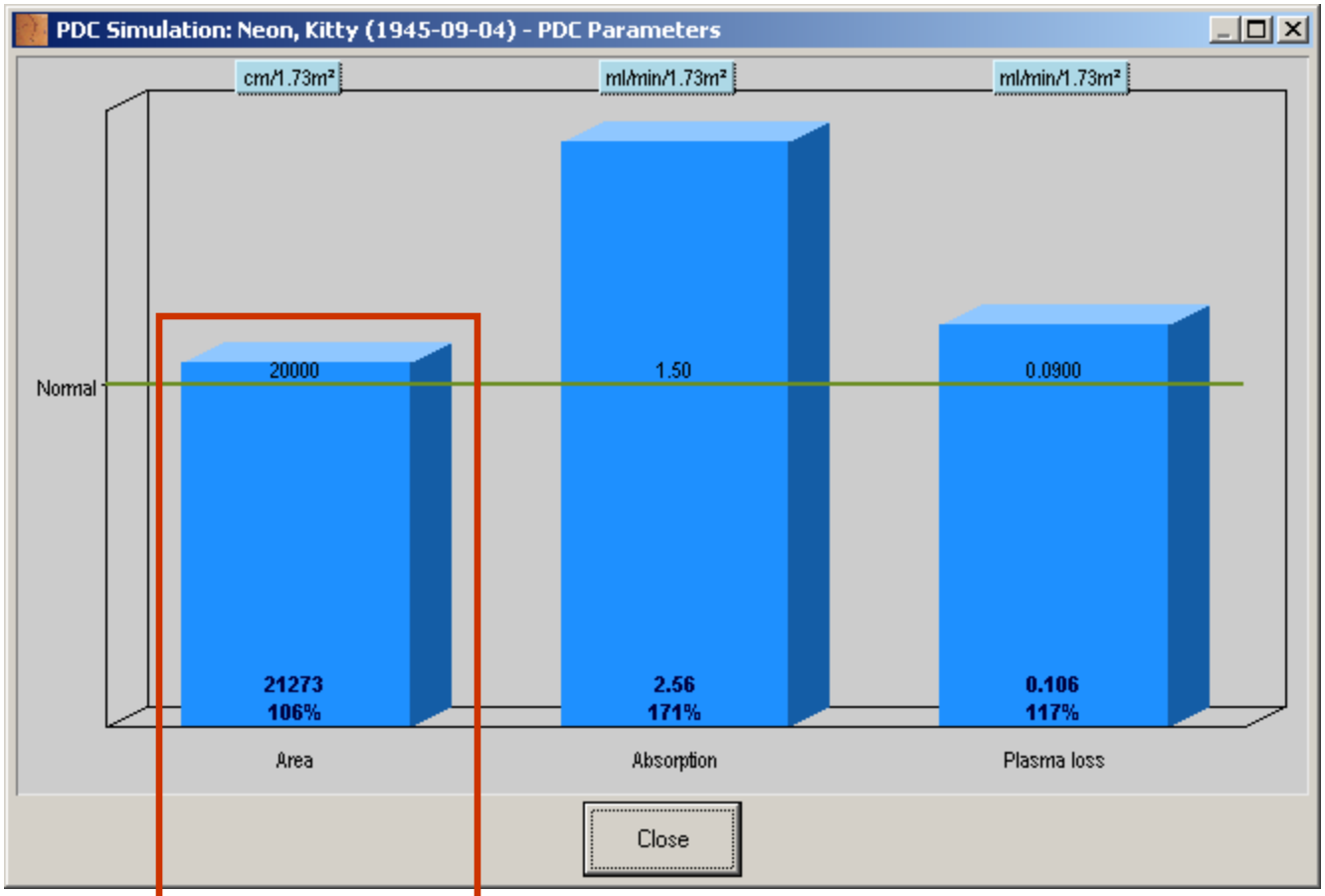
Brandes et al, AJKD 25: 603-610, 1995

The PDC test



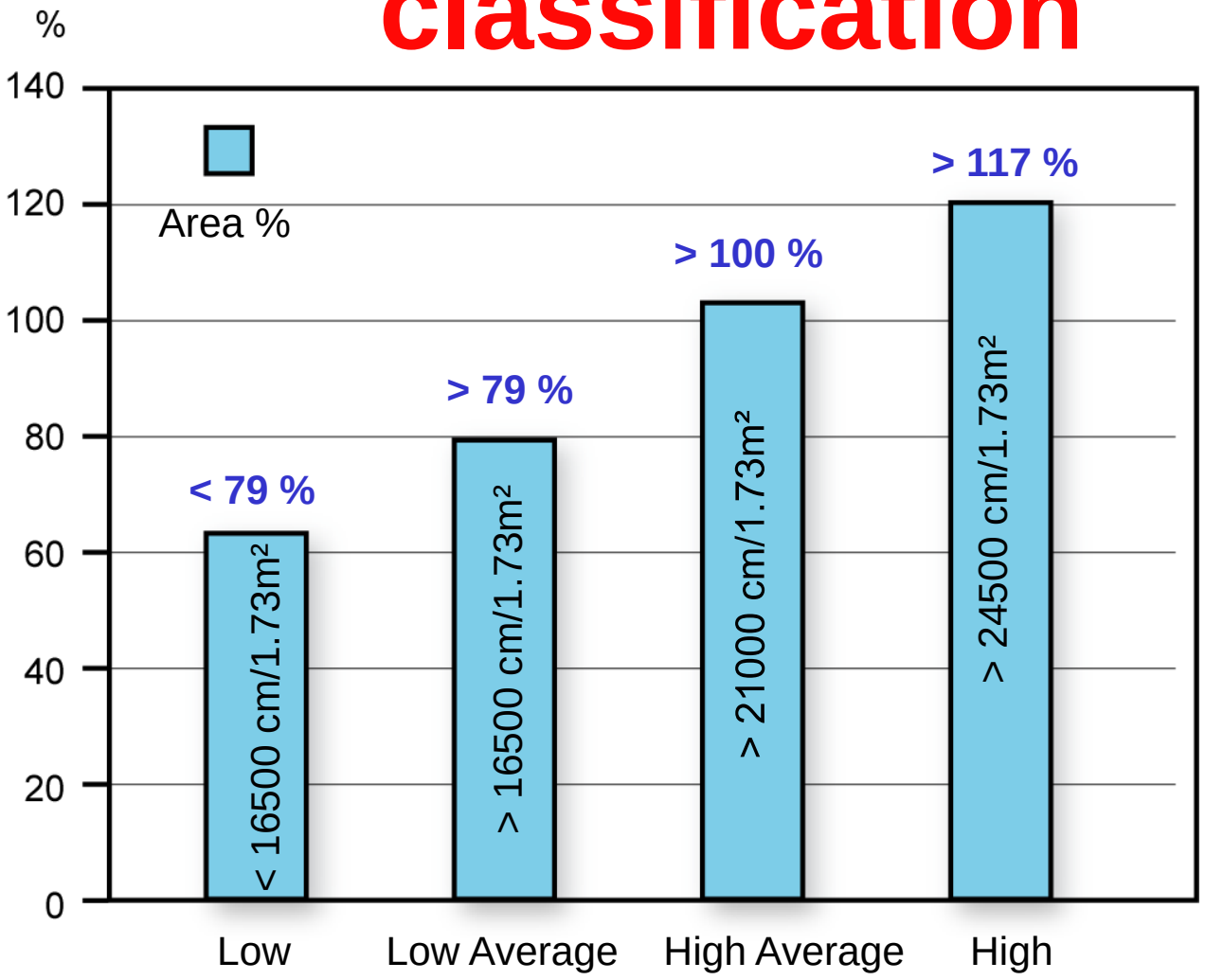
: one blood sample at day 1 (08.00)
: **or** one blood sample at day 2 (08.00)
: **or** one blood sample on day 1 **and** day 2

The PDC parameters – Results of the PDC test

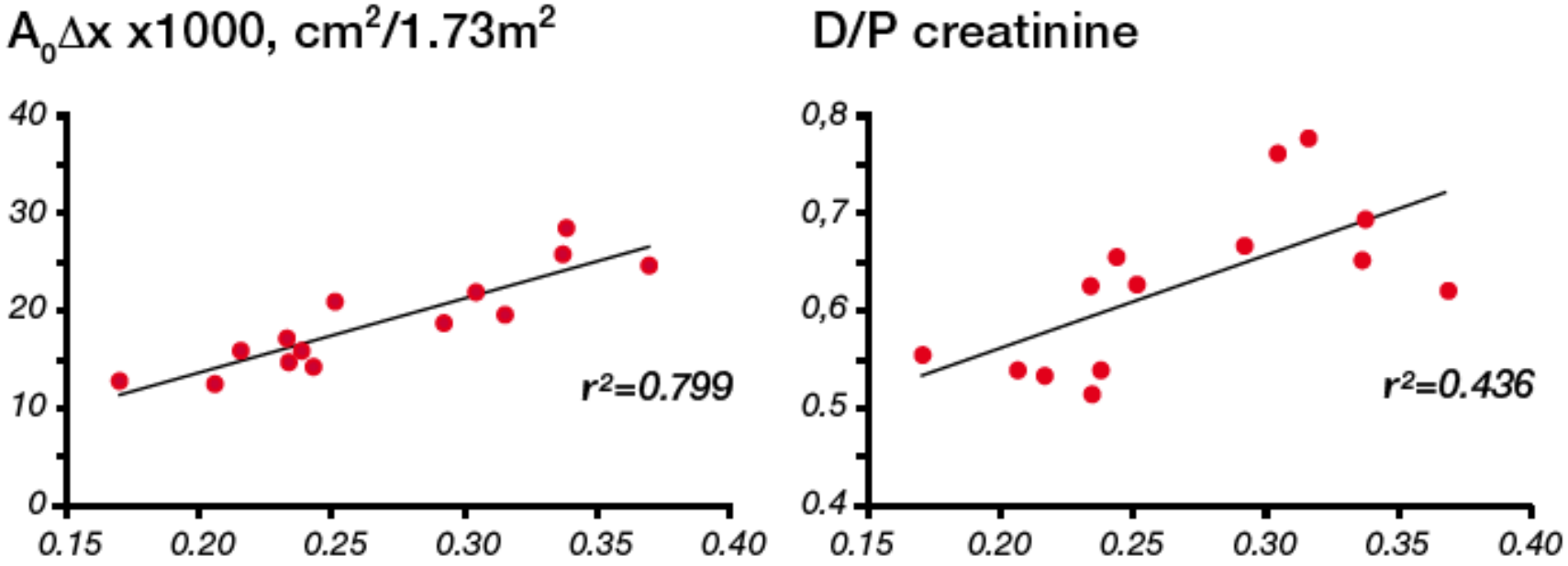


Area parameter

Area parameter vs PET classification



PDC better than PET for evaluation of diffusive transport

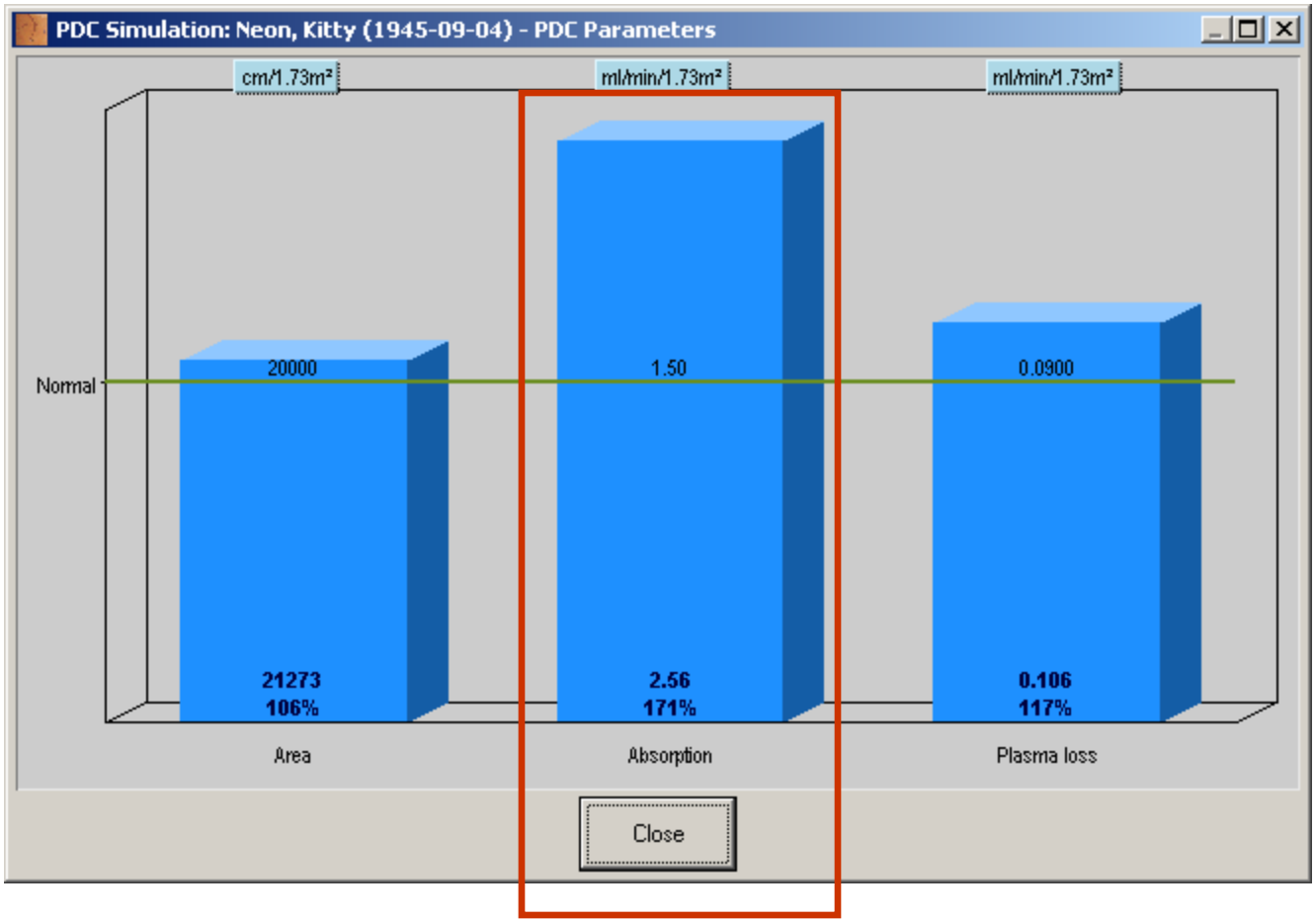


Relative plasma apprearance rate of iohexol after IP administration

Johnson et al, KI 2000

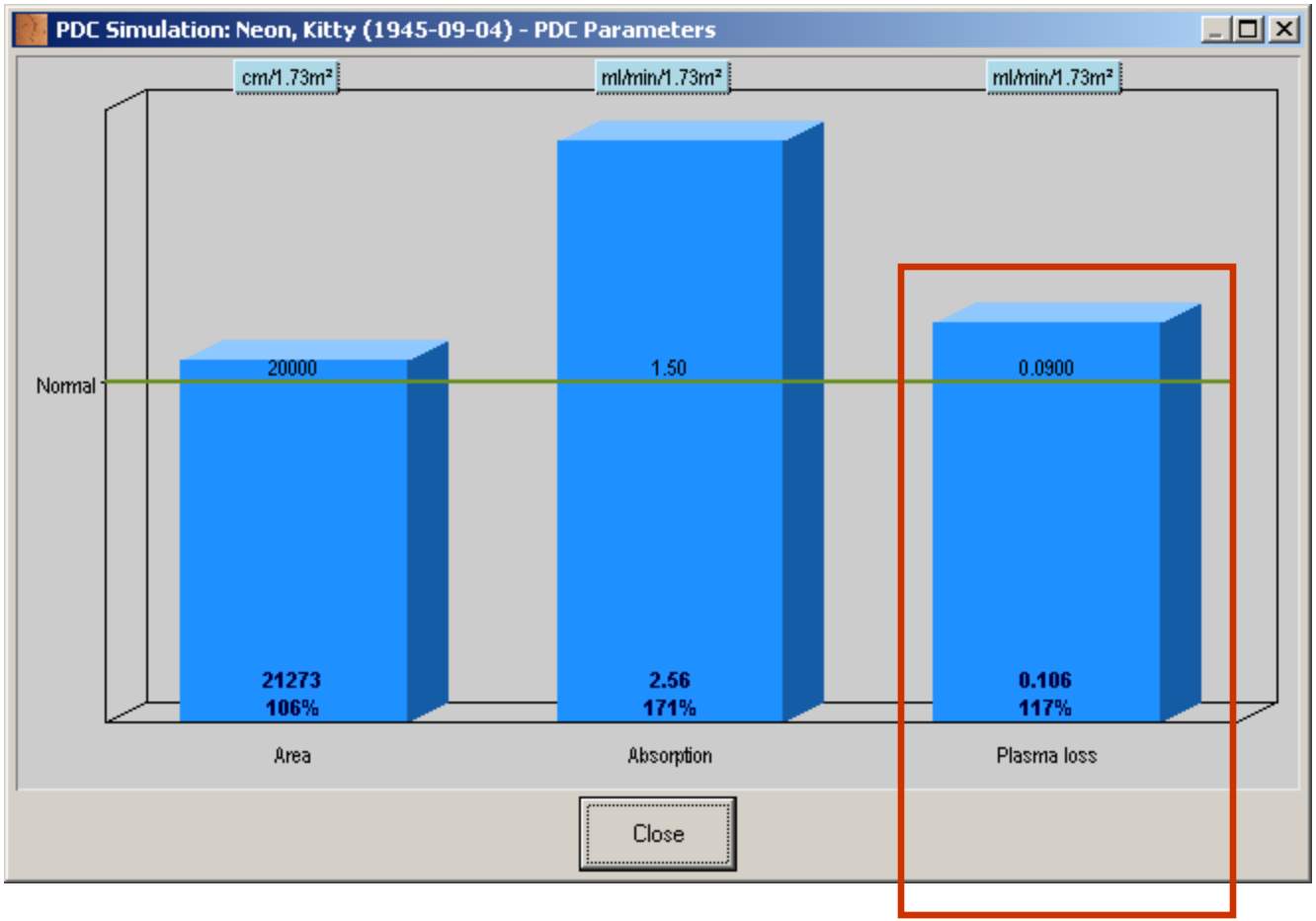
The PDC area parameter is highly correlated to iohexol uptake - PET is not

The PDC parameters – Results of the PDC test



Absorption

The PDC parameters – Results of the PDC test



Plasma Loss

PDC

- Useful test to assess basic transport parameters according to the three-pore model
- Can be used to simulate therapy and therapy optimization
- Seems to be a little more reliable as regards prediction of solute transport and ultrafiltration as compared to the PET

- **2.4 D/P_{urea} shows far less variability between patients than D/P of larger molecules. As such, when formal evaluation of the peritoneal membrane characteristics is required, the use of D/P_{creat} should be preferred to obtain better characterization of the small-solute transport characteristics of the membrane.**
- **2.5 When applying tests of peritoneal membrane characteristics, some methodological caveats should be considered.**

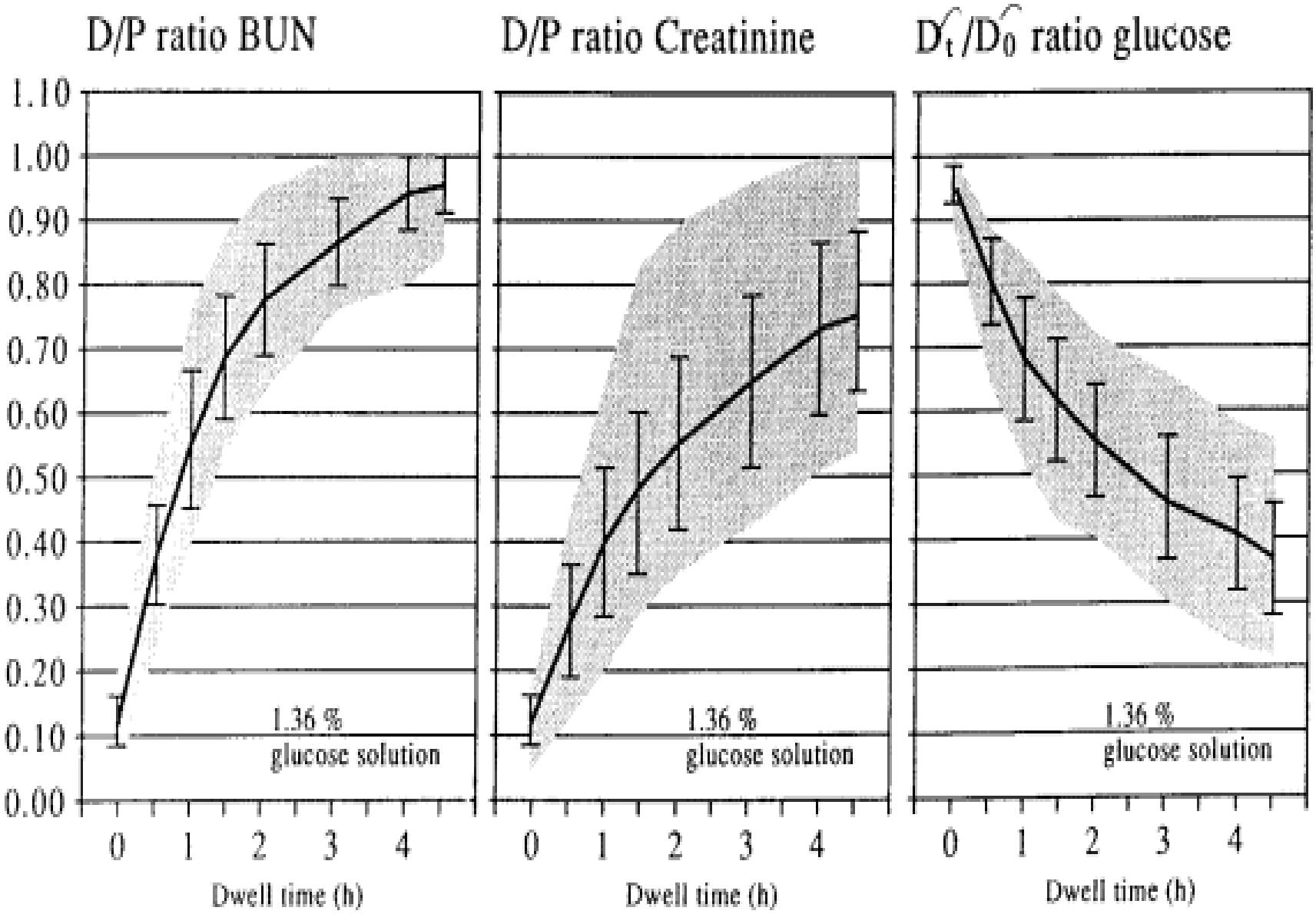


FIGURE 1 Equilibration test in 23 CAPD patients at the beginning of treatment.

Methodological caveats

- **Dialysate creatinine:** Note interference with glucose if the Jaffe method is used for creatinine measurement
- **Dialysate sodium removal and glucose absorption:** Measure Na with flame photometry or indirect ion-selective electrode
- **Net ultrafiltration sodium removal and glucose absorption:** Calculated from mass balance; note the overfill of the bags and the weight of the plastic

2.6 Peritoneal membrane ultrafiltration failure

- **Peritoneal membrane ultrafiltration failure is defined as a drained volume after a 4-h dwell of <2100 ml with a 2.27% glucose solution or one of <2400 ml with a 3.86% glucose solution, respectively (International Society of Peritoneal Dialysis ISPD guideline).**
- **The (theoretical) condition 'ultrafiltration failure' should be distinguished from the (clinical) condition 'overhydration'.**
- **Clinical overhydration is the net result of the volume balance of the patient and, as such, is influenced not only by peritoneal ultrafiltration capacity but also by other factors, such as residual urine production and dietary salt and fluid intake.**

Ultrafiltration Failure (UFF)

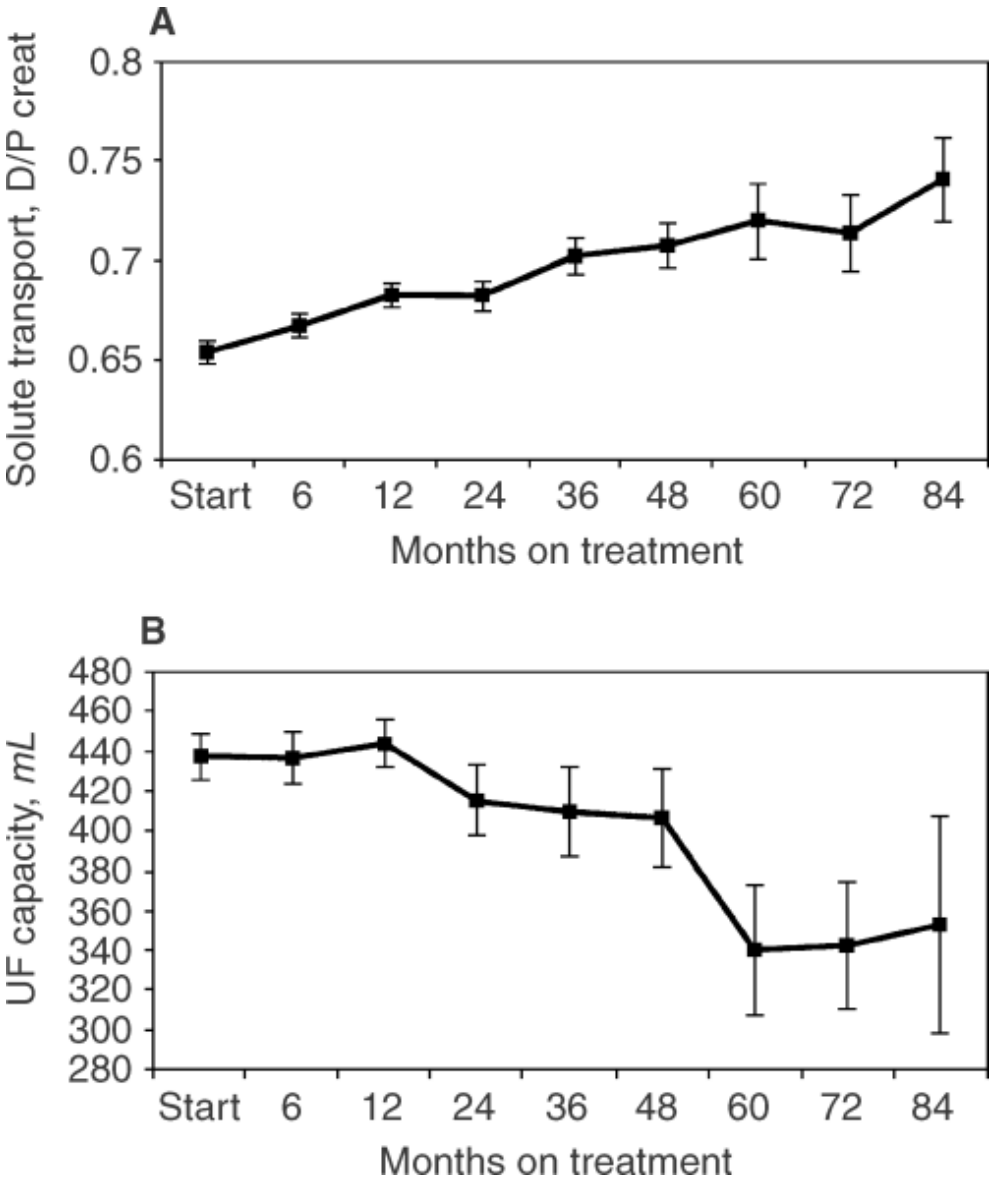
UF volume less than 400 ml in 4 h

for a 4 % (3.86 %) glucose solution

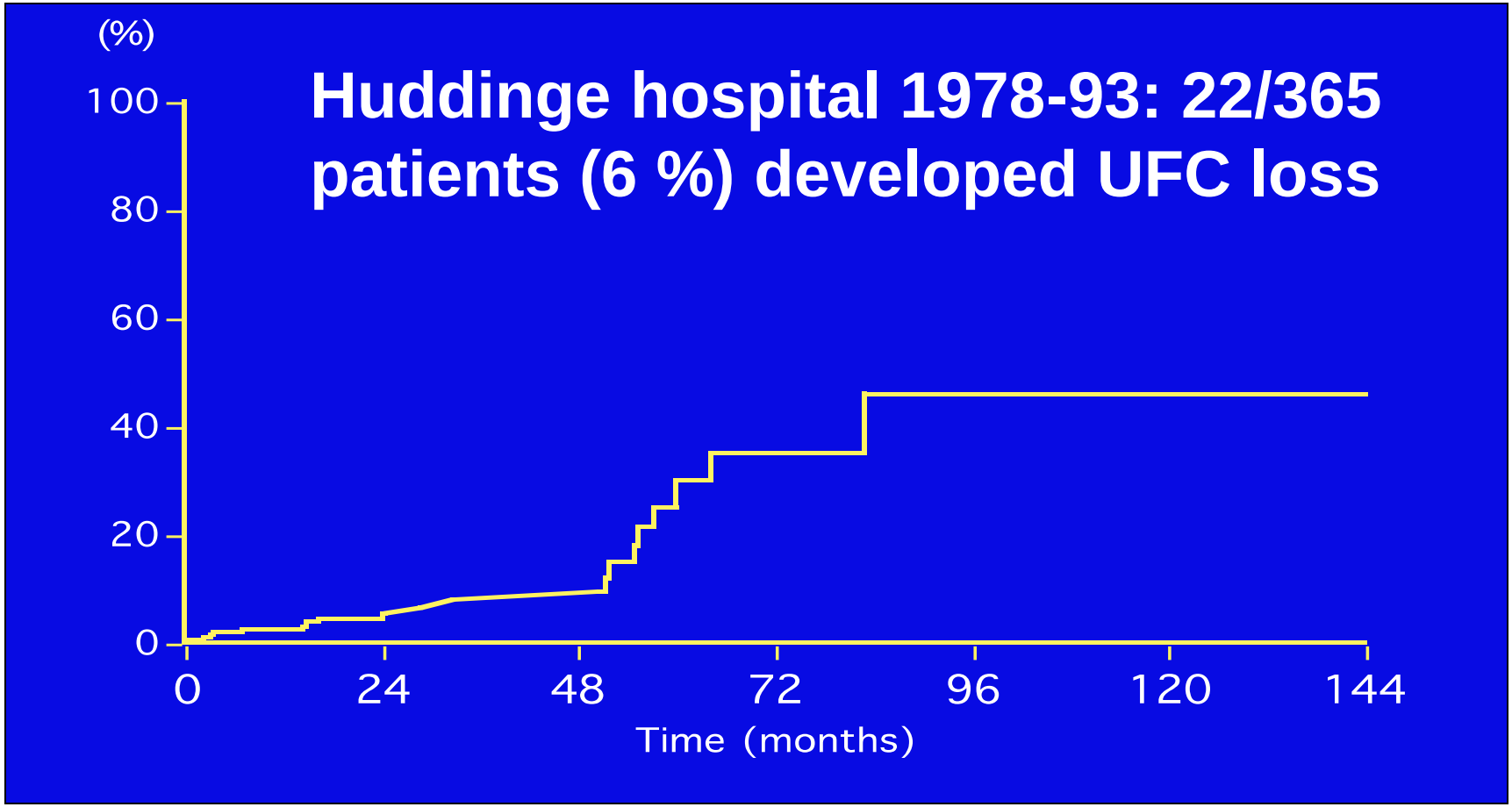
ISPD guidelines

Changes in peritoneal transport with time

Davies SJ, Kidney Int 66:2437-45, 2004



Risk of UF capacity loss vs. time



Heimbürger et al. Perit Dial Int 19 (Suppl 2): S83-S90, 1999

Different transport patterns in patients with loss of UFC

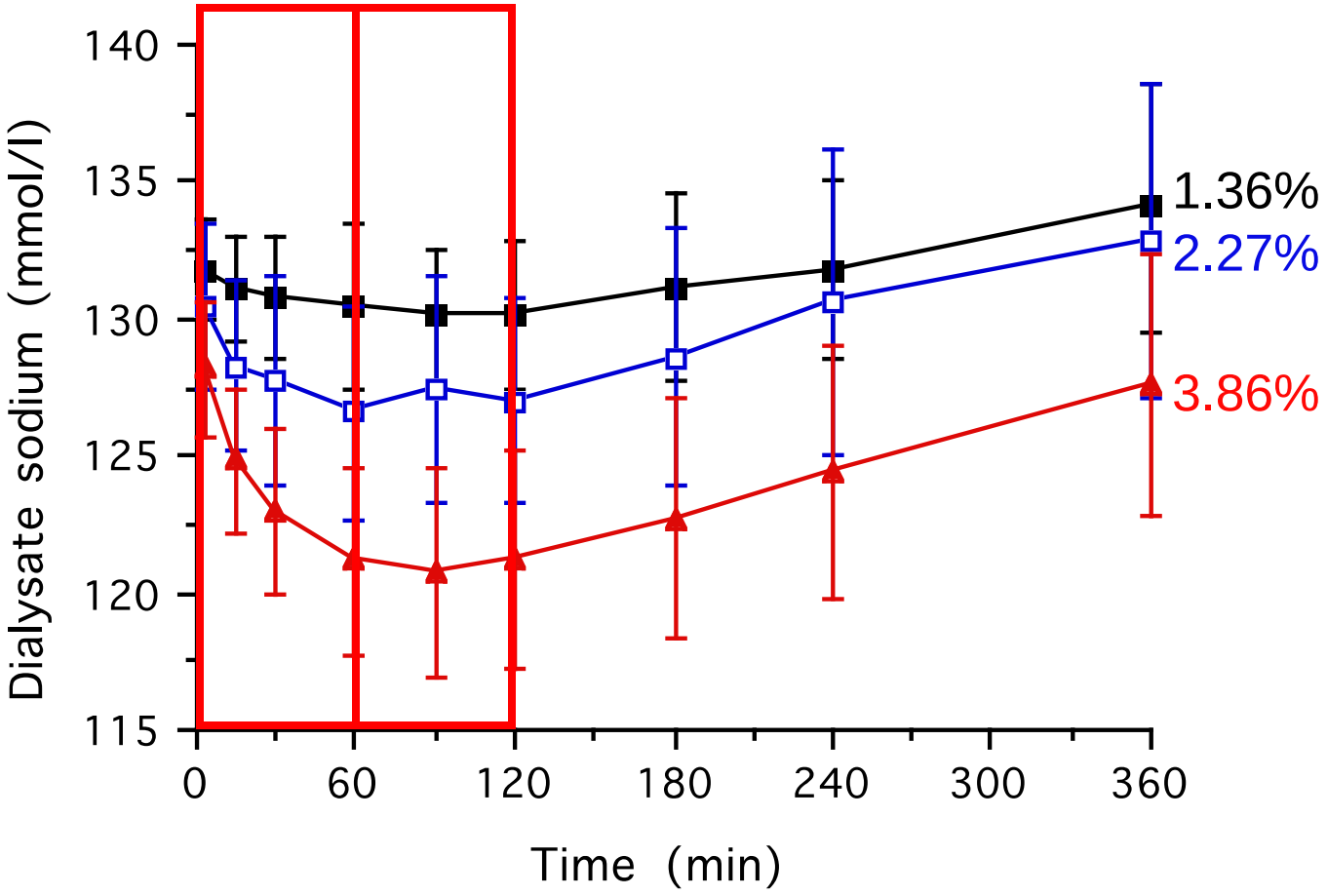
- **Increased diffusive transport *(common)***
  - **Seen in about 80% of patients witn poor UF**
- **Reduced osmotic conductance *(common)***
- **Loss of peritoneal surface area *(extremely rare)***
- **Increased peritoneal fluid absorption *(rare)***

Combinations are common

Decrease of sodium during the initial 90 min of a dwell

- When hypertonic glucose solution is used
- Due to sieving of sodium during the initially high ultrafiltration rate
- Due to water flow through the water channels (aquaporins)
- At low ultrafiltration rate, there is only a small amount of ultrafiltrate that can dilute the dialysate and dialysate sodium will be relatively constant

D-Sodium



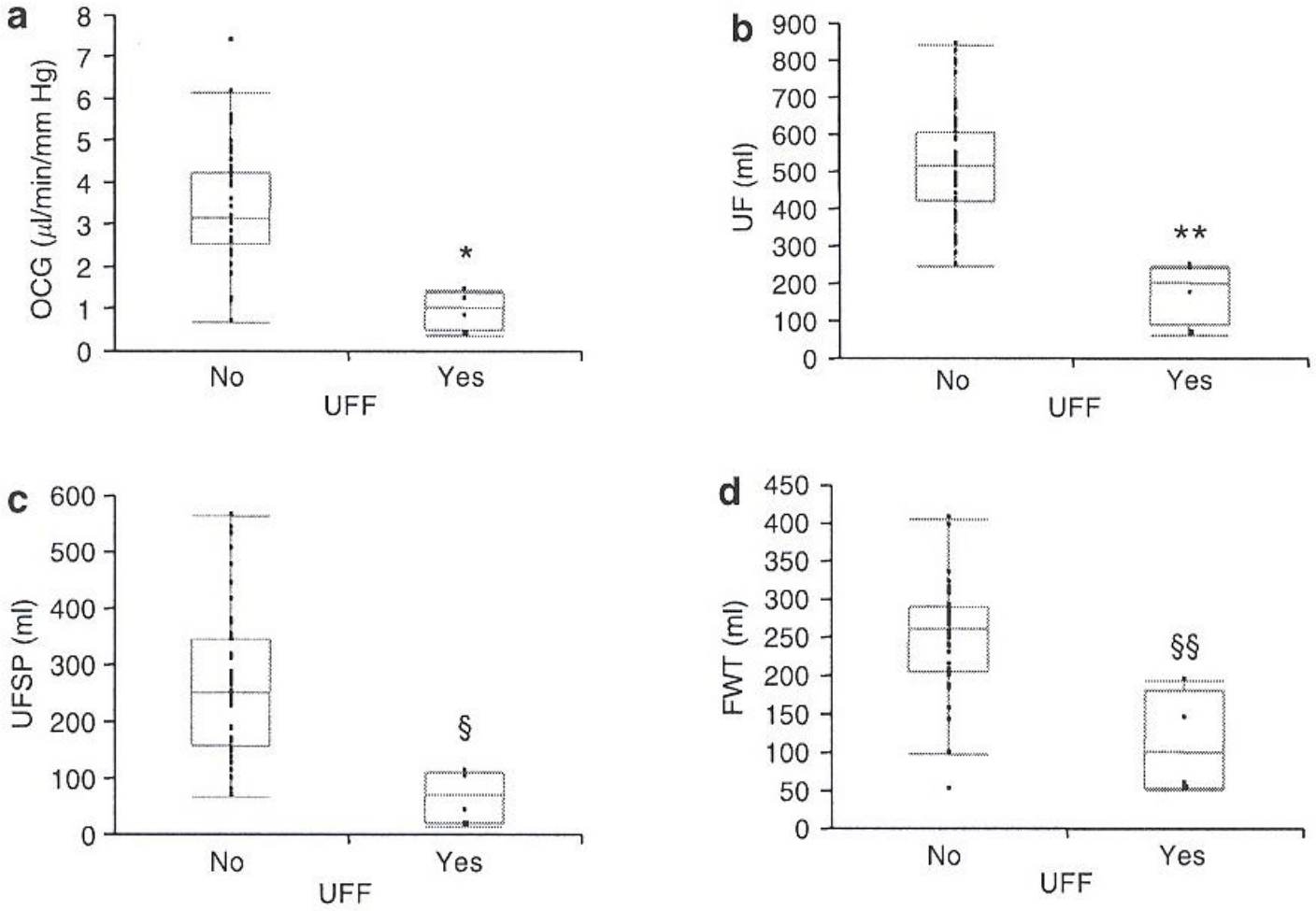
Heimbürger et al. Kidney Int 41: 1320-1332, 1992

Mini-PET, Doubble mini-PET

- **1 hour PET with hypertonic (3.86%/4.25%) glucose solution**
- **UF, D/P creatinine and sodium dip**
- **Doubble mini-PET with 1.36% and 3.86% 1 hour PETs can be used to estimate osmotic conductance for glucose**

La Milia et al NDT 17 (suppl 2):17-18, 2002
Rippe et al, PDI 25: 77-84, 2005
La Milia et al, KI 2006
La Milia et al, KI 2007: 72: 643-650

Difference of a) OCG, b) UF, c) UFSP and d) FWT between the PD patients with and without UFF during the Double Mini-PET



LaMilia et al, Kidney Int 2007;72:643-650

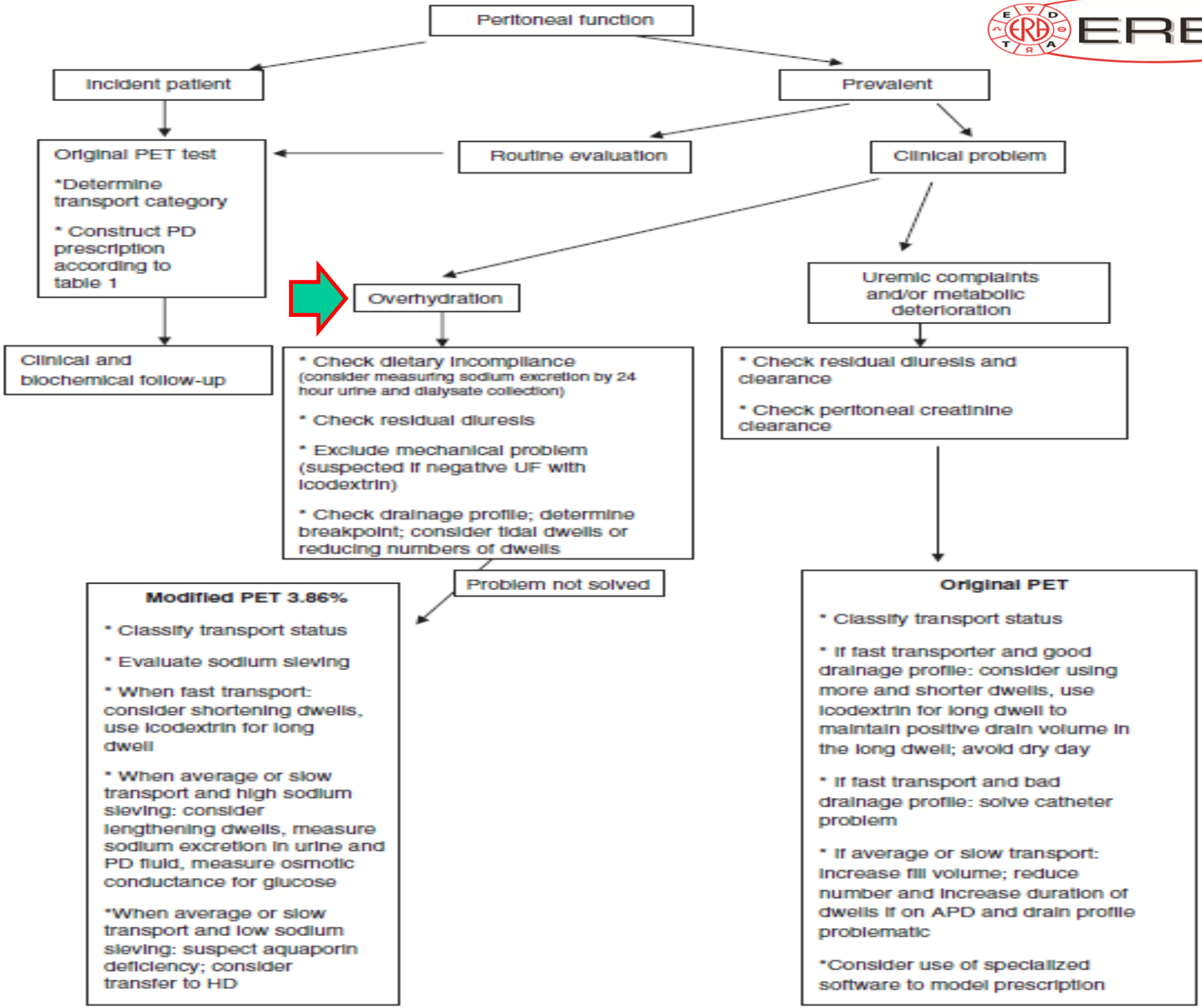


Fig. 1. Flowchart of clinical peritoneal membrane characteristics evaluation.

It dependens on what You want to assess?

- Diffusion?
- Ultrafiltration capacity?
- Free water transport?
- Fluid absorption?
- Macromolecules
- Kt/V, creat-clearance, RRF, PNA (PCR)

- PET, PDC, short PET, (CAPD 24h D/P creat)
- Short dwell 3.86%
- Short dwell 3.86% with d-Na after 1-2 h (=Mini-PET)
- Use a macromolecular tracer, (PDC)
- Albumin clearance, PDC
- 24-h collection of urine and dialysate

24-hour dialysate collection

- **Kt/V urea**
- **Weekly creatinine clearance** (note interference with glucose if the Jaffe method is used for creatinine measurement
- **Pertioneal albumin clearance**
- **Protein intake.** PNA (protein equivalent of nitrogen appearance rate = PCR) calculated from urea and protein excretion in the dialysate and urine
- **Net ultrafiltration** (note the overfill of the bags and the weight of the plastic)
- **Sodium removal and glucose absorption** (calculated from mass balance; note the overfill of the bags and the weight of the plastic). Measure Na with flame photometry or indirect ion-selective electrode
- **Diffusive transport** (D/P creatinine 24 h in CAPD)

Summary

- Peritoneal transport is a complex process
- There is no gold standard for evaluation of peritoneal transport in routine clinical practice
- Computor programmes are valuble for simulations of therapy, but remember the catheter function
- The PET is still a very useful standard test to assess the peritoneal transport charactersitics
- The PDC-test may also may be used to assess the peritoneal transport characterstics, and in some aspects may be better than the PET
- Use of hypertonic glucose (3.86%/4.25%) for the PET includining measurement of dialysate sodium after 1-2 h is recommended for the evaluation of UF capacity loss (which should be distinguished from overhydration)

Remember

- Transport (not permeability)
- Fast transporter (not high)
- Report D/P creatinine, not only transport group
- Osmotic conductance for glucose (not aquaporin function)
- Fluid absorption (not lymphatic)

ispd 2012

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9th-12th September 2012, Kuala Lumpur, Malaysia

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