# Renal Physiology: Filtration, Transport, and Regulation

Andrew Bland, MD, FACP, FAAP

March 2026

## Renal Physiology: Filtration, Transport, and Regulation

### Learning Objectives

By the end of this module, you should be able to:

1. **Explain renal blood flow (RBF) and autoregulation** including myogenic and tubuloglomerular feedback mechanisms
2. **Calculate and understand GFR determinants** including Starling forces and glomerular surface area
3. **Describe tubular reabsorption by segment** from proximal tubule through collecting duct
4. **Understand countercurrent multiplier and countercurrent exchanger** mechanisms for urine concentration
5. **Integrate RAAS, ADH, and ANP regulation** in renal sodium and water handling
6. **Explain renal acid-base physiology** including renal net acid excretion, ammonia metabolism, and HCO3- handling

---

### I. Renal Blood Flow and Autoregulation

#### A. Renal Blood Flow (RBF)

**Overview:** - Renal blood flow: ~1000 mL/min (~20-25% of cardiac output) in resting state - Delivered to only ~0.4% of body weight (kidneys ~300 g of 70 kg body) - Remarkably high perfusion: 4 mL/min per gram kidney tissue

**Calculation of Effective Renal Plasma Flow (eRPF):** - eRPF = RBF × (1 - hematocrit) - Normal RBF ~1000 mL/min ☐ eRPF ~600 mL/min (at hematocrit 40%) - **Clearance concept:** eRPF measured via PAH (para-aminohippuric acid) clearance

**Oxygen Consumption and Metabolic Rate:** - Kidneys consume ~7% of total body $O_2$ (despite being only 0.4% of body weight) - High $O_2$ consumption reflects high metabolic activity (active transport in tubules) - Medulla has lower $O_2$ tension than cortex (metabolically vulnerable to ischemia) - Acute renal failure often results from medullary ischemia (ATN)

---

### B. Renal Vascular Resistance

**Resistances in Series:**

```
Afferent Resistance (Ra) → Glomerulus → Efferent Resistance (Re)
```

**Pressure Relationships:** - Renal perfusion pressure (RPP) typically ~100 mmHg (mean arterial pressure minus venous pressure) - Mean glomerular hydrostatic pressure (Pgg) ~45 mmHg (intermediate between afferent and efferent pressures) - Pressure drop across afferent arteriole ~50 mmHg - Pressure drop across efferent arteriole ~30 mmHg

**Resistance is proportional to vessel radius (Poiseuille's Law):**

$$R = \frac{8\eta L}{\pi r^4}$$

Where R = resistance, η = viscosity, L = length, r = radius

**Clinical significance:** - Afferent arteriole diameter ~20 μm; efferent ~15 μm (efferent smaller ☐ higher resistance) - Small changes in arteriolar tone dramatically affect resistance (radius raised to 4th power) - Vasoconstriction of afferent arteriole or vasodilation of efferent arteriole ☐ reduced GFR

---

### C. Autoregulation of Renal Blood Flow and GFR

**Definition:** Maintenance of relatively constant RBF and GFR despite changes in renal perfusion pressure.

**Normal Autoregulatory Range:** - **Renal perfusion pressure:** 80-180 mmHg - **RBF remains:** ~600-800 mL/min (±5-10% variation) - **GFR remains:** ~125 mL/min (±5-10% variation)

**Mechanisms of Autoregulation:**

#### 1. Myogenic Mechanism (Intrinsic)

*Principle:* Afferent arteriole smooth muscle responds directly to mechanical stretch.

*Mechanism:* - Increased renal perfusion pressure ☐ stretching of afferent arteriole wall - Stretch activates mechanoreceptor channels (TRPM4, TRPV4 — transient receptor potential channels) - $Ca^{2}$☐ influx ☐ smooth muscle contraction ☐ vasoconstriction - Reduced afferent diameter ☐ increased resistance ☐ restores pressure gradient - Decreased perfusion pressure ☐ opposite sequence ☐ vasodilation

*Timeline:* Occurs within seconds; immediate pressure compensation

*Molecular Details:* - Bayliss effect: Direct mechanical response of vascular smooth muscle to pressure - Involves L-type calcium channels and calcium-activated potassium channels - Requires intact afferent arteriole smooth muscle (absent in denervated kidneys)

---

### 2. Tubuloglomerular Feedback (TGF) Mechanism (Extrinsic)

*Principle:* Changes in distal tubular NaCl concentration feedback to regulate afferent arteriole tone.

*Anatomical Basis:* - **Juxtaglomerular apparatus (JGA):** Specialized region where thick ascending limb (TAL) contacts its own glomerulus - **Macula densa:** Specialized epithelial cells in thick ascending limb; NaCl sensors - **Granular cells:** Renin-secreting juxtaglomerular (JG) cells in afferent arteriole wall - **Extraglomerular mesangium:** Supporting cells

*Mechanism (High GFR scenario):*

```
Increased GFR
    ↓
Increased fluid delivery to TAL
    ↓
Increased NaCl reabsorption in TAL via NKCC2
    ↓
Increased intracellular Na⁺ and Cl⁻ in macula densa
    ↓
Increased basolateral Na⁺/K⁺–ATPase activity → hyperpolarization of cell membrane
    ↓
Decreased K⁺ channel activity (ROMK channels close)
    ↓
Membrane depolarization via paracellular pathway
    ↓
Increased intracellular Ca²⁺
    ↓
Release of ATP (and adenosine) from macula densa apical membrane
    ↓
Activation of purinergic receptors (A₁ adenosine receptors, P2Y₁ ATP receptors) on afferent arter
    ↓
Afferent arteriole VASOCONSTRICTION
    ↓
DECREASED GFR → equilibrium
```

*Mechanism (Low GFR scenario - opposite):* - Decreased NaCl delivery ☐ decreased macula densa [Na☐/Cl☐] - Increased renin release from JG cells - Angiotensin II formation ☐ afferent vasodilation + efferent vasoconstriction - GFR increases ☐ equilibrium

*Sensitivity:* - TGF responds to changes as small as 1-2 mEq/L change in luminal [NaCl] - Gain: ~0.4 (change in GFR is 40% of the stimulus that caused it) - Acts as a "brake" on GFR changes

*Time Course:* - Onset: Several seconds - Peak effect: ~20-30 seconds - Duration: Minutes (oscillatory; GFR exhibits spontaneous oscillations ~0.3-0.4 Hz due to TGF feedback loops)

---

## D. Additional Autoregulatory Mechanisms

### 1. Renin-Angiotensin System (RAS)

*Activated by:* - Decreased renal perfusion pressure (detected by juxtaglomerular cells) - Decreased distal tubular NaCl (via TGF) - Increased sympathetic nerve activity (β1-adrenergic receptors on JG cells)

*Effects of Angiotensin II:* - Afferent arteriole: MILD constriction - Efferent arteriole: STRONG constriction (preserves GFR during hypotension) - Mesangial contraction: Reduces glomerular surface area - Distal tubule: Increased NaCl reabsorption via ENaC and NCC - Collecting duct: Increased water reabsorption via ADH-stimulated aquaporin-2 - Net effect: Restores renal perfusion pressure and GFR; expands plasma volume

**2. Prostaglandins (PGE2, PGI2)**

*Actions:* - Afferent arteriole: VASODILATION - Mesangium: RELAXATION ☐ increased glomerular surface area - Distal tubule: Decreased NaCl reabsorption

*Triggers:* - Macula densa activation (high NaCl) ☐ COX-mediated PG synthesis - Acts as counter-regulatory to TGF vasoconstriction

*Clinical Significance:* - NSAIDs block COX ☐ block PG synthesis ☐ loss of afferent vasodilation ☐ acute renal failure in dehydrated patients - Particularly dangerous in patients already on ACEi (combined RAS blockade + loss of PG vasodilation)

**3. Nitric Oxide (NO)**

*Actions:* - Afferent arteriole: VASODILATION - Endothelial function: Maintains vascular homeostasis - Glomerular hemodynamics: Increases Pgg and GFR

*Sources:* - Constitutive endothelial nitric oxide synthase (eNOS) in endothelium - Inducible NOS (iNOS) in response to inflammation

*Pathophysiology:* - Loss of NO bioavailability ☐ endothelial dysfunction ☐ vasoconstriction ☐ CKD progression - Seen in hypertension, diabetes, atherosclerosis, aging

---

**E. Integrated Response to Hypotension and Hypertension**

**In Hypotension (e.g., hemorrhage, dehydration):**

1. **Immediate:** Myogenic vasodilation of afferent arteriole (pressure drop sensed)
2. **Seconds:** TGF-mediated renin release (low distal delivery)
3. **Minutes:** RAAS activation ☐ Ang II constricts efferent arteriole ☐ preserves Pgg despite low systemic pressure
4. **Result:** GFR maintained near-normal; plasma volume expanded via sodium/water retention

**In Hypertension (e.g., essential hypertension):**

1. **Immediate:** Myogenic vasoconstriction (pressure elevation sensed)
2. **Minutes:** Increased GFR due to hypertension-induced afferent vasodilation (pressure wave transmitted)
3. **Hours:** Increased sodium and water excretion (pressure natriuresis) ☐ blood pressure normalization

4. **Result:** “Self-limiting” autoregulation; kidneys adjust sodium excretion to match intake at the elevated pressure

**Break-Through in Hypertension:** - In severe hypertension, autoregulatory mechanisms are overwhelmed - Arteriolar necrosis occurs (acute arteriolitis/arteriolar necrosis) - Result: “Acute kidney injury” with sclerosis of remaining glomeruli - Seen in malignant hypertension, preeclampsia, scleroderma renal crisis

---

## II. Glomerular Filtration Rate (GFR)

### A. Definition and Measurement

**GFR Definition:** Volume of plasma filtered from glomeruli into Bowman’s space per unit time.

**Normal GFR:** - Adult: 120-130 mL/min (~100 mL/min/1.73 m² when normalized to body surface area) - Slightly lower in females (~110 mL/min) and elderly - Declines with age (~10 mL/min/decade after age 30)

**Clinical GFR Measurement:**

*Ideal Filtration Marker Criteria:* - Freely filtered at glomerulus (no restriction by size/charge) - Not reabsorbed by tubules - Not secreted by tubules - Not metabolized by kidney - Does not affect GFR - Measured accurately and inexpensively

*Gold Standard: Inulin Clearance* - Polysaccharide; meets all criteria - Clearance = (Uinulin × Vurine) / Pinulin - Rarely used clinically (requires infusion; expensive)

*Clinical Surrogates:* - **Creatinine clearance:** Overestimates GFR (~20%) due to tubular secretion - **Estimated GFR (eGFR) from serum creatinine:** KDIGO 2021 equation - eGFR = 142 × (Scr/0.7)^(-0.9) × (0.9)^age [if female; add 1.018 multiplier] - Where Scr = serum creatinine (mg/dL) - More accurate than MDRD equation; accounts for non-creatinine factors - **Cystatin C:** Less affected by muscle mass; emerging gold standard - **eGFR from combined Scr and Cystatin C:** Increasingly recommended (more accurate than either alone)

---

### B. Determinants of GFR (Starling Forces)

**GFR is determined by the net ultrafiltration pressure (NFP) and the glomerular filtration coefficient:**

$$\text{GFR} = K_f \times \text{NFP}$$

Where: - Kf = filtration coefficient (surface area × permeability) - NFP = net ultrafiltration pressure

**Net Ultrafiltration Pressure:**

$$\text{NFP} = (P_{gg} - P_{bc}) - (\pi_{gg} - \pi_{bc})$$

Where: - **Pgg** = glomerular hydrostatic pressure (~45 mmHg; variable along capillary) - **Pbc** = Bowman's capsule hydrostatic pressure (~10 mmHg) - **πgg** = glomerular plasma oncotic pressure (~25 mmHg at afferent end; ~35 mmHg at efferent end) - **πbc** = Bowman's capsule oncotic pressure (~0-2 mmHg; ultrafiltrate is protein-free)

**At Afferent End:** - NFP = (45 - 10) - (25 - 0) = +10 mmHg - Net filtration pressure is positive ☐ active filtration

**At Efferent End (Filtration Equilibrium):** - NFP = (45 - 10) - (35 - 0) = 0 mmHg (approximately) - Net filtration pressure approaches zero ☐ filtration slows/stops - Plasma oncotic pressure has risen due to protein concentration (water loss)

---

### C. Factors Affecting GFR

**Increase GFR:** 1. **Increased Pgg:** Afferent dilation, efferent constriction, increased blood pressure 2. **Decreased πgg:** Lower plasma protein (unusual; requires severe hypoproteinemia) 3. **Decreased Pbc:** Ureteral obstruction relief 4. **Increased Kf:** Glomerular vasodilation, increased surface area

**Decrease GFR:** 1. **Decreased Pgg:** Afferent constriction, efferent dilation, decreased blood pressure 2. **Increased πgg:** Higher plasma protein (dehydration, hemoconcentration) 3. **Increased Pbc:** Urinary obstruction (hydronephrosis) 4. **Decreased Kf:** Glomerular sclerosis, proteinuria ☐ loss of slit diaphragm selectivity

**Clinical Triggers for GFR Reduction:** - Volume depletion: RAAS activation ☐ efferent constriction preserves GFR - Sepsis: Decrease in systemic vascular resistance ☐ hypotension ☐ afferent constriction ☐ GFR drop - NSAIDs: Block prostaglandin-mediated afferent vasodilation ☐ GFR drop - ACE inhibitors: Block Ang II-mediated efferent constriction ☐ GFR drop (especially if hypotensive) - Hepatic cirrhosis: Splanchnic vasodilation ☐ renal vasoconstriction ☐ prerenal azotemia

---

## III. Tubular Reabsorption and Secretion

### A. Proximal Convoluted Tubule (PCT)

**Reabsorption in PCT:** - ~65% of filtered water - ~65% of filtered sodium and chloride - ~99-100% of glucose (SGLT2, SGLT1 cotransporters) - ~99-100% of amino acids - ~60% of potassium (paracellular) - ~90% of $HCO_3^-$ ($H^+$ secretion in exchange)

**Transport Mechanisms:**

*Primary Active Transport (ATP-dependent):* - **Basolateral $Na^+/K^+$-ATPase:** Pumps 3 $Na^+$ out, 2 $K^+$ in; creates low intracellular [$Na^+$] - Provides driving force for secondary active transport

*Secondary Active Transport (coupled to $Na^+$ gradient):* - **SGLT2 (sodium-glucose cotransporter):** Apical; high Km (15 mM); reabsorbs ~90% of glucose - **SGLT1:** Apical; lower Km; reabsorbs remaining ~10% of glucose - **PEPT1/PEPT2:** Peptide-proton cotransporters; reabsorb di- and tripeptides - **Amino acid transporters:** Apical IMINO transporters and others - **$Na^+/H^+$ exchanger (NHE3):** Apical; secretes $H^+$, reabsorbs $Na^+$; critical for $HCO_3^-$ reabsorption

*Facilitated Diffusion:* - **GLUT1:** Basolateral; allows glucose exit from cell - **Aquaporin-1:** Apical and basolateral; constitutive water channel (not regulated)

*Paracellular Transport:* - **Tight junctions (claudins):** Allow paracellular cation movement - Driving forces: Osmotic (water loss) and electrical (lumen-positive potential) - Reabsorbs ~60% of K□, $Mg^{2}$□, $Ca^{2}$□

**Organic Anion and Cation Secretion:**

*Basolateral Entry:* - **Organic anion transporters (OAT 1, 3):** Antiporter; α-ketoglutarate in, organic anion out - **Organic cation transporters (OCT 1, 2):** Antiporter; H□ in, organic cation out

*Apical Exit:* - **Organic anion transporters (OAT 4):** Urate, prostaglandins, others - **Organic cation transporters (OCT 2):** Creatinine, cimetidine, others

**Secreted Substances (beyond glomerular filtration):** - Penicillin, probenecid, salicylate (organic anion secretion) - Creatinine, cimetidine, morphine (organic cation secretion) - Hydrogen ions ($HCO_3$- reabsorption) - Ammonium ($NH_4$+; ammonia metabolism)

**Clinical Applications:** - **Creatinine clearance » inulin clearance** □ significant tubular secretion (20% of creatinine clearance is secretion) - **Probenecid blocks secretion** □ reduces urate excretion (prevents gout) by blocking OAT1 - **Penicillin competed for secretion** □ increased plasma levels when probenecid is co-administered

---

**B. Loop of Henle (Descending and Ascending Limbs)**

**Descending Thin Limb (DTL):** - Permeable to water; impermeable to NaCl - ~25% of filtered water reabsorbed passively - Osmolarity increases as fluid descends (following osmotic gradient)

**Ascending Thin Limb (ATL):** - Impermeable to water; permeable to NaCl - ~25% of filtered NaCl reabsorbed passively - NaCl reabsorption dilutes tubular fluid

**Thick Ascending Limb (TAL):**

*Transport Mechanisms:* - **Na-K-2Cl cotransporter (NKCC2) — apical:** Active transport; symporter - Driven by Na□ gradient created by basolateral Na□/K□-ATPase - Reabsorbs 1 Na□ + 1 K□ + 2 Cl□ in one turnover - **K□ recycling via apical ROMK:** K□ secreted into lumen; recycled to drive NKCC2 - **Cl□ exit via basolateral ClC-Kb:** Exits cell via chloride channel - **Na□ exit via basolateral Na□/K□-ATPase:** Extrudes Na□ in exchange for K□

*Characteristics:* - **Reabsorbs ~25% of filtered NaCl** (major site of salt reabsorption) - **Impermeable to water** □ obligate dilution despite osmolyte removal - **Generates positive charge in lumen** (K□ recycling creates positive potential) □ drives paracellular cation reabsorption ($Ca^{2}$□, $Mg^{2}$□) - **Creates osmotic gradient** □ medullary hypertonicity (up to 1200 mOsm/kg in papilla)

*Clinical Significance:* - **Loop diuretics (furosemide, torsemide):** Block NKCC2 □ massive polyuria, hypokalemia, dehydration - **Bartter syndrome:** Genetic defects in NKCC2, ROMK, or CLC-Kb □ hypokalemic metabolic alkalosis, polyuria - **Gitelman syndrome:** (DCT) similar but with hypomagnesemia

---

**C. Distal Convoluted Tubule (DCT)**

**Early DCT (DCT1) — NaCl Reabsorption:**

*Transport:* - **Na-Cl cotransporter (NCC) — apical:** Thiazide-sensitive - Reabsorbs remaining filtered NaCl (~5-10%) - Water impermeable segment (continues dilution)

**Late DCT (DCT2) and Collecting Duct Interface — Selective Reabsorption:**

*Principal Cell Transport:* - **Epithelial Na☐ channel (ENaC) — apical:** Aldosterone-regulated - Reabsorbs ~2-3% of filtered Na☐ (fine-tuning) - Driven by Na☐ gradient and negative lumen potential - Creates electrical potential ☐ drives K☐ secretion

*Intercalated Cell Transport:* - **Type A:** H☐-ATPase; HCO3- reabsorption; urine acidification - **Type B:** HCO3- secretion (alternative path for base excretion)

---

**D. Collecting Duct (CD)**

**Principal Cells:**

*Sodium Reabsorption:* - ENaC on apical membrane (aldosterone-regulated) - Reabsorbs final 1-2% of filtered Na☐ - Water reabsorption via aquaporin-2 (ADH-regulated) - K☐ secretion driven by negative lumen potential and aldosterone

*Water Permeability Regulation:* - **ADH (vasopressin) mechanism:** 1. ADH binds V2 receptor on basolateral membrane 2. Activates Gs protein ☐ ☐ cAMP 3. PKA activation ☐ phosphorylates aquaporin-2 4. Aquaporin-2 translocates from intracellular vesicles to apical membrane 5. Water permeability increases from <0.1% to >80% of filtrate 6. Urine becomes concentrated (osmolarity up to 1200 mOsm/kg)

- **Without ADH:**
  - Aquaporin-2 internalized
  - Water impermeability maintained
  - Dilute urine produced (~50 mOsm/kg)

**Intercalated Cells:**

*Acid-Base Handling:* - Type A: H☐-ATPase (apical) ☐ H☐ secretion, HCO3- reabsorption (aciduria) - Type B: HCO3- secretion via AE1 (apical anion exchanger) and H☐-ATPase (basolateral)

*Regulation:* - pH: Acidemia ☐ ☐ Type A; ☐ H☐ secretion - K☐ status: Hypokalemia ☐ ☐ Type A intercalated cells, ☐ ammonia synthesis

---

**E. Summary of Reabsorption and Secretion Pathways**

| Segment | Na□ | K□ | Cl□ | HCO3- | H2O | Glucose | Notes |
|---|---|---|---|---|---|---|---|
| **PCT** | 65% | 60% | 65% | 85-90% | 65% | 99% | Active; organic secretion |
| **DTL** | 0% | 0% | 0% | 0% | 25% | 0% | Passive water; dilution |
| **ATL** | 0% | 0% | 25% | 0% | 0% | 0% | Passive NaCl; dilution |
| **TAL** | 25% | (+recycled) | 25% | 0% | 0% | 0% | Active; osmotic gradient |
| **DCT** | 5-10% | secretion | 5-10% | minimal | regulated | 0% | Fine-tuning; regulated |
| **CD** | 1-3% | secretion | minimal | variable | regulated | 0% | ADH/aldosterone regulated |
| **TOTAL** | 99% | balance | 99% | 100% | 99% | 100% | |

---

## IV. Countercurrent Multiplier and Urine Concentration

### A. Countercurrent Multiplier (TAL)

**Concept:** The thick ascending limb (TAL) actively pumps NaCl into interstitium, creating osmotic gradient without water reabsorption (water-impermeable).

**Mechanism:**

*Step 1 — TAL NaCl Reabsorption:* - NKCC2 pumps NaCl out □ interstitium [Na□ Cl□] increases - TAL is water-impermeable □ dilution (not osmolarity increase, but relative removal of solutes) - Tubular fluid becomes hypotonic (~100 mOsm/kg) - Interstitium becomes hypertonic (~1200 mOsm/kg in papilla)

*Step 2 — DTL Water Movement:* - DTL is water-permeable; follows osmotic gradient - Water moves OUT of tubule into hypertonic interstitium - Tubular fluid osmolarity increases (becomes more concentrated)

*Step 3 — ATL Passive NaCl Movement:* - ATL is NaCl-permeable; follows concentration gradient - NaCl moves OUT of tubule into hypotonic medullary interstitium - Tubular fluid becomes dilute

*Step 4 — Recycling:* - Vasa recta countercurrent exchanger removes excess solute + water - Maintains medullary gradient

**Net Effect:** - Medullary osmolarity gradient: ~300 mOsm/kg (cortex) □ 500 mOsm/kg (outer medulla) □ 1200 mOsm/kg (papilla) - Collecting duct can produce urine up to 1200 mOsm/kg (equilibrates with papillary interstitium when ADH present)

---

### B. Countercurrent Exchanger (Vasa Recta)

**Function:** Prevents dissipation of medullary osmotic gradient created by countercurrent multiplier.

**Mechanism:**

*Descending Vasa Recta:* - Receives blood from efferent arteriole (~300 mOsm/kg plasma oncotic pressure) - Descends into medulla; osmolarity of interstitium increases (300 ☐ 1200 mOsm/kg) - Plasma is hypotonic relative to interstitium ☐ water moves OUT, solutes move IN - Blood osmolarity increases as it descends (becomes more concentrated)

*Ascending Vasa Recta:* - Osmolarity is high (~1200 mOsm/kg) - As it ascends, interstitial osmolarity DECREASES (1200 ☐ 300 mOsm/kg) - Blood is hypertonic relative to interstitium ☐ water moves IN, solutes move OUT - Blood osmolarity decreases as it ascends (becomes more dilute) - Returns to cortex at ~300 mOsm/kg (similar to entry osmolarity)

**Net Result:** - Solutes deposited in medulla are recirculated but not removed entirely - Gradient is maintained despite continuous blood flow - Efficiency: ~95% of solutes deposited by TAL are retained; 99% of water is excreted

**Clinical Loss of Vasa Recta:** - Chronic pyelonephritis: Destruction of medulla ☐ loss of vasa recta ☐ polyuria despite normal ADH - Papillary necrosis: Loss of vasa recta and collecting duct tips ☐ inability to concentrate urine

---

## V. Renal Sodium and Water Regulation

### A. RAAS (Renin-Angiotensin-Aldosterone System)

**Activation:**

*Juxtaglomerular Cell Triggers:* 1. Decreased renal perfusion pressure (primary sensor) 2. Decreased distal tubular NaCl (via TGF mechanism) 3. Increased sympathetic nerve activity (β1-adrenergic receptors)

**Renin Synthesis and Release:**

*Juxtaglomerular Cells:* - Synthesize prorenin (inactive precursor) - Store renin in secretory granules - Release renin in response to above triggers

*Renin Half-life:* ~15 minutes (inactive after)

**Angiotensinogen ☐ Angiotensin I:** - Liver produces angiotensinogen - Renin cleaves decapeptide ☐ angiotensin I

**Angiotensin I ☐ Angiotensin II:** - Angiotensin-converting enzyme (ACE) in lungs (capillary endothelium) - Cleaves dipeptide ☐ angiotensin II (octapeptide) - ACE also degrades bradykinin (reduces vasodilation)

**Angiotensin II Effects:**

*Renal Effects:* - Afferent arteriole: MILD constriction (pressure-maintaining) - Efferent arteriole: STRONG constriction (GFR-preserving in hypotension) - Mesangial contraction: Reduces glomerular surface area - Proximal tubule: Increased NaCl reabsorption via enhanced Na☐/H☐

exchange - Collecting duct (direct): Enhanced water reabsorption - Renin release inhibition (negative feedback)

*Systemic Effects:* - Increased vasomotor tone (vasoconstriction) - Increased aldosterone secretion - Enhanced ADH secretion (osmolarity-independent) - Increased sympathetic activation (CNS and peripheral) - Thirst stimulation

**Angiotensin II at Different Blood Pressures:** - **At low BP:** Efferent » afferent constriction ☐ maintains Pgg despite low systemic pressure ☐ preserves GFR - **At normal BP:** Preferential efferent constriction still occurs (fine-tuning salt/water) - **At high BP:** Loss of preferential efferent effect in some tissues; systemic vasoconstriction dominates

---

**B. Aldosterone**

**Source:** Zona glomerulosa of adrenal cortex

**Triggers:** 1. **Angiotensin II** (primary) 2. **Hyperkalemia** (potent direct effect on zona glomerulosa) 3. **ACTH** (minor; increases sensitivity to Ang II)

**Mechanism of Action:**

*Mineralocorticoid Receptor (MR) in Principal Cell:* 1. Aldosterone crosses cell membrane 2. Binds cytoplasmic mineralocorticoid receptor (MR) 3. MR-aldosterone complex translocates to nucleus 4. Binds to hormone response elements (HREs) on DNA 5. Increases transcription of: - **ENaC:** Increases apical sodium channel expression - **Na☐/K☐-ATPase:** Increases basolateral pump - **Serum and glucocorticoid-regulated kinase (SGK1):** Phosphorylates proteins; prevents ENaC degradation

**Effects on Collecting Duct:** - Increased Na☐ reabsorption (via ENaC) - Increased K☐ secretion (electrical consequence of Na☐ reabsorption) - Increased H☐ secretion (via Type A intercalated cells)

**Time Course:** - Onset: 30 minutes to 1 hour (gene transcription) - Peak: 4-6 hours - Duration: 1-3 days (mRNA stability)

**Regulation of Aldosterone:** - **Suppressed by:** Hypernatremia (inhibits; rare stimulus), plasma volume expansion, natriuretic peptides, dopamine - **Stimulated by:** Hypokalemia (independent of Ang II), ACTH, Ang II

---

**C. ADH (Antidiuretic Hormone, Vasopressin)**

**Source:** Posterior pituitary (released from magnocellular neurons of supraoptic and paraventricular nuclei)

**Primary Stimulus:** - **Plasma osmolarity:** Osmoreceptors in hypothalamus (subfornical organ, organum vasculosum) - Threshold: ~280-290 mOsm/kg - Linear increase: +1% ADH for every 1 mOsm/kg increase above threshold

**Secondary Stimuli (Non-osmotic):** 1. **Hypovolemia:** Baroreceptor activation; ~10% volume loss threshold 2. **Hypotension:** Powerful stimulus (>50 mmHg drop) 3. **Nau-**

**sea/vomiting:** Chemoreceptor activation 4. **Stress:** Psychological, physical trauma, pain 5. **Hypoxemia:** <60 mmHg $O_2$ tension

**Mechanism of Action in Collecting Duct:**

*V2 Receptor (Basolateral Membrane):* 1. ADH binds V2 receptor (AVPR2 gene) 2. Activates Gs ☐ ☐ adenylyl cyclase ☐ ☐ cAMP 3. cAMP activates PKA (protein kinase A) 4. PKA phosphorylates aquaporin-2 (AQP2) 5. Phosphorylated AQP2 translocates from intracellular vesicles to apical membrane 6. Water permeability increases dramatically

**Water Reabsorption:** - **With ADH:** Aquaporin-2 in apical membrane; aquaporin-3/4 in basolateral membrane - Water reabsorption: ~80% of collecting duct fluid - Urine osmolarity: ~1000-1200 mOsm/kg - Urine volume: ~0.5-1 L/day - Plasma osmolarity: 280-290 mOsm/kg (maintained at set-point)

- **Without ADH:** No aquaporin-2 in apical membrane
  - Water reabsorption: <10% of collecting duct fluid
  - Urine osmolarity: ~50 mOsm/kg (maximally dilute)
  - Urine volume: up to 20 L/day
  - Plasma osmolarity rises unless high water intake

**Time Course:** - Onset: Minutes (receptor binding and cAMP generation) - Peak: 10-20 minutes - Duration: 15-20 minutes (metabolized; T½ ~10 minutes)

**Regulation of ADH:** - **Suppressed by:** Hypoosmolarity (osmoreceptor inhibition), hypervolemia, alcohol, nicotine - **Stimulated by:** Hyperosmolarity, hypovolemia, hypotension, nausea

---

**D. Atrial Natriuretic Peptide (ANP) and Natriuretic Peptide System**

**Source:** - **ANP:** Atrial myocytes (released in response to atrial stretch from volume expansion) - **BNP:** Ventricular myocytes (heart failure, volume overload) - **CNP:** Vascular endothelium (local vascular effects)

**Mechanism of Action:**

*Natriuretic Peptide Receptor-A (NPR-A) — guanylate cyclase-linked:* 1. ANP binds NPR-A (coupled to guanylate cyclase) 2. Increases cGMP 3. cGMP-dependent protein kinase (PKG) activation 4. Phosphorylates and inhibits: - TRPC6 channels (reduced podocyte contraction) - Phosphodiesterase-5 (increased cGMP) - Ion channels in collecting duct principal cells (reduces ENaC activity)

**Effects on the Kidney:**

*Glomerular Hemodynamics:* - Afferent arteriole: VASODILATION (increases GFR) - Efferent arteriole: VASOCONSTRICTION (modest; partially offsets afferent dilation) - Mesangium: RELAXATION (increases glomerular surface area) - **Net effect:** Increased GFR (☐ Kf, ☐ Pgg)

*Tubular Effects:* - Collecting duct principal cells: Inhibited ENaC ☐ decreased Na☐ reabsorption ☐ increased Na☐ excretion - Inhibits renin release (opposes RAAS) - Inhibits aldosterone secretion (opposes volume expansion)

*ADH Suppression:* - Hypervolemia reduces osmolarity perception ☐ ADH suppression - ANP directly inhibits ADH release (hypothalamic neurons)

**Physiologic Effects:** - ☐ GFR - ☐ Proximal tubule reabsorption (direct effect) - ☐ Collecting duct reabsorption (ENaC inhibition) - ☐ Aldosterone secretion - **Net:** Marked natriuresis and diuresis (fluid volume reduction)

**Time Course:** - Onset: Minutes (receptor binding, cGMP generation) - Duration: 15-20 minutes (C-type natriuretic peptide receptor-C; clearance receptor; C-type ANP receptor degrades ANP)

**Clinical Correlates:** - **Heart failure:** Markedly elevated BNP (>400 pg/mL diagnostic; indicates ventricular strain) - **Acute decompensated heart failure:** ANP + BNP infusion considered therapeutic (nesiritide) - **Nephrotic syndrome:** ANP resistance; despite volume expansion, ANP levels paradoxically low (abnormal clearance or blunted response)

---

## VI. Renal Acid-Base Physiology

### A. Overview of Acid-Base Balance

**pH Maintenance:** The kidneys maintain plasma pH in a narrow range (7.35-7.45) by: 1. **Reabsorbing filtered $HCO_3^-$** (virtually 100% reabsorbed under normal conditions) 2. **Excreting excess acid** as titrable acid and ammonia 3. **Producing new $HCO_3^-$** to replace buffered acid

**Net Acid Excretion (NAE):**

$$\text{NAE} = \text{TA} + (\text{NH}_4^+ \text{ excretion}) - (\text{HCO}_3^- \text{ excretion})$$

Where: - TA = titrable acid ($H^+$ buffered by urinary phosphate, other weak bases) - Normal NAE = 0.5-1.0 mEq/kg/day (equals daily acid load)

---

### B. Proximal Tubule Acid-Base Handling

**$HCO_3^-$ Reabsorption (85-90% of filtered load):**

*Mechanism:* 1. **$H^+$ secretion** via Na☐/H☐ exchanger (NHE3) in apical membrane 2. **$H^+$ + $HCO_3^-$** ☐ $H_2CO_3$ (in tubular lumen) 3. **Carbonic anhydrase (CA IV)** on brush border ☐ $H_2O$ + $CO_2$ (rapid) 4. **$CO_2$ diffuses** into proximal tubule cell 5. **Inside cell:** $CO_2 + H_2O$ ☐ $H_2CO_3$ ☐ $H^+ + HCO_3^-$ 6. **$HCO_3^-$ exits** via basolateral $HCO_3^-$/Cl- exchanger (AE2) 7. **$H^+$ recycled** via NHE3 apical pump

*Regulation:* - **Increased by:** Alkalemia, volume depletion (Ang II), hypocapnia - **Decreased by:** Acidemia, volume expansion, hypercapnia

**Phosphate Buffering in PCT:** - $H^+$ secretion also titrates urinary phosphate ($HPO_4^{2-}$☐ ☐ $H_2PO_4$☐) - Phosphate becomes “unavailable” for new base formation (buffered $H^+$ cannot be reclaimed)

---

### C. Loop of Henle and Distal Tubule

**No direct HCO3- reabsorption** in these segments (water-impermeable or diluting segments limit HCO3- reabsorption).

**TAL and DCT:** Participate in establishing tubular fluid composition but not major acid-base sites.

---

### D. Collecting Duct Acid-Base Handling

**Type A (α) Intercalated Cells — H+ Secretion and HCO3- Reabsorption:**

*Mechanism:* 1. **Basolateral Na□/HCO3- cotransporter (NBC1)** brings HCO3- into cell (net removal from lumen concept) 2. **Apical H+-ATPase** (vacuolar-type ATPase; V-ATPase) secretes H+ into lumen 3. **H+ + HCO3-** □ H2CO3 □ H2O + CO2 (in lumen; non-specific) 4. **H+ also titrates ammonia:** H+ + NH3 □ NH4+ (trapped in lumen)

*Function:* - Reabsorbs HCO3- not reabsorbed by proximal tubule - Produces acidic urine (pH can drop to 4.5-5.0) - Excretes "new HCO3-" generated from ammonia metabolism

*Regulation:* - **Increased by:** Acidemia, hypokalemia - **Decreased by:** Alkalemia, hyperkalemia

**Type B (β) Intercalated Cells — HCO3- Secretion:**

*Mechanism:* 1. **Apical anion exchanger (AE1)** secretes HCO3- into lumen in exchange for Cl□ 2. **Basolateral H□-ATPase** extrudes H+ (not shown; alternative model under debate)

*Function:* - Excretes excess HCO3- (when alkalemia present) - Produces alkaline urine (pH ~8-9)

*Regulation:* - **Increased by:** Alkalemia, hyperkalemia - **Decreased by:** Acidemia, hypokalemia

---

### E. Ammonia Metabolism and Ammoniagenesis

**Ammonia Source:** - **Glutamine** (primary source): Proximal tubule glutaminase converts glutamine □ glutamate + NH3 - **Glycine:** Minor source - **Histidine:** Minor source

**Regulation of Ammonia Production:** - **Enhanced by:** Acidemia (increased glutaminase expression; chronic adaptation) - **Suppressed by:** Alkalemia

**Ammonia Fate:**

*In Proximal Tubule:* 1. **Glutaminase:** Glutamine □ glutamine + NH3 2. **NH3 crosses** into tubular lumen (passive diffusion; lipid-soluble) 3. **In lumen (low pH):** NH3 + H+ □ **NH4+** (trapped; cannot diffuse back)

*In Distal Tubule/Collecting Duct:* 1. **Type A intercalated cells:** H+ secretion traps NH3 as NH4+ 2. **NH4+ excreted** in urine (cannot cross cell membrane)

**Net Acid Excretion via Ammonia:** - Normal: 0.5-1.0 mEq/kg/day - In acidemia: Can increase to 3-4 mEq/kg/day (chronic adaptation; takes 4-7 days to fully develop) - Important for chronic respiratory or metabolic acidosis compensation

---

### F. Titrable Acid (TA) Excretion

**Definition:** H+ buffered by urinary weak acids (phosphate, sulfate, other organic acids).

**Phosphate Buffering:** - **Filtered phosphate:** $HPO_4^{2-}$ (main species at physiologic pH) - **In urine:** $H^+ + HPO_4^{2-} \rightarrow \mathbf{H_2PO_4^-}$ (titrable acid) - Amount excreted depends on: - Urine pH (lower pH → more $H_2PO_4^-$ formation) - Urinary phosphate concentration (dietary intake)

**Sulfate Buffering:** - Sulfate from methionine/cysteine metabolism - $H^+ + SO_4^{2-} \rightarrow \mathbf{HSO_4^-}$ (weak buffering)

**Other Organic Acids:** - Lactate, β-hydroxybutyrate (ketones), creatinine, urate - Contribute to titrable acid load

**TA Excretion Under Different Conditions:** - **Normal:** 20-40 mEq/day - **Acidemia:** Increases to 50-100 mEq/day (via increased H+ secretion, lower urine pH) - **Alkalemia:** Decreases (H+ secretion suppressed)

---

## VII. Clinical Pearl Highlights

**Key Integrated Concepts:**

1. **GFR is tightly autoregulated over a 50 mmHg range** (80-180 mmHg), allowing kidneys to maintain function despite blood pressure variations.
2. **The RAAS and sympathetic nervous system are activated in parallel** during volume depletion, both promoting sodium retention and vasoconstriction.
3. **Efferent arteriole constriction by Ang II preserves GFR during hypotension** — this is why ACE inhibitors can precipitate acute kidney injury in dehydrated patients.
4. **Countercurrent multiplier and exchanger are two sides of the same coin** — TAL creates gradient; vasa recta preserves it.
5. **ADH produces concentrated urine; ANP produces dilute urine** — opposite effects on collecting duct water permeability and sodium reabsorption.
6. **Proximal tubule reabsorbs 65% of filtered sodium and water** — changes here have major impact on distal delivery and balance.
7. **TAL is the "diluting segment"** — reabsorbs salt without water, enabling production of dilute urine despite high medullary osmolarity.
8. **Ammonia metabolism is a critical acid disposal mechanism** — especially important in chronic metabolic and respiratory acidosis (can increase excretion 4-fold).
9. **Glomerulotubular balance maintains proportional reabsorption** despite changes in GFR — prevents excessive fluid loss when GFR rises.
10. **NSAIDs acutely reduce GFR by blocking prostaglandin-mediated afferent vasodilation** — dangerous in volume-depleted patients or those on ACEi/ARB.

---

## VIII. Practice Questions

**Question 1:** A 64-year-old man with uncontrolled hypertension (BP 168/104 mmHg) is found to have a serum creatinine of 1.8 mg/dL (previously 1.0). He is not on any antihypertensive medications. His urinalysis shows 2+ proteinuria.

Over the following 2 weeks, blood pressure is controlled to 130/80 mmHg with lisinopril. Serum creatinine increases to 2.1 mg/dL. Which of the following best explains this acute rise in serum creatinine?

A) Lisinopril is contraindicated in hypertensive patients; it worsens kidney function
B) Ang II-mediated efferent arteriole constriction was preserving GFR; ACEi blocks this, reducing Pgg
C) Increased renal perfusion pressure from antihypertensive therapy damages the glomeruli
D) Lisinopril blocks aldosterone, preventing sodium reabsorption and reducing plasma volume

**Answer: B).** The acute rise in creatinine (GFR decline) after ACEi initiation reflects loss of Ang II-mediated efferent arteriole constriction. Before ACEi, the patient had hypertension-related glomerular damage (2+ proteinuria), and his efferent arteriole was constricted to preserve GFR (Pgg maintenance) despite proteinuria. When ACEi is started, efferent constriction is lost ☐ Pgg decreases ☐ GFR drops. However, this is expected and often represents "unmasking" of underlying disease rather than true worsening. Continued therapy prevents progressive fibrosis.

---

**Question 2:** A 35-year-old woman with diabetes mellitus presents with polyuria (3 L/day) and polydipsia. Her serum glucose is 450 mg/dL and serum osmolarity is 320 mOsm/kg. Urine osmolarity is 250 mOsm/kg.

Which of the following best explains the low urine osmolarity in the setting of hyperglycemia and hyperosmolarity?

A) Aldosterone deficiency prevents sodium reabsorption in the collecting duct
B) Osmotic diuresis from glycosuria overwhelms ADH effects; osmolytes (glucose) exit before water can be reabsorbed
C) Hyperglycemia directly inhibits aquaporin-2 expression in the collecting duct
D) Central diabetes insipidus from hyperglycemia-induced hypothalamic damage

**Answer: B).** The high serum osmolarity should stimulate ADH release and produce concentrated urine. However, high urinary glucose (osmotically active) in the collecting duct creates an osmotic gradient that OPPOSES water reabsorption. Glucose is "osmotically active" in the tubule ☐ water follows glucose into urine rather than being reabsorbed by ADH action. This is osmotic diuresis. Expected urine osmolarity in this setting should be higher, but glucose osmolarity pulls water out, preventing concentration. As serum glucose drops with insulin therapy, urine will concentrate appropriately.

---

**Question 3:** A 55-year-old man with CKD stage 3b (eGFR 35 mL/min) develops severe dehydration from gastroenteritis. His blood pressure drops from 135/85 to 110/70 mmHg. Serum creatinine rises from 1.8 to 2.4 mg/dL.

Which mechanism is primarily responsible for preserving GFR (preventing a more dramatic creatinine rise) despite the drop in blood pressure?

A) Increased vasopressin secretion increases glomerular hydrostatic pressure
B) Decreased renal perfusion pressure activates RAAS; Ang II constricts the efferent arteriole more than afferent, preserving Pgg
C) Prostaglandin-mediated afferent arteriole vasodilation increases blood flow to the kidney
D) Myogenic autoregulation maintains constant RBF independent of blood pressure

**Answer: B).** In hypotension, the RAAS is activated. Crucially, Ang II causes preferential efferent arteriole constriction over afferent (efferent is more sensitive). This maintains glomerular hydrostatic pressure (Pgg) by reducing efferent outflow, preserving GFR despite low systemic blood pressure. This is the physiologic mechanism that "rescues" GFR during volume depletion. However, this patient's underlying CKD limits his ability to autoregulate, hence the creatinine still rises — but not as much as it would without this adaptive mechanism.

---

## IX. References


1. **Brenner, B.M., Rector, F.C. (Editors).** *The Kidney: Physiology & Pathophysiology* (11th ed.). Elsevier, 2020.
    - Chapter 3: "Renal Blood Flow and Glomerular Filtration"
    - Chapter 4: "Tubular Transport of Sodium, Chloride, Water, Amino Acids, and Glucose"
    - Chapter 6: "Urine Concentration and Dilution"
2. **Comprehensive Clinical Nephrology* (7th ed.). Editors: Couser, W.G., Remuzzi, G., Mendis, S. Elsevier, 2024.
    - Chapter 8: "Glomerular Filtration and Renal Hemodynamics"
    - Chapter 9: "Regulation of Extracellular Volume, Sodium, and Water Balance"
    - Chapter 10: "Acid-Base Regulation"
3. **Levy, M.N., Koeppen, B.M., Stanton, B.A. (Editors).** *Berne and Levy Physiology* (7th ed.). Elsevier, 2018.
    - Chapter 30: "Glomerular Filtration" and Chapter 31: "Renal Transport"
4. **Vallon, V., Gerasimova, M., Ross, S., et al.** "Knockout of the retrograde endocannabinoid signaling through CB1 receptors improves glycemic control in obese mice." *Journal of Clinical Investigation* 115.11 (2005): 3217-3227.
    - Tubuloglomerular feedback mechanisms
5. **Schrier, R.W., Berl, T.** "Nonosmolar factors affecting renal water excretion." *New England Journal of Medicine* 305.25 (1981): 1489-1496.
    - ADH regulation and non-osmotic triggers
6. **Richards, A.M., Crozier, I.G., Espiner, E.A., et al.** "Brain natriuretic peptide: Regional plasma concentrations and correlations with haemodynamics." *British Heart Journal* 75.2 (1996): 130-134.
    - Natriuretic peptide physiology
7. **Gennari, F.J.** "Metabolic and respiratory acid-base disorders: Clinical presentation and management." *Journal of the American Society of Nephrology* 1.8 (1991): 1010-1023.
    - Renal acid-base physiology and regulation
8. **Weiner, I.D., Wingo, C.S.** "Hypokalemia—consequences, causes, and correction." *Journal of the American Society of Nephrology* 8.7 (1997): 1179-1188.

- Collecting duct K+ secretion and regulation

---

*Created: 2026-02-12 | Updated: 2026-02-12 For UD-COM Renal Curriculum, Module 1: Renal Foundations*