EVALUATION OF KIDNEY FUNCTION

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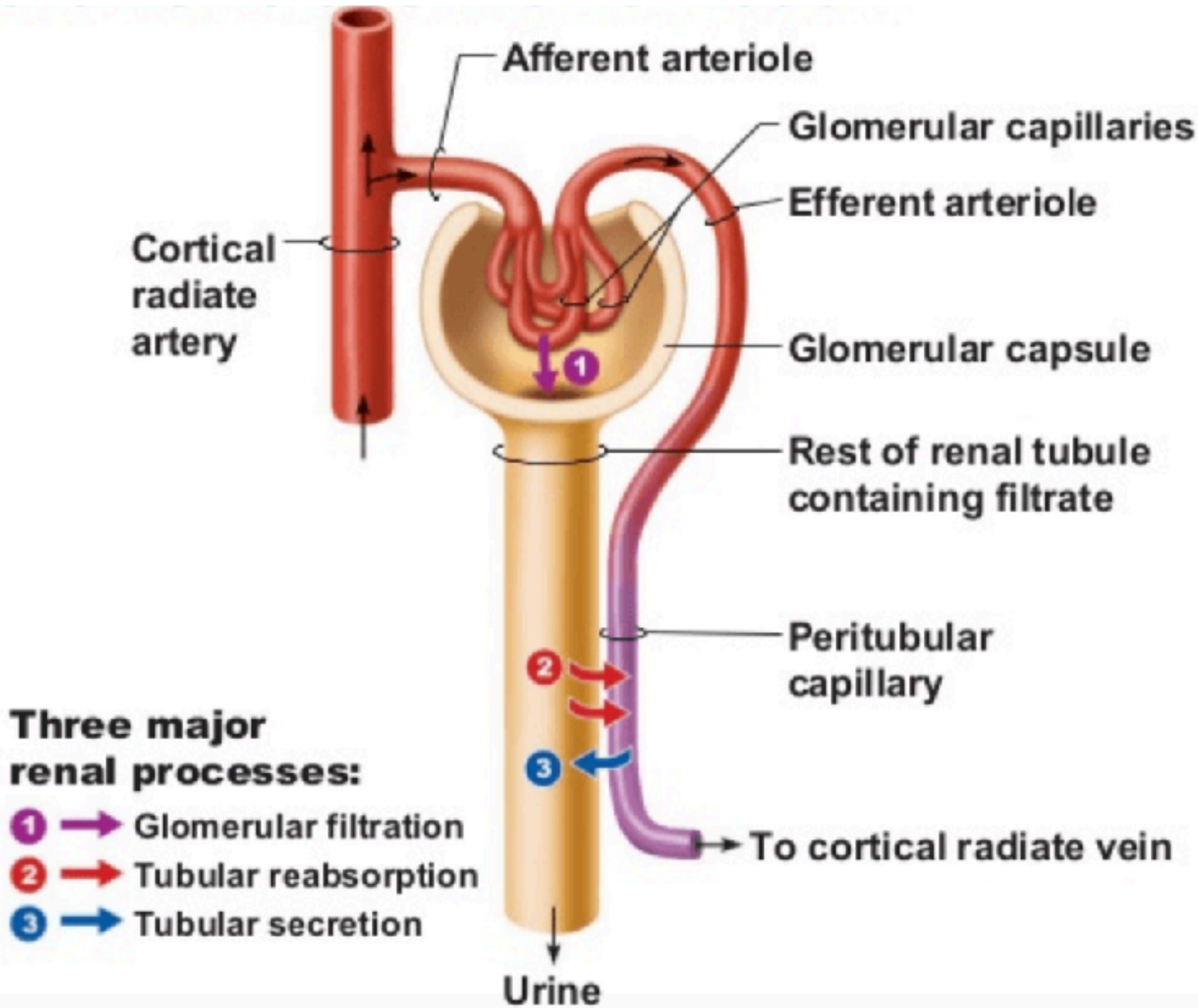
OUTLINE

- Glomerular filtration rate
- Renal plasma flow
- Autoregulation of renal blood flow and glomerular filtration rate
- Assessment of glomerular filtration rate in acute and chronic setting
- proteinuria evaluation

MECHANISM OF URINE FORMATION



GLOMERULAR FILTRATION RATE (GFR)

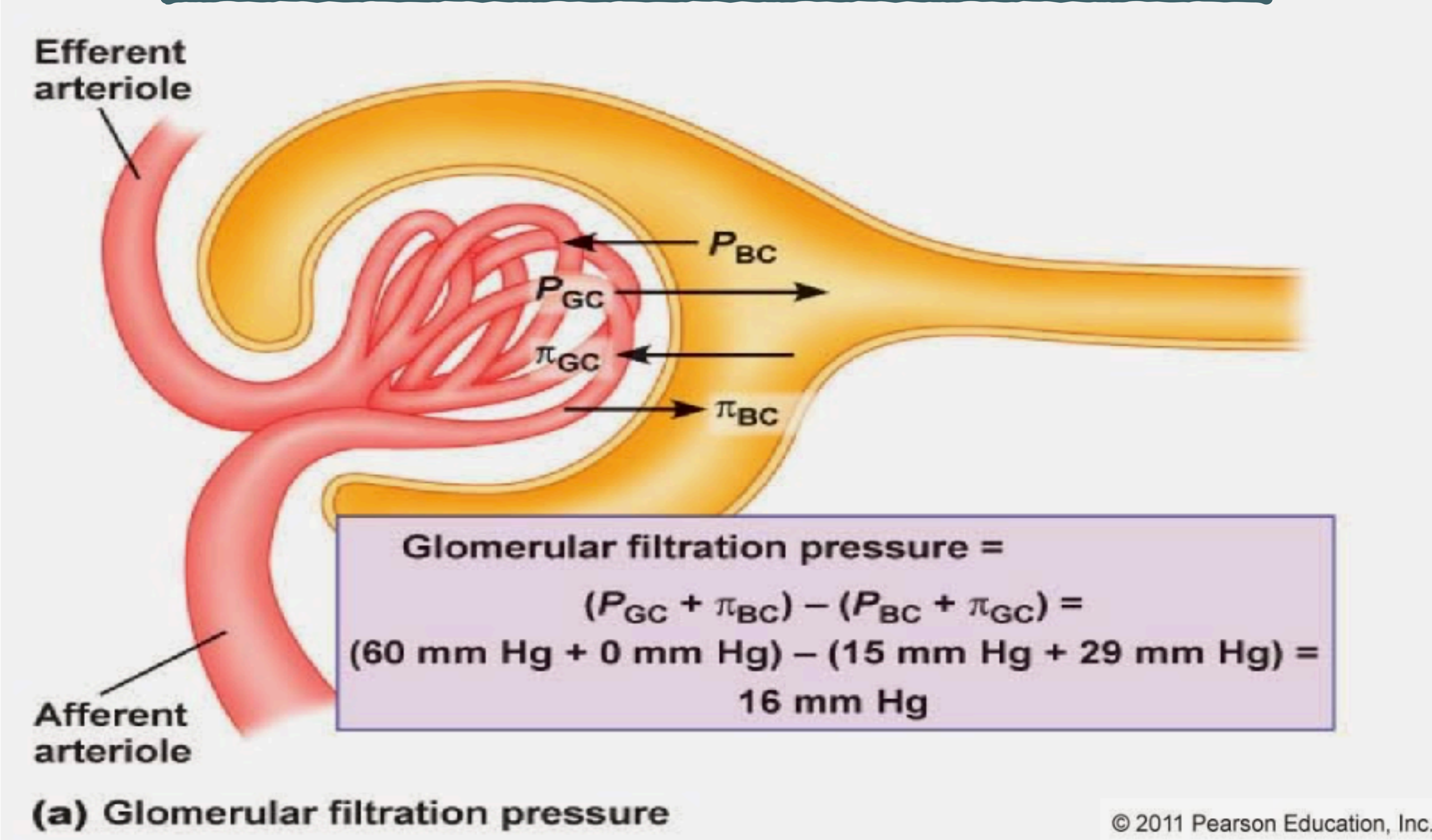
- Average filtration rate of

Single nephron GFR (SNGFR) x number of nephrons in both kidneys

- Normal level of GFR
    - men : 130 ml/min/1.73 m2
    - women : 120 ml/min/1.73 m2

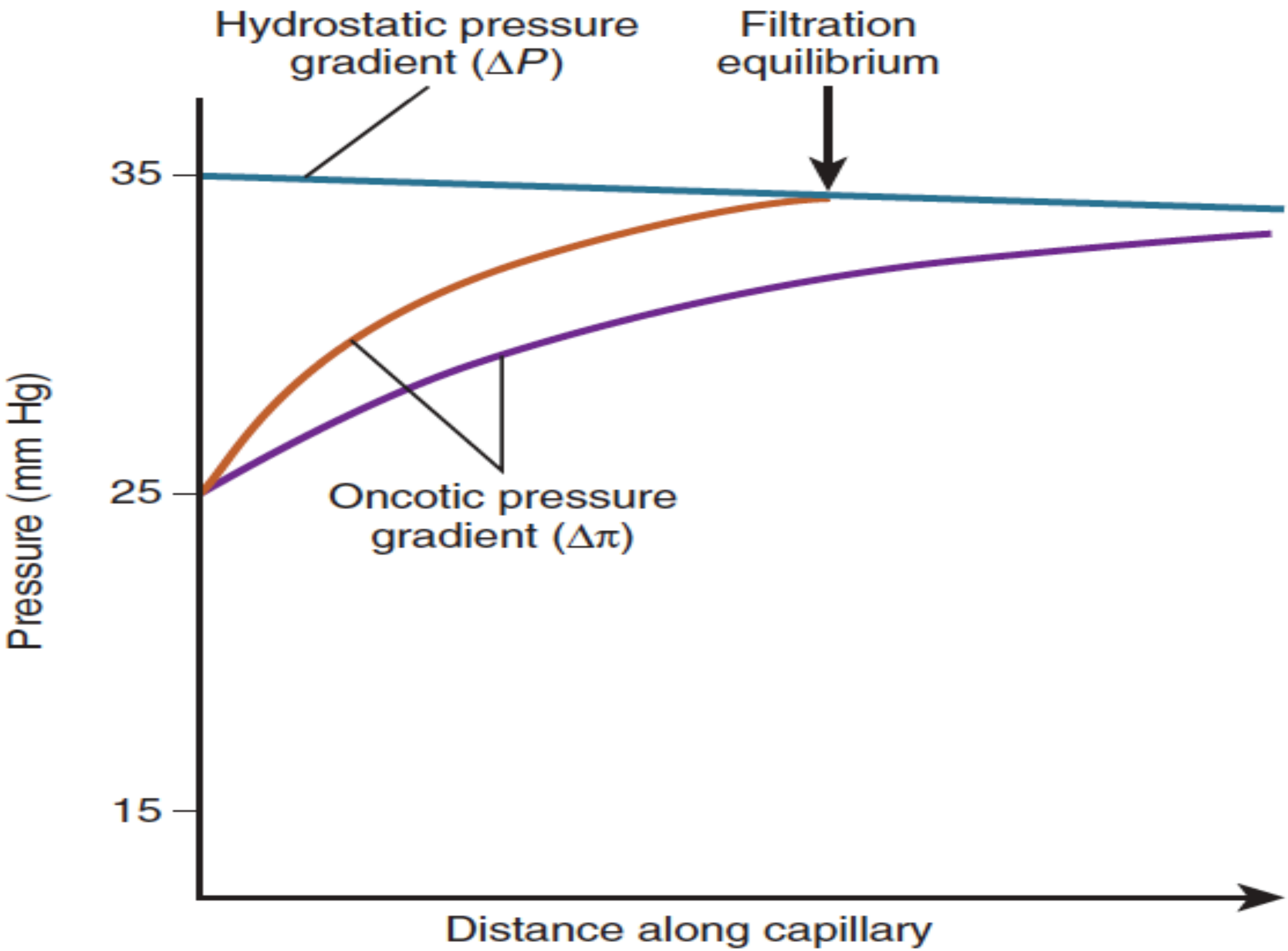
SINGLE NEPHRON GLOMERULAR FILTRATION RATE (SNGFR)

$$SNGFR = Kf\ [(Pgc - Pbc) - (\pi\ gc - \pi\ bc)]$$



(a) Glomerular filtration pressure

GLOMERULAR FILTRATION PRESSURE



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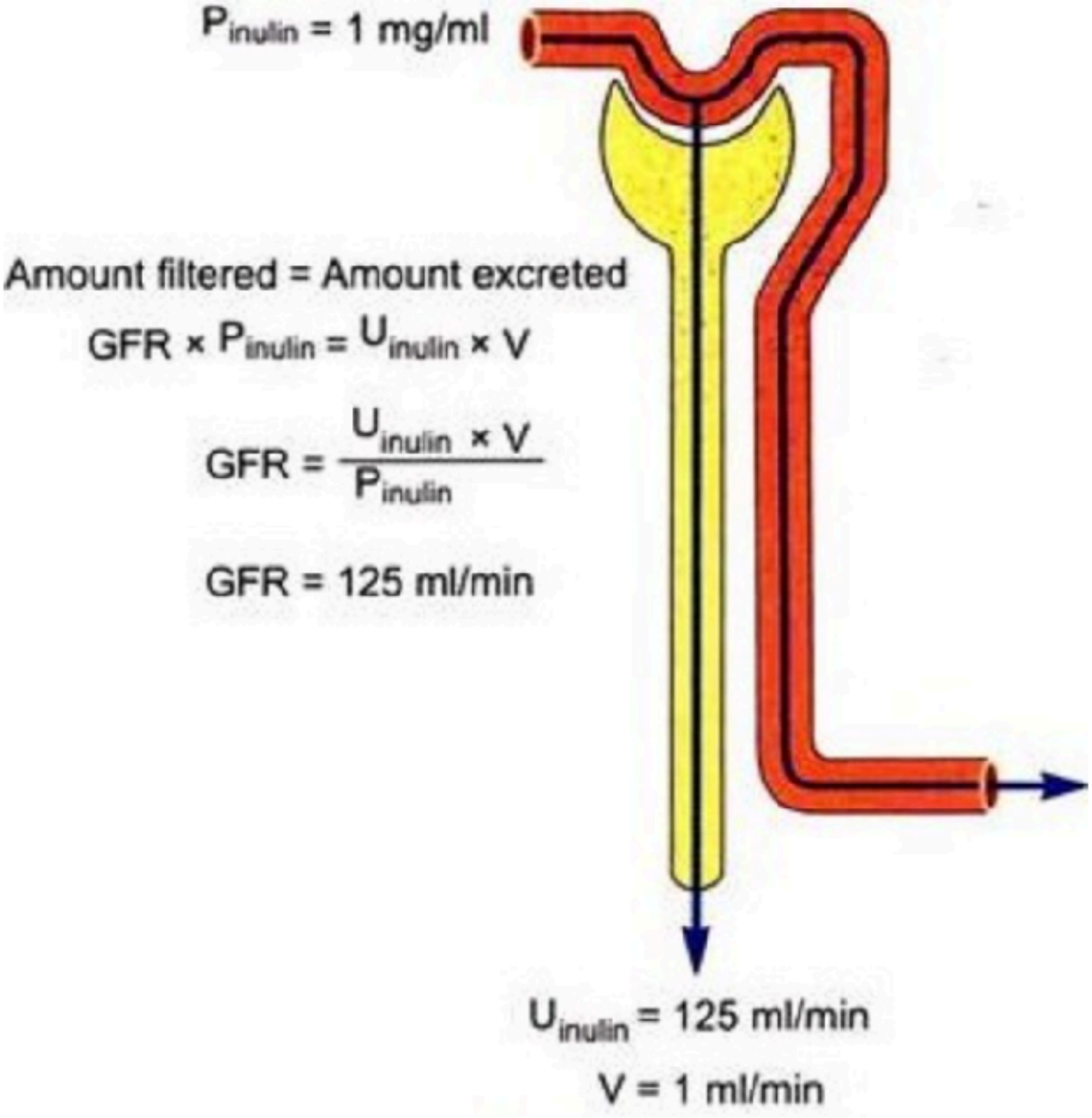
RENAL CLEARANCE= GFR (SUBSTANCE NOT SECRETE/REABSORB)

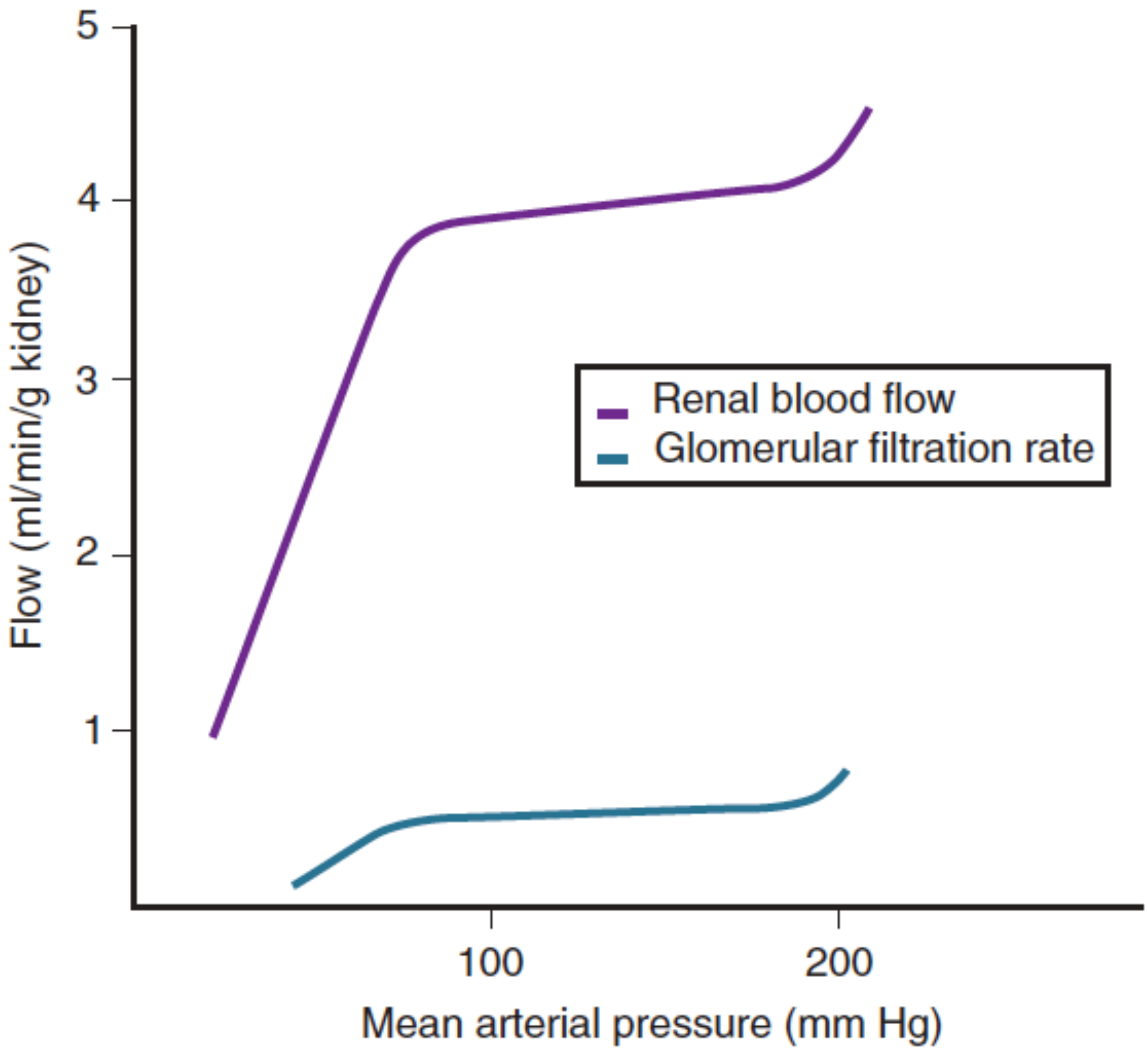


MEASUREMENT OF RENAL PLASMA FLOW (RPF)

- Para-aminohippuric acid (PAH):
  - glomerular filtration and tubular secretion

- $RPF \times P_{PAH} = U_{PAH} \times V$
- $RPF = (U_{PAH} \times V)/P_{PAH}$ = PAH clearance
- Renal blood flow (RBF) = RPF/(1-Hct)
  - RBF normally 20% of Cardiac output (1-1.2 L/min)

RENAL AUTOREGULATION



Fluctuation in BP:
Small effect on
RBF and GFR

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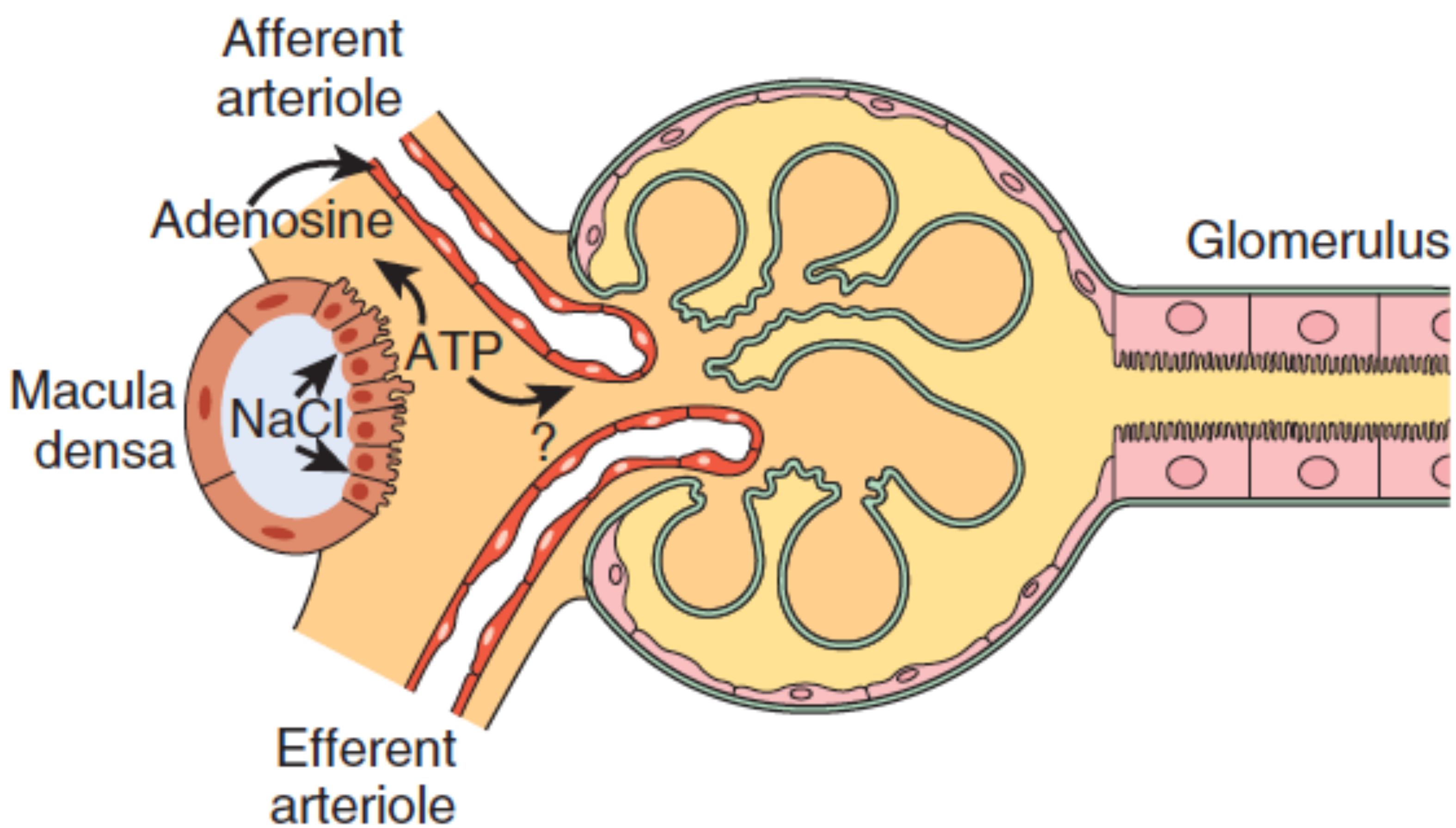
AUTOREGULATION MECHANISM

- myogenic reflex: Afferent arteriole constrict automatically with rising renal perfusion pressure
- Tubuloglomerular feedback (TGF)— ↑ATP, angiotensin II, NO



Afferent arteriole constriction

- Alteration of Kf : mesangial cell contraction/relaxation

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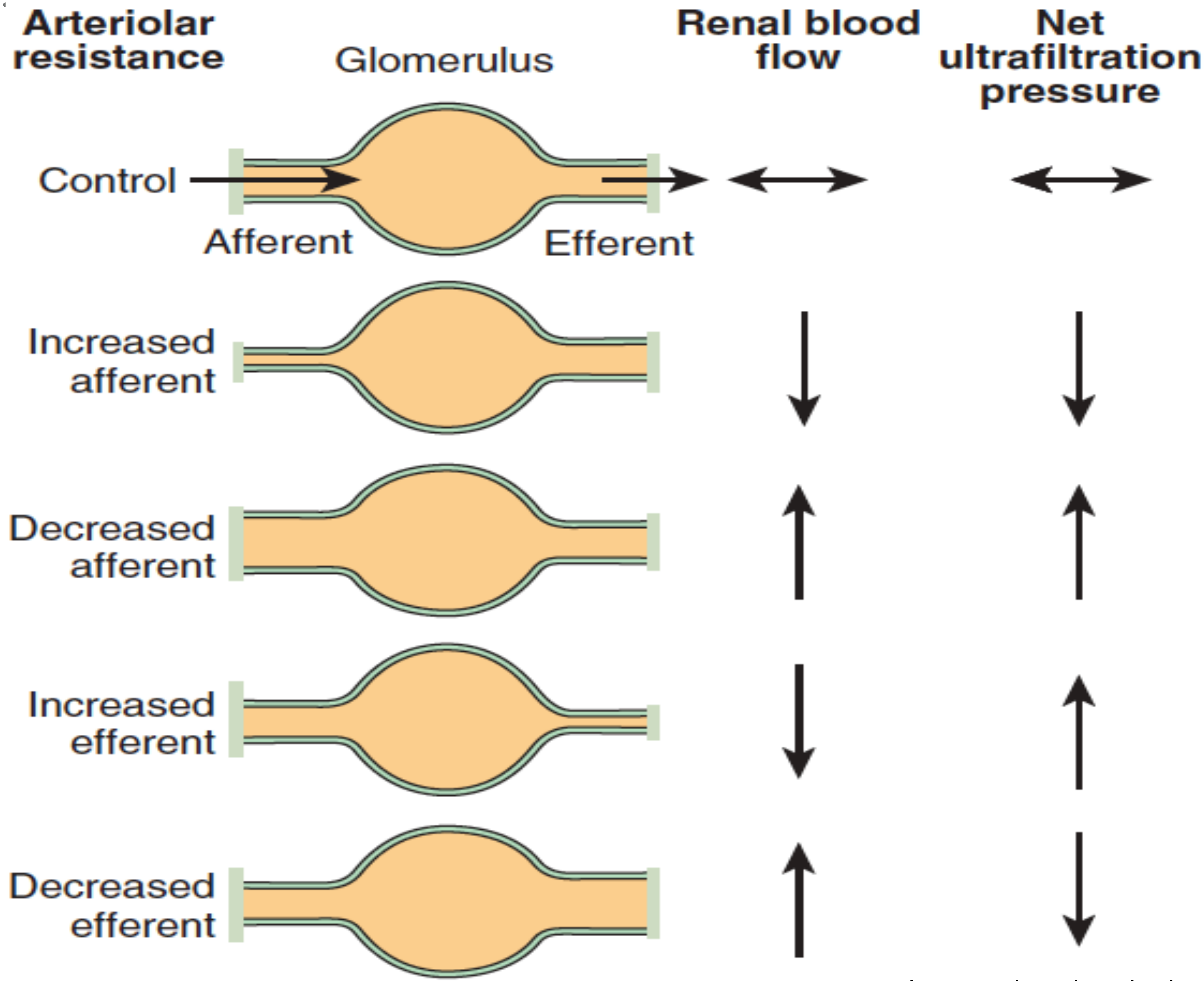
GLOMERULAR HEMODYNAMICS



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PHYSIOLOGIC AND PHARMACOLOGIC INFLUENCE ON GLOMERULAR HEMODYNAMICS

	Arteriolar Resistance					
	Afferent	*Efferent*	*Renal Blood Flow*	*Net Ultrafiltration Pressure*	K_f	*GFR*
Renal sympathetic nerves	↑↑	↑	↓	↓	↓	↓
Epinephrine	↑	↑	↓	→	?	↓
Adenosine	↑	→	↓	↓	?	↓
Cyclosporine	↑	→	↓	↓	?	↓
NSAIDs	↑↑	↑	↓	↓	?	↓
Angiotensin II	↑	↑↑	↓	↑	↓	↓→
Endothelin-1	↑	↑↑	↓	↑	↓	↓
High-protein diet	↓	→	↑	↑	→	↑
Nitric oxide	↓	↓	↑	?	↑	↑(?)
ANP (high dose)	↓	→	↑	↑	↑	↑
PGE_2/PGI_2	↓	↓(?)	↑	↑	?	↑
Calcium channel blockers	↓	→	↑	↑	?	↑
ACE inhibitors, ARBs	↓	↓↓	↑	↓	↑	?*

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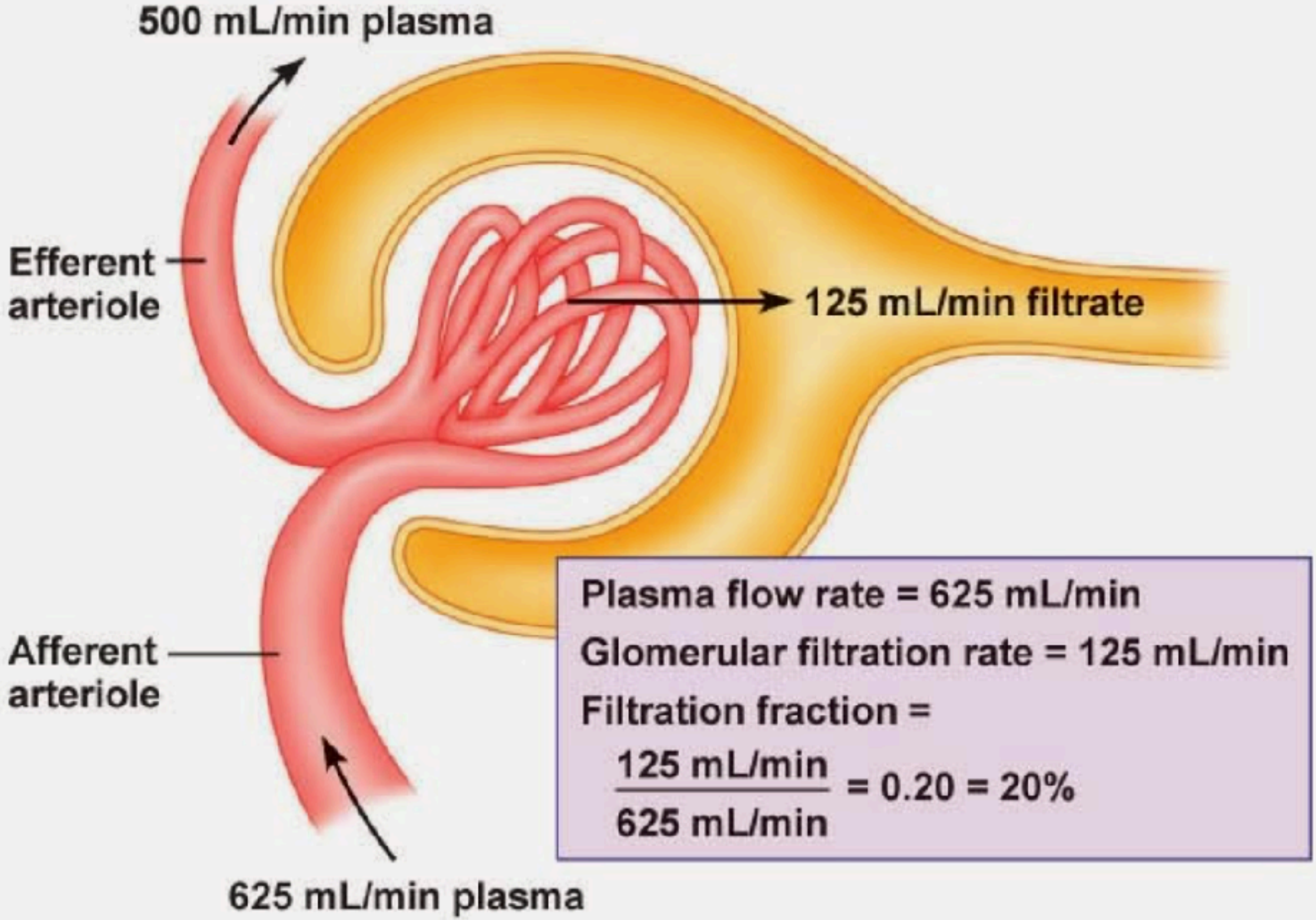


(b) Glomerular filtration rate and filtration fraction

KEY EVENT : GFR MEASUREMENT

- 1884 Jaffe developed methods to assay creatinine
- 1940 Homer Smith developed method to measure GFR
- 1943 Construction of the first working dialyzer
- 1971 First equation estimating GFR from creatinine clearance published (Jeliffe)
- 1989 United States Renal Data systems produced its first annual data report
- 1999 MDRD study equation for GFR estimation published

KEY EVENT

- 2002 Kidney Disease Outcome Quality Initiative (KDOQI) Guideline for the definition, classification and stratification of Chronic Kidney Disease published
- 2003 National Kidney Disease Education Program formed. Laboratory Working Group coordinates standardization of creatinine assays in the United States and works with national laboratory service providers to report estimated GFR whenever serum creatinine is ordered
- 2009 CKD-EPI equation published
- 2012 CKD-EPI creatinine and cystatin-creatinine equation published

GLOMERULAR FILTRATION RATE (GFR)

- Clearance of a substance: volume of plasma cleared of a marker by excretion per unit of time.
- Variation : age, gender, body size, physical activity, diet, pharmacotherapy and physiologic state such as pregnancy
- To standardize kidney function for differences in kidney size > GFR is adjusted for body surface area : 1.73 m2 BSA
- Diurnal variation : 10% lower at midnight compare to afternoon
- After age 40 years : GFR decline 0.75 ml/min/yr

ASSESSMENT OF GFR

- Direct measured GFR
  - Exogenous filtration markers
  - Endogenous Filtration markers: Urinary clearance of Cr, average Cr and Urea if GFR <20 ml/min/1.73 m2
- Calculated GFR : estimated GFR from plasma level
  - Endogenous Filtration markers

EXOGENOUS FILTRATION MARKERS FOR ESTIMATION OF GFR

Marker	Method of Administration	Characteristics
Inulin	Continuous IV infusion	Gold standard
Iothalamate	Bolus IV or subQ	Can be administered with ^{125}I. Secreted>overestimated GFR
99mTc-DTPA	Bolus IV	underestimated GFR
51Cr-EDTA	Bolus IV	10% lower clearance than inulin
Iohexol	Bolus IV	Lower incidence of AE to inulin expensive, difficult to perform

CALCULATE GFR FROM 24 HR URINE COLLECTION

- Serum BUN 50 mg/dL, Cr 4.2 mg/dL
- Urine Volume 4750 ml
- Urine creatinine 1511 mg/24 hr
- Urine Urea 440 mg/dL

CREATININE URINE EXCRETION RATE

- Healthy young men: 20-25 mg/kg/day
- Healthy young women: 15-20 mg/kg/day

CALCULATE GFR FROM 24 HR URINE COLLECTION

- Clearance of Cr (ml/min) = $\dfrac{U_{Cr}\,(mg/dL)\ V(ml)}{P_{Cr}(mg/dL)\ T(min)}$

  $= \dfrac{(1{,}511/4.75x10)\ (4750)}{(4.2)\ (24x60)} = 24.98\ ml/min$

- Clearance of Urea (ml/min) = $\dfrac{U_{Urea}\,(mg/dL)\ V(ml)}{P_{Urea}(mg/dL)\ T(min)}$

  $= \dfrac{(440)\ (4750)}{(50)\ (24x60)} = 29.02\ ml/min$

- Average CCr and CUrea = $\dfrac{24.98+29.02}{2} = 27\ ml/min$

INDICATION FOR MEASURED GFR

- Extremes of age and body size
- Severe malnutrition or obesity
- Disease of skeletal muscle
- Paraplegia or quadriplegia
- Evaluation for kidney donation
- Vegetarian diet
- Before administration of prolonged courses of toxic medications

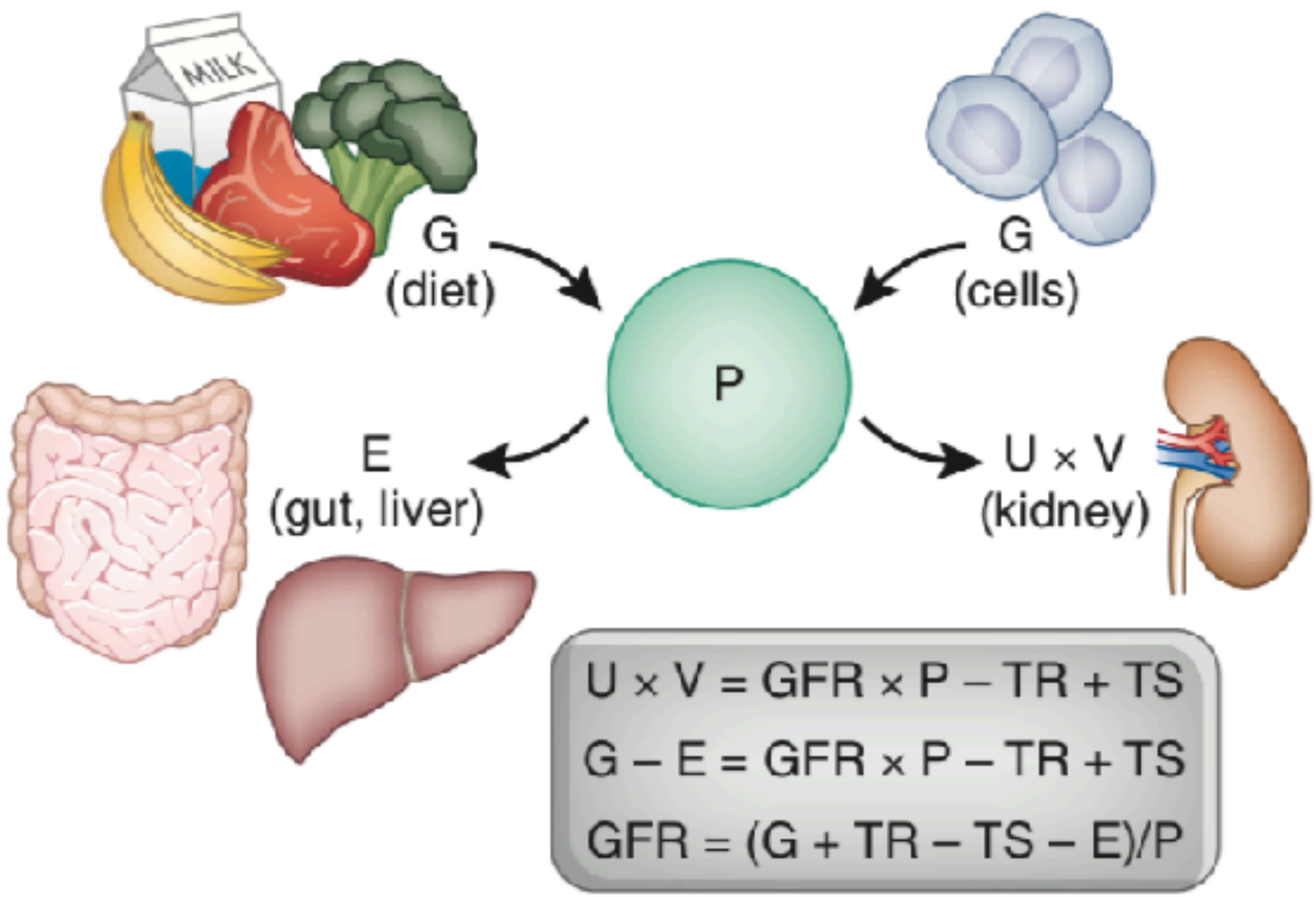
J Am Soc Nephrol 20: 2305–2313, 2009

ENDOGENOUS FILTRATION MARKERS

- Urea
- Creatinine
- Cystatin C

ENDOGENOUS FILTRATION MARKERS

- Substances generated in the body at constant rate and eliminate largely by glomerular filtration



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Comparison of Creatinine, Urea, and Cystatin C as Filtration Markers

Variable	Creatinine	Urea	Cystatin C
Molecular Properties			
Weight (d)	113	60	13,000
Structure	Amino acid derivative	Organic molecular product of protein metabolism	Nonglycosylated basic protein
Physiologic Determinants of Serum Level			
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and whites	Varies, according to dietary protein intake and catabolism	Thought to be mostly constant by all nucleated cells; increases in hyperthyroid state and with steroid use; lower in elderly persons and women
Handling by kidney	Filtered, secreted, and excreted in urine	Filtered, reabsorbed, and excreted in urine	Filtered, reabsorbed, and catabolized
Extrarenal elimination	Yes; increases at reduced GFR	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR
Use In Estimating Equations for GFR			
Demographic and clinical variables as surrogates for physiologic determinants	Age, gender, and race; related to muscle mass	Not applicable	Age, gender
Accuracy	Accurate for GFR <60 ml/min/1.73 m^2	Not applicable	Unknown
Assay			
Method	Colorimetric or enzymatic	Direct measurement, enzymatic colorimetric and electrochemical	PENIA, PETIA, or ELISA
Assay precision	Very good except at low range	Precise throughout range	Precise throughout range
Clinical laboratory practice	Multiple assays; widely used nonstandard calibration	Multiple assays; enzymatic and colorimetric more common	Not on most autoanalyzers; not standardized
Standardized recommendation materials (SRMs)	SRM 967	SRM 912a	ERM-DA471/IFCC
Reference assay	IDMS	IDMS	PENIA, PETIA, or ELISA

Table 3-2 Comparison of creatinine, urea, and cystatin C as filtration markers. *ELISA,* Enzyme-linked immunosorbent assay; *GFR,* glomerular filtration rate; *IDMS,* isotope-dilution–mass spectroscopy; *PENIA,* particle-enhanced nephelometric immunoassay; *PETIA,* particle-enhanced turbidimetric immunoassay. *(Modified with permission from reference 2.)*

CREATINE ASSAY

- Alkaline picrate (Jaffe) assay : color reaction
  - chromogen other than creatinine: interfere with the assay
  - falsely higher creatinine approximately 20%
- Modern enzymatic assays
  - do not detect non creatinine chromogens
- Standardize creatinine measurements
  - Fresh frozen serum pool with known creatinine level trace to isotope-dilution-mass spectrometry (IDMS) reference

Factors Affecting Serum Creatinine Concentration

Factors	Effect on Creatinine	Mechanism/Comment
Age	Decrease	Reduced creatinine generation caused by age-related decline in muscle mass
Female gender	Decrease	Reduced creatinine generation caused by reduced muscle mass
Race		
African American	Increase	Higher creatinine generation caused by higher average muscle mass in African Americans; not known how muscle mass in other races compares with that of African Americans or Caucasians
Diet		
Vegetarian	Decrease	Decrease in creatinine generation
Ingestion of cooked meats and creatinine supplements	Increase	Transient increase in creatinine generation, although this may be blunted by transient increase in GFR
Body Habitus		
Muscular	Increase	Increased muscle generation caused by increased muscle mass and/or increased protein intake
Malnutrition, muscle wasting, amputation	Decrease	Reduced creatinine generation caused by reduced muscle mass and/or reduced protein intake
Obesity	No change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation.
Medications		
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil	Increase	Reduced tubular secretion of creatinine
Keto acids, some cephalosporins	Increase	Interference with alkaline picrate assay for creatinine

ESTIMATED GLOMERULAR FILTRATION RATE FROM SERUM CREATININE

- Cockcroft-Gault Formula
- Modification of Diet in Renal Disease Study (MDRD)
- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

COCKCROFT-GAULT FORMULA

Male

$$C_{cr}(ml/min) = \frac{(140 - Age) \times Weight}{72 \times S_{cr}(mg/dl)}$$

Female

$$C_{cr}(ml/min) = \frac{(140 - Age) \times Weight \times 0.85}{72 \times S_{cr}(mg/dl)}$$

Limitation

- not precise if GFR >60ml/min
- estimate CCr, overestimate GFR especially obese, edematous pt
- the formula derived by older assay methods for SCr

MDRD

- equation use age, gender, race and standardized SCr
- Derived from a study population with CKD
- underestimate the measured GFR in population with high level of GFR
  - GFR < 60 : report as a value
  - GFR > 60 : report “greater than 60 ml/min/1.73 m2”
- not validated in children or pregnant woman
- MDRD for Thai people

CKD-EPI

- equation use age, gender, race and standardized SCr
- Derived from a study population with CKD, non CKD, DM, history of organ transplant
- CKD-EPI as accurate as MDRD at eGFR <60 and more accurate at higher than 60
- Current recommendation for eGFR

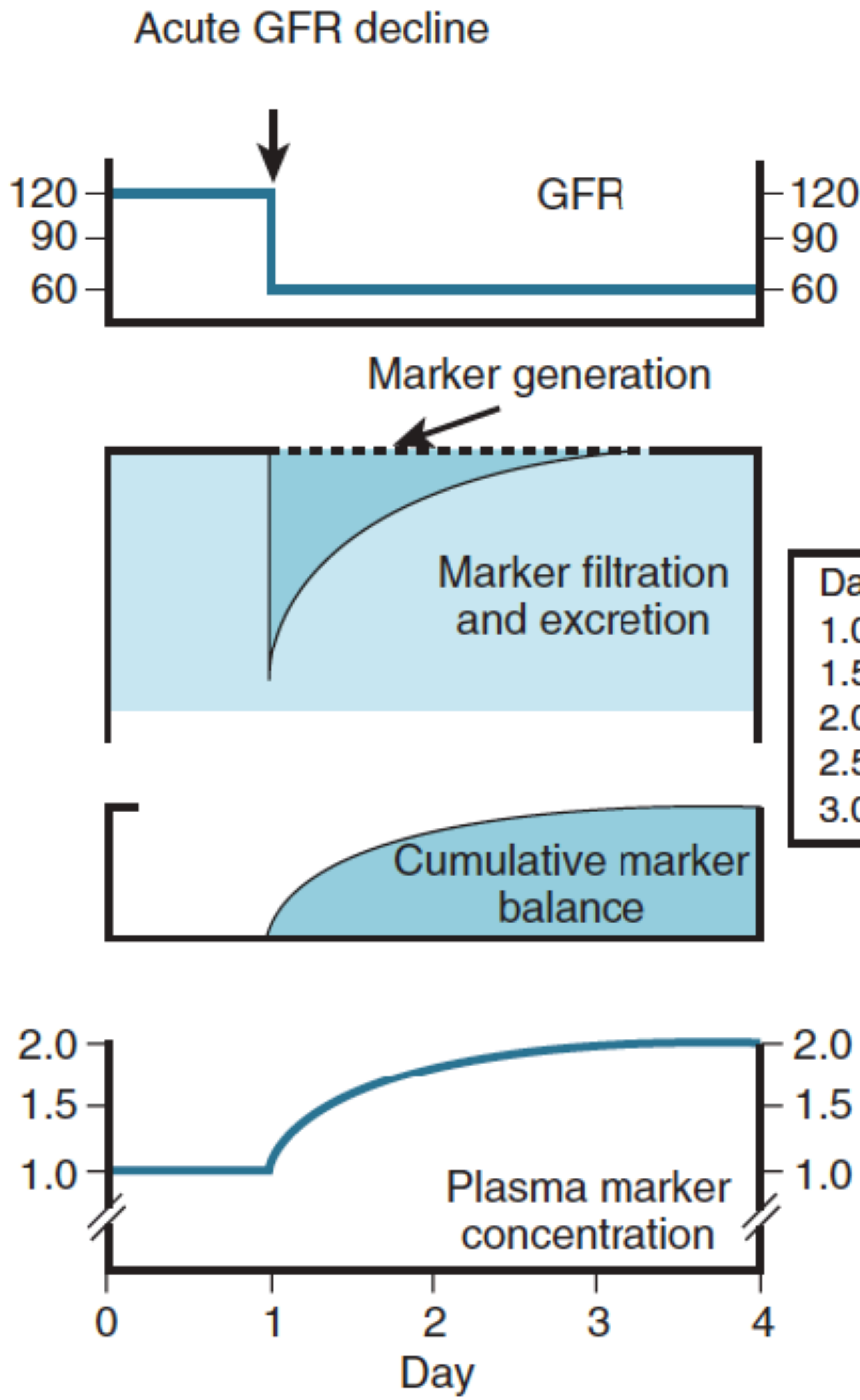
UREA

- tubular reabsorption : underestimated GFR
- widely variable non-GFR determinants
- Increase urea generation
  - protein loading from GI tract
  - absorption of blood after GI bleeding
  - Catabolic states : infection, corticosteroid, chemotherapy
- Decrease urea generation
  - severe malnutrition and liver disease

CYSTATIN C

- constant level from 1-50 years of age
- produced at a constant rate by gene expressed in all nucleated cells.
- 99% of the filtered cystatin C, reabsorbed and catabolized at proximal tubule—not excrete in the urine
- non GFR determinants of cystatin C: inflammation, adiposity, thyroid disease, malignant neoplasm, use of glucocorticoid
- key factors for high cystatin : older age, male, fat mass, white race, diabetes, higher CRP, increased WBC, lower albumin
- **Estimated GFR : CKD-EPI Cystatin-Cr**

AKI



Day	P_{marker}	eGFR
1.0	1.0	120
1.5	1.6	79
2.0	1.8	69
2.5	1.9	65
3.0	2.0	60

When eGFR reaches a new steady state,

accurately reflects measured GFR

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CKD

Prognosis of CKD by GFR Â and Albuminuria Categories: KDIGO 2012

				Albuminuria Categories, Â Description and Range		
				A1	A2	A3
				normal to mildly	moderately increased	severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Categories, Description and Range (mL/min/ 1.73 m²)	G1	normal or high	>90			
	G2	mildly decreased	60-89			
	G3a	mildly to moderately	45-59			
	G3b	moderately to severely	30-44			
	G4	severely decreased	15-29			
	G5	kidney failure	<15			

THANK YOU