Renal Physiology I

Jason Ryan, MD, MPH

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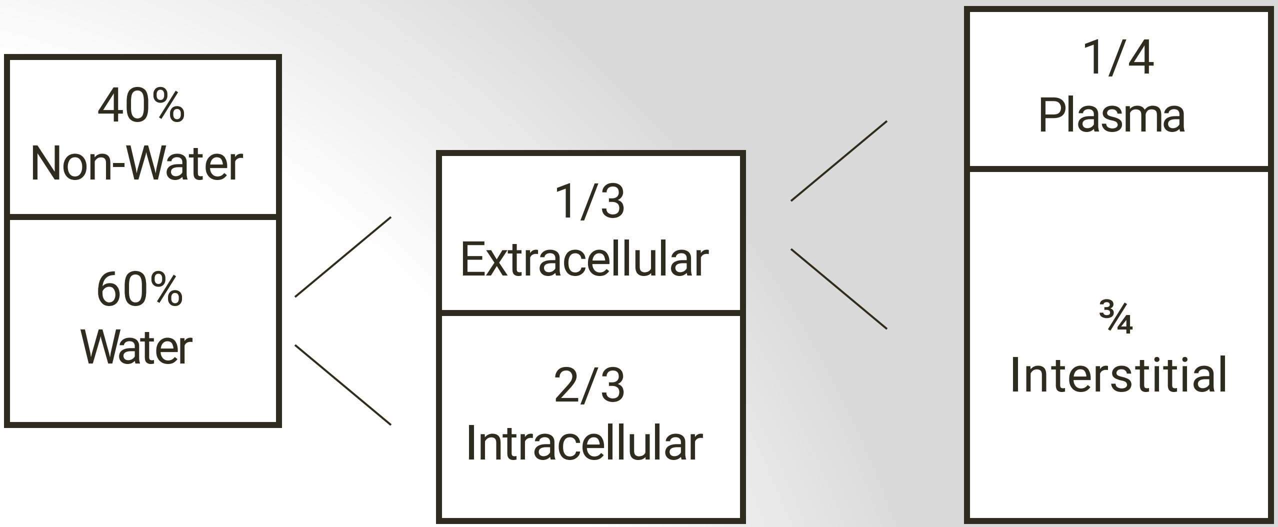
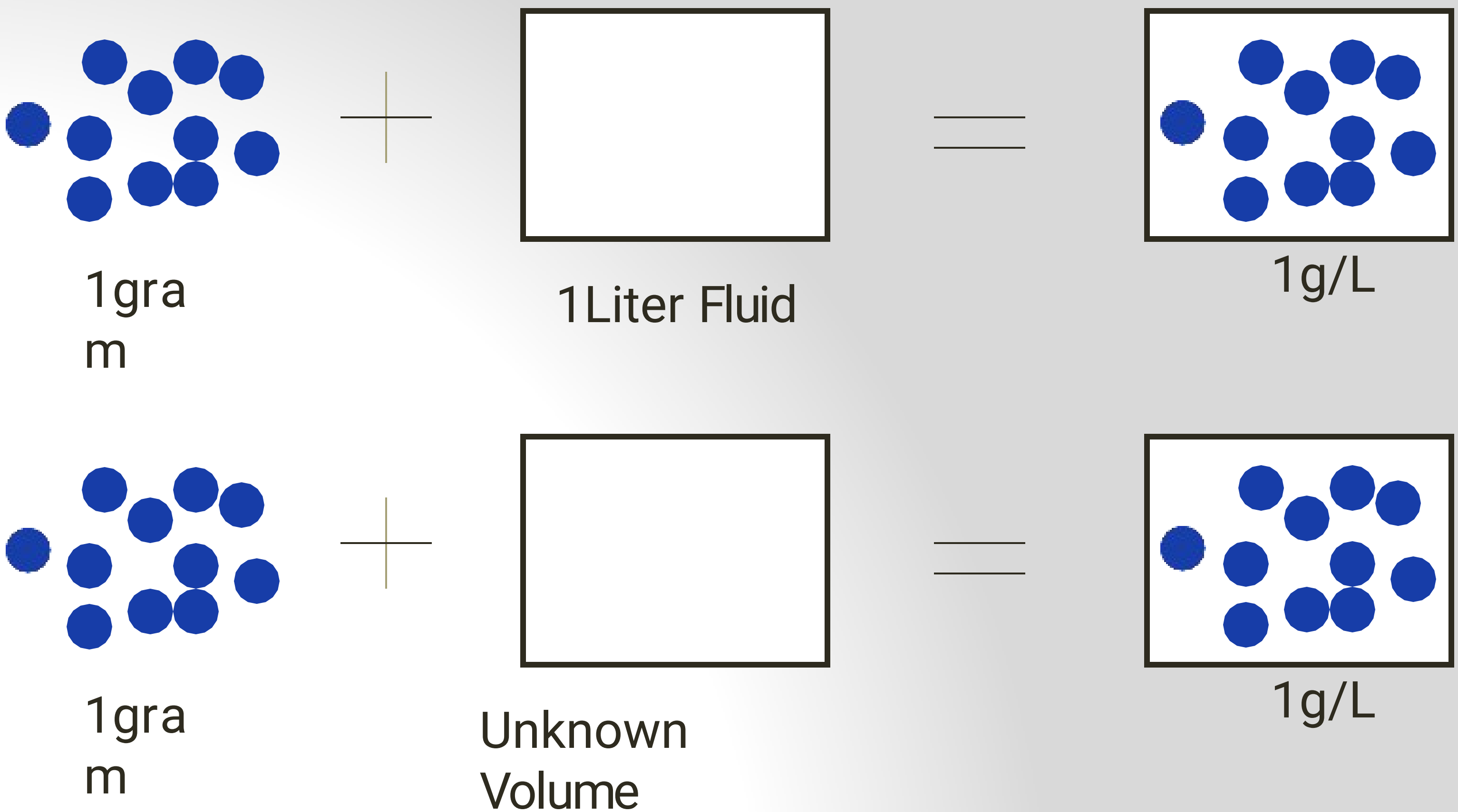
Fluid Compartments



Determining Fluid Volume



Fluid Compartments

Inulin

40% Non-Water

60% Water

1/3 Extracellular

2/3 Intracellular

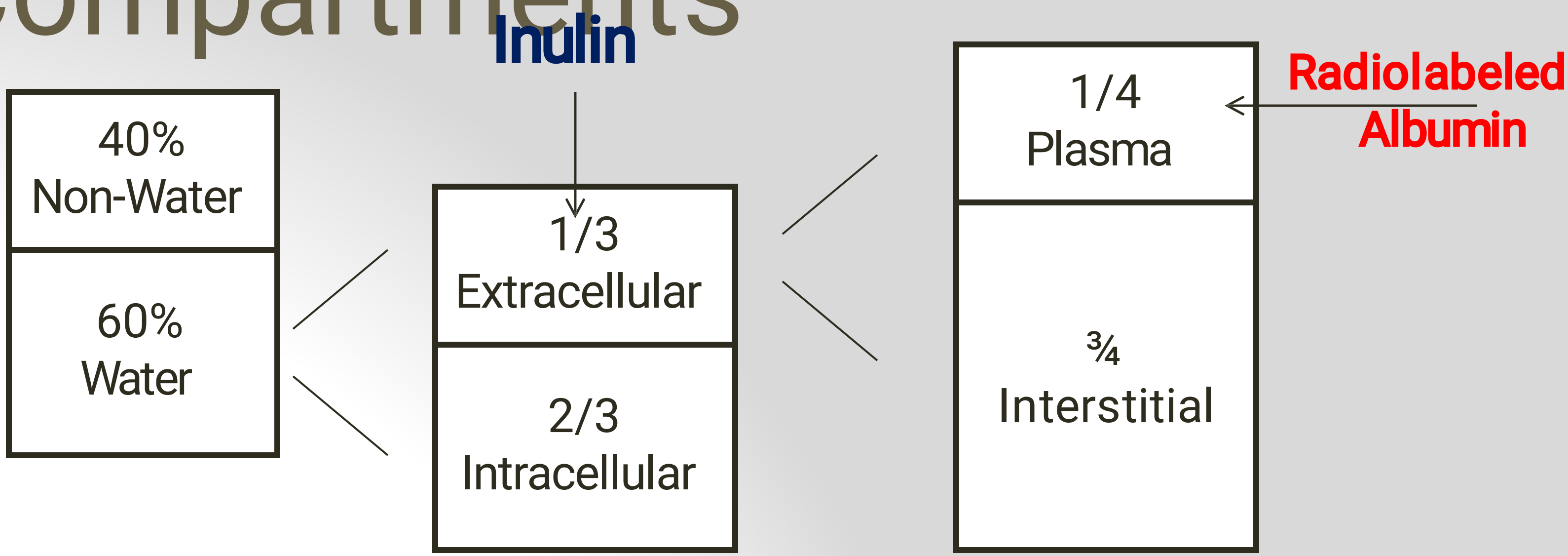
Radiolabeled Albumin

1/4 Plasma

¾ Interstitial

X grams Inulin infused
Equilibrium concentration = Y g/L
ECF = X/Y (Liters)

Fluid Compartments



10 grams Inulin infused

Equilibrium concentration = 0.25 g/L

ECF = 10/0.25 = 40L

Sample Question

A patient is administered 120mg of inulin. An hour later, the patient has excreted 20mg of inulin in the urine. The plasma inulin concentration is 1mg/100ml. What is the extracellular fluid volume for the patient?

Amount of inulin in body = 120mg – 20mg = 100mg Concentration = 1mg/100ml

$$ECF = \frac{100mg}{0.01mg/ml} = 10000ml = 10L$$

Fluid Compartment Shifts

- Plasma osmolarity about 300mosm/kg
- Equilibrium between cells and extracellular fluid
- **Fluid shifts only if difference in osmolarity**

Fluid Compartment Shifts

- Addition/loss of **isotonic fluid**
  - Change in ECF volume
  - No change in ICF volume
- Example: **Hemorrhage**
  - Loss of ECF, no change ICF
- Example: **Infusion of normal saline**
  - Increase ECF, no change ICF

Fluid Compartment Shifts

Example: **Infusion of 5% dextrose**

- Isotonic fluid
- Dextrose metabolized free water remains
- Increase in ECF volume
- Increase in ICF volume

Fluid Compartment Shifts

Example: **Mannitol infusion**

- Raises osmolarity
- Does not cross cell membranes
- Remains in the extracellular space
- Decrease in ICF volume
- Increase in ECF volume

Effective Circulating Volume

- Extracellular fluid contained in arterial system
- Maintains tissue perfusion
- Not necessarily correlated with total body water
- Modified by:
  - Volume
  - Cardiac output
  - Vascular resistance

BP = CO X TPR

Effective Circulating Volume

Low ECV leads to low blood pressure

Low ECV activates:

- **Sympathetic nervous system**
- **Renin-angiotensin-aldosterone system**

Condition	ECV	TBW
Volume Depletion	↓	↓
Heart Failure (low CO)	↓	↑
Cirrhosis (low SVR)	↓	↑

Evaluating Kidney Function

- **Glomerular filtration rate**
  - How much liquid passes through the filter (i.e. glomerulus)?
  - Determined from plasma, urine measurements
  - GFR falls as kidneys fail
- Renal Blood/Plasma Flow
  - How much blood enters kidney
- Filtration Fraction
  - GFR/RPF

Measuring GFR

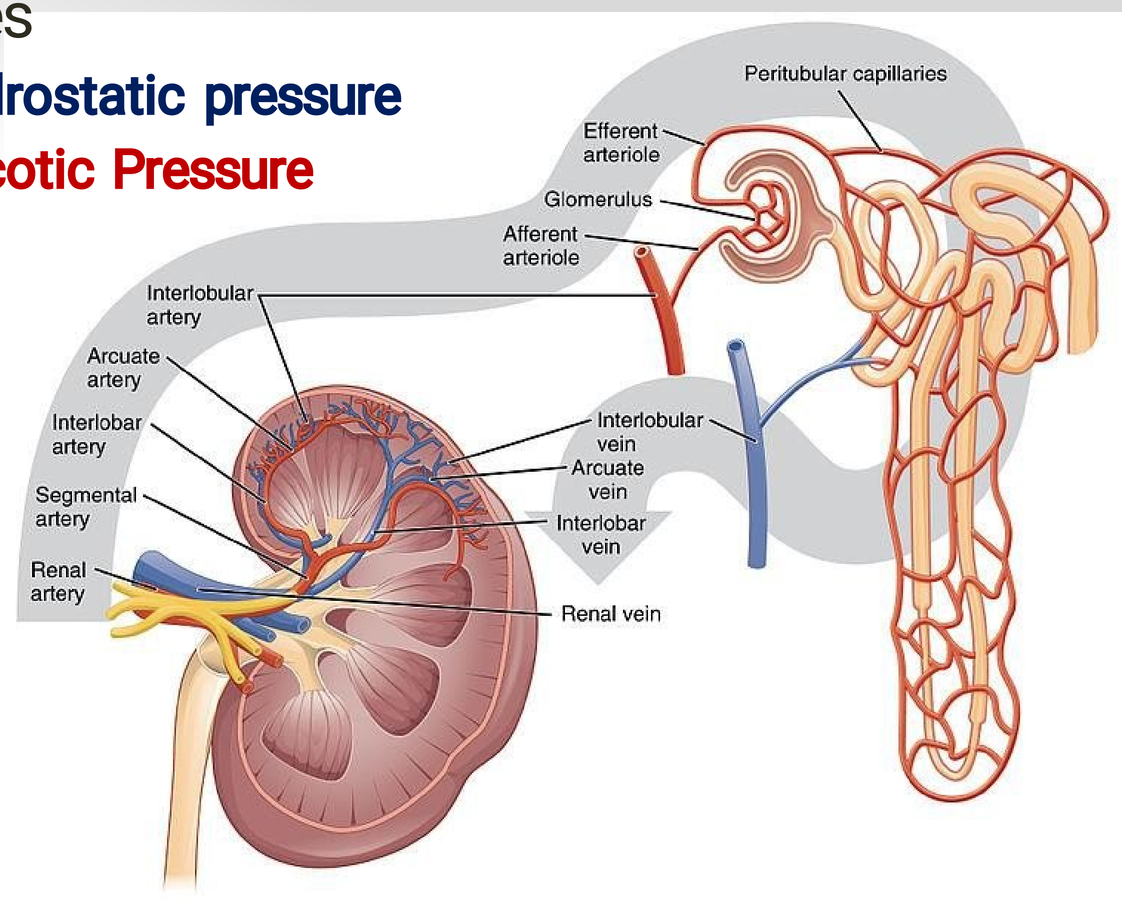
- Theoretical determination
  - Need to know pressures in capillary, Bowman's capsule
- Clinical determination
  - Need to know plasma concentrations solutes, urine flow

Theoretical Determination GFR

Filtration Driving Forces

Hydrostatic pressure

Oncotic Pressure



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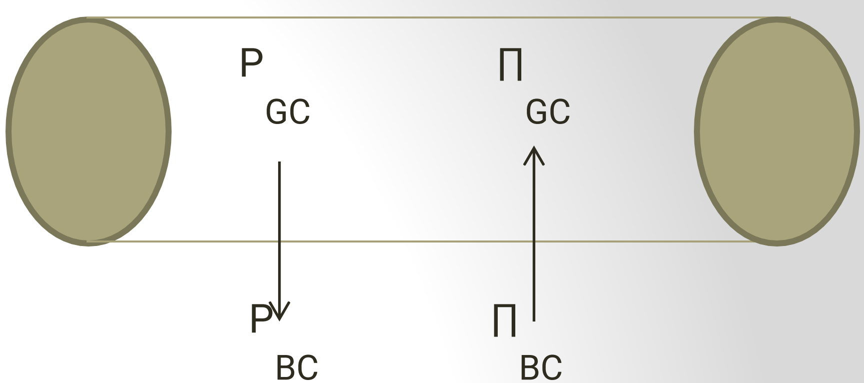
Capillary Fluid Exchange

Hydrostatic pressure – fluid PUSHING against walls

- High pressure drives fluid TOWARD low pressure

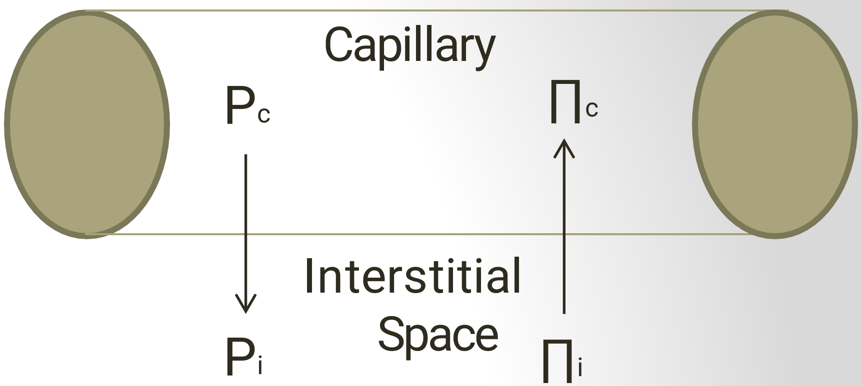
Oncotic pressure – concentrated solution PULLING fluid in

- High pressure draws fluid AWAY from low pressure

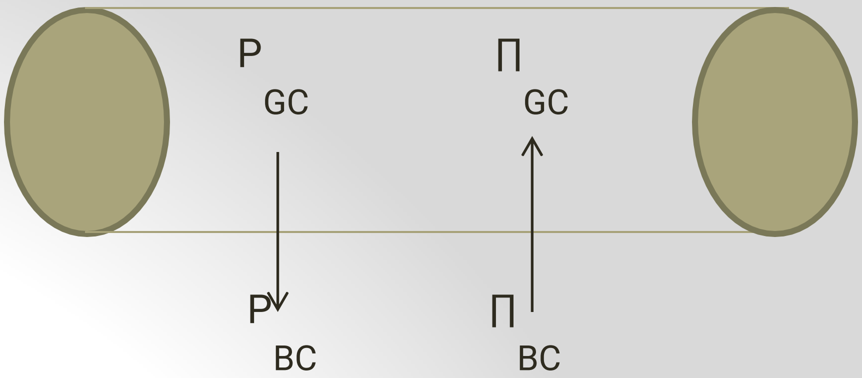


Capillary Fluid Exchange

- Two forces drive fluid into or out of capillaries
- Hydrostatic pressure (P)
  - Molecules against capillaries walls
  - Pushes fluid out
- Oncotic pressure (∏)
  - Solutes (albumin) drawing fluid into capillaries



Glomerular Filtration Rate

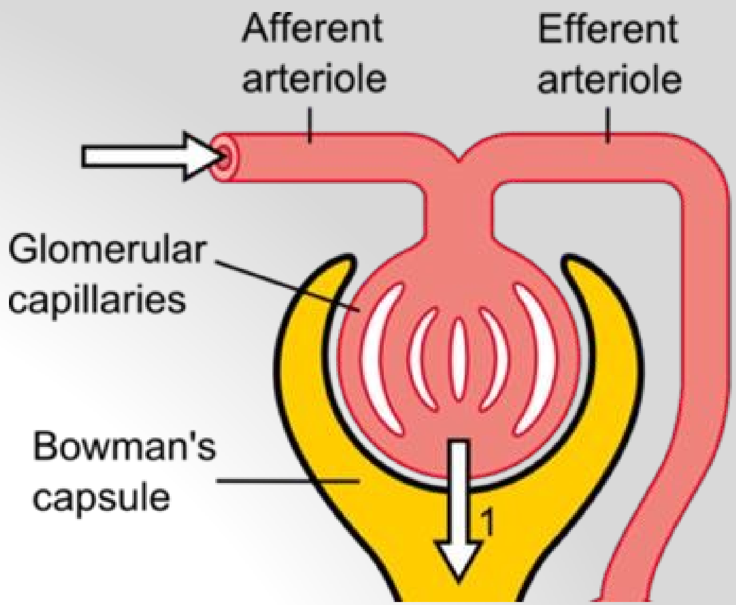


To change GFR:

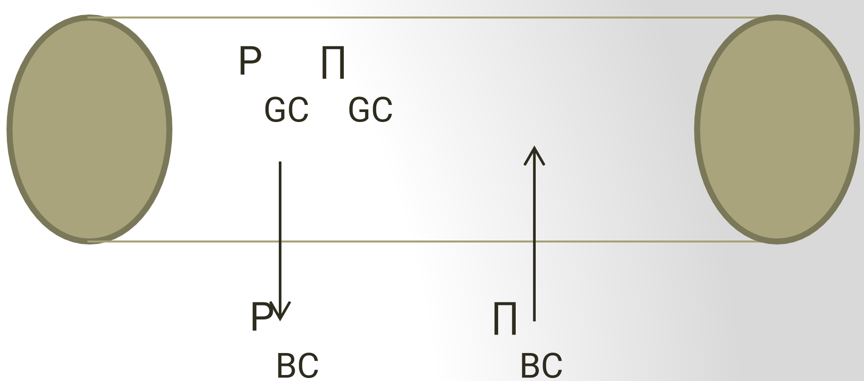
Change P_{GC} or P_{BC} Change Π_{GC} or Π_{BC}

Arterioles

Efferent & Afferent



Madhero88/Wikipedia

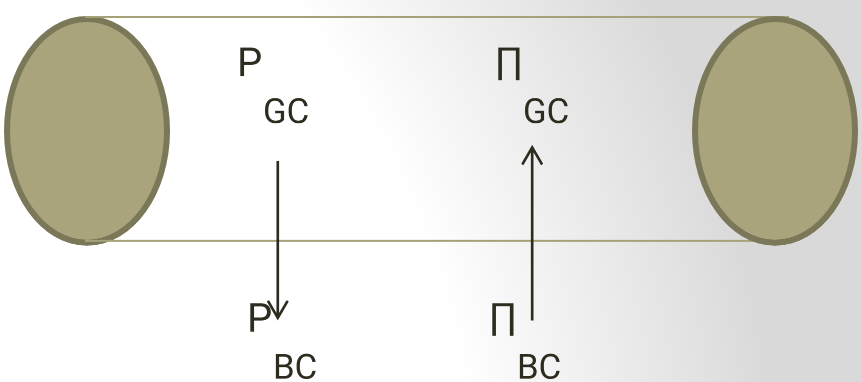


Raise P_{GC}

Increase GFR

Dilate afferent arteriole

- More blood IN
- Increase RPF
- Increase P_{GC}
- Increase GFR
- No change FF

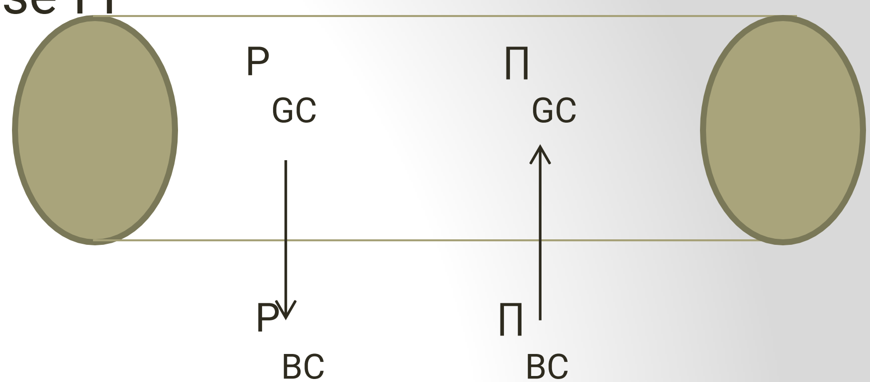


Raise P_{GC}

Increase GFR

Constrict efferent arteriole

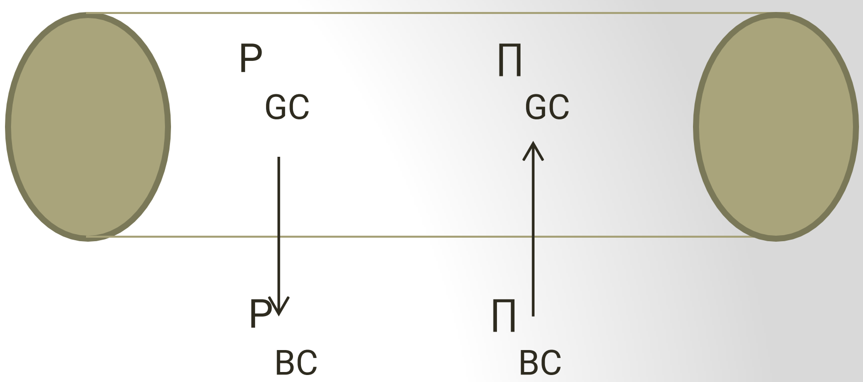
- Blood backs up behind constricted arteriole
- Less blood out
- Decreased RPF
- Increase P_{GC}
- Increase GFR
- Increase FF



Raise Π_{GC}

Increase protein levels in blood

- Less blood drawn into proximal tubule
- Lower GFR
- No change RPF
- Decrease FF



Change P_{BC}

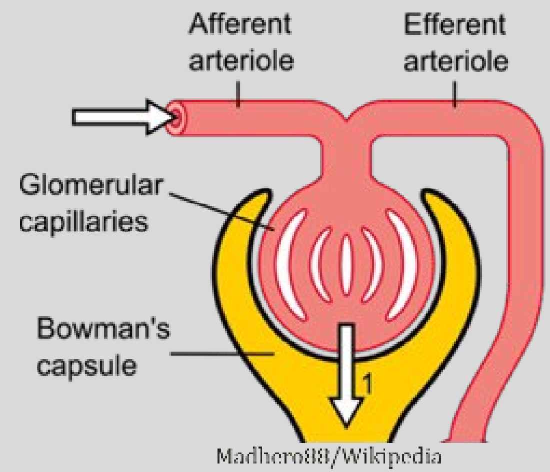
Obstruct ureter Increase P_{BC}

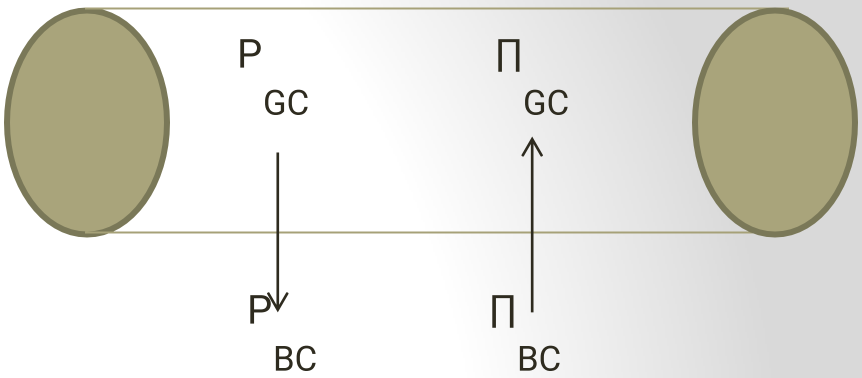
Urine backs up behind obstruction

Less GFR

No effect RPF

Decrease FF





Glomerular Flow Dynamics

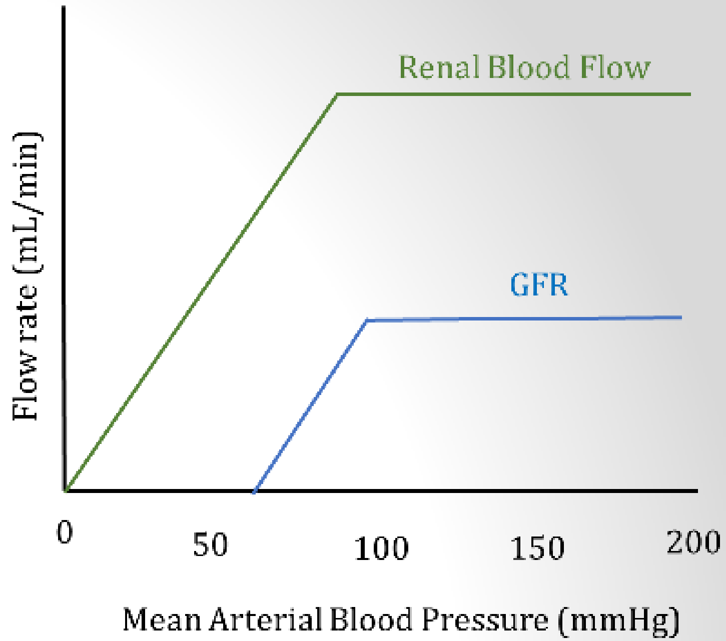
	RPF	GFR	FF
Afferent Dilation	↑	↑	--
Efferent Constriction	↓	↑	↑
↑ plasma proteins	--	↓	↓
Ureter obstruction	--	↓	↓

Autoregulation

Constant GFR/RBF over range of blood pressures

#1: Myogenic mechanism

#2: Tubuloglomerular feedback



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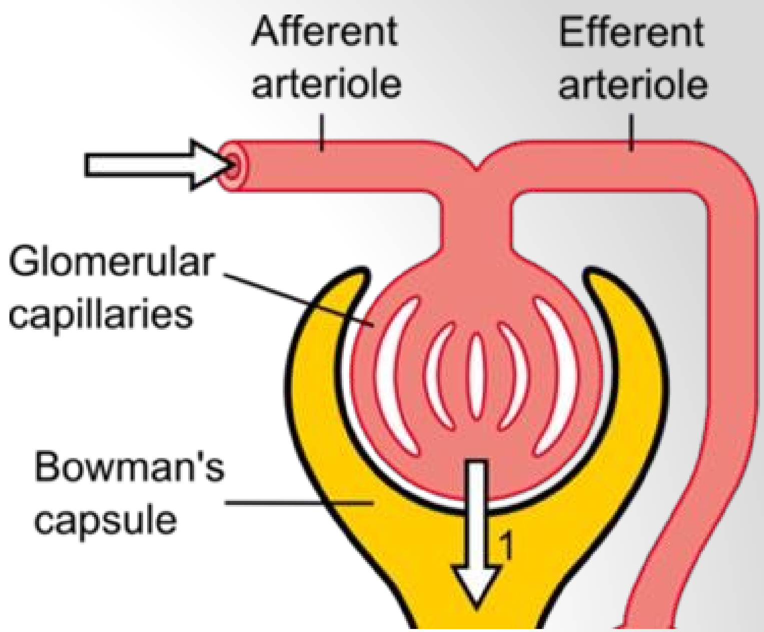
Myogenic Mechanism

Afferent arteriole constricts with high pressure

Responds to changes in stretch

Result is maintenance of normal GFR/RPF



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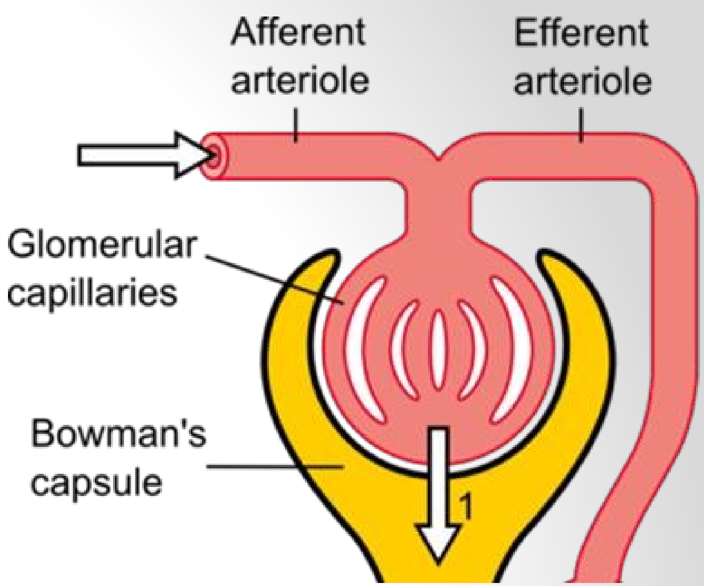
Tubuloglomerular Feedback

↑ urinary flow in tubule ↑ NaCl to distal tubule

NaCl sensed by **macula densa** (part of JG apparatus)

Macula Densa **vasoconstriction afferent arteriole**



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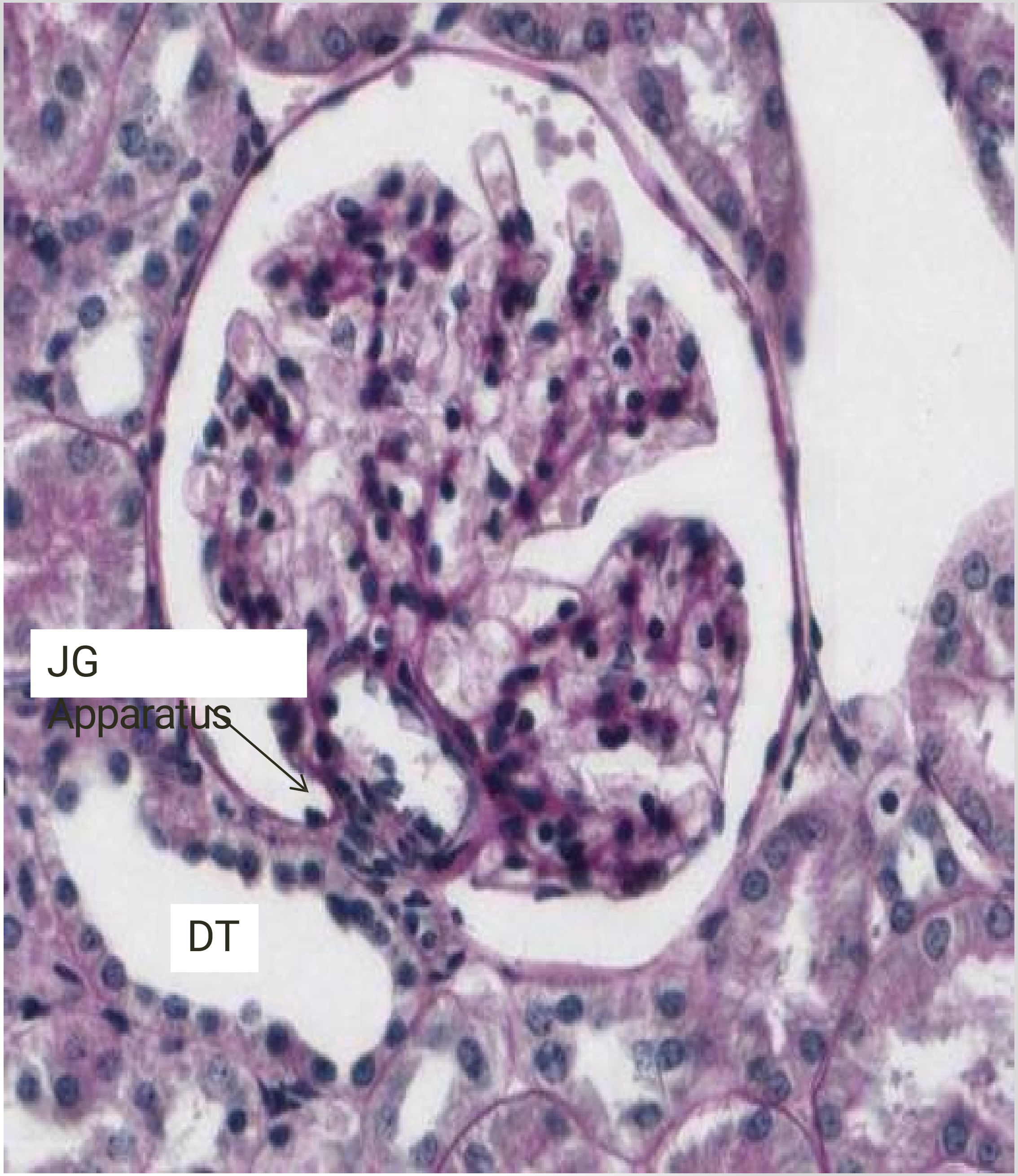
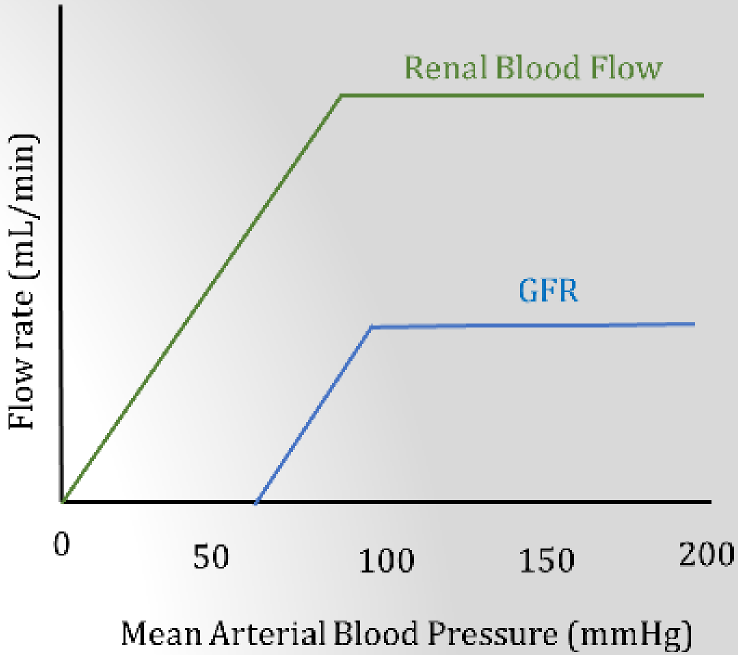

JG
Apparatus
DT

Severe Volume Loss

- Profound loss of fluid (vomiting, diarrhea, etc.)
- Renal plasma flow falls significantly
- **Auto-regulatory mechanisms overwhelmed**
- ↓GFR
- ↑BUN/Cr
- Pre-renal failure



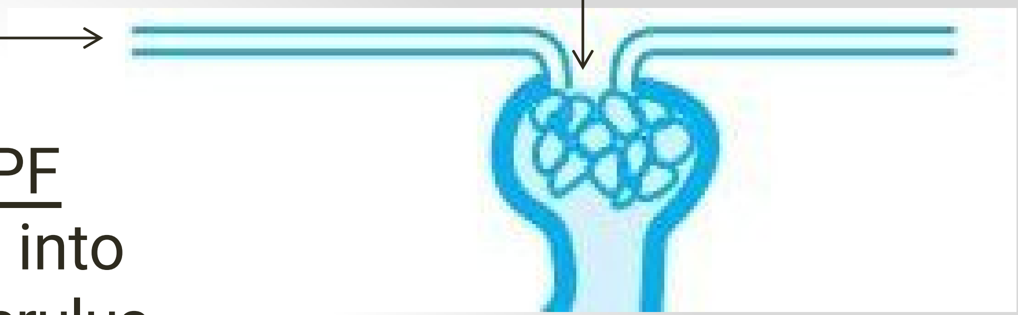
Renal Physiology II

Jason Ryan, MD, MPH

Renal Function Measurements

- Glomerular filtration rate
  - How much liquid passes through the filter (i.e. glomerulus)?
- Renal plasma flow
  - How much liquid does the kidney handle?
- Filtration fraction
  - Of all substance X entering kidney, what % gets filtered?
- Renal clearance
  - How much of each blood component gets removed?

Renal Function Measurements

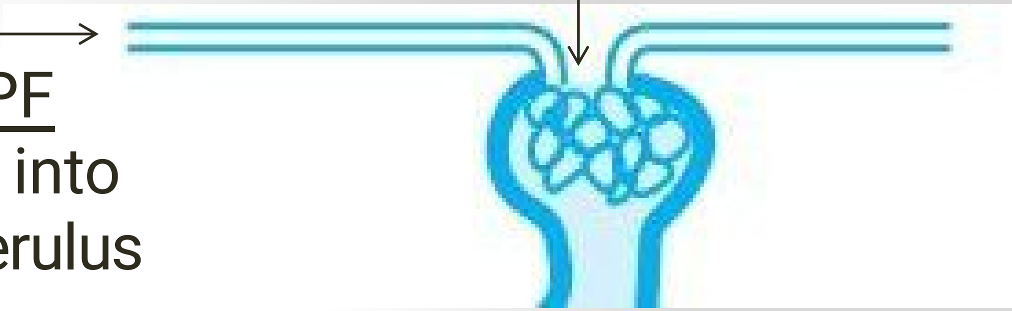


GFR
Fluid across Glomerulus

RPF
Fluid into Glomerulus

Urine Flow
Fluid out of kidney

Renal Function Measurements



GFR
Fluid across Glomerulus

RPF
Fluid into Glomerulus

Urine Flow
Fluid out of kidney

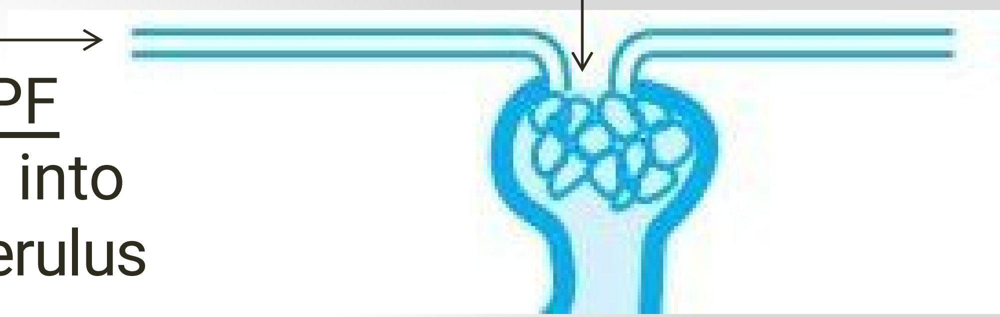
RPF = 5L/min GFR = 2L/min

Filtration Fraction=2/5=40%

Renal Function Measurements

<u>GFR</u>
Fluid across Glomerulus

<u>RPF</u>
Fluid into Glomerulus



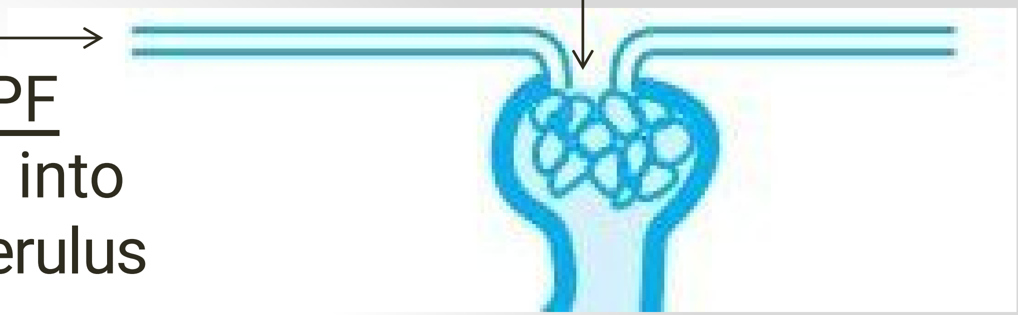
GFR = 2L/min
[Na] = 2g/L
Filtered Load Na
= 2*2= 4g/min

<u>Urine Flow</u>
Fluid out of kidney

Renal Function Measurements

GFR
Fluid across Glomerulus

RPF
Fluid into Glomerulus



Urine Flow = 100cc/hr Urine [K] = 10meq/cc Excretion K = 100 * 10 = 1000meq/hr

Urine Flow
Fluid out of kidney

Measured Variables

1. Plasma concentration (P_x = mg/l)
   i.e. Na, Glucose
2. Urine concentration (U_x = mg/l)
3. Urine flow rate (V = l/min)

Use these measured variables to get RPF, GFR, etc.

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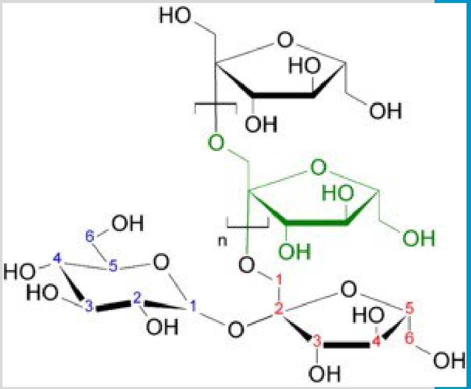
Renal Clearance

- Number determined for blood substance (Na, Glucose)
- Volume of blood "cleared" of substance X
- Volume of blood that contained amount of X excreted
- Reported liters/min (volume flow)

$$C_x = \frac{U_x * V}{P_x}$$

Determining GFR



- **Inulin clearance** used to determine GFR
- Inulin neither secreted or resorbed
- **All inulin filtered goes out**
- Amount blood "cleared" of inulin is amount of blood filtered by glomerulus
- **Clearance of inulin (liters/min) = GFR**

$$C_{inulin} = \frac{U_{inulin} * V}{P_{inulin}} = GFR$$

Creatinine

- Breakdown product muscle metabolism
- **Closest naturally occurring substance to inulin**
  - Inulin = All filtered goes out, no secretion/resorption
  - Creatinine = All filtered goes out, small amount secretion
- Using Cr instead of inulin:
  - Secreted Cr will be counted as filtered
  - This will slightly overestimate GFR

Creatinine

$$C_x = \frac{U_x * V}{P_x}$$

Special formulas to convert Cr to GFR

- Cockcroft-Gault formula
- Modification of Diet in Renal Disease (MDRD) formula
- Use age, gender, Cr level to estimate GFR

<u>Cockcroft-Gault</u>

CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

P_{Cr}/GFR Relationship

Amount of Cr out in urine

Equal to amount produced

$$C_{Cr} = \frac{\overbrace{U_{Cr} * V}}{P_{Cr}} = GFR$$

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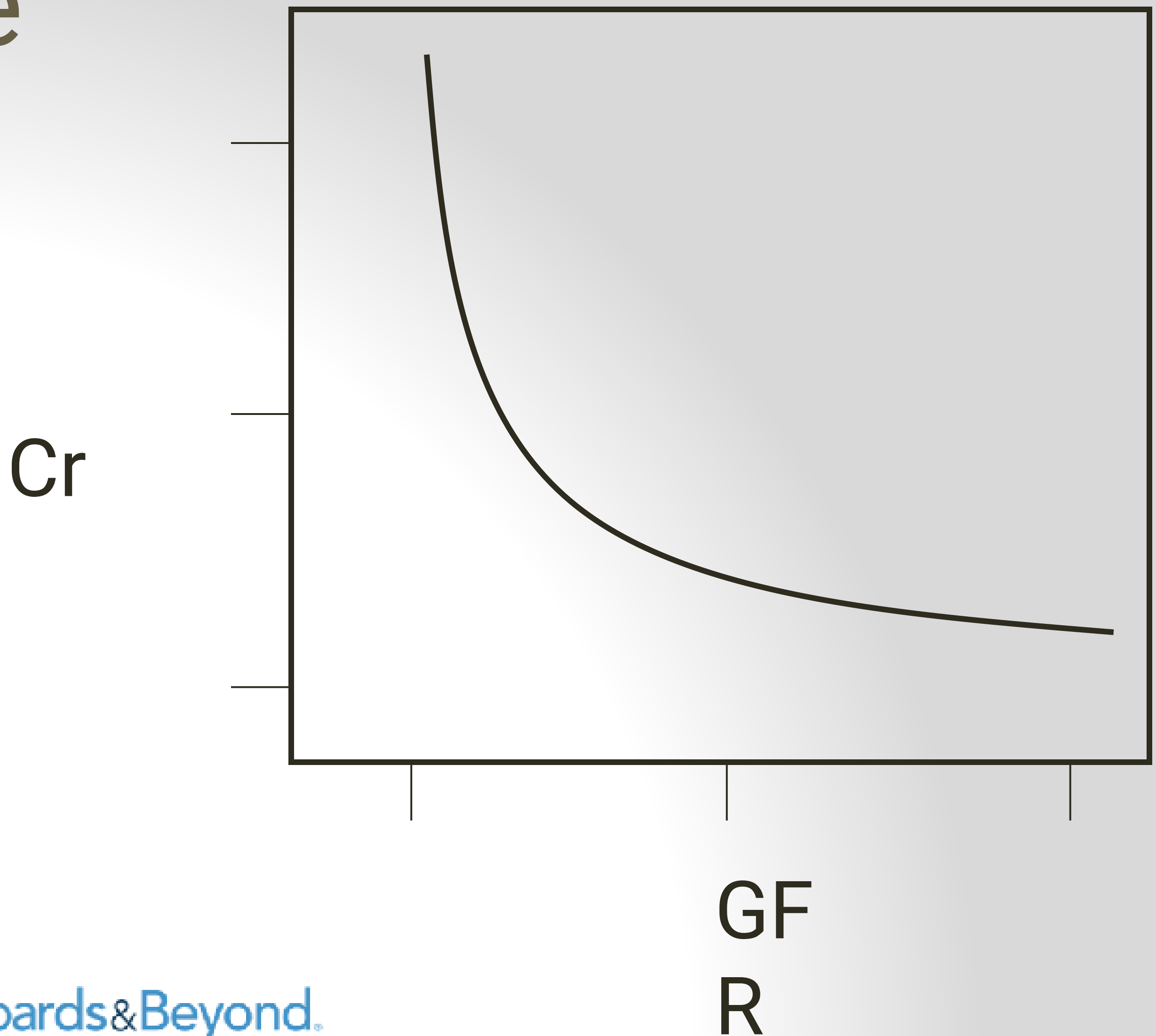
Creatinine Clearance

$$C_{Cr} = \frac{\text{Constant}}{P_{Cr}} \approx GFR$$

Double [Cr] (1.0 to 2.0) Half the GFR

Creatinine



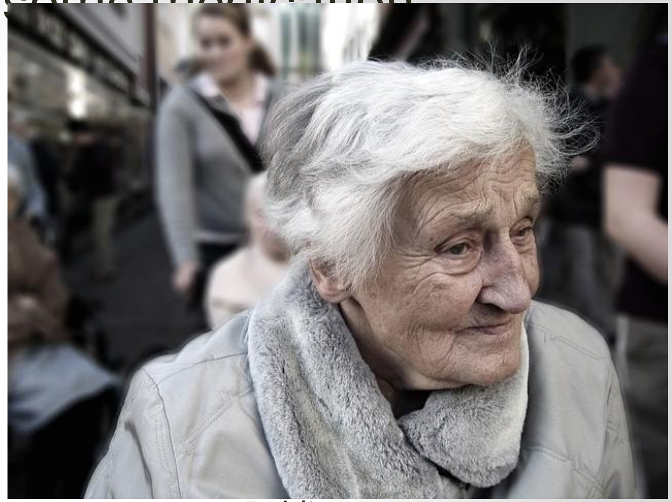
Creatinine

- Worsening renal function = high blood Cr level
- Some sample values:
  - Normal kidney function Cr = 0.8 mg/dl
  - Chronic kidney disease Cr = 2.0 mg/dl
  - End stage renal disease (dialysis) Cr = 4.0mg/dl

Creatinine

GFR declines with age

- Not always accompanied by rise in Cr
- Use of formulas is key
- Must adjust some medication dosages



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<u>Cockcroft-Gault</u>

CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

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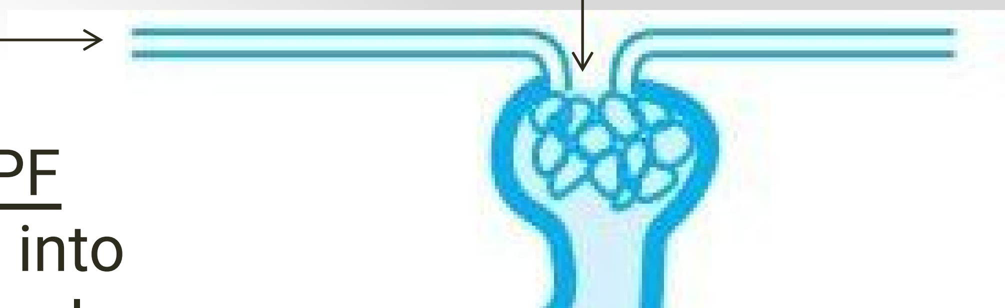
Renal Function Measurements

<u>GFR</u>
Fluid across Glomerulus

<u>RPF</u>
Fluid into Glomerulus

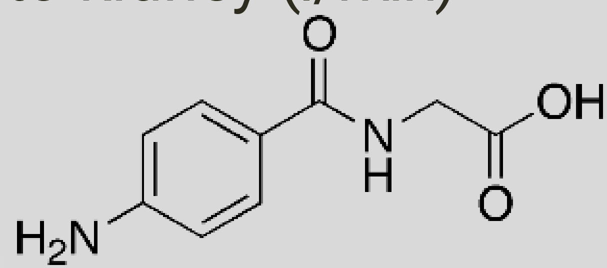


<u>Urine Flow</u>
Fluid out of kidney

Renal Plasma Flow (RPF)

- Use **para-aminohippuric acid (PAH)** to estimate RPF
- PAH is filtered and secreted
- 100% of PAH that enters kidney leaves blood in urine
- Clearance PAH (l/min) = Plasma to kidney (l/min)

$$C_{PAH} = \frac{U_{PAH} * V}{P_{PAH}} = RPF$$



PAH

*PAH clearance underestimates RPF by 10%

Not all renal plasma/blood to glomeruli

Plasma versus Blood

- Blood = Plasma + cells/proteins
- Renal Blood Flow > Renal Plasma Flow
- Separate calculations RBF vs. RPF

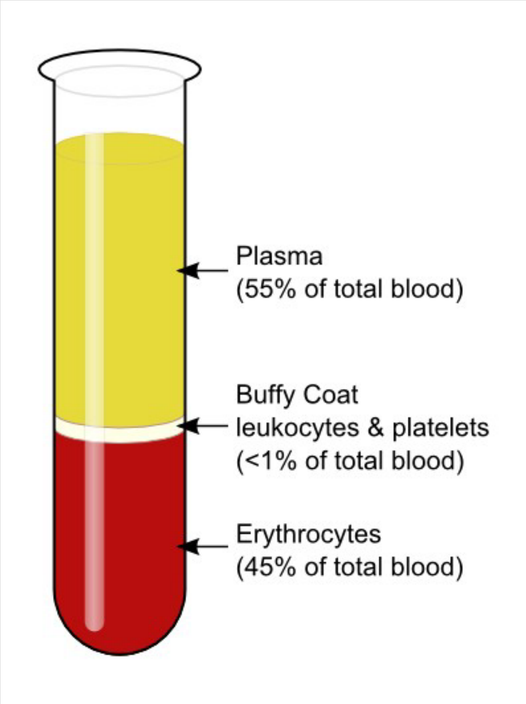


Image courtesy of KnuteKnudsen

Renal Blood Flow (RBF)

RBF determined from RPF

Blood = Plasma + Cells/ Proteins

Cells/Proteins (%) ≈ Hct (%)

RPF = RBF (1-Hct)

RBF = 10cc/min
40% of cells (Hct) 60% RBF is plasma

RPF = 10 (1- 0.4) = 10 (0.6) = 6cc/min

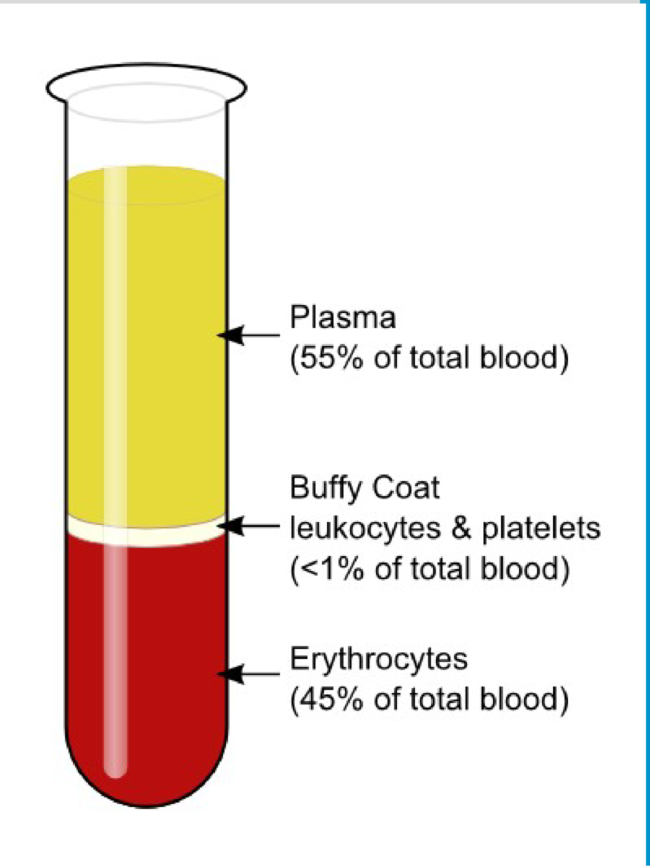


Image courtesy of KnuteKnudsen

Renal Blood Flow (RBF)

RBF determined from RPF

Blood = Plasma + Cells/ Proteins

Cells/Proteins (%) ≈ Hct (%)

$$RPF = RBF\,(1 - Hct)$$

$$RBF = \frac{RPF}{1 - Hct}$$

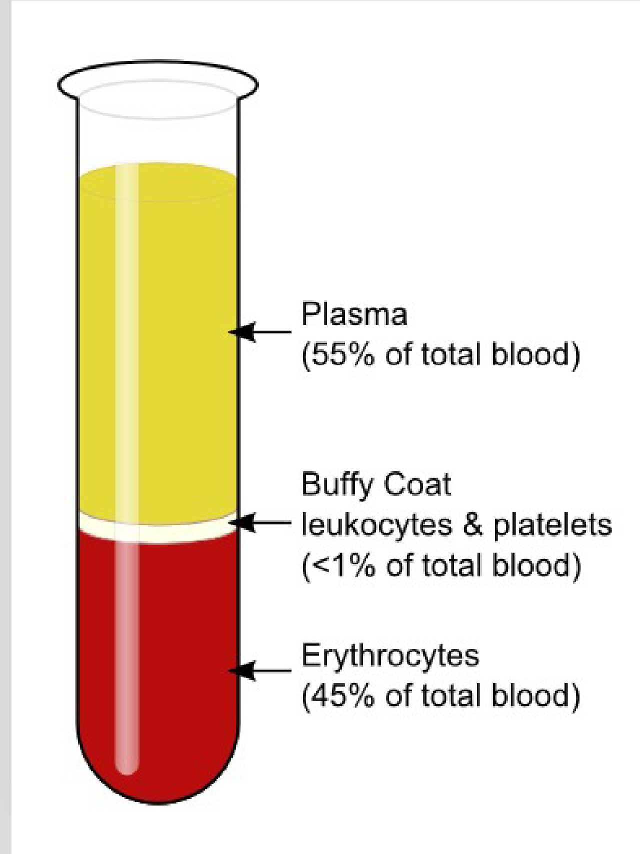


Image courtesy of KnuteKnudsen

Renal Blood Flow (RBF)

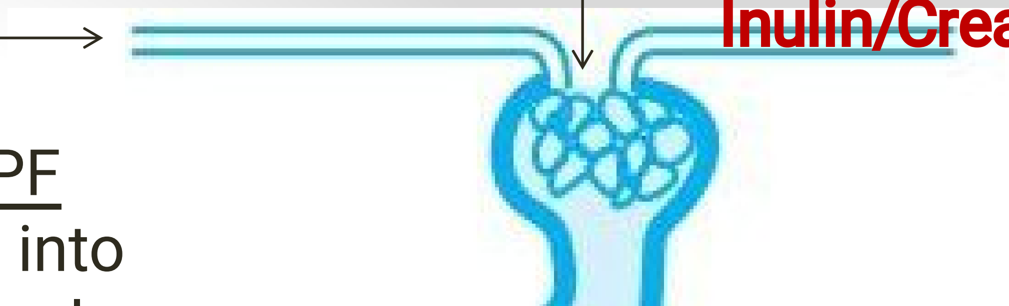
RPF = 1 liter/min

Hct = 40%

$$RBF = \frac{1}{1-Hct} = \frac{1}{0.6} = 1.6 \text{ l/min}$$

Renal Function Measurements

GFR
Fluid across Glomerulus
Inulin/Creatinine



RPF
Fluid into Glomerulus
PAH

Urine Flow
Fluid out of kidney

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Other Renal Function Variables

Filtration Fraction

- How much of plasma to kidney gets filtered?
- GFR/RPF
- Normal = 20%

Filtered Load X

- How much of substance X gets filtered?
- P_x * GFR
- Amount of X delivered to proximal tubule

Quantifying Kidney Function

Measured Variables

Urine Flow (l/min)

Plasma Conc X (mg/l)

Urine Conc X (mg/l)

→

Determined Variables

Renal clearance

Renal plasma flow

Renal Blood Flow

Glomerular filtration rate

Filtration fraction

Inulin Clearance = GFR

PAH Clearance = RPF

Prostaglandins and NSAIDs

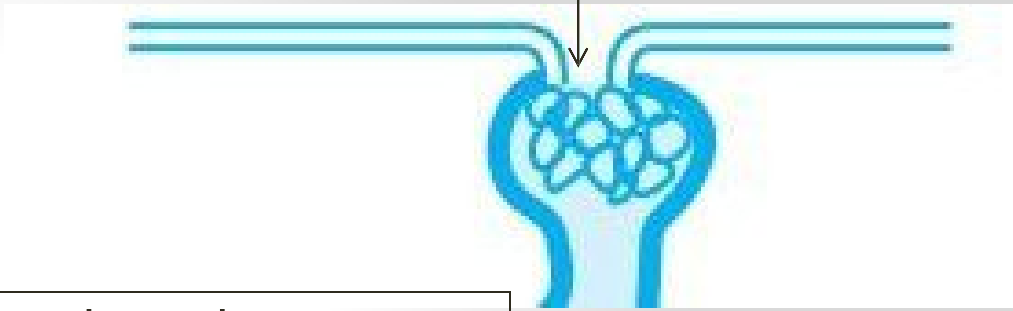
- Prostaglandins **dilate afferent arteriole** ↑RPF
- NSAIDs (ibuprofen) block PG production
- Afferent arteriole constricts
- ↓RPF ↓GFR -- FF
- Clinical effects:
  - Acute renal failure
  - Acute heart failure

ACE Inhibitors

- AII constricts most blood vessels
- AII **constricts efferent arteriole** preferentially
- ACE inhibitors blunt AII effects
- ↓GFR ↑RPF ↓FF

Secretion and Absorption

<u>GFR</u>
Fluid across Glomerulus $GFR*P_x$ = Filtered Load



What if Filtered Load ≠ Excretion

<u>Urine Flow</u>
Fluid out of kidney $V*U_x$ = Excretion

Secretion and Absorption

Excreted = Filtered – Reabsorbed + Secreted

Amount filtered (X) = GFR * P_x

Amount excreted (X) = V * U_x

Example:
10mgX/min filtered, 20mgX/min excreted Additional 10mgX/min must be secreted

Secretion and Absorption

Filtered = Excreted if no secretion/ resorption

Filtered < Excreted if some secreted

Filtered > Excreted if some resorbed

Example #1:

Filtered = 100mg/min
Excreted = 120mg/min

Additional 20mg/min must be secreted

Example #2:

Filtered = 100mg/min
Excreted = 80mg/min
20mg/min must be resorbed

Secretion and Absorption

If clearance (x) = GFR   no secretion/ resorption

GFR<Cx   secretion

GFR>Cx   resorption

Example #1:
GFR = 100ml/min Cx = 120ml/min
Additional 20ml/min “cleared” by secretion

Example #2:
GFR = 100ml/min Cx = 80ml/min
Additional 20ml/min “uncleared” by resorption

Intake and Output

- Amount of any substance in must equal amount out
- When insults occur (renal failure, diarrhea), there is a transient imbalance that alters plasma levels
- Steady state returns
- Eat 10grams per day salt excrete 10grams per day

Solutes in Renal Failure

Regulated solutes (Na/K): No concentration change

Unregulated solutes (Cr/Urea): ↑plasma level

	Normal GFR=100	GFR=50	Filtered Load	Excretion	Fractional Excretion
K	4.5	4.5	↓	--	↑
Na	145	145	↓	--	↑
Urea	20	40	--	--	--

Question 1

A patient has a urine output of 4800cc/day (200cc/hr). Plasma concentration of substance X is 4mg/dL. Urine concentration of X is 8mg/dL. What is the clearance of substance X?

$$C_x = \frac{U_x * V}{P_x} = \frac{8 * 200}{4} = \mathbf{400cc/hr}$$

Question 2

A patient is infused with inulin. At steady state, plasma concentration of inulin is 3mg/dl and urine concentration is 6mg/dl. If the GFR is 200ml/hr, what is the urine flow rate?

$$GFR = \frac{U_{inulin} * V}{P_{inulin}} = C_{inulin}$$

$$V = \frac{GFR * P_{inulin}}{U_{inulin}} = \frac{200 * 3}{6} = \mathbf{100ml/hr}$$

Question 3

A patient is infused with PAH. At steady state, plasma concentration of PAH is 5mg/dl. Urine concentration is 10mg/dl. If the urine flow rate is 200ml/hr and the hematocrit is 0.50, what is the renal blood flow?

$$C_{PAH} = \frac{U_{PAH} * V}{P_{PAH}} = RPF \qquad RBF = \frac{RPF}{1-Hct}$$

$$RPF = \frac{10 * 200}{5} = 400 \qquad RBF = \frac{400}{1-0.5} = \underline{\mathbf{800ml/hr}}$$

Question 4

A lab animal has an inulin clearance of 100cc/hr. Plasma concentration of substance X is 4mg/mL. It is known that substance X is not reabsorbed, but is secreted at a rate of 25mg/hr. What is the excretion rate of substance X?

Amount filtered (X) = GFR * P_x

Excreted = Filtered – Reabsorbed + Secreted

Question 4

A lab animal has an inulin clearance of 100cc/hr. Plasma concentration of substance X is 4mg/mL. It is known that substance X is not reabsorbed, but is secreted at a rate of 25mg/hr. What is the excretion rate of substance X?

Amount filtered (X) = GFR * P_x = 100 * 4 = 400mg/hr Excreted = Filtered – Reabsorbed + Secreted

Excreted = 400 - 0 + 25

425mg/hr

Key Points

- If given inulin clearance, that is GFR
- GFR used to calculate filtered load of other substances
- Just need plasma concentration (P_x)

Key Points

Amount filtered = GFR * P_x

Amount excreted = V * U_x

Excreted = Filtered + Secreted - Resorbed

For Inulin Filtered = Excreted