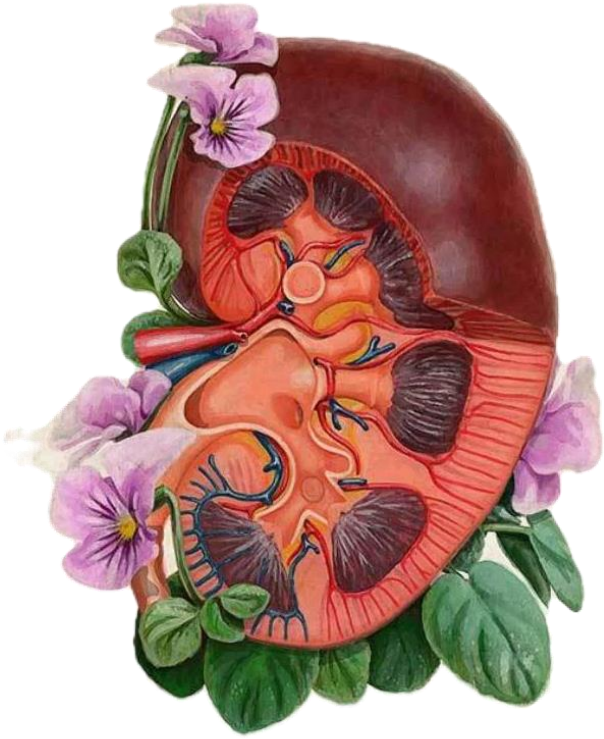
UGS Physiology Sheet 3 - V1



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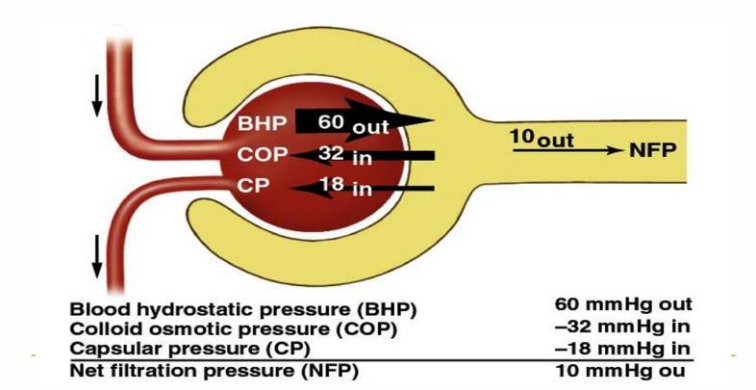
Glomerular Filtration Rate

GFR = Driving Force (NFP) × Permeability Coefficient (K_f)

- GFR represents a bulk fluid flow that is driven by **Starling forces** and opposed by vascular resistance.
- Instead of using resistance, it is physiologically more practical to use **permeability**, because Permeability = 1 / Resistance.
- Permeability is directly proportional to the surface area of the membrane and inversely proportional to its thickness (**Permeability** ∝ **Area / Thickness**).
- Recall the four Starling forces are: capillary hydrostatic pressure (**Pc**) and capillary oncotic pressure (**πc**), which act within the capillary, and interstitial hydrostatic pressure (**Pi**), interstitial oncotic pressure (**πi**), which act in the surrounding interstitium. The summation of these forces determines whether net filtration or net reabsorption will occur.

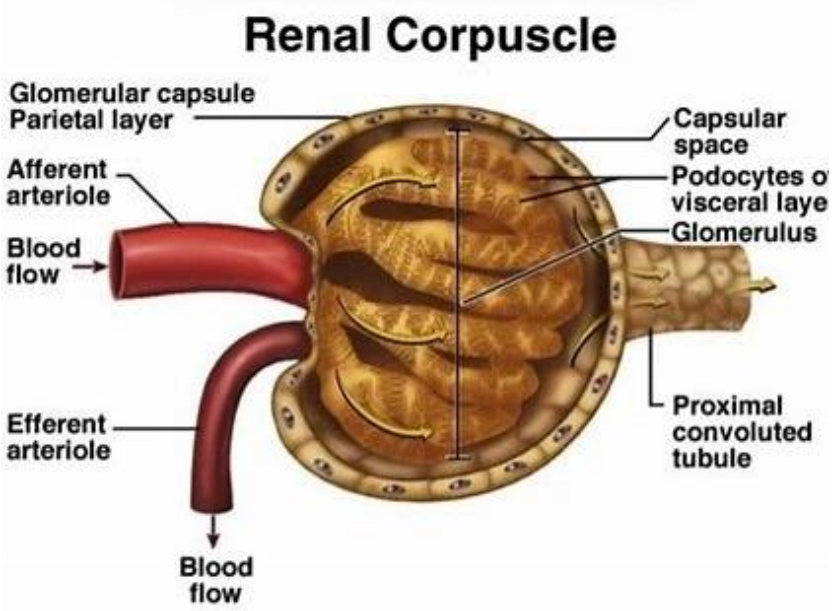


Starling Forces in the Glomerulus

Unlike systemic capillaries which operate on four Starling forces, the kidney operates on only **three active forces** because proteins are generally not filtered into Bowman's space, making the capsular colloid osmotic pressure zero.

The forces are:

- **Blood Hydrostatic Pressure (BHP):** 60 mmHg directed *outward* (promoting filtration). This is exceptionally high compared to systemic capillaries (~30 mmHg).
- **Colloid Osmotic Pressure (COP):** 32mmHg acting inward to oppose filtration (favoring absorption) and is proportional to the difference in protein concentration (ΔC) across the capillary wall.
- **Capsular Pressure (CP):** 18 mmHg directed *inward* (opposing filtration).



Renal Corpuscle & Vascular Pressures

The renal corpuscle comprises the afferent and efferent arterioles, the glomerulus, the visceral layer (podocytes), the parietal layer (glomerular capsule), and the capsular space where filtrate collects before flowing into the proximal convoluted tubule.

- The uniquely high capillary hydrostatic pressure (60 mmHg) is maintained because the **efferent arteriole has a smaller diameter than the afferent arteriole**, acting similarly to venoconstriction.
- The afferent and efferent arterioles contribute approximately **50% of the total renal vascular resistance**.
- **Pressure Drop Pathway:** Aortic pressure (~100 mmHg) → Renal artery (~95 mmHg) ⟶ Afferent arteriole drops from 85 to 60 mmHg ⟶ Glomerular capillary sits at 59 mmHg ⟶ Efferent arteriole drops from 59 down to 18 mmHg⟶ Peritubular capillaries sit at 18 mmHg, dropping to 4 mmHg in venules.

Most of the renal vascular resistance resides in three major segments:
interlobular arteries, **afferent arterioles, and efferent arterioles**.
The afferent arteriole drop is 25 mmHg, and the efferent arteriole drop is 41 mmHg. If total resistance = 100 units, approximately 69% of resistance resides in the afferent and efferent arterioles combined.

Table 27-3 Approximate Pressures and Vascular Resistances in the Circulation of a Normal Kidney

Vessel	*Pressure in Vessel (mm Hg)* Beginning	End	Percent of Total Renal Vascular Resistance
Renal artery	100	100	≈0
Interlobar, arcuate, and interlobular arteries	≈100	85	≈16
Afferent arteriole	85	60	≈26
Glomerular capillaries	60	59	≈1
Efferent arteriole	59	18	≈43
Peritubular capillaries	18	8	≈10
Interlobar, interlobular, and arcuate veins	8	4	≈4
Renal vein	4	≈4	≈0

Because **20% of plasma is filtered** out of the **glomerulus** (compared to 0.5% in systemic capillaries), the remaining proteins become concentrated. This causes the Colloid Osmotic Pressure to rise from 28 mmHg at the afferent end to 36 mmHg at the efferent end, averaging 32 mmHg. As a result the relationship between **π** and **protein concentration** to be nonlinear — the curve is shifted to the left, meaning small increases in protein concentration produce disproportionately large rises in oncotic pressure.

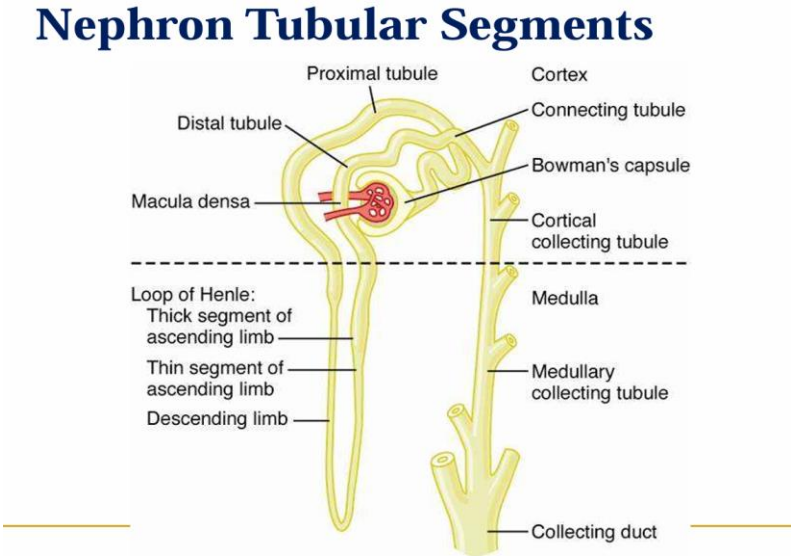
The Filtration Barrier & Molecular Permeability

- The filtration barrier is composed of three layers (endothelium, basement membrane, and epithelium/podocytes) and is **entirely negatively charged**. Filterability depends heavily on:
    - **Molecular Size/Weight:** Larger molecules inherently have a lower chance of being filtered.
    - **Electrical Charge:** Negatively charged molecules are repelled by the barrier.
  - **Albumin** (Molecular Weight ~70,000) is small enough to potentially filter but is repelled completely because it is negatively charged.
  - **Dextran** filterability varies strictly by charge: positively charged (polycationic) dextran **filters easily**, neutral dextran filters **moderately**, and negatively charged (polyanionic) dextran has extremely **poor filterability.**
  - **Hemoglobin** (Molecular Weight 64,500) is usually bound to proteins and not filtered. However, during severe hemolysis (e.g., G6PD deficiency / Favism), free hemoglobin leaks into the filtrate, causing hemoglobinuria (pink urine).

1. ***Net Filtration Pressure (NFP)*** *= Blood Hydrostatic Pressure - (Colloid Osmotic Pressure + Capsular Pressure)*
    - *NFP=60−(32+18) =10 mmHg outwards*

2. ***GFR*** *= Driving Force (NFP) × Permeability Coefficient*
- Using normal physiological values ($125\ \text{ml/min}$ for GFR and $10\ \text{mmHg}$ for NFP):
- $125=10\times Permeability$
- *Permeability Coefficient (K_f) = 12.5 ml/min/mmHg*

3. ***Filtered Load*** *= GFR × Plasma Concentration of a substance* (e.g., glucose). If the filtered load **exceeds** the reabsorption capacity of the proximal tubule, **the substance is lost in the urine.**

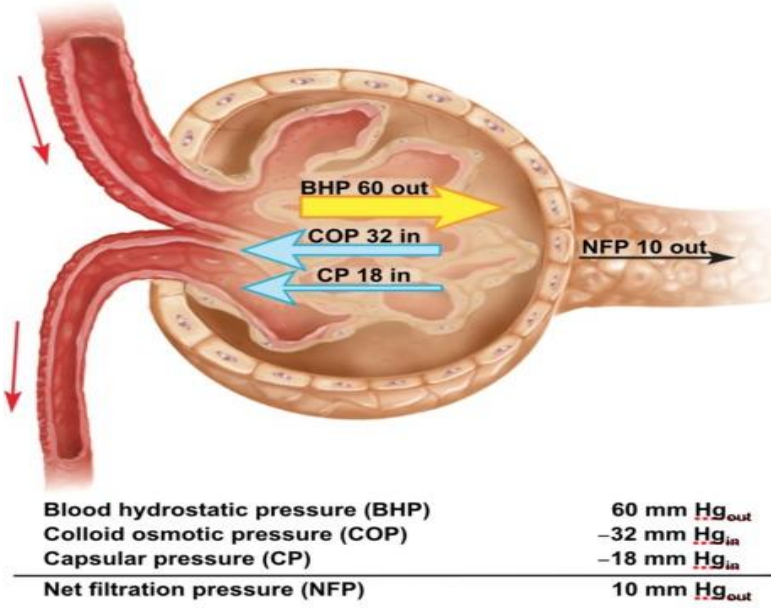


- The nephron physically spans the cortex and medulla. The tubule consists of the proximal tubule, the descending limb, the thin and thick segments of the ascending Loop of Henle, the macula densa, the distal tubule, and the collecting ducts.
- The outer diameter of the proximal tubule is roughly $60\mu m$, while the outer diameter of the Loop of Henle is exceptionally narrow at just $11\mu m$.
- Because the Loop of Henle is so narrow, a **drop** in GFR slows down the flow rate dramatically, increasing the risks for **sodium and calcium crystallization**. This can create an irreversible, **unflushable** obstruction.

Pathologies & Clinical Correlates

- **Uncontrolled Diabetes**
  Diabetic nephropathy, chronic hyperglycemia, thickens the glomerular basement membrane and expands the mesangium, increasing permeability, causing proteinuria. Early on, GFR actually rises (hyperfiltration). Over time, glomerulosclerosis destroys nephron mass, and GFR ultimately falls — accounting for approximately 90% of renal failure cases alongside hypertension.
  Patients must maintain an *HbA1c around 6-6.5* to prevent nephropathy and the leakage of albumin into the urine.
- **Renal Failure Classifications**:
  - *Prerenal:* Caused by issues before the kidney, such as severe dehydration.
  - *Intrarenal:* Damage to the actual kidney structures.
  - *Postrenal (~10% of cases):* Caused by blockages like prostate hypertrophy or stones in the renal pelvis, calyces, ureter, or bladder.

Postrenal Failure: Obstructions cause retrograde (backward) fluid flow, which drastically increases the Capsular Hydrostatic Pressure (e.g., raising it from 18 up to 28 mmHg). This effectively reduces the Net Filtration Pressure to zero, entirely **stopping GFR and leading to rapid kidney destruction (hydronephrosis).**



(COP) is primarily determined by plasma protein concentration (especially albumin) and is normally relatively **constant**.

(BHP) is regulated and can be modulated by changes in ***afferent*** *arteriolar tone:*

- *Prostaglandins* — Protective Dilation
  Prostaglandins help maintain dilation of the afferent arteriole, thereby preserving renal blood flow and glomerular filtration rate (GFR), especially during stress conditions.
- *Sympathetic Stimulation* — Constriction
  In contrast, sympathetic stimulation (e.g., via epinephrine) causes constriction of the afferent arteriole, which reduces GFR. This effect is minimal under resting conditions but becomes significant during severe stress such as bleeding.

A marked reduction in GFR can lead to acute kidney injury due to decreased renal perfusion, potentially resulting in permanent damage if not corrected.

Response To Significant Bleeding

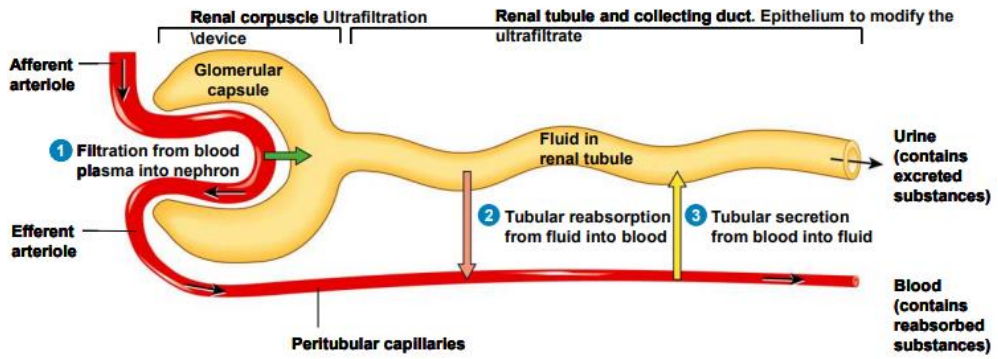
In patients with significant bleeding, cardiac output and renal perfusion decrease, leading to a reduction in GFR, which reduces the delivery of Na+, K+, Cl- and Ca+ to the distal tubule. This is detected by the macula densa, specialized sensory cells located in the distal tubule adjacent to the afferent arteriole (juxtaglomerular apparatus). In response, the macula densa activates two mechanisms:

- Dilation of the **afferent** arteriole to help restore GFR.
- Stimulation of juxtaglomerular (granular) cells to release **renin** into the bloodstream.

The Renin–Angiotensin–Aldosterone Cascade

Renin then acts on angiotensinogen from the liver, converting it into angiotensin I, which is further converted in the lungs by angiotensin-converting enzyme (ACE) into angiotensin II. Angiotensin II increases blood pressure and *preferentially constricts the efferent arteriole*, thereby increasing glomerular capillary pressure and helping maintain GFR, which is essential for continued elimination of waste products such as urea and creatinine.

Fluid Conservation & Peritubular Capillary Dynamics



At the same time, the body must conserve fluid during bleeding, so urine output decreases (e.g., from about 1.5 L/day ≈ 60 mL/hour to about 0.5 L/day ≈ 20 mL/hour).

Constriction of the efferent arteriole increases pressure within the glomerular capillaries while decreasing hydrostatic pressure and increasing oncotic pressure in the peritubular capillaries, these changes in the peritubular capillary environment (**low hydrostatic pressure + high oncotic pressure**) enhance reabsorption of water and solutes from the proximal tubule into the peritubular capillaries.

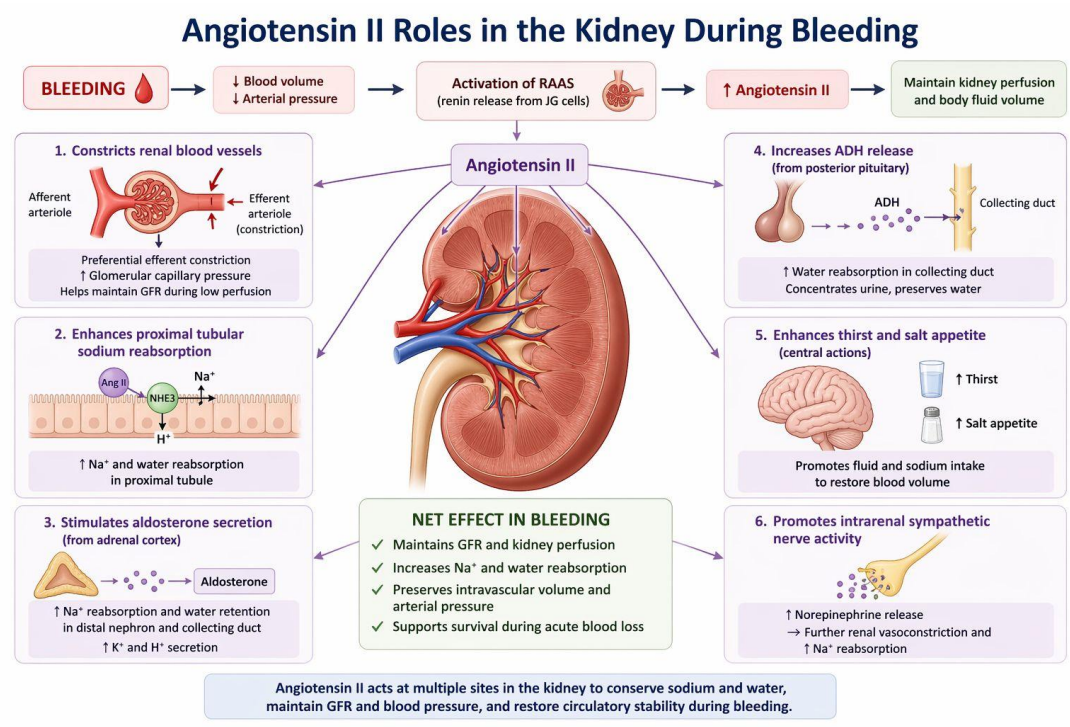
In addition, angiotensin II stimulates:

- Sodium reabsorption in the proximal tubule.
- Aldosterone secretion from the adrenal cortex (zona glomerulosa), which further increases sodium reabsorption in the distal tubule, with water following sodium osmotically due to the established osmotic gradient.

These coordinated mechanisms allow the body to **maintain GFR** while **reducing urine output** and conserving fluid during bleeding.

However, excessive constriction of the efferent arteriole can eventually decrease GFR, since vascular resistance is inversely proportional to the fourth power of the vessel radius, so only moderate constriction is beneficial.

📌 *additional figure.*



Emergency Management: IV Saline

In such cases of patients with significant bleeding, rapid administration of intravenous isotonic saline (0.9% NaCl) is essential to maintain intravascular volume and renal perfusion until definitive fluid or blood replacement is achieved, as delayed intervention may lead to circulatory collapse and organ damage.

NSAIDs & Renal Risk

Drugs such as NSAIDs (e.g., aspirin) inhibit prostaglandin synthesis and may cause constriction of the afferent arteriole, leading to a decrease in GFR and a rise in plasma creatinine levels, particularly in high-risk patients. Therefore, kidney function should be monitored by measuring **serum creatinine** and assessing trends relative to the patient's baseline, rather than relying on fixed values or arbitrary time intervals.

Interpreting Serum Creatinine

Normal serum creatinine ranges from approximately 0.7–1.2 mg/dL, but interpretation depends on the patient's baseline value and clinical context:

- An increase from 0.7 → 1.1 mg/dL over one month is clinically significant and suggests a possible decline in renal function, although it is not sufficient alone to diagnose kidney injury without further assessment of GFR and clinical status.
- A small change such as 0.7 → 0.8 mg/dL may still be within normal biological and laboratory variation and can be influenced by factors such as hydration status or dietary intake.

Clinically, kidney injury is better defined by relative changes from baseline (e.g., ≥1.5× increase in creatinine or a rise of ≥0.3 mg/dL within 48 hours) rather than small isolated differences within the normal range.

GFR, Age, Sex & Muscle Mass

📌 *The following table is not for memorization*

Age	GFR/1.73 m^2	
	Males	Females
20-29	94-140	72-110
30-39	59-137	71-121
40-49	76-120	50-102
50-59	67-109	50-102
60-69	54-98	45-75
70-79	49-79	37-61
80-89	30-60	27-55
90-99	26-44	26-42

- Muscle mass decreases with age, leading to reduced creatinine production, so serum creatinine levels may remain normal or even decrease despite a decline in GFR — which can mask underlying kidney dysfunction.
- Serum creatinine is strongly influenced by muscle mass, individuals with low muscle mass (e.g., elderly) may have normal or low serum creatinine despite reduced GFR, potentially masking kidney dysfunction.
- Conversely, individuals with high muscle mass (e.g., bodybuilders) may have higher serum creatinine without true impairment. Therefore, serum creatinine alone may be misleading across different body compositions and age groups.
    - For example, a serum creatinine of 0.8 mg/dL may be normal in a young adult but could underestimate impaired kidney function in an elderly female due to reduced muscle mass.

GFR Estimation Equations: 📌 *These equations are not required*

1. **MDRD Equation**

Used in adults with chronic kidney disease; does not include body weight and is less accurate at near-normal GFR levels.

$$GFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if female)$$

(Some versions include an additional correction factor for race.)

2. **Cockcroft–Gault Equation**, Estimates creatinine clearance (CrCl); accounts for body weight as an indirect measure of muscle mass.

$$CrCl = \frac{(140 - Age) \times Weight\ (kg) \times (0.85\ if female)}{72 \times SCr\ (mg/dL)}$$

3. **Schwartz Formula (Pediatric)**, Uses height as a surrogate for body size in children.

$$GFR = \frac{k \times Height\ (cm)}{SCr\ (mg/dL)}$$

Various validated equations — such as MDRD and CKD-EPI — are used in clinical practice to estimate GFR, incorporating factors such as age, sex, serum creatinine, and sometimes race, to improve accuracy. However, they do not fully account for individual variations in muscle mass.

Changes from V0 -> V1

- Page 9 ----- The paragraph on the relationship between creatinine and age has been removed, as it is already covered in Sheet 2.
- Page 10 ----- an additional explanatory note has been included in grey and GFR estimation equations are not required.