ULTRAFILTRATION FAILURE

WESTERN CANADA PD DAYS

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HOME DIALYSIS

OUTLINE/OBJECTIVES

- Definition and causes of ultrafiltration failure (UFF)
- Risks associated with inadequate ultrafiltration and persistent volume overload
- Early versus late ultrafiltration failure
- How to maintain normal volume status in the face of UFF

NOT TO GET TOO PHILOSOPHICAL, BUT…

HOW DO YOU DEFINE ULTRAFILTRATION FAILURE?

- fluid removal doesn't keep up with fluid intake?
- so is "fluid overload" the same thing as ultrafiltration failure?
- some people assume that ultrafiltration failure means peritoneal membrane failure
  - not the same thing
  - peritoneal membrane failure is just one cause of ultrafiltration failure
  - example: someone ultrafilters 1000 ml/day, but takes a high salt diet and copious fluids, and is edematous
    - is this ultrafiltration "failure"?

DEFINITION: ULTRAFILTRATION FAILURE

"Ultrafiltration Failure"

→ Fluid overload (from any cause)

→ Peritoneal membrane failure

CAUSES OF FLUID OVERLOAD

- congestive heart failure
- excessive salt and water intake
- decline of residual kidney salt and water excretion
- reluctance to use more hypertonic dialysis fluid or icodextrin
- mechanical problems with the dialysis
- **true peritoneal membrane failure**

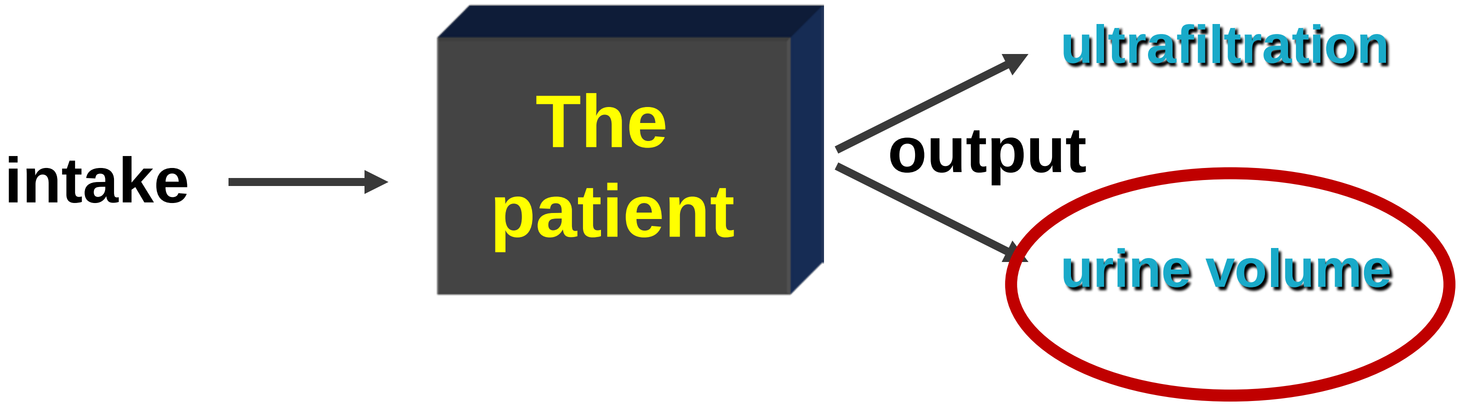
Dynamics of Fluid Balance in the Dialysis Patient

Dynamics of Fluid Balance in the Dialysis Patient

VOLUME OVERLOAD - INTAKE

- excessive salt and water consumption
  - PD has often been "advertised" as allowing a more liberal dietary intake
  - patients with high salt intake are protected from volume overload while they have residual renal function (RRF)
    - *once urine volume diminishes, patient may develop fluid overload*

Dynamics of Fluid Balance in the Dialysis Patient



The Association of Residual Renal Function, but Not Dose of PD, with Survival

Table 5. Association of Weekly Peritoneal (Kp_{cr}) and Residual Renal (Kr_{cr}) Creatinine Clearance With Odds of Death: Three Logistic Models

	Kp_{cr} Only (N = 673)			Kr_{cr} Only (N = 559)			Kpr_{cr} (N = 443)		
Variable	χ^2	*P*	OR	χ^2	*P*	OR	χ^2	*P*	OR
Age (yr)	30.2	<0.001	1.046	26.8	<0.001	1.054	13.2	<0.001	1.042
Sex (male)	1.7	NS	0.750	2.1	NS	0.691	1.7	NS	0.689
Race (nonwhite)	2.5	NS	1.512	3.8	0.050	1.833	2.8	0.092	1.881
Diabetes (no)	11	<0.001	2.023	12.0	<0.001	2.431	14.4	<0.001	2.991
Kp_{cr} (L/wk)	1	**NS**	1.009				0.5	**NS**	1.008
Kr_{cr} (mL/min)				12.7	**<0.001**	**0.876**	8.9	**0.003**	**0.887**

Peritoneal clearance

Renal clearance

Diaz-Buxo et al. Am J Kidney Dis 1999

The CANUSA Study: Renal vs Peritoneal Contribution to Mortality

Variable	Relative Mortality Risk
Peritoneal CrCl	1.00
Renal GFR(per 5L/wk)	0.88
Urine volume (per 250 ml)	0.64

Bargman J Am Soc Nephrol 2001

Preservation of Residual Renal Function

- Avoid nephrotoxic drugs
  - NSAID's and especially COX-2 inhibitors
    - most aches and pains are non-inflammatory anyway, and can be managed by acetaminophen
  - prolonged courses of aminoglycosides
  - avoid fibrates if possible *(my opinion)*

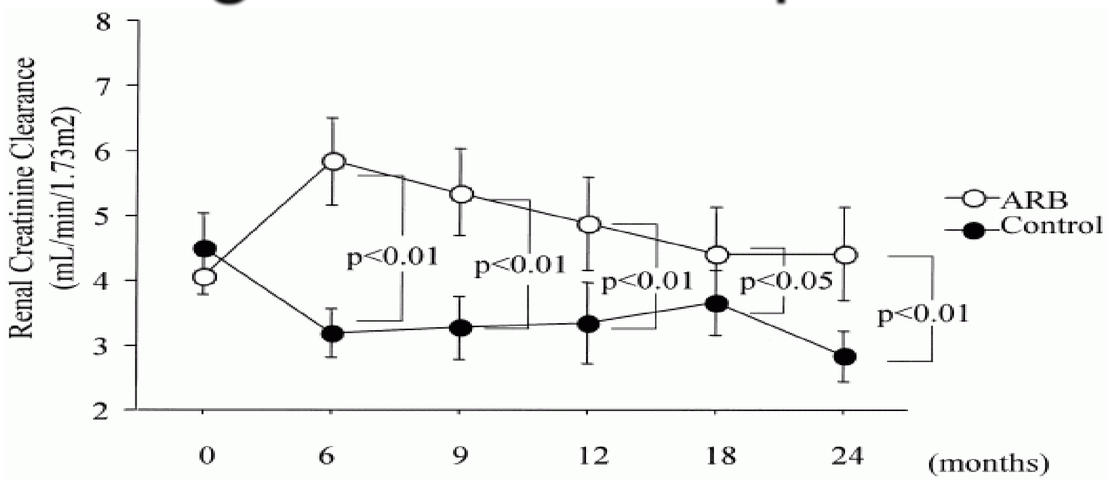
Preservation of Residual Renal Function

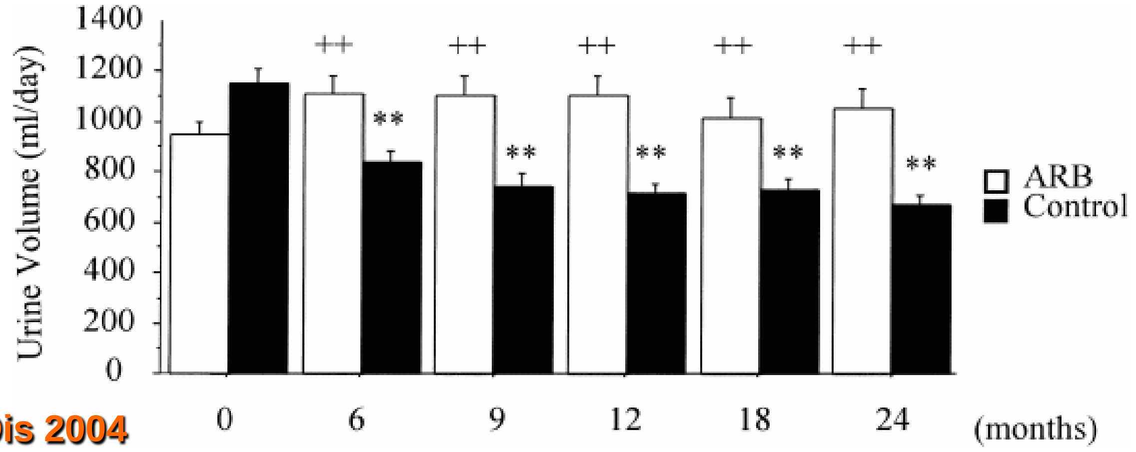
- Avoid intravenous dye studies
  - consider necessity of the study
  - can alternative to dye be used?
    - Dobutamine stress echo
  - use iso-osmolar, nonionic dye, keep patient hydrated
  - use N-Acetyl Cystine (my opinion)
  - minimize volume of dye
    - eg don't image the left ventricle

Preservation of Residual Renal Function

- ACE inhibitors and angiotensin receptor blockers (ARB’s) can slow down deterioration of renal function

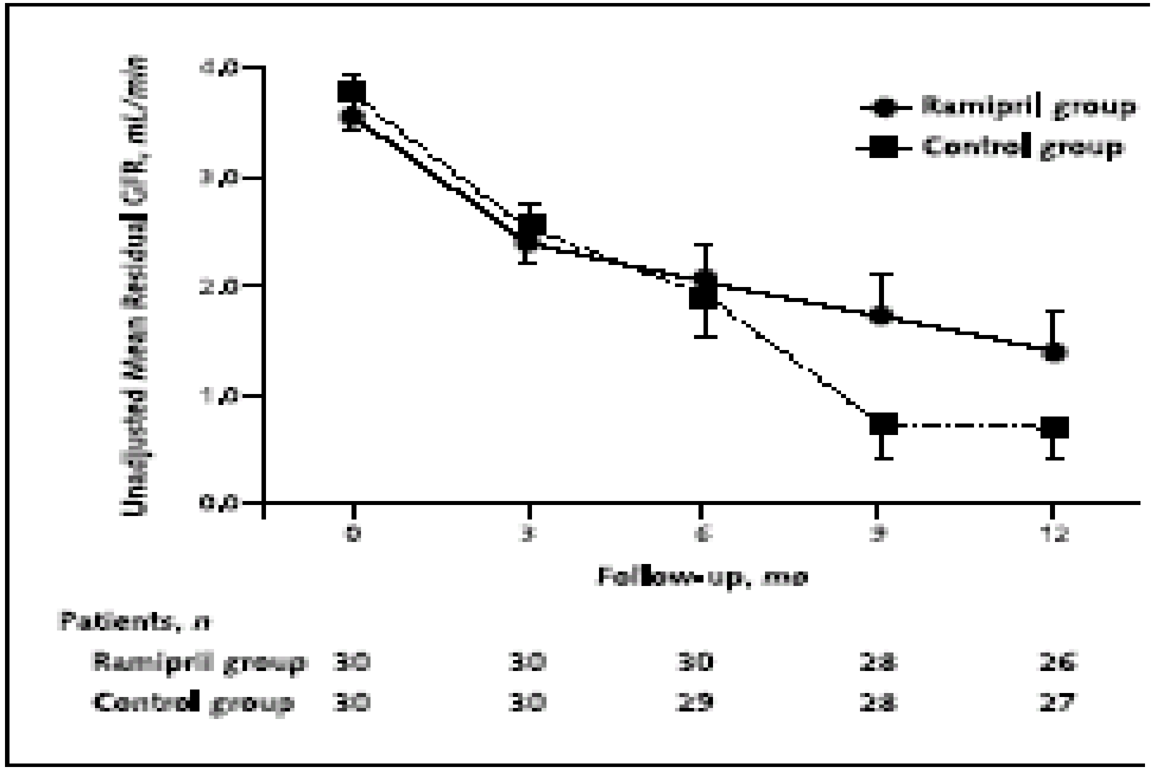
Preservation of Residual Kidney Function with Angiotensin Receptor Blockers





Suzuki et al, Am J Kidney Dis 2004

Preservation of Residual Kidney Function with ACE Inhibition



Li et al, Ann Int Med 2003

PRESERVATION OF RESIDUAL KIDNEY FUNCTION BY ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

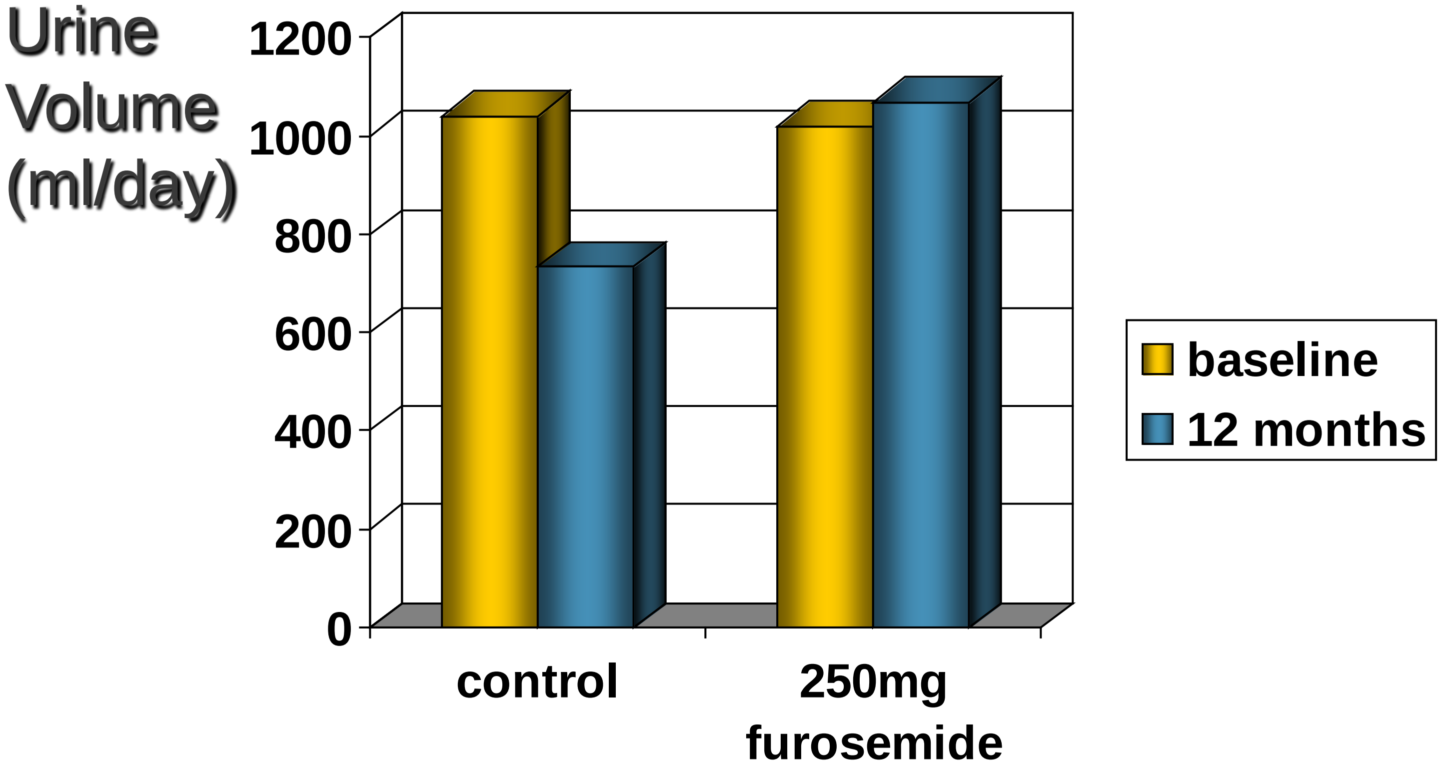
- preservation of 1 ml/min – *so what?*

  - most studies show that each ml/min of residual GFR associated with 15 – 25% reduction in annual mortality
  - this is theoretically as life-prolonging as results seen in the ACE-I, statin or spironolactone trials for heart disease

Preservation of Residual Kidney Function: What About Diuretics?

- diuretics increase renal salt and water excretion
- they do not acutely change GFR
- no evidence over longer term that they either improve or worsen GFR
- after 1 year: preservation of urine *volume*
- but this is important for management of volume status

Effect of Daily Furosemide on Urine Volume: Results After 1 Year

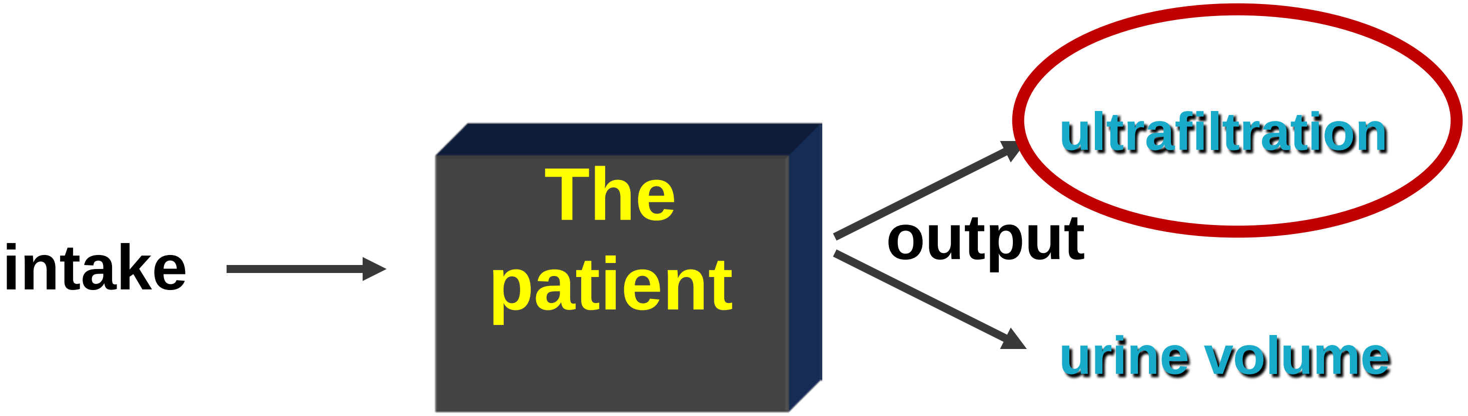


Medcalf Kidney Int 2001

OTHER WAYS TO PRESERVE RESIDUAL KIDNEY FUNCTION

- Continue immunosuppression in “failed” renal transplants
  - **Davies Perit Dial Int 2001**
  - **Jassal et al Am J Kidney Dis 2002**

Dynamics of Fluid Balance in the Dialysis Patient

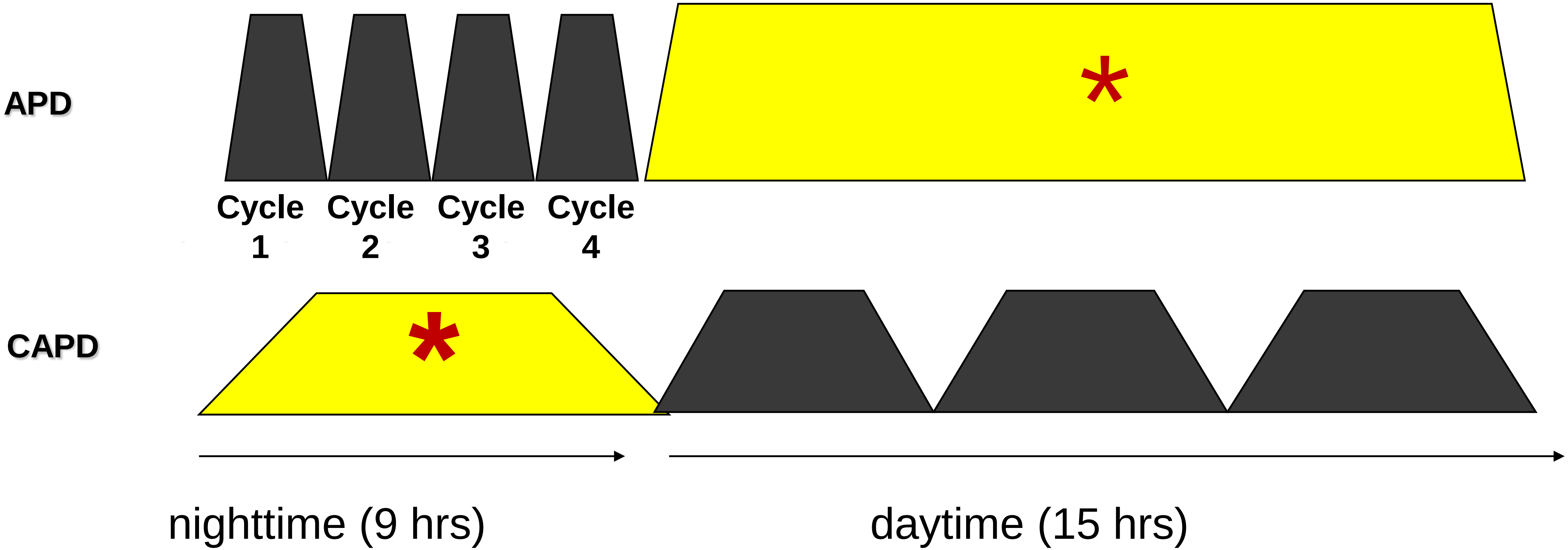


“ULTRAFILTRATION FAILURE”

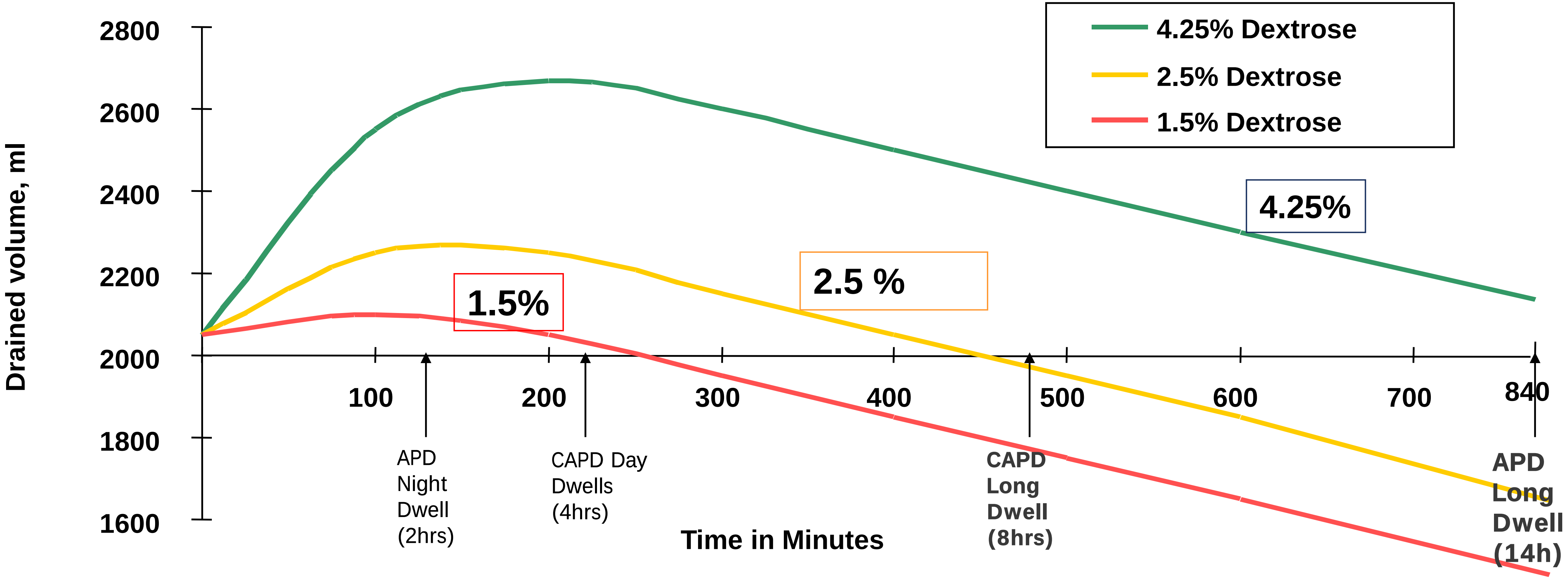
Use of the wrong type of PD fluid

- usually this means failure to account for the long dwell
- reluctance to use hypertonic fluid because of perception that it will hurt the peritoneal membrane

Temporal Profiles of APD and CAPD



Ultrafiltration Profiles of Dextrose-Based Solutions



Rippe, et.al. 2000.

ULTRAFILTRATION FAILURE – OTHER CAUSES

- failure of the peritoneal membrane to respond to UF conditions (true membrane failure)
- mechanical failure of dialysis procedure

FAILURE OF THE PERITONEAL MEMBRANE

Definition: Inability to maintain volume homeostasis despite the use of hypertonic dialysate solutions (3 or more daily)

or

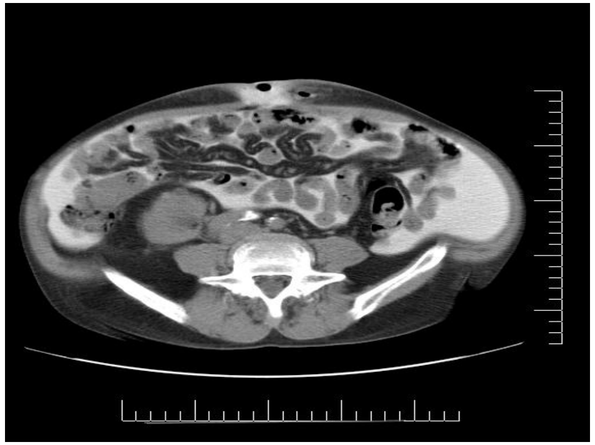
- Failure to ultrafilter > 400 ml using a 4.25% bag for 4 hours (the Rule of 4's)

TRUE PERITONEAL MEMBRANE FAILURE

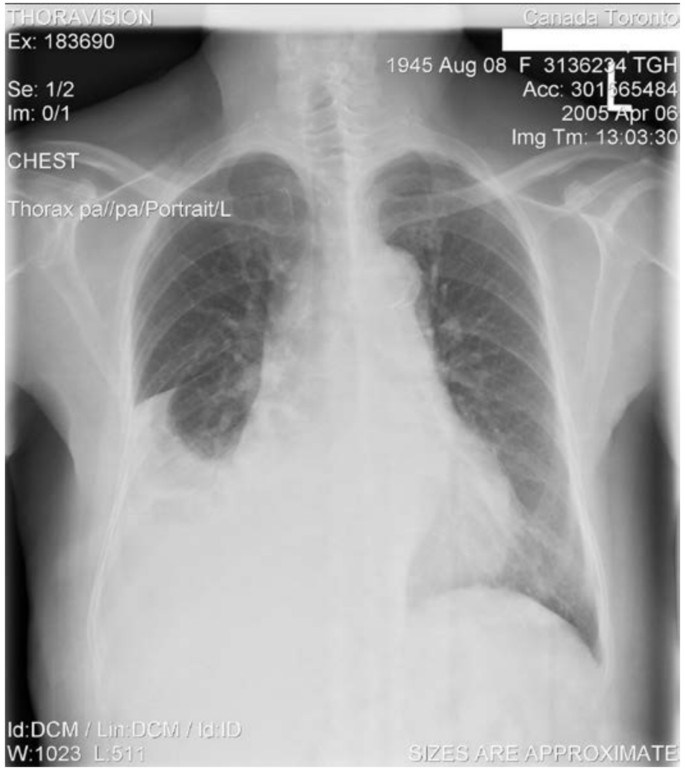
- on PET test, D/P creatinine is high
- these high transporters have rapid absorption of glucose across peritoneal membrane
- rapid dissipation of osmotic gradient
- poor ultrafiltration

MECHANICAL FAILURE OF THE DIALYSIS PROCEDURE

- diminished effluent return because the dialysis fluid is leaving the peritoneal cavity
- PET test is unchanged



MECHANICAL FAILURE OF THE DIALYSIS PROCEDURE



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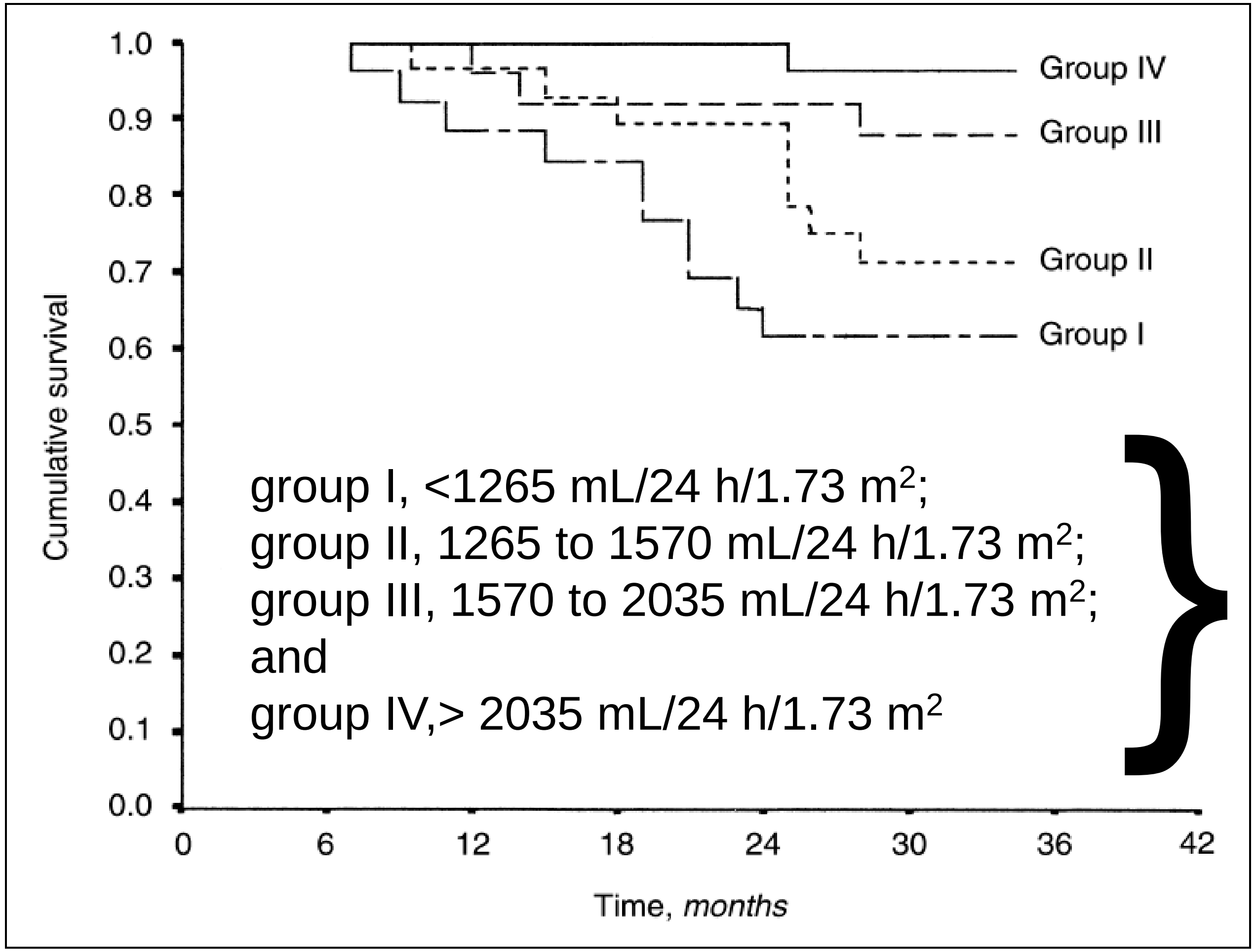
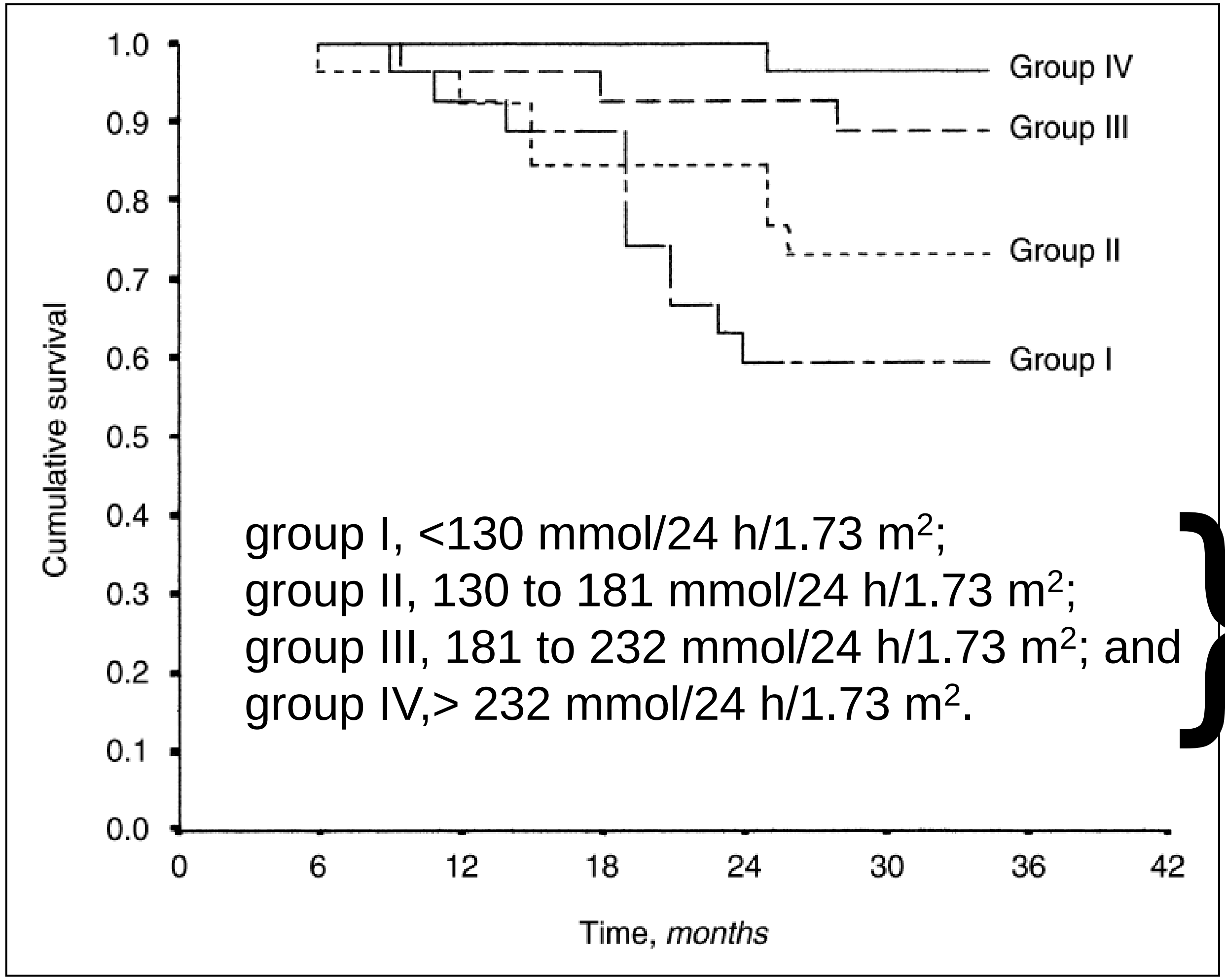
PD ULTRAFILTRATION AND SURVIVAL



Daily UF volume

Ates, et al. *Kidney Int.* 2001;60:767-776.

PD NA+ REMOVAL AND SURVIVAL



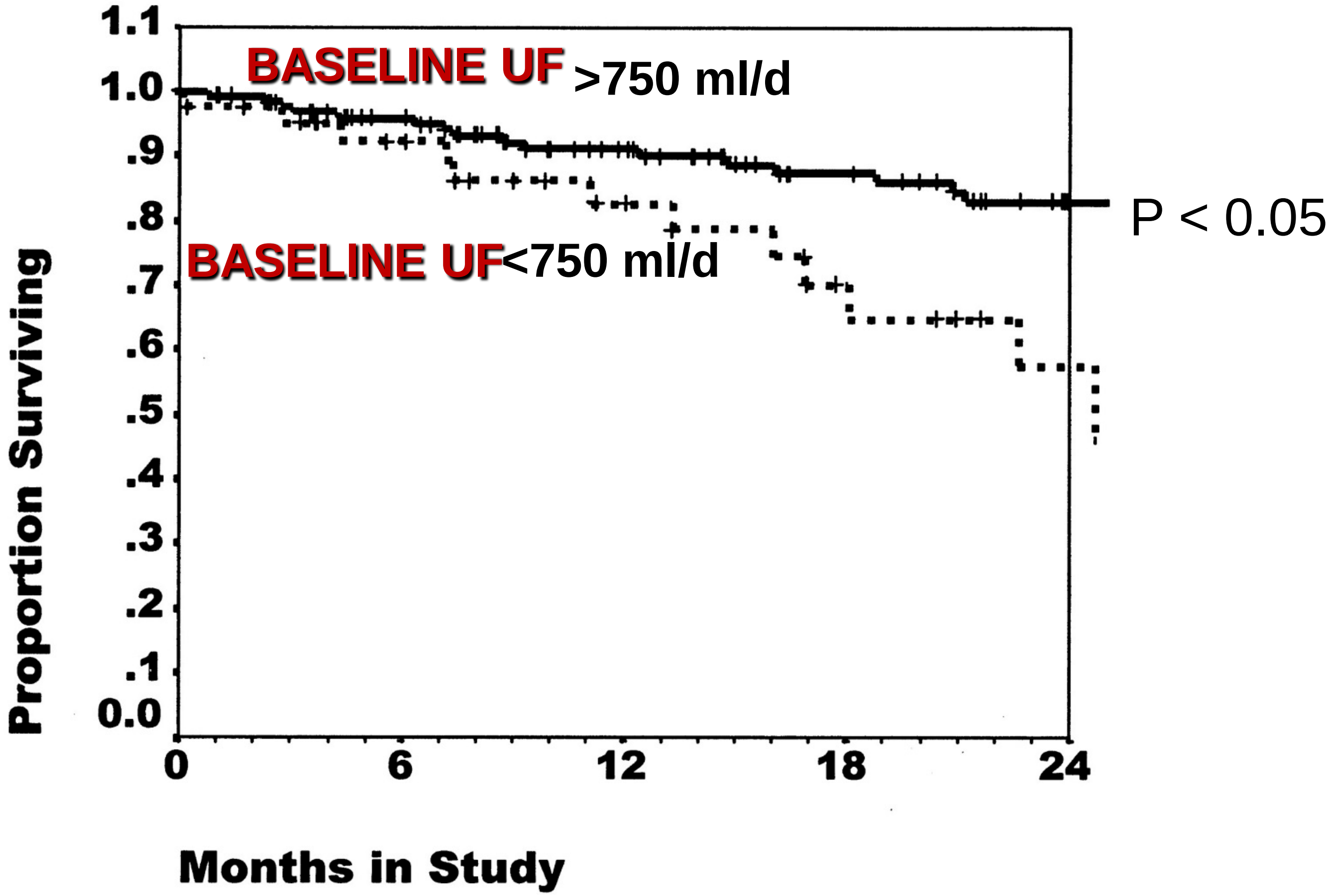
Daily Na+ removal

Ates, et al. *Kidney Int.* 2001;60:767-776.

THE IMPORTANCE OF ULTRAFILTRATION: THE EAPOS STUDY

- multi-centre study in Europe examining predictors of outcome in anuric APD patients
- small solute clearance parameters did not predict survival
- baseline ultrafiltration volume significantly predicted survival
- time-dependent ultrafiltration volume was also of borderline statistical significance

FLUID REMOVAL AND SURVIVAL IN EAPOS



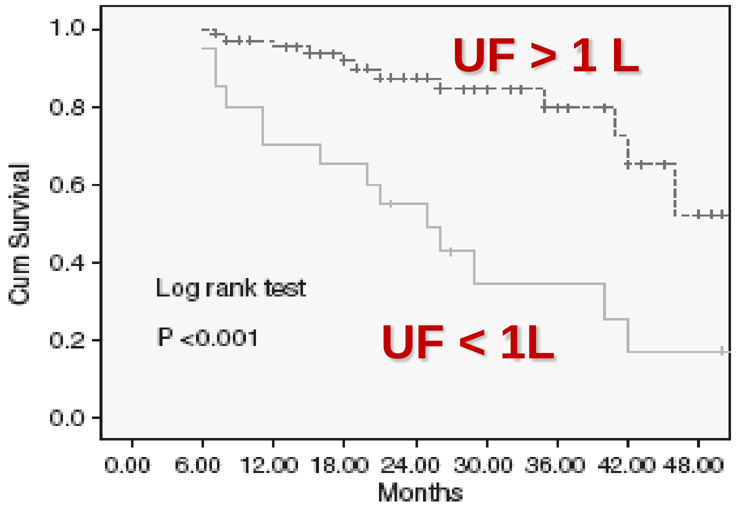
Brown et al, J Am Soc Nephrol 14:2948-2957, 2003

PREDICTORS OF SURVIVAL IN ANURIC PD PATIENTS

- recent study of anuric PD patients in Shanghai
- similar to EAPOS, ultrafiltration volume was an important predictor of survival

Table 4. Multivariate Cox regression analysis showing independent predictors of mortality in 86 anuric PD patients followed up for a median of 25.3 months (range, 6 to 54 months)

	RR	95% CI	*P*-value
Age (1 year)	1.064	1.019–1.111	0.005
Serum albumin (1 g/L)	0.850	0.744–0.973	0.018
*UF(t) (100 ml/24 h)	0.800	0.709–0.901	0.000



Lin et al Neph Dial Transpl 2010

THE IMPORTANCE OF SODIUM AND WATER REMOVAL

- evidence suggests that ultrafiltration volume and euvolemia are important for survival
- this makes sense physiologically, given risks of chronic volume overload
  - LVH
  - increased sympathetic tone
  - congestive heart failure

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Early vs Late Ultrafiltration (Membrane) Failure

- some patients have problems with ultrafiltration at the start of PD
- other patients develop it over the course of PD

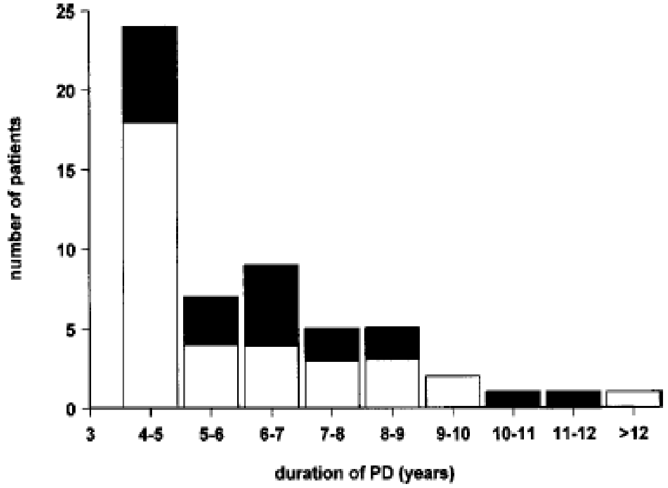


Figure 1 — Frequency distribution of the number of patients with (black boxes) and without (open boxes) ultrafiltration failure and the duration of peritoneal dialysis (PD; months).

Smit et al. Perit Dial Int 2004

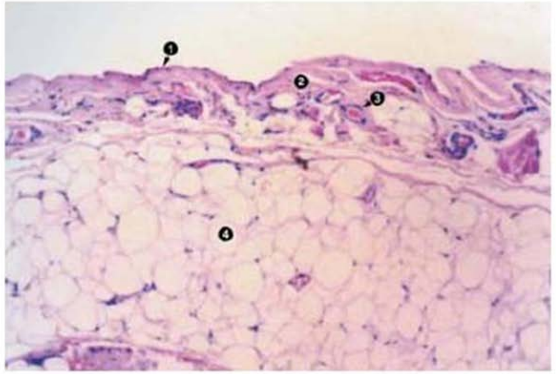
EARLY VS LATE ULTRAFILTRATION FAILURE

- early UF failure is probably a marker of inflammation
- these patients are rapid transporters from the beginning
- late UF failure a marker of a change in the structure of the peritoneal membrane

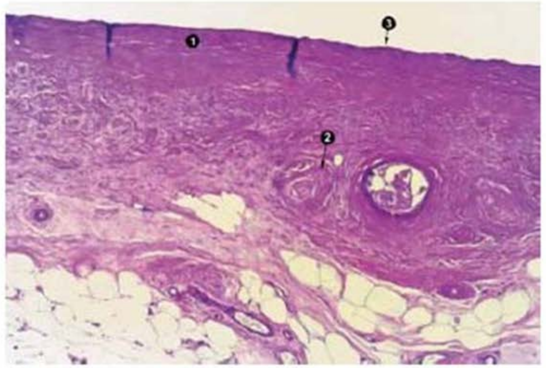
WHAT HAPPENS TO THE PERITONEAL MEMBRANE OVER TIME?

- new blood vessel formation
  - this makes the patient a more rapid transporter
- submesothelial fibrosis
  - this leads to diminished osmotic conductance

early

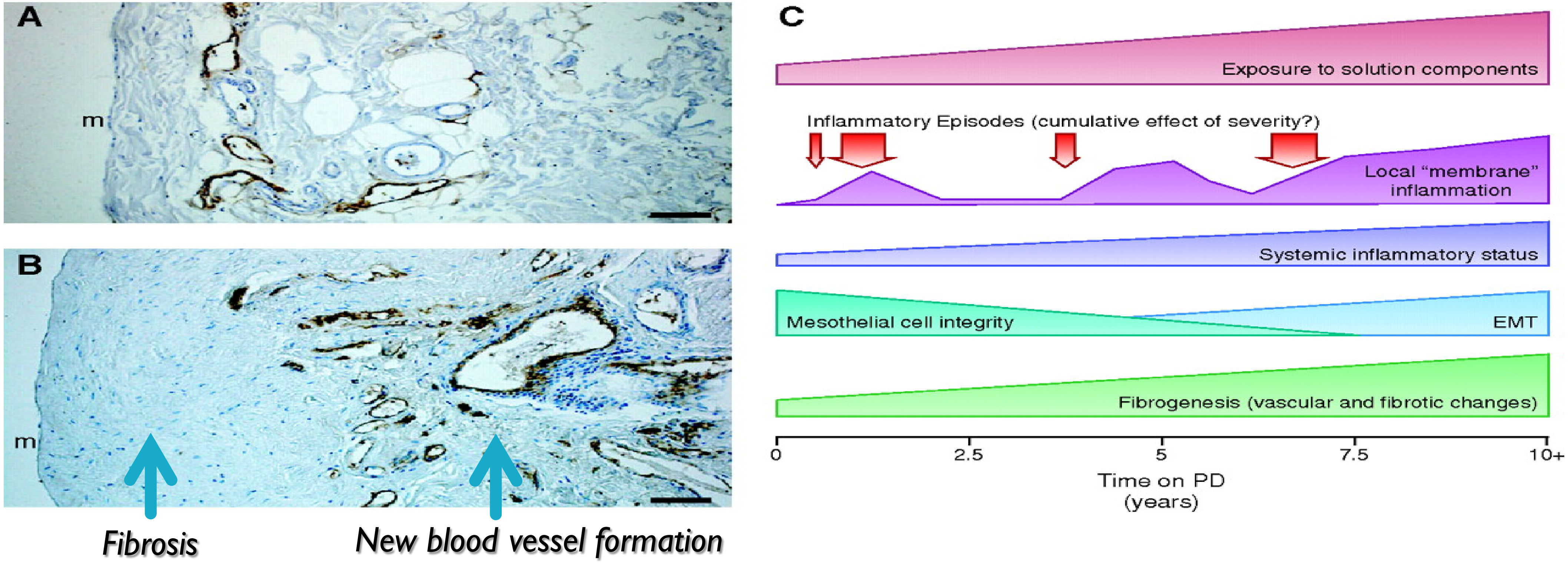


late



Slides courtesy of Peter Margetts

LONG-TERM CHANGES IN THE PERITONEAL MEMBRANE

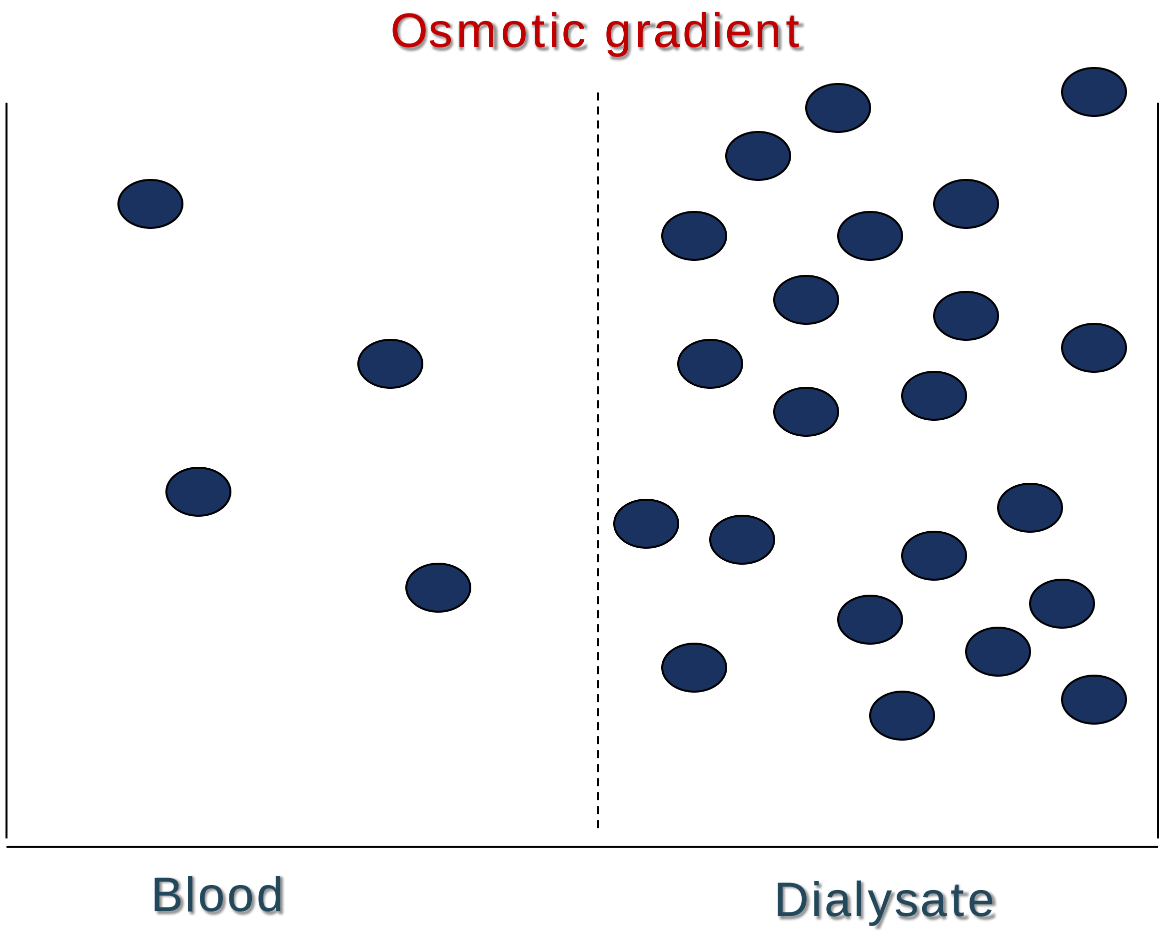


Devuyst O et al. JASN 2010;21:1077-1085

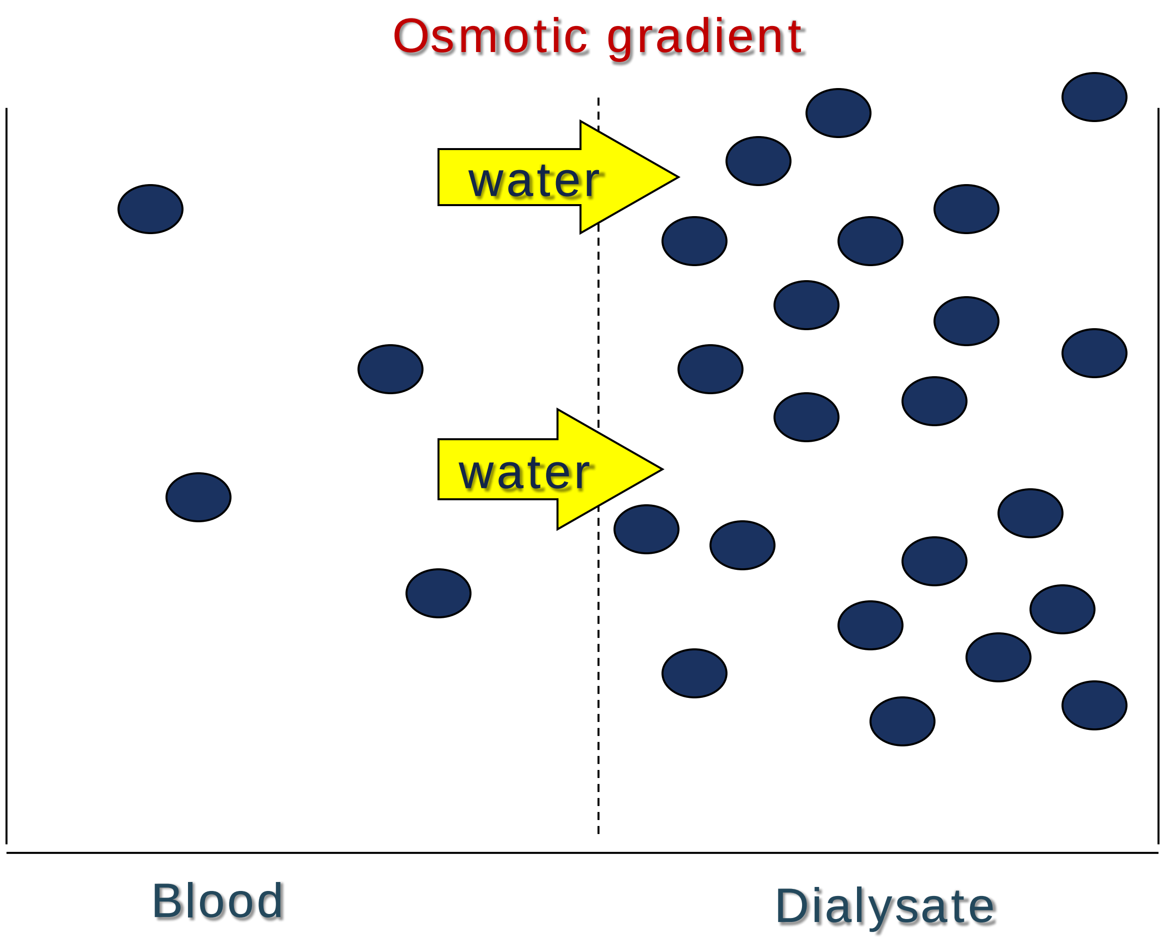
LONG-TERM CHANGES IN THE PERITONEAL MEMBRANE: RESULTS

- acquisition of rapid transport status
  - reduction in ultrafiltration
- diminished osmotic conductance
  - reduced ultrafiltration for any given osmotic gradient

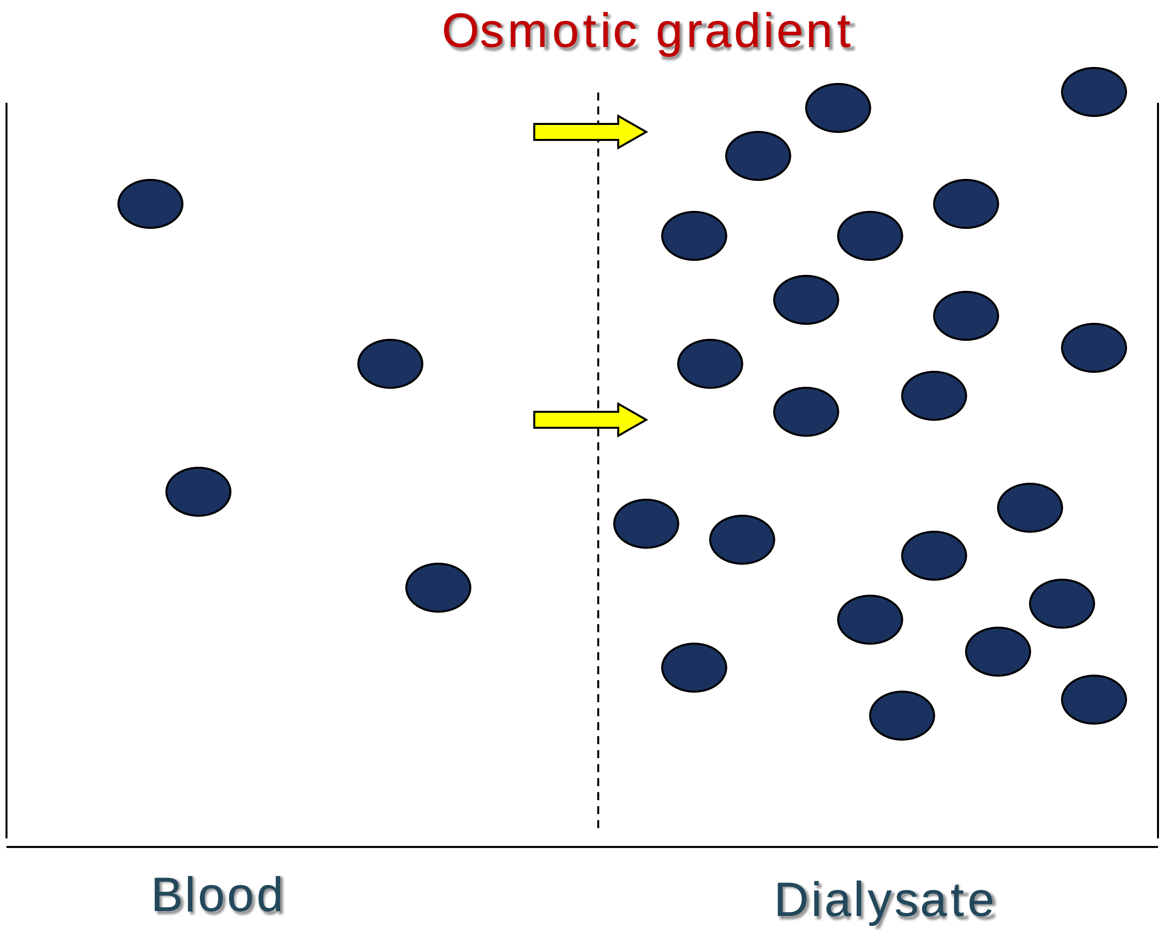
WHAT IS OSMOTIC CONDUCTANCE?



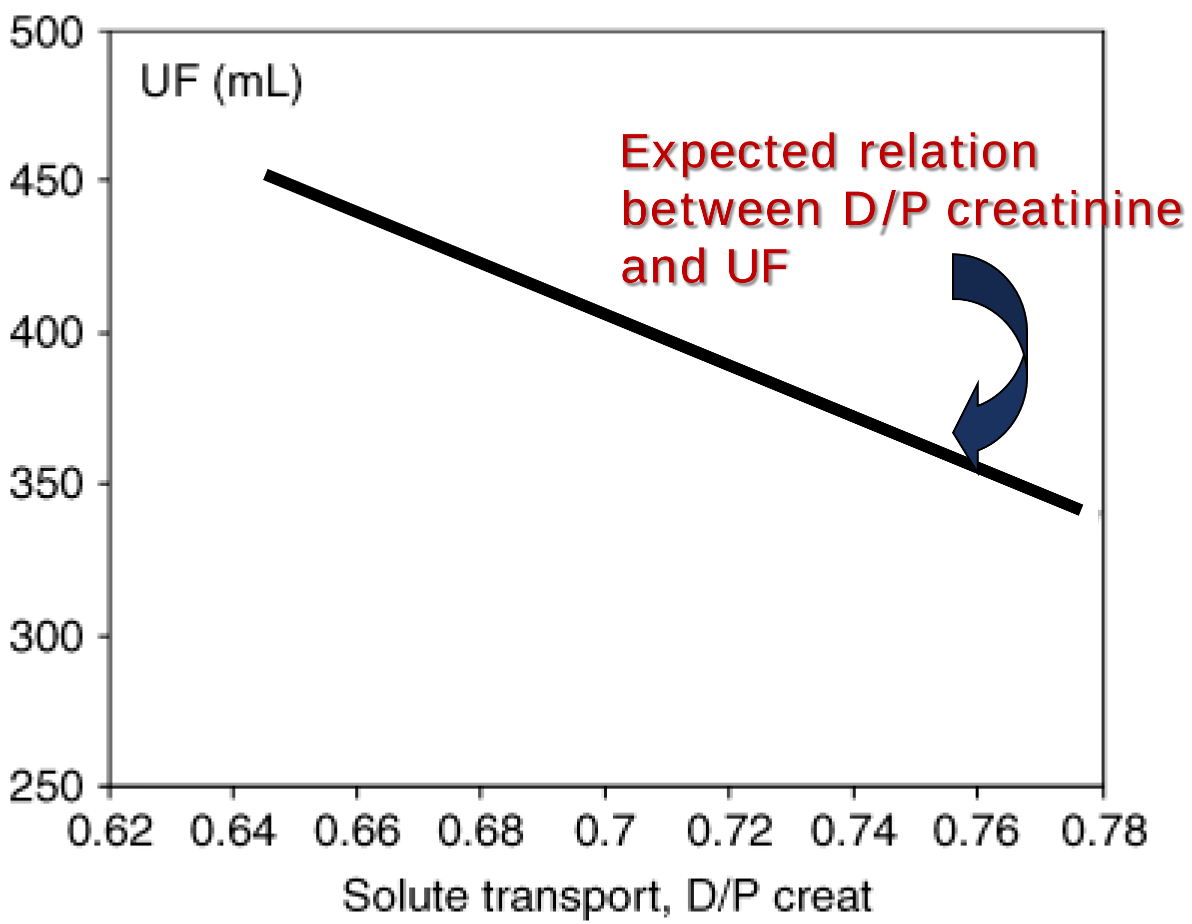
WHAT IS OSMOTIC CONDUCTANCE?



LOW OSMOTIC CONDUCTANCE: FOR A GIVEN OSMOTIC GRADIENT, LESS WATER MOVEMENT

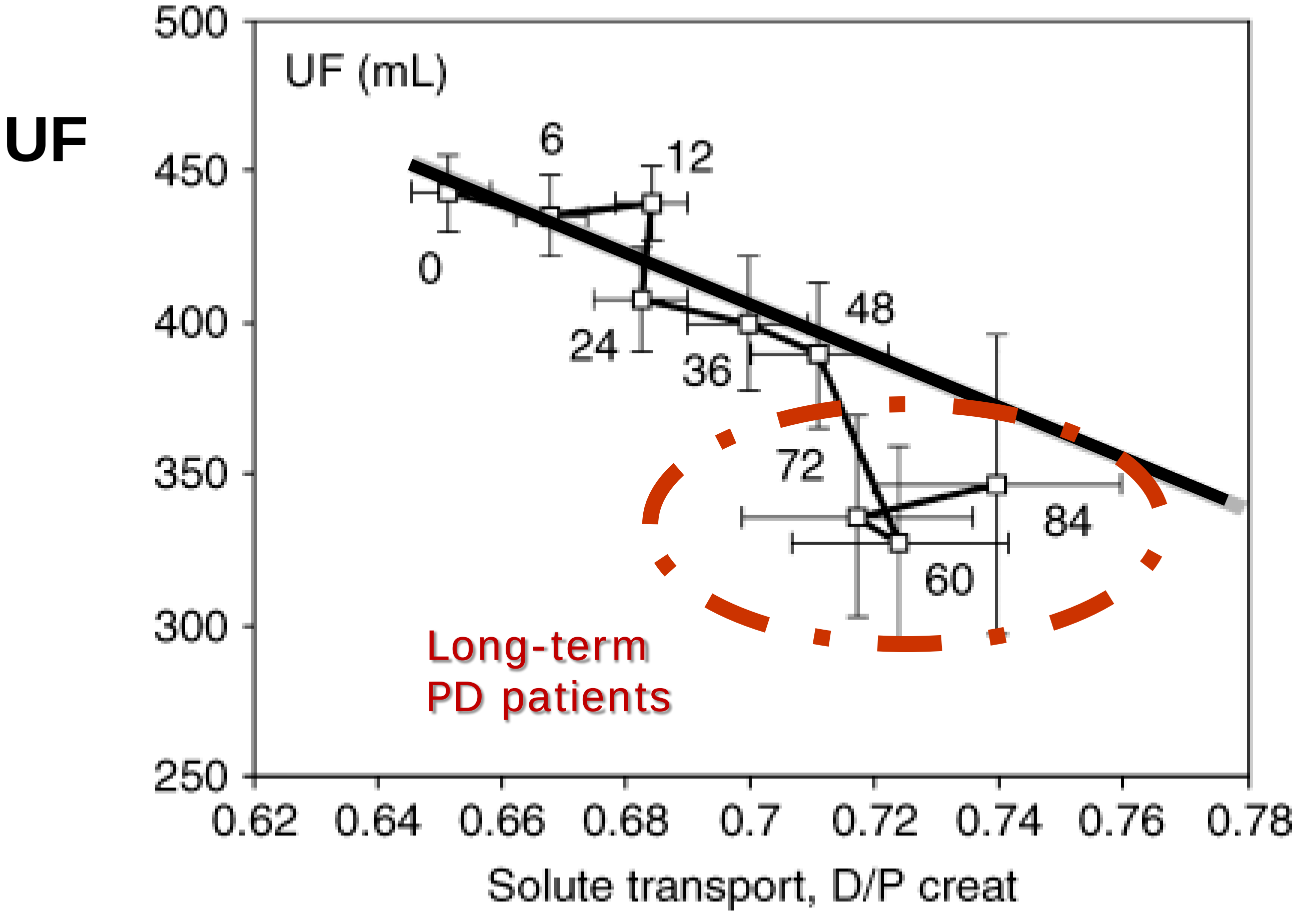


Transport Status and Ultrafiltration



Davies et al, *Kidney International* (2004) 66, 2437–2445

Long-Term PD Patients: Transport Status and Ultrafiltration



Davies et al, *Kidney International* (2004) 66, 2437–2445

LATE ULTRAFILTRATION FAILURE: THE DOUBLE WHAMMY!

- there is a tendency for some patients to become more rapid transporters over time
- in addition, for whatever osmotic gradient there is, less ultrafiltration occurs

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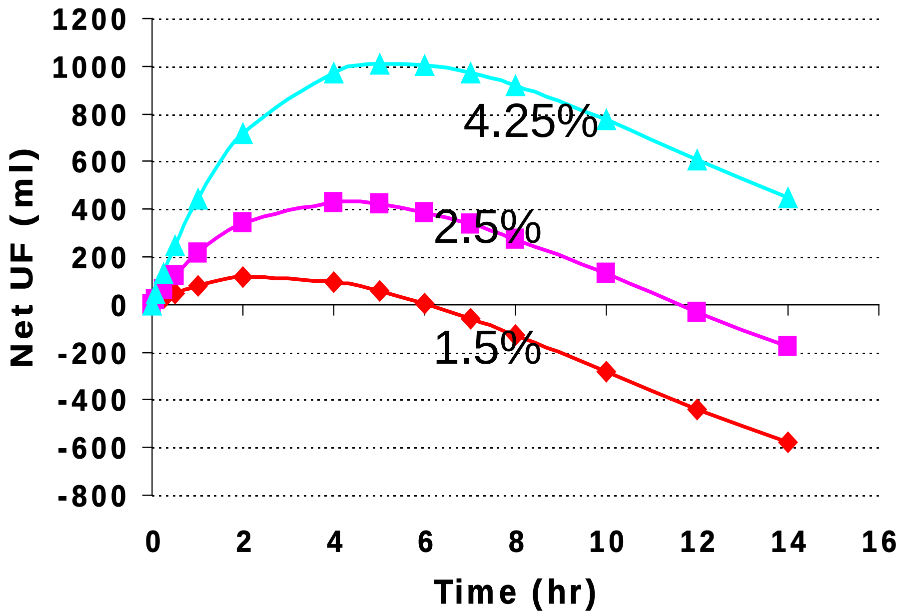
MANAGEMENT OF RAPID TRANSPORTERS (I)

- reinforce salt and water restriction
- use more hypertonic dialysate
- icodextrin can be quite helpful here (*as effective in high transporters as other transport types*)

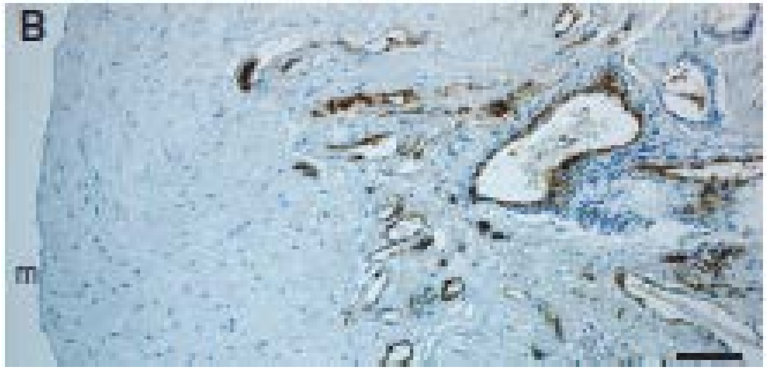
HYPERTONIC DEXTROSE-BASED SOLUTIONS

- hypertonic dialysate will result in more UF and convective removal of solute



USE OF HYPERTONIC DIALYSIS SOLUTIONS

- there is a metabolic "cost" to this:
  - to the patient (calories, lipids, etc)
  - *maybe* to the peritoneal membrane



ICODEXTRIN: A DIFFERENT APPROACH TO ULTRAFILTRATION

- macromolecules that are absorbed more slowly from the peritoneal cavity
- induces water transport across small intercellular pores
- works more efficiently in rapid transporters: enhances UF with increased vascular surface area (more pores)

REMEMBER THE HARE AND THE TORTOISE?

- the hare ran quickly but soon grew tired
- the tortoise, slow and steady, won the race

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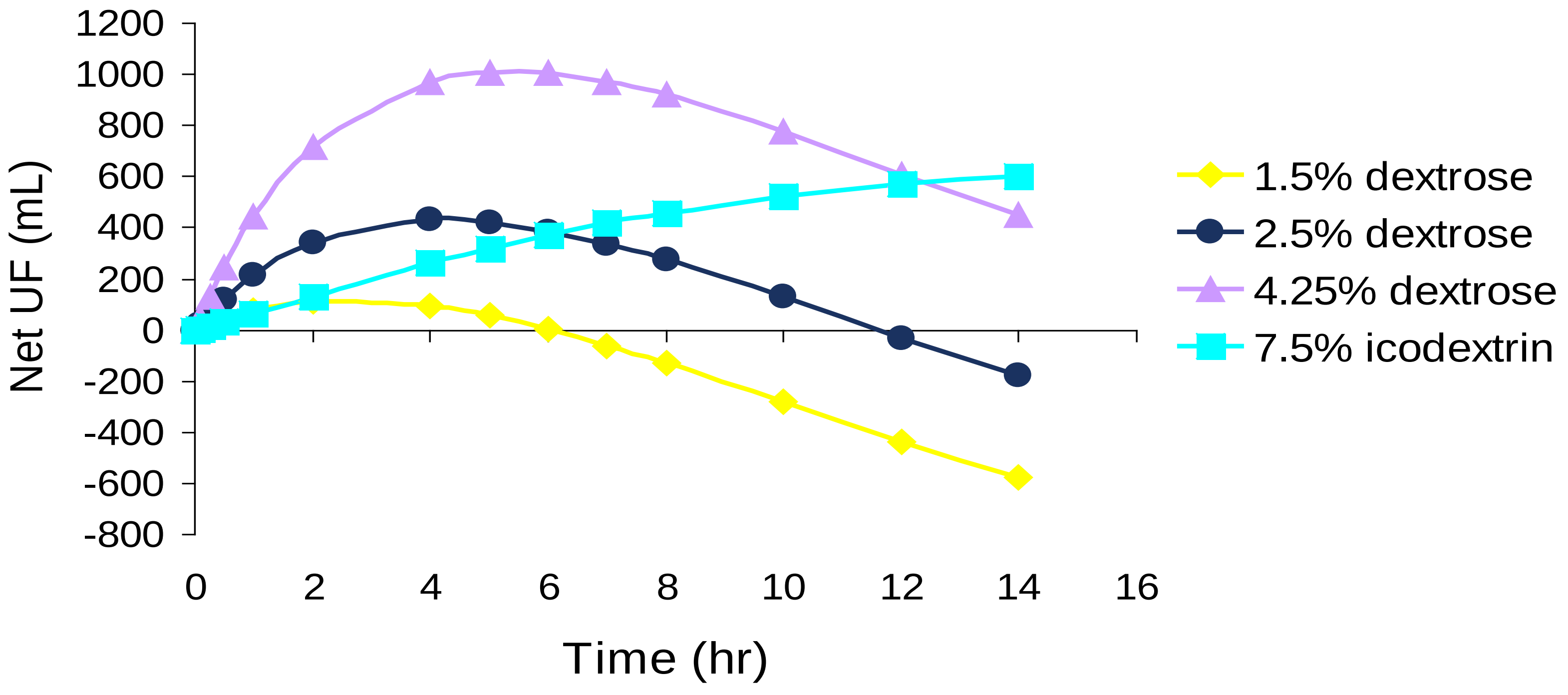
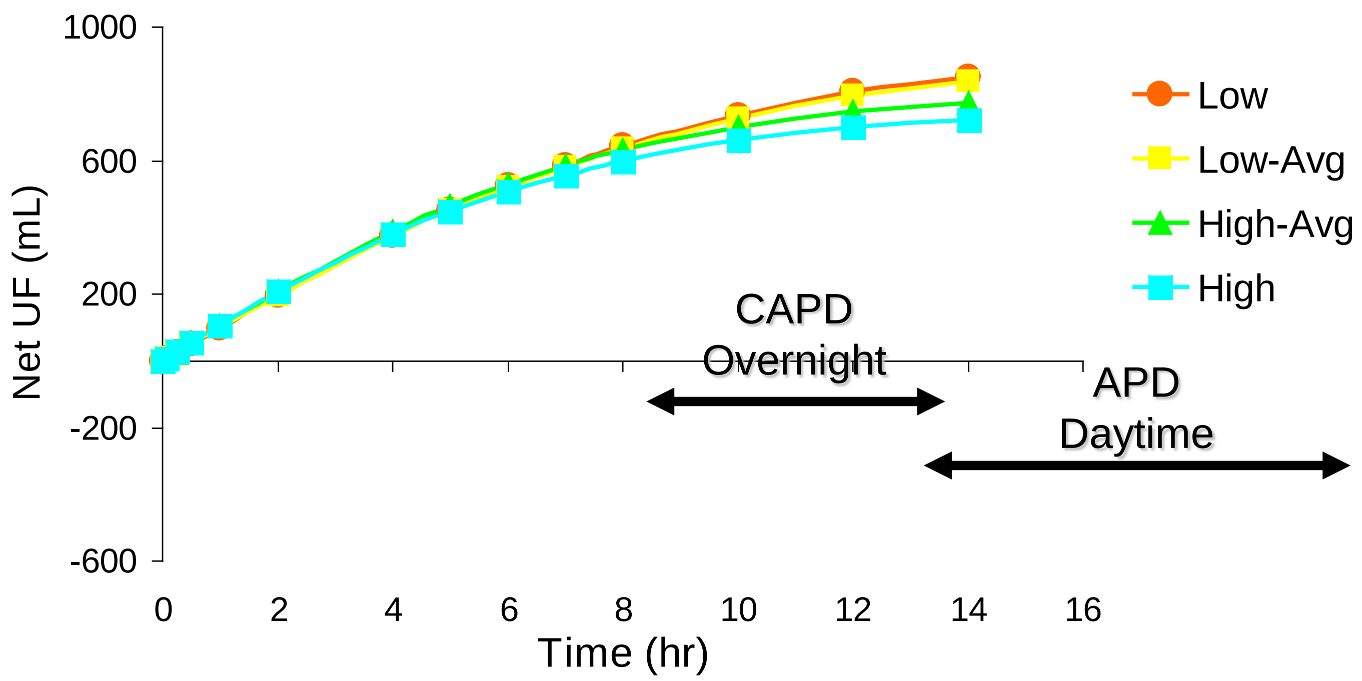
SUSTAINED ULTRAFILTRATION: ICODEXTRIN VS DEXTROSE



Mujais S, Vonesh E. *Kidney Int*. 2002;62(suppl 81):S17-S22.

ICODEXTRIN WORKS WELL IN ALL TRANSPORT TYPES

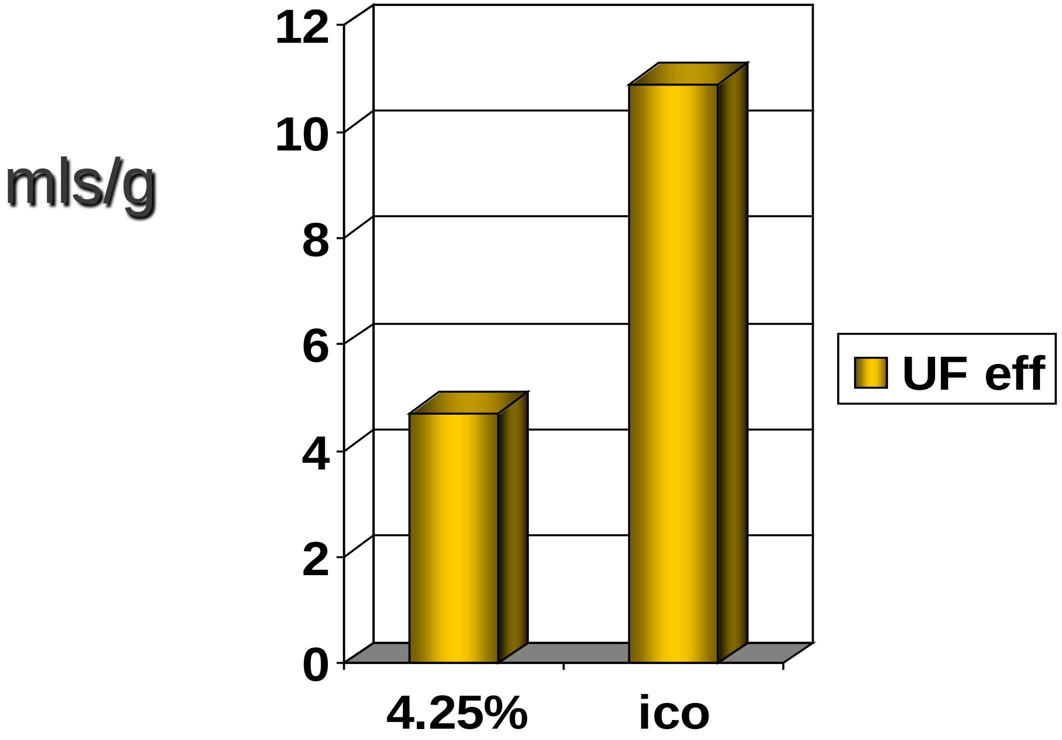


Mujais S, Vonesh E. *Kidney Int*. 2002;62(suppl 81):S17-S22.

ULTRAFILTRATION EFFICIENCY RATIO: THE "METABOLIC COST" OF UF

- Icodextrin leads to more ultrafiltration per gram of carbohydrate absorbed

  (expressed as mls ultrafiltered / g carbohydrate absorbed



Finkelstein et al J Am Soc Nephrol 2005

BUT ICODEXTRIN HAS A CALORIC LOAD TOO

- amount of calories absorbed from icodextrin ~ number of calories absorbed from a 2.5% dextrose solution

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- amount of calories absorbed from icodextrin ~ number of calories absorbed from a 2.5% dextrose solution

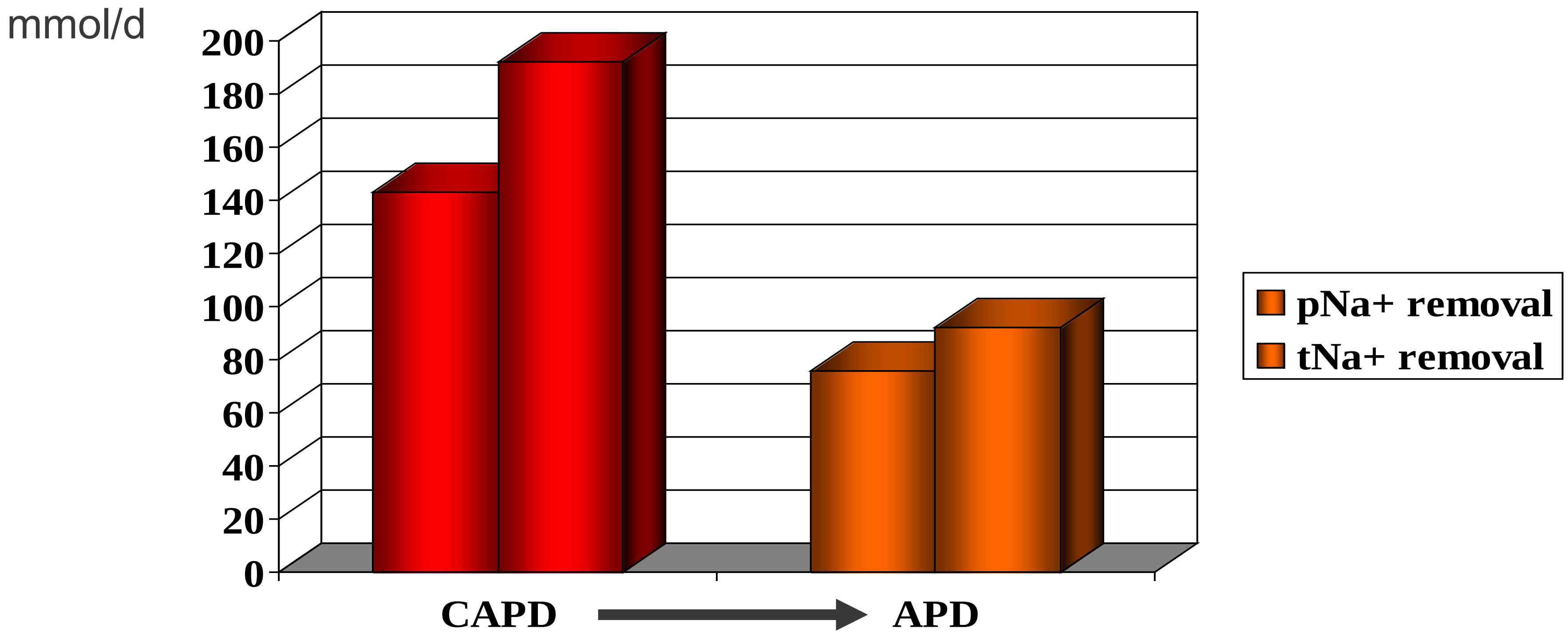
USE OF ICODEXTRIN TO ACHIEVE EUVOLEMIA

- more costly (but cheaper than changing to HD)
- 2 icodextrins/day *(off-label!)* associated with more UF but higher blood concentrations of metabolites

SHORTENED DWELL TIMES AND/OR SWITCH TO APD

- shortened dwell times allow for less dissipation of the glucose osmotic gradient
- this will lead to increased ultrafiltration and less opportunity for reabsorption
- if dwell times too short, water may be ultrafiltered faster than sodium is removed
- this *sodium sieving* can impair salt and water removal
- and you still have to deal with the long(er) dwell!

SODIUM REMOVAL IN PATIENTS TRANSFERRED FROM CAPD TO APD



(Rodriguez-Carmona 2002)

SHORTER DWELL TIME AND/OR CONVERSION TO APD

- in CAPD this necessitates more frequent exchanges and risk of burnout
- APD is not a “magic bullet”!
  - risk of sodium sieving
  - absorption during the long day dwell
- in anuric patients dry abdomen should be avoided in both CAPD and APD

WHAT ABOUT THE LONG DWELL?

1. use icodextrin or a more hypertonic dialysate (e.g. 2.5%)
2. break up the long dwell
   - day dry (only if there is a lot of RRF)
   - "mid-day" exchange in APD
   - drain out day exchange in APD after a few hours

MANAGEMENT OF RAPID TRANSPORTERS (II)

- “push” residual urine output (diuretics)
- APD with dry day, or drain out last fill at lunch (if enough RRF)
- once anuric, watch closely for volume overload
- *consider transfer to hemodialysis if patient is chronically overloaded*
  (start talking about fistula placement with the patient)

MY OPINION: WHAT WORKS FOR UF

CAPD — 1.5% — 2.5% — 1.5% — Icodextrin

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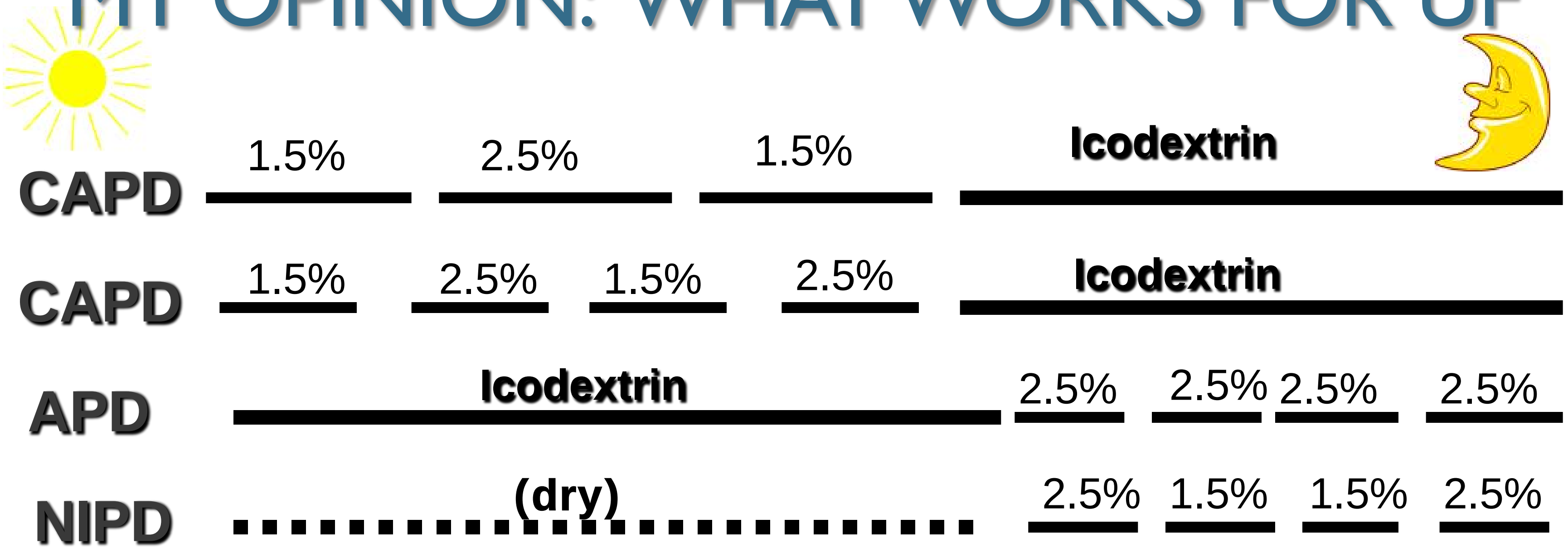

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APD: Icodextrin | 2.5% | 2.5% | 2.5% | 2.5%

NIPD: (dry) | 2.5% | 1.5% | 1.5% | 2.5%

and maybe…

APD: Icodextrin | Icodextrin | 2.5% | 1.5% | 2.5%

SUMMARY

- Attainment of normal volume status is important for the well-being of our dialysis patients
- There is a differential diagnosis in the volume-overloaded PD patient – don't assume it is membrane failure
- Early versus late ultrafiltration failure have different causes
- Management includes dietary sodium restriction, pushing urine output with diuretics, and changes to the PD prescription
- Consider a transition to hemodialysis if the patient remains chronically volume overloaded despite these interventions