1

Physiology of Body Fluids

OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

- How do body fluid compartments differ with respect to their volumes and their ionic compositions?
- What are the driving forces responsible for movement of water across cell membranes and the capillary wall?
- How do the volumes of the intracellular and extracellular fluid compartments change under various pathophysiologic conditions?

In addition, the student should be able to define and understand the following properties of physiologically important solutions and fluids:

- Molarity and equivalence
- Osmotic pressure
- Osmolarity and osmolality
- Oncotic pressure
- Tonicity

KEY TERMS

Steady-state balance
Positive balance
Negative balance
Molarity
Equivalence
Osmosis
Osmotic pressure
van't Hoff's law
Osmolarity
Osmolality
Tonicity (isotonic, hypotonic, and hypertonic)
Isosmotic
Permeable
Impermeable
Effective osmole
Ineffective osmole
Reflection coefficient
Osmotic coefficient
Oncotic pressure
Specific gravity
Total body water
Intracellular fluid (ICF)
Extracellular fluid (ECF)
Interstitial fluid
Plasma
Third space
Ascites
Capillary wall
Starling forces
Capillary filtration coefficient (K_f)
Aquaporin (AQP)

One of the major functions of the kidneys is to maintain the volume and composition of the body's fluids constant despite wide variation in the daily intake of water and solutes. In this chapter, the concept of steady-state balance is introduced. Also, the volume and composition of the body's fluids are discussed to provide a background for the study of the kidneys as regulatory organs. Some of the basic principles, terminology, and concepts related to the properties of solutes in solution also are reviewed.

CONCEPT OF STEADY-STATE BALANCE

The human body is an "open system," meaning that substances are added to the body each day, and similarly substances are lost from the body each day. The amounts added to or lost from the body can vary widely depending on the environment, access to food and water, disease processes, and even cultural norms. In such an open system, the volume and composition of the body fluids is maintained through the process of **steady-state balance**.

The concept of steady-state balance can be illustrated by considering a river on which a dam is built to create a manmade lake. Each day, water enters the lake from the various streams and rivers that feed it. In addition, water is added by underground springs, rain, and snow. At the same time water is lost through the spillways of the dam and by the process of evaporation. For the level of the lake to remain constant (i.e., steady-state balance), the rate at which water is added, regardless of source, must be exactly matched by the amount of water lost, again by whichever route. Because the addition of water is not easily controlled, nor can the loss by evaporation be controlled, the only way to maintain the level of the lake constant is to regulate the amount that is lost through the spillways.

To understand steady-state balance as it applies to the human body, the following key concepts are important.

1. There must be a *set-point* from which deviations can be monitored (e.g., the level of the lake in the previous example or setting the temperature in a room by adjusting the thermostat).
2. The sensors that monitor deviations from the set-point must generate *effector signals* that can lead to changes in either input or output, or both, to maintain the desired set-point (e.g., electrical signals to adjust the spillway in the dam analogy or electrical signals sent to either the furnace or air conditioner to maintain the proper room temperature).
3. *Effector organs* must respond in an appropriate way to the effector signals generated by the set-point monitor (e.g., the spillway gates must operate and the furnace or air conditioner must turn on and off as appropriate).
4. The sensitivity of the system (i.e., how much of a deviation away from the set-point is tolerated) depends on several factors, including the nature of the sensor (i.e., how much of a deviation from the set-point is needed for the sensor to detect the deviation), the time necessary for generation of the effector signals, and how rapidly the effector mechanisms respond to the effector signals.

It is important to recognize that deviations from steady-state balance do occur. When input is greater than output, a state of **positive balance** exists. When input is less than output, a state of **negative balance** exists. Although transient periods of imbalance can be tolerated, prolonged states of extreme positive or negative balance are generally incompatible with life.

PHYSICOCHEMICAL PROPERTIES OF ELECTROLYTE SOLUTIONS

Molarity and Equivalence

The amount of a substance dissolved in a solution (i.e., its concentration) is expressed in terms of either **molarity** or **equivalence**. Molarity is the amount of a substance relative to its molecular weight. For example, glucose has a molecular weight of 180 g/mol. If 1 L of water contains 1 g of glucose, the molarity of this glucose solution would be determined as:

$$\frac{1\ \text{g/L}}{180\ \text{g/mol}} = 0.0056\ \text{mol/L or } 5.6\ \text{mmol/L} \qquad \textbf{(1.1)}$$

For uncharged molecules, such as glucose and urea, concentrations in the body fluids are usually expressed in terms of molarity.[a] Because many of the substances of biologic interest are present at very low concentrations, units are more commonly expressed in the millimolar range (mmol/L).

The concentration of solutes, which normally dissociate into more than one particle when dissolved in solution (e.g., sodium chloride [NaCl]), is usually expressed in terms of equivalence. *Equivalence* refers to the stoichiometry of the interaction between cation and anion and is determined by the valence of these ions. For example, consider a 1 L solution containing 9 g of NaCl (molecular weight = 58.4 g/mol). The molarity of this solution is 154 mmol/L. Because NaCl dissociates into Na^+ and Cl^- ions, and assuming complete dissociation, this solution contains 154 mmol/L of Na^+ and 154 mmol/L of Cl^-. Because the valence of these ions is 1, these concentrations also can be expressed as milliequivalents of the ion per liter (i.e., 154 mEq/L for Na^+ and Cl^-, respectively).

For univalent ions such as Na^+ and Cl^-, concentrations expressed in terms of molarity and equivalence are identical. However, this is not true for ions having valences greater than 1. Accordingly, the concentration of Ca^{++} (molecular weight = 40.1 g/mol and valence = 2) in a 1 L solution containing 0.1 g of this ion could be expressed as:

$$\begin{aligned} &\frac{0.1\ \text{g/L}}{40.1\ \text{g/mol}} = 2.5\ \text{mmol/L} \\ &2.5\ \text{mmol/L} \times 2\ \text{Eq/mol} = 5\ \text{mEq/L} \end{aligned} \qquad \textbf{(1.2)}$$

Although some exceptions exist, it is customary to express concentrations of ions in milliequivalents per liter.

[a] The units used to express the concentrations of substances in various body fluids differ among laboratories. The system of international units (SI) is used in most countries and in most scientific and medical journals in the United States. Despite this convention, traditional units are still widely used. For urea and glucose, the traditional units of concentration are milligrams per deciliter (mg/dL, or 100 mL), whereas the SI units are millimole per liter (mmol/L). Similarly, electrolyte concentrations are traditionally expressed as milliequivalent per liter (mEq/L), whereas the SI units are mmol/L (see Appendix B).

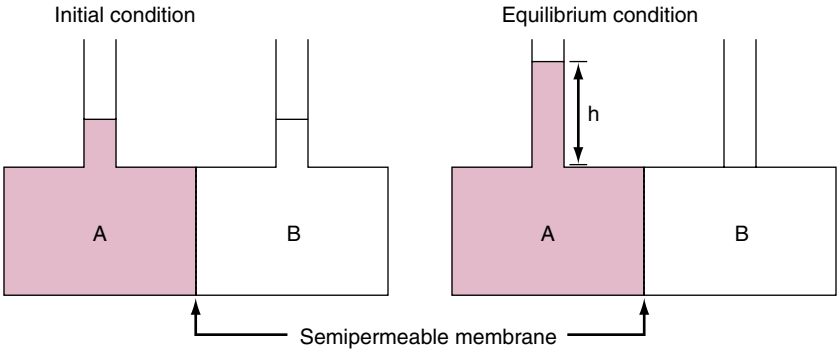

Fig. 1.1 Schematic representation of osmotic water movement and the generation of an osmotic pressure. Compartment A and compartment B are separated by a semipermeable membrane (i.e., the membrane is highly permeable to water but impermeable to solute). Compartment A contains a solute, whereas compartment B contains only distilled water. Over time, water moves by osmosis from compartment B to compartment A. (Note: This water movement is driven by the concentration gradient for water. Because of the presence of solute particles in compartment A, the concentration of water in compartment A is less than that in compartment B. Consequently, water moves across the semipermeable membrane from compartment B to compartment A down its gradient). This causes the level of fluid in compartment A to rise and the level in compartment B to fall. At equilibrium, the hydrostatic pressure exerted by the column of water *(h)* stops the movement of water from compartment B to A. Thus, at equilibrium, the hydrostatic pressure generated by the height *(h)* of the column of water in compartment A is equal and opposite to the osmotic pressure generated by the solute particles in compartment A.

Osmosis and Osmotic Pressure

The movement of water across cell membranes occurs by the process of **osmosis**. The driving force for this movement is the osmotic pressure difference across the cell membrane. Fig. 1.1 illustrates the concept of osmosis and the measurement of the osmotic pressure of a solution.

Osmotic pressure is determined solely by the number of solute particles in the solution. It is not dependent on factors such as the size of the solute particles, their mass, or their chemical nature (e.g., valence). Osmotic pressure (π), measured in atmospheres (atm), is calculated by **van't Hoff's law** as:

$$\pi = nCRT \qquad \textbf{(1.3)}$$

where n is the number of dissociable particles per molecule, C is total solute concentration, R is gas constant, and T is temperature in degrees Kelvin (°K).

For a molecule that does not dissociate in water, such as glucose or urea, a solution containing 1 mmol/L of these solutes at 37°C can exert an osmotic pressure of 2.54×10^{-2} atm as calculated by Eq. (1.3) using the following values: n is 1, C is 0.001 mol/L, R is 0.082 atm L/mol, and T is 310°K.

Because 1 atm equals 760 mm Hg at sea level, π for this solution also can be expressed as 19.3 mm Hg. Alternatively, osmotic pressure is expressed in terms of osmolarity (see the following discussion). Thus a solution containing 1 mmol/L of solute particles exerts an osmotic pressure of 1 milliosmole per liter (1 mOsm/L).

For substances that dissociate in a solution, n of Eq. (1.3) has a value other than 1. For example, a 150 mmol/L solution of NaCl has an osmolarity of 300 mOsm/L because each molecule of NaCl dissociates into a Na^+ and a Cl^- ion (i.e., $n = 2$). If dissociation of a substance into its component ions is not complete, n is not an integer. Accordingly, osmolarity for any solution can be calculated as:

$$\text{Osmolarity} = \text{Concentration} \times \text{Number of dissociable particles}$$
$$\text{mOsm/L} = \text{mmol/L} \times \text{number of particles/mol} \qquad \textbf{(1.4)}$$

Osmolarity and Osmolality

Osmolarity and **osmolality** are often confused and incorrectly interchanged. *Osmolarity* refers to the number of solute particles per 1 L of solvent, whereas *osmolality* is the number of solute particles in 1 kg of solvent. For dilute solutions, the difference between osmolarity and osmolality is insignificant. Measurements of osmolarity are temperature dependent, because the volume of solvent varies with temperature (i.e., the volume is larger at higher temperatures). In contrast, osmolality, which is based on the mass of the solvent, is temperature independent. For this

TABLE 1.1 Units of Measurement for Physiologically Significant Substances

Substance	Atomic/Molecular Weight	Equivalents/Mol	Osmoles/Mol
Na^+	23.0	1	1
K^+	39.1	1	1
Cl^-	35.4	1	1
HCO_3^-	61.0	1	1
Ca^{++}	40.1	2	1
Phosphate (P_i)	95.0	3	1
NH_4^+	18.0	1	1
NaCl	58.4	2*	2†
$CaCl_2$	111	4‡	3
Glucose	180	—	1
Urea	60	—	1

$CaCl_2$, Calcium chloride; *HCO_3^-*, bicarbonate; *K^+*, potassium; *NH_4^+*, ammonium.
*One equivalent each from Na^+ and Cl^-.
†NaCl does not dissociate completely in solution. The actual Osm/mol volume is 1.88. However, for simplicity, a value of 2 often is used.
‡Ca^{++} contributes two equivalents, as do the Cl^- ions.

reason, *osmolality* is the preferred term for biologic systems and is used throughout this and subsequent chapters. Osmolality has the units of Osm/kg H_2O. Because of the dilute nature of physiologic solutions and because water is the solvent, osmolalities are expressed as milliosmoles per kilogram of water (mOsm/kg H_2O).

Table 1.1 shows the relationships among molecular weight, equivalence, and osmoles for a number of physiologically significant solutes.

Tonicity

The **tonicity** of a solution is related to its effect on the volume of a cell. Solutions that do not change the volume of a cell are said to be **isotonic**. A **hypotonic** solution causes a cell to swell, whereas a **hypertonic** solution causes a cell to shrink. Although it is related to osmolality, tonicity also takes into consideration the ability of the solute to cross the cell membrane.

Consider two solutions: a 300 mmol/L solution of sucrose and a 300 mmol/L solution of urea. Both solutions have an osmolality of 300 mOsm/kg H_2O and therefore are said to be **isosmotic** (i.e., they have the same osmolality). When red blood cells (which, for the purpose of this illustration, also have an intracellular fluid osmolality of 300 mOsm/kg H_2O) are placed in the two solutions, those in the sucrose solution maintain their normal volume, but those placed in urea swell and eventually burst. Thus the sucrose solution is isotonic and the urea solution is hypotonic. The differential effect of these solutions on red blood cell volume is related to the permeability of the plasma membrane to sucrose and urea. The red blood cell membrane contains uniporters for urea (see Chapter 4). Thus urea easily crosses the cell membrane (i.e., the membrane is **permeable** to urea), driven by the concentration gradient (i.e., extracellular [urea] > intracellular [urea]). In contrast, the red blood cell membrane does not contain sucrose transporters and sucrose cannot enter the cell (i.e., the membrane is **impermeable** to sucrose).

To exert an osmotic pressure across a membrane, a solute must not cross the membrane. Because the red blood cell membrane is impermeable to sucrose, it exerts an osmotic pressure equal and opposite to the osmotic pressure generated by the contents of the red blood cell (in this case, 300 mOsm/kg H_2O). In contrast, urea is readily able to cross the red blood cell membrane and it cannot exert an osmotic pressure to balance that generated by the intracellular solutes of the red blood cell. Consequently, sucrose is termed an **effective osmole** and urea is termed an **ineffective osmole**.

To account for the effect of a solute's membrane permeability on osmotic pressure, it is necessary to rewrite Eq. (1.3) as:

$$\pi = \sigma\,(nCRT) \qquad \textbf{(1.5)}$$

where σ is the **reflection coefficient** or **osmotic coefficient** and is a measure of the relative ability of the solute to cross a cell membrane.

For a solute that can freely cross the cell membrane (such as urea in this example), σ = 0 and no effective osmotic pressure is exerted. Thus urea is an ineffective osmole for red blood cells. In contrast, σ = 1 for a solute

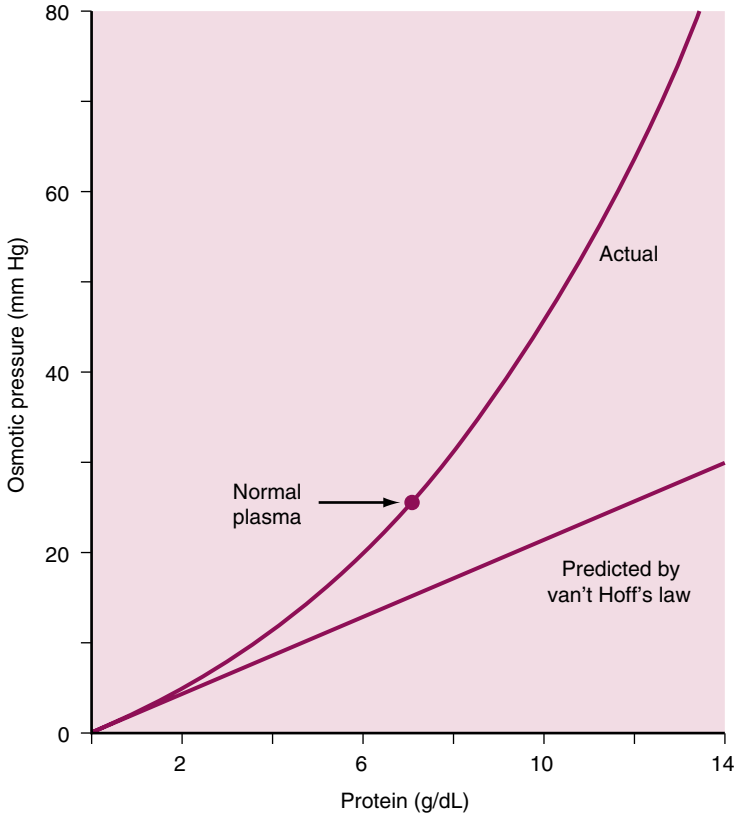

Fig. 1.2 Relationship between the concentration of plasma proteins in solution and the osmotic pressure (oncotic pressure) they generate. Protein concentration is expressed as grams per deciliter. Normal plasma protein concentration is indicated. Note that the actual pressure generated exceeds that predicted by van't Hoff's law.

that cannot cross the cell membrane (e.g., sucrose). Such a substance is said to be an effective osmole. Many solutes are neither completely able nor completely unable to cross cell membranes (i.e., $0 < \sigma < 1$) and generate an osmotic pressure that is only a fraction of what is expected from the molecules' concentration in solution.

Oncotic Pressure

Oncotic pressure is the osmotic pressure generated by large molecules (especially proteins) in solution. As illustrated in Fig. 1.2, the magnitude of the osmotic pressure generated by a solution of protein does not conform to van't Hoff's law. The cause of this anomalous relationship between protein concentration and osmotic pressure is not completely understood but appears to be related to the size and shape of the protein molecule. For example, the correlation to van't Hoff's law is more precise with small, globular proteins than with larger protein molecules.

The oncotic pressure exerted by proteins in human plasma has a normal value of approximately 26 to 28 mm Hg. Although this pressure appears to be small when considered in terms of osmotic pressure (28 mm Hg ≈ 1.4 mOsm/kg H_2O), it is an important force involved in fluid movement across capillaries (details of this topic are presented in the following section on fluid exchange between body fluid compartments).

Specific Gravity

The total solute concentration in a solution also can be measured as **specific gravity**. Specific gravity is defined as the weight of a volume of solution divided by the weight of an equal volume of distilled water. Thus the specific gravity of distilled water is 1. Because biologic fluids contain a number of different substances, their specific gravities are greater than 1. For example, normal human plasma has a specific gravity in the range of 1.008 to 1.010.

IN THE CLINIC

The specific gravity of urine is sometimes measured in clinical settings and used to assess the concentrating ability of the kidney, which can be altered by diseases that alter the ability of the posterior pituitary gland to secrete arginine vasopressin (see Chapter 5 for details). The specific gravity of urine varies in proportion to its osmolality. However, because specific gravity depends on both the number of solute particles and their weight, the relationship between specific gravity and osmolality is not always predictable. For example, patients who have been injected with radiocontrast dye (molecular weight > 500 g/mol) for radiographic studies can have high values of urine-specific gravity (1.040–1.050), even though the urine osmolality is similar to that of plasma (e.g., 300 mOsm/kg H_2O).

VOLUMES OF BODY FLUID COMPARTMENTS

Water makes up approximately 60% of the body's weight, with variability among individuals being a function of the amount of adipose tissue that is present. Because the water content of adipose tissue is lower than that of other tissue, increased amounts of adipose tissue reduce the fraction of total body weight attributed to water. The percentage of body weight attributed to water also varies with age. In newborns, it is approximately 75%. This percentage decreases to the adult value of 60% by 1 year of age.

As illustrated in Fig. 1.3, **total body water** is distributed between two major compartments, which are divided by the cell membrane.[b] The **intracellular fluid (ICF)** compartment is the larger compartment and contains approximately two-thirds of the total body water. The remaining one-third of the body water is contained in the **extracellular fluid (ECF)** compartment. Expressed as percentages of body weight, the volumes of total body water, ICF, and ECF are:

$$\begin{aligned} \text{Total body water} &= 0.6 \times (\text{body weight}) \\ \text{ICF} &= 0.4 \times (\text{body weight}) \\ \text{ECF} &= 0.2 \times (\text{body weight}) \end{aligned} \qquad (1.6)$$

The ECF compartment is further subdivided into **interstitial fluid** and **plasma**, which are separated by the capillary wall. The ECF also includes water contained within the bone and dense connective tissue, as well as the cerebrospinal fluid. The interstitial fluid surrounds the cells in the various tissues of the body and constitutes three-fourths of the ECF volume. Plasma is contained within the vascular compartment and represents the remaining one-fourth of the ECF. Under some pathologic conditions, additional fluid may accumulate in what is referred to as a **third space**. Third space collections of fluid are part of the ECF and include, for example, the accumulation of fluid in the peritoneal cavity (**ascites**) of persons with liver disease.

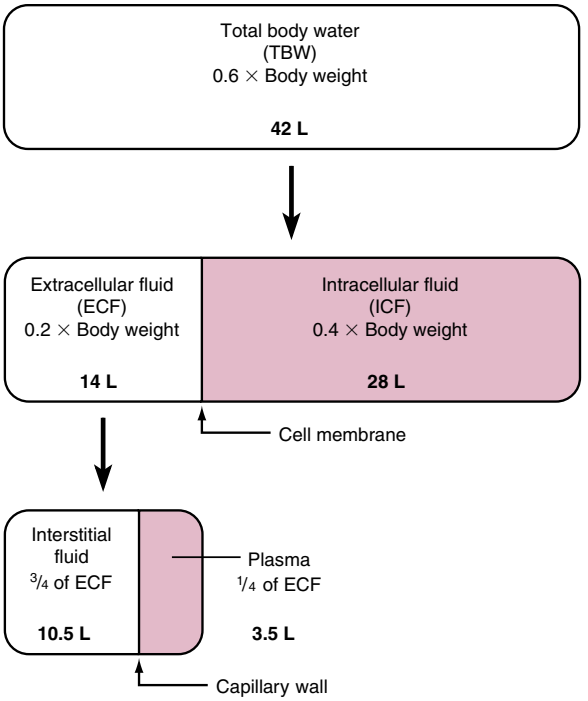

Fig. 1.3 Relationship between the volumes of the major body fluid compartments. The actual values shown are calculated for an individual who weighs 70 kg.

COMPOSITION OF BODY FLUID COMPARTMENTS

The composition of the ECF and ICF differ considerably. The ICF has significantly more proteins and macromolecules than the ECF. There are also differences in the concentrations of many ions (Table 1.2). The composition of the ICF is maintained by the action of several cell membrane transport proteins. Principal among these transporters is the sodium–potassium–adenosine triphosphatase pump (Na^+-K^+-ATPase), which converts the energy in adenosine triphosphate (ATP) into ion and electrical gradients, which

[b] In these and all subsequent calculations, it is assumed that 1 L of fluid (e.g., ICF and ECF) has a mass of 1 kg. This allows conversion from measurements of body weight to volume of body fluids.

TABLE 1.2 Ionic Composition of the ECF and ICF

	Extracellular Fluid	Intracellular Fluid
Na^+ (mEq/L)	135–147	10–15
K^+ (mEq/L)	3.5–5.0	120–150
Cl^- (mEq/L	95–105	20–30
HCO^-_3 (mEq/L)	22–28	12–16
Ca^{++} (mmol/L)*	2.1–2.8 (total)	
	1.1–1.4 (ionized)	~10^{-7} M (ionized)
P_i (mmol/L)*	1.0–1.4 (total)	
	0.5–0.7 (ionized)	0.5–0.7 (ionized)

*Ca^{++} and P_i ($H_2PO_4^-/HPO_4^{-2}$) are bound to proteins and other organic molecules. In addition, large amounts of Ca^{++} can be sequestered within cells. Large amounts of P_i are present in cells as part of organic molecules (e.g., adenosine triphosphate).

can in turn be used to drive the transport of other ions and molecules by means of ion channels and solute carriers (see Chapter 4).

Sodium is the major cation of the ECF, and Cl^- and bicarbonate (HCO_3^-) are the major anions. The ionic composition of the plasma and interstitial fluid compartments of the ECF is similar because they are separated only by the capillary endothelium, a barrier that in many tissues is freely permeable to small ions. The major difference between the interstitial fluid and plasma is that the latter contains significantly more protein. This differential concentration of protein can affect the distribution of cations and anions between these two compartments (i.e., the Gibbs-Donnan effect), because plasma proteins have a net negative charge that tends to increase the cation concentrations and reduce the anion concentrations in the plasma compartment. However, this effect is small, and the ionic compositions of the interstitial fluid and plasma can be considered identical. Because of its abundance, Na^+ (and its attendant anions, primarily Cl^- and HCO_3^-) is the major determinant of ECF osmolality. Accordingly, a rough estimate of the ECF osmolality can be obtained by simply doubling the sodium concentration [Na^+]. For example, if the plasma [Na^+] is 145 mEq/L, the osmolality of plasma and ECF can be estimated as:

$$\text{Plasma osmolality} = 2\,(\text{plasma}\,[Na^+]) = 290\ \text{mOsm/kg}H_2O \quad \textbf{(1.7)}$$

Because water is in osmotic equilibrium across the capillary endothelium and the plasma membrane of cells, measurement of the plasma osmolality also provides a measure of the osmolality of the ECF and ICF.

IN THE CLINIC

In clinical situations a more accurate estimate of the plasma osmolality is obtained by also considering the contribution of glucose and urea to the plasma osmolality. Accordingly, plasma osmolality can be estimated as:

$$\text{Plasma osmolality} = 2\,(\text{plasma}\,[Na^+]) + \frac{[\text{glucose}]}{18} + \frac{[\text{urea}]}{2.8} \quad \textbf{(1.8)}$$

The glucose and urea concentrations are expressed in units of milligrams per deciliter (dividing by 18 for glucose and 2.8 for urea[c] allows conversion from the units of milligrams per deciliter to millimoles per liter and thus to milliosmoles per kilogram of water). This estimation of plasma osmolality is especially useful when dealing with patients who have an elevated plasma [glucose] level because of uncontrolled diabetes mellitus and patients with chronic renal failure whose plasma [urea] level is elevated.

[c]The [urea] in plasma is measured as the nitrogen in the urea molecule, or blood urea nitrogen (BUN).

In contrast to the ECF, where the [Na^+] is approximately 145 mEq/L, the [Na^+] of the ICF is only 10 to 15 mEq/L. K^+ is the predominant cation of the ICF, and its concentration is approximately 150 mEq/L. This asymmetric distribution of Na^+ and K^+ across the plasma membrane is maintained by the activity of the Na^+-K^+-ATPase. By its action, Na^+ is extruded from the cell in exchange for K^+. The anion composition of the ICF differs from that of the ECF. For example, Cl^- and HCO_3^- are the predominant anions of the ECF, and organic molecules and the negatively charged groups on proteins are the major anions of the ICF.

FLUID EXCHANGE BETWEEN BODY FLUID COMPARTMENTS

Water moves freely and rapidly between the various body fluid compartments. Two forces determine this movement: hydrostatic pressure and osmotic pressure. Hydrostatic pressure from the pumping of the heart (and the effect of gravity on the column of blood in the vessel) and osmotic pressure exerted by plasma proteins (oncotic pressure) are important determinants of fluid movement across the capillary wall. By contrast, because hydrostatic pressure gradients are not present across the cell membrane, only osmotic pressure differences between ICF and ECF cause fluid movement into and out of cells.

Capillary Fluid Exchange

The movement of fluid across a **capillary wall** is determined by the algebraic sum of the hydrostatic and oncotic pressures (the so-called **Starling forces**) as expressed by the following equation:

$$\text{Filtration rate} = K_f\,[(P_c - P_i) - \sigma\,(\pi_c - \pi_i)] \qquad \textbf{(1.9)}$$

where the *filtration rate* is the volume of fluid moving across the capillary wall (expressed in units of either volume/capillary surface area or volume/time) and where K_f is the filtration coefficient of the capillary wall, P_c is hydrostatic pressure within the capillary lumen, π_c is oncotic pressure of the plasma, P_i is hydrostatic pressure of the interstitial fluid, π_i is oncotic pressure of the interstitial fluid, and σ is the reflection coefficient for proteins across the capillary wall.[d]

The Starling forces for capillary fluid exchange vary between tissues and organs. They also can change in a given capillary bed under physiologic conditions (e.g., exercising muscle) and pathophysiologic conditions (e.g., congestive heart failure). Fig. 1.4 illustrates these forces for a capillary bed located in skeletal muscle at rest.

The **capillary filtration coefficient (K_f)** reflects the intrinsic permeability of the capillary wall to the movement of fluid, as well as the surface area available for filtration. The K_f varies among different capillary beds. For example, the K_f of glomerular capillaries in the kidneys is approximately 100 times greater in magnitude than that of skeletal muscle capillaries. This difference in K_f accounts for the large volume of fluid filtered across glomerular capillaries compared with the amount filtered across skeletal muscle capillaries (see Chapter 3).

The hydrostatic pressure within the lumen of a capillary (P_c) is a force promoting the movement of fluid from the lumen into the interstitium. Its magnitude depends on arterial pressure, venous pressure, and precapillary (arteriolar) and postcapillary (venular and small vein) resistances. An increase in the arterial or venous pressures results in an increase in P_c, whereas a decrease in these pressures has the opposite effect. P_c increases with either

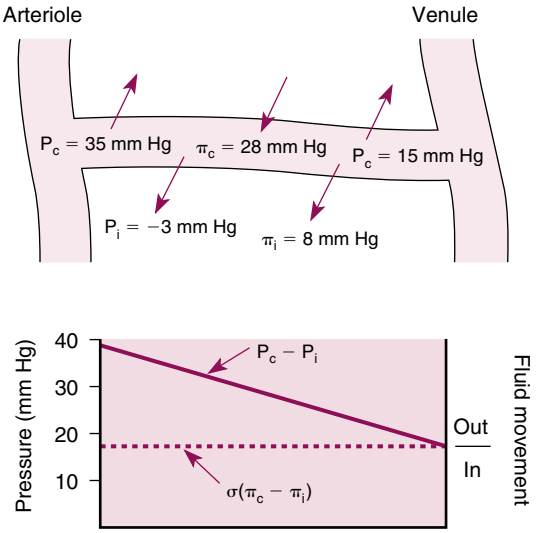

Fig. 1.4 *Top,* Schematic representation of the Starling forces responsible for the filtration and absorption of fluid across the wall of a typical skeletal muscle capillary. Note that P_c decreases from the arteriole end to the venule end of the capillary, whereas all the other Starling forces are constant along the length of the capillary. Some of the fluid filtered into the interstitium returns to the circulation via postcapillary venules, and some is taken up by lymphatic vessels and returned to the vascular system (not shown). *Bottom,* Graph of hydrostatic and oncotic pressure differences along the capillary (in this example, σ = 0.9). Net fluid movement across the wall of the capillary also is indicated. Note that fluid is filtered out of the capillary except at the venous end, where the net driving forces are zero. P_c, Capillary hydrostatic pressure; P_i, interstitial hydrostatic pressure; π_c, capillary oncotic pressure; π_i, interstitial oncotic pressure.

a decrease in precapillary resistance or an increase in postcapillary resistance. Likewise, an increase in precapillary resistance or a decrease in postcapillary resistance decreases P_c. For virtually all capillary beds, precapillary resistance is greater than postcapillary resistance, and thus the precapillary resistance plays a greater role in determining P_c. An important exception is the glomerular capillaries, where both precapillary and postcapillary resistances modulate P_c (see Chapter 3). The magnitude of P_c varies not only among tissues but also among capillary beds within a given tissue; it also is dependent on the physiologic state of the tissue.

Precapillary sphincters control the hydrostatic pressure within an individual capillary and the number of perfused capillaries in the tissue. For example, in skeletal muscle at rest, not all capillaries are perfused. During exercise, relaxation of precapillary sphincters allows perfusion of

[d]The osmotic pressure of plasma is in the range of 280 to 295 mOsm/kg H_2O. Most of these osmoles reflect the presence of small molecules (e.g., glucose) and ions. The plasma proteins only contribute 1 to 2 mOsm/kg H_2O (26 to 28 mm Hg). However, because the walls of most capillaries are highly permeable to small molecules and ions, they are essentially ineffective osmoles and therefore do contribute to the movement of fluid across the capillary wall. It is the small but important osmotic pressure gradient created by proteins (oncotic pressure gradient) that is an important determinant for capillary fluid movement.

more capillaries. The increased number of perfused capillaries reduces the diffusion distance between the cells and capillaries and thereby facilitates the exchange of O_2 and cellular metabolites (e.g., carbon dioxide [CO_2] and lactic acid).

The hydrostatic pressure within the interstitium (P_i) is difficult to measure, but in the absence of edema (i.e., abnormal accumulation of fluid in the interstitium), its value is near zero or slightly negative. Thus under normal conditions it causes fluid to move out of the capillary. However, when edema is present, P_i can become positive, and when it does, it opposes the movement of fluid out of the capillary (see Chapter 6).

The oncotic pressure of plasma proteins (π_c) retards the movement of fluid out of the capillary lumen. At a normal plasma protein concentration, π_c has a value of approximately 26 to 28 mm Hg. The degree to which oncotic pressure influences capillary fluid movement depends on the permeability of the capillary wall to protein molecules. If the capillary wall is highly permeable to protein, the protein concentration of the interstitial fluid is essentially the same as that of plasma. Thus σ is near zero and the oncotic pressure generated by plasma proteins plays little or no role in capillary fluid exchange. This situation is seen in the capillaries of the liver (i.e., hepatic sinusoids), which are highly permeable to proteins. Accordingly, in liver sinusoids, fluid movement across the sinusoidal wall is driven solely by the hydrostatic pressure gradient. In contrast, the capillaries of skeletal muscle are much less permeable to plasma proteins, such that the protein concentration in plasma is greater than that of the interstitial fluid. Because σ is approximately 0.9 in skeletal muscle, plasma protein oncotic pressure plays an important role in fluid movement across these capillary beds.

The proteins that are in the interstitium exert an oncotic pressure (π_i) that promotes the movement of fluid out of the capillary lumen. In skeletal muscle capillaries under normal conditions, π_i is small and has a value of only 8 mm Hg.

As depicted in Fig. 1.4, the balance of Starling forces across muscle capillaries causes fluid to leave the lumen (filtration) along its entire length. Some of this filtered fluid reenters the vasculature across the postcapillary venule, where the Starling forces are reversed (i.e., the net driving force for fluid movement is into the vessel). The remainder of the filtered fluid is returned to the circulation through the lymphatics.

Normally, 8 to 12 L/day of fluid moves across capillary beds throughout the body and is collected by lymphatic vessels. This lymphatic fluid flows first to lymph nodes, where most of the fluid is returned to the circulation. Fluid not returned to the circulation at the lymph nodes (1 to 4 L/day) reenters the circulation through the thoracic and right lymphatic ducts. However, under conditions of increased capillary filtration, such as that which occurs in individuals with congestive heart failure, thoracic and right lymphatic duct flow can increase 10-fold to 20-fold.

Cellular Fluid Exchange

Osmotic pressure differences between ECF and ICF are responsible for fluid movement between these compartments. Because the plasma membrane of cells contains water channels (aquaporins), water can easily cross the membrane. Thus a change in the osmolality of either ICF or ECF results in rapid movement (i.e., in minutes) of water between these compartments. Thus, except for transient changes, the ICF and ECF (plasma and interstitial fluid) are in osmotic equilibrium.

AT THE CELLULAR LEVEL

Water movement across the plasma membrane of cells occurs through a class of membrane proteins called **aquaporins (AQPs)**. Although water can cross the membrane through other transporters (e.g., Na^+-glucose symporter), AQPs are the main route of water movement into and out of cells. These AQPs can be divided into two subgroups. One group, which includes the AQP involved in the regulation of water movement across the apical membrane of renal collecting duct cells by arginine vasopressin (AQP-2) (see Chapter 5), is permeable only to water. The second group is permeable not only to water but also to low-molecular-weight substances, including gases and metalloids. Because glycerol can cross the membrane via this group of aquaporins, they are termed *aquaglyceroporins*. AQPs exist in the plasma membrane as a homotetramer, with each monomer functioning as a water channel (see Chapter 4).

In contrast to the movement of water, the movement of ions across cell membranes is more variable from cell to cell and depends on the presence of specific membrane transport proteins. Consequently, as a first approximation, fluid exchange between the ICF and ECF under pathophysiologic conditions can be analyzed by assuming that appreciable shifts of ions between the compartments do not occur.

BOX 1.1 Principles for Analysis of Fluid Shifts Between ICF and ECF

- The volumes of the various body fluid compartments can be estimated in a healthy adult as shown in Fig. 1.3.
- All exchanges of water and solutes with the external environment occur through the ECF (e.g., intravenous infusion and intake or loss via the gastrointestinal tract). Changes in the ICF are secondary to fluid shifts between the ECF and the ICF. Fluid shifts occur only if the perturbation of the ECF alters its osmolality.
- Except for brief periods of seconds to minutes, the ICF and the ECF are in osmotic equilibrium (within the ECF, plasma and interstitial fluid are also in osmotic equilibrium). A measurement of plasma osmolality provides a measure of both the ECF (including interstitial fluid) and the ICF osmolality.
- For the sake of simplification, it can be assumed that equilibration between the ICF and the ECF occurs only by movement of water and not by movement of osmotically active solutes.
- Conservation of mass must be maintained, especially when considering either addition or removal of water or solutes from the body.

A useful approach for understanding the movement of fluids between the ICF and the ECF is outlined in Box 1.1. To illustrate this approach, consider what happens when solutions containing various amounts of NaCl are added to the ECF.[e]

Example 1: Addition of Isotonic NaCl to ECF

The addition of an isotonic NaCl solution (e.g., intravenous infusion of 0.9% NaCl, osmolality ≈ 290 mOsm/kg H_2O, to a patient)[f] to the ECF increases the volume of this compartment by the volume of fluid administered. Because this fluid has the same osmolality as ECF and therefore also has the same osmolality as ICF, no driving force for fluid movement between these compartments exists and the volume of ICF is unchanged. Although Na^+ can cross cell membranes, it is effectively restricted to the ECF by the activity of Na^+-K^+-ATPase, which is present in the plasma membrane of all cells. Therefore no net movement of the infused NaCl into the cells occurs.

[e] In clinical settings, electrolyte solutions (e.g., isotonic NaCl) are often administered intravenously. When isotonic NaCl is infused by this route, rapid equilibration occurs (i.e., within minutes) between plasma and the interstitial fluid. Thus these fluids are essentially added to the entire ECF.

[f] A 0.9% NaCl solution (0.9 g NaCl/100 mL) contains 154 mmol/L of NaCl. Because NaCl does not dissociate completely in solution (i.e., 1.88 Osm/mol), the osmolality of this solution is 290 mOsm/kg H_2O, which is very similar to that of normal ECF.

IN THE CLINIC

Neurosurgical procedures and cerebrovascular accidents (strokes) often result in the accumulation of interstitial fluid in the brain (i.e., edema) and swelling of neurons. Because the brain is enclosed within the skull, edema can raise intracranial pressure and thereby disrupt neuronal function, leading to coma and death. The blood-brain barrier, which separates the cerebrospinal fluid and brain interstitial fluid from blood, is permeable to water but not to most other substances. As a result, excess fluid in brain tissue can be removed by imposing an osmotic gradient across the blood-brain barrier. Mannitol can be used for this purpose. Mannitol is a sugar (molecular weight = 182 g/mol) that does not readily cross the blood-brain barrier and membranes of cells (neurons as well as other cells in the body). Therefore mannitol is an effective osmole, and intravenous infusion results in the movement of fluid from the brain tissue by osmosis.

Example 2: Addition of Hypotonic NaCl to ECF

The addition of a hypotonic NaCl solution to the ECF (e.g., intravenous infusion of 0.45% NaCl, osmolality < 145 mOsm/kg H_2O, to a patient) decreases the osmolality of this fluid compartment, resulting in the movement of water into the ICF. After osmotic equilibration, the osmolalities of ICF and ECF are equal but lower than before the infusion, and the volume of each compartment is increased. The increase in ECF volume is greater than the increase in ICF volume.

Example 3: Addition of Hypertonic NaCl to ECF

The addition of a hypertonic NaCl solution to the ECF (e.g., intravenous infusion of 3% NaCl, osmolality ≈ 1000 mOsm/kg H_2O, to a patient) increases the osmolality of this compartment, resulting in the movement of water out of cells. After osmotic equilibration, the osmolalities of ECF and ICF are equal but higher than before the infusion. The volume of the ECF is increased, whereas that of the ICF is decreased.

IN THE CLINIC

Fluid and electrolyte disorders often are encountered in clinical practice (e.g., in patients with vomiting and/or diarrhea). In most instances these disorders are self-limited, and correction of the disorder occurs without need for intervention. However, more severe or prolonged disorders may require fluid replacement therapy. Such therapy may be administered orally with special electrolyte solutions, or intravenous fluids may be administered.

Intravenous solutions are available in many formulations (Table 1.3). The type of fluid administered to a particular patient is dictated by the patient's need. For example, if an increase in the patient's vascular volume is necessary, a solution containing substances that do not readily cross the capillary wall is infused (e.g., 5% albumin solution). The oncotic pressure generated by the albumin molecules retains fluid in the vascular compartment, expanding its volume. Expansion of ECF is accomplished most often by using isotonic saline solutions (e.g., 0.9% NaCl).

As already noted, administration of an isotonic NaCl solution does not result in the development of an osmotic pressure gradient across the plasma membrane of cells. Therefore the entire volume of the infused solution remains in the ECF. Patients whose body fluids are hyperosmotic need hypotonic solutions. These solutions may be hypotonic NaCl (e.g., 0.45% NaCl or 5% dextrose in water [D_5W]). Administration of D_5W is equivalent to infusion of distilled water, because the dextrose is metabolized to CO_2 and water. Administration of these fluids increases the volumes of both the ICF and ECF. Finally, patients whose body fluids are hypotonic need hypertonic solutions, which typically are solutions that contain NaCl (e.g., 3% and 5% NaCl). These solutions expand the volume of the ECF but decrease the volume of the ICF. Other constituents, such as electrolytes (e.g., K^+) or drugs, can be added to intravenous solutions to tailor the therapy to the patient's fluid, electrolyte, and metabolic needs.

TABLE 1.3 Intravenous Solutions

Solution	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Ca^{++} (mEq/L)	Lactate (mmol/L)	Glucose	Osmolality (mOsm/kg H_2O)	Other
0.45% NaCl (½ NSS)	77	77	0	0	0	0	154	0
0.9% NaCl (NSS)	154	154	0	0	0	0	308	0
3% NaCl (hypertonic saline solution)	513	513	0	0	0	0	1024	0
Lactated Ringer's solution	130	109	4	3	28*	0	275	
D_5W	0	0	0	0	0	50 g/L†	280	0
Dextrose (½ NSS)	77	77	0	0	0	50 g/L†	406	0
5% albumin in NSS	145	145	<1	0	0	0	309	50 g/L albumin

D_5W, 5% dextrose in water; *NSS*, normal saline solution.
*Metabolized to HCO_3^-.
†Metabolized to CO_2 and H_2O.

SUMMARY

1. Water, which is a major constituent of the human body, accounts for 60% of the body's weight. Body water is divided between two major compartments: ICF and ECF. Two-thirds of the water is in the ICF, and one-third is in the ECF. Osmotic pressure gradients between ICF and ECF drive water movement between these compartments. Because the plasma membrane of cells is highly permeable to water, ICF and ECF are in osmotic equilibrium.
2. The ECF is divided into a vascular compartment (plasma) and an interstitial fluid compartment. Starling forces across capillaries determine the exchange of fluid between these compartments.
3. Sodium is the major cation of ECF, and potassium is the major cation of the ICF. This asymmetric distribution of Na^+ and K^+ is maintained by the activity of Na^+-K^+-ATPase.

SELF-STUDY PROBLEMS

1. Calculate the molarity and osmolality of a 1 L solution containing the following solutes. Assume complete dissociation of all electrolytes.

	Molecular Weight (g/mol)	Molarity (mmol/L)	Osmolality (mOsm/kg H_2O)
9 g NaCl	58.4	_____	_____
72 g Glucose	180.2	_____	_____
22.2 g $CaCl_2$	111.0	_____	_____
3 g Urea	60.1	_____	_____
8.4 g $NaHCO_3$	84.0	_____	_____

2. The intracellular contents of a cell generate an osmotic pressure of 300 mOsm/kg H_2O. The cell is placed in a solution containing 300 mmol/L of a solute *(x)*. If solute *x* remains as a single particle in solution and has a reflection coefficient of 0.5, what happens to the volume of the cell in this solution? What would be the composition of an isotonic solution (i.e., a solution that does not cause a change in the volume of the cell) containing substance *x*?

3. A person's plasma [Na^+] is measured and found to be 130 mEq/L (normal = 145 mEq/L). What is the person's estimated plasma osmolality? What effect does the lower than normal plasma [Na^+] have on water movement across cell plasma membranes and across the capillary endothelium?

4. Fig. 1.4 illustrates the normal values for the Starling forces involved in fluid movement across a typical skeletal muscle capillary. Draw the new hydrostatic ($P_c - P_i$) and oncotic $\sigma(\pi_c - \pi_i)$ pressure curves if P_c at the venous end of the capillary was increased to 20 mm Hg. What effect would this increase have on fluid exchange across the capillary wall?

Note: For questions 5 through 8, for ease of calculation, the composition and osmolality of the infused solutions that are provided are slightly different from the solutions used clinically (see Table 1.3).

5. A healthy volunteer (body weight = 50 kg) is infused with 1 L of a 5% dextrose in water solution (D_5W, osmolality ~ 290 mOsm/kg H_2O). What would be the immediate and long-term effects (i.e., several hours after the dextrose has been metabolized) of this infusion on the following parameters? Assume an initial plasma [Na^+] of 145 mEq/L and, for simplicity, no urine output.

Immediate Effect:
ECF volume: _____ L
ICF volume: _____ L
Plasma [Na^+]: _____ mEq/L
Long-term Effect:
ECF volume: _____ L
ICF volume: _____ L
Plasma [Na^+]: _____ mEq/L

6. A second healthy volunteer (body weight = 50 kg) is infused with 1 L of a 0.9% NaCl solution (isotonic saline, osmolality ~ 290 mOsm/kg H_2O). What would be the immediate and long-term effects (i.e., several hours) of this infusion on the following parameters? Assume an initial plasma [Na^+] of 145 mEq/L and, for simplicity, no urine output.

Immediate Effect:
ECF volume: _____ L
ICF volume: _____ L
Plasma [Na^+]: _____ mEq/L
Long-term Effect:
ECF volume: _____ L
ICF volume: _____ L
Plasma [Na^+]: _____ mEq/L

7. A person who weighs 60 kg has an episode of gastroenteritis with vomiting and diarrhea. Over a 2-day period this person loses 4 kg of body weight. Before becoming ill, this individual had a plasma [Na^+] of 140 mEq/L, which was unchanged by the illness. Assuming the entire loss of body weight represents the loss of fluid (a reasonable assumption), estimate the following values:

Initial Conditions (Before Gastroenteritis):
Total body water: _____ L
ICF volume: _____ L

ECF volume: _____ L
Total body osmoles: _____ mOsm
ICF osmoles: _____ mOsm
ECF osmoles: _____ mOsm

New Equilibrium Conditions (After Gastroenteritis):

Total body water: _____ L
ICF volume: _____ L
ECF volume: _____ L
Total body osmoles: _____ mOsm
ICF osmoles: _____ mOsm
ECF osmoles: _____ mOsm

8. A person who weighs 50 kg with a plasma $[Na^+]$ of 145 mEq/L is infused with 5 g/kg of mannitol (molecular weight of mannitol = 182 g/mol) to reduce brain swelling after a stroke. After equilibration, estimate the following values, assuming mannitol is restricted to the ECF compartment, no excretion occurs, and the infusion volume of the mannitol solution is negligible (i.e., total body water is unchanged):

Initial Conditions (Before Mannitol Infusion):

Total body water: _____ L
ICF volume: _____ L
ECF volume: _____ L
Total body osmoles: _____ mOsm
ICF osmoles: _____ mOsm
ECF osmoles: _____ mOsm

New Equilibrium Conditions (After Mannitol Infusion):

Total body water: _____ L
ICF volume: _____ L
ECF volume: _____ L
Total body osmoles: _____ mOsm
ICF osmoles: _____ mOsm
ECF osmoles: _____ mOsm
Plasma osmolality: _____ mOsm/kg H_2O
Plasma Na^+: _____ mEq/L

9. Two healthy individuals (body weight = 60 kg) have the following urine output over the same period.
Subject A: 1 L of urine with an osmolality of 1000 mOsm/kg H_2O
Subject B: 4 L of urine with an osmolality of 400 mOsm/kg H_2O
If both individuals have no fluid intake, what is their plasma osmolality? Hint: Assume that both individuals have an initial plasma $[Na^+]$ of 145 mEq/L and thus a plasma osmolality of approximately 290 mOsm/kg H_2O.
Subject A:_____
Subject B:_____