Lec1: Introduction and anatomy

I. Overview of the Urinary System:
Main Components:
1. Kidneys (x2) – Filter blood, form urine, maintain fluid/electrolyte balance.
Kidney Hilum Contains:
- Renal artery
- Renal vein
- Ureter
- Lymphatics and nerves

2. Ureters (x2) – Transport urine to the bladder via peristalsis.
3. Urinary Bladder (x1) – Stores urine.
4. Urethra (x1) – Discharges urine from the body.

II. Functions of the Urinary System
1. Excretion of Waste Products
Eliminates nitrogenous wastes: creatinine (from muscles), urea and ammonia (broken down amino acids), uric acid (broken down nucleic acids).
Excretes hormone metabolites, drugs, toxins and foreign substances.
Involves filtration, reabsorption, and secretion.

2. Conservation of Nutrients
Reabsorbs glucose, amino acids, etc.
Performs gluconeogenesis during fasting using glutamine.

3. Electrolyte (Ion) Balance
Regulates Na^+, K^+, Cl^-, and other ion levels via tubular reabsorption/secretion.

4. Regulation of Blood pH
Controls H^+ and HCO_3^- ion excretion.
Works with lungs to maintain pH balance.

5. Blood Volume and Pressure Regulation
Adjusts urine output.
Releases renin to activate RAAS → vasoconstriction + aldosterone release.
1. Renin converts angiotensinogen to angiotensin 1
2. ACE converts angiotensin 1 to angiotensin 2
3. Angiotensin 2 stimulates aldosterone release from adrenal glands
4. Aldosterone increases sodium and water reabsorption in the kidneys, raising BP

6. Red Blood Cell Production
Secretes erythropoietin in response to hypoxia.
Stimulates hematopoiesis in bone marrow.

7. Urine Storage
Bladder stores urine produced continuously by the kidneys.

8. Urine Excretion
Urethra discharges urine during micturition reflex.

9. Hormone Production (Endocrine Functions)
Calcitriol: Active vitamin D → increases Ca^{2+} absorption from GIT and deposition in bones.
Renin: Activates RAAS & regulating blood Na+ & K+.
Prostaglandins/Bradykinin: Affect renal/systemic blood flow.
Erythropoietin: Stimulates RBC production.

III. Urine Formation – 3 Main Mechanisms
1. Filtration (in glomerulus): Passive, non-selective, somewhat variable (excludes proteins/cells) (water and smaller molecules will leave the glomerular capillaries to the capsular space, which make the composition of the filtrate similar to that of plasma except for the proteins).
2. Reabsorption: Selective, highly variable recovery of electrolytes, glucose, water (from tubules to vessels).
3. Secretion: Active, highly variable, rapid excretion of some waste products (H^+) and removal of toxins, drugs (from vessels to tubules).
4. Final step: Urine excretion.

IV. Kidney Structure
- Cortex: Outer layer.
- Medulla: Inner layer made of renal pyramids.
  Papilla: Tip of pyramid → empties urine into calyces → renal pelvis.
- Renal Columns: Between pyramids.
- Protected by a renal capsule.

V. The Nephron: Functional Unit
- ~1 million per kidney.
- Parts:

1. Renal Corpuscle = Bowman's Capsule + Glomerulus
2. Renal Tubules: PCT, Loop of Henle, DCT, Connecting tubule, Cortical collecting tubule, Medullary collecting tubule, Collecting Duct.

- Types of Nephrons
  1. Cortical Nephrons (85%) – Mostly in cortex, short loops of henle in medulla.
  2. Juxtamedullary Nephrons (15%) – Long loops deep in medulla; associated with vasa recta for urine concentration. The rest in the cortex.

🛑 Nephron damage is irreversible; number declines with age (10% per decade after 40).

VI. Renal Blood Supply
25% of cardiac output reaches the kidneys through renal arteries.

1. Renal artery → Segmental → Interlobar → Arcuate → Interlobular
2. Afferent arteriole → Glomerulus → Efferent arteriole
3. Efferent arteriole → Peritubular capillaries, in juxtaglomerular nephrons peritubular capillaries will also surround loop of henle forming Vasa recta

> ➤ Two capillary beds in series = crucial for filtration & reabsorption.

VII. Detailed Nephron Histology

1. Renal Corpuscle:

A. Bowman's capsule:

- Parietal layer of bowman's capsule: Simple squamous
- Visceral layer of bowman's capsule: Podocytes with pedicles wrapped around basement membranes of capillaries
- Capsular space between the two layers: Filled with filtrate

B. Juxtaglomerular cells + Macula densa = Juxtaglomerular apparatus.

- Juxtaglomerular cells: Modified smooth muscle cells (secrete renin) in arterioles, proximal to macula densa.
- Macula Densa: Cells in the final part of ascending loop of henle. Sense Na^+ in DCT
- Mesangial cells: Contractile cells found in spaces between afferent and efferent arterioles, Adjust blood flow via contraction.

2. Tubules:

- PCT: Simple Cuboidal + Brush border
- Loop of Henle:
  Thin limb: Simple squamous
  Thick limb: Simple Cuboidal
- DCT: Simple cuboidal
- Last part of DCT and CD:
  Simple cuboidal consisting of:
  - Principal cells: Receptors for ADH/aldosterone
  - Intercalated cells: Regulate pH

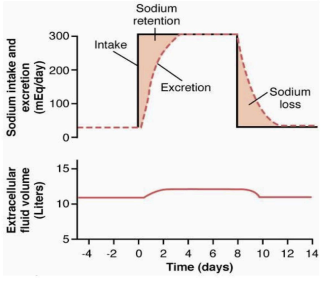
VIII. Micturition (Urination)

Detrusor muscle contracts bladder.
Bladder capacity varies between males and females 700-800mL) but stretch (200–400 mL) triggers spinal reflex:

- Parasympathetic input: Bladder contracts, internal sphincter relaxes.
- Voluntary control: External sphincter (skeletal muscle).

! Micturition center = in the spinal cord.

IX. Regulation of Sodium & ECF Volume



Sudden Na^+ intake → temporary sodium retention until the kidneys compensate to balance between input and output → increased ECF, Kidneys gradually balance excretion with intake. Upon sudden Na^+ reduction, kidneys continue excreting until new balance is reached. (Kidney adapts over several days to maintain fluid homeostasis).

❓ Common Question
Q: Can someone live with one kidney?
A: Yes, a healthy kidney can fully compensate.

Lec2: GFR + RBF 1

I. Mechanisms of Urine Formation

Equation:
Excretion = Filtration – Reabsorption + Secretion

1. Filtration
Occurs at the glomerulus.
Passive, not selective (except for size/charge).
Filters ~20% of plasma.
Excludes large proteins and cells.
2. Reabsorption
Highly selective: glucose, amino acids, ions reabsorbed via specialized transporters.
Waste products are poorly reabsorbed.
3. Secretion
Active process for rapid removal of substances like H^+, drugs, and toxins.
4. Excretion
What remains after the above processes is excreted as urine.

II. Nephron and Filtration Barrier Structure

- Nephron Composition:
  ~1 million per kidney
  Divided into:
  Vascular part: afferent arteriole → glomerulus → efferent arteriole
  Tubular part: Bowman's capsule surrounding the glomerulus → PCT → Loop of Henle → DCT → Collecting ducts.
- Filtration Barrier in corpuscle (3 layers):

1. Fenestrated endothelium: negatively charged, size-limited pores
2. Basal lamina: negatively charged proteoglycans
3. Podocytes (visceral layer of Bowman's capsule): pedicels form filtration slits, charge- and size-selective

These 3 layers prevent protein filtration because proteins are large and negatively charged (especially albumin).

IV. Renal Handling of Key Substances

Substance	Filtered	Reabsorbed	Excreted
Water (L/day)	180	179	1
Na^+ (mmol/day)	25,560	25,410	150
Glucose (gm/day)	180 g	180	0
Creatinine (gm/day)	1.8 g	0	1.8

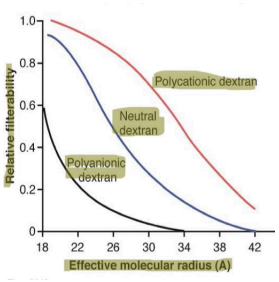
Summary:
Water: filtered and mostly reabsorbed; filtered about 60x/day (180 L/day while we have 3L of plasma, which indicates that:
A. Waste is filtered efficiently and rapidly. B. Precise control of Extracellular fluid and blood volume daily.)
Na^+: most reabsorbed; variable depending on intake.
Glucose: completely reabsorbed unless plasma level exceeds renal threshold (as in diabetes).
Creatinine: filtered & secreted; no reabsorption → good GFR marker.

V. Scenarios of Substance Handling

1. Filtration only (not present in the body): no reabsorption or secretion (e.g. creatinine-like)
2. Filtration + partial reabsorption: Na^+, Cl^-, water
3. Filtration + complete reabsorption: glucose, amino acids
4. Filtration + secretion (not present in the body): close to toxins, drugs (e.g. para-aminobenzoic acid)

VI. Factors Affecting Filtration

Factor	Effect on Filterability
Size	↑ size = ↓ filterability
Charge	+ve = easier filtration –ve = repelled by filtration barrier



Albumin is small enough but negatively charged, so it doesn't filter.
Diseases that remove this –ve charge (e.g. minimal change disease) → albuminuria

VIII. Clinical Application: When Filtration Goes Wrong

Damaged glomerular membrane → protein leakage → ↓ blood colloid pressure & ↑ bowman's capsule colloid pressure →

1. ↑ fluid loss from plasma to bowman's capsule → ↑ filtered fluid
2. ↑ fluid loss from plasma to interstitium → edema (e.g. ankle swelling)

Common in Glomerulonephritis, Nephrotic syndrome, and Heart failure.

Lec3: GFR + RBF 2

I. Review of Key Concepts

Filtration membrane damage (e.g. loss of podocytes or –ve charge) → proteinuria.
Microalbuminuria (30–150 mg/day albumin) is an early marker of kidney disease, especially in:
Diabetes mellitus (DM) (diabetic patients with microalbuminuria are 10-20 fold more likely to develop persistent protienuria)
Hypertension
Glomerular hyperfiltration
Pregnancy (preeclampsia risk)

II. Renal Blood & Plasma Flow

Plasma = ~55% of blood
If renal plasma flow (PF) = 625 mL/min:
➢Renal Blood flow (BF) = PF / 0.55 ≈ 1140 mL/min
Kidneys receive 22.8% of cardiac output
[note that this percentage was mentioned as 20% sometimes throughout the lectures]
! High blood flow is essential to maintain GFR.

III. Glomerular Filtration Rate (GFR) Basics

GFR = The volume of fluid filtered through all the corpuscles of both kidneys per minute
Total GFR ≈ 180 L/day while we have 3 liters of plasma → plasma is filtered ~60×/day.
[note that 180 L/day = 125 mL/min]

Functions:

1. Efficient waste removal
2. Precise plasma composition regulation

Why kidneys filter so much?

- High hydrostatic pressure
- High renal plasma flow (20% of CO)
- Highly permeable filtration membrane

IV. Filtration fraction

Filtration fraction (FF) is the fraction of blood plasma in the afferent arterioles that becomes filtrate.

FF = GFR/RPF

Normal FF = (125 mL/min) / (625 mL/min) = 0.2 which means that 20% of plasma that enters the afferent tubules is filtered.
[Renal blood flow of 1140 mL/min (22.8% of cardiac output) is required to have GFR of 125 mL/min]
Homeostasis of body fluids requires constant GFR by kidneys.

V. Importance of GFR Homeostasis

GFR Status	Result
↑ GFR	Excess loss of needed substances (e.g. water, electrolytes)
↓ GFR	Toxin accumulation, poor waste clearance

📌 Both high and low GFR can disrupt body fluid balance.

VI. Determinants of GFR

1. Net Filtration Pressure (NFP)

Filtration Pressures

Pressure Type	Value (mmHg)	Effect
Glomerular hydrostatic (PG)	+60	Promotes filtration
Capsular hydrostatic (PB)	–18	Opposes filtration
Glomerular oncotic (πG)	–32	Opposes filtration
Capsular oncotic (πB)	~0	Negligible

Net Filtration Pressure (NFP):

NFP = (PG + πB) – (PB + πG)

NFP = (60 + 0) – (18 + 32) = +10 mmHg

Filtration is directly proportional to NFP.

GFR = NFP × Kf (filtration coefficient)

Kf in kidneys = GFR/NFP = 125/10 = 12.5 mL/min/mmHg

Kidney Kf is ~400× greater than other organs

and this maybe due to:

- the characteristics of the filtration membrane (surface area and permeability)
- Net filtration forces
- the high renal blood flow that comes to the tissues.

Kf = hydraulic conductivity x surface area hence it depends on;

- Filtration surface area
- Permeability

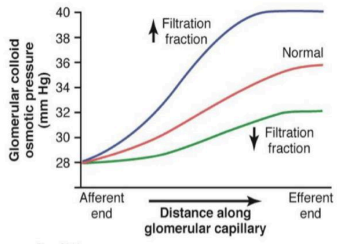
! Kf is constant, it is not physiologically regulated to control GFR, but decreases in pathological conditions that damage the capillaries leading to thickening of basement membrane like:

- Diabetes
- Hypertension
- Glomerulonephritis

2. Bowman's Capsule Hydrostatic Pressure (PB)
Pathological increases (e.g. obstruction from stones/tumors/necrosis/prostate hypertrophy) → ↑PB → ↓NFP → ↓GFR
🧠 Not a physiological regulator of GFR because normally, it changes as a function of GFR

3. Glomerular Capillary Oncotic Pressure (πG)
Increases from afferent → efferent end of glomerulus.
Factors affecting πG:

- Arterial plasma oncotic pressure (direct relation)
- Filtration Fraction (FF) = GFR / RPF
    - ➤ ↑FF → ↑πG
    - ➤ ↓FF → ↓πG



🛑 πG is not a physiological regulator of GFR (depends on GFR like PB).

4. Glomerular Hydrostatic Pressure (PG)
Main regulator of GFR
The determinant of GFR most subject to physiological control
Since PG is constant and the oncotic pressure increases, the net filtration pressure decreases along the length of the capillary.

Factors that affect PG:

A. Arterial pressure (effect buffered by autoregulation)
B. Afferent arteriolar pressure
C. Efferent arteriolar pressure

A. Arterial pressure and Autoregulation of Renal Blood Flow

Logically we expect that as blood pressure increases PG increases, however it was found that when the blood pressure is between 60 mmHg to 140 mmHg, the PG was nearly constant (plateau), and this is due to an autoregulation process in the kidneys to resist changes in pressure inside the glomerular capillaries
• The direct relationship between blood pressure and PG is only true for extreme changes in pressure (lower than 60 mmHg or higher than 140 mmHg).
• The autoregulation process is an intrinsic regulation done by the kidney to stabilize PG, so that changes that affect arterial pressure will not affect GFR.

PG remains stable within 60–140 mmHg mean arterial pressure → maintains constant GFR
Outside that range:
↓ BP → ↓ PG → ↓ GFR
↑ BP → ↑ PG → ↑ GFR
In renal disease, autoregulation fails → GFR becomes BP-dependent.

Autoregulation maintains stable GFR and RBF BUT: Urine output increases with BP due to RAAS and hormonal reabsorption control.

📌 Autoregulation affects filtration, not urine volume.
📌 The kidney adjusts resistance in afferent and efferent arterioles to stabilize GFR despite changes in systemic BP.

B&C: Resistance in Afferent & Efferent Arterioles

Resistance Change	Effect on RBF	Effect on PG	Effect on GFR
↑ Afferent Resistance	↓ RBF	↓ PG	↓ GFR
↑ Efferent Resistance	↓ RBF	↑ PG	Mixed/↑ GFR

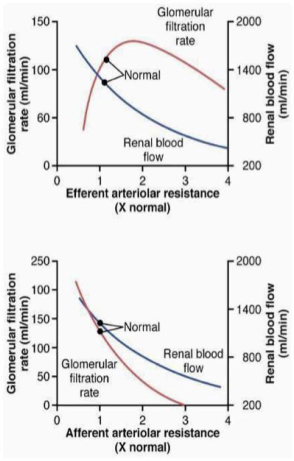
The kidney adjusts resistance in these vessels to stabilize GFR.

Lec4: GFR + RBF 3

I. Key ideas

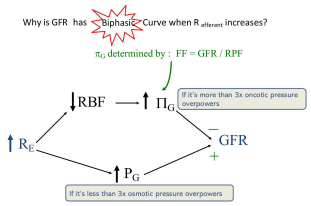
As mentioned previously, PG is the main determinant of GFR, PG is affected by:

A. Mean arterial pressures (not between 60-140 mmHg)
B. Afferent arteriolar resistance (*or pressure, not that big of a difference ;)*)
   A modest increase in afferent arteriolar resistance → Decreased renal blood flow (RBF) due to blood flow impedance. → decrease in GFR.
C. Efferent Arteriolar Resistance:
   Biphasic Response:
   1. First Phase: Increase in resistance one to three times causes an increase in GFR (hydrostatic pressure buildup), reducing RBF while GFR would increase/be mixed.
   2. Second Phase: Over 3x increase of resistance, glomerular oncotic pressure overpowers hydrostatic pressure, leading to a decrease in GFR, and an even greater decrease in RBF, increasing FF.



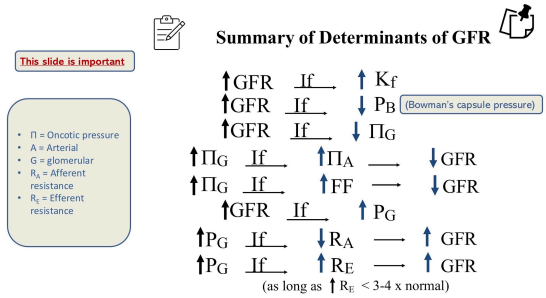
Summary:

- *↑Ra → ↓RBF → ↓PG → ↓NFP → ↓GFR*
- *↑Re (1-3x) → ↓RBF & ↑PG → ↑NFP → mixed/↑GFR*
- *↑Re (>3x) → ↓↓RBF & ↑PG → ↑↑↑ΠG → ↓NFP → ↓GFR but ↑FF*



II. Determinants of GFR

Summary of Determinants of GFR:



*Remember: GFR=[(PG + ΠB) - (ΠG + PB)] * Kf*
Then remember the factors that affect each one of these :)

GFR: Determined by afferent and efferent resistance, hydrostatic pressure, and oncotic pressure.

III. Determinants of Renal Blood Flow (RBF)

Equation for RBF:
RBF = ΔP/R
Where:

ΔP = Difference between renal artery pressure and renal vein pressure.
R = Total renal vascular resistance (Ra + Re + Rv).

Renal Blood Flow Details:

- High blood flow (~22% of cardiac output) is necessary for high GFR.
- Excess oxygen and nutrients are delivered to kidneys for function, not metabolic needs.
- Renal Oxygen Consumption: Primarily related to sodium reabsorption because it relies on active mechanisms which consume oxygen for ATP production.

IV. Control of GFR and Renal Blood Flow

Types of Control:

A. Neurohumoral: External regulation.
B. Local (Intrinsic): Kidney's self-regulation.

A. Neurohormonal control:

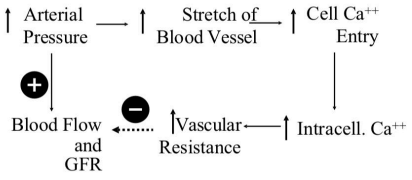
Summary of Neurohumoral Control of GFR and RBF

Regulator	effects	cause for release	notes
Sympathetic stimulation 1. Sympathetic Nervous System /catecholamine ↑↑ R_A + ↑ R_E ⟶ ↓ GFR + ↓↓ RBF e.g. severe hemorrhage	**Mild:** maintains GFR by equally affecting both resistances. **Severe:** Epinephrine increases afferent and efferent resistances, which reduces both RBF and GFR.	Severe stimulation in hemorrhage	
Angiotensin II: 2. Angiotensin II ↑ R_E ⟶ ↔GFR + ↓ RBF (prevents a decrease in GFR) e.g. low sodium diet, volume depletion	increases both afferent and efferent resistances, but efferent resistance to a greater extent, which elevates GFR	When BP decreases, GFR decreases as well, juxtaglomerular cells sense this decrease and activate RAAS system, angiotensin II elevates GFR back to normal e.g., low sodium diet, volume depletion,	Angiotensin II direct effect: increased GFR net effect: normal GFR
Prostaglandins 3. Prostaglandins ↓↓R_A + ↓R_E ⟶ ↑GFR + ↑↑ RBF Blockade of prostaglandin synthesis → ↓ GFR • This is usually important only when there are other disturbances that are already tending to lower GFR • e.g. nonsteroidal antiinflammatory drugs in a • volume depleted patient, or a patient with heart failure, • cirrhosis, etc	dilating afferent arterioles more than efferent and maintaining GFR.	Prostaglandins work as protective procedure: When patients have impaired GFR, prostaglandins help the kidney to elevate it back to normal (prevent further decline in GFR).	PG blockers like NSAIDS are contraindicated in patients with low GFR
Endothelial-Derived Nitric Oxide (EDRF): 4. Endothelial-Derived Nitric Oxide (EDRF) ↓↓R_A + ↓R_E ⟶ ↑ GFR + ↑↑RBF • Protects against excessive vasoconstriction • Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR in response to stimuli such as volume depletion	EDRF causes vasodilation in afferent more than efferent arterioles, which reduces Ra, increasing RBF and GFR.	Protection against excessive vasoconstriction	Patients with endothelial dysfunction *(no sufficient release of EDRF)* have greater risk for excessive decrease in GFR in response to stimuli like volume depletion
Endothelin: 5. Endothelin ↑↑ R_A + ↑ R_E ⟶ ↓ GFR + ↓↓ RBF • Hepatorenal syndrome – decreased renal function in cirrhosis or liver disease? • Acute renal failure (e.g. contrast media nephropathy)? • Hypertensive patients with chronic renal failure? Endothelin antagonists may be useful in these conditions Note about the last sentence: • You give the patient endothelin antagonists, and then discover if the endothelin is the cause of GFR decreasing or not. • Because there are many factors other than endothelin.	Vasoconstriction of afferent arterioles decreases GFR.		Endothelin antagonists are useful in conditions like cirrhosis, hypertensive kidney damage, and acute renal failure.

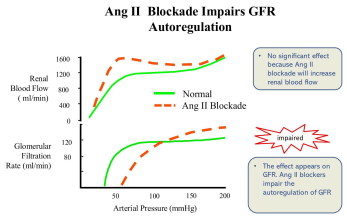
A. Local Control of GFR and Renal Blood Flow

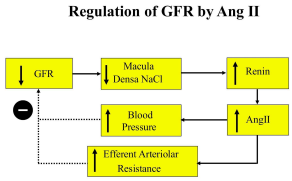
1. Myogenic Mechanism:

Smooth muscle cells in afferent arterioles respond to stretch due to changes in pressure. Constriction decreases GFR to prevent excessive flow.



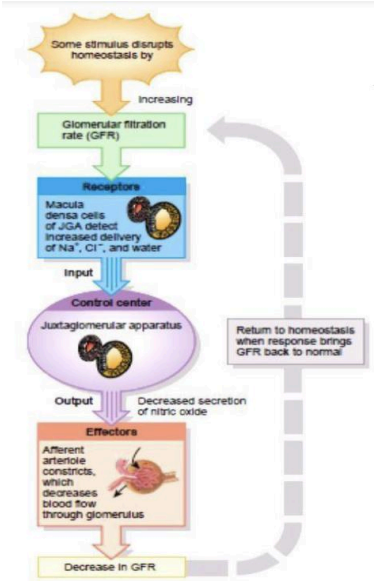
2. Regulation by Angiotensin II:
   Constricts efferent arterioles mainly, raising GFR.
   Ang II Blockade: Impairs autoregulation by increasing RBF but decreasing GFR.





3. Macula Densa Feedback (tubuloglomerular feedback = distal tubule to glomerulus):
   Senses Na+ and Cl- delivery in the distal tubule and adjusts GFR accordingly.
   - If they are decreased, it stimulates ang II release to increase systemic BP, PG and GFR
   - If they are increased, it sends signals to juxtaglomerular cells to reduce RBF by:
     - NO (vasodilator) release inhibition
     - renin inhibition

   So, what factors control renin secretion?
   1. Perfusion Pressure: low perfusion in afferent arterioles stimulates renin secretion while high perfusion inhibits renin secretion.
   2. Sympathetic nerve activity: Activation of the sympathetic nerve fibers in the afferent arterioles increases renin secretion.
   3. NaCl delivery to macula densa: When NaCl is decreased, Renin secretion is stimulated and vice versa. (Tubuloglomerular Feedback)



V. Renal Autoregulation and Pressure Response

Response to Renal Artery Pressure:

Any sudden increase or decrease in renal artery pressure will result in sudden increase or decrease in GFR and RBF respectively. Those changes will be autoregulated subsequently.

Decreased BP (80 mmHg): GFR initially drops but normalizes within 2 minutes even if the BP remains low.

Increased BP (120 mmHg): GFR initially increases but returns to normal quickly even if the BP remains high.

📌 Remember that autoregulation affects RBF & GFR but NOT urine output.