Fluid and Electrolyte physiology

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COMPOSITION OF BODY FLUIDS

- Water is the most abundant constituent in the body, comprising ~50% of body weight in women and 60% in men.
- Total-body water is distributed in two major compartments:

➢ 55–75% is intracellular [ICF],

➢and 25–45% is extracellular [ECF] .

- The ECF is further subdivided into intravascular (plasma water) and extravascular (interstitial) spaces in a ratio of 1:3.

- Fluid movement between the intravascular and interstitial spaces occurs across the capillary wall and is determined by Starling forces, capillary hydraulic pressure and colloid osmotic pressure.
- The transcapillary hydraulic pressure gradient exceeds the corresponding oncotic pressure gradient, thereby favoring the movement of plasma ultrafiltrate into the extravascular space.
- The return of fluid into the intravascular compartment occurs via lymphatic flow.

- The solute or particle concentration of a fluid is known as its osmolality, expressed as milliosmoles per kilogram of water (mOsm/kg). Water easily diffuses across most cell membranes to achieve osmotic equilibrium (ECF osmolality = ICF osmolality).
- Notably, the extracellular and intracellular solute compositions differ considerably owing to the activity of various transporters, channels, and ATP-driven membrane pumps.
- The major ECF particles are Na and its accompanying anions Cl and HCO , whereas K and organic phosphate esters (ATP, creatine phosphate, and phospholipids) are the predominant ICF osmoles.
- Solutes that are restricted to the ECF or the ICF determine the “tonicity” or effective osmolality of that compartment.
- Certain solutes, particularly urea, do not contribute to water shifts across most membranes and are thus known as ***ineffective osmoles***

Water Balance

- Vasopressin secretion, water ingestion, and renal water transport collaborate to maintain human body fluid osmolality between 280 and 295 mOsm/kg.
- Vasopressin (AVP) is synthesized in magnocellular neurons within the hypothalamus; the distal axons of these neurons project to the posterior pituitary or neurohypophysis, from which AVP is released into the circulation.
- A network of central “osmoreceptor” neurons, which includes the AVP-expressing magnocellular neurons themselves, sense circulating osmolality via nonselective, stretch-activated cation channels.
- These osmoreceptor neurons are activated or inhibited by modest increases and decreases in circulating osmolality, respectively; activation leads to AVP release and thirst

- AVP secretion is stimulated as systemic osmolality increases above a threshold level of ~285 mOsm/kg, above which there is a linear relationship between osmolality and circulating AVP .
- Thirst and thus water ingestion are also activated at ~285 mOsm/kg, beyond which there is an equivalent linear increase in the perceived intensity of thirst as a function of circulating osmolality.
- Changes in blood volume and blood pressure are also direct stimuli for AVP release and thirst, albeit with a less sensitive response profile.
- Of perhaps greater clinical relevance to the pathophysiology of water homeostasis, ECF volume strongly modulates the relationship between circulating osmolality and AVP release, such that hypovolemia reduces the osmotic threshold and increases the slope of the response curve to osmolality; *hypervolemia* has an opposite effect, increasing the osmotic threshold and reducing the slope of the response curve

- Water transport across apical and basolateral aquaporin-1 water channels in the descending thin limb of the loop of Henle is thus involved, as is passive absorption of Na -Cl by the thin ascending limb, via apical and basolateral CLC-K1 chloride channels and paracellular Na transport.
- Renal urea transport in turn plays important roles in the generation of the medullary osmotic gradient and the ability to excrete solute-free water under conditions of both high and low protein intake.
- AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the CD, resulting in transepithelial water absorption down the medullary osmotic gradient

- Under “antidiuretic” conditions, with increased circulating AVP, the kidney reabsorbs water filtered by the glomerulus, equilibrating the osmolality across the CD epithelium to excrete a hypertonic, “concentrated” urine (osmolality of up to 1200 mOsm/kg).

- In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the CD is essentially abolished, resulting in secretion of a hypotonic, dilute urine (osmolality as low as 30–50 mOsm/kg).

- Abnormalities in this “final common pathway” are involved in most disorders of water homeostasis, a reduced or absent insertion of active aquaporin-2 water channels into the membrane of principal cells in diabetes insipidus (DI).

Maintenance of Arterial Circulatory Integrity

- Sodium is actively pumped out of cells by the Na /K -ATPase membrane pump. In consequence, 85–90% of body Na is extracellular, and the ECF volume (ECFV) is a function of total-body Na content.
- Arterial perfusion and circulatory integrity are, in turn, determined by renal Na retention or excretion, in addition to the modulation of systemic arterial resistance.
- Within the kidney, Na is filtered by the glomeruli and then sequentially reabsorbed by the renal tubules. The Na cation is typically reabsorbed with the chloride anion (Cl), and, thus, chloride homeostasis also affects the ECFV.
- On a quantitative level, at a glomerular filtration rate (GFR) of 180 L/d and serum Na of ~140 m*M*, the kidney filters some 25,200 mmol/d of Na . This is equivalent to ~1.5 kg of salt, which would occupy roughly 10 times the extracellular space; 99.6% of filtered Na -Cl must be reabsorbed to excrete 100 m*M* per day. Minute changes in renal Na -Cl excretion will thus have significant effects on the ECFV, leading to edema syndromes or hypovolemia.

- Approximately two-thirds of filtered Na -Cl is reabsorbed by the renal proximal tubule, via both paracellular and transcellular mechanisms.
- The TALH subsequently reabsorbs another 25–30% of filtered Na -Cl via the apical, furosemide-sensitive Na -K -2Cl cotransporter.
- The adjacent aldosterone-sensitive distal nephron, comprising the distal convoluted tubule (DCT), connecting tubule (CNT), and CD, accomplishes the “fine-tuning” of renal Na -Cl excretion.
- The thiazide-sensitive apical Na -Cl cotransporter (NCC) reabsorbs 5–10% of filtered Na -Cl in the DCT.
- Principal cells in the CNT and CD reabsorb Na via electrogenic, amiloride-sensitive epithelial Na channels (ENaC).

- Renal tubular reabsorption of filtered Na -Cl is regulated by multiple circulating and paracrine hormones, in addition to the activity of renal nerves.

- Angiotensin II activates proximal Na –Cl reabsorption, as do adrenergic receptors under the influence of renal sympathetic innervation; locally generated dopamine, in contrast, has a *natriuretic* effect.
- Aldosterone primarily activates Na –Cl reabsorption within the aldosterone-sensitive distal nephron.
- In particular, aldosterone activates the ENaC channel in principal cells, inducing Na absorption and promoting K excretion

- Circulatory integrity is critical for the perfusion and function of vital organs.
- “Underfilling” of the arterial circulation is sensed by ventricular and vascular pressure receptors, resulting in a neurohumoral activation (increased sympathetic tone, activation of the renin-angiotensin-aldosterone axis, and increased circulating AVP) that synergistically increases renal Na -Cl reabsorption, vascular resistance, and renal water reabsorption.
- This occurs in the context of decreased cardiac output, as occurs in hypovolemic states, low-output cardiac failure, decreased oncotic pressure, and/or increased capillary permeability. Alternatively, excessive arterial vasodilation results in *relative* arterial underfilling, leading to neurohumoral activation in the defense of tissue perfusion.

HYPOVOLEMIA

Etiology

- True volume depletion, or hypovolemia, generally refers to a state of combined salt and water loss,leading to contraction of the ECFV.
- The loss of salt and water may be renal or nonrenal in origin.

RENAL CAUSES

- Excessive urinary Na -Cl and water loss is a feature of several conditions:

❖ A high filtered load of endogenous solutes, such as glucose and urea, can impair tubular reabsorption of Na -Cl and water, leading to an osmotic diuresis.

❖ Exogenous mannitol, often used to decrease intracerebral pressure, is filtered by glomeruli but not reabsorbed by the proximal tubule, thus causing an osmotic diuresis.

❖ Pharmacologic diuretics selectively impair Na -Cl reabsorption at specific sites along the nephron, leading to increased urinary Na -Cl excretion.

❖ Other drugs can induce natriuresis as a side effect. For example, acetazolamide can inhibit proximal tubular Na -Cl absorption via its inhibition of carbonic anhydrase; other drugs, such as the antibiotics trimethoprim (TMP) and pentamidine, inhibit distal tubular Na reabsorption through the amiloride-sensitive ENaC channel, leading to urinary Na –Cl loss.

❖ Hereditary defects in renal transport proteins are also associated with reduced reabsorption of filtered Na -Cl and/or water.

❖ Alternatively, mineralocorticoid defficiency, mineralocorticoid resistance, or inhibition of the mineralocorticoid receptor (MLR) can reduce Na -Cl reabsorption by the aldosterone-sensitive distal nephron.

❖ Finally, tubulointerstitial injury, as occurs in interstitial nephritis, acute tubular injury, or obstructive uropathy, can reduce distal tubular Na -Cl and/or water absorption

- Excessive excretion of free water. water without electrolytes, can also lead to hypovolemia. However, the effect on ECFV is usually less marked, given that two-thirds of the water volume is lost from the ICF.
- Excessive renal water excretion occurs in the setting of decreased circulating AVP or renal resistance to AVP (central and nephrogenic DI, respectively).

EXTRARENAL CAUSES

- Nonrenal causes of hypovolemia include fluid loss from the gastrointestinal tract, skin, and respiratory system.
- Accumulations of fluid within specific tissue compartments, typically the interstitium, peritoneum, or gastrointestinal tract, can also cause hypovolemia.
- Approximately 9 L of fluid enter the gastrointestinal tract daily, 2 L by ingestion and 7 L by secretion; almost 98% of this volume is absorbed, such that daily fecal fluid loss is only 100–200 mL.
- Impaired gastrointestinal reabsorption or enhanced secretion of fluid can cause hypovolemia.
- Because gastric secretions have a low pH (high H concentration), whereas biliary, pancreatic, and intestinal secretions are alkaline (high HCO concentration), vomiting and diarrhea are often accompanied by metabolic alkalosis and acidosis, respectively

- Evaporation of water from the skin and respiratory tract (so-called “insensible losses”) constitutes the major route for loss of solute-free water, which is typically 500–650 mL/d in healthy adults.
- This evaporative loss can increase during febrile illness or prolonged heat exposure. Hyperventilation can also increase insensible losses via the respiratory tract, particularly in ventilated patients; the humidity of inspired air is another determining factor.
- In addition, increased exertion and/or ambient temperature will increase insensible losses via sweat, which is hypotonic to plasma. Profuse sweating without adequate repletion of water and Na -Cl can thus lead to both hypovolemia and hypertonicity.
- Alternatively, replacement of these insensible losses with a surfeit of free water, without adequate replacement of electrolytes, may lead to hypovolemic hyponatremia.

- Excessive fluid accumulation in interstitial and/or peritoneal spaces can also cause intravascular hypovolemia.
- Increases in vascular permeability and/or a reduction in oncotic pressure (hypoalbuminemia) alter Starling forces, resulting in excessive “third spacing” of the ECFV.
- This occurs in sepsis syndrome, burns, pancreatitis, nutritional hypoalbuminemia, and peritonitis.
- Alternatively, distributive hypovolemia can occur due to accumulation of fluid within specific compartments, for example within the bowel lumen in gastrointestinal obstruction or ileus.
- Hypovolemia can also occur after extracorporeal hemorrhage or after significant hemorrhage into an expandable space, for example, the retroperitoneum.

Diagnostic Evaluation

- A careful history will usually determine the etiologic cause of hypovolemia.
- Symptoms of hypovolemia are nonspecific and include fatigue, weakness, thirst, and postural dizziness; more severe symptoms and signs include oliguria, cyanosis, abdominal and chest pain, and confusion or obtundation.
- Associated electrolyte disorders may cause additional symptoms, for example, muscle weakness in patients with hypokalemia.
- On examination, diminished skin turgor and dry oral mucous membranes are less than ideal markers of a decreased ECFV in adult patients; more reliable signs of hypovolemia include a decreased jugular venous pressure (JVP), orthostatic tachycardia (an increase of >15–20 beats/min upon standing), and orthostatic hypotension (a >10–20 mmHg drop in blood pressure on standing).
- More severe fluid loss leads to hypovolemic shock, with hypotension, tachycardia, peripheral vasoconstriction, and peripheral hypoperfusion; these patients may exhibit peripheral cyanosis, cold extremities, oliguria, and altered mental status.

- Routine chemistries may reveal an increase in blood urea nitrogen (BUN) and creatinine, reflective of a decrease in GFR.
- Creatinine is the more dependable measure of GFR,
- because BUN levels may be influenced by an increase in tubular reabsorption (“prerenal azotemia”), an increase in urea generation in catabolic states, hyperalimentation, or gastrointestinal bleeding, and/or a decreased urea generation in decreased protein intake.
- In hypovolemic shock, liver function tests and cardiac biomarkers may show evidence of hepatic and cardiac ischemia, respectively.
- Routine chemistries and/or blood gases may reveal evidence of acid-base disorders. For example, bicarbonate loss due to diarrheal illness is a very common cause of metabolic acidosis; alternatively, patients with severe hypovolemic shock may develop lactic acidosis with an elevated anion gap.

- The neurohumoral response to hypovolemia stimulates an increase in renal tubular Na and water reabsorption.
- Therefore, the urine Na concentration is typically <20 m*M* in nonrenal causes of hypovolemia, with a urine osmolality of >450 mOsm/kg.
- The reduction in both GFR and distal tubular Na delivery may cause a defect in renal potassium excretion, with an increase in plasma K concentration.
- Of note, patients with hypovolemia and a hypochloremic alkalosis due to vomiting, diarrhea, or diuretics will typically have a urine Na concentration >20 m*M* and urine pH of >7.0, due to the increase in filtered HCO ; the urine Cl concentration in this setting is a more accurate indicator of volume status, with a level <25 m*M* suggestive of hypovolemia.
- The urine Na concentration is often >20 m*M* in patients with *renal* causes of hypovolemia, such as acute tubular necrosis; similarly, patients with DI will have an inappropriately dilute urine.

TREATMENT

- The therapeutic goals in hypovolemia are to restore normovolemia and replace ongoing fluid losses.
- Mild hypovolemia can usually be treated with oral hydration and resumption of a normal maintenance diet.
- More severe hypovolemia requires intravenous hydration, tailoring the choice of solution to the underlying pathophysiology.
- Isotonic, “normal” saline (0.9% NaCl, 154 m*M* Na) is the most appropriate resuscitation fluid for normonatremic or hyponatremic patients with severe hypovolemia; colloid solutions such as intravenous albumin are not demonstrably superior for this purpose.

TREATMENT

- Hypernatremic patients should receive a hypotonic solution, 5% dextrose if there has only been water loss (as in DI), or hypotonic saline (1/2 or 1/4 normal saline) if there has been water and Na -Cl loss; changes in free water administration should be made if necessary, based on frequent measuring of serum chemistries.
- Patients with bicarbonate loss and metabolic acidosis, as occur frequently in diarrhea, should receive intravenous bicarbonate, either an isotonic solution (150 meq of Na -HCO in 5% dextrose) or a more hypotonic bicarbonate solution in dextrose or dilute saline.
- Patients with severe hemorrhage or anemia should receive red cell transfusions, without increasing the hematocrit beyond 35%.