

**Pathophysiology**  
**Introduction/ Renal Anatomy and Function**

- I. Functions of the kidney
  - A. Maintaining homeostasis of a large number of solutes and water is the main job of the kidney. Total body contents stay normal even if dietary intake or endogenous production changes.
    1. components of the body that are regulated by the kidney
      - a. electrolytes
        - (1) sodium, the main osmole in the extracellular space
        - (2) potassium, the major intracellular cation
        - (3) chloride, the major extracellular anion
      - b. total body water (and therefore osmolality)
      - c. pH
        - (1) by excreting hydrogen ions
        - (2) by regulating the concentration of  $\text{HCO}_3^-$ , the major extracellular buffer
      - d. minerals
        - (1) calcium
        - (2) phosphorus
        - (3) magnesium
      - e. endogenously produced waste materials
        - (1) urea—major end product of protein catabolism
        - (2) creatinine—produced by skeletal muscle
        - (3) uric acid—nucleic acid breakdown product
    - B. The kidney also performs a number of endocrine functions.
      1. The kidney is the sole source of erythropoietin
        - a. released in response to hypoxia; necessary to mobilize iron in bone marrow to produce hemoglobin for red blood cell production
        - b. therefore, reduced number of functional nephrons leads to less erythropoietin\_ low reticulocyte count; normocytic, normochromic anemia
        - c. the anemia caused by kidney failure can be corrected by administration of exogenous erythropoietin
      2. Kidney is also the only significant site of production of 1- $\alpha$ -hydroxylase
        - a. the final enzyme necessary to produce the active component of the vitamin D system,  $1,25\text{-(OH)}_2\text{D}_3$ .
        - b. loss of renal mass leads to lack of active vitamin D and thus hypocalcemia
      3. Also the sole source of renin
    - C. There are also a number of paracrine substances in the kidney that regulate homeostasis within the kidney
      1. bradykinin
      2. prostaglandins (esp.  $\text{PGE}_2$  and  $\text{PGI}_2$ , natriuretic and vasodilatory)
      3. endothelial factors
        - a. NO, which causes vasodilation and natriuresis

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- b. endothelin
  - (1) also produced by endothelial cells, but usually only in response to injury
  - (2) the most potent vasoconstrictor known
- D. The kidney is a critical organ in the maintenance of normal blood pressure for a number of reasons:
  - 1. regulates water and sodium, so controls blood volume (most important mechanism for regulating blood pressure)
  - 2. controls renin-angiotensin-aldosterone axis
  - 3. produces some vasodilatory substances
- E. Involved in catabolism of small peptide hormones such as insulin
- F. Can produce glucose via gluconeogenesis during fasting
- G. Responsible for elimination of many drugs. Changes in kidney function will change plasma concentration of these drugs.
- H. the concept of balance
  - 1. Neutral balance means dietary intake + endogenous production = excretion rate by the kidney. Total body content of the solute stays stable.
  - 2. Positive balance means intake + endogenous production > excretion. Total body content increases.
  - 2. Negative balance means intake + endogenous production < excretion. Total body content decreases.
- II. Mechanisms of function
  - A. The kidney produces an enormous amount of ultrafiltrate across the glomerulus
    - 1. approximately 180 L/day (60X total plasma volume)
    - 2. this enormous amount of filtrate is produced passively at the glomerulus due to Starling forces, and therefore requires an enormous amount of blood flow to the kidneys
      - a. the kidneys receive about 20% of total cardiac output (10% to ea. kidney)
      - b. 98-99% of this filtrate must be reabsorbed; otherwise we would lose our volume, go into shock, and die within minutes
      - c. we only make 1-2 L of urine per day
    - 3. kidney uses processes of selective reabsorption and secretion at tubular level to determine final contents of the urine and maintain homeostasis
  - B. Important processes involved in renal function
    - 1. Filtration—the first step. Huge blood flow reaches kidney and deposits a protein-free ultrafiltrate of plasma coming from the glomerular capillaries into Bowman's space. A passive process driven by Starling forces.
    - 2. Then it's in the tubule and we either reabsorb it or excrete it
    - 3. Things that are reabsorbed are things that are needed to maintain homeostasis such as salt and water. These are reabsorbed from tubular fluid \_renal epithelial cells\_ interstitium \_peritubular capillaries.
    - 4. Substances that are secreted not only can enter the tubular fluid by glomerular filtration, but also by active secretion from the peritubular capillaries directly into the renal tubules to enhance elimination from the body (e.g., potassium, many drugs)

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5. Excretion—what ends up in the urine
6. The glomerulus and the tubule must operate jointly. If one quits working, the other quits working.
7. Remember this: **Glomerular filtration rate (GFR) is the best overall index of kidney function and renal mass.** Normal GFR is 120 mL/min. All kidney functions, including endocrine, are related to GFR.

### III. Renal Anatomy

- A. The kidneys are paired retroperitoneal organs
  1. each weighs about 150 grams
  2. located roughly between T12 and L3
- B. Two major portions
  1. Cortex—rim just under the fibrous capsule
    - a. 90% of renal blood flow goes to the cortex
    - b. most highly perfused tissue per gram of any organ
    - c. all glomeruli are located in the cortex (about 1 million per kidney)
  2. Medulla
    - a. extends all the way to the renal pelvis
    - b. receives only 10% of renal blood flow, so perfusion is similar to other tissues
- C. Urine flow
  1. leaves end of the collecting ducts at tips of the renal papillae
  2. enters the minor calices
  3. minor calices join to form about three major calices
  4. major calices come together to form renal pelvis
  5. renal pelvis becomes the ureter, which descends paraspinally in the retroperitoneum to enter the urinary trigone of the bladder
  6. bladder stores urine
  7. urine leaves the bladder through the urethra
    - a. urethra is much shorter in females\_ more ascending UTI's in females
    - b. urethra passes through prostate in males\_potential site of obstruction (benign prostatic hypertrophy is the most common cause of urinary obstruction in older males)
    - c. several points along course of urethra are relatively narrow and therefore prone to obstruction in males and females (e.g., with stones)
      - (1) junction of the ureter and renal pelvis
      - (2) where ureter crosses over pelvic brim
      - (3) where ureter enters trigone of the bladder
    - d. obstruction causes an increase of tubular pressure, which causes a loss of GFR due to disturbed Starling forces
- D. Renal Blood Flow
  1. each kidney is perfused by a single main renal artery which branches at the hilum into 3 to 4 segmental branches
  2. segmental branches give off interlobar arteries which course between lobes up to the corticomedullary junction
  3. at the corticomedullary junction, the interlobar vessels give off perpendicular branches called arcuate arteries
    - a. run along corticomedullary junction and perpendicular to interlobar artery

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- b. arcuate arteries are end arteries; if one is occluded, the part of the kidney it perfuses will be infarcted
4. ascending perpendicular branches off the arcuate arteries are called interlobular arteries
5. afferent arterioles branch off the interlobular arteries
6. afferent arterioles branch into glomerular capillaries
7. glomerular capillaries re-form into efferent arterioles—a unique situation where capillaries have arterioles on either side (pre- and post-capillary)
- E. Two types of nephrons in the kidney
  1. cortical (short-looped) nephrons—close to cortex
    - a. 85% of all nephrons
    - b. afferent arteriole comes off the interlobular vessel closer to the capsule (farther from main artery)
    - c. therefore perfusion pressure is less and filtration rate is less
    - d. have a shorter loop of Henle (does not descend deep into inner medulla) and shorter thick ascending limb, and therefore are not nearly as important in concentrating the urine or reabsorbing sodium or avidly conserving sodium
    - e. these never operate at full capacity, but always have some reserve left so that they can further increase GFR when needed (such as after a high-protein meal)
  2. juxtamedullary (long-looped) nephrons—close to corticomedullary junction
    - a. 15% of all nephrons
    - b. afferent arteriole comes off the interlobular vessel close to the corticomedullary junction
    - c. therefore perfusion pressure is higher and filtration rate is higher
    - d. slightly larger than short-looped
    - e. because these nephrons have a long loop of Henle (descends deep into medulla) and a long thick ascending limb (major site of salt transport), they play a very important role in conserving sodium and concentrating urine
    - f. always function at full capacity
- F. Microcirculation of cortical nephrons
  1. the afferent arteriole becomes the glomerulus
  2. the glomerulus then reforms an efferent arteriole
  3. the efferent arteriole then breaks down into the peritubular capillary network
  4. peritubular capillaries reabsorb 98-99% of glomerular filtrate
- G. Microcirculation of the juxtamedullary nephrons
  1. the afferent arteriole forms the glomerulus, which then converges to form efferent arteriole
  2. the efferent arteriole becomes the descending vasa recta
    - a. vasa recta are the sole blood supply to the medulla
    - b. vasa recta function as a countercurrent exchange system
      - i. solute material can move from descending to ascending vasa recta and vice versa
      - ii. there is also countercurrent exchange of oxygen, such that the oxygen tension decreases the deeper you extend into the

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medulla. Therefore, the medulla is at increased risk for hypoxic injury when there is prolonged shock or hypoxemia.

### IV. Production of Glomerular Filtrate

#### A. Glomerulus

1. is a ball of capillaries invaginated into the beginning of the proximal tubule
2. This ball of glomerular capillaries is surrounded by a fibrous capsule called Bowman's Capsule that is lined by epithelial cells called parietal epithelial cells
3. Glomerular filtrate is made from capillary loops into Bowman's space; the most important factor in filtration is the glomerular capillary pressure
4. This space is contiguous with the tubule system, where materials are selectively absorbed and secreted

#### B. Mesangium—the skeletal support system that holds all of the capillary loops in place. Loops exit off mesangial structure like clover leaves.

1. Composed of resident mesangial cells which produce a matrix composed primarily of proteoglycans and type IV collagen
2. The mesangial cells contain actin and myosin, so they contract to control the number of capillary loops that are open and thus the surface area available for filtration.
3. A part of each capillary loop is adjacent to the mesangium. This part of the loop is not covered by basement membrane. Therefore, the mesangium is exposed to inflammatory mediators or immune complexes in plasma
4. Mesangial cells function as phagocytic cells, and thus frequently ingest immune complexes. This can turn on an inflammatory cascade, so that mesangial inflammation is often a component of glomerulonephritis.

#### C. Glomerular capillary wall

1. The filtrate has to pass through this to get into the urinary space
2. Glomerular capillaries are perfused by higher pressure than systemic capillaries
3. Anatomy
  - a. Endothelial cell—lines glomerular capillary wall. Glomerular capillary endothelial cells have larger fenestrations than other fenestrated capillaries.
  - b. Endothelial cells are surrounded by the basement membrane, which prevents passage of protein and cells
  - c. Unique to the glomerular capillaries is a third layer composed of visceral epithelial cells, or podocytes, that produce foot processes that attach at the external part of the glomerular basement membrane
  - d. Between the foot processes are small slit diaphragms
  - e. Three-layered capillary wall very efficiently prevents loss of cells and large molecules like protein into urine, but allows small-molecular weight molecules like water and electrolytes to pass through.
  - f. All three layers are rich in negative charges from sialic acid residues and heparan sulfate, so that besides acting as a simple size barrier that prevents larger molecules from passing, they also act as a charge barrier

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- g. Positively charged substances move most readily across the capillary, neutral substances move less readily than positive substances, and negatively-charged substances move least readily.
- h. The major plasma protein is albumin—a polyvalent anion. The negative charge barrier is an important way to keep albumin in the plasma where it belongs.
- 3. There are three places in the glomerulus that immune complexes can deposit
  - a. sub-epithelial
  - b. sub-endothelial
  - c. mesangium
- D. The Juxtaglomerular Apparatus (JGA)
  - 1. The macula densa
    - a. The macula densa is at the end of the cortical thick ascending limb. It is adjacent to the afferent and efferent arterioles of the *same nephron*.
      - i. everything before the macula densa is considered proximal nephron; everything after the macula densa is considered distal nephron
      - ii. the macula densa cells function as sensors to determine how much filtrate is being delivered from the glomerulus
    - b. The proximal tubule is the bulk reabsorber (90% of filtrate). The distal tubule is only responsible for reabsorption of about 10% of filtrate, so the distal tubule is more for fine-tuning.
    - c. The macula densa is important for regulating the amount of filtrate reaching the distal tubule so that it is not overwhelmed with more than it can reabsorb
    - d. if the macula densa senses too much filtrate being delivered to the distal nephron, it feeds back to the afferent arteriole via autocrine mechanisms to cause vasoconstriction, which will reduce capillary pressure and filtration rate
    - e. this mechanism is called tubuloglomerular feedback
    - f. through tubuloglomerular feedback, each nephron can influence the rate of filtration at its glomerulus
  - 2. the afferent arteriole
    - a. functions as a baroreceptor
      - (1) responds to stretch and pressure by myogenic mechanisms
      - (2) if pressure is increased, afferent arteriole will vasoconstrict to prevent injury to the kidney and keep GFR constant
      - (3) if pressure is decreased, afferent arteriole will vasodilate to keep GFR constant
    - b. also functions as an endocrine structure
      - (1) produces renin
      - (2) renin is released in response to reduced pressure or  $\alpha_1$ -adrenergic stimulation
      - (3) renin release is inhibited in response to increased pressure
- V. Filtrate formation
  - A. Fluid movement across the glomerular capillary is a passive process governed by Starling's law, which says that movement is determined by capillary

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surface area and permeability and hydrostatic and oncotic pressure gradients.

$$\text{GFR} = L_p S (\Delta P - \Delta \Pi)$$

1.  $L_p$  = capillary wall permeability
2.  $S$  = surface area available for filtration
3.  $\Delta P$  = hydrostatic pressure gradient between capillary and Bowman's space
4.  $\Delta \Pi$  = oncotic pressure gradient between capillary and Bowman's space

### B. Summary of forces

1. Hydrostatic pressure is high in the capillary and low in Bowman's space because of continuous reabsorption in the proximal tubule; this drives filtration into Bowman's space.
2. There is virtually no oncotic pressure in Bowman's space due to the lack of protein, while oncotic pressure is high in the capillary. This would tend to favor fluid movement into the capillary.
3. Filtration rate is determined by the pressure gradients between the two spaces. In the proximal part of the capillary, the hydrostatic pressure gradient favoring filtration is much greater than the oncotic pressure gradient opposing filtration, resulting in the huge amount of filtrate. In the distal capillary, where much of the fluid has crossed into Bowman's space and all of the protein remains, the oncotic pressure gradient becomes equal to the hydrostatic pressure gradient. At this point, net filtration stops.

## VI. Autoregulation of GFR via afferent and efferent arterioles

- A. Recall that glomerular capillaries have resistance vessels on either side—an afferent arteriole carrying blood to the capillary and an efferent arteriole carrying blood away
- B. Changes in resistance of either vessel → change in capillary pressure → change in GFR
  1. Vasodilation of the afferent arteriole results in increased renal blood flow and increases GFR
  2. Vasoconstriction of the afferent arteriole decreases renal blood flow and decreases GFR
  3. Vasodilation of the efferent arteriole will raise renal blood flow, but decrease capillary pressure and thus GFR
  4. Vasoconstriction of the efferent arteriole reduces renal blood flow, but increases capillary pressure and GFR
- C. The above mechanisms operate together to maintain GFR
- D. In response to a dramatic drop in cardiac output, kidney would vasodilate afferent arteriole and vasoconstrict efferent arteriole to maintain GFR
- E. Through autoregulation, renal blood flow and GFR can be kept constant over a very wide range of arterial pressures
- F. Urine flow rate is **not** autoregulated
  1. therefore, urine flow is not a good index of GFR or overall kidney function (more urine does not necessarily mean better kidney function)
  2. increased arterial pressure results in increased urine flow rate; this is known as pressure natriuresis (as pressure increases, sodium excretion increases, which obligates water excretion)

## VII. Definitions and formulas

- A. Filtered load—how much solute gets filtered at the glomerulus per unit time

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1. filtered load (mg/min) =  $[P_x] * GFR$ , where  $[P_x]$  is the plasma concentration of substance x
2. this assumes the substance is small enough to be filtered at the glomerulus
- B. Excretion rate—how much gets excreted in urine per unit of time; excretion rate (mg/min) =  $[U_x] * V$ , where V is the urine flow rate (ml/min) and  $[U_x]$  is the urine concentration of substance x
- C. To measure GFR, we need a compound with the following properties:
  1. present in plasma at constant concentration
  2. freely filtered at glomerulus
  3. not reabsorbed or secreted (filtered load = excretion rate)
  4. inulin is an exogenous substance with these properties, but must be administered continuously to the patient and therefore is difficult to work with
  5. creatinine is the only endogenous substance with these properties
    - a. is produced at a constant rate by skeletal muscle, so the amount produced is proportional to lean body mass
    - b. is freely filtered and is not reabsorbed
    - c. actually, creatinine is secreted in small amounts; therefore it overestimates GFR slightly (not significantly)
- D. Calculating GFR
  1. If filtered load = excretion rate, then  $[P_x] * GFR = [U_x] * V$
  2. solving for GFR:  
 **$GFR \text{ (ml/min)} = ([U_x] * V) / [P_x] = \text{clearance of substance x}$**   
*As long as substance x is handled in the kidney like inulin or creatinine.*
- E. Renal Clearance
  1. like GFR, has units of ml/min
  2. tells what volume of plasma was cleared of the substance in question per unit time
  3. **renal clearance =  $[(U_x) * V] / [P_x]$**
  4. note that the formula looks the same as the GFR formula! For substances like inulin and creatinine with the properties described in VII. C. 1-3, renal clearance = GFR
  5. clearance ratio = clearance of a substance / GFR
    - a. clearance ratio of inulin is 1 (freely filtered, no reabsorption or secretion)
    - b. if clearance ratio > 1, then substance is actively secreted (e.g. potassium)
    - c. if clearance ratio < 1, then substance is reabsorbed (e.g. sodium)
    - d. if clearance ratio = 0, substance was either too big to be filtered (e.g. protein) or was completely reabsorbed (e.g. glucose, amino acids)
- F. Measuring renal plasma flow (RPF)
  1. No endogenous substance can be used to measure renal plasma flow
  2. An exogenous substance, paraaminohippurate (PAH) is used to measure renal plasma flow
    - a. freely filtered
    - b. also very actively secreted
    - c. in one pass through kidney, over 90% of PAH is cleared into urine
    - d. therefore, renal clearance of PAH estimates renal plasma flow
- G. Filtration fraction =  $GFR/RPF * 100\%$

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1. normal GFR is about 120 mL/min
2. normal RPF is about 600 mL/min
3. therefore, normal filtration fraction is 20% (in other words, 20% of renal plasma flow becomes filtrate)
4. fairly constant as long as volume is normal