CHAPTER 49

Management of Patients with Fluid & Electrolyte Disturbances

KEY CONCEPTS

1. Osmotic pressure is generally dependent only on the number of nondiffusible solute particles. This is because the average kinetic energy of particles in solution is similar regardless of their mass.
2. Potassium is the most important determinant of intracellular osmotic pressure, whereas sodium is the most important determinant of extracellular osmotic pressure.
3. Fluid exchange between the intracellular and interstitial spaces is governed by the osmotic forces created by differences in nondiffusible solute concentrations.
4. Serious manifestations of hyponatremia are generally associated with plasma sodium concentrations <120 mEq/L.
5. Very rapid correction of hyponatremia has been associated with demyelinating lesions in the pons (central pontine myelinolysis), resulting in serious permanent neurological sequelae.
6. The major hazard of increases in extracellular volume is impaired gas exchange due to pulmonary interstitial edema, alveolar edema, or large collections of pleural or ascitic fluid.
7. Intravenous replacement of potassium chloride is usually reserved for patients with, or at risk for, significant cardiac manifestations or severe muscle weakness.
8. Because of its lethal potential, hyperkalemia exceeding 6 mEq/L should always be corrected.
9. Symptomatic hypercalcemia requires rapid treatment. The most effective initial treatment is rehydration followed by a brisk diuresis (urinary output 200–300 mL/h) utilizing administration of intravenous saline infusion and a loop diuretic to accelerate calcium excretion.
10. Symptomatic hypocalcemia is a medical emergency and should be treated immediately with intravenous calcium chloride (3–5 mL of a 10% solution) or calcium gluconate (10–20 mL of a 10% solution).
11. Some patients with severe hypophosphatemia may require mechanical ventilation postoperatively because of muscle weakness.
12. Marked hypermagnesemia can lead to respiratory and cardiac arrest.
13. Isolated hypomagnesemia should be corrected prior to elective procedures because of its potential for causing cardiac arrhythmias.

Fluid and electrolyte disturbances are extremely common in the perioperative period. Large volumes of intravenous fluids are frequently required to correct fluid deficits and compensate for blood loss during surgery. Major disturbances in fluid and electrolyte balance can rapidly alter cardiovascular, neurological, and neuromuscular functions, and anesthesia providers must have a clear understanding of normal water and electrolyte physiology. This chapter examines the body's fluid compartments and common water and electrolyte derangements, their treatment, and anesthetic implications. Acid–base disorders and intravenous fluid therapy are discussed in other chapters.

Nomenclature of Solutions

The system of international units (SI) has still not gained universal acceptance in clinical practice, and many older expressions of concentration remain in common use. Thus, for example, the quantity of a solute in a solution may be expressed in grams, moles, or equivalents. To complicate matters further, the concentration of a solution may be expressed either as quantity of solute per volume of solution or quantity of solute per weight of solvent.

MOLARITY, MOLALITY, & EQUIVALENCY

One mole of a substance represents 6.02×10^{23} molecules. The weight of this quantity in grams is commonly referred to as gram-molecular weight. Molarity is the standard SI unit of concentration that expresses the number of moles of solute per *liter* of solution. Molality is an alternative term that expresses moles of solute per *kilogram* of solvent. Equivalency is also commonly used for substances that ionize: the number of equivalents of an ion in solution is the number of moles multiplied by its charge (valence). Thus, a 1 M solution of $MgCl_2$ yields 2 equivalents of magnesium per liter and 2 equivalents of chloride per liter.

OSMOLARITY, OSMOLALITY, & TONICITY

Osmosis is the net movement of water across a semipermeable membrane as a result of a difference in nondiffusible solute concentrations between the two sides. *Osmotic pressure* is the pressure that must be applied to the side with more solute to prevent a net movement of water across the membrane to dilute the solute.

1 Osmotic pressure is generally dependent only on the number of nondiffusible solute particles. This is because the average kinetic energy of particles in solution is similar regardless of their mass. One osmole equals 1 mol of nondissociable substances. For substances that ionize, however, each mole results in *n* Osm, where *n* is the number of ionic species produced. Thus, 1 mol of a highly ionized substance such as NaCl dissolved in solution should produce 2 Osm; in reality ionic interaction between the cation and anion reduces the effective activity of each such that NaCl behaves as if it is only 75% ionized. A difference of 1 mOsm/L between two solutions results in an osmotic pressure of 19.3 mm Hg. The osmolarity of a solution is equal to the number of osmoles per *liter* of solution, whereas its osmolality equals the number of osmoles per *kilogram* of solvent. *Tonicity,* a term that is often used interchangeably with osmolarity and osmolality, refers to the effect a solution has on cell volume. An *isotonic* solution has no effect on cell volume, whereas *hypotonic* and *hypertonic* solutions increase and decrease cell volume, respectively.

Fluid Compartments

Body water is distributed between two major fluid compartments separated by cell membranes: intracellular fluid (ICF) and extracellular fluid (ECF). The latter can be further subdivided into intravascular and interstitial compartments. The interstitium includes all fluid that is both outside cells and outside the vascular endothelium. The relative contributions of each compartment to total body water (TBW) and body weight are delineated in **Table 49–1**.

TABLE 49–1 Body fluid compartments (based on average 70-kg male).

Compartment	Fluid as Percent Body Weight (%)	Total Body Water (%)	Fluid Volume (L)
Intracellular	40	67	28
Extracellular			
Interstitial	15	25	10.5
Intravascular	5	8	3.5
Total	60	100	42

The volume of fluid (water) within a compartment is determined by its solute composition and concentrations (Table 49–2). Differences in solute concentrations are largely due to the characteristics of the physical barriers that separate compartments (see below). The osmotic forces created by "trapped" solutes govern the distribution of water between compartments and ultimately each compartment's volume.

INTRACELLULAR FLUID

The outer membrane of cells plays an important role in regulating intracellular volume and composition. A membrane-bound adenosine triphosphate (ATP)–dependent pump exchanges Na^+ for K^+ in a 3:2 ratio. Because cell membranes are relatively impermeable to sodium and (to a lesser extent) potassium ions, potassium is concentrated intracellularly, whereas sodium is concentrated extracellularly. As a result, potassium is the most important determinant of intracellular osmotic pressure, whereas sodium is the most important determinant of extracellular osmotic pressure.

2

The impermeability of cell membranes to most proteins results in a high intracellular protein concentration. Because proteins act as nondiffusible solutes (anions), the unequal exchange ratio of 3 Na^+ for 2 K^+ by the cell membrane pump is critical in preventing relative intracellular hyperosmolality. Interference with Na^+–K^+-ATPase activity, as occurs during ischemia or hypoxia, results in progressive swelling of cells.

EXTRACELLULAR FLUID

The principal function of ECF is to provide a medium for delivery of cell nutrients and electrolytes and for removal of cellular waste products. Maintenance of a normal extracellular volume—particularly the circulating component (intravascular volume)—is critical. For the reasons described

TABLE 49–2 The composition of fluid compartments.

			Extracellular	
	Gram-Molecular Weight	Intracellular (mEq/L)	*Intravascular (mEq/L)*	*Interstitial (mEq/L)*
Sodium	23.0	10	145	142
Potassium	39.1	140	4	4
Calcium	40.1	<1	3	3
Magnesium	24.3	50	2	2
Chloride	35.5	4	105	110
Bicarbonate	61.0	10	24	28
Phosphorus	31.0[1]	75	2	2
Protein (g/dL)		16	7	2

[1] PO_4^{3-} is 95 g.

above, sodium is quantitatively the most important extracellular cation and the major determinant of extracellular osmotic pressure and volume. Changes in ECF volume are therefore related to changes in total body sodium content. The latter is a function of sodium intake, renal sodium excretion, and extrarenal sodium losses (see below).

Interstitial Fluid

Very little interstitial fluid is normally in the form of free fluid. Most interstitial water is in chemical association with extracellular proteoglycans, forming a gel. Interstitial fluid pressure is generally thought to be negative (about −5 mm Hg). As interstitial fluid volume increases, interstitial pressure also rises and eventually becomes positive. When the latter occurs, the free fluid in the gel increases rapidly and appears clinically as edema.

Because only small quantities of plasma proteins can normally cross capillary clefts, the protein content of interstitial fluid is relatively low (2 g/dL). Protein entering the interstitial space is returned to the vascular system via the lymphatic system.

Intravascular Fluid

Intravascular fluid, commonly referred to as plasma, is restricted to the intravascular space by the vascular endothelium. Most electrolytes (small ions) freely pass between plasma and the interstitium, resulting in nearly identical electrolyte composition. However, the tight intercellular junctions between adjacent endothelial cells impede the passage of plasma proteins to outside the intravascular compartment. As a result, plasma proteins (mainly albumin) are the only osmotically active solutes in fluid not normally exchanged between plasma and interstitial fluid.

Increases in extracellular volume are normally proportionately reflected in intravascular and interstitial volume. However, when interstitial pressure becomes positive, continued increases in ECF result in expansion of only the interstitial fluid compartment (Figure 49–1). In this way, the interstitial compartment acts as an overflow reservoir for the intravascular compartment. This is seen clinically in the form of tissue edema.

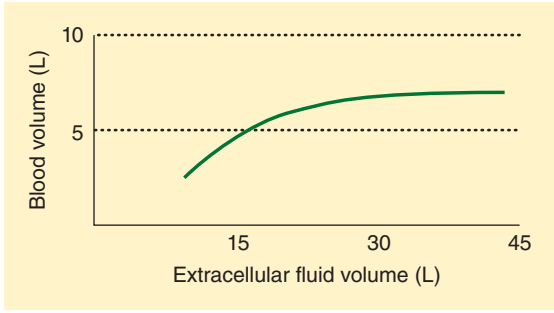

FIGURE 49–1 The relationship between blood volume and extracellular fluid volume. (Modified and reproduced, with permission, from Guyton AC: *Textbook of Medical Physiology,* 7th ed. W.B. Saunders, 1986.)

EXCHANGE BETWEEN FLUID COMPARTMENTS

Diffusion is the random movement of molecules due to their kinetic energy and is responsible for the majority of fluid and solute exchange between compartments. The rate of diffusion of a substance across a membrane depends upon (1) the permeability of that substance through that membrane, (2) the concentration difference for that substance between the two sides, (3) the pressure difference between either side because pressure imparts greater kinetic energy, and (4) the electrical potential across the membrane for charged substances.

Diffusion Through Cell Membranes

Diffusion between interstitial fluid and ICF may take place by one of several mechanisms: (1) directly through the lipid bilayer of the cell membrane, (2) through protein channels within the membrane, or (3) by reversible binding to a carrier protein that can traverse the membrane (facilitated diffusion). Oxygen, CO_2, water, and lipid-soluble molecules penetrate the cell membrane directly. Cations such as Na^+, K^+, and Ca^{2+} penetrate the membrane poorly because of the cell transmembrane voltage potential (which is positive to the outside) created by the Na^+–K^+ pump. Therefore, these cations can diffuse only through specific protein channels. Passage through these channels is

dependent on membrane voltage and the binding of ligands (such as acetylcholine) to the membrane receptors. Glucose and amino acids diffuse with the help of membrane-bound carrier proteins.

3 Fluid exchange between the intracellular and interstitial spaces is governed by the osmotic forces created by differences in nondiffusible solute concentrations. Relative changes in osmolality between the intracellular and interstitial compartments result in a net water movement from the hypoosmolar to the hyperosmolar compartment.

Diffusion Through Capillary Endothelium

Capillary walls are typically 0.5 µm thick, consisting of a single layer of endothelial cells with their basement membrane. Intercellular clefts, 6–7 nm wide, separate each cell from its neighbors. Oxygen, CO_2, water, and lipid-soluble substances can penetrate directly through both sides of the endothelial cell membrane. Only low-molecular-weight water-soluble substances such as sodium, chloride, potassium, and glucose readily cross intercellular clefts. High-molecular-weight substances such as plasma proteins penetrate the endothelial clefts poorly (except in the liver and the lungs, where the clefts are larger).

Fluid exchange across capillaries differs from that across cell membranes in that it is governed by significant differences in hydrostatic pressures in addition to osmotic forces (Figure 49–2). These forces are operative on both arterial and venous ends of capillaries, with a tendency for fluid to move out of capillaries at the arterial end and back into capillaries at the venous end. Moreover, the magnitude of these forces differs between the various tissue beds. Arterial capillary pressure is determined by precapillary sphincter tone. Thus capillaries that require a high pressure such as glomeruli have low precapillary sphincter tone, whereas the normally low-pressure capillaries of muscle have high precapillary sphincter tone. Normally, all but 10% of the fluid filtered is reabsorbed back into capillaries. What is not reabsorbed (about 2 mL/min) enters the interstitial fluid and is then returned by lymphatic flow to the intravascular compartment.

Disorders of Water Balance

The human body at birth is approximately 75% water by weight. By 1 month this value decreases to 65%, and by adulthood to 60% for males and 50% for females. The higher fat content in females decreases water content. For the same reason, obesity and advanced age further decrease water content.

NORMAL WATER BALANCE

The normal adult daily water intake averages 2500 mL, which includes approximately 300 mL as a byproduct of the metabolism of energy substrates. Daily water loss averages 2500 mL and is typically accounted for by 1500 mL in urine, 400 mL in respiratory tract evaporation, 400 mL in skin evaporation, 100 mL in sweat, and 100 mL in feces. Evaporative loss is very important in thermoregulation because this mechanism normally accounts for 20–25% of heat loss.

Both ICF and ECF osmolalities are tightly regulated to maintain normal water content in tissues. Changes in water content and cell volume can induce serious impairment of function, particularly in the brain (see below).

RELATIONSHIP OF PLASMA SODIUM CONCENTRATION, EXTRACELLULAR OSMOLALITY, & INTRACELLULAR OSMOLALITY

The osmolality of ECF is equal to the sum of the concentrations of all dissolved solutes. Because Na^+ and its anions account for nearly 90% of these solutes, the following approximation is valid:

$$\text{Plasma osmolality} = 2 \times \text{Plasma sodium concentration}$$

Moreover, because ICF and ECF are in osmotic equilibrium, plasma sodium concentration $[Na^+]_{plasma}$ generally reflects total body osmolality:

$$\text{Total body osmolality} = \frac{\text{Extracellular solutes} + \text{intracellular solutes}}{\text{TBW}}$$

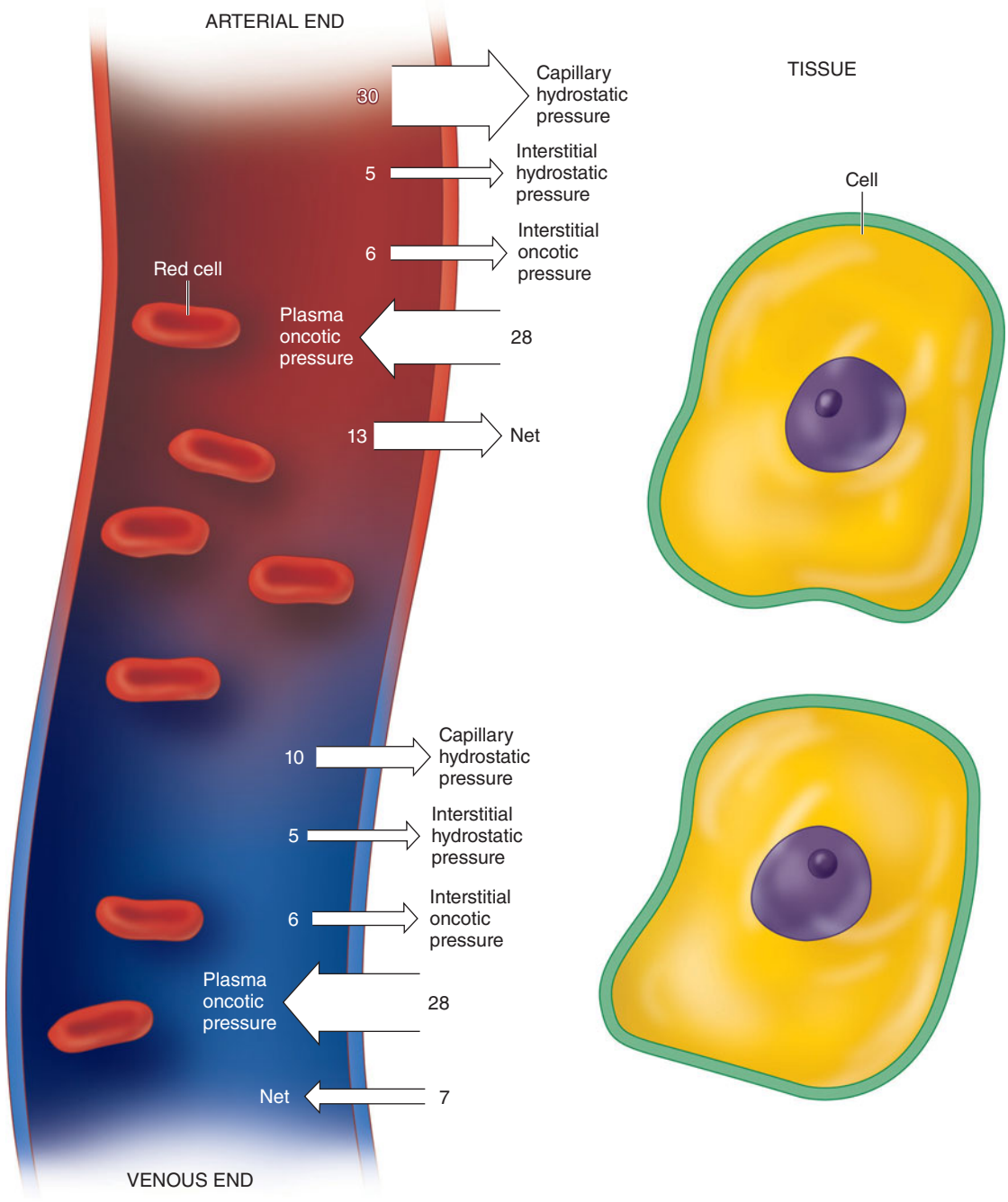

FIGURE 49–2 Capillary fluid exchange. The numbers in this figure are in mm Hg and indicate the pressure gradient for the respective pressures. "Net" refers to the net pressure at either end of the capillary, ie, 13 mm Hg at the arterial and 7 mm Hg at the venous end of the capillary.

Because sodium and potassium are the major intra- and extracellular solutes, respectively:

$$\text{Total body osmolality} = \frac{(Na^+_{\text{extracellular}} \times 2) + (K^+_{\text{intracellular solutes}} \times 2)}{\text{TBW}}$$

Combining the two approximations:

$$[Na^+]_{\text{plasma}} \approx \frac{Na^+_{\text{extracellular}} + K^+_{\text{intracellular}}}{\text{TBW}}$$

Using these principles, the effect of isotonic, hypotonic, and hypertonic fluid loads on compartmental water content and plasma osmolality can be calculated (**Table 49–3**). The potential importance of intracellular potassium concentration is readily apparent from this equation. Thus significant potassium losses may contribute to hyponatremia.

In pathological states, glucose and—to a much lesser extent—urea can contribute significantly to extracellular osmolality. A more accurate approximation of plasma osmolality is therefore given by the following equation:

$$\text{Plasma osmolality (mOsm/kg)} = [Na^+] \times 2 + \frac{\text{BUN}}{2.8} + \frac{\text{glucose}}{18}$$

where $[Na^+]$ is expressed as mEq/L and blood urea nitrogen (BUN) and glucose as mg/dL. Urea is an ineffective osmole because it readily permeates cell membranes and is therefore frequently omitted from this calculation:

$$\text{Effective plasma osmolality} = [Na^+] \times 2 + \frac{\text{glucose}}{18}$$

Plasma osmolality normally varies between 280 and 290 mOsm/L. Plasma sodium concentration decreases approximately 1 mEq/L for every 62 mg/dL increase in glucose concentration. A discrepancy between the measured and calculated osmolality is referred to as an *osmolal gap*. Significant osmolal gaps indicate a high concentration of an abnormal osmotically active molecule in plasma such as ethanol, mannitol, methanol, ethylene glycol, or isopropyl alcohol. Osmolal gaps may also be seen in patients with chronic kidney failure (attributed to retention of small solutes), patients with ketoacidosis (as a result of a high concentration of ketone bodies), and those receiving large amounts of glycine (as during transurethral resection of the prostate). Lastly, osmolal gaps may also be present in patients with marked hyperlipidemia or hyperproteinemia. In such instances, the protein or lipid

TABLE 49–3 Effect of different fluid loads on extracellular and intracellular water contents.[1]

A. Normal
Total body solute = 280 mOsm/kg × 42 kg = 11,760 mOsm
Intracellular solute = 280 mOsm/kg × 25 kg = 7000 mOsm
Extracellular solute = 280 mOsm/kg × 17 kg = 4760 mOsm
Extracellular sodium concentration = 280 ÷ 2 = 140 mEq/L

	Intracellular	Extracellular
Osmolality	280	280
Volume (L)	25	17
Net water gain	0	0

B. Isotonic load: 2 L of Isotonic saline (NaCl)
Total body solute = 280 mOsm/kg × 44 kg = 12,320 mOsm
Intracellular solute = 280 mOsm/kg × 25 kg = 7000 mOsm
Extracellular solute = 280 mOsm/kg × 19 kg = 5320 mOsm

	Intracellular	Extracellular
Osmolality	280	280
Volume (L)	25	19
Net water gain	0	2

Net effect: Fluid remains in extracellular compartment.

C. Free water (hypotonic) load: 2 L water
New body water = 42 + 2 = 44 kg
New body osmolality = 11,760 mOsm ÷ 44 kg = 267 mOsm/kg
New intracellular volume = 7000 mOsm ÷ 267 mOsm/kg = 26.2 kg
New extracellular sodium concentration = 267 ÷ 2 = 133 mEq/L

	Intracellular	Extracellular
Osmolality	267.0	267.0
Volume (L)	26.2	17.8
Net water gain	+1.2	+0.8

Net effect: Fluid distributes between both compartments.

D. Hypertonic load: 600 mEq NaCl (no water)
Total body solute = 11,760 + 600 = 12,360 mOsm/kg
New body osmolality = 12,360 mOsm/kg ÷ 42 kg = 294 mOsm
New extracellular solute = 600 + 4760 = 5360 mOsm
New extracellular volume = 5360 mOsm ÷ 294 mOsm/kg = 18.2 kg
New intracellular volume = 42 – 18.2 = 23.8 kg
New extracellular sodium concentration = 294 ÷ 2 = 147 mEq/L

	Intracellular	Extracellular
Osmolality	294.0	294.0
Volume (L)	23.8	18.2
Net water gain	–1.2	+1.2

Net effect: An intracellular to extracellular movement of water.

[1]Based on a 70-kg adult male.

part of plasma contributes significantly to plasma volume; although plasma [Na^+] is decreased, [Na^+] in the water phase of plasma (true plasma osmolality) remains normal. The water phase of plasma is normally only 93% of its volume; the remaining 7% consists of plasma lipids and proteins.

CONTROL OF PLASMA OSMOLALITY

Plasma osmolality is closely regulated by osmoreceptors in the hypothalamus. These specialized neurons control both the secretion of antidiuretic hormone (ADH) and the thirst mechanism. Plasma osmolality is therefore maintained within relatively narrow limits by varying both water intake and water excretion.

Secretion of Antidiuretic Hormone

Specialized neurons in the supraoptic and paraventricular nuclei of the hypothalamus are very sensitive to changes in extracellular osmolality. When ECF osmolality increases, these cells shrink and release ADH from the posterior pituitary. ADH markedly increases water reabsorption in renal collecting tubules (see Chapter 29), which tends to reduce plasma osmolality back to normal. Conversely, a decrease in extracellular osmolality causes osmoreceptors to swell and suppresses the release of ADH. Decreased ADH secretion allows a water diuresis, which tends to increase osmolality to normal. Peak diuresis occurs once circulating ADH is metabolized (90–120 min). With complete suppression of ADH secretion, the kidneys can excrete up to 10–20 L of water per day.

Nonosmotic Release of Antidiuretic Hormone

The carotid baroreceptors and probably atrial stretch receptors can also stimulate ADH release following a 5–10% decrease in blood volume. Other nonosmotic stimuli include pain, emotional stress, and hypoxia.

Thirst

Osmoreceptors in the lateral preoptic area of the hypothalamus are also very sensitive to changes in extracellular osmolality. Activation of these neurons by increases in ECF osmolality induces thirst and causes the individual to drink water. Conversely, hypoosmolality suppresses thirst. Thirst is the major defense mechanism against hyperosmolality and hypernatremia, because it is the only mechanism that increases water intake.

HYPEROSMOLALITY & HYPERNATREMIA

Hyperosmolality occurs whenever total body solute content increases relative to TBW and is usually, but not always, associated with hypernatremia ([Na^+] > 145 mEq/L). Hyperosmolality without hypernatremia may be seen during marked hyperglycemia or following the accumulation of abnormal osmotically active substances in plasma (see above). In the latter two instances, plasma sodium concentration may actually decrease as water is drawn from the intracellular to the extracellular compartment. For every 100 mg/dL increase in plasma glucose concentration, plasma sodium decreases approximately 1.6 mEq/L.

Hypernatremia is nearly always the result of either a relative loss of water in excess of sodium (hypotonic fluid loss) or the retention of large quantities of sodium. Even when renal concentrating ability is impaired, thirst is normally highly effective in preventing hypernatremia. Hypernatremia is therefore most commonly seen in debilitated patients who are unable to drink, the very aged, the very young, and patients with altered consciousness. Patients with hypernatremia may have a low, normal, or high total body sodium content (Table 49–4).

Hypernatremia & Low Total Body Sodium Content

These patients have lost both sodium and water, but the water loss is in relative excess to that of the sodium loss. Hypotonic losses can be renal (osmotic diuresis) or extrarenal (diarrhea or sweat). In either case, patients usually manifest signs of hypovolemia (see Chapter 51). Urinary sodium concentration is generally greater than 20 mEq/L with renal losses and less than 10 mEq/L with extrarenal losses.

TABLE 49–4 Major causes of hypernatremia.

Impaired thirst
Coma
Essential hypernatremia
Solute diuresis
Osmotic diuresis: diabetic ketoacidosis, nonketotic hyperosmolar coma, mannitol administration
Excessive water losses
Renal
Neurogenic diabetes insipidus
Nephrogenic diabetes insipidus
Extrarenal
Sweating
Combined disorders
Coma plus hypertonic nasogastric feeding

Hypernatremia & Normal Total Body Sodium Content

This group of patients generally manifests signs of water loss without overt hypovolemia unless the water loss is massive. Total body sodium content is generally normal. Nearly pure water losses can occur via the skin, respiratory tract, or kidneys. Occasionally transient hypernatremia is observed with movement of water into cells following exercise, seizures, or rhabdomyolysis. The most common cause of hypernatremia in conscious patients with normal total body sodium content is **diabetes insipidus**. Diabetes insipidus is characterized by marked impairment in renal concentrating ability that is due either to decreased ADH secretion (central diabetes insipidus) or failure of the renal tubules to respond normally to circulating ADH (nephrogenic diabetes insipidus). Rarely, "essential hypernatremia" may be encountered in patients with central nervous system disorders. These patients appear to have "reset" osmoreceptors that function at a higher baseline osmolality.

A. Central Diabetes Insipidus

Lesions in or around the hypothalamus and the pituitary stalk frequently produce diabetes insipidus. Diabetes insipidus often develops with brain death. Transient diabetes insipidus is also commonly seen following neurosurgical procedures and head trauma. The diagnosis is suggested by a history of polydipsia, polyuria (often >6 L/d), and the absence of hyperglycemia. In the perioperative setting, the diagnosis of diabetes insipidus is suggested by marked polyuria without glycosuria and a urinary osmolality lower than plasma osmolality. The absence of thirst in unconscious individuals leads to marked water losses and can rapidly produce hypovolemia. The diagnosis of central diabetes insipidus is confirmed by an increase in urinary osmolality following the administration of exogenous ADH. Aqueous vasopressin (5–10 units subcutaneously or intramuscularly every 4–6 h) is the treatment of choice for acute central diabetes insipidus. Vasopressin in oil (0.3 mL intramuscularly every day) is longer lasting but is more likely to cause water intoxication. Desmopressin (DDAVP), a synthetic analogue of ADH with a 12- to 24-h duration of action, is available as an intranasal preparation (10–40 mcg/d either as a single daily dose or divided into two doses) that can be used in both ambulatory and perioperative settings.

B. Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus can be congenital but is more commonly secondary to other disorders, including chronic kidney disease, hypokalemia and hypercalcemia, sickle cell disease, and hyperproteinemias. Nephrogenic diabetes insipidus can also be secondary to the side effects of some drugs (amphotericin B, lithium, demeclocycline, ifosfamide, mannitol). ADH secretion in nephrogenic diabetes insipidus is normal, but the kidneys fail to respond to ADH; urinary concentrating ability is therefore impaired. The mechanism may be either a decreased response to circulating ADH or interference with the renal countercurrent mechanism. The diagnosis is confirmed by failure of the kidneys to produce hypertonic urine following the administration of exogenous ADH. Treatment is generally directed at the underlying illness and ensuring an adequate fluid intake. Volume depletion by a thiazide diuretic can paradoxically decrease urinary output by reducing water delivery to collecting tubules. Sodium and protein restriction can similarly reduce urinary output.

Hypernatremia & Increased Total Body Sodium Content

This condition most commonly results from the administration of large quantities of hypertonic saline solutions (3% NaCl or 7.5% $NaHCO_3$). Patients with primary hyperaldosteronism and Cushing's syndrome may also have elevations in serum sodium concentration along with signs of increased sodium retention.

Clinical Manifestations of Hypernatremia

Neurological manifestations predominate in patients with hypernatremia and are generally thought to result from cellular dehydration. Restlessness, lethargy, and hyperreflexia can progress to seizures, coma, and ultimately death. Symptoms correlate more closely with the rate of movement of water out of brain cells than with the absolute level of hypernatremia. Rapid decreases in brain volume can rupture cerebral veins and result in focal intracerebral or subarachnoid hemorrhage. Seizures and serious neurological damage are common, particularly in children with acute hypernatremia when plasma [Na^+] exceeds 158 mEq/L. Chronic hypernatremia is usually better tolerated than the acute form. After 24–48 h, intracellular osmolality begins to rise as a result of increases in intracellular inositol and amino acid (glutamine and taurine) concentrations. As intracellular solute concentration increases, neuronal water content slowly returns to normal.

Treatment of Hypernatremia

The treatment of hypernatremia is aimed at restoring plasma osmolality to normal as well as correcting the underlying cause. Water deficits should generally be corrected over 48 h with a hypotonic solution such as 5% dextrose in water (see below). Abnormalities in extracellular volume must also be corrected (Figure 49–3). Hypernatremic patients with decreased total body sodium should be given isotonic fluids to restore plasma volume to normal *prior* to treatment with a hypotonic solution. Hypernatremic patients with increased total body sodium should be treated with a loop diuretic along with intravenous 5% dextrose in water. The treatment of diabetes insipidus is discussed above.

Rapid correction of hypernatremia can result in seizures, brain edema, permanent neurological damage, and even death. Serial Na^+ osmolalities should be obtained during treatment. In general, decreases in plasma sodium concentration should not proceed at a rate faster than 0.5 mEq/L/h.

Example

A 70-kg man is found to have a plasma [Na^+] of 160 mEq/L. What is his water deficit?

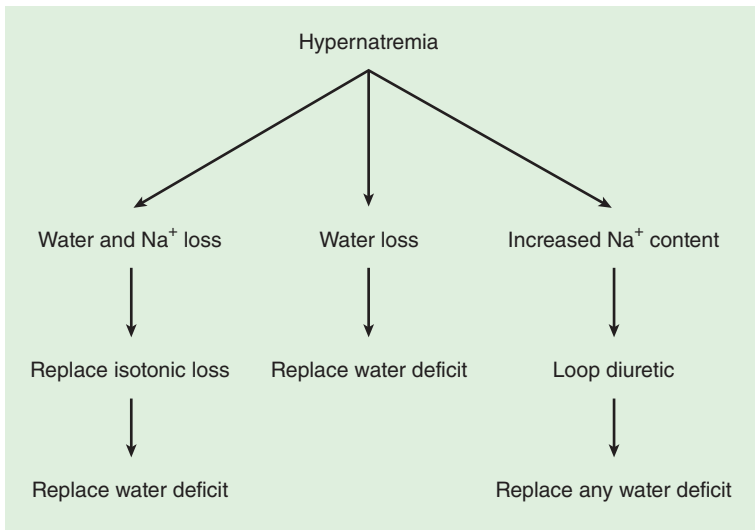

FIGURE 49–3 Algorithm for treatment of hypernatremia.

If one assumes that hypernatremia in this cases represents water loss only, then total body osmoles are unchanged. Thus, assuming a normal [Na^+] of 140 mEq/L and TBW content that is 60% of body weight:

$$\text{Normal TBW} \times 140 = \text{present TBW} \times [Na^+]_{plasma} \text{ or}$$

$$(70 \times 0.6) \times 140 = \text{present TBW} \times 160$$

Solving the equation:

$$\text{Present TBW} = 36.7 \text{ L}$$

$$\text{Water deficit} = \text{normal TBW} - \text{present TBW or}$$

$$(70 \times 0.6) - 36.7 = 5.3 \text{ L}$$

To replace this deficit over 48 h, it is necessary to give 5% dextrose in water intravenously, 5300 mL over 48 h, or 110 mL/h.

Note that this method ignores any coexisting isotonic fluid deficits, which if present should be replaced with an isotonic solution.

Anesthetic Considerations

Hypernatremia has been demonstrated to increase the minimum alveolar concentration for inhalation anesthetics in animal studies, but its clinical significance is more closely related to the associated fluid deficits. Hypovolemia accentuates any vasodilation or cardiac depression from anesthetic agents and predisposes to hypotension and hypoperfusion of tissues. Decreases in the volume of distribution for drugs necessitate dose reductions for most intravenous agents, whereas decreases in cardiac output enhance the uptake of inhalation anesthetics.

Elective surgery should be postponed in patients with significant hypernatremia (>150 mEq/L) until the cause is established and fluid deficits are corrected. Both water and isotonic fluid deficits should be corrected prior to elective surgery.

HYPOOSMOLALITY & HYPONATREMIA

Hypoosmolality is nearly always associated with hyponatremia ([Na^+] < 135 mEq/L). Table 49–5 lists rare instances in which hyponatremia does not necessarily reflect hypoosmolality (*pseudohyponatremia*). Routine measurement of plasma osmolality in hyponatremic patients rapidly excludes pseudohyponatremia.

TABLE 49–5 Causes of pseudohyponatremia.[1]

Hyponatremia with a normal plasma osmolality
Asymptomatic
Marked hyperlipidemia
Marked hyperproteinemia
Symptomatic
Marked glycine absorption during transurethral surgery
Hyponatremia with an elevated plasma osmolality
Hyperglycemia
Administration of mannitol

[1]Adapted from Rose RD: *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 3rd ed. McGraw-Hill, 1989.

Hyponatremia invariably reflects water retention from either an absolute increase in TBW or a loss of sodium in relative excess to loss of water. The kidneys' normal capacity to produce dilute urine with an osmolality as low as 40 mOsm/kg (specific gravity 1.001) allows them to excrete over 10 L of free water per day if necessary. Because of this tremendous reserve, hyponatremia is nearly always the result of a defect in urinary diluting capacity (urinary osmolality > 100 mOsm/kg or specific gravity > 1.003). Rare instances of hyponatremia without an abnormality in renal diluting capacity (urinary osmolality < 100 mOsm/kg) are generally attributed to primary polydipsia or reset osmoreceptors; the latter two conditions can be differentiated by water restriction.

Clinically, hyponatremia is best classified according to total body sodium content (Table 49–6). Hyponatremia associated with transurethral resection of the prostate is discussed in Chapter 31.

Hyponatremia & Low Total Body Sodium

Progressive losses of both sodium and water eventually lead to extracellular volume depletion. As the intravascular volume deficit reaches 5–10%, nonosmotic ADH secretion is activated (see above). With further volume depletion, the stimuli for nonosmotic ADH release overcome any hyponatremia-induced suppression of ADH. Preservation of circulatory volume takes place at the expense of plasma osmolality.

TABLE 49–6 Classification of hypoosmolal hyponatremia.

Decreased total sodium content
Renal
Diuretics
Mineralocorticoid deficiency
Salt-losing nephropathies
Osmotic diuresis (glucose, mannitol)
Renal tubular acidosis
Extrarenal
Vomiting
Diarrhea
Integumentary loss (sweating, burns)
"Third-spacing"
Normal total sodium content
Primary polydipsia
Syndrome of inappropriate antidiuretic hormone
Glucocorticoid deficiency
Hypothyroidism
Drug-induced
Increased total sodium content
Congestive heart failure
Cirrhosis
Nephrotic syndrome

Fluid losses resulting in hyponatremia may be renal or extrarenal in origin. Renal losses are most commonly related to thiazide diuretics and result in a urinary [Na^+] greater than 20 mEq/L. Extrarenal losses are typically gastrointestinal and usually produce a urinary [Na^+] of less than 10 mEq/L. A major exception to the latter is hyponatremia due to vomiting, which can result in a urinary [Na^+] greater than 20 mEq/L. In those instances, bicarbonaturia from the associated metabolic alkalosis obligates concomitant excretion of Na^+ with HCO_3 to maintain electrical neutrality in the urine; urinary chloride concentration, however, is usually less than 10 mEq/L.

Hyponatremia & Increased Total Body Sodium

Edematous disorders are characterized by an increase in both total body sodium and TBW. When the increase in water exceeds that in sodium, hyponatremia occurs. Edematous disorders include congestive heart failure, cirrhosis, kidney failure, and nephrotic syndrome. Hyponatremia in these settings results from progressive impairment of renal free water excretion and generally parallels underlying disease severity. Pathophysiological mechanisms include nonosmotic ADH release and decreased delivery of fluid to the distal diluting segment in nephrons (see Chapter 29). The "effective" circulating blood volume is reduced.

Hyponatremia with Normal Total Body Sodium

Hyponatremia in the absence of edema or hypovolemia may be seen with glucocorticoid insufficiency, hypothyroidism, drug therapy (chlorpropamide and cyclophosphamide), and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The hyponatremia associated with adrenal hypofunction may be due to cosecretion of ADH with corticotropin-releasing factor (CRF). Diagnosis of SIADH requires exclusion of other causes of hyponatremia and the absence of hypovolemia, edema, and adrenal, renal, or thyroid disease. Various malignant tumors, pulmonary diseases, and central nervous system disorders are commonly associated with SIADH. In most such instances, plasma ADH concentration is not elevated but is inadequately suppressed relative to the degree of hypoosmolality in plasma; urine osmolality is usually greater than 100 mOsm/kg and urine sodium concentration is greater than 40 mEq/L.

Clinical Manifestations of Hyponatremia

Symptoms of hyponatremia are primarily neurological and result from an increase in intracellular water. Their severity is generally related to the rapidity with which extracellular hypoosmolality develops. Patients with mild to moderate hyponatremia ([Na^+] > 125 mEq/L) are frequently asymptomatic. Early symptoms are typically nonspecific and may include anorexia, nausea, and weakness. Progressive cerebral edema, however, results in lethargy, confusion, seizures, coma, and finally death.

4 Serious manifestations of hyponatremia are generally associated with plasma sodium concentrations less than 120 mEq/L. Compared with

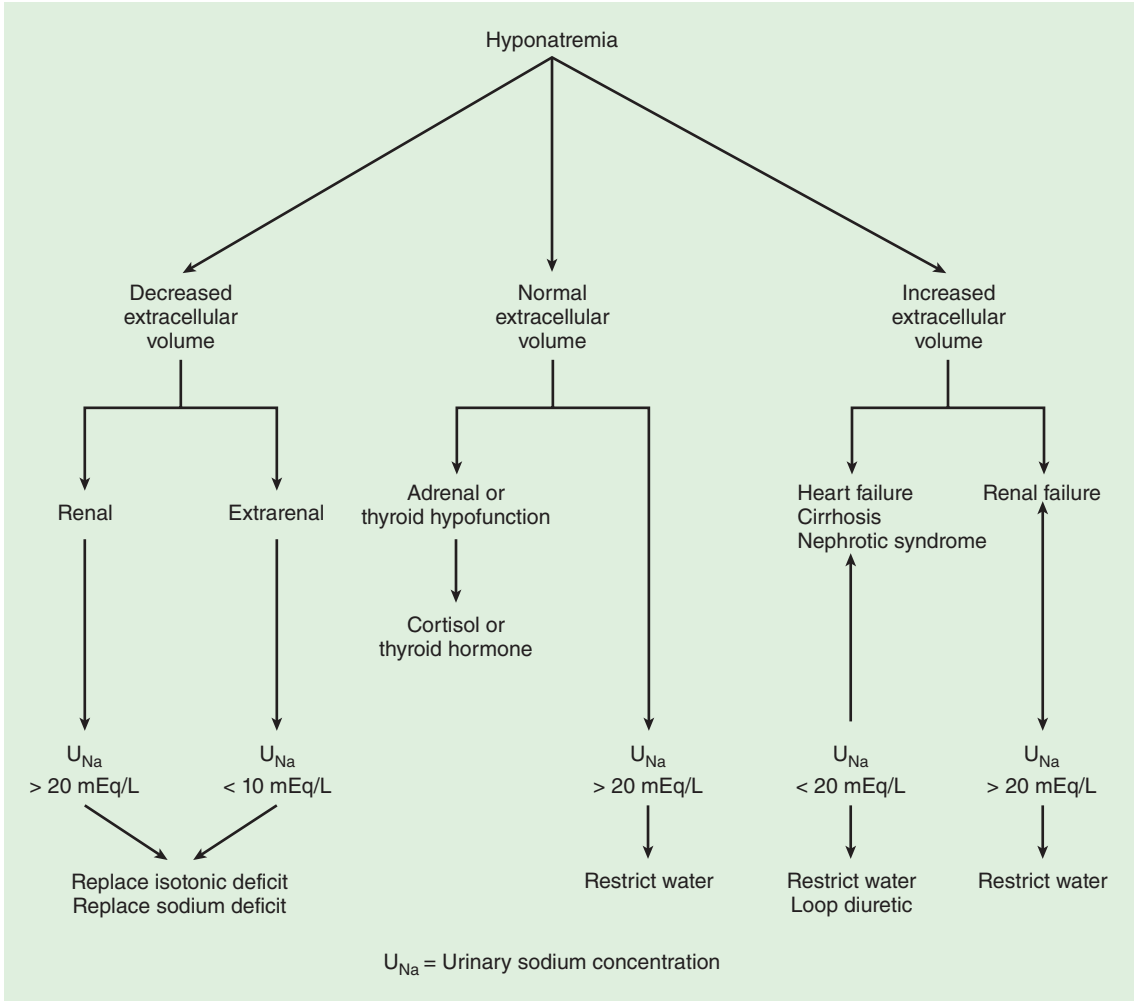

FIGURE 49–4 Algorithm for treatment of hyponatremia.

men, premenopausal women appear to be at greater risk of neurological impairment and damage from hyponatremia.

Patients with slowly developing or chronic hyponatremia are generally less symptomatic, probably because the gradual compensatory loss of intracellular solutes (primarily Na^+, K^+, and amino acids) restores cell volume to near normal. Neurological symptoms in patients with chronic hyponatremia may be related more closely to changes in cell membrane potential (due to a low extracellular [Na^+]) than to changes in cell volume.

Treatment of Hyponatremia

As with hypernatremia, the treatment of hyponatremia (Figure 49–4) is directed at correcting both the underlying disorder as well as the plasma [Na^+]. **Isotonic saline is generally the treatment of choice for hyponatremic patients with decreased total body sodium content.** Once the ECF deficit is corrected, spontaneous water diuresis returns plasma [Na^+] to normal. Conversely, water restriction is the primary treatment for hyponatremic patients with normal or increased total body sodium. More

specific treatments such as hormone replacement in patients with adrenal or thyroid hypofunction and measures aimed at improving cardiac output in patients with heart failure may also be indicated. Demeclocycline, a drug that antagonizes ADH activity at the renal tubules, has proved to be a useful adjunct to water restriction in the treatment of patients with SIADH.

Acute symptomatic hyponatremia requires prompt treatment. In such instances, correction of plasma [Na^+] to greater than 125 mEq/L is usually sufficient to alleviate symptoms. The amount of NaCl necessary to raise plasma [Na^+] to the desired value, the Na^+ deficit, can be estimated by the following formula:

$$Na^+ \text{ deficit} = TBW \times (\text{desired } [Na^+] - \text{present } [Na^+])$$

5 Excessively rapid correction of hyponatremia has been associated with demyelinating lesions in the pons (*central pontine myelinolysis*), resulting in permanent neurological sequelae. The rapidity with which hyponatremia is corrected should be tailored to the severity of symptoms. The following correction rates have been suggested: for mild symptoms, 0.5 mEq/L/h or less; for moderate symptoms, 1 mEq/L/h or less; and for severe symptoms, 1.5 mEq/L/h or less.

Example

An 80-kg woman is lethargic and is found to have plasma [Na^+] of 118 mEq/L. How much NaCl must be given to raise her plasma [Na^+] to 130 mEq/L?

$$Na^+ \text{ deficit} = TBW \times (130 - 118)$$

TBW is approximately 50% of body weight in females:

$$Na^+ \text{ deficit} = 80 \times 0.5 \times (130 - 118) = 480 \text{ mEq}$$

Because normal (isotonic) saline contains 154 mEq/L, the patient should receive 480 mEq ÷ 154 mEq/L, or 3.12 L of normal saline. For a correction rate of 0.5 mEq/L/h, this amount of saline should be given over 24 h (130 mL/h).

Note that this calculation does not take into account any coexisting isotonic fluid deficits, which, if present, should also be replaced. More rapid correction of hyponatremia can be achieved by giving a loop diuretic to induce water diuresis while replacing urinary Na^+ losses with isotonic saline. Even more rapid corrections can be achieved with intravenous hypertonic saline (3% NaCl). Hypertonic saline may be indicated in markedly symptomatic patients with plasma [Na^+] less than 110 mEq/L. Three percent NaCl should be given cautiously as it can precipitate pulmonary edema, hypokalemia, hyperchloremic metabolic acidosis, and transient hypotension; bleeding has been associated with prolongation of the prothrombin time and activated partial thromboplastin time.

Anesthetic Considerations

Hyponatremia is often a manifestation of a serious underlying disorder and requires careful preoperative evaluation. A plasma sodium concentration greater than 130 mEq/L is usually considered safe for patients undergoing general anesthesia. In most circumstances, plasma [Na^+] should be corrected to greater than 130 mEq/L for elective procedures, even in the absence of neurological symptoms. Lower concentrations may result in significant cerebral edema that can be manifested intraoperatively as a decrease in minimum alveolar concentration or postoperatively as agitation, confusion, or somnolence. Patients undergoing transurethral resection of the prostate can absorb signi cant amounts of water from irrigation fluids (as much as 20 mL/min) and are at high risk for rapid development of profound acute water intoxication.

Disorders of Sodium Balance

ECF volume is directly proportionate to total body sodium content. Variations in ECF volume result from changes in total body sodium content. A positive sodium balance increases ECF volume, whereas a negative sodium balance decreases ECF volume. It is important to reemphasize that *extracellular (plasma)* Na^+ *concentration is more indicative of water balance than total body sodium content.*

NORMAL SODIUM BALANCE

Net sodium balance is equal to total sodium intake (adults average 170 mEq/d) minus both renal sodium

excretion and extrarenal sodium losses. (One gram of sodium yields 43 mEq of Na^+ ions, whereas 1 g of sodium chloride yields 17 mEq of Na^+ ions.) The kidneys' ability to vary urinary Na^+ excretion from less than 1 mEq/L to more than 100 mEq/L allows them to play a critical role in sodium balance (see Chapter 29).

REGULATION OF SODIUM BALANCE & EXTRACELLULAR FLUID VOLUME

Because of the relationship between ECF volume and total body sodium content, regulation of one is intimately tied to the other. This regulation is achieved via sensors (see below) that detect changes in the most important component of ECF, namely, the "effective" intravascular volume. The latter correlates more closely with the rate of perfusion in renal capillaries than with measurable intravascular fluid (plasma) volume. Indeed, with edematous disorders (heart failure, cirrhosis, and kidney failure), "effective" intravascular volume can be independent of the measurable plasma volume, ECF volume, and even cardiac output.

ECF volume and total body sodium content are ultimately controlled by appropriate adjustments in renal Na^+ excretion. In the absence of kidney disease, diuretic therapy, and selective renal ischemia, urinary Na^+ concentration reflects "effective" intravascular volume. A low urine Na^+ concentration (<10 mEq/L) is therefore generally indicative of a low "effective" intravascular fluid volume and reflects secondary retention of Na^+ by the kidneys.

Control Mechanisms

The multiple mechanisms involved in regulating ECF volume and sodium balance normally complement one another but can function independently. In addition to altering renal Na^+ excretion, some mechanisms also produce more rapid compensatory hemodynamic responses when "effective" intravascular volume is reduced.

A. Sensors of Volume

Baroreceptors are the principal volume receptors in the body. Because blood pressure is the product of cardiac output and systemic vascular resistance (see Chapter 20), significant changes in intravascular volume (preload) not only affect cardiac output but also transiently affect arterial blood pressure. Thus, the baroreceptors at the carotid sinus and afferent renal arterioles (juxtaglomerular apparatus) indirectly function as sensors of intravascular volume. Changes in blood pressure at the carotid sinus modulate sympathetic nervous system activity and nonosmotic ADH secretion, whereas changes at the afferent renal arterioles modulate the renin–angiotensin–aldosterone system. Stretch receptors in both atria are affected by changes in intravascular volume, and the degree of atrial distention modulates the release of atrial natriuretic hormone and ADH.

B. Effectors of Volume Change

Regardless of the mechanism, effectors of volume change ultimately alter urinary Na^+ excretion. Decreases in "effective" intravascular volume decrease urinary Na^+ excretion, whereas increases in the "effective" intravascular volume increase urinary Na^+ excretion. These mechanisms include the following:

1. Renin–angiotensin–aldosterone—Renin secretion increases the formation of angiotensin II. The latter increases the secretion of aldosterone and has a direct effect in enhancing Na^+ reabsorption in the proximal renal tubules. Angiotensin II is also a potent direct vasoconstrictor and potentiates the actions of norepinephrine. Secretion of aldosterone enhances Na^+ reabsorption in the distal nephron (see Chapter 29) and is a major determinant of urinary Na^+ excretion.

2. Atrial natriuretic peptide (ANP)—This peptide is normally released from both right and left atrial cells following atrial distention. ANP appears to have two major actions: arterial vasodilation and increased urinary sodium and water excretion in the renal collecting tubules. Na^+-mediated afferent arteriolar dilation and efferent arteriolar constriction can also increase glomerular filtration rate (GFR). Other effects include the inhibition of both renin and aldosterone secretion and antagonism of ADH.

3. Brain natriuretic peptide (BNP)—ANP, BNP, and C-type natriuretic peptide are structurally related peptides. BNP is released by the ventricles in response to increased ventricular volume and pressure, and

ventricular overdistention, and also by the brain in response to increased blood pressure. BNP levels are usually approximately 20% of ANP levels, but during an episode of acute congestive heart failure BNP levels may exceed those of ANP. BNP levels can be measured clinically, and a recombinant form of BNP, nesiritide (Natrecor), is available to treat acute decompensated congestive heart failure.

4. Sympathetic nervous system activity— Enhanced sympathetic activity increases Na^+ reabsorption in the proximal renal tubules, resulting in Na^+ retention, and increases renal vasoconstriction, which reduces renal blood flow (see Chapter 29). Conversely, stimulation of left atrial stretch receptors results in decreases in renal sympathetic tone and increases in renal blood flow (cardiorenal reflex) and glomerular filtration.

5. Glomerular filtration rate and plasma sodium concentration—The amount of Na^+ filtered in the kidneys is directly proportionate to the product of the GFR and plasma Na^+ concentration. Because GFR is usually proportionate to intravascular volume, intravascular volume expansion can increase Na^+ excretion. Conversely, intravascular volume depletion decreases Na^+ excretion. Similarly, even small elevations of blood pressure can result in a relatively large increase in urinary Na^+ excretion because of the resultant increase in renal blood flow and glomerular filtration rate. Blood pressure–induced diuresis (*pressure natriuresis*) appears to be independent of any known humorally or neurally mediated mechanism.

6. Tubuloglomerular balance—Despite wide variations in the amount of Na^+ filtered in nephrons, Na^+ reabsorption in the proximal renal tubules is normally controlled within narrow limits. Factors considered to be responsible for tubuloglomerular balance include the rate of renal tubular flow and changes in peritubular capillary hydrostatic and oncotic pressures. Altered Na^+ reabsorption in the proximal tubules can have a marked effect on renal Na^+ excretion.

7. Antidiuretic hormone—Although ADH secretion has little effect on Na^+ excretion, nonosmotic secretion of this hormone (see above) can play an important part in maintaining extracellular volume with moderate to severe decreases in the "effective" intravascular volume.

TABLE 49–7 Osmoregulation versus volume regulation.[1]

	Volume Regulation	Osmoregulation
Purpose	Control extracellular volume	Control extracellular osmolality
Mechanism	Vary renal Na^+ excretion	Vary water intake Vary renal water excretion
Sensors	Afferent renal arterioles Carotid baroreceptors Atrial stretch receptors	Hypothalamic osmoreceptors
Effectors	Renin-angiotensin-aldosterone Sympathetic nervous system Tubuloglomerular balance Renal pressure natriuresis Atrial natriuretic peptide Antidiuretic hormone Brain natriuretic peptide	Thirst Antidiuretic hormone

[1]Adapted from Rose RD: *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 3rd ed. McGraw-Hill, 1989.

Extracellular Osmoregulation versus Volume Regulation

Osmoregulation protects the normal ratio of solutes to water, whereas extracellular volume regulation preserves absolute solute and water content (Table 49–7). As noted previously, volume regulation generally takes precedence over osmoregulation.

Anesthetic Implications

Problems related to altered sodium balance result from its manifestations as well as the underlying disorder. Disorders of sodium balance present either as hypovolemia (sodium deficit) or hypervolemia (sodium excess). Both disturbances should be corrected prior to elective surgical procedures. Cardiac, liver, and renal function should also be carefully evaluated in the presence of sodium excess (generally manifested as tissue edema).

Hypovolemic patients are sensitive to the vasodilating and negative inotropic effects of vapor anesthetics, propofol, and agents associated with histamine release (morphine, meperidine). Dosage

requirements for other drugs must also be reduced to compensate for decreases in their volume of distribution. Hypovolemic patients are particularly sensitive to sympathetic blockade from spinal or epidural anesthesia. If an anesthetic must be administered prior to adequate correction of hypovolemia, etomidate or ketamine may be the induction agents of choice for general anesthesia.

6 Hypervolemia should generally be corrected preoperatively with diuretics. The major hazard of increases in extracellular volume is impaired gas exchange due to pulmonary interstitial edema, alveolar edema, or large collections of pleural or ascitic fluid.

Disorders of Potassium Balance

Potassium plays a major role in the electrophysiology of cell membranes as well as in carbohydrate and protein synthesis (see below). The resting cell membrane potential is normally dependent on the ratio of intracellular to extracellular potassium concentrations. Intracellular potassium concentration is estimated to be 140 mEq/L, whereas extracellular potassium concentration is normally about 4 mEq/L. Under some conditions, a redistribution of K^+ between the ECF and ICF compartments can result in marked changes in extracellular [K^+] without a change in total body potassium content.

NORMAL POTASSIUM BALANCE

Dietary potassium intake averages 80 mEq/d in adults (range, 40–140 mEq/d). About 70 mEq of that amount is normally excreted in urine, whereas the remaining 10 mEq is lost through the gastrointestinal tract.

Renal excretion of potassium can vary from as little as 5 mEq/L to over 100 mEq/L. Nearly all the potassium filtered in glomeruli is normally reabsorbed in the proximal tubule and the loop of Henle. The potassium excreted in urine is the result of distal tubular secretion. Potassium secretion in the distal tubules is coupled to aldosterone-mediated reabsorption of sodium (see Chapter 29).

REGULATION OF EXTRACELLULAR POTASSIUM CONCENTRATION

Extracellular potassium concentration is determined by cell membrane Na^+–K^+-ATPase activity and plasma [K^+], and is influenced by the balance of potassium intake and excretion. Cell membrane Na^+–K^+-ATPase activity regulates the distribution of potassium between cells and ECF, whereas plasma [K^+] is the major determinant of urinary potassium excretion.

INTERCOMPARTMENTAL SHIFTS OF POTASSIUM

Intercompartmental shifts of potassium are known to occur following changes in extracellular pH (see Chapter 50), circulating insulin levels, circulating catecholamine activity, plasma osmolality, and possibly hypothermia. Insulin and catecholamines are known to directly affect Na^+–K^+-ATPase activity and decrease plasma [K^+]. Exercise can also transiently increase plasma [K^+] as a result of the release of K^+ by muscle cells; the increase in plasma [K^+] (0.3–2 mEq/L) is proportionate to the intensity and duration of muscle activity. Intercompartmental potassium shifts are also thought to be responsible for changes in plasma [K^+] in syndromes of periodic paralysis (see Chapter 35).

Because the ICF may buffer up to 60% of an acid load (see Chapter 50), changes in extracellular hydrogen ion concentration (pH) directly affect extracellular [K^+]. In the setting of acidosis, extracellular hydrogen ions enter cells, displacing intracellular potassium ions; the resultant movement of potassium ions out of cells maintains electrical balance but increases extracellular and plasma [K^+]. Conversely, during alkalosis, extracellular potassium ions move into cells to balance the movement of hydrogen ions out of cells; as a result, plasma [K^+] decreases. Although the relationship is variable, a useful rule of thumb is that plasma potassium concentration changes approximately 0.6 mEq/L per 0.1 unit change in arterial pH (range 0.2–1.2 mEq/L per 0.1 unit).

Changes in circulating insulin levels can directly alter plasma [K^+] independent of that hormone's effect on glucose transport. Insulin enhances the activity of membrane-bound Na^+–K^+-ATPase, increasing cellular uptake of potassium in the liver and in skeletal muscle, and insulin secretion may play an important role in the basal control of plasma potassium concentration and in the physiological response to increased potassium loads.

Sympathetic stimulation also increases intracellular uptake of potassium by enhancing Na^+–K^+-ATPase activity. This effect is mediated through activation of β_2-adrenergic receptors. In contrast, α-adrenergic activity may impair the intracellular movement of K^+. Plasma [K^+] often decreases following the administration of β_2-adrenergic agonists as a result of uptake of potassium by muscle and the liver. Moreover, β-adrenergic blockade can impair the handling of a potassium load in some patients.

Acute increases in plasma osmolality (hypernatremia, hyperglycemia, or mannitol administration) may increase plasma [K^+] (about 0.6 mEq/L per 10 mOsm/L). In such instances, the movement of water out of cells (down its osmotic gradient) is accompanied by movement of K^+ out of cells. The latter may be the result of "solvent drag" or the increase in intracellular [K^+] that follows cellular dehydration.

Hypothermia has been reported to lower plasma [K^+] as a result of cellular uptake. Rewarming reverses this shift and may result in transient hyperkalemia if potassium was given during the hypothermia.

Urinary Excretion of Potassium

Urinary potassium excretion generally parallels its extracellular concentration. Potassium is secreted by tubular cells in the distal nephron. Extracellular [K^+] is a major determinant of aldosterone secretion from the adrenal gland. Hyperkalemia stimulates aldosterone secretion, whereas hypokalemia suppresses aldosterone secretion. Renal tubular flow in the distal nephron may also be an important determinant of urinary potassium excretion because high tubular flow rates (as during osmotic diuresis) increase potassium secretion by keeping the capillary to renal tubular gradient for potassium secretion high. Conversely, slow tubular flow rates increase [K^+] in tubular fluid and decrease the gradient for K^+ secretion, thereby decreasing renal potassium excretion.

HYPOKALEMIA

Hypokalemia, defined as plasma [K^+] less than 3.5 mEq/L, can occur as a result of (1) an intercompartmental shift of K^+ (see above), (2) increased potassium loss, or (3) an inadequate potassium intake (Table 49–8). Plasma potassium concentration typically correlates poorly with the total potassium deficit. A decrease in plasma [K^+] from 4 mEq/L to 3 mEq/L usually represents a 100- to 200-mEq deficit, whereas plasma [K^+] below 3 mEq/L can represent a deficit anywhere between 200 mEq and 400 mEq.

TABLE 49–8 Major causes of hypokalemia.

Excess renal loss
Mineralocorticoid excess
Primary hyperaldosteronism (Conn's syndrome)
Glucocorticoid-remediable hyperaldosteronism
Renin excess
Renovascular hypertension
Bartter's syndrome
Liddle's syndrome
Diuresis
Chronic metabolic alkalosis
Antibiotics
Carbenicillin
Gentamicin
Amphotericin B
Renal tubular acidosis
Distal, gradient-limited
Proximal
Ureterosigmoidostomy
Gastrointestinal losses
Vomiting
Diarrhea, particularly secretory diarrheas
ECF → ICF shifts
Acute alkalosis
Hypokalemic periodic paralysis
Barium ingestion
Insulin therapy
Vitamin B_{12} therapy
Thyrotoxicosis (rarely)
Inadequate intake

Hypokalemia due to the Intracellular Movement of Potassium

Hypokalemia due to the intracellular movement of potassium occurs with alkalosis, insulin therapy, β_2-adrenergic agonists, and hypothermia and during attacks of hypokalemic periodic paralysis (see above). Hypokalemia may also be seen following transfusion of previously frozen red cells; these cells lose potassium in the preservation process and take up potassium following reinfusion. Cellular K^+ uptake by red blood cells (and platelets) also accounts for the hypokalemia seen in patients recently treated with folate or vitamin B_{12} for megaloblastic anemia.

Hypokalemia due to Increased Potassium Losses

Excessive potassium losses are usually either renal or gastrointestinal. Renal wasting of potassium is most commonly the result of diuresis or enhanced mineralocorticoid activity. Other renal causes include hypomagnesemia (see below), renal tubular acidosis (see Chapter 29), ketoacidosis, salt-wasting nephropathies, and some drug therapies (carbenicillin and amphotericin B). Increased gastrointestinal loss of potassium is most commonly due to nasogastric suctioning or to persistent vomiting or diarrhea. Other gastrointestinal causes include losses from fistulae, laxative abuse, villous adenomas, and pancreatic tumors secreting vasoactive intestinal peptide.

Chronic increased sweat formation occasionally causes hypokalemia, particularly when potassium intake is limited. Dialysis with a low-potassium-containing dialysate solution can also cause hypokalemia. Uremic patients may actually have a total body potassium deficit (primarily intracellular) despite a normal or even high plasma concentration; the absence of hypokalemia in these instances is probably due to an intercompartmental shift from the acidosis. Dialysis in these patients unmasks the total body potassium deficit and often results in hypokalemia.

Urinary $[K^+]$ less than 20 mEq/L is generally indicative of increased extrarenal losses, whereas concentrations greater than 20 mEq/L suggest renal wasting of K^+.

Hypokalemia due to Decreased Potassium Intake

Because of the kidney's ability to decrease urinary potassium excretion to as low as 5–20 mEq/L, marked reductions in potassium intake are required to produce hypokalemia. Low potassium intakes, however, often accentuate the effects of increased potassium losses.

Clinical Manifestations of Hypokalemia

Hypokalemia can produce widespread organ dysfunction (Table 49–9). Most patients are asymptomatic until plasma $[K^+]$ falls below 3 mEq/L. Cardiovascular effects are most prominent and include an abnormal ECG (Figure 49–5), arrhythmias, decreased cardiac contractility, and a labile arterial blood pressure due to autonomic dysfunction. Chronic hypokalemia has also been reported to cause myocardial fibrosis. **ECG manifestations are primarily due to delayed ventricular repolarization and include T-wave flattening and inversion, an increasingly prominent U wave, ST-segment depression, increased P-wave amplitude, and prolongation of the P–R interval.**

TABLE 49–9 Effects of hypokalemia.[1]

Cardiovascular
Electrocardiographic changes/arrhythmias
Myocardial dysfunction
Neuromuscular
Skeletal muscle weakness
Tetany
Rhabdomyolysis
Ileus
Renal
Polyuria (nephrogenic diabetes insipidus)
Increased ammonia production
Increased bicarbonate reabsorption
Hormonal
Decreased insulin secretion
Decreased aldosterone secretion
Metabolic
Negative nitrogen balance
Encephalopathy in patients with liver disease

[1]Adapted from Schrier RW, ed: *Renal and Electrolyte Disorders*, 3rd ed. Little, Brown and Company, 1986.

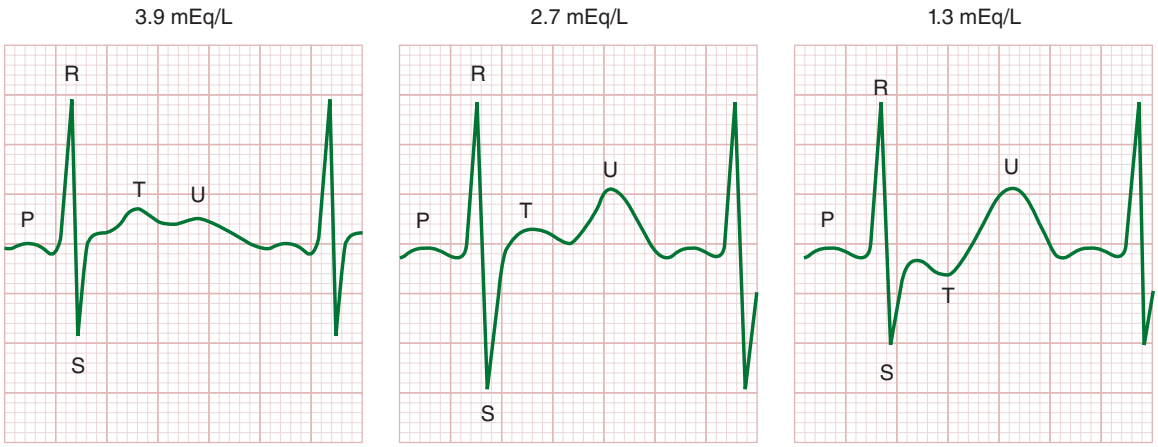

FIGURE 49–5 Electrocardiographic effects of acute hypokalemia. Note progressive flattening of the T wave, an increasingly prominent U wave, increased amplitude of the P wave, prolongation of the P–R interval, and ST-segment depression.

Increased myocardial cell automaticity and delayed repolarization promote both atrial and ventricular arrhythmias.

Neuromuscular effects of hypokalemia include skeletal muscle weakness, flaccid paralysis, hyporeflexia, muscle cramping, ileus, and, rarely, rhabdomyolysis. Hypokalemia induced by diuretics is often associated with metabolic alkalosis; as the kidneys absorb sodium to compensate for intravascular volume depletion and in the presence of diuretic-induced hypochloremia, bicarbonate is absorbed. The end result is hypokalemia and hypochloremic metabolic alkalosis. Renal dysfunction is seen due to impaired concentrating ability (resistance to ADH, resulting in polyuria) and increased production of ammonia resulting in impairment of urinary acidification. Increased ammonia production represents intracellular acidosis; hydrogen ions move intracellularly to compensate for intracellular potassium losses. The resulting metabolic alkalosis, together with increased ammonia production, can precipitate encephalopathy in patients with advanced liver disease. Chronic hypokalemia has been associated with renal fibrosis (tubulointerstitial nephropathy).

Treatment of Hypokalemia

The treatment of hypokalemia depends on the presence and severity of any associated organ dysfunction. Significant ECG changes such as ST-segment changes or arrhythmias mandate continuous ECG monitoring, particularly during intravenous K^+ replacement. Digoxin therapy—as well as the hypokalemia itself—sensitizes the heart to changes in potassium ion concentration. Muscle strength should also be periodically assessed in patients with weakness.

In most circumstances, the safest method by which to correct a potassium deficit is oral replacement over several days using a potassium chloride solution (60–80 mEq/d). Intravenous replacement of potassium chloride is usually be reserved for patients with, or at risk for, significant cardiac manifestations or severe muscle weakness. The goal of intravenous therapy is to remove the patient from immediate danger, not to correct the entire potassium deficit. Because of potassium's irritative effect on peripheral veins, peripheral intravenous replacement should not exceed 8 mEq/h. Dextrose-containing solutions should generally be avoided because the resulting hyperglycemia and secondary insulin secretion may actually worsen the low plasma $[K^+]$. More rapid intravenous potassium replacement (10–20 mEq/h) requires central venous administration and close monitoring of the ECG. Intravenous replacement should generally not exceed 240 mEq/d.

Potassium chloride is the preferred potassium salt when a metabolic alkalosis is also present because it also corrects the chloride deficit discussed above. Potassium bicarbonate or equivalent (K^+ acetate or K^+ citrate) is preferable for patients with metabolic acidosis. Potassium phosphate is a suitable alternative with concomitant hypophosphatemia (diabetic ketoacidosis).

Anesthetic Considerations

Hypokalemia is a common preoperative finding. The decision to proceed with elective surgery is often based on lower plasma [K^+] limits somewhere between 3 and 3.5 mEq/L. The decision, however, should also be based on the rate at which the hypokalemia developed as well as the presence or absence of secondary organ dysfunction. In general, chronic mild hypokalemia (3–3.5 mEq/L) without ECG changes does not substantially increase anesthetic risk. The latter may not apply to patients receiving digoxin, who may be at increased risk of developing digoxin toxicity from the hypokalemia; plasma [K^+] values above 4 mEq/L are desirable in such patients.

The intraoperative management of hypokalemia requires vigilant ECG monitoring. Intravenous potassium should be given if atrial or ventricular arrhythmias develop. Glucose-free intravenous solutions should be used and hyperventilation avoided to prevent further decreases in plasma [K^+]. Increased sensitivity to neuromuscular blockers (NMBs) may be seen; therefore dosages of NMBs should be reduced 25–50%, and a nerve stimulator should be used to follow both the degree of paralysis and the adequacy of reversal.

HYPERKALEMIA

Hyperkalemia exists when plasma [K^+] exceeds 5.5 mEq/L. Hyperkalemia rarely occurs in normal individuals because of the kidney's capability to excrete large potassium loads. When potassium intake is increased slowly, the kidneys can excrete as much as 500 mEq of K^+ per day. The sympathetic nervous system and insulin secretion also play important roles in preventing acute increases in plasma [K^+] following acquired potassium loads.

TABLE 49–10 Causes of hyperkalemia.

Pseudohyperkalemia
Red cell hemolysis
Marked leukocytosis/thrombocytosis
Intercompartmental shifts
Acidosis
Hypertonicity
Rhabdomyolysis
Excessive exercise
Periodic paralysis
Succinylcholine
Decreased renal potassium excretion
Renal failure
Decreased mineralocorticoid activity and impaired Na^+ reabsorption
Acquired immunodeficiency syndrome
Potassium-sparing diuretics
Spironolactone
Eplerenone
Amiloride
Triamterene
ACE[1] inhibitors
Nonsteroidal antiinflammatory drugs
Pentamidine
Trimethoprim
Enhanced Cl^- reabsorption
Gordon's syndrome
Cyclosporine
Increased potassium intake
Salt substitutes

[1]ACE, angiotensin-converting enzyme.

Hyperkalemia can result from (1) an intercompartmental shift of potassium ions, (2) decreased urinary excretion of potassium, or, rarely, (3) an increased potassium intake (Table 49–10). Measurements of plasma potassium concentration can be spuriously elevated if red cells hemolyze in a blood specimen. In vitro release of potassium from white cells in a blood specimen can also falsely indicate increased levels in the measured plasma [K^+] when the leukocyte count exceeds $70{,}000 \times 10^9$/L. A similar release of potassium from platelets occurs when the platelet count exceeds $1{,}000{,}000 \times 10^9$/L.

Hyperkalemia due to Extracellular Movement of Potassium

Movement of K^+ out of cells can be seen with acidosis, cell lysis following chemotherapy, hemolysis,

rhabdomyolysis, massive tissue trauma, hyperosmolality, digitalis overdoses, during episodes of hyperkalemic periodic paralysis, and with administration of succinylcholine, β_2-adrenergic blockers, and arginine hydrochloride. The average increase in plasma [K^+] of 0.5 mEq/L following succinylcholine administration can be exaggerated in patients with large burns or severe muscle trauma and in those with muscle denervation, and its use in these settings should be avoided.

β_2-Adrenergic blockade accentuates the increase in plasma [K^+] that occurs following exercise. Digoxin inhibits Na^+–K^+-ATPase in cell membranes, and digoxin overdose has been reported to cause hyperkalemia in some patients. Arginine hydrochloride, which is used to treat metabolic alkalosis, evaluate pituitary growth hormone reserve, and as a performance-enhancing supplement by athletes, can cause hyperkalemia as the cationic arginine ions enter cells and potassium ions move out to maintain electroneutrality.

Hyperkalemia due to Decreased Renal Excretion of Potassium

Decreased renal excretion of potassium can result from (1) marked reductions in glomerular filtration, (2) decreased aldosterone activity, or (3) a defect in potassium secretion in the distal nephron.

Glomerular filtration rates less than 5 mL/min are nearly always associated with hyperkalemia. Patients with lesser degrees of renal impairment can also readily develop hyperkalemia when faced with increased potassium loads (dietary, catabolic, or iatrogenic). Uremia may also impair Na^+–K^+-ATPase activity.

Hyperkalemia due to decreased aldosterone activity can result from a primary defect in adrenal hormone synthesis or a defect in the renin–aldosterone system. Patients with primary adrenal insufficiency (Addison's disease) and those with isolated 21-hydroxylase adrenal enzyme deficiency have marked impairment of aldosterone synthesis. Patients with the syndrome of isolated hypoaldosteronism (also called hyporeninemic hypoaldosteronism, or type IV renal tubular acidosis) are usually diabetics with some degree of renal impairment; they have an impaired ability to increase aldosterone secretion in response to hyperkalemia. Although usually asymptomatic, these patients develop hyperkalemia when they increase their potassium intake or when given potassium-sparing diuretics. They also often have varying degrees of Na^+ wasting and a hyperchloremic metabolic acidosis. Similar findings have been reported in patients with AIDS who have relative adrenal insufficiency due to cytomegalovirus infection.

Drugs interfering with the renin–aldosterone system have the potential to cause hyperkalemia, particularly in the presence of any degree of renal impairment. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit prostaglandin-mediated renin release. Angiotensin-converting enzyme (ACE) inhibitors interfere with angiotensin II–mediated release of aldosterone. Large doses of heparin can interfere with aldosterone secretion. The potassium-sparing diuretic spironolactone directly antagonizes aldosterone activity at the kidneys.

Decreased renal excretion of potassium can also occur as a result of an intrinsic or acquired defect in the distal nephron's ability to secrete potassium. Such defects may occur even in the presence of normal renal function and are characteristically unresponsive to mineralocorticoid therapy. The kidneys of patients with pseudohypoaldosteronism display an intrinsic resistance to aldosterone. Acquired defects have been associated with systemic lupus erythematosus, sickle cell anemia, obstructive uropathies, and cyclosporine nephropathy in transplanted kidneys.

Hyperkalemia due to Increased Potassium Intake

Increased potassium loads rarely cause hyperkalemia in normal individuals unless large amounts are given rapidly and intravenously. Hyperkalemia, however, may be seen when potassium intake is increased in patients receiving β blockers or in patients with renal impairment. Unrecognized sources of potassium include potassium penicillin, sodium substitutes (primarily potassium salts), and transfusion of stored whole blood. The plasma [K^+] in a unit of whole blood can increase to 30 mEq/L after 21 days of storage. The risk of hyperkalemia from multiple transfusions is reduced, although not

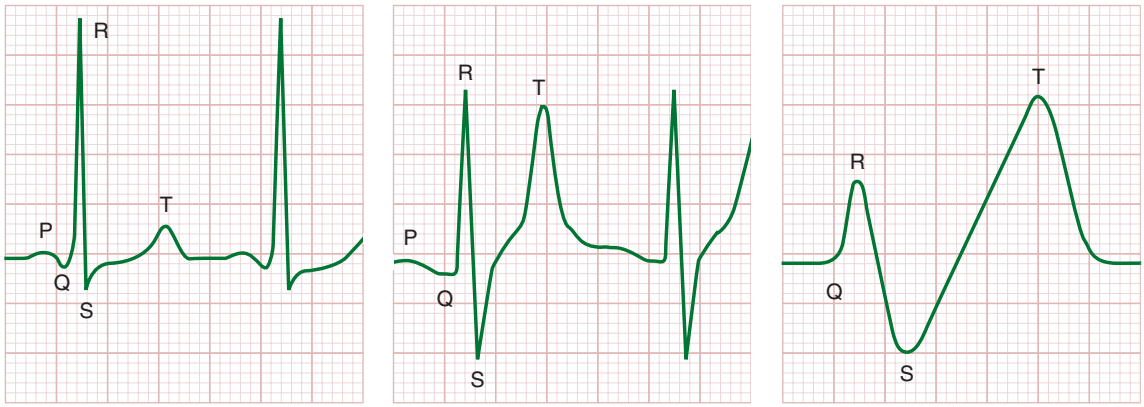

FIGURE 49–6 Electrocardiographic effects of hyperkalemia. Electrocardiographic changes characteristically progress from symmetrically peaked T waves, often with a shortened QT interval, to widening of the QRS complex, prolongation of the P–R interval, loss of the P wave, loss of R-wave amplitude, and ST-segment depression (occasionally elevation)—to an ECG that resembles a sine wave—before final progression into ventricular fibrillation or asystole.

eliminated, by minimizing the volume of plasma given through the use of packed red blood cell transfusions (see Chapter 51).

Clinical Manifestations of Hyperkalemia

The most important effects of hyperkalemia are on skeletal and cardiac muscle. Skeletal muscle weakness is generally not seen until plasma [K^+] is greater than 8 mEq/L, and is due to sustained spontaneous depolarization and inactivation of Na^+ channels of muscle membrane, eventually resulting in paralysis. Cardiac manifestations (Figure 49–6) are primarily due to delayed depolarization, and are consistently present when plasma [K^+] is greater than 7 mEq/L. ECG changes characteristically progress sequentially from symmetrically peaked T waves (often with a shortened QT interval) → widening of the QRS complex → prolongation of the P–R interval → loss of the P wave → loss of R-wave amplitude → ST-segment depression (occasionally elevation) → an ECG that resembles a sine wave, before progression to ventricular fibrillation and asystole. Contractility may be relatively well preserved until late in the course of progressive hyperkalemia. Hypocalcemia, hyponatremia, and acidosis accentuate the cardiac effects of hyperkalemia.

Treatment of Hyperkalemia

8 Because of its lethal potential, hyperkalemia exceeding 6 mEq/L should always be corrected. Treatment is directed to reversal of cardiac manifestations and skeletal muscle weakness, and to restoration of normal plasma [K^+]. Therapeutic modalities employed depend on the cause of hyperkalemia and the severity of manifestations. Hyperkalemia associated with hypoaldosteronism can be treated with mineralocorticoid replacement. Drugs contributing to hyperkalemia should be discontinued and sources of increased potassium intake reduced or stopped.

Calcium (5–10 mL of 10% calcium gluconate or 3–5 mL of 10% calcium chloride) partially antagonizes the cardiac effects of hyperkalemia and is useful in patients with marked hyperkalemia. Its effects are rapid but short lived. Care must be exercised in administering calcium to patients taking digoxin, as calcium potentiates digoxin toxicity.

When metabolic acidosis is present, intravenous sodium bicarbonate (usually 45 mEq) will promote cellular uptake of potassium and can decrease plasma [K^+] within 15 min. β Agonists promote cellular uptake of potassium and may be useful in acute hyperkalemia associated with massive transfusions; low-dose epinephrine infusion often rapidly

decreases plasma [K^+] and provides inotropic support in this setting. An intravenous infusion of glucose and insulin (30–50 g of glucose with 10 units of insulin) is also effective in promoting cellular uptake of potassium and lowering plasma [K^+], but may take up to 1 h for peak effect.

For patients with some renal function, furosemide is a useful adjunct in increasing urinary excretion of potassium. In the absence of renal function, elimination of excess potassium can be accomplished only with nonabsorbable cation-exchange resins such as oral or rectal sodium polystyrene sulfonate (Kayexalate). Each gram of resin binds up to 1 mEq of K^+ and releases 1.5 mEq of Na^+; the oral dose is 20 g in 100 mL of 20% sorbitol.

Dialysis is indicated in symptomatic patients with severe or refractory hyperkalemia. Hemodialysis is faster and more effective than peritoneal dialysis in decreasing plasma [K^+]. Maximal potassium removal with hemodialysis approaches 50 mEq/h, compared with 10–15 mEq/h for peritoneal dialysis.

Anesthetic Considerations

Elective surgery should not be undertaken in patients with significant hyperkalemia. Anesthetic management of hyperkalemic surgical patients is directed at both lowering the plasma potassium concentration and preventing any further increases. The ECG should be carefully monitored. Succinylcholine is contraindicated, as is the use of any potassium-containing intravenous solutions such as lactated Ringer's injection. The avoidance of metabolic or respiratory acidosis is critical to prevent further increases in plasma [K^+]. Ventilation should be controlled under general anesthesia, and mild hyperventilation may be desirable. Lastly, neuromuscular function should be monitored closely, as hyperkalemia can accentuate the effects of NMBs.

Disorders of Calcium Balance

Although 98% of total body calcium is in bone, maintenance of a normal extracellular calcium concentration is critical to homeostasis. Calcium ions are involved in nearly all essential biological functions, including muscle contraction, the release of neurotransmitters and hormones, blood coagulation, and bone metabolism, and abnormalities in calcium balance can result in profound physiological derangements.

NORMAL CALCIUM BALANCE

Calcium intake in adults averages 600–800 mg/d. Intestinal absorption of calcium occurs primarily in the proximal small bowel but is variable. Calcium is also secreted into the intestinal tract; moreover, this secretion appears to be constant and independent of absorption. Up to 80% of the daily calcium intake is normally lost in feces.

The kidneys are responsible for most calcium excretion. Renal calcium excretion averages 100 mg/d but may vary from as low as 50 mg/d to more than 300 mg/d. Normally, 98% of the filterable calcium is reabsorbed. Calcium reabsorption parallels that of sodium in the proximal renal tubules and the ascending loop of Henle. In the distal tubules, however, calcium reabsorption is dependent on parathyroid hormone (PTH) secretion, whereas sodium reabsorption is dependent on aldosterone secretion. Increased PTH levels enhance distal calcium reabsorption and thereby decrease urinary calcium excretion.

Plasma Calcium Concentration

The normal plasma calcium concentration is 8.5–10.5 mg/dL (2.1–2.6 mmol/L). Approximately 50% is in the free ionized form, 40% is protein bound (mainly to albumin), and 10% is complexed with anions such as citrate and amino acids. The free ionized calcium concentration ([Ca^{2+}]) is physiologically most important. Plasma [Ca^{2+}] is normally 4.75–5.3 mg/dL (2.38–2.66 mEq/L or 1.19–1.33 mmol/L). Changes in plasma albumin concentration affect total but not ionized calcium concentrations: for each increase or decrease of 1 g/dL in albumin, the total plasma calcium concentration increases or decreases approximately 0.8–1.0 mg/dL, respectively.

Changes in plasma pH directly affect the degree of protein binding and thus ionized calcium concentration. Ionized calcium increases approximately

0.16 mg/dL for each decrease of 0.1 unit in plasma pH and decreases by the same amount for each 0.1 unit increase in pH.

Regulation of Extracellular Ionized Calcium Concentration

Calcium normally enters ECF by either absorption from the intestinal tract or resorption of bone; only 0.5–1% of calcium in bone is exchangeable with ECF. In contrast, calcium normally leaves the extracellular compartment by (1) deposition into bone, (2) urinary excretion, (3) secretion into the intestinal tract, and (4) sweat formation. Extracellular [Ca^{2+}] is closely regulated by three hormones: parathyroid hormone (parathormone, PTH), vitamin D, and calcitonin. These hormones act primarily on bone, the distal renal tubules, and the small bowel.

PTH is the most important regulator of plasma [Ca^{2+}]. Decreases in plasma [Ca^{2+}] stimulate PTH secretion, while increases in plasma [Ca^{2+}] inhibit PTH secretion. The calcemic effect of PTH is due to (1) mobilization of calcium from bone, (2) enhancement of calcium reabsorption in the distal renal tubules, and (3) an indirect increase in intestinal absorption of calcium via acceleration of 1,25-dihydroxycholecalciferol synthesis in the kidneys (see below).

Vitamin D exists in several forms in the body, but 1,25-dihydroxycholecalciferol has the most important biological activity. It is the product of the metabolic conversion of (primarily endogenous) cholecalciferol, first by the liver to 25-cholecalciferol and then by the kidneys to 1,25-dihydroxycholecalciferol. The latter transformation is enhanced by secretion of PTH as well as hypophosphatemia. Vitamin D augments intestinal absorption of calcium, facilitates the action of PTH on bone, and appears to augment renal reabsorption of calcium in the distal tubules.

Calcitonin is a polypeptide hormone that is secreted by parafollicular cells in the thyroid gland. Its secretion is stimulated by hypercalcemia and inhibited by hypocalcemia. Calcitonin inhibits bone reabsorption and increases urinary calcium excretion.

TABLE 49–11 Causes of hypercalcemia.

Hyperparathyroidism
Malignancy
Excessive vitamin D intake
Paget's disease of bone
Granulomatous disorders (sarcoidosis, tuberculosis)
Chronic immobilization
Milk-alkali syndrome
Adrenal insufficiency
Drug-induced
Thiazide diuretics
Lithium

HYPERCALCEMIA

Hypercalcemia can occur as a result of a variety of disorders (Table 49–11). In *primary hyperparathyroidism*, secretion of PTH is increased and is independent of [Ca^{2+}]. In contrast, in *secondary hyperparathyroidism* (chronic renal failure or malabsorption), the elevated PTH levels are in response to chronic hypocalcemia. Prolonged secondary hyperparathyroidism, however, can occasionally result in autonomous secretion of PTH, resulting in a normal or elevated [Ca^{2+}] (*tertiary hyperparathyroidism*).

Patients with cancer can present with hypercalcemia whether or not bone metastases are present. Most often this is due to direct bony destruction, or secretion of humoral mediators of hypercalcemia (PTH-like substances, cytokines, or prostaglandins), or both. Hypercalcemia due to increased turnover of calcium from bone can also be encountered in patients with benign conditions such as Paget's disease and chronic immobilization. Increased gastrointestinal absorption of calcium can lead to hypercalcemia in patients with the *milk-alkali syndrome* (marked increase in calcium intake), hypervitaminosis D, or granulomatous diseases (enhanced sensitivity to vitamin D).

Clinical Manifestations of Hypercalcemia

Hypercalcemia often produces anorexia, nausea, vomiting, weakness, and polyuria. Ataxia, irritability, lethargy, or confusion can rapidly progress to

coma. Hypertension is often present initially before hypovolemia supervenes. ECG signs include a shortened ST segment and a shortened QT interval. Hypercalcemia increases cardiac sensitivity to digitalis. Pancreatitis, peptic ulcer disease, and kidney failure may also complicate hypercalcemia.

Treatment of Hypercalcemia

9 Symptomatic hypercalcemia requires rapid treatment. The most effective initial treatment is rehydration followed by a brisk diuresis (urinary output 200–300 mL/h) utilizing intravenous saline infusion and a loop diuretic to accelerate calcium excretion. Premature diuretic therapy prior to rehydration may aggravate the hypercalcemia by exacerbating volume depletion. Renal loss of potassium and magnesium usually occurs during diuresis, and laboratory monitoring and intravenous replacement as necessary should be performed. Although hydration and diuresis may remove the potential risk of cardiovascular and neurological complications of hypercalcemia, the serum calcium level usually remains elevated above normal. Additional therapy with a bisphosphonate or calcitonin may be required to further lower the serum calcium level. Severe hypercalcemia (>15 mg/dL) usually requires additional therapy after saline hydration and furosemide calciuresis. Bisphosphonates or calcitonin are preferred agents. Intravenous administration of pamidronate (Aredia) or etidronate (Didronel) is often utilized in this setting. Dialysis is very effective in correcting severe hypercalcemia and may be necessary in the presence of kidney or heart failure. Additional treatment depends on the underlying cause of the hypercalcemia and may include glucocorticoids in the setting of vitamin D–induced hypercalcemia such as granulomatous disease states.

It is necessary to look for the underlying etiology and direct appropriate treatment toward the cause of the hypercalcemia once the initial threat of hypercalcemia has been removed. Approximately 90% of all hypercalcemia is due to either malignancy or hyperparathyroidism. The best laboratory test for discriminating between these two main categories of hypercalcemia is the PTH assay. The serum PTH concentration is usually suppressed in malignancy states and elevated in hyperparathyroidism.

Anesthetic Considerations

Significant hypercalcemia is a medical emergency and should be corrected, if possible, before administration of any anesthetic. Ionized calcium levels should be monitored closely. If surgery must be performed, saline diuresis should be continued intraoperatively with care to avoid hypovolemia; appropriate goal-directed hemodynamic and fluid management therapy (see Chapter 51) should be utilized, especially for patients with cardiac impairment. Serial measurements of $[K^+]$ and $[Mg^{2+}]$ are helpful in detecting iatrogenic hypokalemia and hypomagnesemia. Responses to anesthetic agents are not predictable. Ventilation should be controlled under general anesthesia. Acidosis should be avoided so as to not worsen the elevated plasma $[Ca^{2+}]$.

HYPOCALCEMIA

Hypocalcemia should be diagnosed only on the basis of the plasma ionized calcium concentration. When direct measurements of plasma $[Ca^{2+}]$ are not available, the total calcium concentration must be corrected for decreases in plasma albumin concentration (see above). The causes of hypocalcemia are listed in Table 49–12.

TABLE 49–12 Causes of hypocalcemia.

Hypoparathyroidism
Pseudohypoparathyroidism
Vitamin D deficiency
Nutritional
Malabsorption
Postsurgical (gastrectomy, short bowel)
Inflammatory bowel disease
Altered vitamin D metabolism
Hyperphosphatemia
Precipitation of calcium
Pancreatitis
Rhabdomyolysis
Fat embolism
Chelation of calcium
Multiple rapid red blood transfusions or rapid infusion of large amounts of albumin

Hypocalcemia due to hypoparathyroidism is a relatively common cause of symptomatic hypocalcemia. Hypoparathyroidism may be surgical, idiopathic, part of multiple endocrine defects (most often with adrenal insufficiency), or associated with hypomagnesemia. Magnesium deficiency may impair the secretion of PTH and antagonize the effects of PTH on bone. Hypocalcemia during sepsis is also thought to be due to suppression of PTH release. Hyperphosphatemia (see below) is also a relatively common cause of hypocalcemia, particularly in patients with chronic renal failure. Hypocalcemia due to vitamin D deficiency may be the result of a markedly reduced intake (nutritional), vitamin D malabsorption, or abnormal vitamin D metabolism.

Chelation of calcium ions with the citrate ions in blood preservatives is an important cause of perioperative hypocalcemia in transfused patients; similar transient decreases in [Ca^{2+}] are also possible following rapid infusions of large volumes of albumin. Hypocalcemia following acute pancreatitis is thought to be due to precipitation of calcium with fats (soaps) following the release of lipolytic enzymes and fat necrosis; hypocalcemia following fat embolism may have a similar basis. Precipitation of calcium (in injured muscle) may also be seen following rhabdomyolysis.

Less common causes of hypocalcemia include calcitonin-secreting medullary carcinomas of the thyroid, osteoblastic metastatic disease (breast and prostate cancer), and pseudohypoparathyroidism (familial unresponsiveness to PTH). Transient hypocalcemia may be seen following heparin, protamine, or glucagon administration.

Clinical Manifestations of Hypocalcemia

Manifestations of hypocalcemia include paresthesias, confusion, laryngeal stridor (laryngospasm), carpopedal spasm (Trousseau's sign), masseter spasm (Chvostek's sign), and seizures. Biliary colic and bronchospasm have also been described. ECG may reveal cardiac irritability or QT interval prolongation, which may not correlate in severity with the degree of hypocalcemia. Decreased cardiac contractility may result in heart failure, hypotension, or both. Decreased responsiveness to digoxin and β-adrenergic agonists may also occur.

Treatment of Hypocalcemia

10 Symptomatic hypocalcemia is a medical emergency and should be treated immediately with intravenous calcium chloride (3–5 mL of a 10% solution) or calcium gluconate (10–20 mL of a 10% solution). (Ten milliliters of 10% $CaCl_2$ contains 272 mg of Ca^{2+}, whereas 10 mL of 10% calcium gluconate contains only 93 mg of Ca^{2+}.) To avoid precipitation, intravenous calcium should not be given with bicarbonate- or phosphate-containing solutions. Serial ionized calcium measurements are mandatory. Repeat boluses or a continuous infusion (Ca^{2+} 1–2 mg/kg/h) may be necessary. Plasma magnesium concentration should be checked to exclude hypomagnesemia. In chronic hypocalcemia, oral calcium ($CaCO_3$) and vitamin D replacement are usually necessary.

Anesthetic Considerations

Significant hypocalcemia should be corrected preoperatively. Serial ionized calcium levels should be monitored intraoperatively in patients with a history of hypocalcemia. Alkalosis should be avoided to prevent further decreases in [Ca^{2+}]. Intravenous calcium may be necessary following rapid transfusions of citrated blood products or large volumes of albumin solutions. Potentiation of the negative inotropic effects of barbiturates and volatile anesthetics should be expected. Responses to NMBs are inconsistent and require close monitoring with a nerve stimulator.

Disorders of Phosphorus Balance

Phosphorus is an important intracellular constituent. Its presence is required for the synthesis of (1) the phospholipids and phosphoproteins in cell membranes and intracellular organelles, (2) the phosphonucleotides involved in protein synthesis and reproduction, and (3) ATP used for the storage of energy. Only 0.1% of total body phosphorus is in ECF; 85% is in bone and 15% is intracellular.

NORMAL PHOSPHORUS BALANCE

Phosphorus intake averages 800–1500 mg/d in adults. About 80% of that amount is normally absorbed in the proximal small bowel. Vitamin D increases intestinal absorption of phosphorus. The kidneys are the major route for phosphorus excretion and are responsible for regulating total body phosphorus content. Urinary excretion of phosphorus depends on both intake and plasma concentration. Secretion of PTH can augment urinary phosphorus excretion by inhibiting its proximal tubular reabsorption. The latter effect may be offset by PTH-induced release of phosphate from bone.

Plasma Phosphorus Concentration

Plasma phosphorus exists in both organic and inorganic forms. Organic phosphorus is mainly in the form of phospholipids. Of the inorganic phosphorus fraction, 80% is filterable in the kidneys and 20% is protein bound. The majority of inorganic phosphorus is in the form of $H_2PO_4^-$ and HPO_4^{2-} in a 1:4 ratio. By convention, plasma phosphorus is measured as milligrams of elemental phosphorus. Normal plasma phosphorus concentration is 2.5–4.5 mg/dL (0.8–1.45 mmol/L) in adults and up to 6 mg/dL in children. Plasma phosphorus concentration is usually measured during fasting, because a recent carbohydrate intake transiently decreases the plasma phosphorus concentration. Hypophosphatemia increases vitamin D production, whereas hyperphosphatemia depresses it. The latter plays an important role in the genesis of secondary hyperparathyroidism in patients with chronic kidney failure (see Chapter 30).

HYPERPHOSPHATEMIA

Hyperphosphatemia may be seen with increased phosphorus intake (abuse of phosphate laxatives or excessive potassium phosphate administration), decreased phosphorus excretion (renal insufficiency), or massive cell lysis (following chemotherapy for lymphoma or leukemia).

Clinical Manifestations of Hyperphosphatemia

Although hyperphosphatemia itself does not appear to be directly responsible for any functional disturbances, its secondary effect on plasma $[Ca^{2+}]$ can be important. Marked hyperphosphatemia is thought to lower plasma $[Ca^{2+}]$ by precipitation and deposition of calcium phosphate in bone and soft tissues.

Treatment of Hyperphosphatemia

Hyperphosphatemia is generally treated with phosphate-binding antacids such as aluminum hydroxide or aluminum carbonate.

Anesthetic Considerations

Although specific interactions between hyperphosphatemia and anesthesia are generally not described, renal function should be carefully evaluated. Secondary hypocalcemia should also be excluded.

HYPOPHOSPHATEMIA

Hypophosphatemia is usually the result of either a negative phosphorus balance or cellular uptake of extracellular phosphorus (an intercompartmental shift). Intercompartmental shifts of phosphorus can occur during alkalosis and following carbohydrate ingestion or insulin administration. Large doses of aluminum or magnesium-containing antacids, severe burns, inadequate phosphorus supplementation during hyperalimentation, diabetic ketoacidosis, alcohol withdrawal, and prolonged respiratory alkalosis can all produce a negative phosphorus balance and lead to severe hypophosphatemia (<0.3 mmol/dL or <1.0 mg/dL). In contrast to respiratory alkalosis, metabolic alkalosis rarely leads to severe hypophosphatemia.

Clinical Manifestations of Hypophosphatemia

Mild to moderate hypophosphatemia (1.5–2.5 mg/dL) is generally asymptomatic. In contrast, severe hypophosphatemia (<1.0 mg/dL) is often associated with widespread organ dysfunction. Cardiomyopathy, impaired oxygen delivery (decreased

2,3-diphosphoglycerate levels), hemolysis, impaired leukocyte function, platelet dysfunction, encephalopathy, skeletal myopathy, respiratory failure, rhabdomyolysis, skeletal demineralization, metabolic acidosis, and hepatic dysfunction have all been associated with severe hypophosphatemia.

Treatment of Hypophosphatemia

Oral phosphorus replacement is generally preferable to parenteral replacement because of the increased risk of phosphate precipitation with calcium, resulting in hypocalcemia, and also because of the increased risks of hyperphosphatemia, hypomagnesemia, and hypotension. Accordingly, intravenous replacement therapy is usually reserved for instances of symptomatic hypophosphatemia and extremely low phosphate levels (<0.32 mmol/L). In situations where oral phosphate replacement is utilized, vitamin D is required for intestinal phosphate absorption.

Anesthetic Considerations

Anesthetic management of patients with hypophosphatemia requires familiarity with its complications (see above). Hyperglycemia and respiratory alkalosis should be avoided to prevent further decreases in plasma phosphorus concentration. Neuromuscular function must be monitored carefully when NMBs are given. Some patients with severe hypophosphatemia may require mechanical ventilation postoperatively because of muscle weakness.

Disorders of Magnesium Balance

Magnesium is an important intracellular cation that functions as a cofactor in many enzyme pathways. Only 1–2% of total body magnesium stores is present in the ECF compartment; 67% is contained in bone, and the remaining 31% is intracellular. Magnesium has been reported to decrease anesthetic requirements, attenuate nociception, blunt the cardiovascular response to laryngoscopy and intubation, and potentiate NMBs. Suggested mechanisms of action include altering central nervous system neurotransmitter release, moderating adrenal medullary catecholamine release, and antagonizing the effect of calcium on vascular smooth muscle. Magnesium impairs the calcium-mediated presynaptic release of acetylcholine and may also decrease motor end-plate sensitivity to acetylcholine and alter myocyte membrane potential.

In addition to the treatment of magnesium deficiency, administration of magnesium is utilized therapeutically for preeclampsia and eclampsia, torsades de pointes and digoxin-induced cardiac tachyarrhythmias, and status asthmaticus.

NORMAL MAGNESIUM BALANCE

Magnesium intake averages 20–30 mEq/d (240–370 mg/d) in adults. Of that amount, only 30–40% is absorbed, mainly in the distal small bowel. Renal excretion is the primary route for elimination, averaging 6–12 mEq/d. Magnesium reabsorption by the kidneys is very efficient. Twenty-five percent of filtered magnesium is reabsorbed in the proximal tubule, whereas 50–60% is reabsorbed in the thick ascending limb of the loop of Henle. Factors known to increase magnesium reabsorption in the kidneys include hypomagnesemia, PTH, hypocalcemia, ECF depletion, and metabolic alkalosis. Factors known to increase renal excretion include hypermagnesemia, acute volume expansion, hyperaldosteronism, hypercalcemia, ketoacidosis, diuretics, phosphate depletion, and alcohol ingestion.

Plasma Magnesium Concentration

Plasma [Mg^{2+}] is closely regulated between 1.7 and 2.1 mEq/L (0.7–1 mmol/L or 1.7–2.4 mg/dL) through interaction of the gastrointestinal tract (absorption), bone (storage), and the kidneys (excretion). Approximately 50–60% of plasma magnesium is unbound and diffusible.

HYPERMAGNESEMIA

Increases in plasma [Mg^{2+}] are nearly always due to excessive intake (magnesium-containing antacids or laxatives), renal impairment (GFR < 30 mL/min), or both. Less common causes include adrenal

insufficiency, hypothyroidism, rhabdomyolysis, and lithium administration. Magnesium sulfate therapy for preeclampsia and eclampsia can cause hypermagnesemia in the mother as well as in the fetus.

Clinical Manifestations of Hypermagnesemia

Symptomatic hypermagnesemia typically presents with neurological, neuromuscular, and cardiac manifestations, including hyporeflexia, sedation, muscle weakness, and respiratory depression. Vasodilation, bradycardia, and myocardial depression may cause hypotension. ECG signs may include prolongation of the P–R interval and widening of the QRS complex. Marked hypermagnesemia can lead to respiratory and cardiac arrest.

Treatment of Hypermagnesemia

With relatively mild hypermagnesemia, all that is usually necessary is to discontinue source(s) of magnesium intake (most often antacids). In cases of relatively high [Mg^{2+}], and especially in the presence of clinical signs of magnesium toxicity, intravenous calcium can temporarily antagonize most of the effects of clinical toxicity. A loop diuretic in conjunction with intravenous fluid replacement enhances urinary magnesium excretion in patients with adequate renal function. When diuretic administration with intravenous infusion is used to enhance magnesium excretion, serial measurements of [Ca^{2+}] and [Mg^{2+}] should be obtained, a urinary catheter is required, and goal-directed hemodynamic and fluid management should be considered. Dialysis may be necessary in patients with marked renal impairment. In cases of severe magnesium toxicity, ventilatory or circulatory support, or both, may be necessary.

Anesthetic Considerations

Hypermagnesemia requires close monitoring of the ECG, blood pressure, and neuromuscular function. Potentiation of the vasodilatory and negative inotropic properties of anesthetics should be expected. Dosages of nondepolarizing NMBs should be reduced.

TABLE 49–13 Causes of hypomagnesemia.

Inadequate intake
Nutritional
Reduced gastrointestinal absorption
Malabsorption syndromes
Small bowel or biliary fistulas
Prolonged nasogastric suctioning
Severe vomiting or diarrhea
Chronic laxative abuse
Increased renal losses
Diuresis
Diabetic ketoacidosis
Hyperparathyroidism
Hyperaldosteronism
Hypophosphatemia
Nephrotoxic drugs
Postobstructive diuresis
Multifactorial
Chronic alcoholism
Protein–calorie malnutrition
Hyperthyroidism
Pancreatitis
Burns

HYPOMAGNESEMIA

Hypomagnesemia is a common and frequently overlooked problem, particularly in critically ill patients, and is often associated with deficiencies of other intracellular components such as potassium and phosphorus. It is commonly found in patients undergoing major cardiothoracic or abdominal operations, and its incidence among patients in intensive care units may exceed 50%. Deficiencies of magnesium are generally the result of inadequate intake, reduced gastrointestinal absorption, and increased renal excretion (Table 49–13). Drugs that cause renal wasting of magnesium include ethanol, theophylline, diuretics, cisplatin, aminoglycosides, cyclosporine, amphotericin B, pentamidine, and granulocyte colony-stimulating factor.

Clinical Manifestations of Hypomagnesemia

Most patients with hypomagnesemia are asymptomatic, but anorexia, weakness, fasciculation, paresthesias, confusion, ataxia, and seizures may be

encountered. Hypomagnesemia is frequently associated with both hypocalcemia (impaired PTH secretion) and hypokalemia (due to renal K^+ wasting). Cardiac manifestations include electrical irritability and potentiation of digoxin toxicity; both factors are aggravated by hypokalemia. Hypomagnesemia is associated with an increased incidence of atrial fibrillation. Prolongation of the P–R and QT intervals may also be present.

Treatment of Hypomagnesemia

Asymptomatic hypomagnesemia can be treated orally or intramuscularly. Serious manifestations such as seizures should be treated with intravenous magnesium sulfate, 1–2 g (8–16 mEq or 4–8 mmol) given slowly over 15–60 min.

Anesthetic Considerations

Although no specific anesthetic interactions are described, coexistent electrolyte disturbances such as hypokalemia, hypophosphatemia, and hypocalcemia are often present and should be corrected prior to surgery. Isolated hypomagnesemia should be corrected prior to elective procedures because of its potential for causing cardiac arrhythmias. Moreover, magnesium appears to have intrinsic antiarrhythmic properties and possibly cerebral protective effects (see Chapter 26). It is frequently administered preemptively to lessen the risk of postoperative atrial fibrillation in patients undergoing cardiac surgery.

CASE DISCUSSION

Electrolyte Abnormalities Following Urinary Diversion

A 70-year-old man with carcinoma of the bladder presents for radical cystectomy and ileal loop urinary diversion. He weighs 70 kg and has a 20-year history of hypertension. Preoperative laboratory measurements revealed normal plasma electrolyte concentrations and a blood urea nitrogen (BUN) of 20 mg/dL with a serum creatinine of 1.5 mg/dL. The operation lasts 4 h and is performed under uncomplicated general anesthesia. The estimated blood loss is 900 mL. Fluid replacement consists of 3500 mL of lactated Ringer's injection and 750 mL of 5% albumin.

One hour after admission to the postanesthesia care unit, the patient is awake, his blood pressure is 130/70 mm Hg, and he appears to be breathing well (18 breaths/min, Fio_2 = 0.4). Urinary output has been only 20 mL in the last hour. Laboratory measurements are as follows: Hb, 10.4 g/dL; plasma Na^+, 133 mEq/L; K^+, 3.8 mEq/L; Cl^-, 104 mEq/L; total CO_2, 20 mmol/L; Pao_2, 156 mm Hg; arterial blood pH, 7.29; $Paco_2$, 38 mm Hg; and calculated HCO_3^-, 18 mEq/L.

What is the most likely explanation for the hyponatremia?

Multiple factors tend to promote hyponatremia postoperatively, including nonosmotic antidiuretic hormone (ADH) secretion (surgical stress, hypovolemia, and pain), large evaporative and functional fluid losses (tissue sequestration), and the administration of hypotonic intravenous fluids. Hyponatremia is particularly common postoperatively in patients who have received relatively large amounts of lactated Ringer's injection ([Na^+] 130 mEq/L); the postoperative plasma [Na^+] generally approaches 130 mEq/L in such patients. (Fluid replacement in this patient was appropriate considering basic maintenance requirements, blood loss, and the additional fluid losses usually associated with this type of surgery.)

Why is the patient hyperchloremic and acidotic (normal arterial blood pH is 7.35–7.45)?

Operations for supravesical urinary diversion utilize a segment of bowel (ileum, ileocecal segment, jejunum, or sigmoid colon) that is made to function as a conduit or reservoir. The simplest and most common procedure utilizes an isolated loop of ileum as a conduit: the proximal end is anastomosed to the ureters, and the distal end is brought through the skin, forming a stoma.

Whenever urine comes in contact with bowel mucosa, the potential for significant fluid and electrolyte exchange exists. The ileum actively absorbs chloride in exchange for bicarbonate, and sodium in exchange for potassium

or hydrogen ions. When chloride absorption exceeds sodium absorption, plasma chloride concentration increases, whereas plasma bicarbonate concentration decreases—a hyperchloremic metabolic acidosis is established. In addition, the colon absorbs NH^{4+} directly from urine; the latter may also be produced by urea-splitting bacteria. Hypokalemia results if significant amounts of Na^+ are exchanged for K^+. Potassium losses through the conduit are increased by high urinary sodium concentrations. Moreover, a potassium deficit may be present—even in the absence of hypokalemia—because movement of K^+ out of cells (secondary to the acidosis) can prevent an appreciable decrease in extracellular plasma [K^+].

Are there any factors that tend to increase the likelihood of hyperchloremic metabolic acidosis following urinary diversion?

The longer the urine is in contact with bowel, the greater the chance that hyperchloremia and acidosis will occur. Mechanical problems such as poor emptying or redundancy of a conduit—along with hypovolemia—thus predispose to hyperchloremic metabolic acidosis. Preexisting renal impairment also appears to be a major risk factor and probably represents an inability to compensate for the excessive bicarbonate losses.

What treatment, if any, is required for this patient?

The ileal loop should be irrigated with saline—through the indwelling catheter or stent—to exclude partial obstruction and ensure free drainage of urine. Hypovolemia should be considered and treated based on goal-directed hemodynamic and fluid therapy or the response to a fluid challenge (see Chapter 51). A mild to moderate systemic acidosis (arterial pH > 7.25) is generally well tolerated by most patients. Moreover, hyperchloremic metabolic acidosis following ileal conduits is often transient and usually due to urinary stasis. Persistent or more severe acidosis requires treatment with sodium bicarbonate. Potassium replacement may also be required if hypokalemia is present.

Are electrolyte abnormalities seen with other types of urinary diversion?

Procedures employing bowel as a conduit (ileal or colonic) are less likely to result in hyperchloremic metabolic acidosis than those in which bowel functions as a reservoir. The incidence of hyperchloremic metabolic acidosis approaches 80% following ureterosigmoidostomies.

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