

Pathophysiology Sodium and Water Balance

I. History of Salt and Water

- A. Fascination with salt is evident in writings throughout world history.
 - 1. Venice, AD 523: Some persons may not seek gold, but never was there a man who does not desire salt. (paraphrased)
 - 2. Rome: Soldiers were paid in salt; hence the origination of the word “salary” and the expression “he is worth his salt”
 - a. Salted greens to counter bitterness → “salad”
 - 3. France: salted husband (slap it on front and back) to make them more virile.

II. The importance of sodium in the regulation of ECF volume

- A. Primarily important for ECF volume maintenance- via osmolality effects
- B. Sodium is the most abundant osmotically active cation in the extra cellular fluid (ECF)
- C. Sodium accounts for almost half of the osmolality of ECF
 - 1. Actually, sodium plus its anion account for 90 – 95% of the total extra cellular osmolality
- D. “Exchangeable sodium”= sodium that is osmotically active.
 - 1. There is also non-exchangeable sodium that is bound tightly in the bone
 - 2. The exchangeable Na⁺, such as in plasma, interstitial fluid, dense CT and cartilage, exchangeable bone Na⁺, transcellular fluid (e.g., CSF, pleural, peritoneal fluid), and intracellular contributes to osmolar pool of body

II. Defense of Osmolality

- A. The quantity of water consumed (thirst) and retained (Vasopressin) is adjusted around the quantity of exchangeable sodium in the body to maintain normal osmolality.
- B. Osmolality is defended to avoid changes in cell volume and solute concentrations that might interfere in essential cell function and metabolism.
- C. Purpose: to maintain normal Extracellular osmolality
 - 1. Changes in osmolality → changes in cell volume → changes in cell metabolism/functions

III. Set Point for ECF Volume

- A. When sodium intake is severely restricted, organ and tissue perfusion is preserved by sodium retaining mechanisms that are capable of reducing urinary sodium excretion to negligible quantities
- B. “Set Point” is the point at which sodium excretion virtually ceases and ECF volume is maintained in the absence of sodium intake.

IV. Renal Responses to changes in sodium concentrations

- A. Na⁺ Deprivation
 - 1. In the absence of sodium intake, sodium excretion is reduced to negligible quantities. The urine can become virtually sodium free
 - 2. The kidneys are able to efficiently conserve sodium in response to low sodium intake.
 - 3. ECF volume is reduced to threshold level.
 - 4. Study measuring Na⁺, K⁺, Cl⁻, Nitrogen, Creatinine clearance, and Weight variances in obese patients, who were starved(no caloric intake) for 28 days. (See figure 1)

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- a. Patients were given ONLY multivitamins, K⁺ (because K⁺ is not efficiently conserved), and black coffee. (Mmmmmm)
- b. initially (first 5 days) there was about 300meq of sodium lost
- c. NO sodium loss thereafter!
- d. The point: The body turned on its defense mechanisms, and the Set Point is reached in order to maintain ECF volume and preserve tissue perfusion.
- e. FYI: the patients lost 1lb/day, and stopped complaining of severe hunger after the first few days.

Figure 1-

Results of starvation study, showing excretion levels of Na⁺, K⁺, Cl⁻, Nitrogen.

- notice Urine Sodium levels virtually disappear
- K⁺ continues to be excreted
- negative nitrogen balance

B. Increased Na⁺ intake

1. Increased intake increases the urinary excretion of sodium
2. BUT, the excretion does not equal the intake until positive sodium balance is achieved and ECF volume is increased.
3. Positive balance is achieved mainly by retaining excess total body sodium
 - a. this probably has protective value
 - b. serves as a buffer for to prevent volume depletion
 - c. **Figure 2:** Notice that Na⁺ excretion lags behind Na⁺ intake in order to preserve volume

V. Volume-Sensing Mechanisms Affecting Sodium and Water Excretion

Note: Sodium is regulated by mechanisms which are VOLUME sensitive.

Vasopressin is primarily regulated by mechanisms which are OSMOLALITY sensitive (via osmoreceptors in the hypothalamus.)

- A. Volume is a reflection of total body sodium
- B. Atrial Receptors (sensors) monitor atrial filling [intravascular volume] and modulate urinary sodium excretion via sympathetic neural pathways and release of ANP

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1. ANP is predominately produced and released from the right atrium wall cells
 2. Is released under conditions of atrial stretch and inhibited when atrial volume is decreased
 3. ANP acts on collecting ducts to increase sodium excretion
- C. Sensors with similar functions have been identified in ventricles, juxtapulmonary capillary interstitium and arteries.
- D. Renal Sensors in the JG apparatus modulate urinary sodium excretion via effects on renin release
1. There is a lag period before this sensor comes into play, as opposed to the other mechanisms, which are fairly rapid responses.
 2. Renin-Angiotensin system plays a major role in defense mechanisms and in making the urine sodium free when necessary.
- E. Sodium is sometimes lost regardless of these mechanisms. It is important to recognize the clinical signs. . .

VI. Clinical Recognition of Sodium Depletion

- A. Reduction in blood pressure from previously known levels and/or orthostatic reduction in blood pressure
- B. Tachycardia, especially in erect posture
- C. Poor skin turgor, dry mucous membranes, absence of dependent edema
- D. Disproportionate increase in BUN relative to increase in serum creatinine concentration
- E. Increased Hematocrit
- F. Reduced Urine sodium concentration (<20mep/l in the absence of renal disease or diuretic administration)
- G. **Serum sodium concentration normal, low, or increased. Serum sodium concentration alone is NOT indicative of the state of the total body sodium.**

VII. Causes of Sodium Depletion

- A. Renal sodium loss:
1. Renal Parenchymal disease affecting tubular handling of sodium
 2. Deficiency of mineralcorticoid (aldosterone)
 3. Persistent solute diuresis (glucosuria)
 4. **Diuretic therapy** – most common
- B. Extra renal sodium loss:
1. Vomiting and/or diarrhea
 2. Nasogastric tube drainage
 3. Ileostomy output
 4. Profuse sweating
 - a. rarely in hardcore athletes and steel mill workers
 - b. story time: Gatorade was invented by a nephrologist at the U of Florida to prevent this cause of sodium loss. It was named after the Florida GATORS.
- C. Study: Diuretic induced sodium depletion
1. The subject lost 50lbs (>20kg)
 2. Serum sodium concentration did not change during the weight loss due to volume expansion

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3. When the body reached the threshold and the circulatory unit was in jeopardy, there was an increase in Vasopressin secretion → increased water retention → HYPONATREMIA due to water retention. (See Figure 3)
4. Hyponatremia in patients that are sodium depleted is dependent on NON-OSMOTIC stimulation of Vasopressin (VP) Release. (Occurs only after excessive Na⁺ deficit, usually after set point is exceeded and volume depleted)

**Figure 3-Serum sodium levels
In Patient with Diuretic induced
Hyponatremia**
- notice the dramatic Na⁺ decline
due to VP

VIII. Hyponatremia

- A. Sodium depletion with non-osmotic stimulation of VP release resulting in retention of water in defense of ECF volume
- B. Water retention as a primary abnormality resulting in negative sodium balance and development of hyponatremia with only a moderate sodium deficit.
- C. Retention of both sodium and water in which the latter is sufficient to lower the sodium concentration despite the increase in total body sodium.
- D. Low sodium concentration due to expansion of ECF volume associated with increased concentration of other osmotically active extracellular solute, usually glucose.
- E. Low sodium concentration due to the presence of high molecular weight solute in plasma usually lipid. Plasma water sodium concentration is normal.

IX. Water Retention (SIADH)

- A. Normal or expanded ECF Volume
 1. Expansion slight; no edema
- B. No signs of dehydration
- C. Normal or slightly increased GFR
 1. Reduced Serum Urea Nitrogen (SUN); normal or low serum creatinine
- D. Normal Hematocrit
- E. Sodium excretion greater than in sodium deficiency- because there is no volume deficit
- F. Excretion of administered sodium
- G. SIADH is associated with the following: (*last years notes)
 1. Neoplasms (bronchogenic carcinoma, and other solid tumors)
 2. Inflammatory pulmonary diseases (TB, pneumonia)
 3. CNS (hypothalamus/ brain base, glucocorticoid deficiency, hyperpituitarism)
 4. Miscellaneous (drugs)

X. Congestive Heart Failure [increased total body Na⁺ → so, why the Na⁺ retention?]

- A. Extracellular fluid volume is expanded, but “effective” arterial blood volume is reduced
 1. Some tissues are not well perfused → i.e. decreased “effective” volume

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B. Volume sensing mechanisms normally involved in the regulation of urinary sodium excretion are activated by the *perception* of a low volume status, resulting in ongoing sodium retention.

Note: If generalized, dependent edema is present (as in CHF or Cirrhosis of the liver), there is NO sodium deficit—no matter what the sodium concentration.

XI. Congestive Heart Failure and Hepatic Cirrhosis

A. Common mechanisms in sodium and water retention

1. SNS activated due to decreased effective BV
2. Renin/Angiotensin- due to dec. renal blood flow
3. Reduction/redistribution of the renal blood flow
4. Non-osmotic VP release-due to perceived volume inadequacy (will → hyponatremia)

XII. ECF Volume Expansion in Nephrotic Syndrome and other Hypoalbuminemic States

A. $J_v = K_f[(P_c - P_i) - (\pi_c - \pi_i)]$

Figure 4

J_v =fluid flux along the length of a capillary

K_f = the ultrafiltration coefficient

P_c = capillary hydrostatic Pressure

P_i = the interstitial Hydrostatic P

π_c =cap oncotic P

π_i =interstitial Onc. P.

B. Counterregulatory Factors in Interstitial Fluid Accumulation

1. Compliance characteristics of the interstitium
 - a. small increases in interstitial volume result in large increases in interstitial pressure
2. Reduction in interstitial oncotic pressure
 - a. with development of hypoalbuminemia capillary and interstitial oncotic pressures decrease in parallel with no change in capillary tissue gradient
3. Increased Lymph Flow
 - a. Increased egress of tissue albumin via lymphatics increases the fraction of the total albumin pool located in the intravascular compartment.

C. Nephrotic Syndrome

1. Patients losing protein in the urine → hypoalbuminemia
2. In general, the mechanisms that are in place to resist edema formation are sufficient to counter the fall in intravascular oncotic pressure
 - a. thus, edema does not form solely on the fact that there is a reduction in intravascular oncotic pressure
3. In order for edema to form, sodium retention must take place and this is a renal problem
 - a. primary renal sodium retention accounts for the expansion of interstitial volume once the defense mechanisms have been exhausted.
4. The more traditional view of nephrosis deals with a dramatic decrease in oncotic pressure, but cannot always be applied as the explanation
 - a. when the plasma oncotic P becomes extremely low (<2g/dl of albumin) this may be more likely to occur
 - b. this would be defined as secondary renal sodium retention

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5. A decrease in intravascular oncotic pressure may cause a reduction in intravascular volume sufficient enough to turn on the renal sodium retention mechanism
 - a. turning on aldosterone and the SNS can add to the sodium retention that is initiated by a primary renal abnormality in sodium handling
6. **Figure 5:** shows the relationship between plasma and tissue-fluid oncotic pressure (COP) in patients with the nephritic syndrome, at the first visit (O) and during follow up with partial or complete recovery (O).
 - a. notice that plasma COP is greater than tissue COP by about 5mmHg
 - b. Notice that the GRADIENT between tissue and plasma COP is not reduced, because the two change in parallel.

NEPHROTIC PROTEINURIA

HYPOALBUMINEMIA

Oncotic pressure	Oncotic Pressure
Activation of edema Preventing factors	Activation then exhaustion of edema preventing factors
Normal Blood Volume	Blood Volume
Normal AngII, catechols, Aldosterone	AngII, Catechols, Aldo
Mild PRIMARY severe RENAL Na+ RETENTION	SECONDARY RENAL Na+ RETENTION
NO edema	Exhaustion of Edema preventing factors

EDEMA

FIGURE 6- outline of nephritic proteinuria

XIII. Summary

- A. Sodium is a primary determinant of ECF volume
- B. Under normal conditions sodium is tightly conserved to maintain effective hemodynamic and metabolic status when sodium intake is restricted
- C. Increments in total body sodium above the “set point” are a reflection of dietary sodium intake and provide a buffer against sudden loss of volume

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- D. Serum sodium concentrations in the absence of other observations is not an index of total body sodium
- E. Sodium retaining mechanisms are activated by perceived (not absolute) low volume status in edematous patients with CHF and cirrhosis
- F. Hypoalbuminemia at levels commonly observed in nephrotic syndrome is not a primary factor in the development of edema