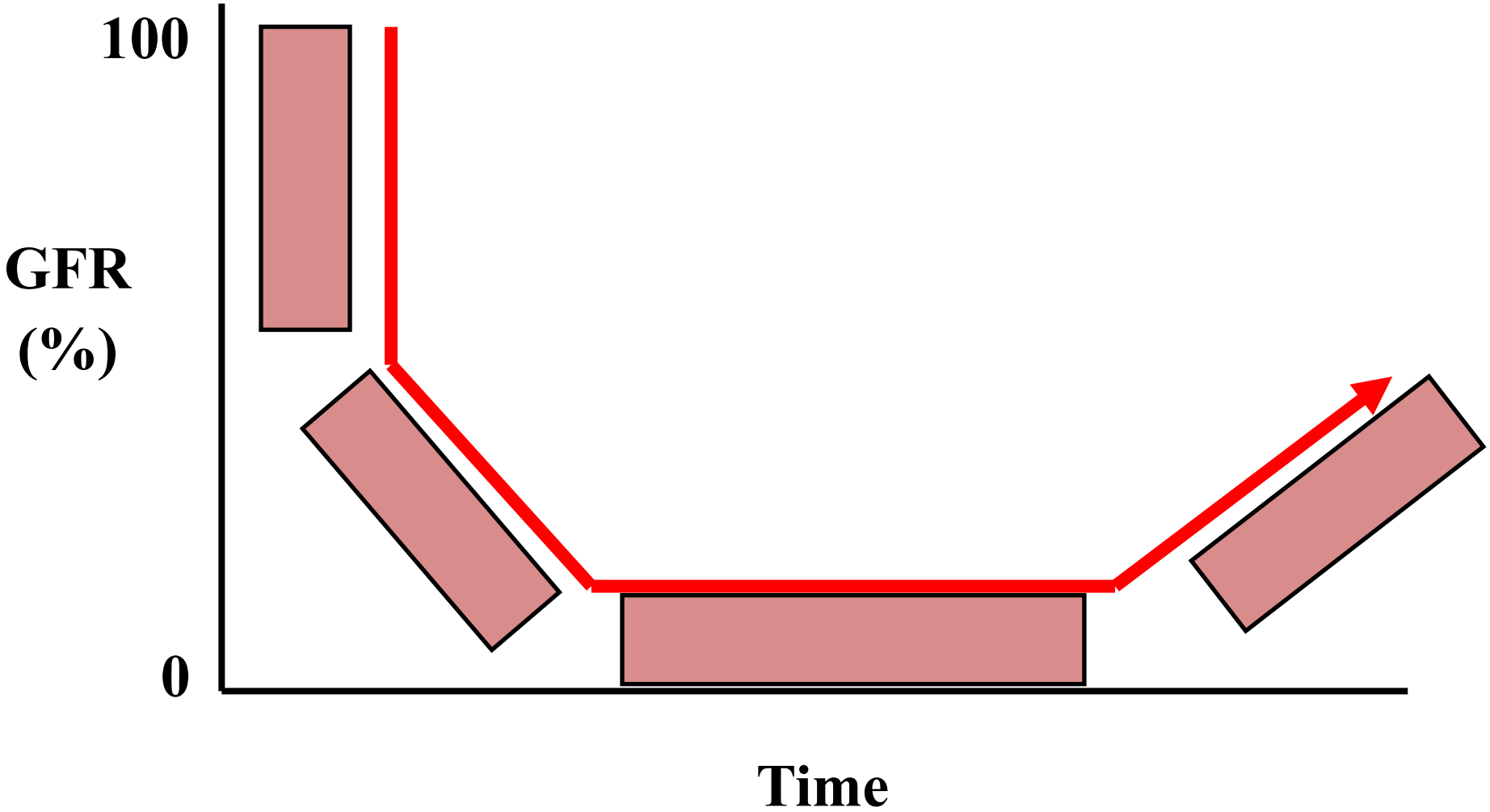
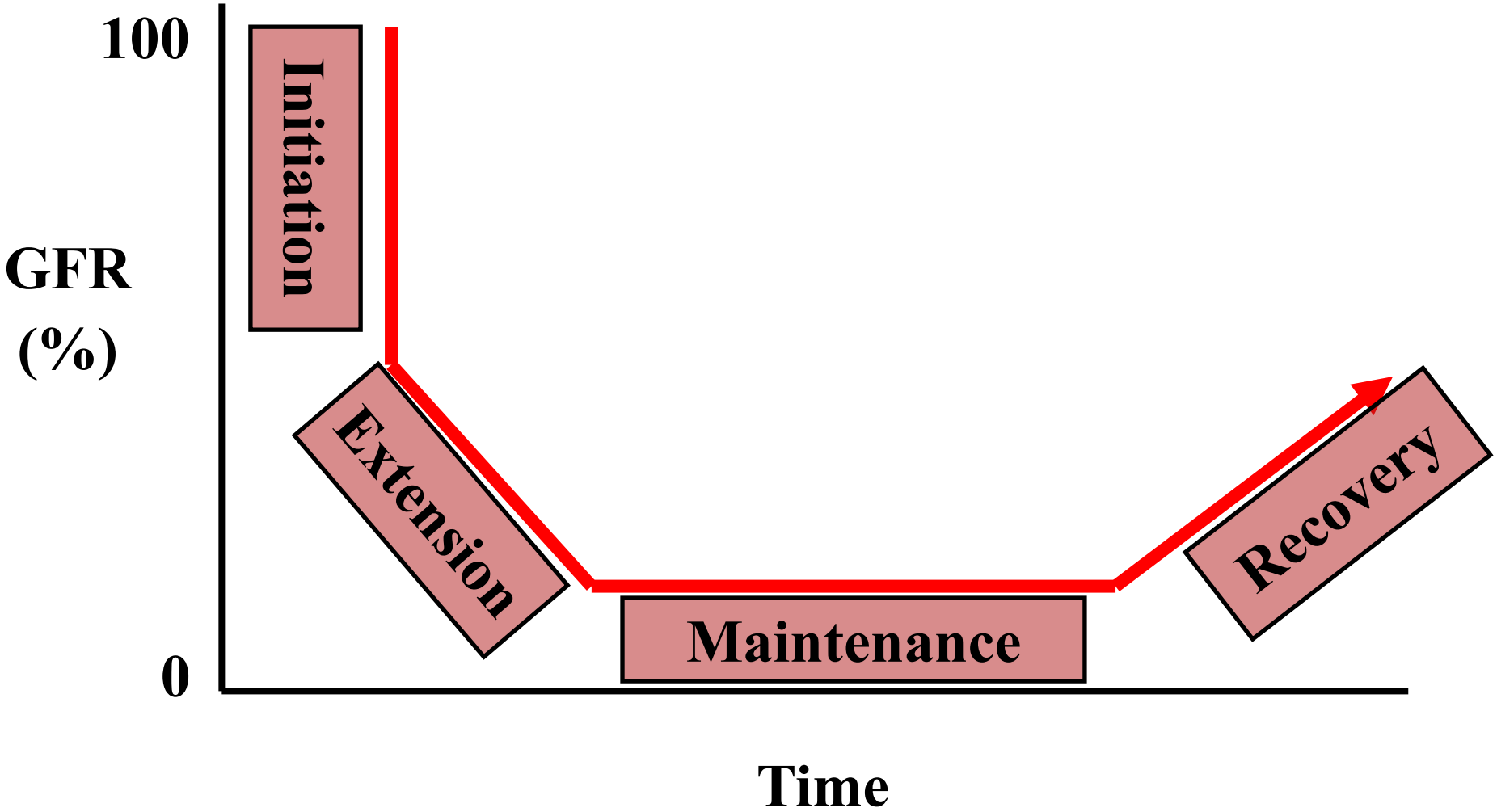
Defending the GFR

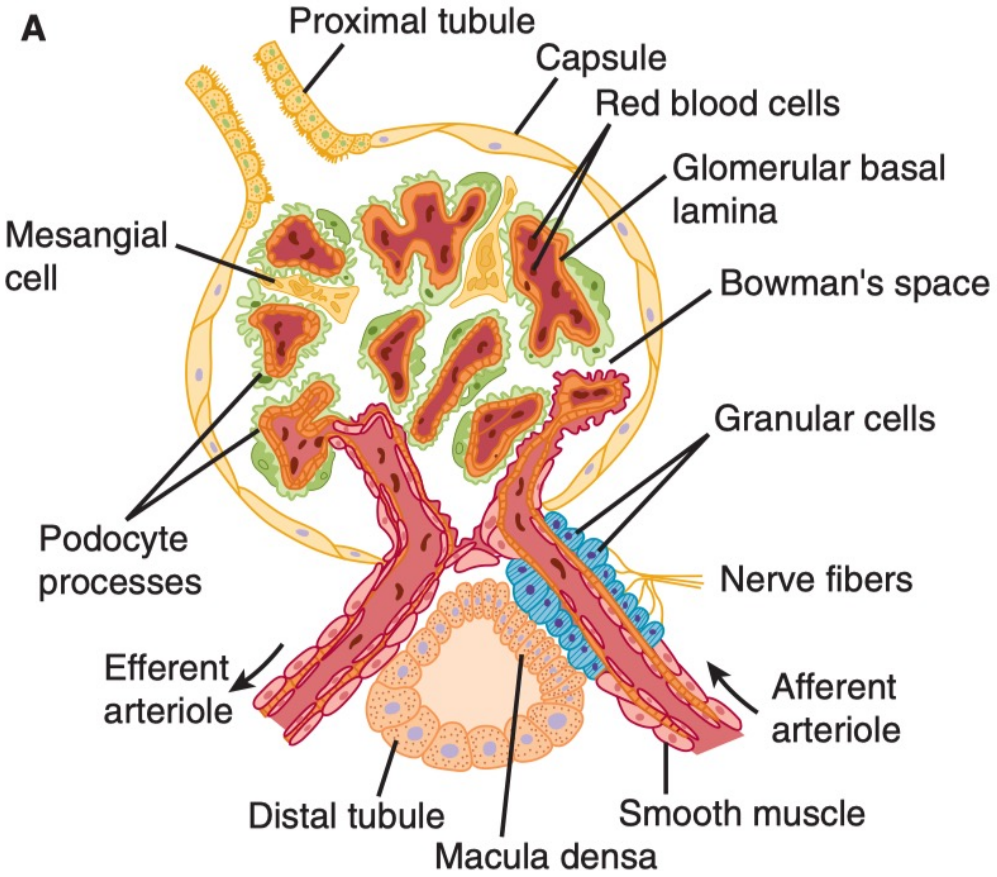
Jethro Forbes, DVM, DACVECC

Feb 7, 2023


100
GFR
(%)
0
Time

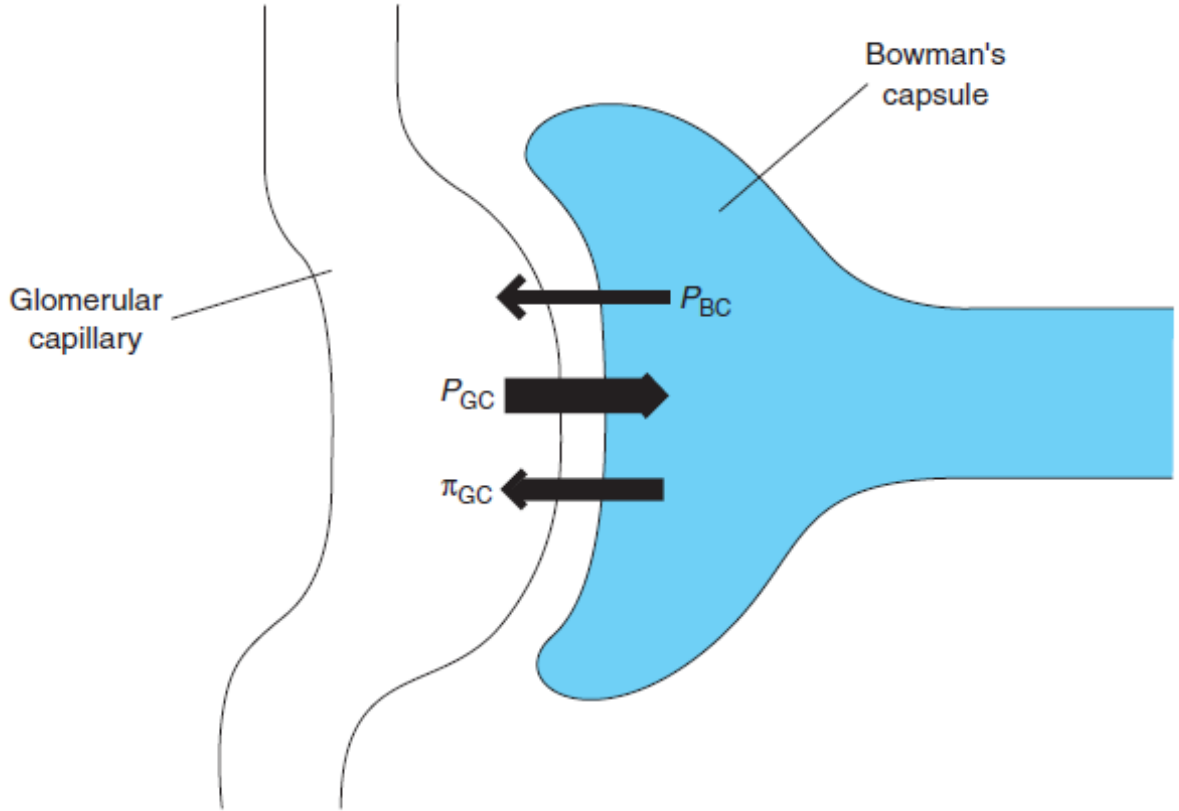

100
GFR
(%)
0
Initiation
Extension
Maintenance
Recovery
Time

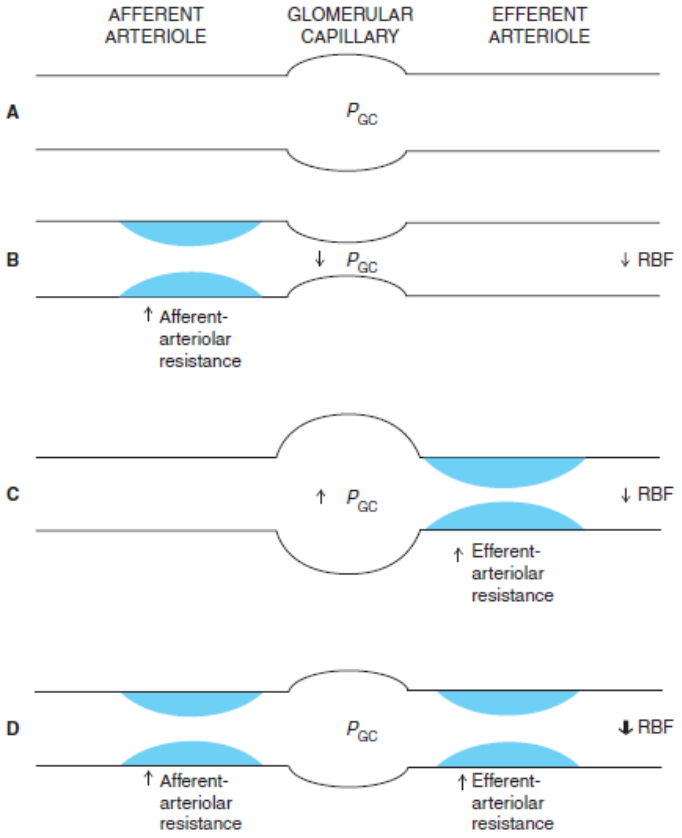
Anatomy of the Glomerulus



Ganong, 24ed Fig 37-2

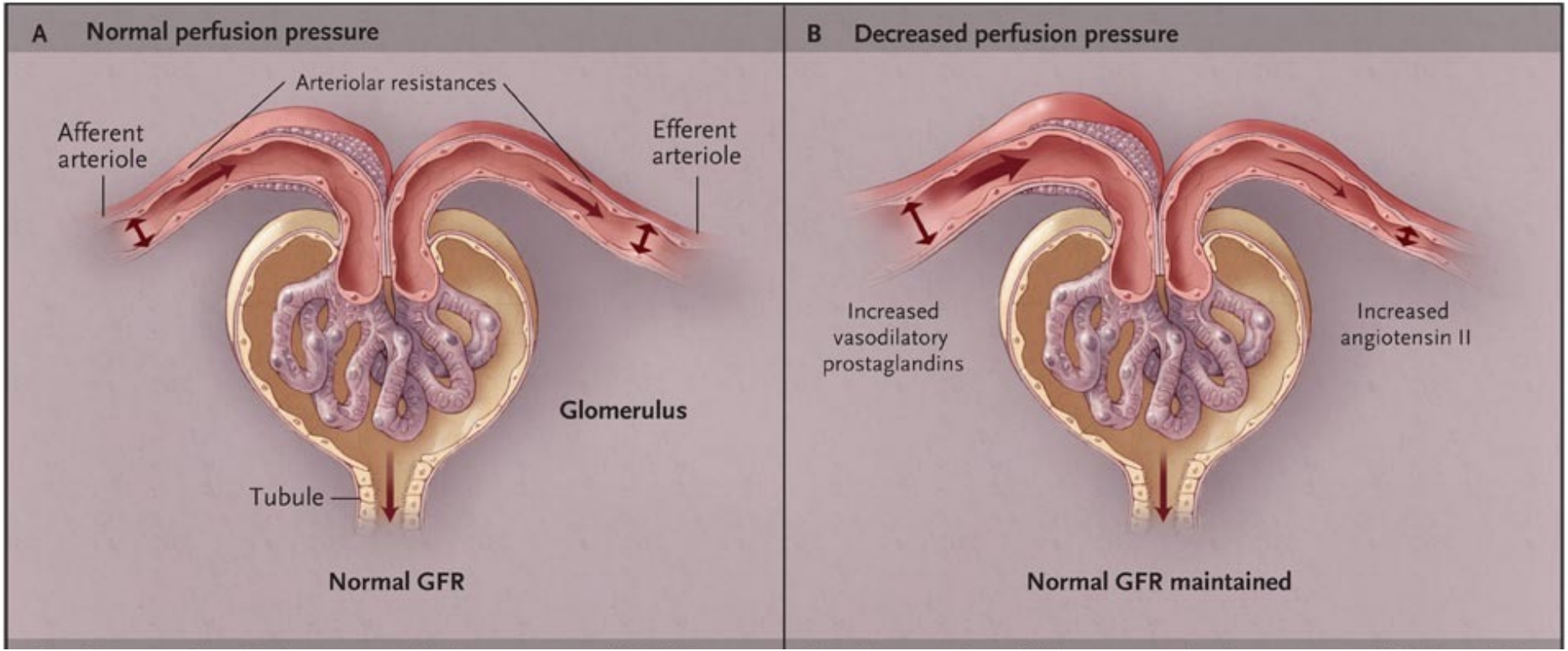
GFR Determination?





Kidney Autoregulation in Health

- Intricate balance of afferent and efferent vessels dilating and constricting in response to local and distant messengers
- Goal: maintain Glomerular filtration Rate (GFR) and Renal Blood Flow (RBF) over a range of perfusion pressures.



N Engl J Med 2007; 357:797-805

Defense of GFR – Autoregulation in Health

- Three Mechanisms?

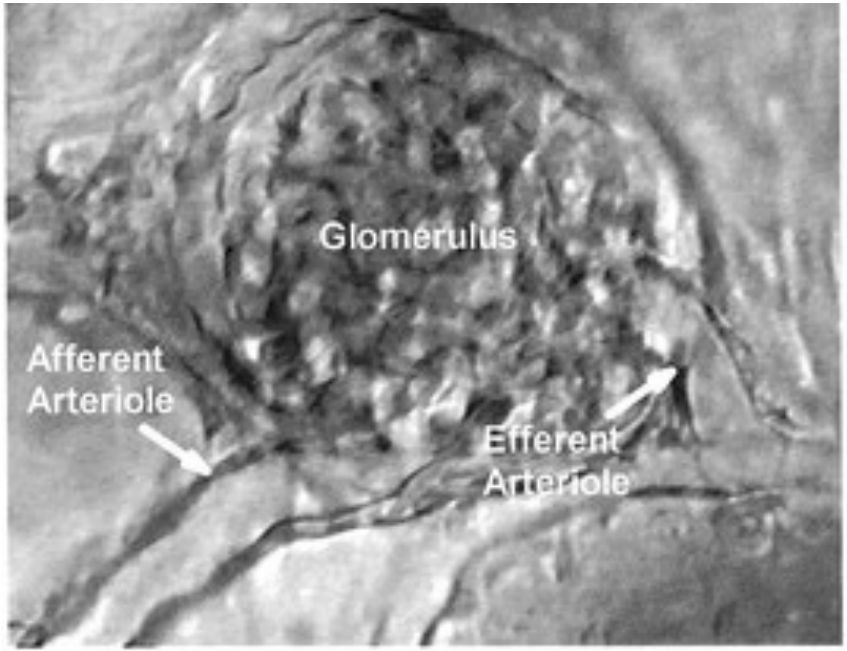
Defense of GFR – Autoregulation in Health

- Three Mechanisms?
- Local Myogenic Response – Baroreceptor Function
- Tubuloglomerular Feedback
- RAAS

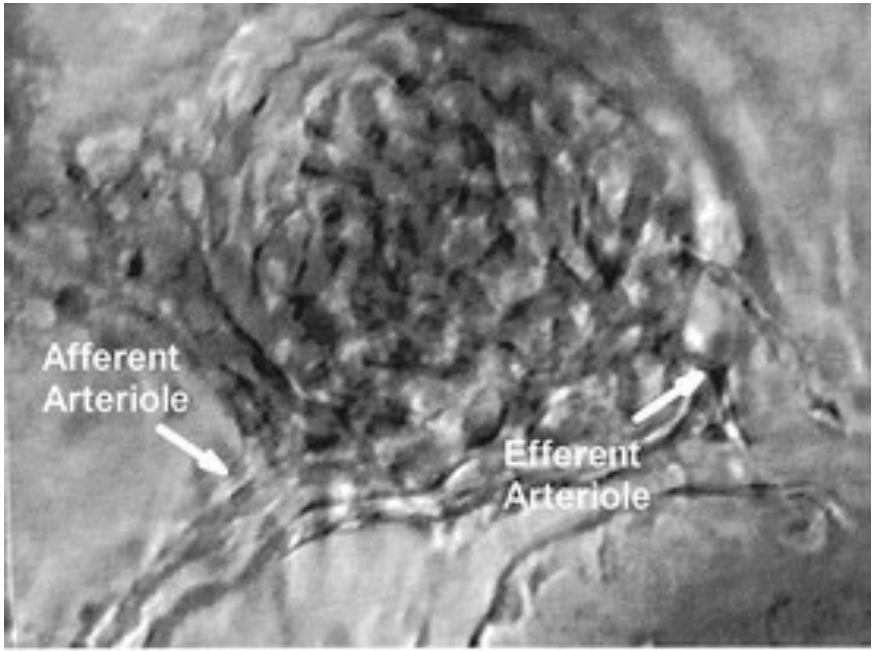
Defense of GFR – Autoregulation in Health

- Local Myogenic Response – Baroreceptor Function
  - Smooth muscle cells of afferent arteriole sense increased pressure/stretch as increased flow > Ca++ influx into smooth muscle cells induces contraction of AA to protect glomerulus from excess flow, maintain stable GFR
  - Smooth muscle cells of afferent arteriole sense decreased pressure/stretch as decreased flow > Prostacyclin (PGI2) induced relaxation of AA to maintain GFR

Myogenic Response



Kidney perfused at 80 mm Hg

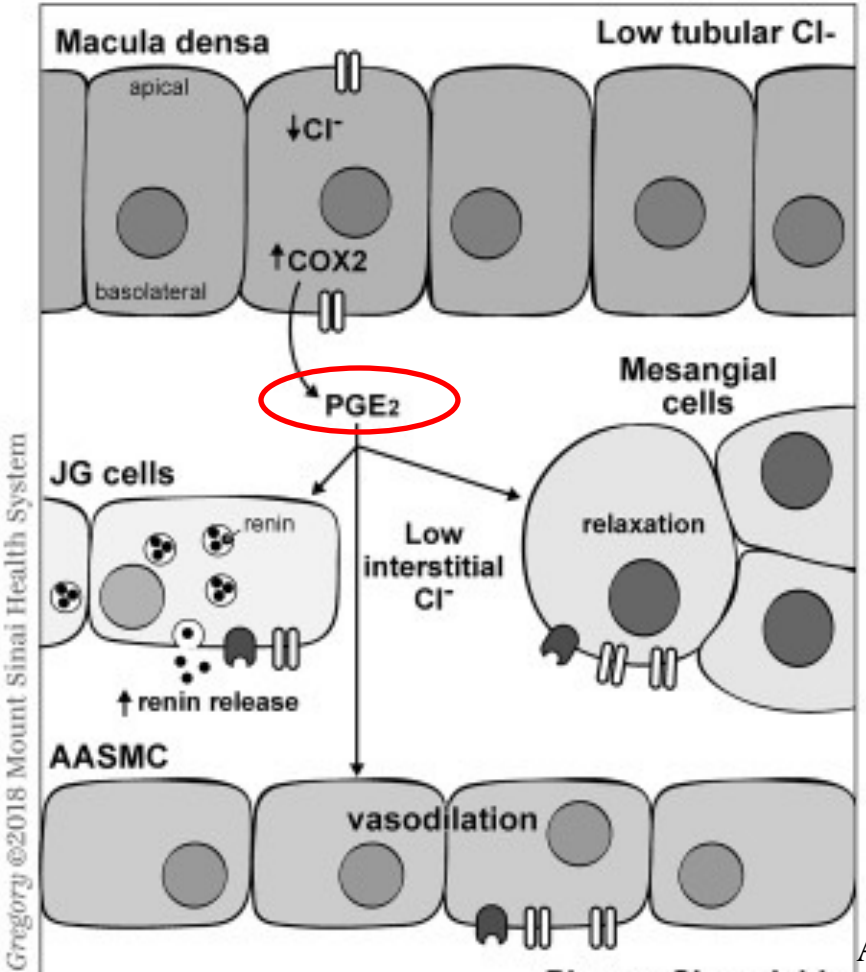


Kidney perfused at 180 mm Hg

Rodger Loutzenhiser. Circulation Research. Renal Myogenic Response, Volume: 90, Issue: 12, Pages: 1316-1324,

Defense of GFR

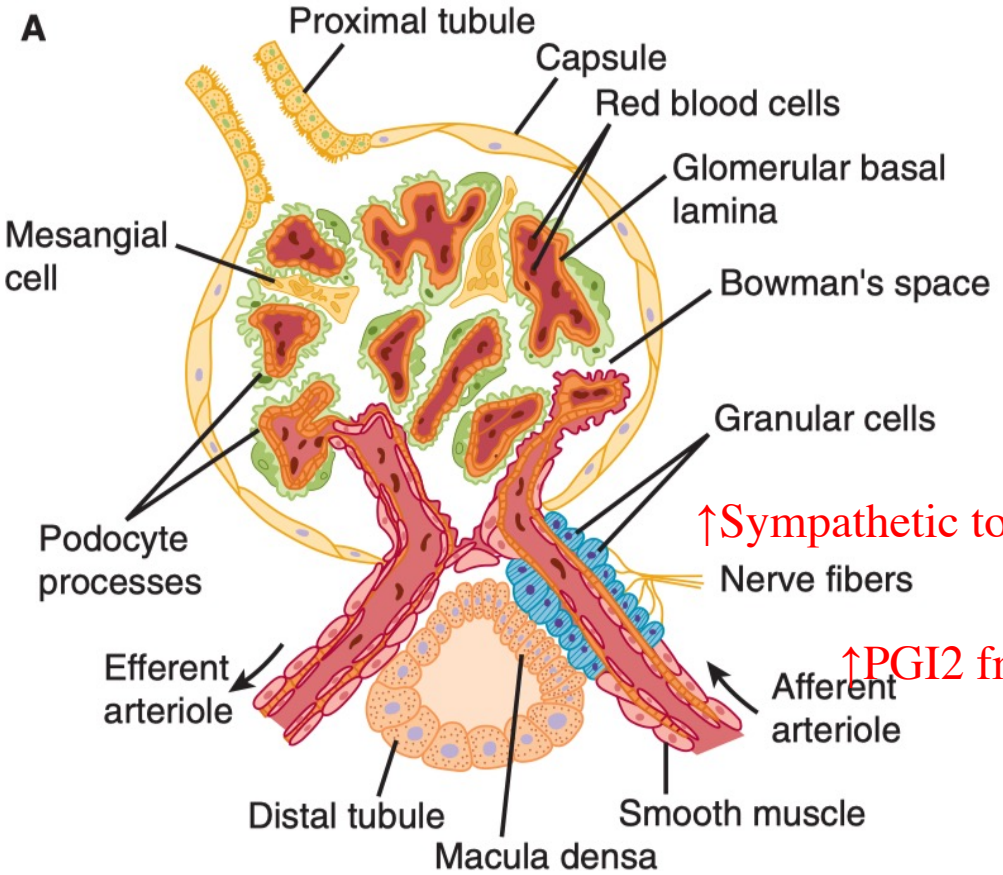
- Tubuloglomerular Feedback
  - Macula Densa senses flow >chloride (sodium) via NKCC transporter
  - Increased flow causes afferent arteriole vasoconstriction
  - Decreased flow causes afferent arteriole vasodilation



Am J Physiol Renal Physiol 316: F587–F605, 2019.

Defense of GFR

- Tubuloglomerular Feedback
  - Macula Densa senses flow >chloride (sodium) via NKCC transporter
  - With lower flow to MD, COX2 mediated increase of PGE2
  - PGE2 acts in paracrine fashion to:
    - stimulate renin release from JG cells
    - relax smooth muscle cells of AA cell walls
    - Cause mesangial relaxation



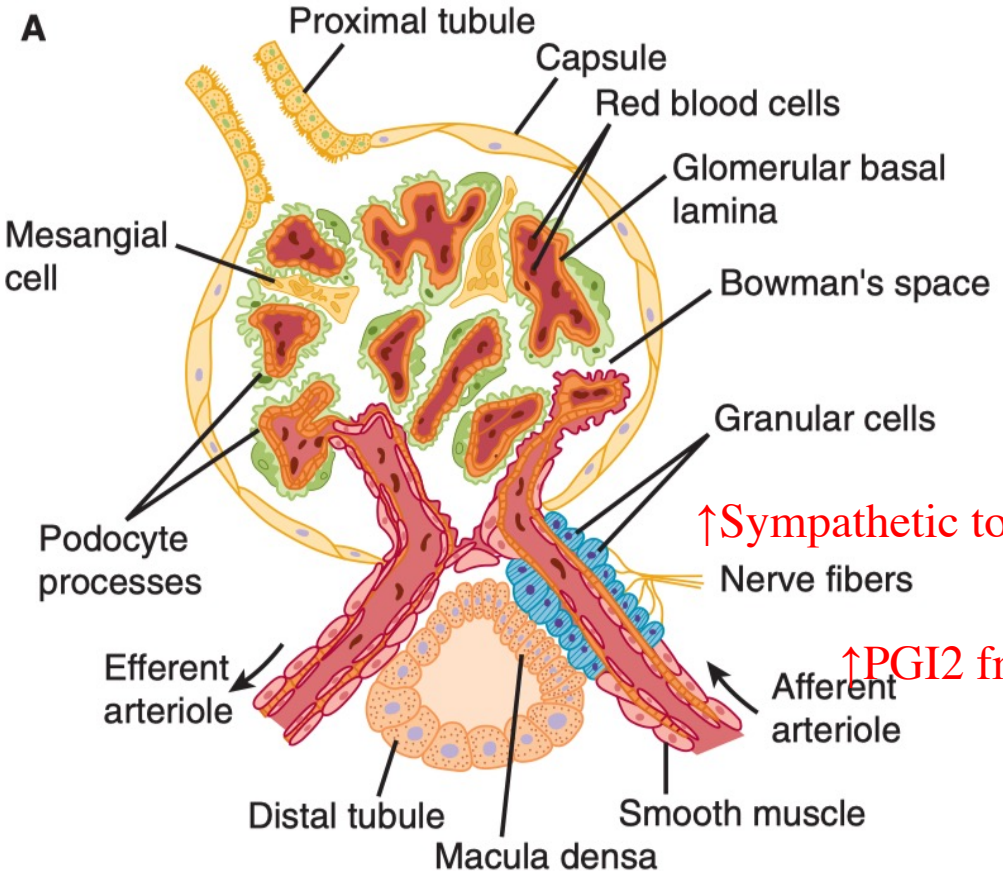
↑↑↑Renin

↑Sympathetic tone

↑PGI2 from ↓Stretch

↑PGE2 from ↓Cl Delivery

Ganong, 24ed Fig 37-2



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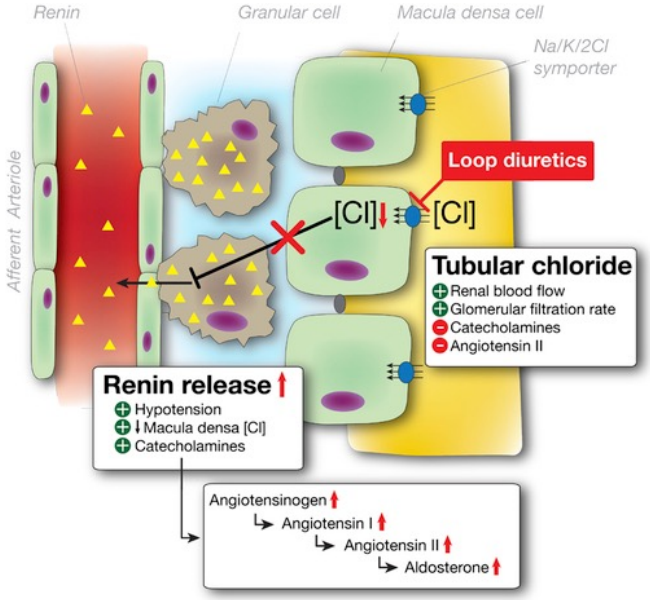
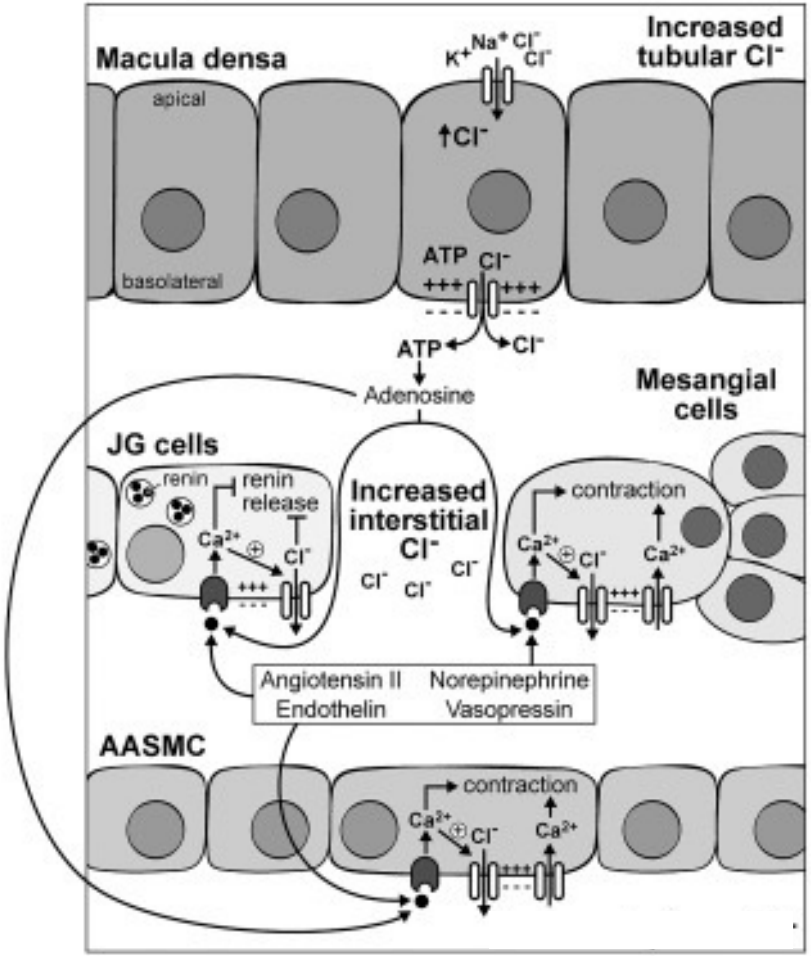


Frederik H. Verbrugge et al. *J Am Coll Cardiol HF* 2014; 3:108-111.



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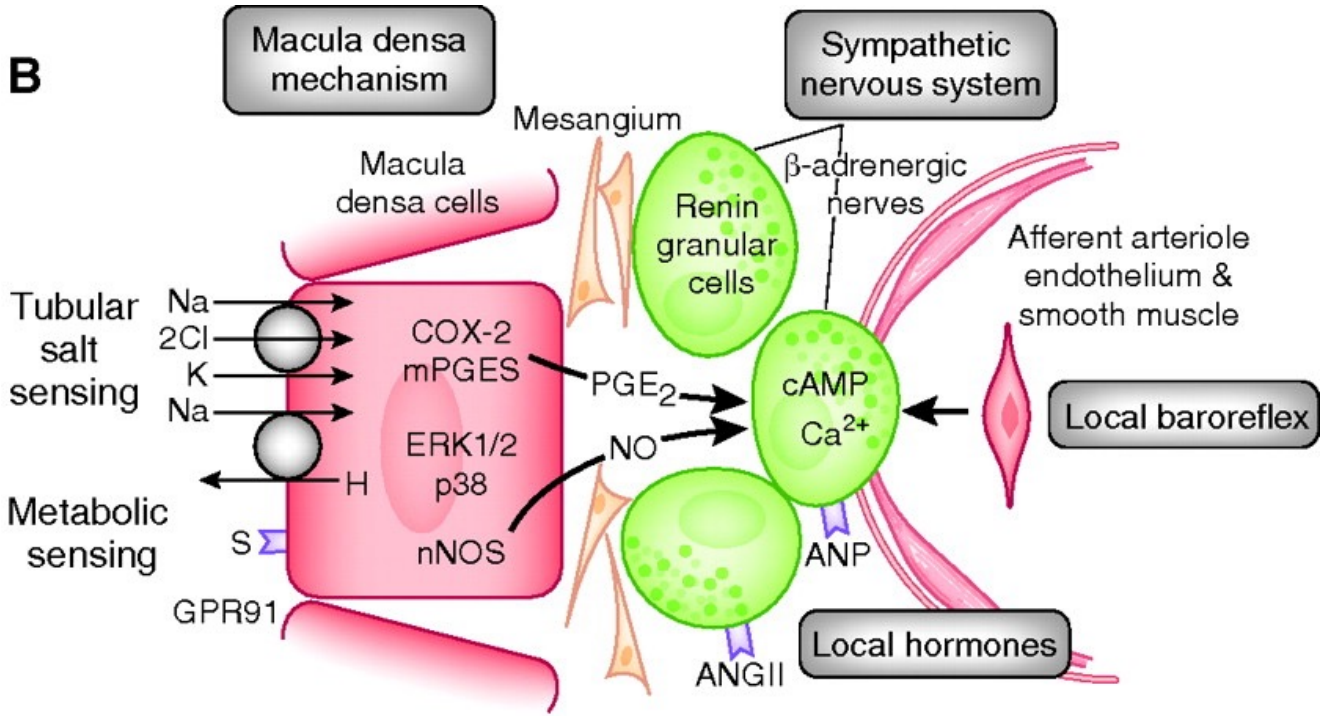
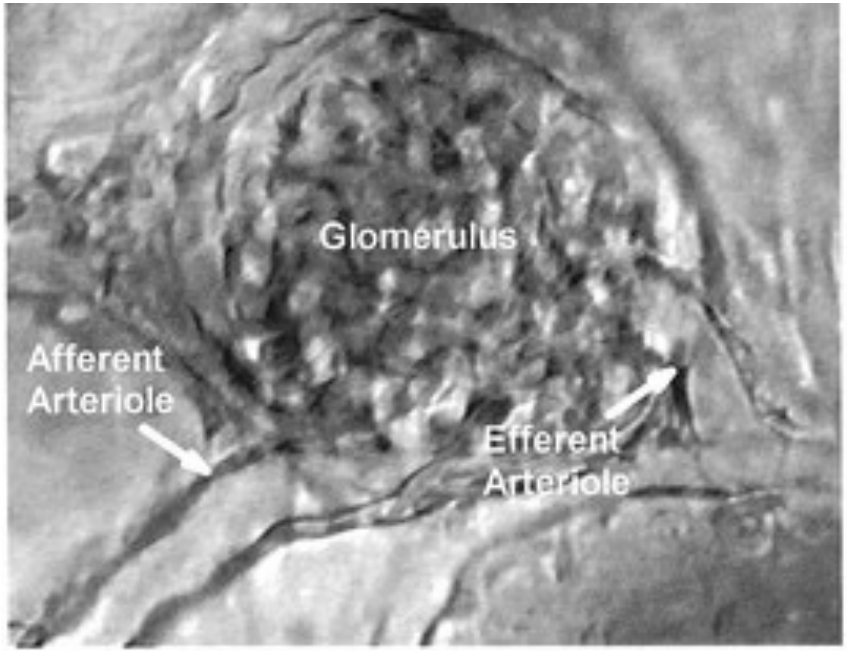


JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY
Peti-Peterdi, J and Harris, RC. JASN 2010;21:1093-1096

Myogenic Response



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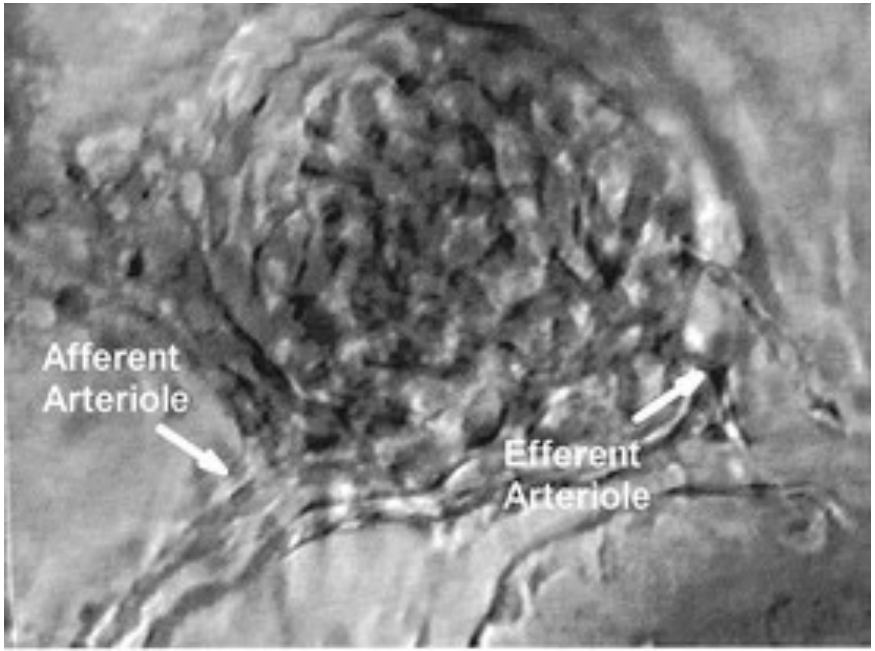


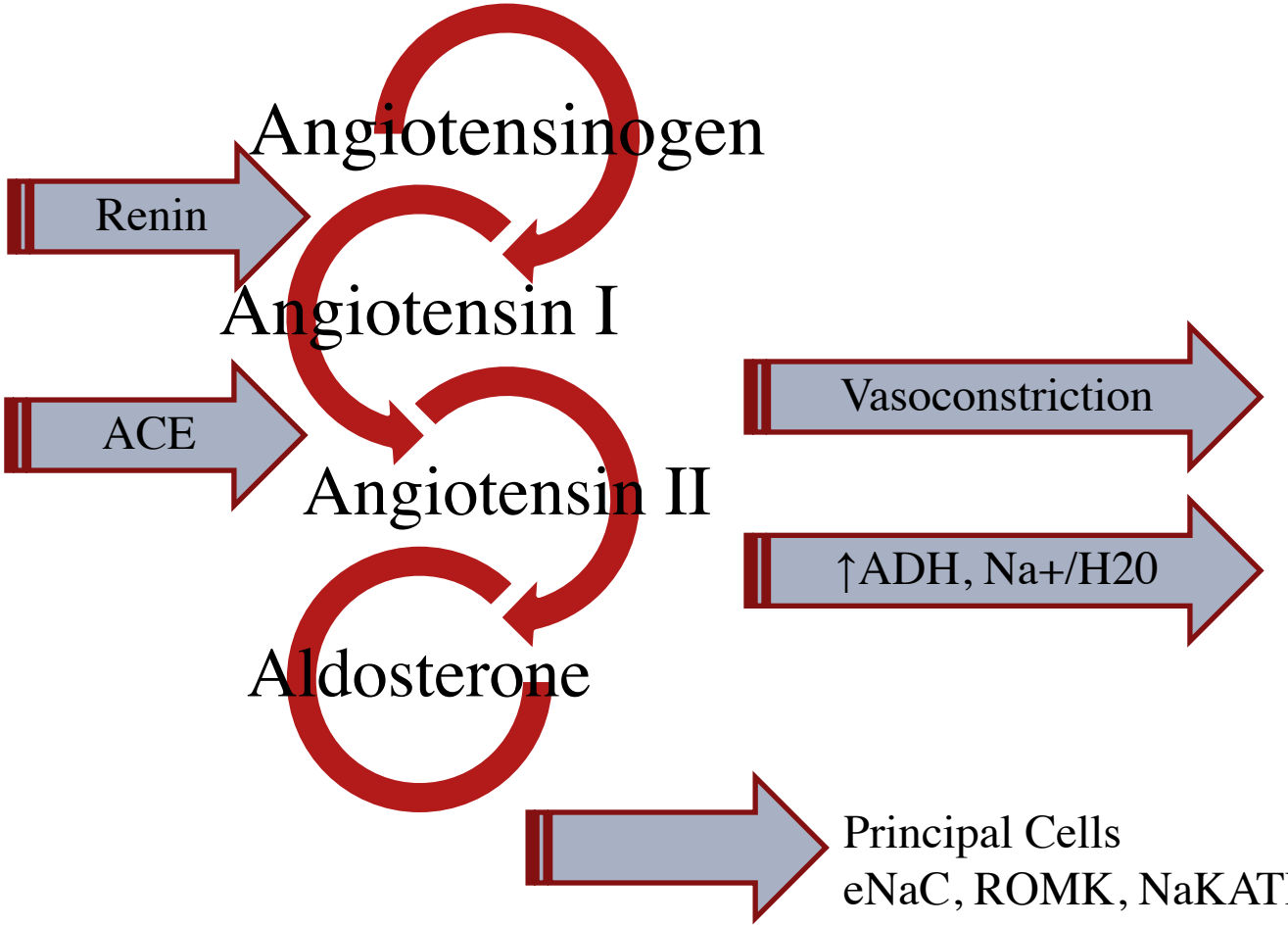
Kidney perfused at 180 mm Hg

Rodger Loutzenhiser. Circulation Research. Renal Myogenic Response, Volume: 90, Issue: 12, Pages: 1316-1324,

”Mushu” 13yr FS DSH

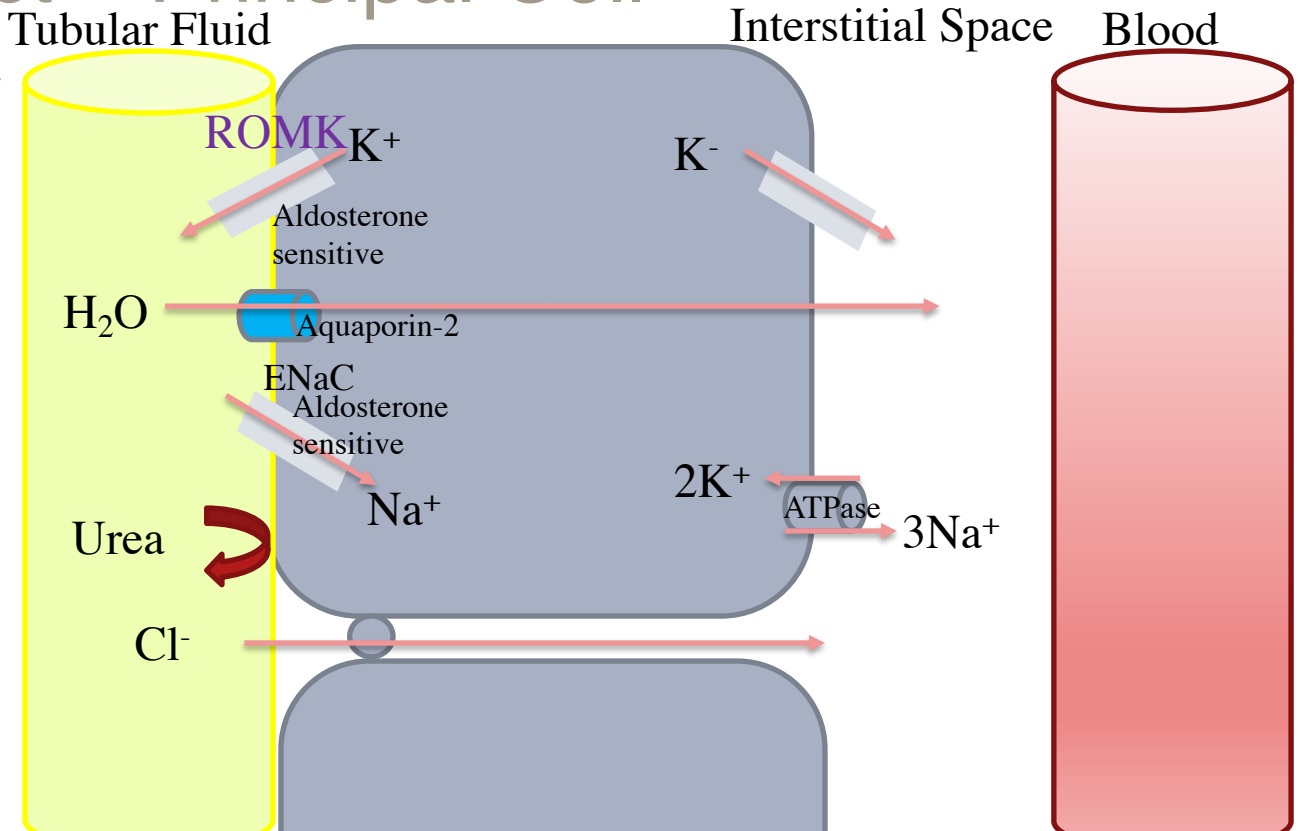
- CC: Vomiting, Anorexia x2d
- Hx: IRIS Stage 2 CKD (creat2.1)
  - Proteinuria and Hypertension
  - ACE-I, Calcium Channel Blocker
- Today BUN 93, Creat 4.5

RAAS


Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Vasoconstriction
↑ADH, Na+/H20
Aldosterone
Principal Cells
eNaC, ROMK, NaKATPase

Collecting Duct – Principal Cell

- Reabsorption of
  - Na^+
  - Cl^-
- K^+ secretion

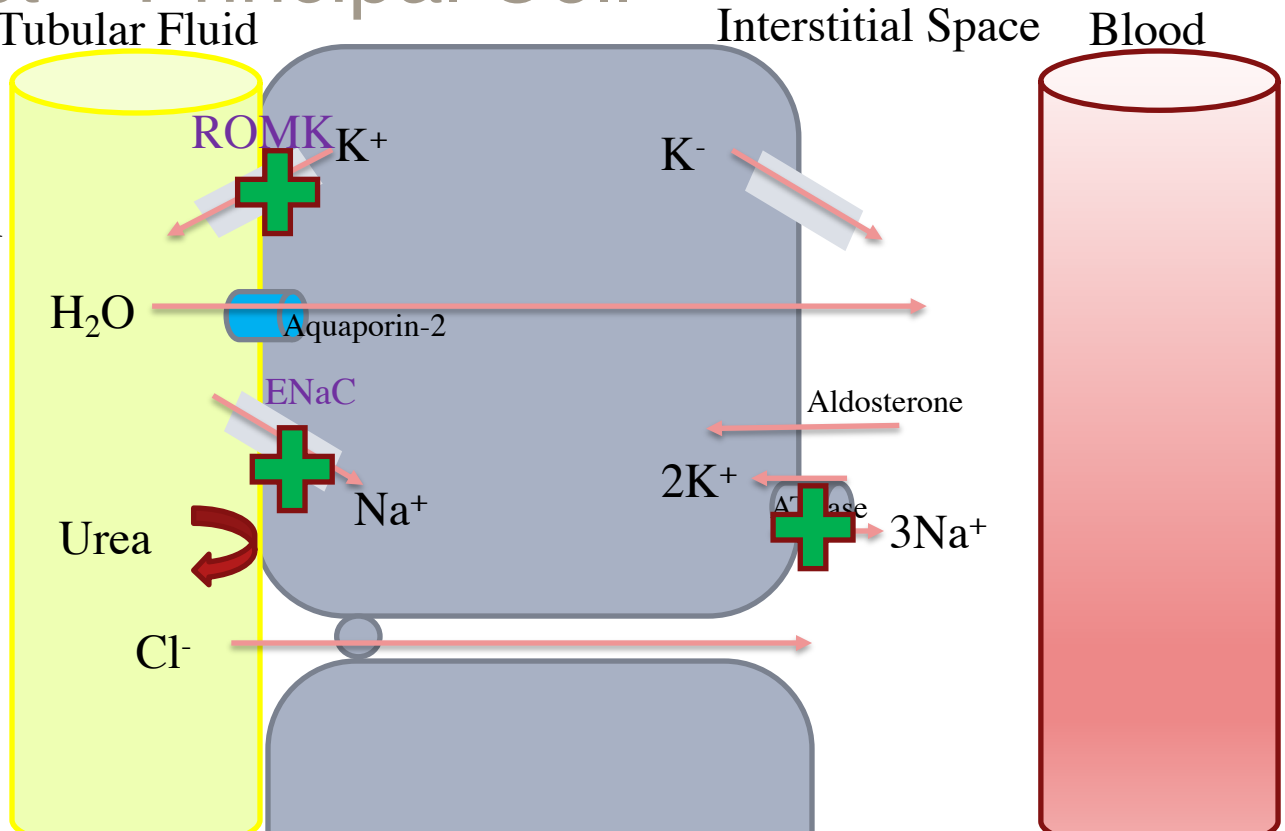


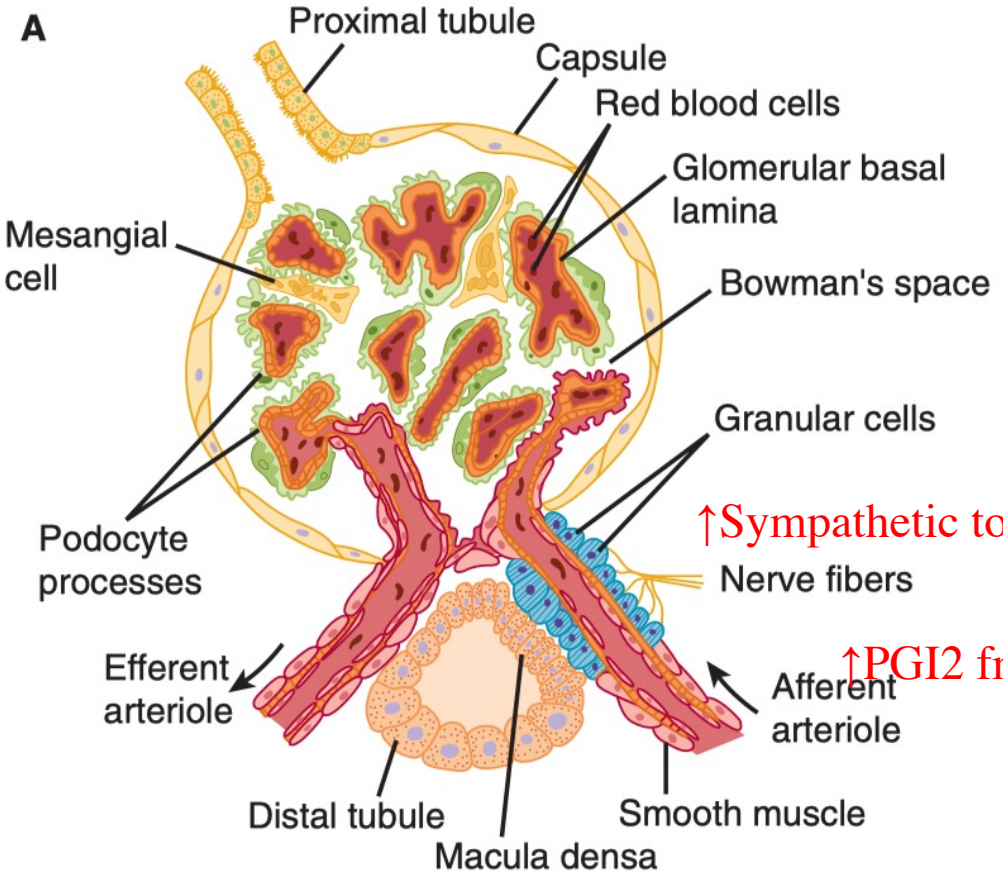
Collecting Duct – Principal Cell

- ↑Aldosterone

↑ Na^+ reabsorption

↑ K^+ secretion





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↑Sympathetic tone

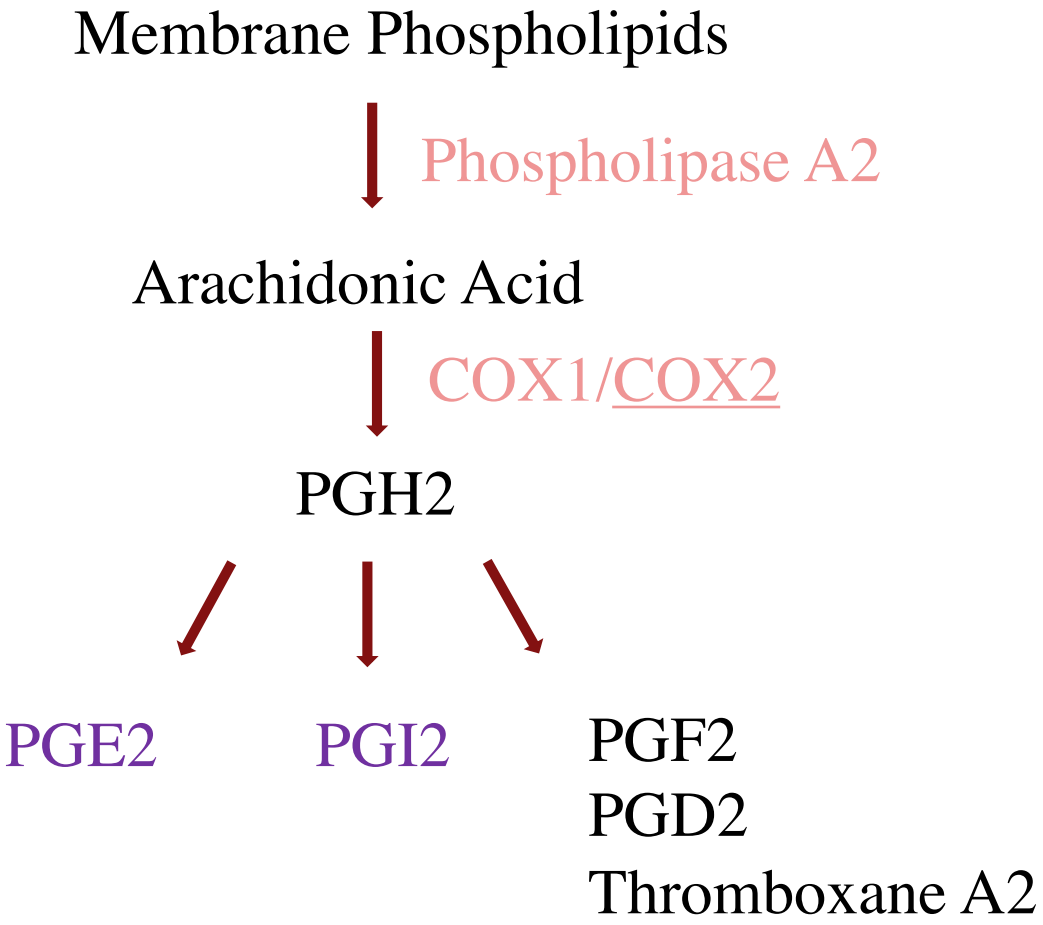
↑PGI2 from ↓Stretch

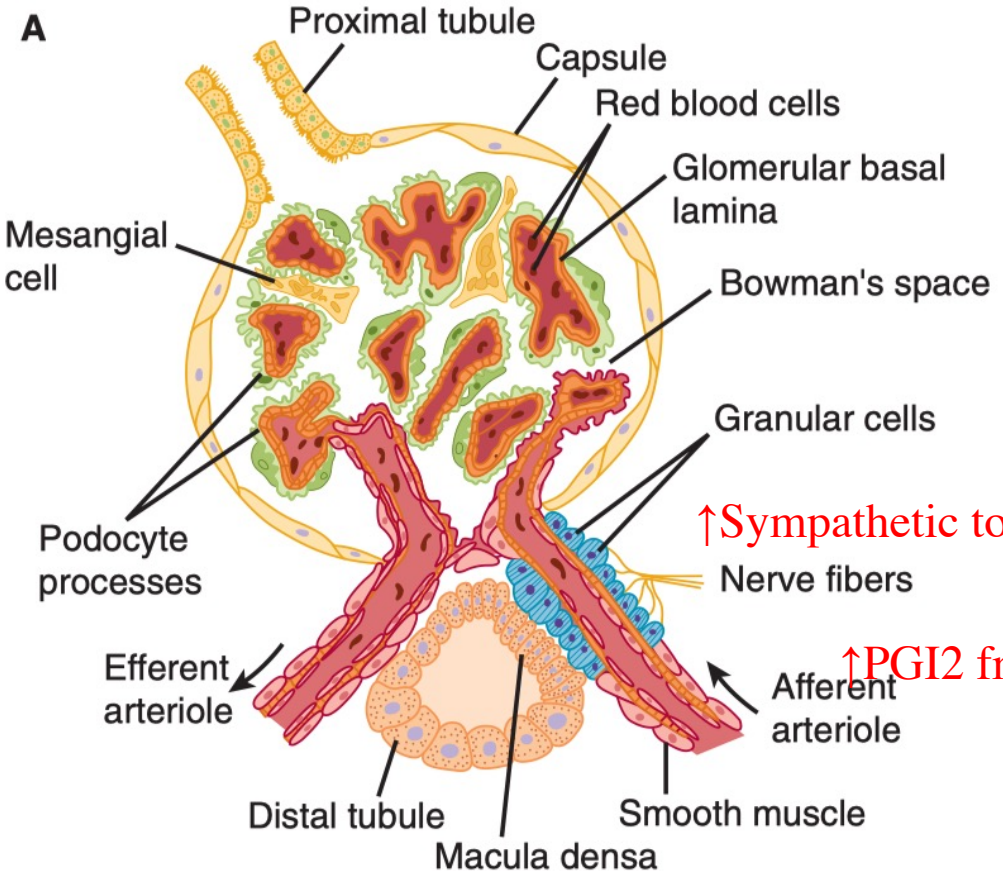
↑PGE2 from ↓Cl Delivery

Ganong, 24ed Fig 37-2

Belle, 7yr FS Lab Retriever

- CC: Acute Pelvic Lameness
- Hx: Chronic OA
  - Carprofen
  - Known IRIS Stage 2 CKD (creat 1.8)
- Dx: TPLO, taken to surgery
- Continue NSAID?


Membrane Phospholipids
Phospholipase A2
Arachidonic Acid
COX1/COX2
PGH2
PGE2
PGI2
PGF2
PGD2
Thromboxane A2



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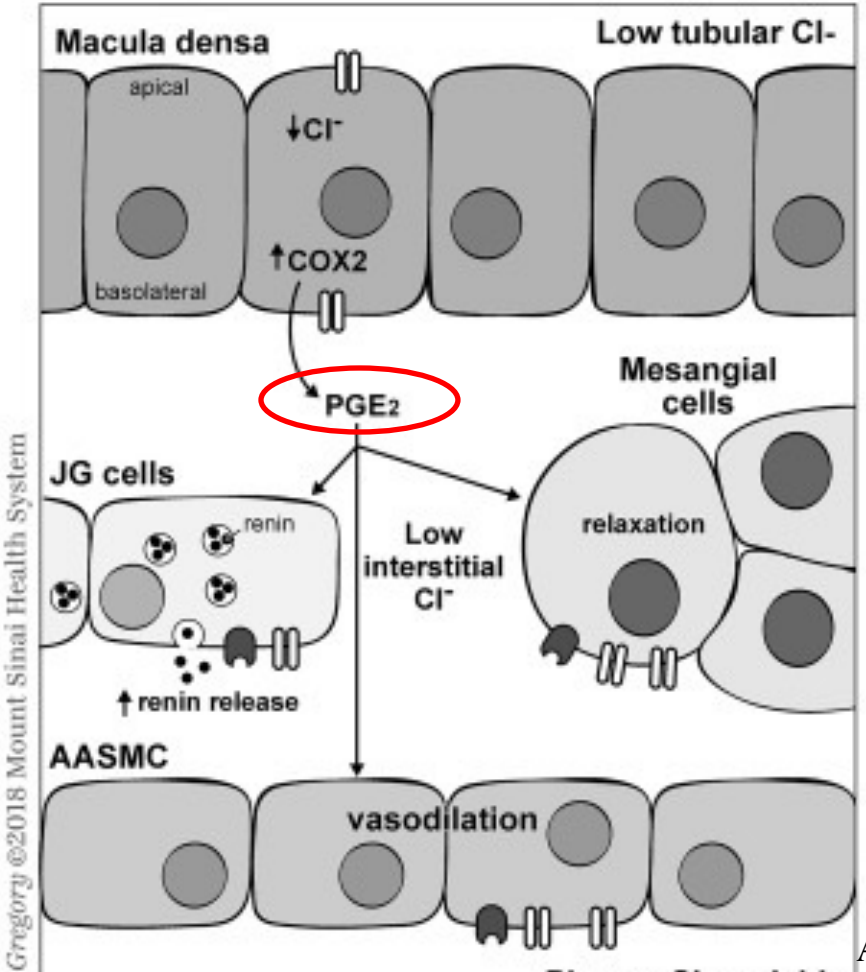

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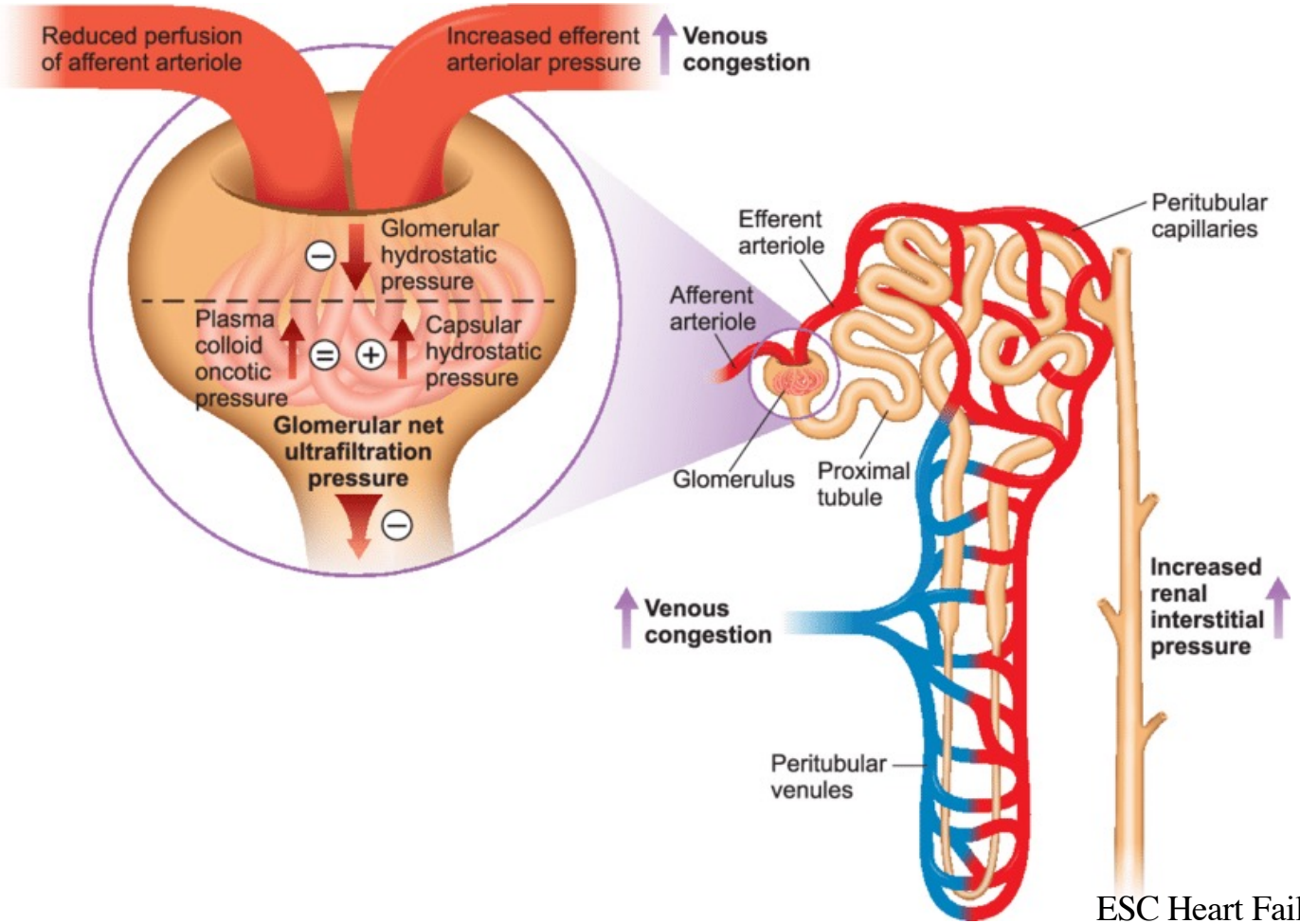
Scruffy 9yr MC Pekingese

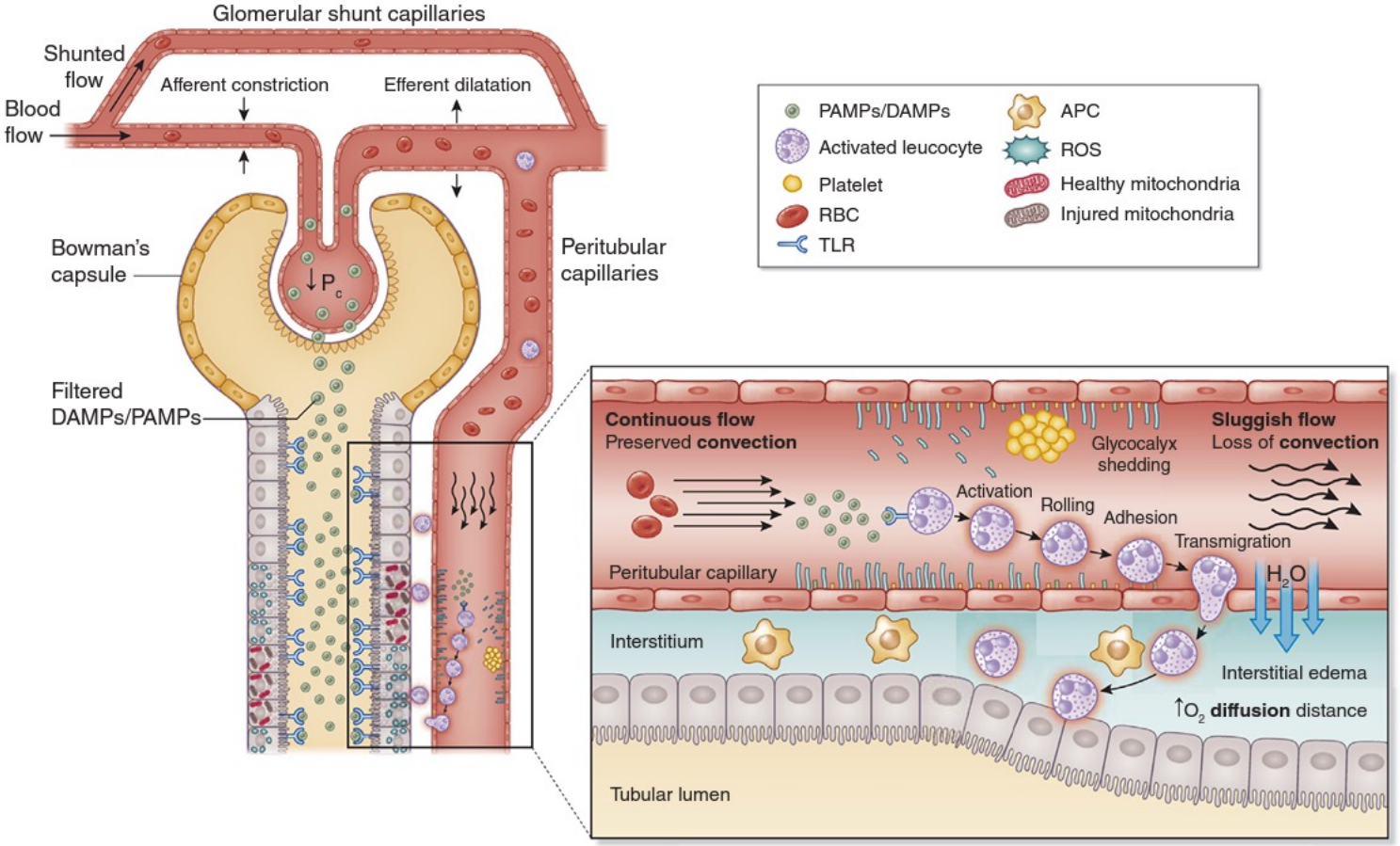
- CC: Respiratory Distress
- History MMVD
  - Furosemide, enalapril, pimobendan
- Thoracic POCUS: Diffuse B-Lines, LA:Ao 2:1
- BUN 80, creat 3.4 (new azotemia today)

Congestive Nephropathy

- Increased tubular flow = TubuloGlomerular Feedback
- Kidney swelling within capsule – interstitial edema
  - Decreased renal blood flow and GFR
  - Congestive nephrosis as venous return is impaired
  - Impaired oxygen transport
  - Tubular obstruction
  - Oligoanuria and worsening azotemia
- Intra-Abdominal Hypertension



ESC Heart Failure 2021; 8: 183–203

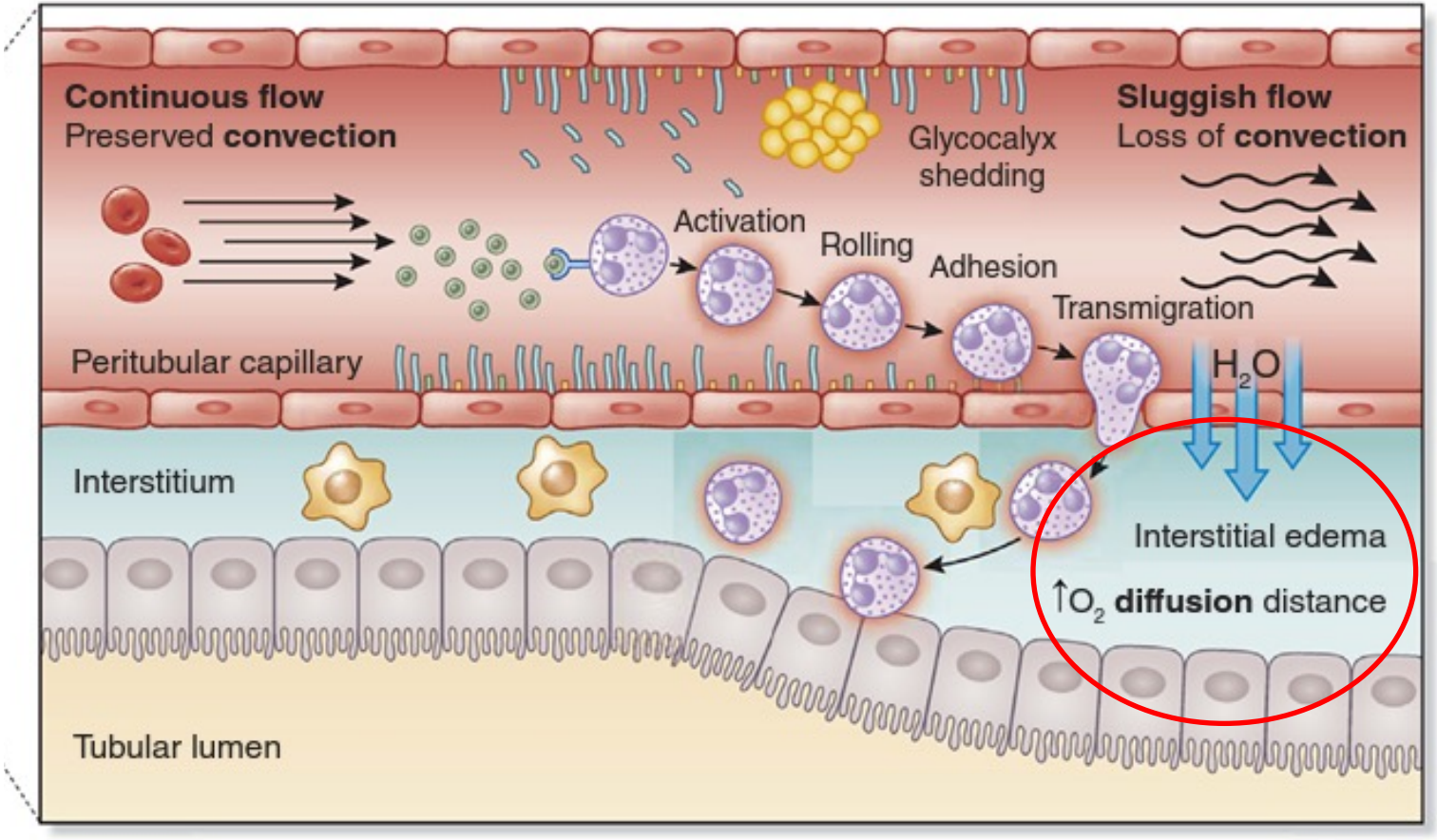


Peerapornratana S, et al. Kidney Int. 2019 Nov;96(5):1083-1099.

Fick's Law of O2 Diffusion

- O2 diffusion is determined by:
  - the O2 gradient between capillary and tissue
  - diffusional distance
  - area available for gas exchange

Fick's Law Diffusion: Diffusion of a gas (O2) is inversely proportional to thickness of the membrane



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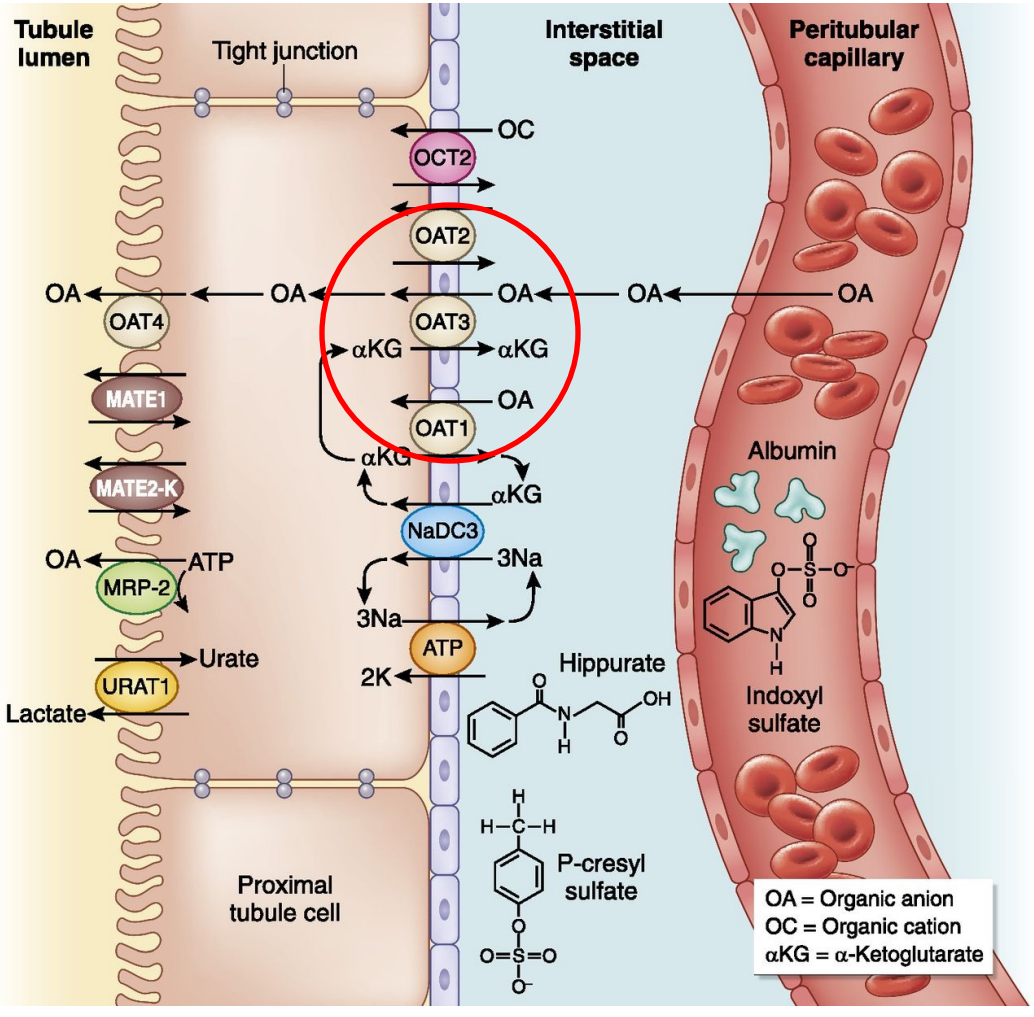
CardioRenal Syndrome

Human Classification	Veterinary Classification	Definition	Conditions
Type 1: Acute cardiorenal syndrome	$CvRD_H$ unstable	Acute impairment of the cardiac function leading to acute kidney injury (AKI)	Acute heart failure Cardiogenic shock
Type 2: Chronic cardiorenal syndrome	$CvRD_H$ stable	Chronic cardiovascular disease causing progressive chronic kidney disease (CKD)	Chronic heart failure “Congestive nephropathy”
Type 3: Acute renocardiac syndrome	$CvRD_K$ unstable	Acute primary worsening of kidney function that leads to cardiac dysfunction	AKI Hyperkalemia, uremia
Type 4: Chronic renocardiac syndrome	$CvRD_K$ stable	Primary CKD that contributes to cardiac dysfunction	Chronic glomerular disease, anemia, systemic hypertension
Type 5: Secondary cardiorenal syndrome	$CvRD_O$	Cardiac and renal dysfunction secondary to an acute or chronic systemic condition	Diabetes mellitus Sepsis

Vet Clin Small Anim 47 (2017) 1083–1102

Loop Diuretics - Furosemide

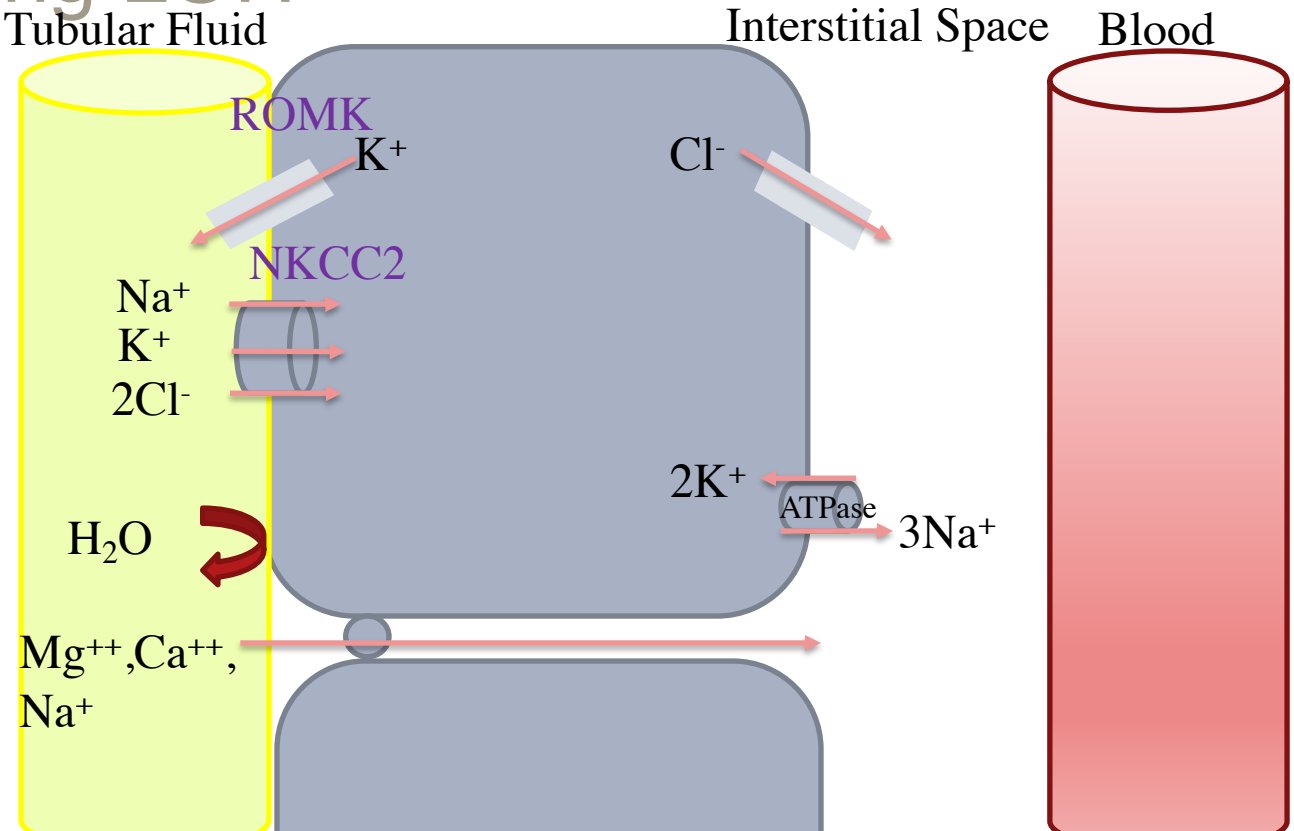
- Highly protein bound (90-95%)
- Not significantly filtered at glomerulus;
- Organic ion transporter (OAT) in basolateral proximal tubular membrane, secretion into proximal tubule
- Carried in tubular filtrate to thick ascending Loop of Henle and macula densa



CJASN
Clinical Journal of the American Society of Nephrology
Wang, K and Kestenbaum, B. CJASN 2018;13:1291-1296

Thick Ascending LOH

- Na^+ 20-30%
- Cl^- 30-40%
- K^+ 20-25%
- Mg^{++} 50-60%
- Ca^{++} 15-25%
- HCO_3^- 5-10%



Thick Ascending LOH

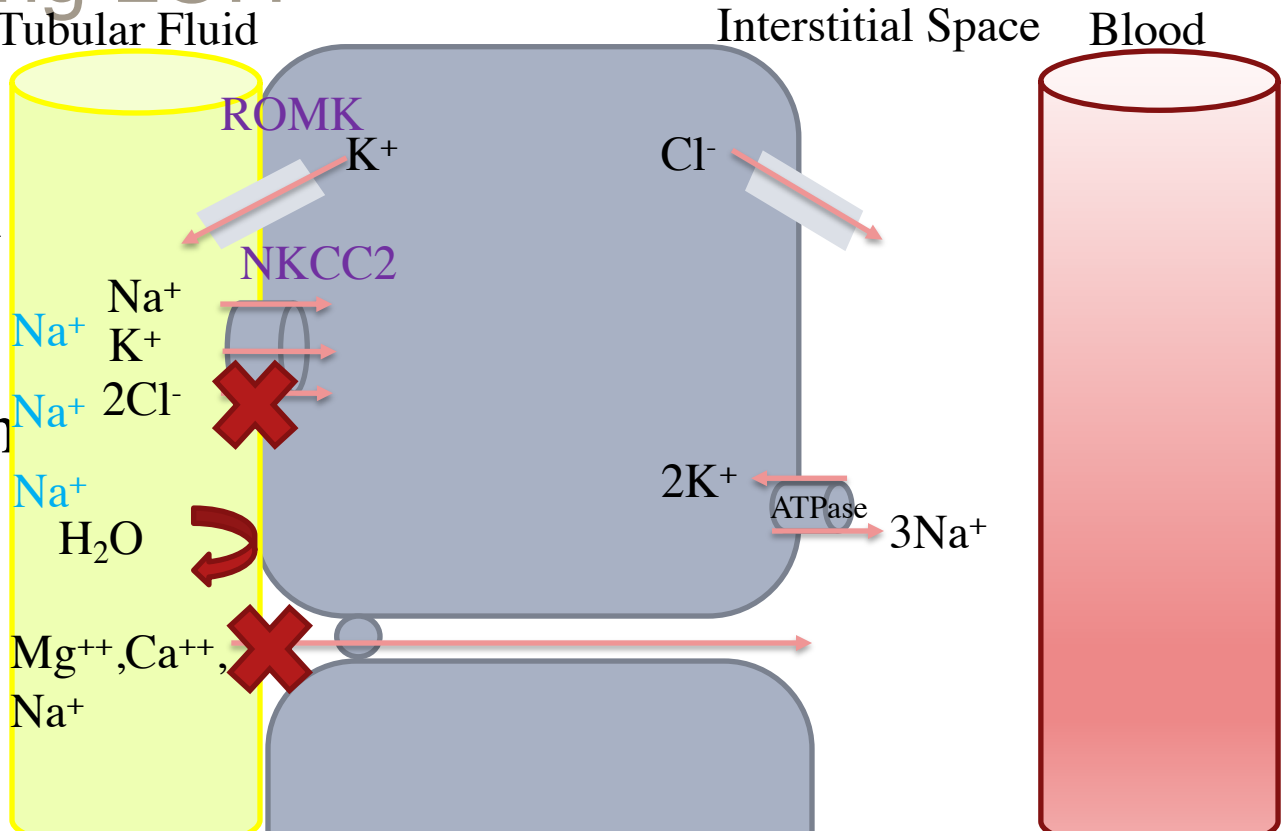
- Loop Diuretics

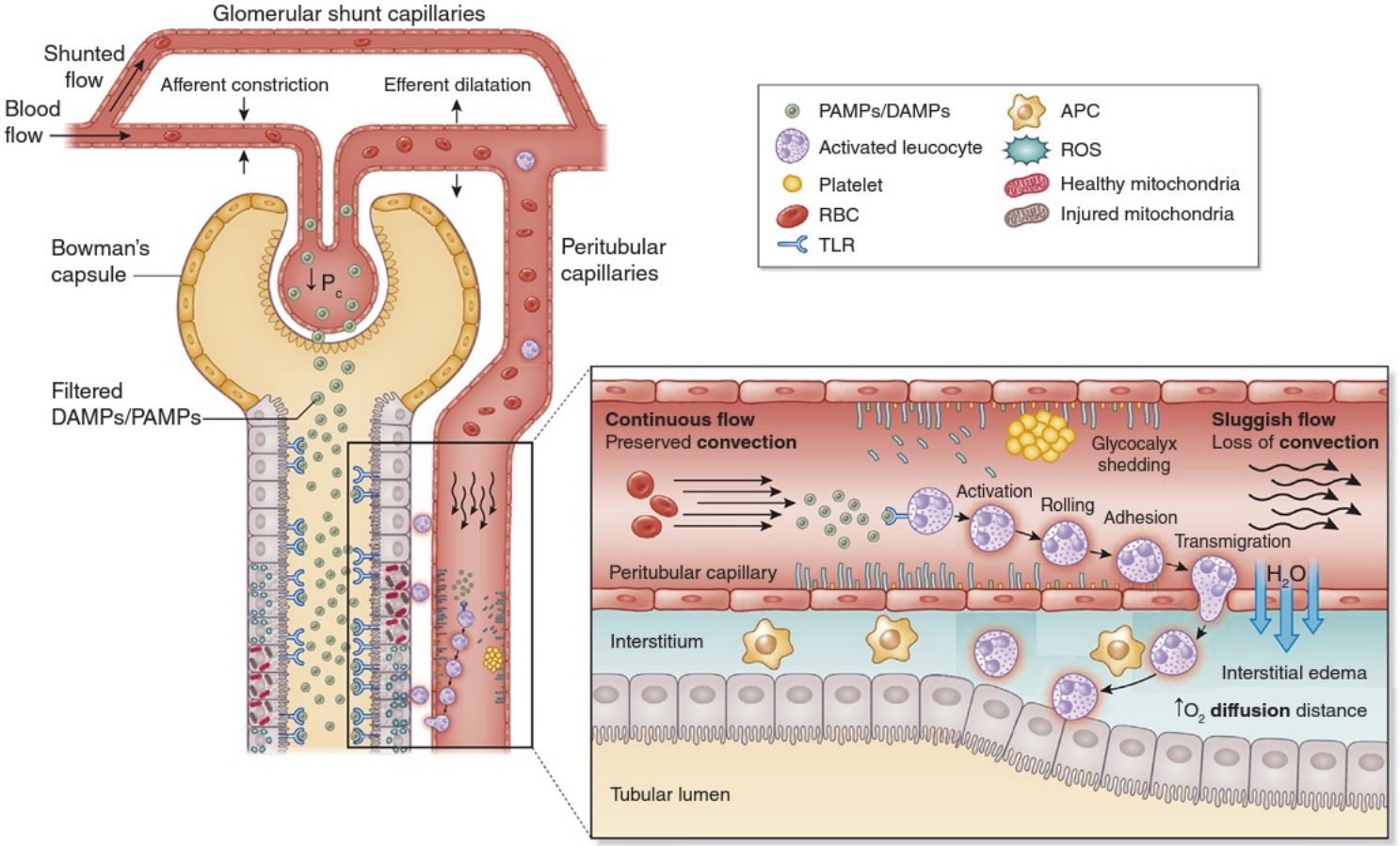
↓ Na reabsorption

↓ K back flow =

↓ Mg reabsorption

↓ Ca reabsorption





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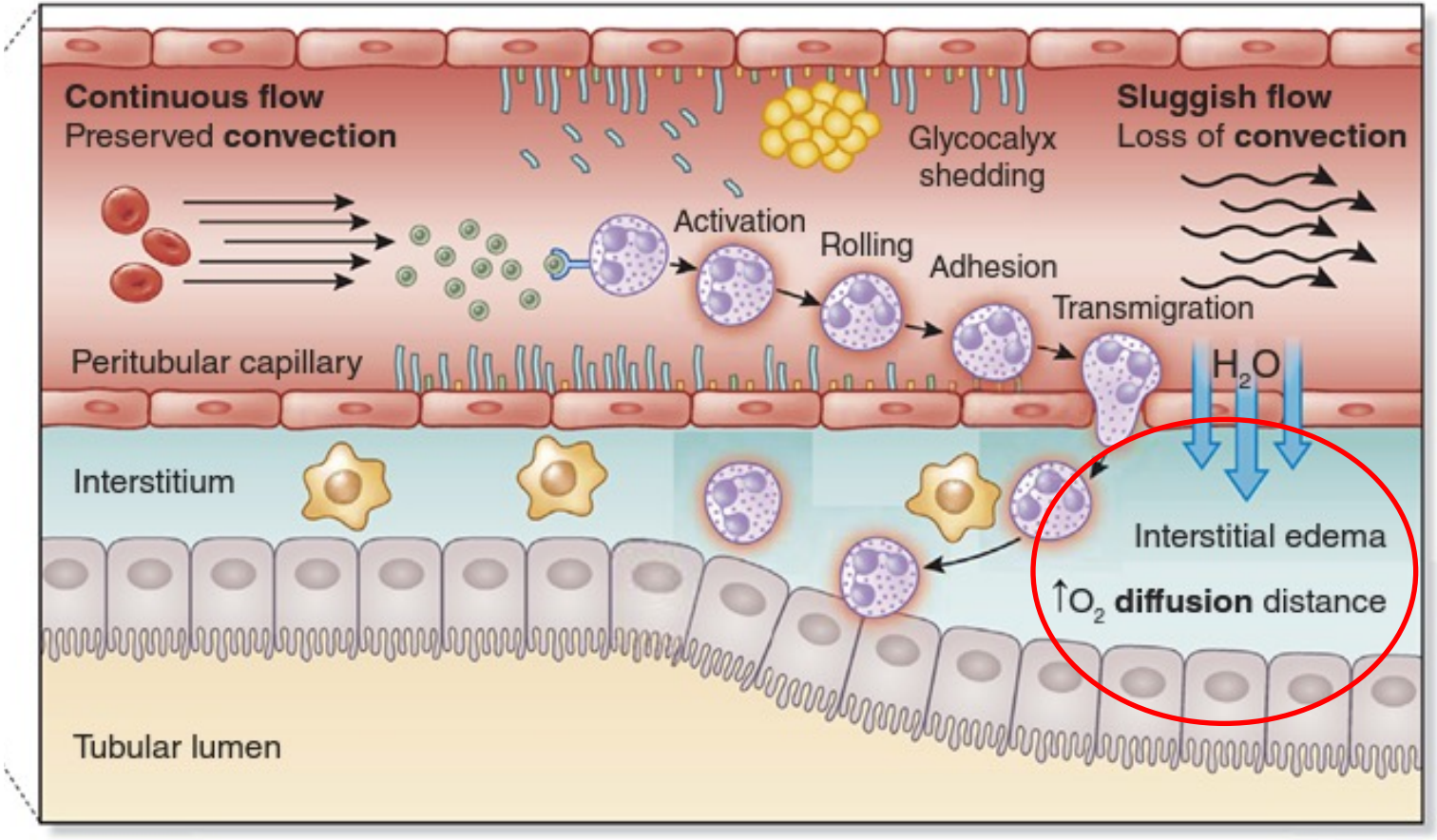

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