PHARMACOKINETICS IN PATIENTS REQUIRING RENAL REPLACEMENT Rx

PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

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JOHN JACOB ABEL
1857 - 1938

FIRST DESCRIPTION OF HEMODIALYSIS IN ANIMALS*

ON THE REMOVAL OF DIFFUSIBLE SUBSTANCES FROM THE CIRCULATING BLOOD OF LIVING ANIMALS BY DIALYSIS

JOHN J. ABEL, LEONARD G. ROWNTREE AND B. B. TURNER

From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, December 18, 1913

CONTENTS

I. Introductory..... 275
II. The method..... 277
III. The apparatus: Types and methods of construction..... 278
IV. Technique of the experiments..... 295
V. Preparation of the leech extract..... 302
VI. Employment of the apparatus not detrimental to life..... 305
VII. Quantitative data on the elimination of salicylic acid by the apparatus..... 309
VIII. Qualitative data on constituents of the blood separated by the apparatus..... 314
IX. Summary..... 316

*** From: Abel JJ, et al. J Pharmacol Exp Ther 1914;5:275-317.**

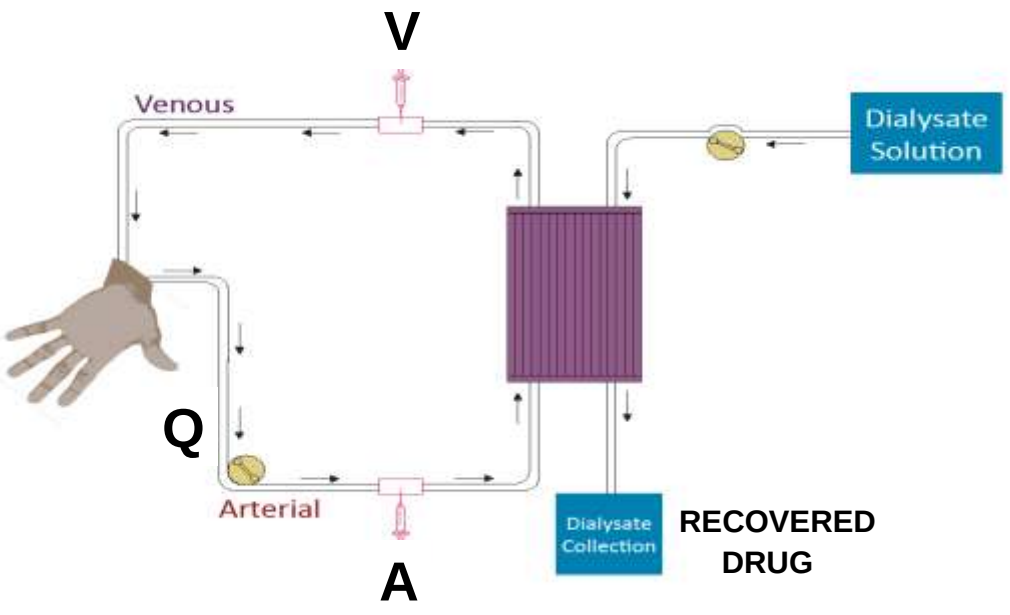
WILLEM J. KOLFF, M.D. (1911 -)

ELIMINATION BY DIFFERENT ROUTES

MEASUREMENTS	RENAL	HEPATIC	DIALYSIS
BLOOD FLOW	+*	+*	+
AFFERENT CONC.	+	+	+
EFFERENT CONC.	0	0	+
ELIMINATED DRUG	+	0	+

*not actually measured in routine PK studies

DATA SOURCES FOR FICK EQUATION



IMPACT OF CL_D

$$CL_E = CL_R + CL_{NR} + CL_D$$

CRITERION FOR DIALYSIS EFFICACY*

$$CL_{EC} > 30\% [CL_R + CL_{NR}]$$

BUT CLEARANCE ESTIMATES MUST BE COMPARABLE

* Levy G. Am J Med 1977;62:461-5.

GOALS OF DIALYSIS DISCUSSION

- DISCUSSION OF DIALYSIS CLEARANCE
  - MECHANISTIC - RENKIN APPROACH
  - EMPIRICAL
    - RECOVERY CLEARANCE
    - FICK EQUATION
- CLINICAL STUDIES OF DIALYSIS PK
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  - TREATMENT OF DRUG TOXICITY
- PHYSIOLOGIC CHANGES DURING DIALYSIS
  - USE OF KINETIC METHODS FOR ANALYSIS
  - PATHOPHYSIOLOGIC CONSEQUENCES

EUGENE RENKIN
PROFESSOR EMERITUS AT UC DAVIS

RENKIN DIALYSIS EQUATION*

$$CL_D = Q(1 - e^{-P \cdot S/Q})$$

Q = DIALYZER BLOOD FLOW

P·S = PERMEABILITY-SURFACE AREA PRODUCT OF DIALYZING MEMBRANE

NEGLECTS: BOUNDARY EFFECTS, ULTRAFILTRATION

* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5

DETERMINANTS OF PERMEABILITY TERM (P or P · S)

- DIALYZER MEMBRANE CHARACTERISTICS
  - MEMBRANE SURFACE AREA
  - MEMBRANE THICKNESS
  - MEMBRANE POROSITY
- DRUG BINDING TO PLASMA PROTEINS
- SOLUTE SIZE AND DIFFUSIVITY

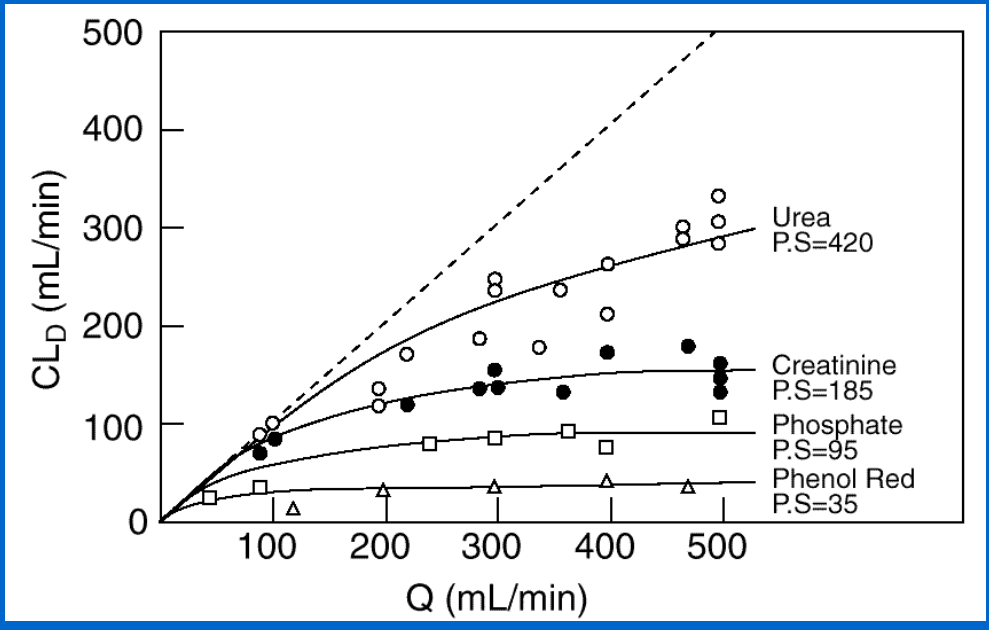
DIALYZER PERMEABILITY VS. FREE WATER DIFFUSION COEFFICIENTS

PROCAINAMIDE/NAPA:

RATIO OF DIALYZER PERMEABILITY COEFFICIENTS*	**1.28 ± 0.23**
RATIO OF FREE WATER DIFFUSION COEFFICIENTS	**1.23**

*** From Gibson TP et al. Clin Pharmacol Ther 1976;20:720-6.**

DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW*



* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5

POSSIBLE USE FOR INTRA-DIALYZER TRANSFER OF RESULTS

- PERFORM PRELIMINARY *IN VITRO* STUDY TO OBTAIN P RATIO FOR DRUG & STANDARD COMPOUND FOR DIALYZER BEING USED IN DIALYSIS STUDY (RECORD Q & RBC/PLASMA).
- THIS RATIO CAN BE USED TO ESTIMATE DRUG CL_D FOR OTHER DIALYZERS AND OTHER Q VALUES IF P OF STANDARD COMPOUND FOR THAT DIALYZER IS KNOWN.
- NEED TO SELECT APPROPRIATE STANDARD COMPOUND (? CREATININE).

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RECOVERY CLEARANCE

THE GOLD STANDARD

$$CL_D = \frac{C_D \cdot Vol_D}{\overline{A} \cdot t}$$

$$CL_D = \frac{C_D \cdot Vol_D}{AUC_A}$$

A-V DIFFERENCE METHOD [FICK EQUATION]

$$CL = Q\left[\frac{A - V}{A}\right]$$

$$E = \left[\frac{A - V}{A}\right]$$

Q = DIALYZER BLOOD FLOW
A = CONCENTRATION IN BLOOD COMING TO DIALYZER
V = CONCENTRATION IN BLOOD LEAVING DIALYZER
E = EXTRACTION RATIO

EXTRACTION RATIO

Renkin Equation :

$$E = 1 - e^{-P/Q}$$

Fick Equation :

$$E = \left[\frac{A - V}{A} \right]$$

In Each Case :

$$CL = Q \bullet E$$

TWO DIALYSIS MYTHS

- NEED TO USE BLOOD CONCENTRATIONS WHEN CALCULATING BLOOD CLEARANCE

  BUT PLASMA CONCENTRATIONS PROPORTIONAL TO BLOOD CONCENTRATIONS, SO MAKES NO DIFFERENCE IN A/[A + V] RATIO

- NEED TO USE PLASMA FLOW WHEN CALCULATING PLASMA CLEARANCE

PLASMA VS. BLOOD CLEARANCE

RECOVERY : $CL_P = \frac{U \bullet V}{P}$ $CL_B = \frac{U \bullet V}{B}$

FICK : $CL_P = Q_{PK}\left(\frac{A-V}{A}\right)$ $CL_B = Q_B\left(\frac{A-V}{A}\right)$

IF $B > P$: $CL_P > CL_B$, SO: $Q_{PK} > Q_B > Q_P$

NAPA IN RBC IS DIALYZED

FLOW PARAMETER	MEAN VALUE mL/min
Q_{PK}	223
Q_{MEAS}	195 ($p < 0.2$)
Q_{EFF}*	217 ($p > 0.2$)

* $Q_{EFF} = [(1 - Hct) + (RBC/P) (HCT)] Q_{MEAS}$

DIALYSIS SATURATION VS. RECOVERY CLEARANCE

DIALYSIS SATURATION ($EC = C_d/C_p$):

$$CL_D = Q_d \frac{C_d}{C_p}$$

RECOVERY CLEARANCE:

$$CL_D = \frac{UV}{P\tau} = \frac{C_d V_d}{C_p \tau}$$

BUT:

$$Q_d = \frac{V_d}{\tau}$$ ***SO EXPRESSION S ARE EQUIVALENT***

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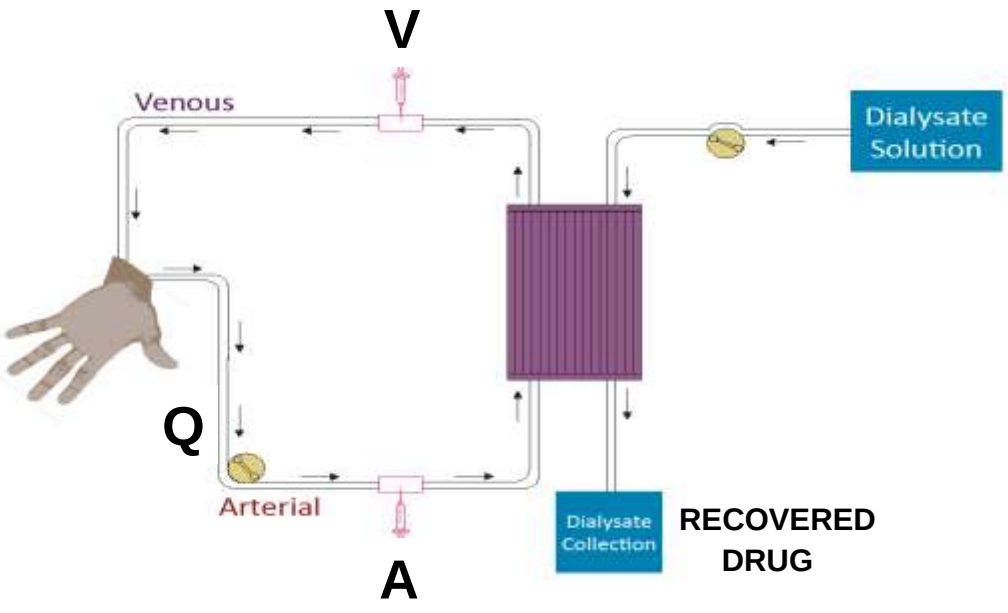
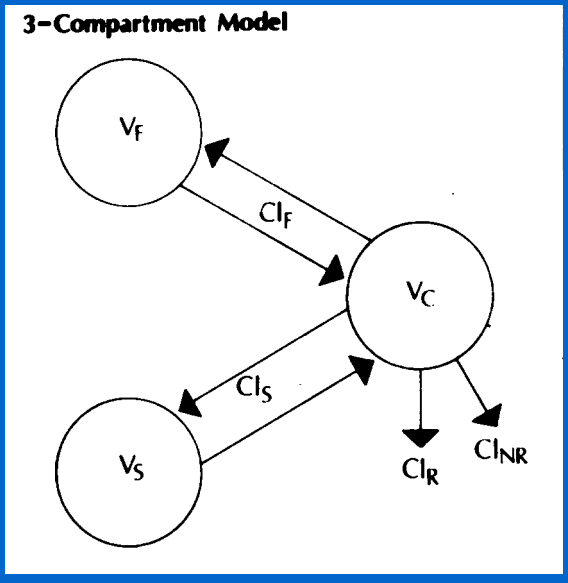
DATA SOURCES FOR FICK EQUATION

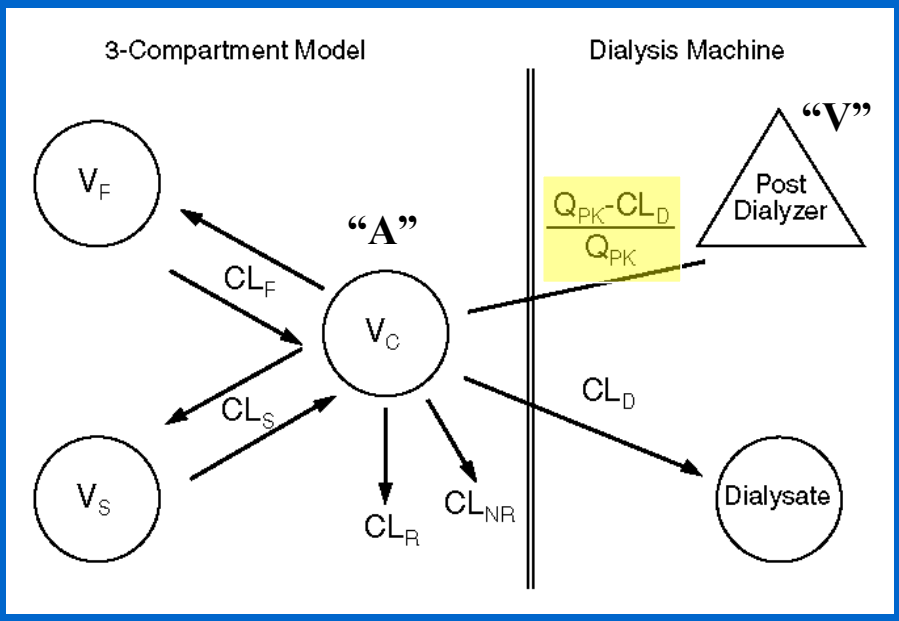


KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

FICK CLEARANCE EQUATION

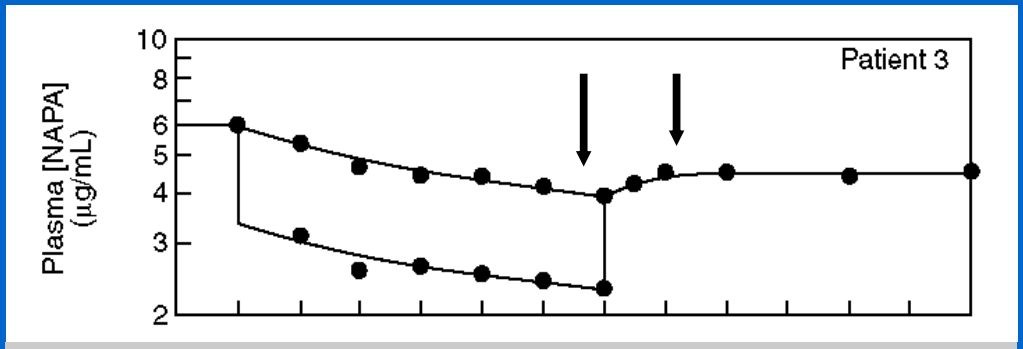
$$CL = Q\left[\frac{A - V}{A}\right]$$

$$CLA = QA - QV$$

$$QV = QA - CLA$$

$$V = \left[\frac{Q - CL}{Q}\right]A$$

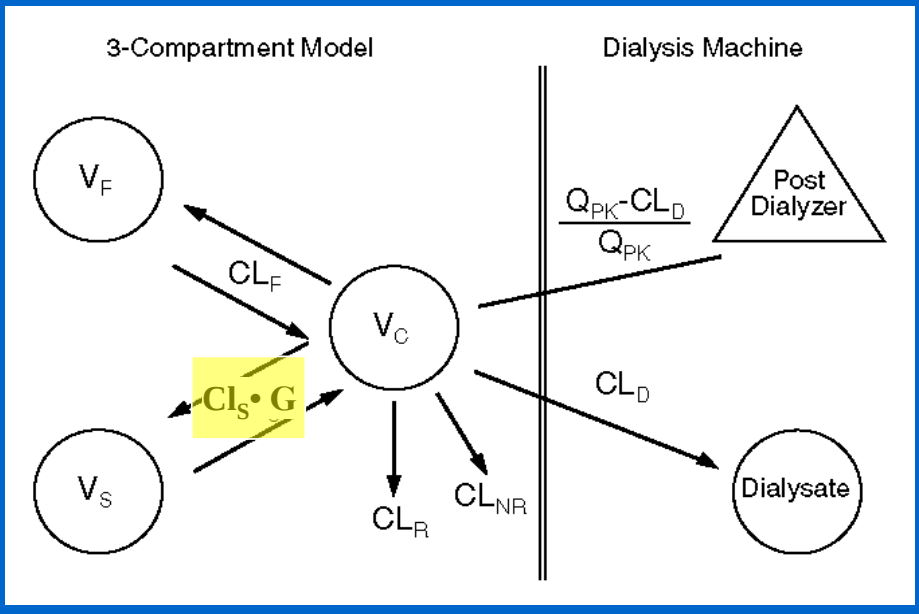
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*



1. **DURING DIALYSIS: [A] AND [V] DROP MORE THAN EXPECTED FROM DRUG RECOVERY**
2. **AFTER DIALYSIS: CONCENTRATION REBOUND IS LESS THAN EXPECTED**

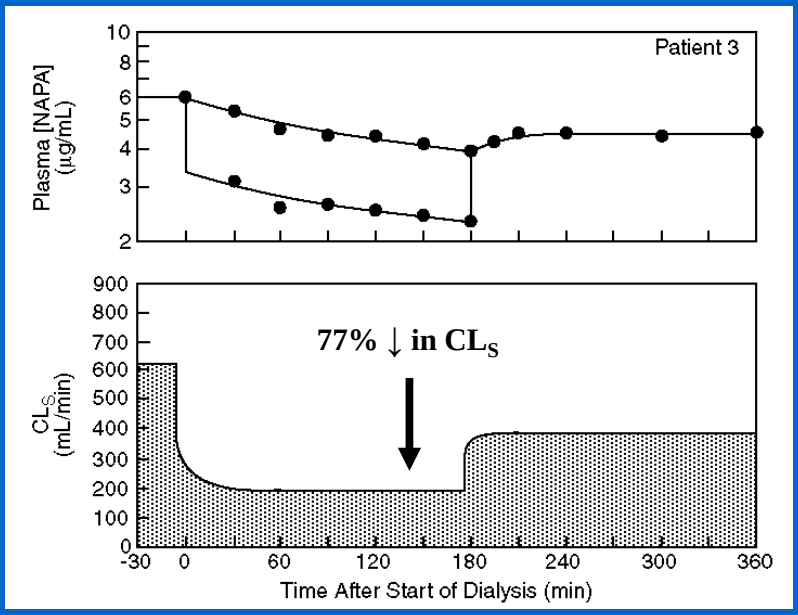
* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

REDUCTION IN CL_S DURING AND AFTER HEMODIALYSIS*



* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

CONDUCT OF PK STUDIES IN HEMODIALYSIS PATIENTS

Chapter 6 – Principles of Clinical Pharmacology

Atkinson AJ Jr, Umans JG: Pharmacokinetic Studies in Hemodialysis Patients. Clin Pharmacol Ther 2009;86:548-52.

CDER, FDA: Draft Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling. http://www.fda.gov downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM204959.pdf

GOALS OF DIALYSIS DISCUSSION

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CASE HISTORY

A 67 year-old woman became lethargic and confused and developed hypotension, renal insufficiency, junctional tachycardia and intraventricular conduction delay after ingesting an estimated 7gm of procainamide (PA). Plasma PA and NAPA concentrations were 57 µg/mL and 55 µg/mL, respectively.

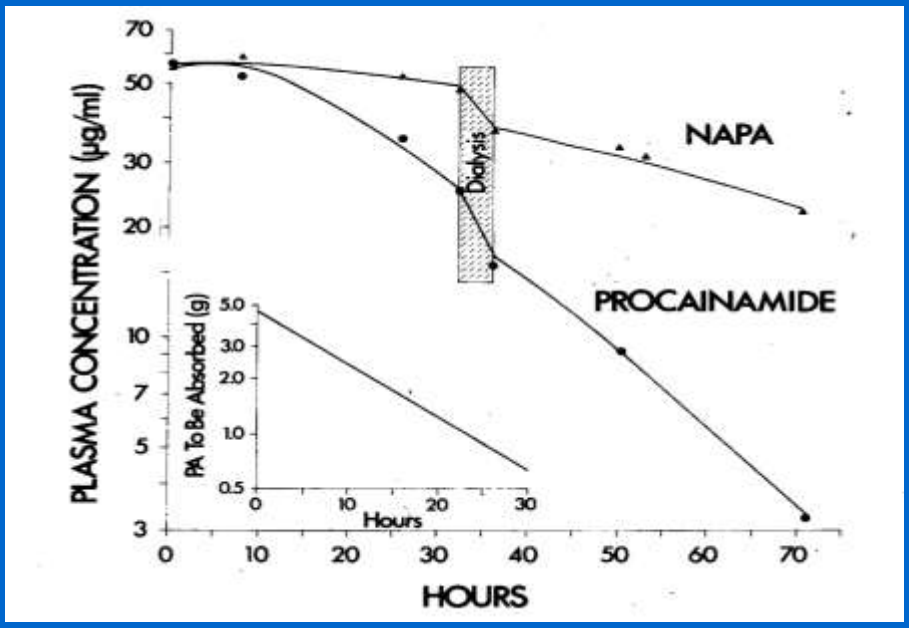
CASE HISTORY (cont.)

Hemodialysis was performed for 4 hr. By the end of the second hour BP was maintained in the range of 110/80 mm Hg without vasopressor therapy. At the end of dialysis, the patient was alert and oriented although only 340 mg of PA and 470 mg of NAPA had been removed by this procedure.

DIALYSIS CASE HISTORY (cont.)

Fifteen hours after dialysis, PA and NAPA levels were 9.2 µg/mL and 33 µg/mL, respectively. The patient had returned to normal sinus rhythm with QRS = 0.12 sec.

KINETIC ANALYSIS OF HEMODIALYSIS FOR PROCAINAMIDE TOXICITY*



*** From: Atkinson AJ Jr, et al. Clin Pharmacol Ther 1976;20:585-92.**

CRITERION FOR DIALYSIS EFFICACY*

$$CL_{EC} > 30\% [CL_R + CL_{NR}]$$

* Levy G. Am J Med 1977;62:461-5.

WAS DIALYSIS EFFICACIOUS?

- **DIALYSIS INCREASED DRUG CLEARANCE**
  - **PA – TWO FOLD**
  - **NAPA – 3.8 FOLD**
- **BUT 4 hr OF DIALYSIS REMOVED < 1 gm of 7 gm DOSE**
  - **340 mg PA**
  - **470 mg NAPA**
- **HOWEVER, BLOOD LEVELS FELL SUBSTANTIALLY**
  - **PA: 25.7 µg/mL → 15.5 µg/mL**
  - **NAPA: 47.0 µg/mL → 35.5 µg/mL**

***AND* PATIENT'S CONDITION STABILIZED**

PA & NAPA KINETICS IN TOXIC PATIENT

	NORMAL		PATIENT	
	PA	NAPA	PA	NAPA
$t_{1/2}$ (hr)	2.5	6.2	10.5	35.9
CL_E (mL/min)	590	233	66.8	16.1
CL_D (mL/min)			68.3	45.8
$V_{d\beta}$ (L/kg)	1.80	1.76	0.76	0.63

ESTIMATION OF V_d

Question: Why was distribution volume estimate so much lower in patient than in normal subjects?

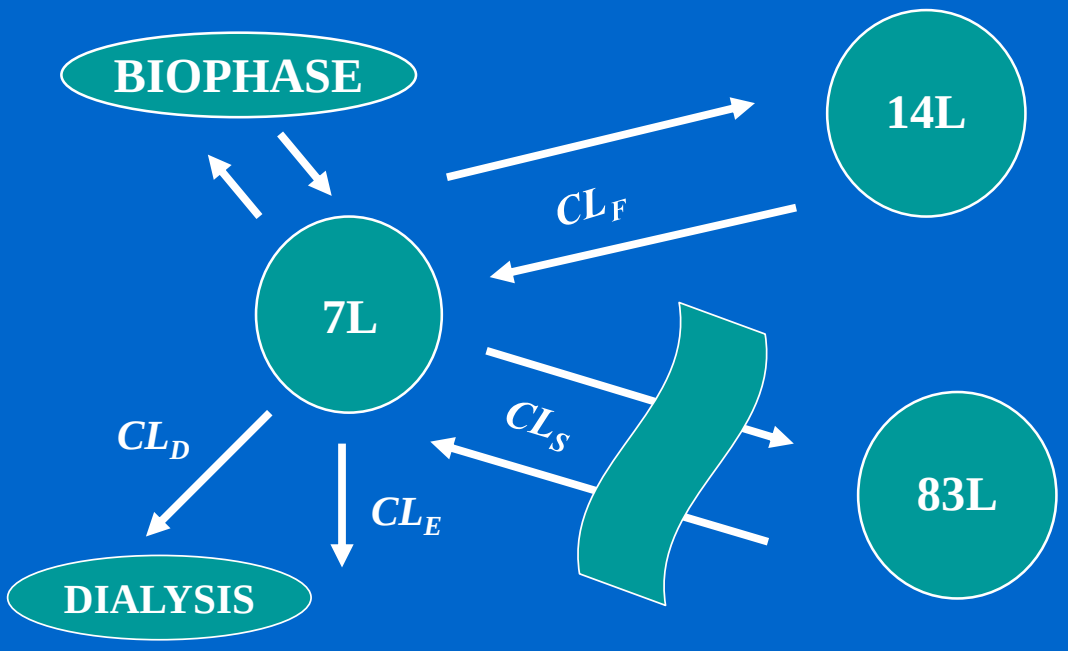
USUAL V_d ESTIMATE :

$$V_d = \frac{\text{DOSE GIVEN}}{\Delta \text{ CONCENTRAT ION}}$$

DIALYSIS V_d ESTIMATE :

$$V_d = \frac{\text{DRUG REMOVED}}{\Delta \text{ CONCENTRAT ION}}$$

SEQUESTRATION OF DRUG IN SOMATIC TISSUES



EFFICACY OF EXTRACORPOREAL TREATMENT OF DRUG TOXICITY

- TOTAL EXTENT OF DRUG REMOVAL MAY BE COMPROMIZED BY ↓ CL_S.
- ↓ CL_S FROM SOMATIC TISSUES CAN ACCELERATE ↓ IN DRUG CONCENTRATION TO WHICH VITAL ORGANS (CNS, HEART) ARE EXPOSED AND RESULT IN A BENEFICIAL CLINICAL RESPONSE > EXTENT OF DRUG REMOVAL.
- ↓ CL_S FROM SOMATIC TISSUES ALSO ATTENUATES POST-DIALYSIS REBOUND.

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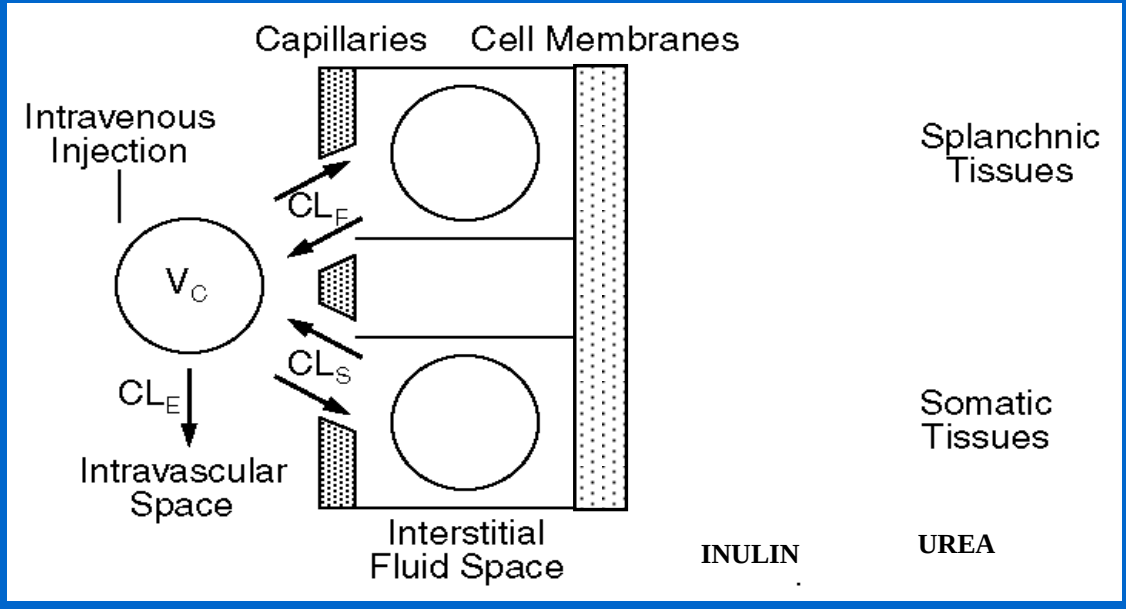
WHY DOES $CL_S \downarrow$ DURING DIALYSIS ?

$$CL = Q(1 - e^{-P \bullet S/Q})$$

POSSIBILITIES:

- CAPILLARY BLOOD FLOW (Q) DECREASES
- CAPILLARY P S PRODUCT DECREASES
- BOTH DECREASE

MULTICOMPARTMENTAL MODEL OF INULIN AND UREA KINETICS*

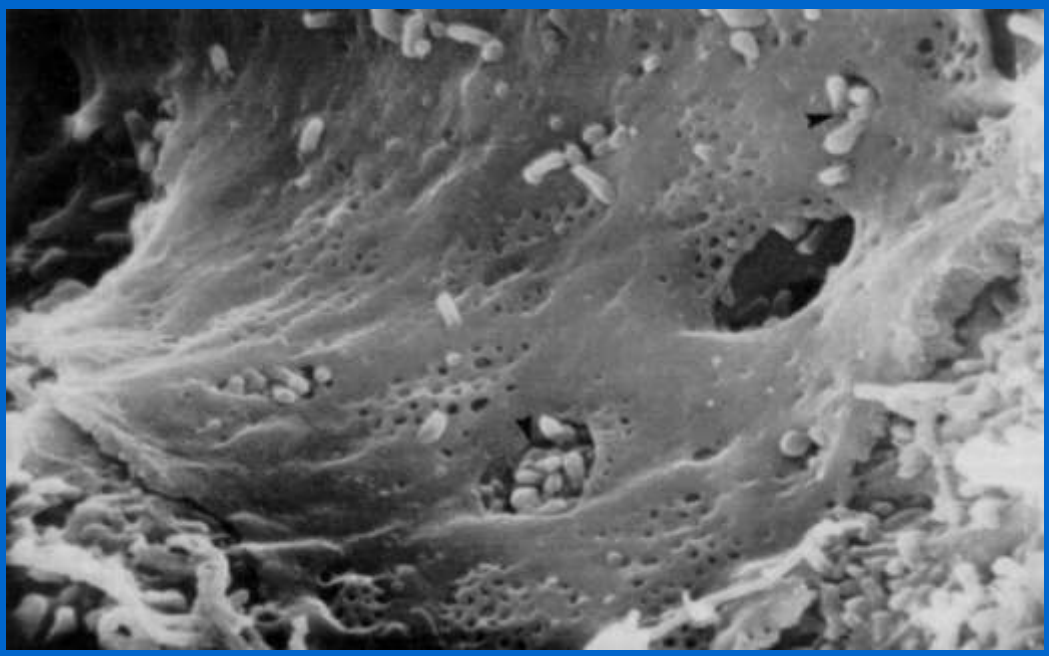


*** From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

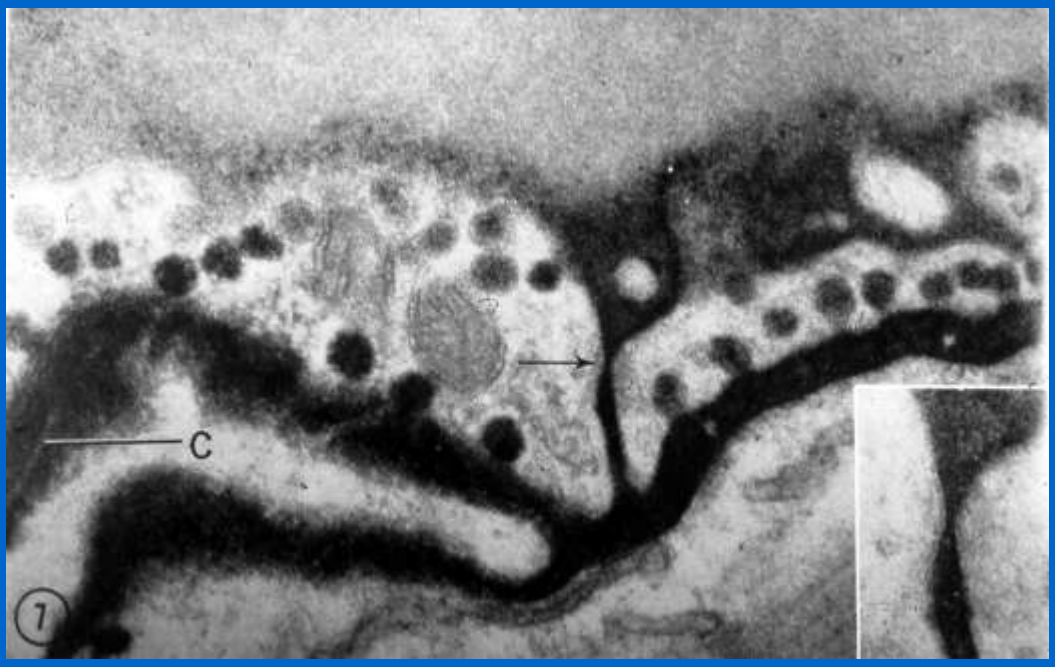
BASIS FOR KINETIC HETEROGENETIY OF INTERSTITIAL FLUID SPACE

EFFECTIVE PORE SIZE	CAPILLARY STRUCTURE	PRIMARY LOCATION
LARGE	FENESTRATED	SPLANCHNIC BED
SMALL	CONTINUOUS	SOMATIC TISSUES

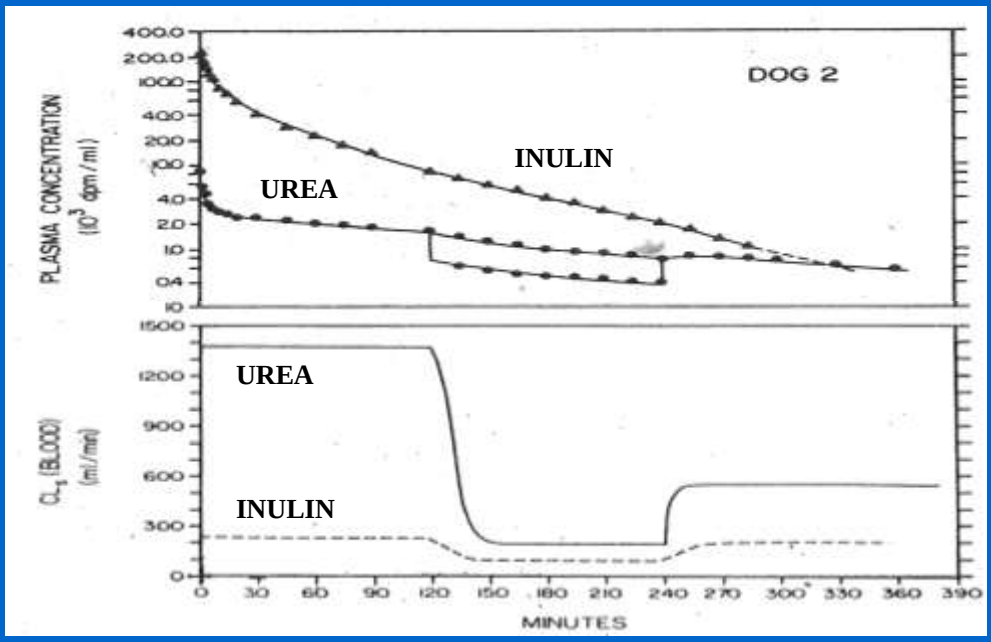
ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS



INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

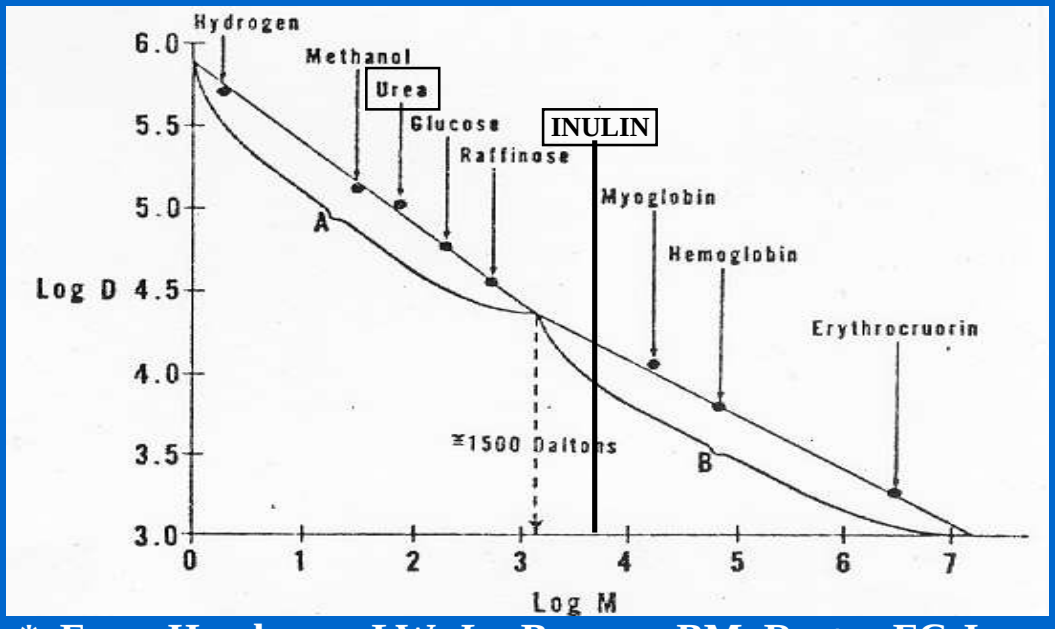


UREA (●) AND INULIN (▲) KINETICS DURING AND AFTER HEMODIALYSIS*



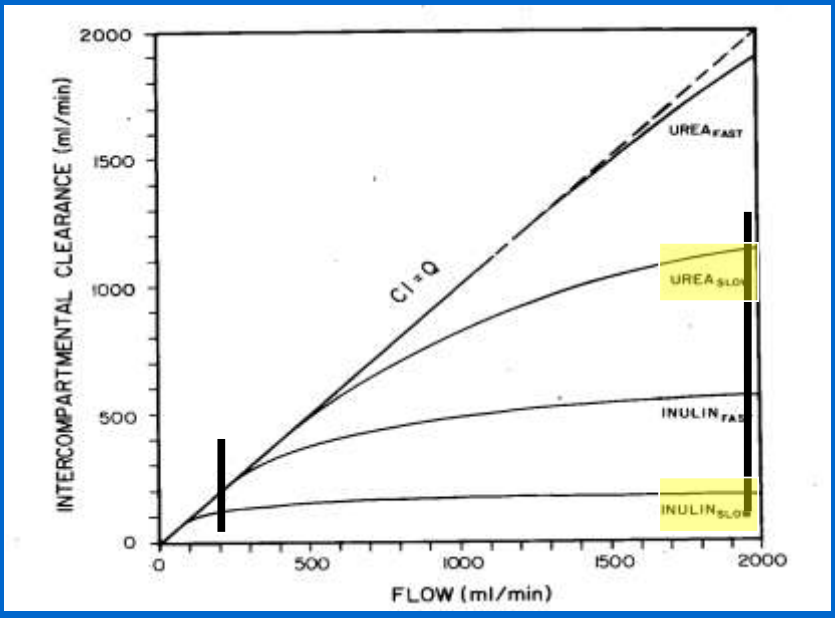
*** From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.**

EFFECT OF MOLECULAR WEIGHT (M) ON SOLUTE DIFFUSIVITY (D)*



* From Henderson LW: *In*: Brenner BM, Rector FC Jr. The Kidney. 1976, p. 1643-71.

RELATIONSHIP BETWEEN BLOOD FLOW (Q) AND CL_I *



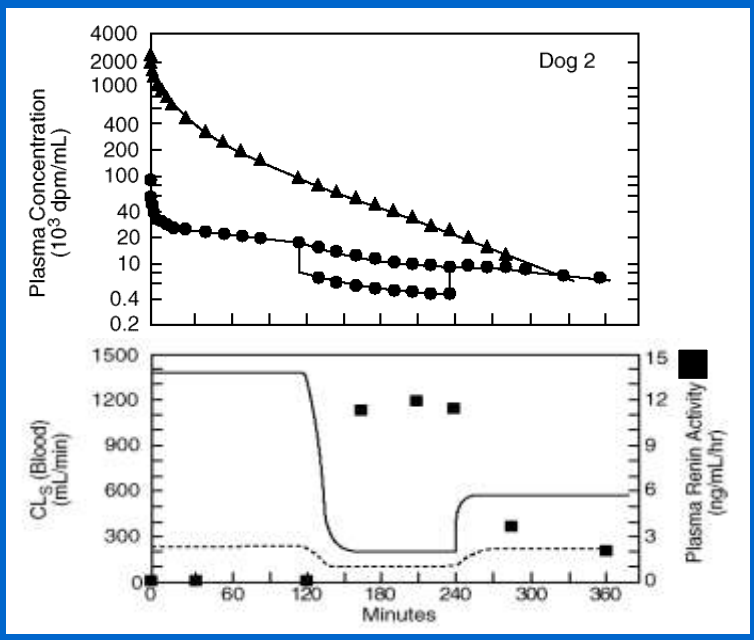
*** From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.**

UREA AND INULIN KINETICS DURING AND AFTER HEMODIALYSIS

PARAMETER	BEFORE	DURING	AFTER
BLOOD FLOW			
Q_S (mL/min)	1991	199	405
Q_F (mL/min)	2332	2591*	2965*
C.O. (mL/min)	4399	2790	3370
PS			
INULIN (mL/min)	186	169	238
UREA (mL/min)	1649	1541	2164

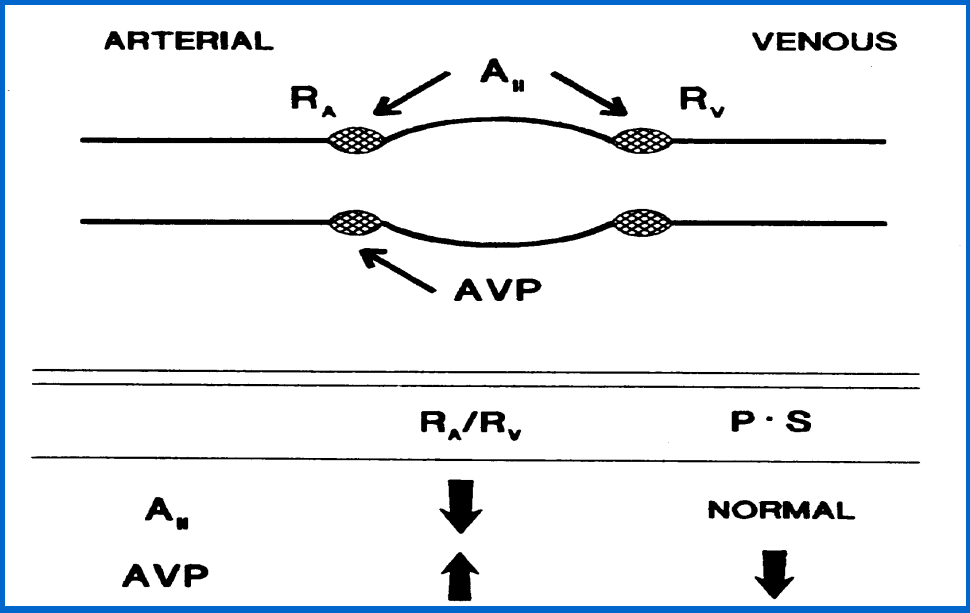
* ESTIMATED AS C.O. - Q_S

RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*



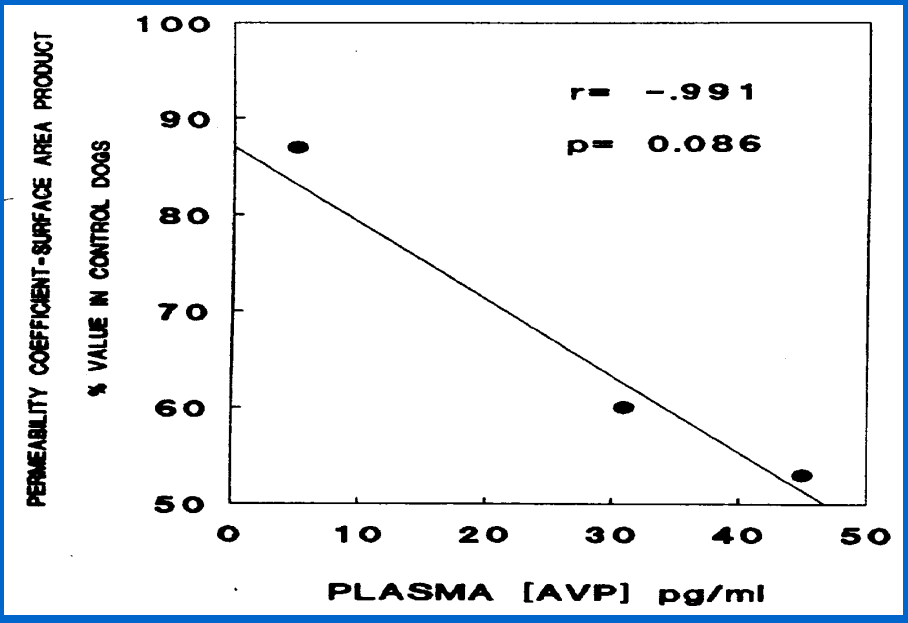
*** From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.**

DIFFERENT MICROCIRCULATORY ACTIONS OF ANGIOTENSIN II AND AVP*



* From Atkinson AJ Jr: The Pharmacologist 1989;31:229-34.

EFFECT OF ARGININE VASOPRESSIN (AVP) ON P• S*



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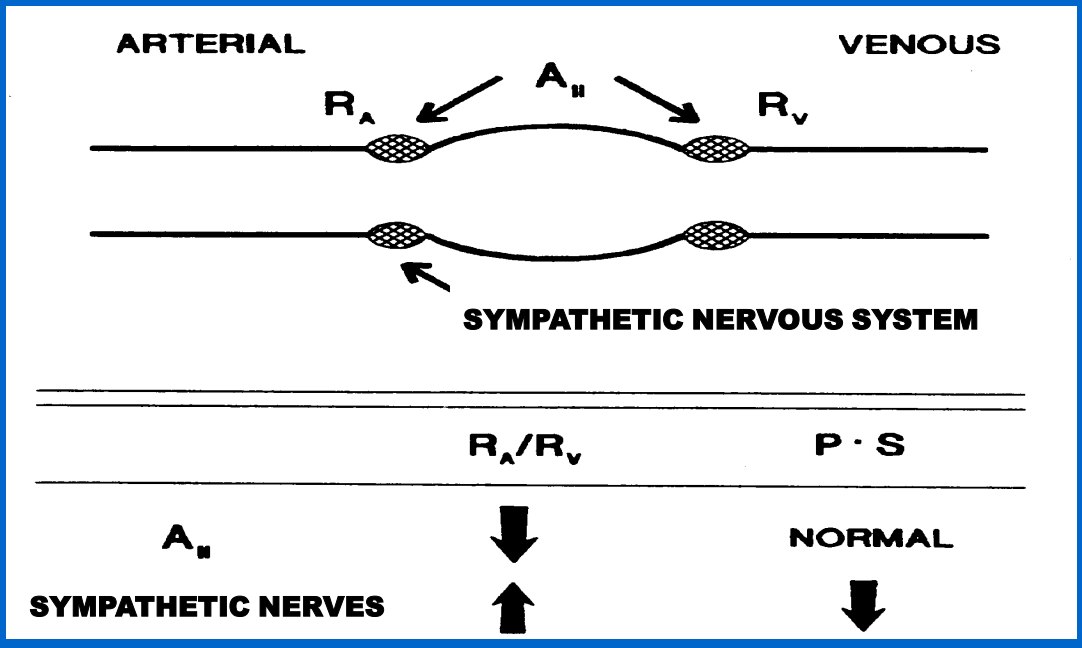
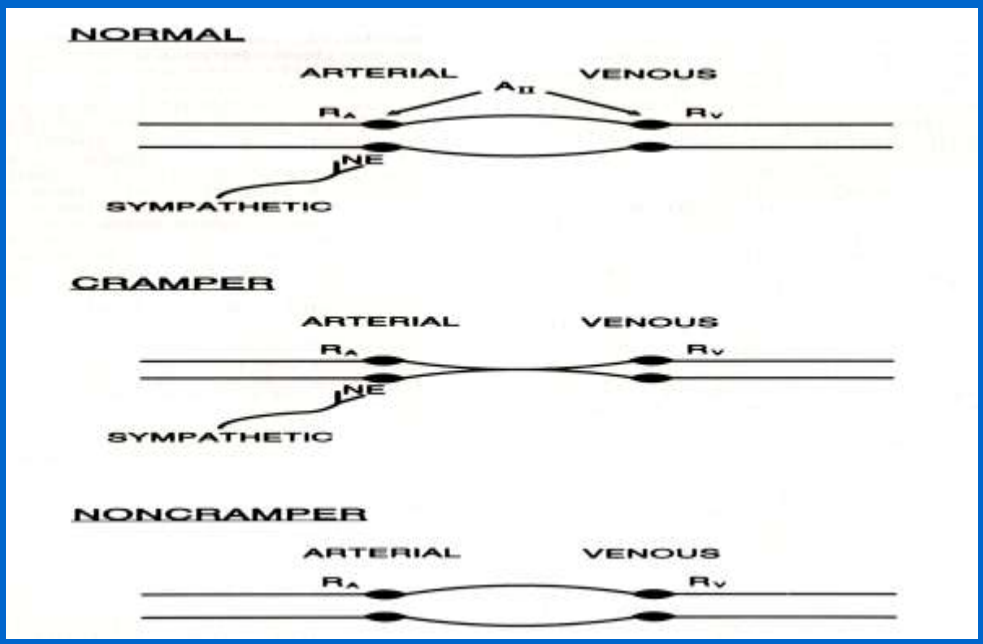
HEMODIALYSIS-ASSOCATED SKELETAL MUSCLE CRAMPS

- COMPLICATE MORE THAN 20% OF HEMODIALYSIS SESSIONS
- PATHOGENESIS UNCLEAR
- SYMPTOMATIC THERAPY: NaCl, MANNITOL
- PREVENTIVE THERAPY: NaCl INFUSION
- OCCUR MORE FREQUENTLY IN SOME PATIENTS THAN OTHERS

ACTIONS OF ANGIOTENSIN II & SYMPATHETIC NERVOUS SYSTEM

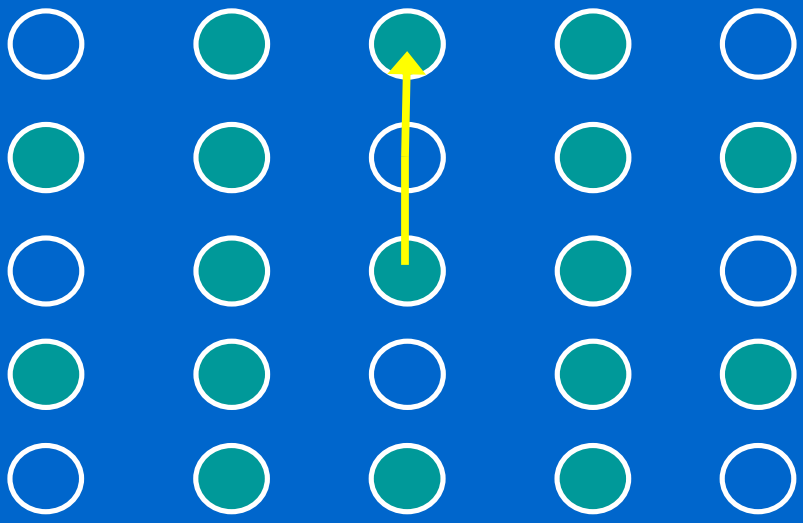


ONLY SOME PATIENTS HAVE DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS*

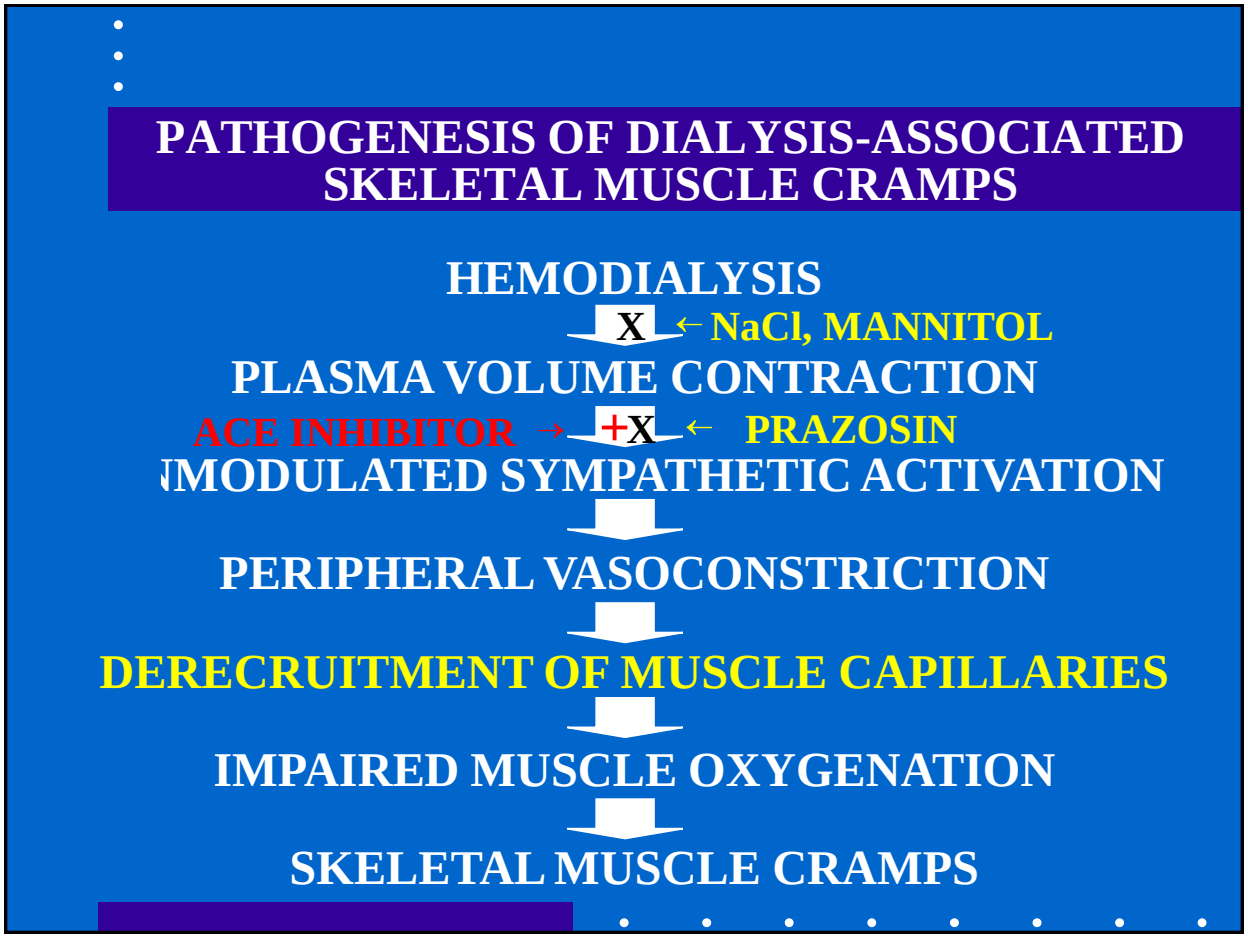


*** Sidhom OA, et al. Clin Pharmacol Ther 1994;56:445-51**

CAPILLARY DERECRUITMENT (OPEN (O) & CLOSED (●) CAPILLARIES)



- OPEN CAPILLARIES IN MUSCLE CROSS SECTION


PATHOGENESIS OF DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS
HEMODIALYSIS
X
NaCl, MANNITOL
PLASMA VOLUME CONTRACTION
ACE INHIBITOR
+X
PRAZOSIN
IMODULATED SYMPATHETIC ACTIVATION
PERIPHERAL VASOCONSTRICTION
DERECRUITMENT OF MUSCLE CAPILLARIES
IMPAIRED MUSCLE OXYGENATION
SKELETAL MUSCLE CRAMPS

CONCLUDING THOUGHT

ALTHOUGH NON-COMPARTMENTAL ANALYSIS OF PK DATA IS CURRENTLY IN VOGUE, IT IS UNABLE TO PROVIDE INSIGHT INTO SOME IMPORTANT PHENOMENA:

- **IMPACT OF DIALYSIS-ASSOCIATED HEMODYNAMIC CHANGES ($\downarrow CL_S$)**
- **IMPACT OF $\downarrow$ SPLANCHNIC BLOOD FLOW ($\downarrow CL_F$) ON BIOAVAILABILITY**