Residual Renal Function and Dialysis Adequacy in ESRD Patients

History and Mathematics

History and Mathematics

- "History is a tragedy for those who feel and a comedy for those who think."

(quoted by Will Durant in History of Civilization)

- "The application of mathematics in nephrology is a tragedy for those who feel and a comedy for those who think."

  *(own observation)

*Everything in blue in this lecture relates to my own observations/thoughts

Part I. Theoretical Considerations

- Importance of Residual Renal Function (RRF) in Urea Kinetic Modeling
- Basic Assumptions of Urea Kinetic Modeling
- Importance of ignoring the terms relating to Residual Renal Function during Urea Kinetic Modeling

Once upon a time….

Since:
low flux, low efficiency dialysis improve

1. Hyperkalemia
2. Volume overload
3. Acidosis
4. Encephalopathy
5. Pericarditis
6. Bleeding Diathesis
7. Severe nausea

Therefore:
low flux, low efficiency dialysis must remove

1. Potassium
2. Salt, water
3. Acid
4. Other low molecular, free solutes such as urea that we can name "uremic toxins"

Decrease in Urea Concentration as surrogate marker of Toxin Removal

1. Behave like other known poisons: effect is concentration dependent
2. Plasma concentration is reflective of tissue toxicity, toxins diffuse rapidly between tissues
3. Uremic toxins are small and not largely protein-bound
4. Most of the removal of uremic toxins occurs during dialysis in a concentration and time dependent fashion -all dialyses are created equal
5. Patients on chronic dialysis are in steady state: i.e. in a net zero nitrogen balance
6. Urea generation is largely independent of urea removal

1. Several toxins: do all behave the same? Urea is not a toxin!
2. Do tissues have different sensitivity, variable clearances: reservoir effect, compartment effect?
3. Are some toxins large and/or protein-bound?
4. What about variability of residual clearance, frequency, speed and method of dialysis?
5. Are most patients in steady state?
6. Is toxin generation independent of removal

The Fateful Assumption

alias

"Let us start the battle and then we shall see!"

(Napoléon)

- **Change in urea concentration during dialysis can approximate "dialysis dose"**
- Sargent & Gotch 1975: concentration change during dialysis equals generation during dialysis minus removal during dialysis
- As concentration of urea changes from C_0 to C_t during dialysis from time t_0 to t_d then:

$$\int_{Co}^{Ct} V dC / [G - (K_d + K_r) C] = \int_{to}^{td} dt$$

where V = distribution volume of urea

Co= pre BUN

Ct = post BUN

G = urea generation during dialysis

Kd= dialyzer clearance

Kr= residual renal function during dialysis

t = time from beginning to end of dialysis

Simple Math

- Using **basic** calculus rule $\int dx/a+bx = 1/b \ln(a+bx)$ we get:

$$-V/(K_d+K_r) \ln(G-(K_d+K_r)C) \mid C_o \rightarrow C_t = t \mid t_o \rightarrow td$$

- From above we express Ct as:

$$Ct = Co\, e^{-(Kd+Kr)\, td /V} + G/(K_d+K_r)\,(1 - e^{-(Kd+Kr)\, td /V})$$

- In an anephric patient ignoring generation:

$Ct = Co\, e^{-Kd\, td /V}$ or $\underline{\ln(Co/Ct) = Kt/V}$

- By **analogy** during the interdialytic interval we get:

$$Co = Ct\, e^{-Kr\, tid /V} + G/K_r\,(1 - e^{-Kr\, tid /V})$$

where id= interdialytic

- In an anephric patient then: $\underline{Co = Ct + G\, tid/V}$

Pay Attention Here!

$$Ct = Co\, e^{-(Kd+Kr)\, td\, /V} + G/(K_d+K_r)\,(1- e^{-(Kd+Kr)\, td\, /V})$$

$$Co = Ct\, e^{-Kr\, tid\, /V} + G/K_r\,(1- e^{-Kr\, tid\, /V})$$

- **These equations implicitly assume the *equivalence of 2 different clearing processes Kd and Kr!!!!***

- **There are too many unknowns!**

  We know these:

  Ct, Co, Kr, td, tid

  (although: Ct and Co may not be constant, Kr may be variable, td may not be as we assume, tid likewise)

  We do not know these:

  Kd, G, V

How do you solve 2 Equations for 3 Unknowns?

Introduce more assumptions!

- Kd can be estimated from the following variables:

-manufacturer's estimate on urea clearance

-blood flow

-dialysate flow

-hematocrit (viscosity)

-ultrafiltration volume

(but how about: needle position, needle size, needle distance, recirculation, inadequate anticoagulation, reuse, calibration problems, alarms, low blood pressure, not to mention sampling errors….)

- Or V can be estimated from anthropometric formulae

Practical solutions….

- Estimate Kd then solve equations for G and V or estimate V and solve for Kd and G
- Kt/V includes an estimated term with all the pitfalls of estimation
- Does Watson volume apply for all dialysis patients?
- Since a 24 hour urine collection is a hassle and the equations are much simpler

  $Co = Ct + G\ tid/V$ **versus** $Co = Ct\ e^{-Kr\ tid/V} + G/K_r\ (1 - e^{-Kr\ tid/V})$

  Kr terms can be conveniently **ignored**
- Over-rely on a simplified *estimated* goal ignoring *how one gets there*
- It saves time/easier and is seemingly more objective to document a lab report, a number than global subjective assessment of dialysis tolerance and effect

On Mental Inertia

- Lao Tsu Zhong VIIth Century Ch'an-Buddhist Scholar:

  "As to those who believe that the Great Void equals vacuity and that cessation of discriminative thought equals cessation of all mind function (with them) I have no patience. For nothing hinders the realization of Essential Wisdom more than inertia and confusion. A pure mental state requires the utmost concentration and active effort."

On Plagiarism

- Ludwig von Schaum XIXth century German scholar (from the *Wissenschaftliche Beschreibung der Moralischen Philosophie)*

“The sources for mental corruption are the following: confusion, laziness and the consequent over-reliance on and indiscriminate plagiarism of the thoughts of others. This latter is commonly due to lack of dedication, easy compromising as well as authoritative thinking.”

A word or two on G…..

- NPCR and G are directly correlated- underestimation of G may lead to underestimation of NPCR as well and vice versa
- *In anephric patients* NPCR can be fairly well estimated by pre-BUN (own observation)
- Remember that pre-BUN is a function of not only the protein intake in the interdialytic period but also of the metabolic state (catabolism, liver function, GI bleed etc) *as well as Residual Renal Function*
- Biologically, urea generation and urea removal may not be independent at all: a malnourished patient may have more chronic inflammation and not be in steady state; a patient better dialyzed may progressively eat more and gain weight

"Reverse epidemiology" in ESRD patients

- Non-ESRD: BMI>40 associated with relative risk of death of >2.2
- ESRD: progressive increase of BMI above 25 is associated with a RR of death ~ 0.6-0.8 (cross-sectional study!!!!!!)
- Is ability to gain/maintain weight a surrogate marker of dialysis quality?

(own observation)

What does dialysis do?

- Dialysis removes things
- When it removes salt and water, we call that ultrafiltration
- When it removes mysterious uremic toxins, we call that clearance
- Why are salt, water, phosphorus, simple acids, potassium not included in the category of uremic toxins? Unlike urea they are actually toxic!!!!

Dialysis does not equal Urea removal

(alias let us subscribe to NDT)

- My summary of Depner on clearance (NDT 1998):

  Urea diffuses freely between tissue compartments as it is unbound, has no charge and special transport pathways facilitate its movement. Uremic toxins do not appear to behave this way. Urea removal may not be a good model of uremic toxin removal. If a uremic toxin diffuses less than urea, the limitations of intermittent dialysis is even more pronounced in reality.
- My summary of Locatelli on fluid removal (NDT 1999):

  There is a concern in Japanese and Italian nephrologists following the path of Americans disregarding the importance of slow removal of fluid. Kt/V pushed high by increasing efficiency and decreasing dialysis time may kill more patients as dialysis tolerance is mainly driven by toleration of ultrafiltration rate.

Intermittent versus Continuous Clearance
alias Kd vs. Kr

- Residual Renal Function:

-is continuous therefore does not share rapid loss of efficiency of intermittent techniques

-no compartment effects

-removes middle, large and protein-bound molecules

-does not decrease blood pressure

-perfectly biocompatible

-does not require access and anticoagulation so……

The Great Enigma

(the "go and see the real world" slide)

- Why on Earth did anyone ever think that Residual Renal Function clearance is equivalent to dialysis clearance?
- Why on Earth would anyone think that a "standardized" Kt/V (a given Kt/V necessary to keep average peak urea concentration a given level ***irrespective of how*** urea is cleared) is a predictor of mortality?
- Why do we use Kt/V as quality indicator when not a single large-scale prospective study ever verified this except a post-hoc analysis of the NCDS? (In fact 2 recent large prospective studies showed the exact opposite)
- NCDS: at extremely inefficient dialysis easy to remove small solute clearance (potassium, acid) may be important, at more efficient dialysis (HEMO, ADEMEX) other factors become important such as tolerance and other functions of the dialysis treatment (large molecule removal, UFR, maintenance of RRF)

We are not alone…

* **"Frequent dialyses (four or more sessions per week) with total weekly dialysis time sufficient to allow gentle ultrafiltration rates provide the best clinical results…. Kt/V urea should be abandoned as a measure of dialysis quality."**
- KDOQI 2006 finally admitted that irrespective of Kt/V there should be a minimum time for 3x/week dialysis sessions in patients with low RRF
- Several alternative modalities: Tassin, frequent daily dialysis, hemodiafiltration- qualitatively different

*Int J Artif Organs. 2004 Jun;27(6)
Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance.
***Twardowski ZJ*.**

We are not alone…2

"The casual use of mathematical models can mislead unwary clinicians and compromise quality enhancement."

Semin Nephrol. 1996 May;16(3):242-62.

Thoughts about judging dialysis treatment: mathematics and measurements, mirrors in the mind.

Lowrie EG

History and Mathematics

Vitéz Zsombory Alajos Hungarian philosopher XXIst century:

"History and mathematics share a major fallacy: they are both commonly used for simplified description of infinitely complex systems."

The Great Questions

- A concentration of urea achieved by 20% contribution of RRF and 80% dialysis contribution- is this really equivalent to 0% and 100% respectively? (Kd?=Kr)
- If not then why not regularly measure *and maintain Residual Renal Function*?
- Ideal dialysis:

1. removes all toxins (including phosphorus, larger and protein-bound molecules etc),
2. is well tolerated (UFR, *rate* of removal of osmoles and potassium….) and
3. *maintains Residual Renal Function* ultimately allowing patients to gain weight (SGA)

Part II. Clinical Studies

- Clinical studies concerning the maintenance and importance of RRF often done in the PD setting as reliance on RRF here has been historically more important than in HD
- Main issues are:

  -clinical evidence of importance of RRF

  -natural history of decline and associated factors

  -how to preserve RRF

JASN 12:2158-2162, 2001

American Society of Nephrology

Relative Contribution of Residual Renal Function and Peritoneal Clearance to Adequacy of Dialysis: A Reanalysis of the *CANUSA Study

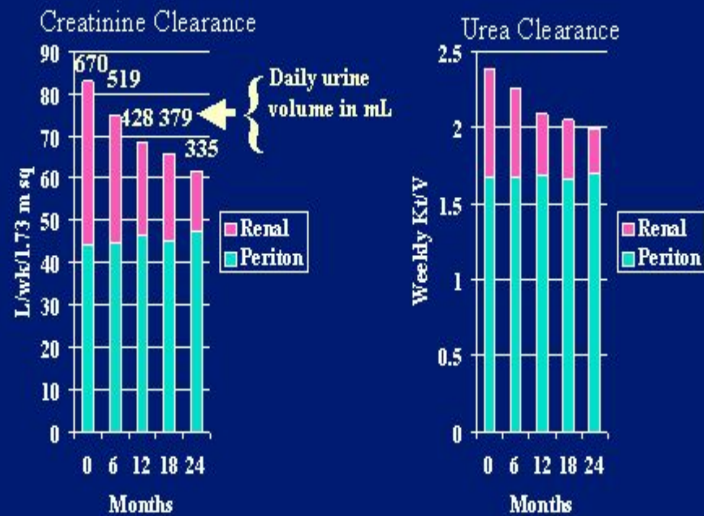
JOANNE M. BARGMAN, KEVIN E. THORPE, DAVID N. CHURCHILL and the CANUSA Peritoneal Dialysis Study Group

**originally did not address RRF*

Re-CANUSA Introduction

- "....recommendations proposed by the Dialysis Outcome Quality Initiative in the United States. These recommendations assume an equivalence between clearance of small molecules by the native kidneys and by the peritoneal membrane…"
- CANUSA: a multi-center study aiming at determining association of patient mortality, dialysis dose and nutritional status in PD patients
- JASN abstract in 1996: "improved clinical outcomes were associated with increased adequacy and better nutritional status"
- Small reports: Kd ≠ Kr
- Authors re-analyzed database 5 years later (almost as in: NCDS and mechanistic analysis….), they discovered that actually RRF was measured at 6 monthly intervals
- Cox-proportional hazard model: GFR (RRF) and Kd creatinine as time dependent covariates

A Striking Observation



- GFR: 37.7 → 14.8 L/week over 24 months
  Kd : 44.3 → 47.2 L/week over 24 months
- In the 90s CAPD prescription was relatively uniform
- Main difference of achieved Kt/V between study groups was due to: differences in RRF

Relative Risk of Mortality

- *SGA 0.740 0.647-0.842
- Kd creatinine 1.000 0.898-1.105
  (each 5 L/wk per 1.73 m2 greater)
- RRF 0.88 0.829-0.943
  (each 5 L/wk per 1.73 m2 greater)

*Subjective global assessment by a dietician

Non-equivalence of Clearances….

Fresenius Medical Care Data Base
Diaz-Buxo et al, AJKD 33:523, 1999

	Peritoneal and renal clearance model	
	P	Death OR
Age (yr)	<.001	1.042
Sex (m)	NS	0.689
Race (nonwhite)	0.09	1.881
DM	<.001	2.991
Peritoneal clearance	NS	1.008
Renal clearance	0.003	0.887

Only prevalent pts, only comorbidity noted is DM, only one clearance data set used

- RRF and PD clearances do not seem to be equivalent for patient death as the outcome (here expressed as odds ratio)
- Kd ≠ Kr

A Chinese Study: a Matter of Range

- 270 CAPD patients followed over 6 years
- Average peritoneal Kt/V throughout the study was 1.59 +/- 0.37 (Kt/V was low); median residual GFR 0.82 mL/minute (very low: 0.82x1.44x7 L/week), **(RRF was also low)**
- sex, age, duration of dialysis, presence of diabetes, serum albumin, dialysate-to-plasma creatinine ratio at 24 hours, **peritoneal Kt/V, residual GFR**, and normalized protein nitrogen appearance were independent factors of both actuarial patient survival and technique survival

**Perit Dial Int. 2004 Jan-Feb;24(1):*
Independent effects of renal and peritoneal clearances on the mortality of peritoneal dialysis patients.
Szeto CC, Wong TY, Chow KM, Leung CB, Law MC, Li PK

J Am Soc Nephrol. 2004 Apr;15(4):1061-70.

- *Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT;* ***NECOSAD Study Group.***

"Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2."

Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam

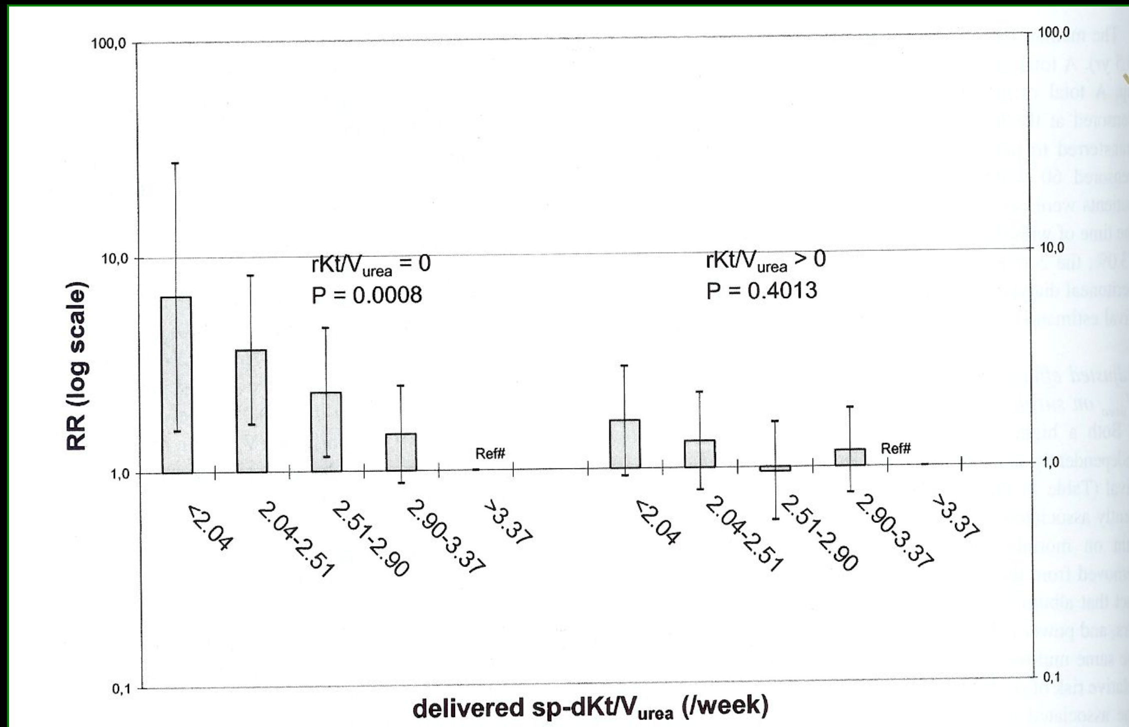
The Dutch again come to our Rescue

- Large multi-center prospective observational study in incident HD patients who survived the first 3 months (n=740)
- Follow-up to 36 months, Cox proportional-hazard model used for patient survival
- RRF measured regularly unless urine output <100 ml/day then entered in a time-dependent Cox regression model

Results

- for each increase of 1/wk in rKt/V, relative risk of death = 0.44 [P < 0.0001), for anuric patients RR=17.66 compared to rKt/V>0.84/week
- dKt/V, relative risk of death = 0.76 [P < 0.01])
- the effect of dKt/V on mortality was strongly dependent on the presence of rKt/V, low values for dKt/V of <2.9/wk being associated with a significantly higher mortality in anuric patients only
- SGA is again an independent predictor of mortality (RR=0.89)
- An excess of ultrafiltration in relation to inter-dialytic weight gain was associated with an increase in mortality independent of dKt/V

Differential Effect of dKt/V in Patients with varying degrees of RRF



- It was only in anephric patients that increasing dialysis dose mattered.
- In patients with existing RRF, RRF was a major determinant of survival
- In all patients excessive ultrafiltration was associated with increased mortality
- Kd ≠ Kr

More Studies in HD Patients

RRF Is Important in HD

- Shemin et al AJKD 38:85, 2001. Single center, 114 HD pts followed for 2 yrs showed the presence of RRF ($\geq$ 100 mL/d) lowered risk of death by 56% adjusted for duration of HD, age, smoking, DM, CV disease, albumin and URR.
- Suda et al NDT 15:396, 2000. Single center study of 41 pts on HD at least 2 yrs. Renal weekly but not dialytic Kt/V was correlated to albumin. If urine output was > 200mL/d the nPCR was significantly higher.

- Kd ≠ Kr

Still not Convinced?

- Nephrol Dial Transplant. 2004: **Important differentiation of factors that predict outcome in peritoneal dialysis patients with different degrees of residual renal function.**
  Yee-Moon Wang A, Woo J, Wang M, Man-Mei Sea M, Sanderson JE, Lui SF, Kam-Tao Li P.

- "Our study demonstrates more adverse cardiovascular, inflammatory, nutritional and metabolic profiles as well as higher mortality in anuric PD patients. Furthermore, factors associated with mortality are also not equivalent for PD patients with and without RRF, suggesting that patients with and without RRF are qualitatively different."

The Belgians come to our Rescue

Kidney Int. 2003 Dec;64(6):2238-43 by ***Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y.***

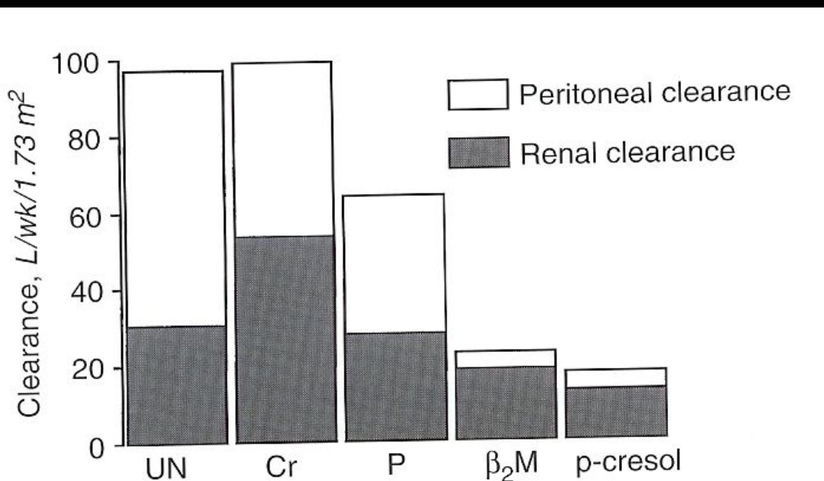


Fig. 1. Peritoneal, renal, and total clearances of urea nitrogen (UN), creatinine (Cr), phosphate (P), β_2-microglobulin (β_2m), and p-cresol. Mean values are illustrated.

- Cross-sectional observational study in 30 “nonanuric” PD patients
- β2M used as a marker of middle molecules
- P-cresol used as a marker of highly protein-bound substances
- Main finding: both markers are cleared mainly by Residual Renal Function
- Kd ≠ Kr

More from Canada….

- Adv Perit Dial. 2002;18:189-91.
  The relationship between residual renal function, protein catabolic rate, and phosphate and magnesium levels in peritoneal dialysis patients.
  P**age DE, Knoll GA, Cheung V.**
- "The very good inverse correlation between RRF and serum phosphate highlights the importance of RRF in the control of serum phosphate."
- Own experience: this is the case in HD patients as well

The Foundations are Shaking

- **“The implications of the ADEMEX study for the peritoneal dialysis prescription: the role of small solute clearance versus salt and water removal.”**

  Curr Opin Nephrol Hypertens. 2003 Nov;12(6):581-5.
- **McCormick BB, Bargman JM.:**

  ”The ADEMEX study and subsequent investigations have changed the way we perceive the optimal peritoneal dialysis prescription. This has resulted in de-emphasis of peritoneal small molecule clearance and increased emphasis on clinical assessment of dialysis adequacy, preservation of residual renal function, and optimization of salt and water removal.”

Still not Convinced?- a slide of 2 studies

Long Term BP Control in PD Cohort Is Dependent on RRF

Menon et al NDT 16:2207, 2001

- 207 incident pts, 91% HT at initiation of PD
- Systolic and MAP fell by 6-12 months and thereafter worsened
- On multivariate linear regression analysis independent associations with poor BP control were:
  - Age
  - Duration of HT prior to dialysis
  - Declining GFR or urine output (all $p < 0.001$)

- Kidney Int. 2002 Aug;62(2):639-47.
  A novel association between residual renal function and left ventricular hypertrophy in peritoneal dialysis patients.
  Wang AY, Wang M, Woo J, Law MC, Chow KM, Li PK, Lui SF, Sanderson JE.

- Conclusions:
  "Other than anemia, hypoalbuminemia and arterial pulse pressure, this study demonstrates an important, novel association between the degree of RRF and severity of LVH in ESRF patients undergoing

Can it be done in HD?

- Int J Artif Organs. 2004 Mar;27(3):251-4.
  Maintenance of residual renal function 10 years after the start of hemodialysis: the advantage of tailored schedules?
  Piccoli GB, Burdese M, Mezza E, Consiglio V, Mangiarotti G, Thea A, Bermond F, Gai M, Lanfranco G, Jeantet A, Segoloni GP.

- "Eighteen months after starting hemodialysis on a conventional thrice weekly schedule, the patient was switched to 2 sessions/week (creatinine clearance increased to 6 ml/min). Thereafter, clearances were checked in alternate months and treatment was tailored to an equivalent renal clearance > or =12 ml/min (1-2 sessions, 2-3.30 hours/week). Ten years after beginning dialysis, he is on a twice weekly schedule (3.30 hours), is normotensive, works full-time and does not want to go on a transplant waiting list."

It can be done….

- ASAIO J. 2002 Jul-Aug;48(4)
  Adjustment of hemodialysis dose for residual renal urea clearance: a two year study of impact on dialysis time.
  Khan MS, Atav AS, Ishler MJ, Rehman A, Lozano JE, Sklar AH.

- "Regression analysis revealed that each 0.10 increment in K(r) t/V urea yielded an actual dialysis time reduction of 12 minutes per week with average cumulative reduction of 80 minutes per week per patient. At approximately 1 year after initiation of dialysis, there were still 10 patients whose dialysis prescriptions were being adjusted on the basis of K(r)t/V urea."

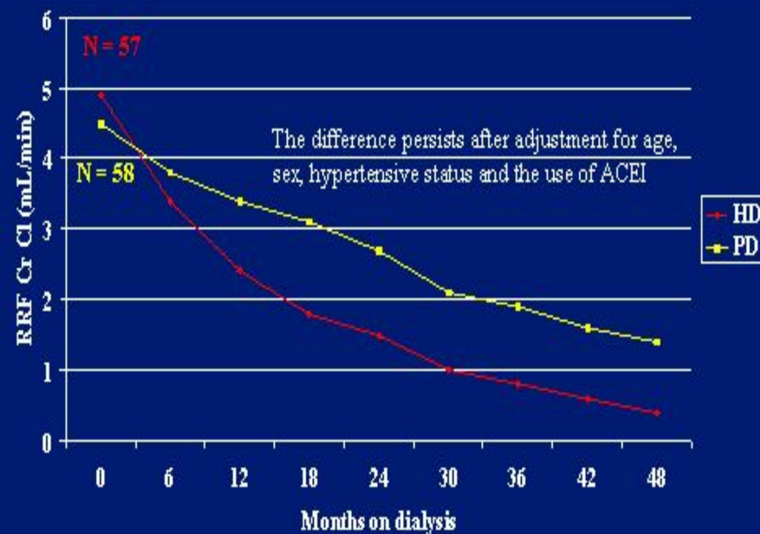
Conclusions I

- The current way we measure the so called "adequacy" of dialysis is gravely suboptimal because of both theoretical (alias simple commonsense) and clinical (alias everyday practice) considerations.
- Residual and dialysis clearances are not equivalent (Kd ≠ Kr).
- Standardized stdKt/V is a clinically invalid approach as it does matter *how* a given urea level is maintained (dialysis tolerance, maintenance of residual function etc).
- The presence of RRF may mean better clearance of middle, large and protein-bound molecules.
- The absence of RRF modifies patient mortality and even other mortality factors, the latter in PD patients.
- It appears to be feasible to adjust dose for RRF even in HD.
- Therefore one has to measure and maintain RRF as long as possible.

Decline of RRF: PD better than HD

The Influence of Dialysis Treatment Modality on Remaining RRF

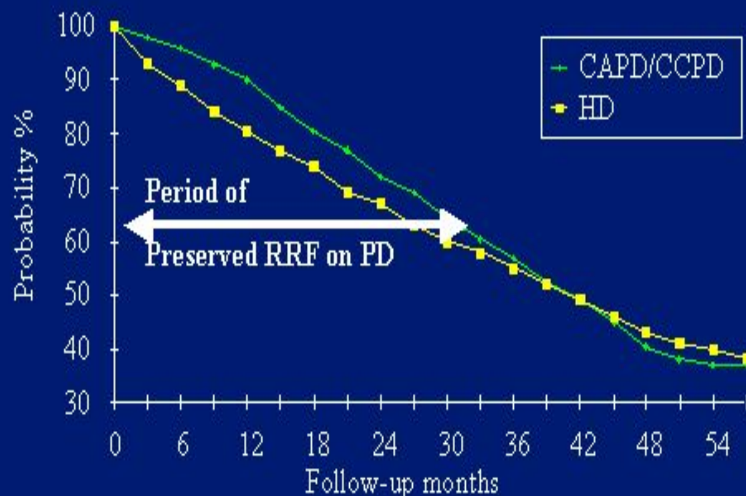
Lysaght MJ, et al, *ASAIO Trans* 37:598, 1996



RRF Under PD vs. Under HD

- Rottembourg, 1982. 25 pts on each followed for 18 months with GFR going from 4.4 to 4.0 in CAPD and from 4.3 to 1.3 in HD ($p < 0.01$). Updated in 1993 with more diabetics, same result.
- Cancarini et al, 1986. The PD pts slower decline of RRF but not for all diagnoses.
- Feber, 1994. Children on PD preserve urine output better on PD, but GFR not preserved.
- Park, 2000. PD pts having HD treatments for a month lost GFR faster than PD pts not needing HD (confirmed X 1)

Importance of Difference in RRF Decline between Modalities



- RRF is relatively preserved in the first 2-4 years after initiating PD
- Survival tends to be better in the first few years on PD then is identical with HD
- Part of this (other possible factors: weight gain, accumulating AGEs, membrane damage etc) may be because of RRF

Another Slide of 2 Studies…

Preservation Of RRF, PD vs HD by Membranes

Lang et al PDI 21:52, 2001

Prospectively 15 incident CAPD pts matched (for cause of ESRD and RRF) by 15 incident polysulfone and 15 cuprophane HD pts

Mean loss of Cr Cl from matched baselines at these time intervals

	6 months	12 months
CAPD	0.6	1.4
Cuprophane HD	3.6	NA
Polysulfone HD	1.9	NA
All HD	2.8	3.7

- Kidney Int. 2002 Jan;61(1):256-65
  Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD.
  McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K.
- *"In hemodialysis using high-flux biocompatible membranes and ultrapure water, residual renal function declines at a rate indistinguishable from that in CAPD"*
- *But: 300 HD 175 PD patients, few diabetics, well controlled BP (<10% hypotensive episodes),*
- *Both modalities: very well maintained urea residual clearance*

RRF Decline and Modality

- PD better: less hemodynamic effects than HD
- PD better: no bio-incompatible membranes
- PD better: better BP control
- PD worse: peritonitis?, dialysate volume?

- In PD additional associated factors:

-diabetes

-male sex?

-impaired LV function

-proteinuria

-BP meds, aminoglycosides,

- NSAIDS statistically not a factor (probably does depend on dose)

RRF Decline-a Study

Factors Associated with Loss of RRF in Combined PD and HD, Multivariate

Variable	Odds Ratio (UV < 200 ml)	P value
Female (vs. male)	1.45	<0.001
Nonwhite (vs. white)	1.57	<0.001
Comorbid diabetes	1.82	0.006
Comorbid CHF	1.32	0.03
CrCl at ESRD onset (ml/min)	0.96	0.04
PD (vs. HD)	0.35	<0.001
ACE inhibitor use	0.68	<0.001
Ca^{++} channel blocker use	0.77	<0.01
Serum Ca^{++}	0.81	0.05

- Moist et al JASN 11:556
- 1819 HD or PD pts
- Endpoint: urine output< 200 ml/day
- 8-18 months follow-up
- The only recent study that included HD patients

The Dutch and the Australians come to our Rescue

Predictors of Decline in RRF in Incident PD Patients

Johnson et al PDI 23:276, 2003

- 146 consecutive PD pts in Brisbane
- Correlation between GFR and urine volume was moderate ($r^2 = 0.55$, $p < 0.001$)
- Because of small numbers they simply split into the 50% with slower and 50% with faster decline
- The more rapid decliners were more likely to be male, non-Caucasion, diabetic, receiving a statin, had higher baseline GFR, had higher $D/P_{creatinine}$
- Anuria predicted by lower baseline RRF, larger size, diabetes, higher protein intake, higher $D/P_{creatinine}$

- NECOSAD-1 (KI 62: 1046, 2002)
- 522 Pts, no effect cause of ESRD
- Positive effect:

-PD versus HD

-better BP diastolic

-less low BP on HD

-less dehydration on PD

-no proteinuria

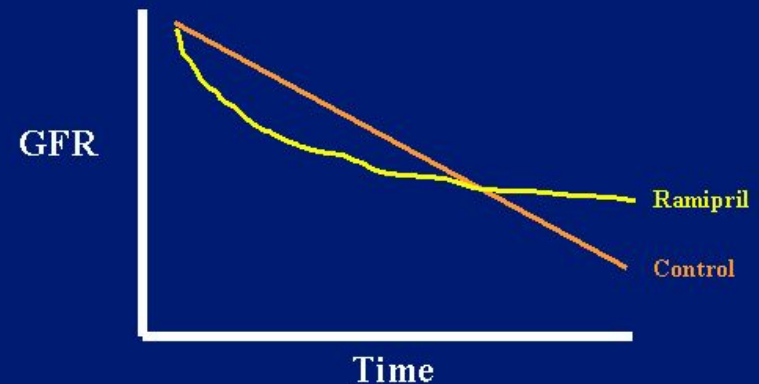
-less comorbidities

ACE Inhibition and RRF in PD Patients

ACE Inhibitors Help Preserve RRF in PD Patients

Li et al, Ann Int Med 139:105, 2003

- 30 pts randomly assigned to 5 mg/d ramipril; 30 to no Rx
- Over 12 months RRF GFR declined
  - 2.07 mL/min/1.73 m^2 in ramipril group
  - 3.00 mL/min/1.73 m^2 in control group ($p < 0.03$)
- Developing anuria at 12 months
  - 14 in ramipril group
  - 22 in control group
- No BP differences (other drugs allowed for BP control)
- Ramipril associated with initial decrement, but long term preservation of RRF



The Japanese come to our Rescue: AIIRB and Preservation of RRF in PD

Am J Kidney Dis. 2004 Jun;43(6):1056-64

- **Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD.**
  Suzuki H, Kanno Y, Sugahara S, Okada H, Nakamoto H.
- 34 patients follow-up up to 2 years, BP kept <130/80 in both groups and was not different
- Valsartan group decreased decline of RRF (3.2 +/- 0.3 to 4.3 +/- 0.7 mL/min/1.73 m2 versus 5.9 +/- 0.5 to 2.8 +/- 0.4 mL/min/1.73 m2)
  (N.B. in the valsartan group GFR increased in the first 6 months then started declining with a less steep slope)

Additional Factors in PD Patients

- Excessive ultrafiltration may lower RRF
- Aminoglycosides: controversial reports
- NSAIDS: no clear evidence (most patients reporting use may do so at low dosages)
- Diuretics: no effect on GFR while positive effect on urine volume (in PD: Van Olden et al PDI 23: 339, 2003 and Medcalf et al KI 59: 1128, 2001)

Conclusions II

- As PD seems to be associated with better preservation of RRF and decreased early mortality, this may be a factor to consider in modality selection.
- In HD, special techniques (biocompatible membranes, ultrapure water, *excellent* BP control, avoidance of low BP) may be associated with RRF preservation that is close to that in PD.
- The main factors in preservation of RRF are: good blood pressure control, control of proteinuria, avoidance of low blood pressure episodes and dehydration, less comorbidities and possibly avoidance of peritonitis.
- Certain blood pressure classes such as ACEI, AIIRB and CCB may be especially beneficial. This is better documented in PD patients.
- Although the evidence is controversial, it makes good sense to try to avoid nephrotoxic substances (mostly aminoglycosides and NSAIDS) in patients with RRF, whereas diuretics are ineffective.
- Time and time again Subjective Global Assessment by a dietician has been shown to be a significant predictor of survival. Why not that of a doctor? Alias

For those who know Latin and Roman History (or have a sharp eye…)

- Ludovicus Giomus Cato
  IIIth century B.C.E.:

“Ceterum censeo Cathepervinem delendam esse!”

(Otherwise I think Kt/V should be abandoned)