Renal Physiology and pathophysiology of the kidney

Alain Prigent
Université Paris-Sud 11

IAEA Regional Training Course on Radionuclides in Nephrourology
Mikulov, 10–11 May 2010

The glomerular filtration rate (GFR) may change with

- The adult age ?

- The renal plasma (blood) flow ?

- The Na^+/water reabsorption in the nephron ?

- The diet variations ?

- The delay after a kidney donation ?

GFR can measure with the following methods

- The Cockcroft-Gault formula ?

- The urinary creatinine clearance ?

- The Counahan-Baratt method in children?

- The Modification on Diet in Renal Disease (MDRD) formula in adults ?

- The MAG 3 plasma sample clearance ?

About the determinants of the renogram curve (supposed to be perfectly « BKG » corrected)

-The uptake (initial ascendant segment) of ^{99m}Tc DTPA depends on GFR

-The uptake (initial ascendant segment) of ^{99m}Tc MAG 3 depends almost only on renal plasma flow

-The uptake (initial ascendant segment) of ^{123}I hippuran depends both on renal plasma flow and GFR

-The height of renogram maximum (normalized to the injected activity) reflects on the total nephron number

-The « plateau » pattern of the late segment of the renogram does mean obstruction ?

Overview of the kidney functions

Regulation of the volume and composition of the body fluids

Body fluid osmolality and volume

electrolyte balance (Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}, HPO_4^{--}/ $H_2PO_4^-$)

acid-base balance (H^+, HCO_3^-)

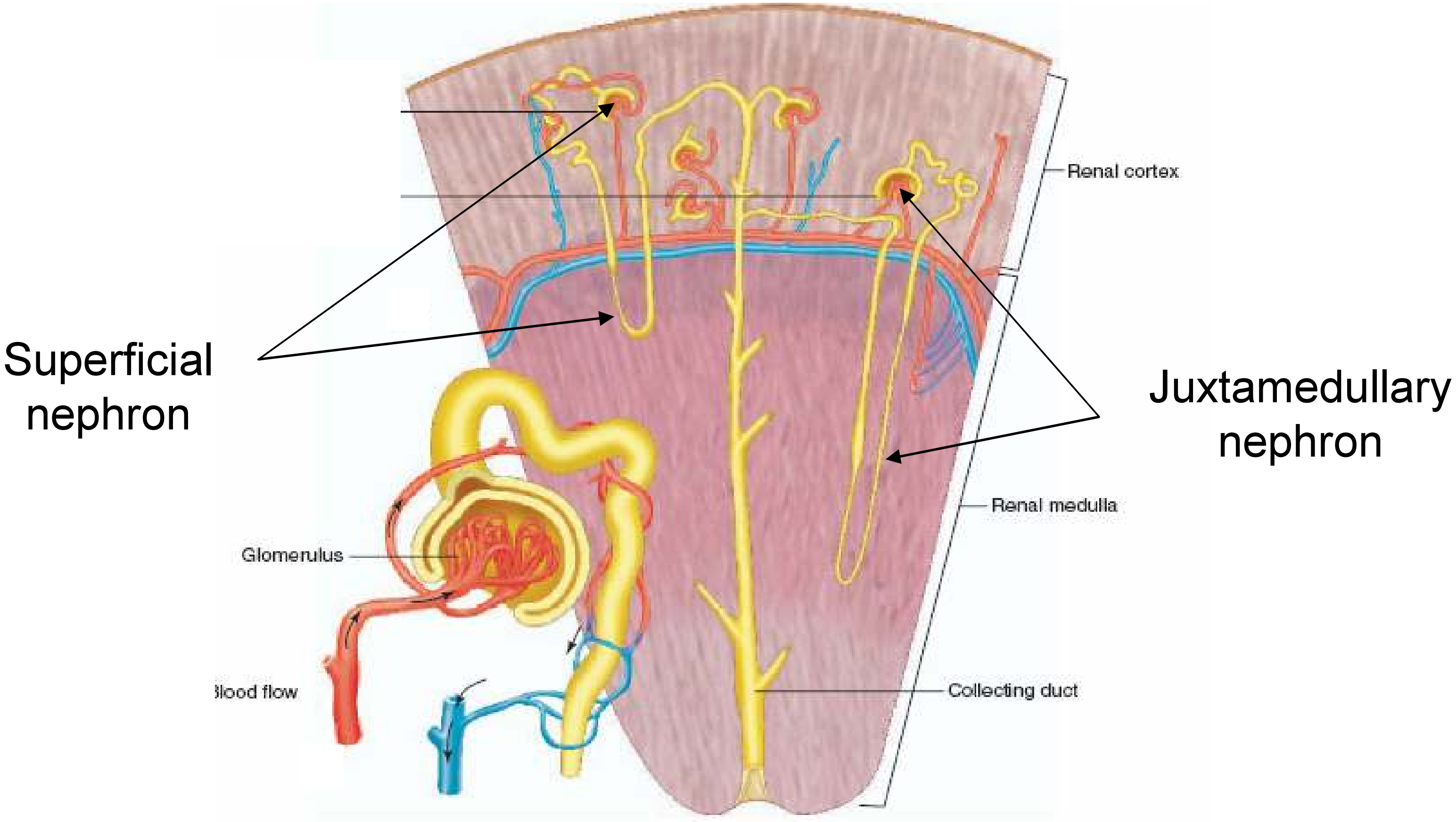
Excretion of metabolic products and xenobiotics

citrate, succinate, urea, uric acid, creatinine, end-products of metabolisms of hemoglobin and hormones, antibiotics, drugs, …

Secretion of hormones

renin, prostaglandins, kinins, 1-25 di-hydroxyvitamin D_3, erythopoietin

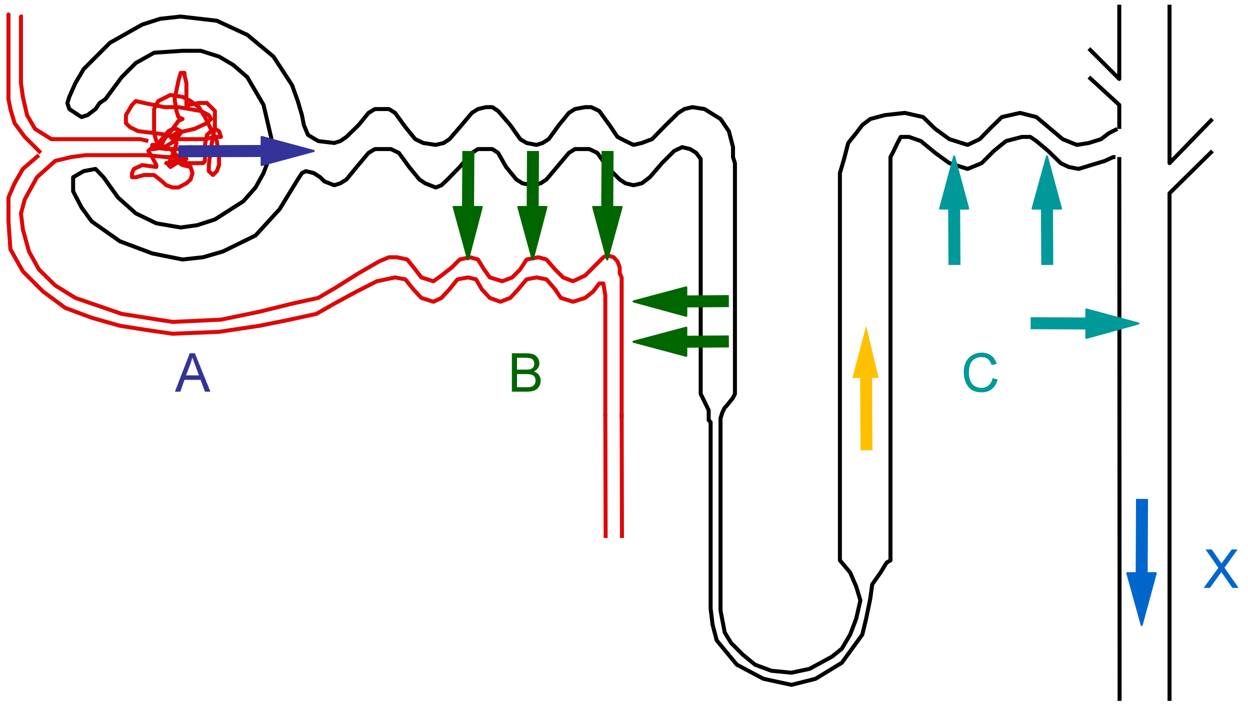
Nephron *Functional unit*



The fluid formed by capillary filtration enters the tubules and is subsequently modified by transport processes, resulting in urine.

Each kidney contains more than a million nephrons.

Processes of kidney function



Excreted amount = Filtrated amount - Reasorbed amount + Secreted amount
X = **A** - **B** + **C**

Summary of renal flow data

RENAL BLOOD FLOW (RBF)

. About 20 % of cardiac output ....# 1-1.2 L/min
. 90 % dedicated to the cortex

RENAL PLASMA FLOW (RPF)

. RPF = RBF (1 - Ht)...# 500 - 600 mL/min

GLOMERULAR FILTRATION RATE (GFR)

. About 20 % of RPF (filtration fraction) ....# 100 - 120 mL/min

TUBULAR FLOW RATE (TFR)

. Primitive urine flow rate (GFR)...# 180 L/day
. Proximal nephron output (ECFV, Na status)..............................# 15 L/day
. Distal nephron output (cortico-medullary gradient, ADH)...........# 1-2 L/day

The classical definition of renal function is glomerular filtartion rate (GFR)

Because of **:**

1. Interdependance of glomerular fitration and tubular Na+ reabsorption

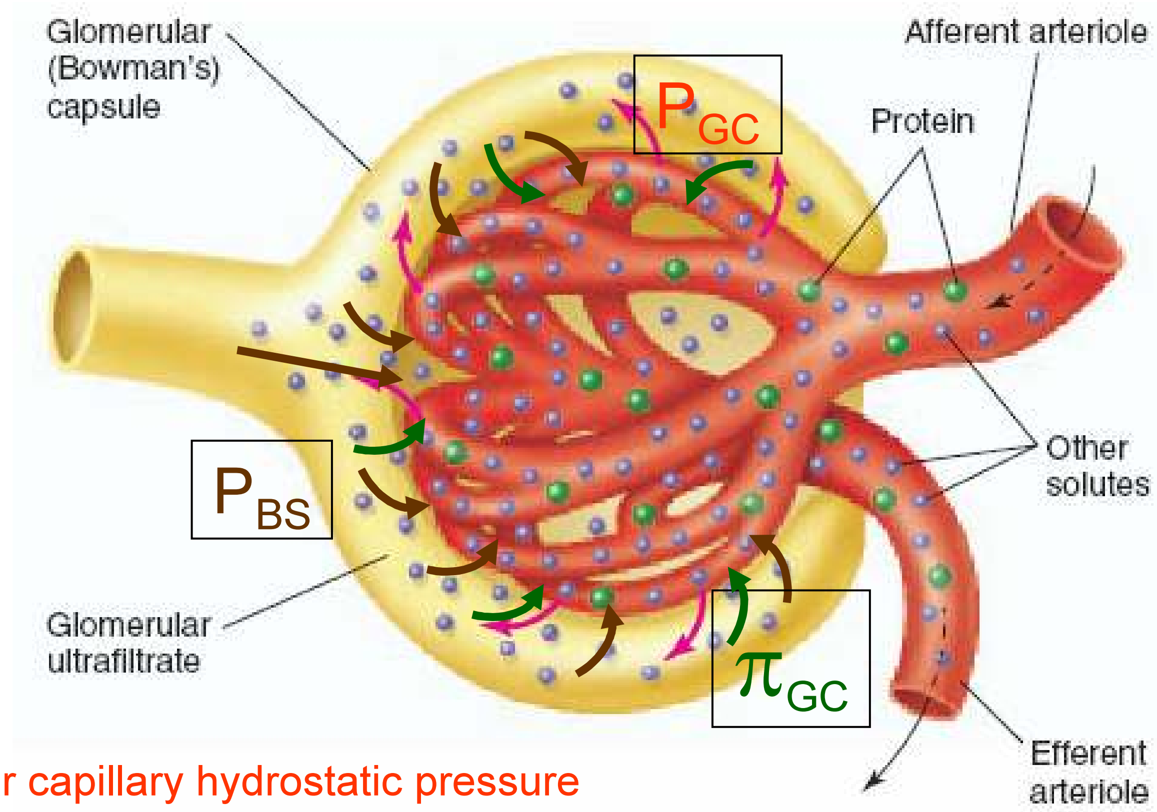
   Glomerulotubular balance

   Tubuloglomerular feed-back

2. Common regulation of GFR and renal blood (or plasma) flow
   (filtration fraction : GFR/RPF about 20 %)

3. Functional pathological correlation

Ultrafiltration of plasma across the glomerular capillary



P_{GC} = glomerular capillary hydrostatic pressure

π_{GC} = glomerular capillary oncotic pressure

P_{BS} = Bowmann's space hydrostatic pressure

$$P_{UF} = P_{GC} - (P_{BS} + \pi_{GC})$$

Main determinants of glomerular ultrafiltration

Glomerular plasma flow rate (Q_A nL/min)

Q_A influences the glomerular capillary profile of π_{GC} and consequently P_{UF}

Glomerular capillary ultrafiltration coefficient (K_f)

$K_f = k.S$

- k = hydraulic permeability (nL/min/mmHg)
- S = surface area of filtration (cm^2)

SNGFR = 45 nL/min when Q_A= 155 nL/min during euvolemia in Munich-Wistar rat
(SNGFR for single nephron GFR)

Normal GFR (adult humans) = 120-130 mL/min/1.73 m2 (# 180 L/day)

Glomerular plasma flow rate (Q_A nL/min) influences the glomerular capillary profile of π_{GC}

$\Delta P = P_{CG} - P_{BS}$

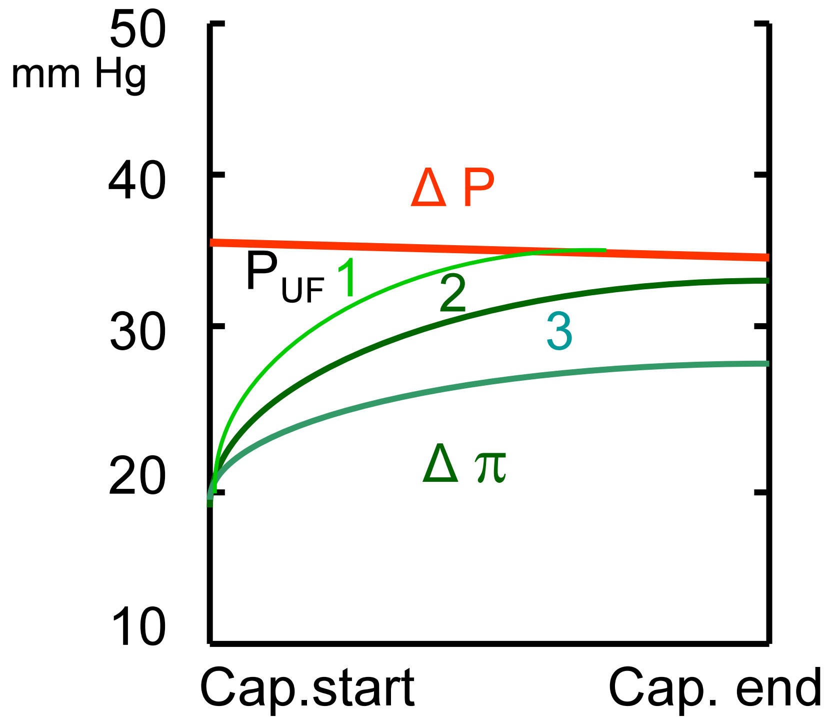
$\Delta \pi = \pi_{GC} - \pi_{BS}$

$P_{UF} = \Delta P - \Delta \pi$

$Q_A1 < Q_A2 < Q_A3$

$P_{UF}1 > P_{UF}2 > P_{UF}3$

SNGFR 1 > SNGFR 2 > SNGFR 3



COUPLING BETWEEN GFR AND TUBULAR FUNCTION

Glomerulotubular balance :

Increase in the filtrated load increases the proximal reabsorption (constant fractional reabsorption)

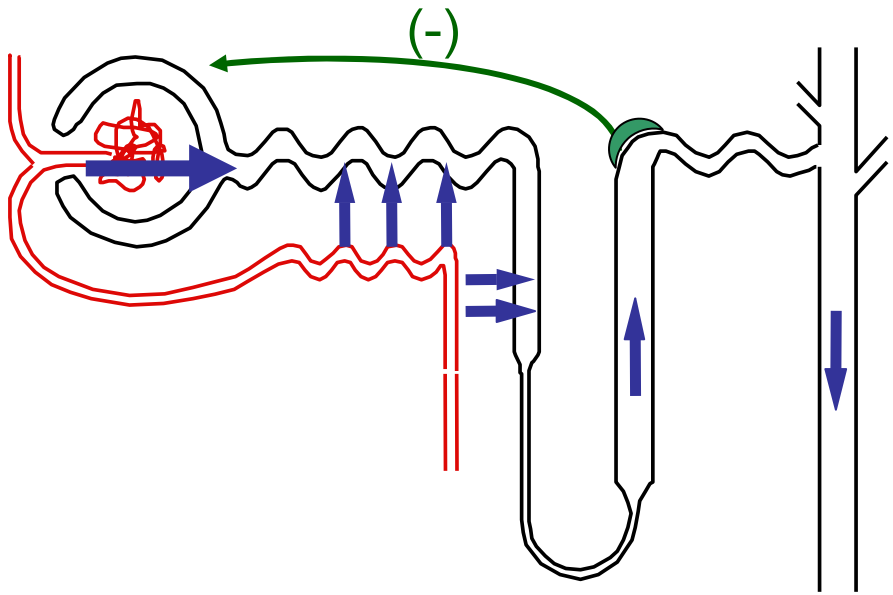
Negative tubulo-glomerular feed-back :

Increase in the water/NaCl delivery rate to the macula densa decreases in the single nephron GFR (flow/NaCl filtrated load) of the same nephron

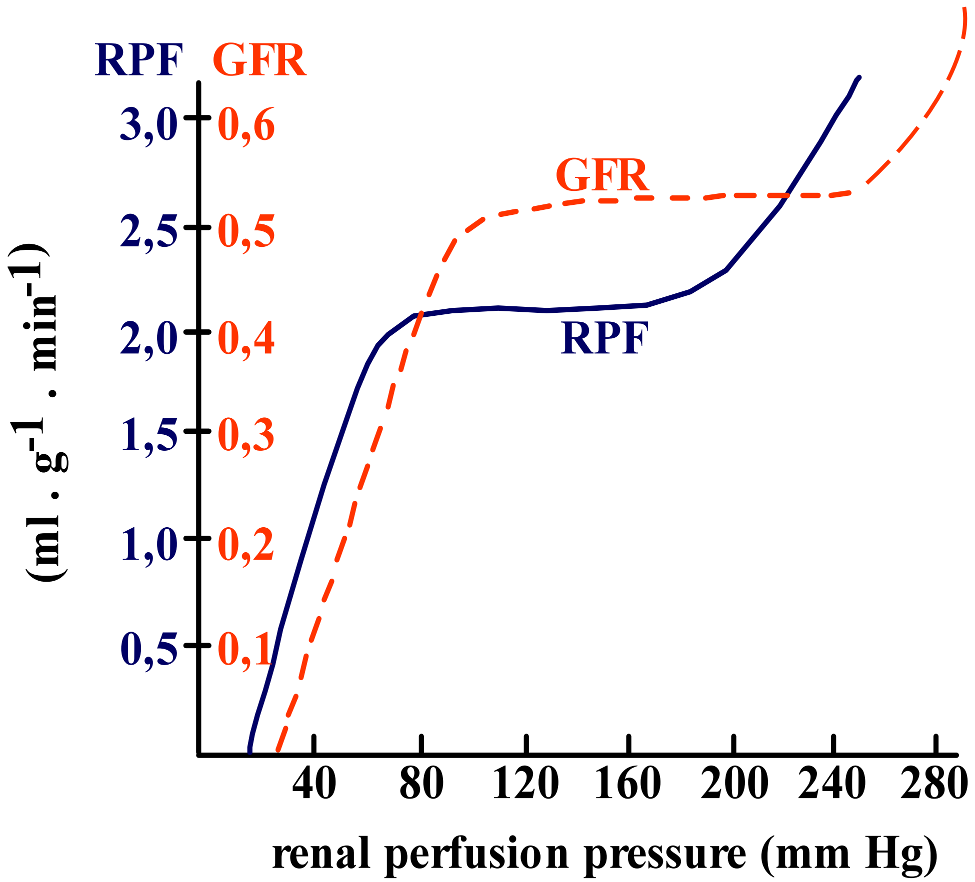
Interdependance of glomerular fitration and tubular Na^+reabsorption

Tubuloglomerular feed-back:

An increase of Na^+ load delivered at the macula densa (distal tubule) induces a decrease in the GFR and filtrated Na^+ and water loads of the same nephron



Common autoregulation* of GFR and RPF



* From about 80 to 160 mm Hg

K/DOQI Guidelines 2002*
*KDIGO** Position Statement 2005*

« Estimates of GFR are the best overall indices of the level of kidney function »

* **National Kidney Fundation - Kidney/Disease Outcomes Quality Initiative**

** **International Board - Kidney Disease:Improving Global Outcomes**

Global assessment of renal function

The concept of renal clearance

Clearance is a « cleaning » index for blood plasma passing the kidney.

Clearance of the substance X (Cl_X) is

- directly proportional to the excretion rate of the substance ($U_X.V$)
- inversely proportional to plasma concentration of the substance (P_X)

$$Cl_X \propto U_X.V / P_X$$

P_X = plasma concentration of the substance X (mg/mL)

U_X = urinary concentration of the substance X (mg/mL)

V = urine flow rate (mL/min)

Global assessment of renal function

Glomerular filtration rate (GFR) and clearance

Substance X (inulin, ^{51}Cr-EDTA, ^{99m}Tc-DTPA, ^{125}I-iothalamate…)

- -freely filtrated by the glomerulus
- -neither reabsorbed, nor secreted
- -neither metabolized, nor produced by the kidney
- -not altering GFR

Filtrated amount = excreted amount

$$GFR.P_X = U_X.V$$

$$GFR_{human} = Cl_X = (U_X.V) / P_X = 120 - 130 \text{ mL/min/1.73 m}^2$$

(about 180 l filtrated per day)

Normal values of GFR (1)

Adults :

- Male = 130 ± 23 mL/min/1.73m²
- Female = 120 ± 16 mL/min/1.73m²

Functional renal reserve (FRR) :

Reactive increase in GFR (120-140 % of baseline) within 2 h after

- meat (300-500 g) meal
- gluconeogenic amino acids (50-75g in 3 h) infusion
- dopamine (1.5-2.0 µg/kg/min for 2 h) infusion

FRR, expressed as a percentage of baseline GFR, does not decrease with renal function

Normal values of GFR (2)

Aging (over 40 y)

- Transversal studies :
  decline of 1 mL/min/year

- Longitudinal studies :
  1/3 pts = stability of the normal GFR value
  1/3 pts = decline to 50-70 % of the maximum GFR value
  1/3 pts = progressive but small decline

Children

- Around 1 month: half the adult value (mean GFR: 55 mL/min/1.73 m^2)

- Progressive increase till 18 months - 2 years

- Over 2 years: adult values (as expressed as mL/min/1.73 m^2)

Physiological variations of GFR

Circadian variations:

maximum around 1 pm
minimum around 1 am
(max-min)/mean = 20 %

Diet variation:

GFR decreases with deficient diet in either calories, proteins, or sodium salts

Pregnancy :

GFR increases (140 %), due to increase in ECFV

Nephrectomy (kidney donors)

1 month later = about 60 % of the predonation value
1 year later = about 70 % of the predonation value

Long-term consequences of kidney donation

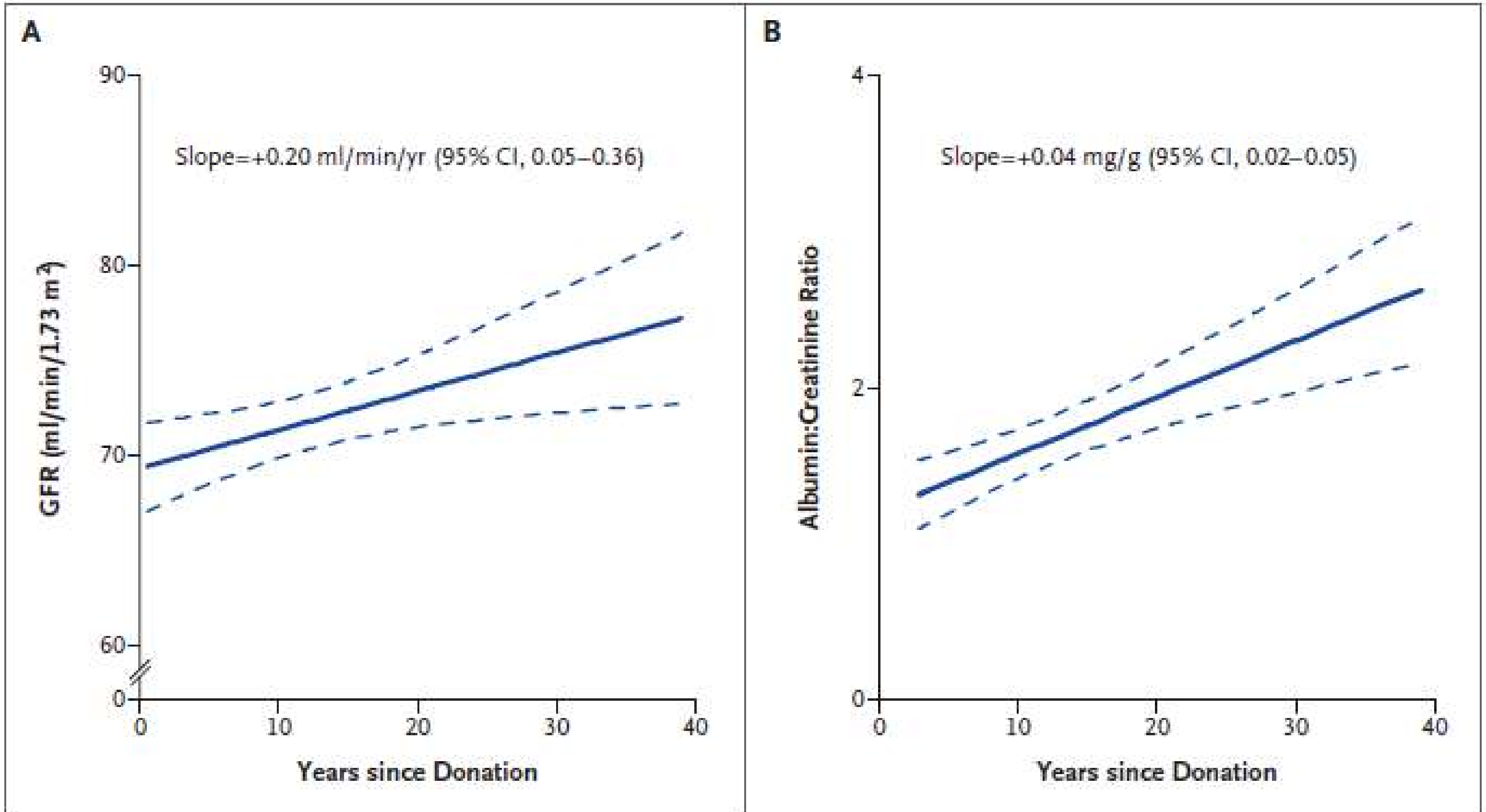


Figure 2. Glomerular Filtration Rate (GFR) and Urinary Albumin Excretion According to Time since Donation.
Panel A shows the GFR, and Panel B shows log-transformed values for the ratio of urinary albumin to creatinine. In each panel, the solid line indicates the regression line, and the dotted line, the 95% confidence interval.

H N Ibrahim et, N Engl J Med, 2009

Definition of chronic kidney disease (CKD)

Guidelines 2002 (NKF/KDOQI)

1. Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with ou without decreased GFR, manifest by either :

   - Pathological abnormalities on kidney biopsy, or

   - Markers of kidney damage, such as proteinuria, abnormal urinary sediment, or abnormalities in imaging tests

2. GFR < 60 mL/min/1.73m² for ≥ 3 months, with or without kidney damage

NKF/KDOQ :National Kidney Fundation - Kidney/Disease Outcomes Quality Initiative

Functional tests for monitoring GFR

Measurements

Inulin: «has long been considered as the gold standard» (The Kidney; B.Brenner-F.Rector, 2005)

- constant infusion, bladder catheterization, expensive, difficult assay

Unlabeled markers:

- X-ray fluorescence needs 30 ml of blood while HPLC is costly
- possible contrast media side-effects

Radiolabeled tracers:

- safe (tracer dose), simple (bolus injection), spontaneous bladder emptying
- accurate with low bias, high precision and good reproducibility

Often albeit wrongly claimed « complexe, expensive, difficult to do in clinical practice »

Functional tests for monitoring GFR

Surrogates for « estimation » | **Serum values of endogenous markers**

- Creatinine clearance (no more recommended)
- Creatinine levels (Scr) and inverse of Scr
- Prediction formulae based on Scr (either creatinine clearance or GFR estimation)
- Cystatin C levels (ScysC)
- Prediction formulae based on ScysC (GFR estimation)

Biomarkers | **Early diagnosis and disease progression**

C-reactive protein (C-RP) and other markers (IL-6, TNF-α, TGF-β)

(A)symmetrical dimethyl arginine (ADMA and SDMA)

Neutrophil gelatinase associated lipocalin (NGAL)

A Prigent, «Monitoring renal function Limitations of renal function tests», *Seminars in nucl Med, 2008*

KDOQI recommendations

Creatinine clearance estimation (ml/min)

Cockcroft-Gault, 1976 (adults)

$$Clcr = \frac{(140 - age) \times weight}{Scr \times 72} \times 0.85 \text{ (if female)}$$

Schwartz, 1976 (children)

$$Clcr = \frac{0.55 \times length}{Scr}$$

Scr, mg/dl
age, years
weight, kg
length, cm

GFR estimation (ml/min/1.73m²)

4v-MDRD, 2005 (adults)

$$DFG = 186.3 \times (Scr)^{*-1.154} \times (age)^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if Afro-American)}$$

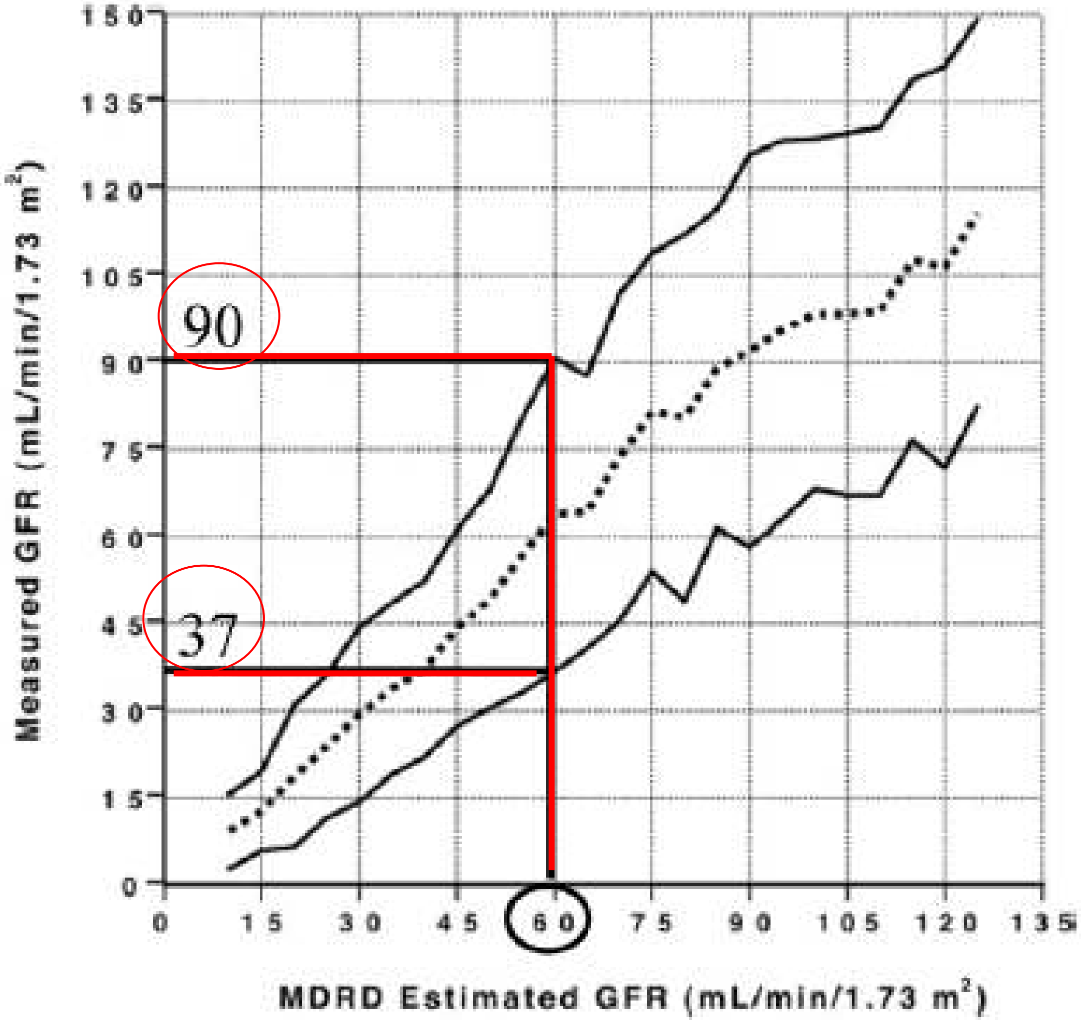
Counahan-Baratt, 1976 (children)

$$DFG = \frac{0.43 \times length}{Scr}$$

* enzymatic assay traceable to isotopic-dilution mass spectrometric assay

Reference method for GFR measurement

^{51}Cr EDTA (Europe) and ^{125}I iothalamate (USA) clearance



Adapted from Froissart et al, 2005

KDIGO recommendations-2007

When clearance measurements may be necessary to estimate GFR ?

Extremes of age (elderly ? children ?)

Extremes of body size (obesity*or low BMI < 18.5 kg/m2)

Severe malnutrition (cirrhosis ?, end-stage renal failure ?, ...)

Grossly abnormal muscle mass (amputation, paralysis, …)

High or low intake of creatinine or creatine (vegetarian diet, dietary supplements)

Pregnancy

Rapidly changing kidney function

Prior to dosing (high toxicity drugs, excreted by the kidney)

Prior to kidney donation

International Board - Kidney Disease: Improving Global Outcomes

Global assessment of renal function
Effective renal plasma flow (ERPF) and clearance

Substance X (PAH, ^{125}I-ortho-iodo-hippurate, ^{Tc99m} MAG3 or LL,EC…)

-filtrated by the glomerulus and secreted by the tubule
-«totally» excreted in one pass through the kidney
-neither metabolized, nor produced by the kidney
-not altering renal plasma (blood) flow

Entering (filtrated and secreted) amount = excreted amount

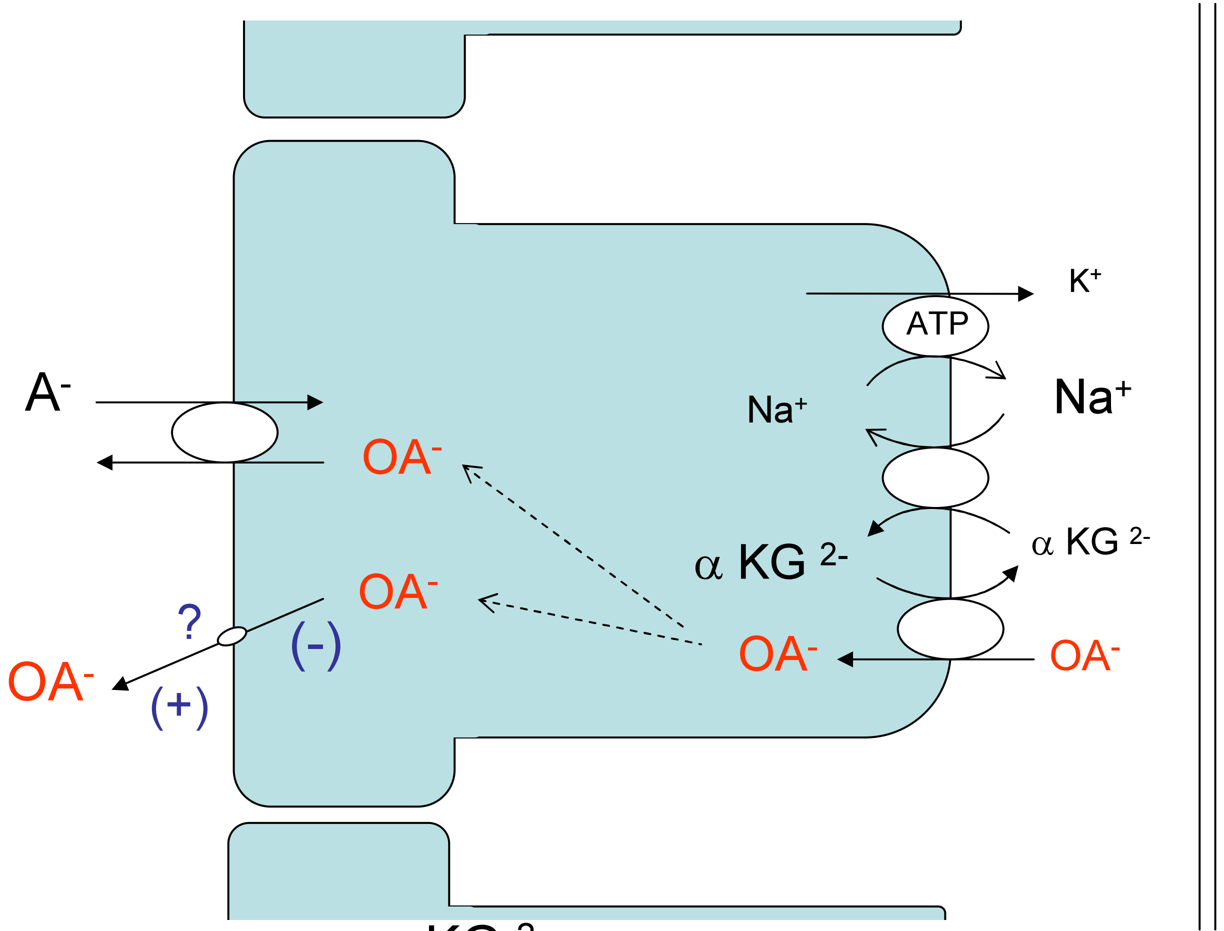
$$RPF.P_X = U_X . V$$

Extraction fraction (EF_X) lower than unity (not «totally» excreted)

$$ERPF = (U_X.V) / P_X \qquad RPF = (U_X .V) / (P_X .EF_X)$$

Proximal tubule secretion of organic anions

A^- (anions): HCO_3^-, Cl^-, …



OA- (organic anions):
PAH, OIH, MAG3, LL,EC, …
fluroescein,urate, diuretics,…

αKG^{2-}: α keto-glutarate (dicarboxylate)

The functional significance of Effective Renal Plasma Flow (ERPF)

$$Cl_{OA} = RPF \times EF_{OA} = ERPF$$

The extraction fraction (EF_{OA}) of an organic anion (e.g., PAH; OIH; MAG3; L,L-EC; ...) depends on:

- -Plasma protein and RBC binding
- -Excretion pathway (tubular secretion with/without filtration of the unbound moiety)
- -Affinity for the nonspecific dicarboxylic acid/organic anion counter-transporter located at the basolateral membrane of the proximal tubular cell (segment S2)
- -Distribution of the RBF between superficial and juxtamedullar glomeruli (medullary RPF not measured)
- -Nature and severity of the disease
- -Administration of vasoactive substances, certain drugs, or iodine contrast media
- -Status of hydration and extracellular volume

Organic anions used in clinical practice

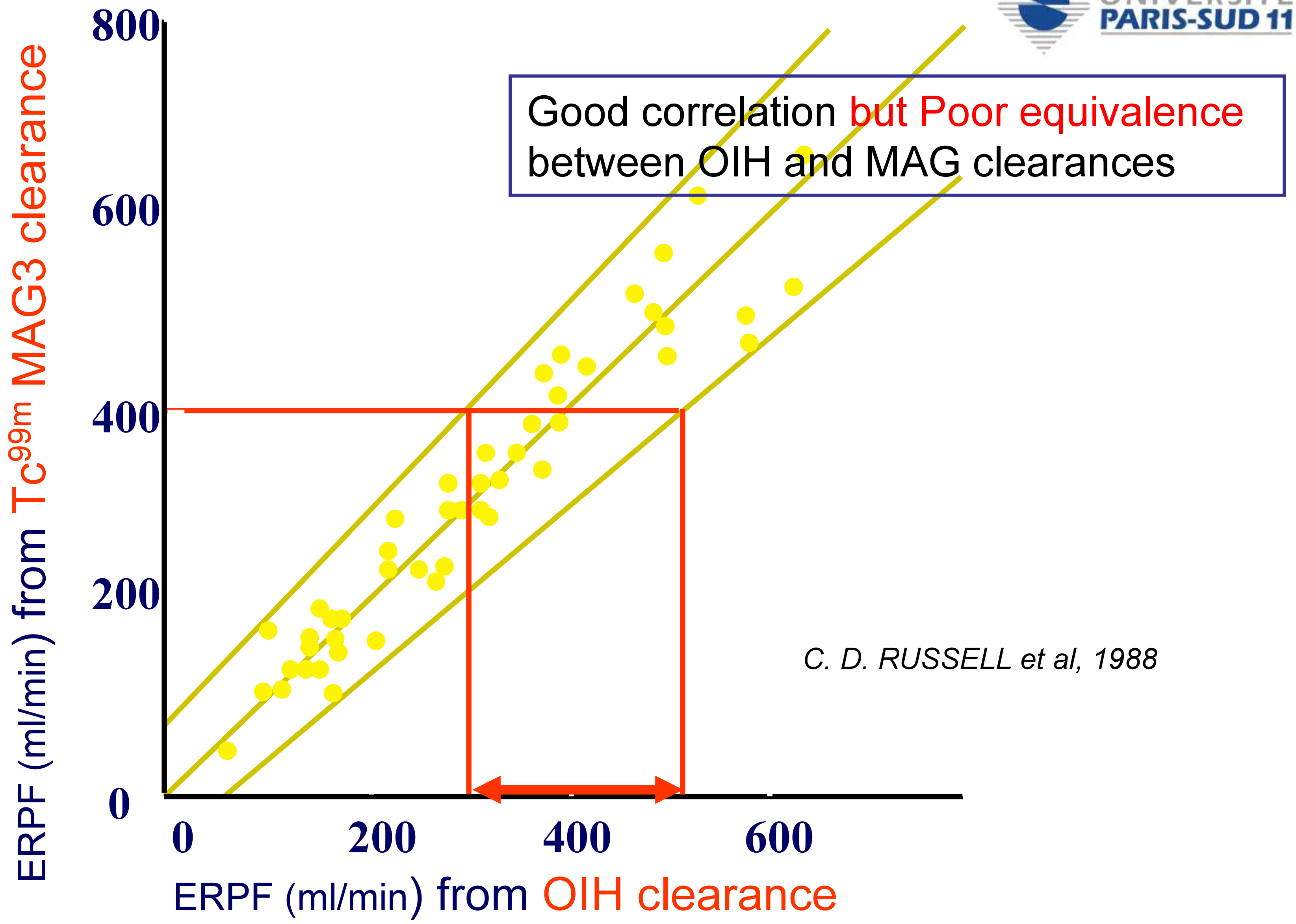
	PAH	I*-OIH	^{99m}Tc-MAG3
Protein binding (%)	25 - 35	60 - 70	80 - 90
RBC binding (%)	5 - 15	10 - 20	< 5
Extraction fraction in normal volunteers	0.90	0.80	0.55
. % filtrated	20	15	5
. % secreted	70	65	50

Variations of the PAH extraction fraction

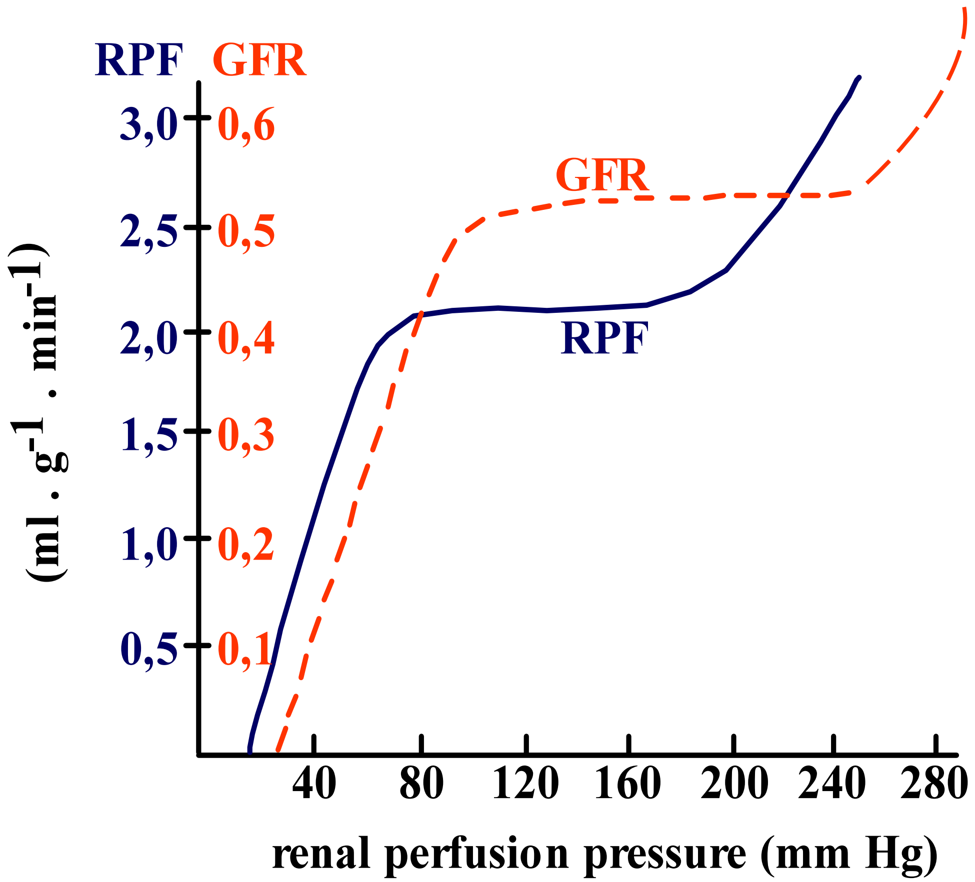
			Mean ±SD
Human volunteer	*(Reubi,*	*1978)*	0.92 ± 0.03
	(Battilana,	*1991)*	0.87 ± 0.11
Essential benign hypertension	*(Reubi,*	*1978)*	0.87 ± 0.06
	(London,	*1988)*	0.81 ± 0.10
Malignant hypertension	*(Reubi,*	*1978)*	0.76 ± 0.11
Heart transplant	*(Myers,*	*1988)*	0.84 ± 0.09
Ciclosporine	*(Battilana,*	*1991)*	0.77 ± 0.14
Proteinuric glomerulopathies	*(Golbetz,*	*1989)*	0.68 ± 0.18
Renovascular hypertension	*(Wenting,*	*1987)*	
- stenostic kidney (+ IEC)			0.54 ± 0.05 (0.34 ± 0.04)
- contralat.kidney (+ IEC)			0.74 ± 0.02 (0.66 ± 0.03)

Other examples of decreased EF_{PAH} :

- fever, ECFV expansion, renal carcinoma *(Aurell, 1978)*
- isotonic glucose infusion *(Lote, 1985)*
- iodine contrast media injection *(Tidgren, 1985)*
- increase in the ureteric pressure *(Nash, 1964)*


800
600
400
200
0
ERPF (ml/min) from Tc99m MAG3 clearance
Good correlation but Poor equivalence
between OIH and MAG clearances
C. D. RUSSELL et al, 1988
0
200
400
600
ERPF (ml/min) from OIH clearance

Common autoregulation* of GFR and RPF



* From about 80 to 160 mm Hg

Hemodynamically significant RAS

Decreased downstream perfusion pressure

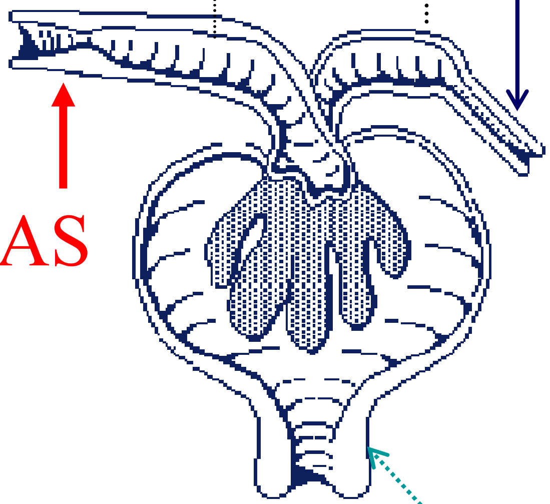
Increased Renin secretion

angiotensinogen

angiotensin I

Angiotensin Converting Enzyme-ACE

angiotensin II



RAS

Vasoconstrict. efferent glomer. arteriole

Increased aldosterone secretion

Increased total peripheral Resistance

Restauration perfusion pressure

Increased Na^+ tubular reabsorption

Na^+ retention
Increased extracell. fluid volume

Restauration of normal to near normal GFR

Decreased tubular flow rate

Systemic hypertension

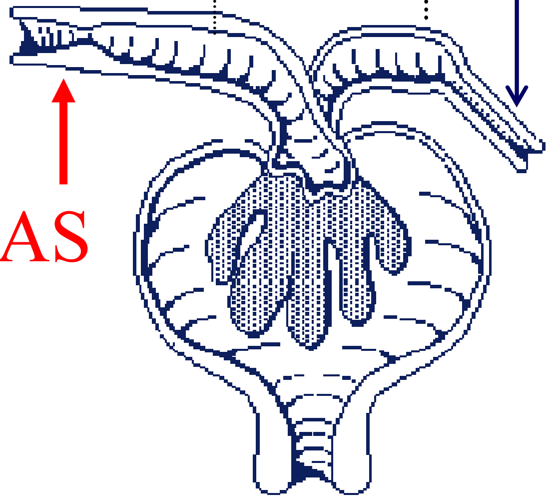
RAS and ACE inhibitor challenge

Decreased downstream perfusion pressure → Increased Renin secretion → angiotensinogen → angiotensin I ✗ (ACE inhibitor) → angiotensin II

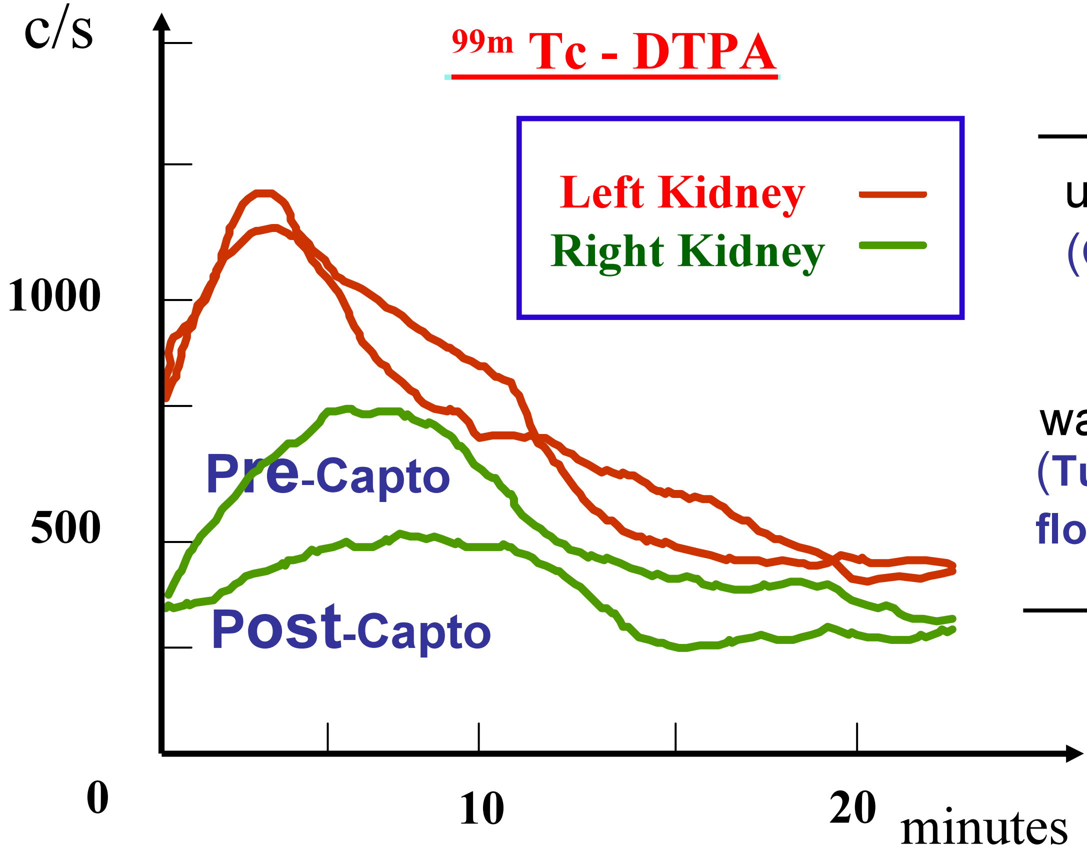
angiotensin II ✗ → Vasodilatation. efferent glomer. arteriole → Drop of perfusion pressure → Decreased GFR → Decreased tubular flow rate

angiotensin II ✗ → Decreased total peripheral Resistance → Control of hypertension

RAS



Captopril isotope renography ^{99m}Tc DTPA

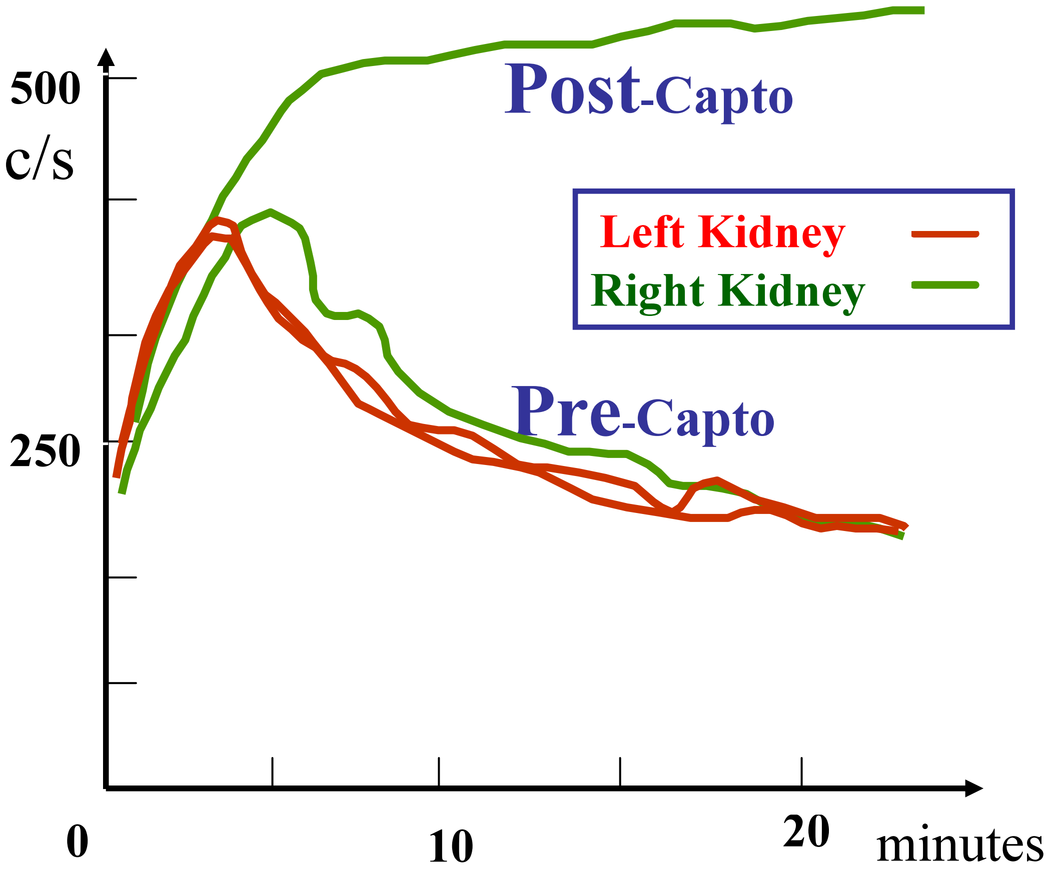


	Stenotic kidney	
	Baseline	Captopril
uptake (GFR)	normal or slightly decreased	markedly decreased
wash out (Tubular flow rate)*	normal or slightly decreased	markedly decreased

* GFR is the primitive tubular flow rate

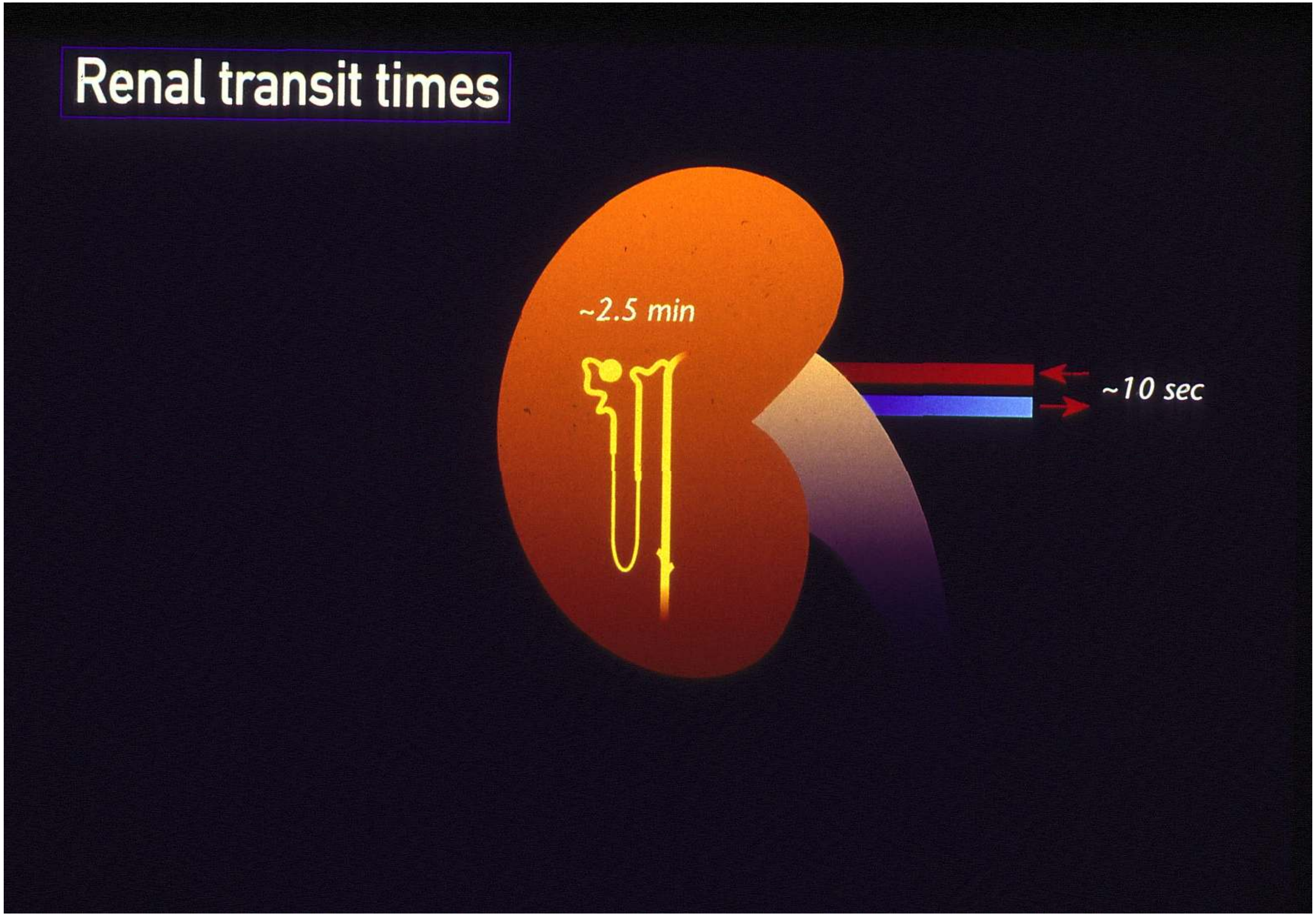
Captopril isotope renography ^{99m}Tc MAG 3

^{99m} Tc - MAG 3



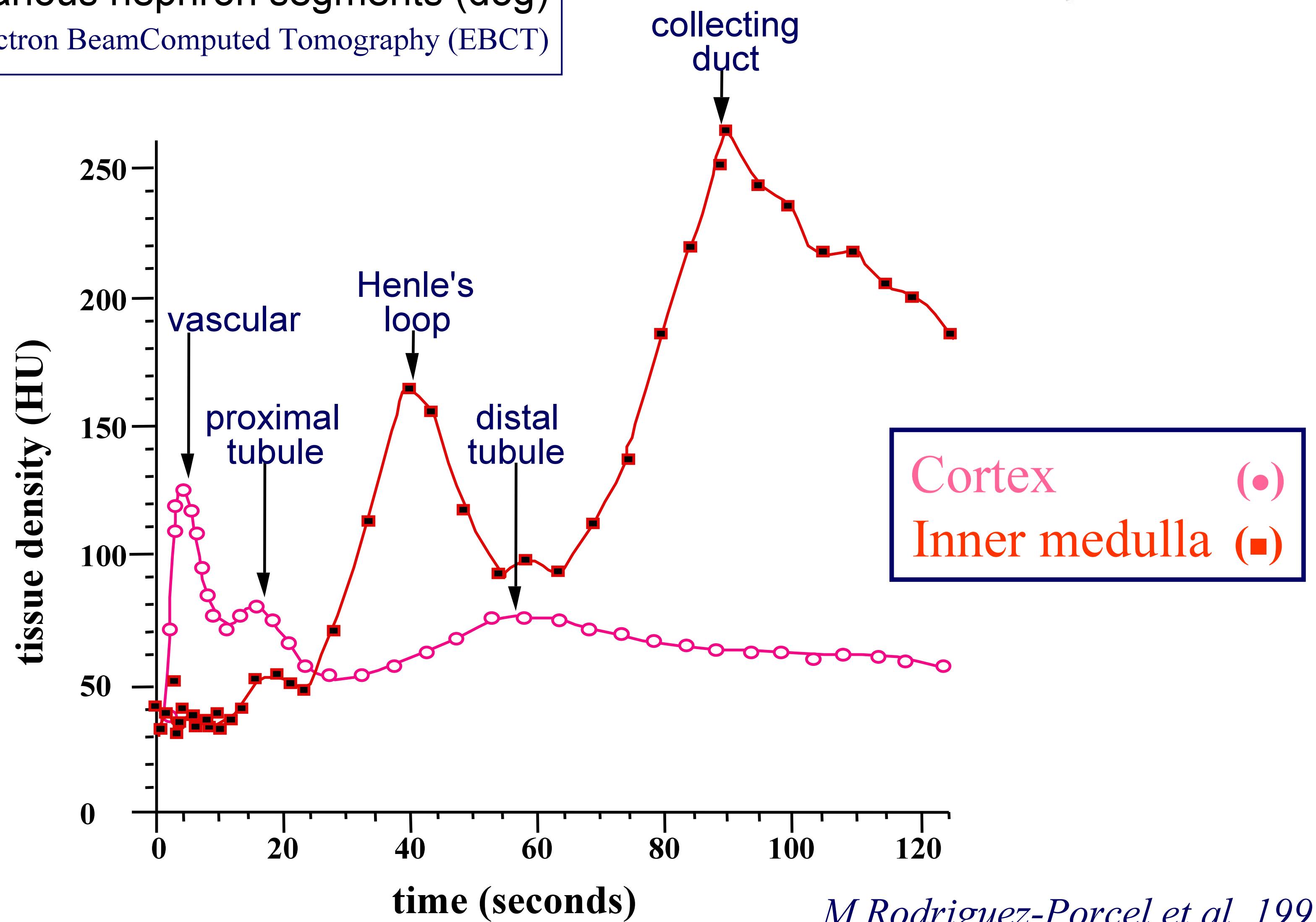
	Stenotic kidney	
	Baseline	Captopril
uptake (E)RPF	normal *	unchanged *
wash out (Tubular flow rate)	normal or slightly decreased	markedly decreased

* rarely slightly decreased


Renal transit times
~2.5 min
~10 sec

Time-density (HU) curves in the various nephron segments (dog)

Electron BeamComputed Tomography (EBCT)



M.Rodriguez-Porcel et al, 1997

Determinants of tubular transit

Short-term (< 10 sec) and long-term changes in blood pressure
(JE Steele et al. Am J Physiol 1993, 265 : F717 - F 722)

Renal perfusion pressure (RPP) changes within the range of autoregulation
(M Rodriguez-Porcel et al. Am J Physiol, 1997, 273 : F667 - 673)

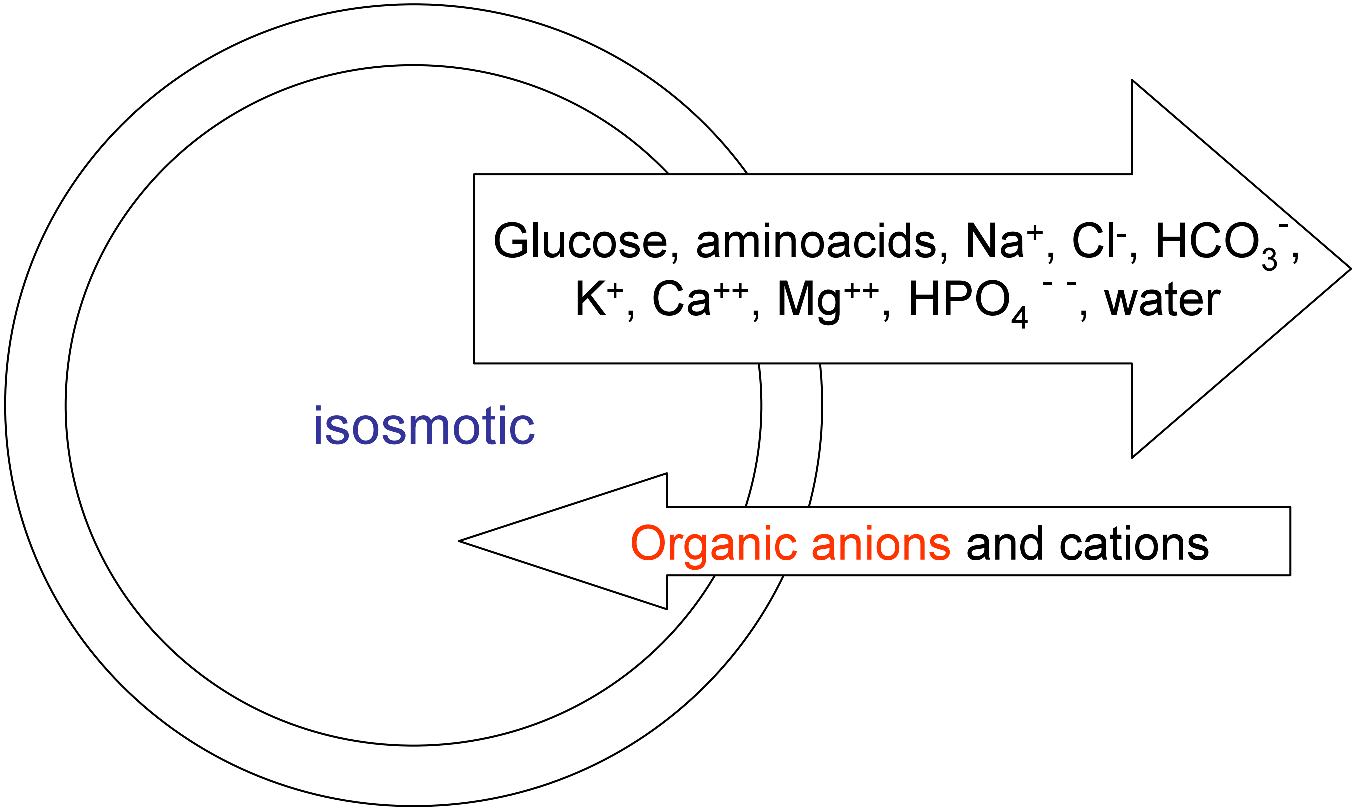
Tubular tracer input (as a function of GFR and proximal secretion)

Proximal fluid reabsorption:
- ECFV status and salt diet
- Filtration fraction

Distal fluid reabsorption:
- Cortico-papillary osmotic gradient
- ADH and water diet

Downward urinary pressure:
- Pelvis compliance and volume
- Obstruction

Proximal tubule reabsorption



65% of filtrated NaCl reabsorbed

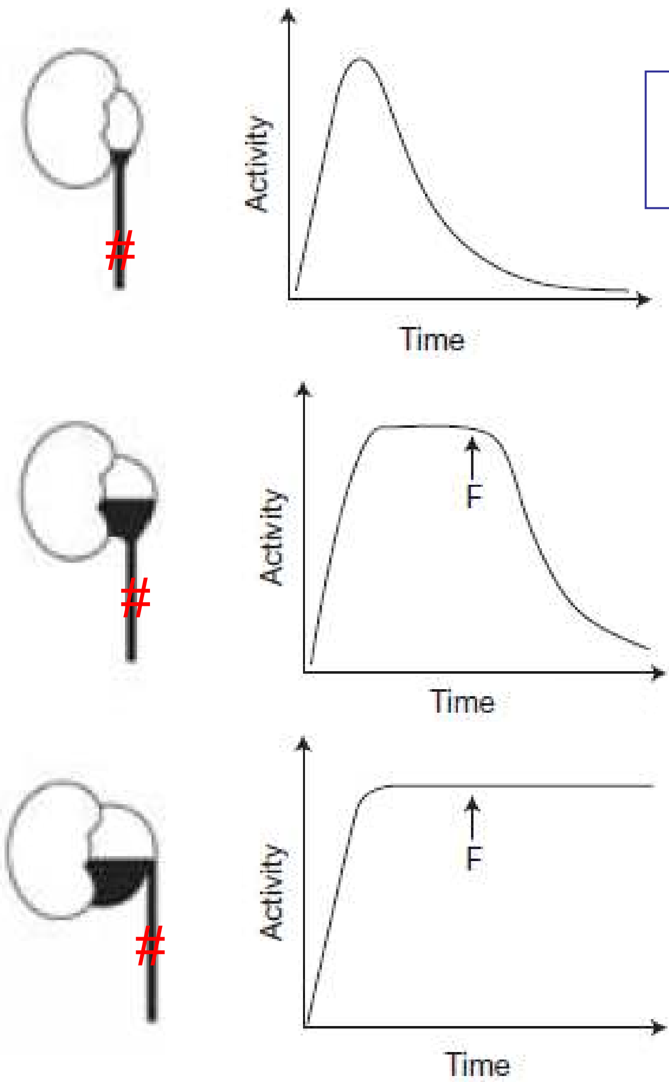
Urine concentration and dilution

Dilution (hypoosmotic urine production):

- reabsorption of solute from tubular fluid without water
- ascending limb of Henle'sloop, distal tubule and collecting duct

Concentration (hyperosmotic urine production):

- reabsorption of water from tubular fluid without solute
- late distal tubule and collecting duct
- main effectors:
  - ~ antidiuretic hormone (ADH) or vasopressin
  - ~ medullary interstitial osmotic gradient
    - .countercurrent multiplication by the loop of Henle
    - .different solute and water permeabilities and transports of the nephron segments



Botn the renal pelvis volume and urinary flow rate influence the shape of the renogram curve !

« The reservoir effect »

The larger the pelvis,
The more diluted is the tracer,
The more prolonged is the drainage

A plateau curve does not represent an true obstruction but a balance between the inflow and outflow rates.

Functional Imaging in Nephro-urology, 2006

Hydration of the patient ? What do you mean ?

Load	1 L H_2O (PO) or 1 L glucose 5% (IV)	9 g NaCl (PO) or 1 L NaCl 0.9 % (IV)
Distribution volume	Intracell. and extracell. volumes	Extracellular volume
Regulated parametrer	Plasma osmolarity $[Na]_{pl}$, mmol/L	Arterial pressure $V_{24h}.[Na]_u$, mmol/day
Hormonal regulation	ADH Peptidic, fast effect	Renin, Angiotensin, Aldosterone Steroïdic, slow effect
Urinary excretion	60% of H_2O load excreted in about the following hour	70% of Na load excreted in about the next 24 hours
Physiological effect	Rapid hyperdiuresis	Slight GFR increase Progressive sodium excretion

Thank you for your attention

Responses to the MCQ !

The glomerular filtration rate (GFR) may change with

- The adult age ?

- The renal plasma (blood) flow ?

- The Na^+/water reabsorption in the nephron ?

- The diet variations ?

- The delay after a kidney donation ?

The glomerular filtration rate (GFR) may change with

-The adult age ?

Yes in longitudinal studies, No in transversal study (only a 1/3 of the patients have a significant decrease)

-The renal plasma (blood) flow ?

Yes, Q_A changes modify $\Delta \pi$ (= π_{GC} - π_{BS}) and P_{UF} and so SNGFR

-The Na^+/water reabsorption in the nephron ?

Yes, glomerulotubular balance and feed-back tubulo-glomerular

-The diet variations ?

Yes, Na^+, protein, calorie intakes

-The delay after a kidney donation ?

Yes, but only a very slight inscrease over time

GFR can measure with the following methods

- The Cockcroft-Gault formula ?

- The urinary creatinine clearance ?

- The Counahan-Baratt method in children?

- The Modification on Diet in Renal Disease (MDRD) formula in adults ?

- The MAG 3 plasma sample clearance ?

GFR can be measured with the following methods

-Cockcroft-Gault formula ?

-No, creatinine clearance estimation

-Urinary creatinine clearance ?

-No, not recommended (day-to-day coefficient of variation as high as 27%)

-The Counahan-Baratt method in children ?

-Yes, according to KDOQI recommendations

-The Modification on Diet in Renal Disease (MDRD) formula in adults ?

-No, it's only an estimation of GRF method, more or less useful for screening ?

-Yes according tthe « initial » KDOQI recommendations

-The MAG 3 plasma sample clearance ?

-No, MAG3 clearance does not estimate ERPF any time (and moreover RPF) and the filtration fraction (GFR/RPF) varies in some diseases (RVH, acute obstruction, acute pyelonephritis…)

About the determinants of the renogram curve (supposed to be perfectly « BKG » corrected)

-The uptake (initial ascendant segment) of ^{99m}Tc DTPA depends on GFR

-The uptake (initial ascendant segment) of ^{99m}Tc MAG 3 depends almost only on renal plasma flow

-The uptake (initial ascendant segment) of ^{123}I hippuran depends both on renal plasma flow and GFR

-The height of renogram maximum (normalized to the injected activity) reflects on the total nephron number

-The « plateau » pattern of the late segment of the renogram does mean obstruction ?

About the determinants of the whole kidney renogram curve
(supposed to be perfectly « BKG » corrected)

-The uptake (initial ascendant segment) of ^{99m}Tc DTPA depends on GFR

Yes, an only filtrated tracer

-The uptake (initial ascendant segment) of ^{99m}Tc MAG 3 depends almost only on renal plasma flow

Yes, only about 5% is filtrated (EF about 55-to60% in normal humans)

-The uptake (initial ascendant segment) of ^{123}I hippuran depends both on renal plasma flow and GFR

Yes, ortho-iodo-hippurate is 15% filtrated and 65% secreted

-The height of renogram maximum (normalized to the injected activity) reflects on the total nephron number

No, many factors intervene (uptake, tubular flow rate,kidney depth, …)

-The « plateau » pattern of the late segment of the renogram does mean obstruction ?

No, a plateau means equilibrium between inflow and outflow from the renal pelvis