Objectives

- 1. Review the role of the renin-angiotensin-aldosterone system, sympathetic nervous system, atrial natriuretic peptide, and pressure natriuresis in the regulation of sodium balance
- 2. Understand the concept of effective circulating volume
- 3. Understand the pathogenesis of edema in congestive heart failure, cirrhosis and nephrotic syndrome
- 4. Understand the mechanisms of action and side effects of diuretics

Readings

Rose and Rennke, pages 97-121. Rennke and Denker, pages 99-125.

I. Sodium Balance

- A. Net sodium balance is determined by sodium intake and sodium excretion.
- B. Sodium excretion predominantly occurs in the kidney such that in the steady state, sodium intake is equal to kidney sodium excretion.
- C. Sodium content is the principal mediator of volume status, and must be rigorously guarded. Sodium content is assessed by evaluating volume status. Plasma sodium concentration has nothing to do with sodium content – it is determined by water content.
- D. Filtered load
 - 1. The filtered load of a substance is equal to the GFR x plasma concentration x the sieving coefficient of that substance (the fraction that comes out of the plasma into an ultrafiltrate). Sodium is freely filtered (sieving coefficient of 1) and thus its filtered load is equal to the GFR x the plasma concentration. In normal subjects, the GFR is 120 ml/min and the plasma sodium is 140 mEq/l, thus the filtered load is 16.8 mEq/minute or over 24,100 mEq/day. The total sodium content of the ECF is approximately 1960 mEq, so the kidney must reabsorb the vast majority to maintain balance.
 - 2. The kidney has a tremendous capacity to regulate sodium content (total body sodium). The kidney is extremely adaptive to extremes of sodium intake. Some cultures have daily intakes of sodium of > 1000 mEq/day, while others ingest less than 22 mEq/day. All maintain balance.

3. The kidney must reabsorb most of the filtered load. The average American intake of sodium is approximately 200 mEq/day. To remain in balance, the kidney can only excrete 200 mEq/day, and reabsorb the remaining filtered load. The amount of filtered sodium that ends up in the urine is called the "fractional excretion of Na⁺".

 $FENa^{+}$ = the urinary sodium excretion rate divided by the filtered load

Since the kidney must typically excretes 200 mEq/day (the result of urine concentration x urine volume) and the filtered load of sodium is 24,100 mEq/day, the fractional excretion of sodium in the steady state is very low.

FENa⁺ = (200 / 24,100) x 100 = 0.82%

Thus, in this typical steady state, the kidney only excretes 0.82% of the filtered load and must reabsorb greater than 99%.

4. By adjusting the fractional excretion of sodium slightly, the kidney can maintain sodium balance in face of large changes in sodium intake. For example, if the intake of sodium increased from 200 mEq all the way to 500 mEq in a day:

 $\text{FENa}^+ = (500/24, 100) \times 100 = 2.07\%$

Even with a tremendous increase in sodium intake, the fractional excretion remains a small part of the filtered load.

E. Tubular reabsorption of sodium

There are four major sites of sodium reabsorption:

- 1. Proximal tubule: 60-70%
- 2. Thick ascending limb of the loop of Henle: 25%
- 3. Distal convoluted tubule: 5%
- 4. Collecting duct: 3%

Sodium reabsorption at these sites occurs actively due to the presence of basolateral Na⁺/K⁺-ATPase creating a driving force for sodium movement from the tubular lumen into the cells.



II. Regulation of Sodium Balance

- A. Sodium is the **primary** ECF solute.
 - 1. Na^+/K^+ -ATPase is a ubiquitous cell membrane protein that partitions Na^+ extracellularly and K^+ intracellularly.
 - 2. Sodium balance determines ECF volume.

Net Na⁺ loss = ECF volume contraction Net Na⁺ retention = ECF volume expansion

Note: this is whole body sodium content, <u>not</u> sodium concentration which is determined by water balance (remember, patients with identical degrees of hyponatremia can be severely orthostatic, euvolemic, or foaming at the mouth from volume overload).

- B. Sensors In order to regulate Na⁺ balance, the body requires volume sensors to monitor intravascular volume status. Volume sensors can be divided into:
 - 1. Low-pressure sensors receptors in the pulmonary circulation and in cardiac atria.
 - 2. High-pressure sensors carotid baroreceptors and kidney baroreceptors (the juxtaglomerular apparatus).
- C. Effectors Once sensing a challenge to volume homeostasis, sodium excretion is increased or decreased. The effectors of Na⁺ regulation include:
 - 1. Filtered load
 - a. Increased sodium intake will increase ECF volume.
 - b. Increased ECF increases cardiac output, systemic pressure, and thus kidney perfusion pressure.
 - c. Increased pressure increases renal blood flow, and to a lesser extent GFR.
 - d. Increased GFR will increase filtered load of sodium. However, modulation of filtered load does not appear to be a major determinant of sodium excretion. Patients with advanced kidney disease and severely reduced GFR can still maintain sodium balance.

Sodium Handling and Volume Regulation

- 2. Renin-Angiotensin-Aldosterone the major player regulating sodium excretion
 - a. The juxtaglomerular apparatus (JGA) senses kidney perfusion pressure.
 - b. When reduced perfusion is sensed by a drop in luminal Cl⁻ delivery to the



macula dense of the distal convoluted tubule, renin is released from the JGA.

- c. Renin is also released in response to direct sympathetic nerve stimulation.
- d. Renin leads to proteolytic cascade with effects mediated by angiotensin II (AII):
 - i. Vasoconstriction
 - aa. Increases systemic blood pressure by increasing SVR (directly binds vascular smooth muscle)
 - bb. Selective efferent artery vasoconstriction, maintains GFR despite reduction in RPF
 - ii. Effects on tubular absorption of sodium
 - aa. AII directly enhances active Na⁺ reabsorption in proximal tubule.
 - bb. Changes in peri-tubular hemodynamics increased filtration fraction increases peri-tubular capillary oncotic pressure and Na⁺ re-uptake.
 - cc. All stimulates aldosterone release from the zona glomerulosa in the adrenal gland. Aldosterone has a target receptor on the basolateral surface of the collecting tubule that greatly enhances distal sodium reabsorption and distal potassium and hydrogen ion excretion.
 - iii. Thirst
- e. The renin system is suppressed by volume expansion.

- 3. Sympathetic Nervous System Sympathetic activity increases in response to decreased circulatory volume sensed at the carotid bodies. Like AII, sympathetic nerve stimulation directly leads to systemic vasoconstriction and stimulates sodium reabsorption. Increased sodium uptake is likely mediated by changes in peritubular hemodynamics and direct effects on proximal tubule sodium transporters. Additionally, beta-adrenergic stimulation results in increased renin release from the juxtaglomerular apparatus. The sympathetic nerves are suppressed by volume expansion.
- 4. Pressure Natriuresis By unclear mechanisms, an increase in kidney perfusion pressure leads to natriuresis. This is believed to be secondary to a reduction in sodium reabsorption in the proximal tubule and loop of Henle with increased tubular flow rates.
- 5. Atrial Natriuretic Peptide
 - a. Sensor atrial stretch
 - b. Effector atrial natriuretic peptide causes increased Na⁺ excretion (direct effect on collecting duct); at higher doses (probably only pharmacologic), it is a vasodilator that can increase RPF and GFR.
- 6. Anti-diuretic hormone (ADH), a.k.a. vasopressin, responds predominantly to osmotic stimulation. It also responds to effective circulating volume depletion by stimulating water reabsorption, and possibly Na⁺ reabsorption. Thirst and water intake are increased.

III. Pathophysiology of Volume Depletion

- A. Volume depletion occurs when Na⁺ losses are greater than Na⁺ intake.
- B. Losses can occur from skin (e.g. excessive sweating, burns), hemorrhage, GI tract (vomiting and diarrhea), and from the kidney (e.g. diuretics or rare salt-wasting nephropathies).
- C. Primarily diagnosed by physical examination poor skin turgor, decreased jugular venous pressure, orthostatic hypotension/tachycardia, shock (low pulmonary capillary wedge pressure)
- D. Labs may show hemoconcentration (high HCT), high BUN/creatinine ratio, decreased GFR (elevated BUN and creatinine), low urine Na⁺, low FENa⁺

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- E. High-pressure sensors are activated leading to increased sympathetic tone and release of renin. Together, norepinephrine, angiotensin II, and aldosterone lead to direct vasoconstriction (only NE and AII) and to marked kidney sodium retention.
- F. Appropriate kidney response
 - 1. $UNa^+ < 20 \text{ mEq/l} (usually < 10 \text{ mEq/l})$
 - 2. $FENa^+ < 1\%$
 - 3. If inappropriate (FENa > 1%), a kidney source of volume loss should be considered.
 - a. diuretics, osmotic diuresis (e.g. mannitol)
 - b. salt losing nephropathy
 - c. hypoaldosteronism
 - d. post-obstructive diuresis
- G. Treatment involves volume replacement
- H. "Effective Circulating Volume"
 - 1. Definition: fluid in vascular space that effectively perfuses tissue.
 - 2. Generally correlates with cardiac output, but not always. With arterio-venous shunting, cardiac output is increased but the blood is short circuiting and not perfusing tissue. An example of this process occurs with early cirrhosis where cardiac output is frequently elevated
 - 3. Clinical situations associated with ineffective arterial perfusion
 - a. Congestive heart failure
 - b. Cirrhosis
 - c. Nephrotic syndrome
- I. Host response to ineffective arterial perfusion is the same as the response to volume depletion

IV. Pathophysiology of Sodium Overload: Edematous States

- A. Pathogenesis of edema
 - 1. Edema is palpable swelling due to expansion of interstitial fluid.
 - 2. Two steps typically involved
 - a. altered capillary hemodynamics or wall permeability (Starling forces)
 - b. Na⁺ retention by the kidney clinical edema requires 2.5-3 L expansion of interstitium. Therefore, the source cannot all be from plasma volume (3 liters total)
 - 3. Cascade to the edematous state:
 - a. movement of fluid into interstitium (disturbed Starling Forces)
 - b. contraction of plasma volume
 - c. triggering of sodium retentive mechanisms (RAAS and SNS)
 - d. expansion of ECF with "normalization" of plasma volume ("appropriate" compensation)
 - e. restoration of tissue perfusion (but now with expanded interstitium, i.e. edema)
 - 4. Primary kidney disorder leading to sodium and water retention differs in that both plasma volume and interstitial volume are expanded "inappropriately"
- B. Capillary hemodynamics



Tufts University School of Medicine Page 7 Net filtration = LpS (Δ hydraulic pressure - Δ oncotic pressure) = LpS [(P_{cap} - P_{is}) - σ ($\Pi_{cap} - \Pi_{is}$)] Where: Lp - hydraulic conductivity (porosity) S - capillary surface area P_{cap} - capillary hydraulic pressure P_{is} - interstitial fluid hydraulic pressure Π_{cap} - capillary oncotic pressure Π_{is} - interstitial fluid oncotic pressure σ - reflection coefficient for proteins

- 1. Edema formation is precipitated by one of the following problems:
 - a. Increased capillary pressure the pre-capillary arteriole auto-regulates capillary pressure. Increases are generally due to increased venous pressure.
 - i. venous obstruction, e.g. venous thrombosis
 - ii. expanded venous blood volume, e.g. HF or kidney failure
 - b. Decreased plasma oncotic pressure hypoalbuminemia generally < 2 g/dl (normal 4-5 g/dl) can be seen with nephrotic syndrome and liver failure.
 - c. Increased capillary permeability augments transit of proteins into interstitium therefore decreases oncotic pressure gradient, e.g. burns, angioedema
- 2. Edema will not appear until the net filtration pressure increases greater than 15 mmHg. This protective threshold is related to:
 - a. Increased lymphatic flow
 - b. Increased filtration dilutes tubular proteins and thus decreases $\Delta \Pi$ by lowering Π_{is}
 - c. Increased filtration increases P_{is} and thus, decreases ΔP

- 3. Despite these safety mechanisms, edema is a very common clinical finding
 - a. Kidney sodium retention is the **most important** factor in sustaining edema
 - i. Normal kidney function with sodium retention "appropriate compensatory response" triggered by ineffective arterial perfusion
 - ii. Abnormal kidney function inability to excrete ingested Na⁺ and water
 - b. Not mutually exclusive as you can have both reduced kidney function and enhanced sodium avidity

V. Edema in Heart Failure

A. Patterns - distribution of edema depends on nature of heart disease

- 1. Left heart failure Coronary artery disease and hypertensive heart disease typically presents with left ventricular dysfunction and pulmonary edema
- 2. Right heart failure Cor pulmonale results in right ventricular dysfunction and presents with peripheral edema and ascites
- 3. Cardiomyopathy affecting both ventricles It is common to see both pulmonary and peripheral edema
- 4. Acute (flash) pulmonary edema after acute myocardial infarction An increased left ventricular end diastolic pressure is transmitted **back** into pulmonary veins and capillaries with a rise in the pulmonary capillary wedge pressure, typically > 18-20 mm Hg (normal 5-12 mm Hg)
- B. "Forward Hypothesis"
 - 1. Primary event is a reduced cardiac output leading to under-perfusion of the kidneys and Na^+ retention by the kidney.
 - a. Stimulation of SNS and RAAS are early events that precede edema formation (unlike flash pulmonary edema)
 - b. With worsening disease, forward flow depends on plasma volume expansion to increase ventricular filling

- 2. Starling curves in patients with heart failure (HF)
- 3. Sequence of events leading to edema in HF:

cardiac dysfunction \rightarrow decreased cardiac output \rightarrow kidney Na⁺ and water retention leading to increased blood volume \rightarrow increased venous pressure \rightarrow increased capillary hydraulic pressure (P_{cap}) \rightarrow increased transcapillary gradient \rightarrow movement of fluid from plasma to interstitium \rightarrow peripheral edema \rightarrow increased left ventricular filling \rightarrow normalization of cardiac output \rightarrow "compensated state"

- 4. As cardiac function continues to worsen, plasma expansion increases to the point of pulmonary edema, leading to impaired gas exchange and dyspnea.
- 5. Treatment of chronic HF
 - a. Improve cardiac function-increase forward flow
 - i. treat underlying disease, e.g. valve replacement
 - ii. improve inotropy, e.g. digoxin, dobutamine
 - iii. improve cardiac output by afterload reduction with vasodilators; e.g. ACE inhibitors (might worsen kidney function if GFR is highly AII dependent)
 - iv. These therapies can initiate a natriures is by decreasing the neurohumoral stimuli for Na^+ retention
 - b. Plasma volume contraction may improve cardiac function
 - i. sodium restriction
 - ii. diuretics
 - iii. These therapies can reduce HF symptoms, but might compromise tissue perfusion due to decreased ventricular filling

VI. Cirrhosis and Ascites

- A. Ascites accumulation of third-spaced fluid in the peritoneal cavity
 - 1. Fluid is derived from the hepatic sinusoids
 - 2. It enters peritoneum by moving across the hepatic capsule

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- 3. Due to post-sinusoidal obstruction from hepatic scarring, and to a lesser extent portal hypertension. Hypoalbuminemia not involved as the sinusoids are freely permeable to proteins
- 4. Safety factors increased lymphatic drainage and increased abdominal pressure (as the cavity fills) temper fluid accumulation
- B. Mechanism of ECF Expansion "overflow" versus "underfill" hypothesis
 - 1. "Overflow" Sodium retention **precedes** the development of ascites despite normal kidney function, absence of edema, appropriate suppression of renin, and no overt change in systemic hemodynamics. Fluid extravagates into abdominal cavity.
 - 2. "Underfill"
 - a. Increased intra-sinusoidal pressure leads to fluid sequestration in the abdomen and ascites formation
 - b. Hypoalbuminemia is related to impaired synthetic function of liver. When severe, it promotes peripheral edema by decreasing Π_{cap} , and decreases plasma volume.
 - c. Peripheral vasodilation occurs from arterio-venous fistulas (e.g. spider angiomata) in patients with cirrhosis. An elevated cardiac output is observed.
 - d. These stimuli activate the typical neurohumoral response to a reduction in effective circulating volume (AII, NE, ADH), and lead to Na⁺ retention by the kidney
 - 3. Degree of neurohumoral stimulation correlates with survival. A $U_{Na} < 10 \text{ mEq/l or}$ $P_{Na} < 125 \text{ mEq/l}$ (impaired water excretion due to high ADH) correlates with a survival of 5-6 months vs. 2 years for patients with ascites alone
 - 4. Treatment
 - a. Improve liver function liver transplantation
 - b. Reduce ECF volume
 - i. Restrict Na⁺ intake
 - ii. Diuretics must use extreme caution to avoid to tissue hypoperfusion
 - iii. Paracentesis
 - iv. Periods of bed rest and leg elevation
 - v. Peritoneo-venous shunt (ascitic fluid reinfused into internal jugular vein)

VII. Nephrotic Syndrome

- A. Characteristics
 - 1. Impaired glomerular barrier function with heavy proteinuria (> 3.5 g/d)
 - 2. Hypoalbuminemia multifactorial (urinary loss and decreased synthesis)
 - 3. Na⁺ retention poorly characterized impairment of sodium excretion that **precedes** the underfilled state due to hypoalbuminemia
 - 4. Underfill usually occurs with albumin < 2 g/dl
- B. Treatment
 - 1. Treat underlying nephrologic disease steroids, cytotoxic agents
 - 2. Decrease urinary protein leak by changing glomerular hemodynamics
 - a. Proteinuria varies closely with P_{GC} . Maneuvers which can decrease P_{GC} (ACE inhibitors reduce AII and therefore efferent arterial tone) reduce level of proteinuria.
 - 3. Decrease ECF volume
 - a. Sodium restriction
 - b. Diuretics

VIII. Principles of Diuretic Therapy

Diuretic usage leads to contraction of the extracellular fluid volume by inducing a loss of Na⁺ in the urine (natriuresis).

A. Classification and mechanism of action

Site of action	Channel inhibited	Percent filtered Na ⁺ excreted
Loop of Henle	Na ⁺ /K ⁺ /2Cl ⁻ -cotransport	Up to 25
Furosemide		
Bumetanide		
Ethacrynic acid		
Distal tubule	Na ⁺ /Cl ⁻ -cotransport	Up to 3 to 5
Thiazides		
Chlorthalidone		
Metolazone		
Cortical collecting tubule	Na ⁺ -channel	Up to 1 to 2
Spironolactone		
Amiloride		
Triamterene		

Physiologic characteristics of commonly-used diuretics



- B. Steady State Following a natriuretic response, a new steady state is rapidly reestablished where sodium intake once again equals sodium excretion.
- C. Physiologic Brakes
 - 1. Diuretic-induced natriuresis induces neurohumoral response to volume contraction.
 - a. Increased proximal Na reabsorption
 - b. AII
 - c. Norepinephrine
 - 2. Increased cortical collecting duct reabsorption due to aldosterone

- D. Reasons to Treat Edematous States with Diuretics
 - 1. pulmonary congestion with impaired oxygenation
 - 2. improve cardiac function by changing point on Starling Curve
 - 3. discomfort of tense ascites
 - 4. cosmetic

Note: The reduction in ECF volume induced by diuretics will lessen left ventricular filling and thus, might compromise tissue perfusion.

E. Pathogenesis and Treatment of Refractory Edema

Problem	Treatment	
Excess sodium intake	Measure urine sodium excretion; attempt more rigorous dietary restriction if greater than 100 meq/day.	
Decreased or delayed intestinal drug absorption	Bowel wall edema can reversibly impair oral drug absorption. Switch to intravenous loop diuretic if megadose oral therapy is ineffective.	
Decreased drug entry into the tubular lumen	Increase to maximum effective dose of a loop diuretic; use of spironolactone in hepatic cirrhosis; mixture of albumin and loop diuretic if marked hypoalbuminemia.	
Increased distal reabsorption	Multiple daily doses if partial diuretic response; add thiazide- type and/or K ⁺ -sparing diuretic.	
Decreased loop sodium delivery due to low GFR and/or enhanced proximal reabsorption	Attempt to increase delivery out of proximal tubule with acetazolamide; diuretic administration in supine posture or head-down tilt; dialysis or hemofiltration if severe kidney or heart failure.	

Table 2

F. Complications of Diuretic Therapy

Fluid and electrolyte complications of diuretic therapy		
Volume depletion		
Azotemia		
Hypokalemia		
Metabolic alkalosis		
Hyperkalemia and metabolic acidosis with K ⁺ -sparing diuretics		
Hyponatremia, especially with the thiazides		
Hyperuricemia		
Hypomagnesemia		