Basics of Fluid Physiology

10

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Introduction

Administration of intravenous fluids is one of the commonest medical acts in hospitalized patients. This chapter will emphasize the physiological role of fluids, principles behind the movement and distribution of water and it solutes, and the characteristics of different kinds of commonly infused fluids. In Chap. 42, use of fluids for both resuscitation and maintenance of normal fluid balance is discussed. Some of these issues have been covered previously (Magder 2001), but in this review the principles are updated. An important influence on this discussion is the excellent review by Bhave and Neilson (Bhave and Neilson 2011a). We will emphasize four basic concepts. (1) Elements, especially sodium ion (Na^+) and chloride ion (Cl^-), have unique importance when compared to metabolizable organic molecules. (2) The amount of an element in the body can be regulated only by absorption or excretion. (3) The vascular space is in a dynamic equilibrium with the interstitial and other "third" spaces, such as the pleural and peritoneal compartments. Because of this, they all have approximately the same osmolality. This means that any administration of resuscitation fluids, or de-resuscitation of fluid, shifts water and elements between all compartments. Thus, volume management must not be confined to just the vascular space. (4) Colloids play a unique role in the maintenance of intravascular and intracellular volumes because they do not readily cross cell membranes.

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What Is the Role of Water in Organisms?

Organic molecules and elements need to be in solution to react with each other and to move by bulk flow or diffusion from one region to another (Rawn 1989). With the odd exception, water is the solvent for all biological solutions. Life as we know it would not exist without water. This is because water has a unique property which readily allows dissolved substances to become part of its structure (Rawn 1989; Ball 2001). Bodily solutions are essentially mixtures of salts, with dissolved proteins, carbohydrates, lipids, and other small organic molecules.

When original cell walls formed, and solutions of organic substances became walled off from the surrounding milieu, regulation of cell volume became an important physiological process. This is because cell walls are imbedded

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with complex protein structures, including channels, exchangers, and receptors (O'Neill 1999). A change in cell volume stresses the cell walls and alters the tertiary structure of these large membrane molecules (Macknight and Leaf 1977). Changes in their shape can lead to intracellular transcriptional and non-transcriptional processes that are directed at restoring steady state volume as part of the body's stress response (O'Neill 1999; Orlov and Hamet 2006). *A key message is that, independent of the role* water has *in altering intravascular volume, infusion of a fluid that results in changes in intracellular volume significantly alters intracellular signaling processes (key messages are listed in* Table 10.1*)* Unfortunately, these processes are complex and not predictable; the consequences can be determined only by empirical studies on whole organisms or cells. These studies likely should be done on human tissues because of species and even cellular specificities.

When multi-celled organisms developed an envelope that excluded interior structures from the surrounding environment, it became necessary to evolve systems to regulate the volume and concentration of substances in this interior space which is inside the outer integument but outside cells (Stein 2002). This is called the interstitial space (Pitts 1968; Magder 2014; Aukland and Nicolaysen 1981). Without regulation of the concentration of electrolytes in this space, water would be lost or gained from the milieu outside the organism's outer barrier. *Thus, a key message is that in fluid management, even though we only make assessments based on the plasma space, consideration must be given to the consequences of administered fluids for the vascular, interstitial, and intracellular spaces.* Furthermore, it needs to be appreciated that the volume in red cells is not part of the extracellular volume, but it is part of the total intracellular volume, although its properties are different from other cells.

Table 10.1 Key principles from physiology of fluid

1. Independent of the role water has in altering intravascular volume, infusion of a fluid that results in changes in intracellular volume significantly alters intracellular signaling processes
2. In fluid management, even though we only make assessments based on the plasma space, consideration must be given to the consequences of administered fluids for the vascular, interstitial, and intracellular spaces
3. A volume bolus of more than 1 to 1.5 L is not likely to remain in the vascular space because the vessels do not have the capacity to hold it
4. When considering volume therapy, the volume and composition of fluids in all extracellular compartments must be considered because they all are in equilibrium with the plasma space in the steady state
5. One must distinguish the concentration of elements from their actual amount in the body. The total amount of an element in the body is related to the total amount of the volume of water and the concentration of the element and the amount only can be regulated by absorption or excretion because elements cannot be created or metabolized
6. Edema can produce further edema, and large volume resuscitation can make things worse

Volume and the Generation of Blood Flow

In small organisms, O_2 and nutrients can be adequately supplied, and waste excreted, by diffusion from the surrounding environment. However, in large multicellular organisms, diffusion is not adequate and a distribution system is required to allow more rapid conductive flow. This was provided by evolution of the cardiovascular system (Bishopric 2005). The role of volume in the regulation of cardiac output is covered in Chap. 2. In essence, cardiac output is controlled by the interaction of the return of blood to the heart (return function) and cardiac function. The primary force in both of these functions is the stretch of the elastic walls of cardiovascular structures by volume.

As emphasized in Chap. 2, some of the blood volume in vessels simply rounds out vessel walls, and some of the volume stretches the walls, but only the portion that stretches the walls produces the elastic recoil force. This is called stressed volume. The remaining volume rounds out vessels but does not stretch their elastic walls; this is called unstressed volume. In a standard size male, total blood volume is approximately 5.5 L. Under resting conditions, about 30%, or 1.3 to 1.4 L, is

stressed and an elastic recoil pressure is created in vessels (Magder and De Varennes 1998). The rest of the volume is unstressed and provides a reserve that can be recruited to produce the equivalent of an auto-transfusion as discussed below. Furthermore, with a hematocrit of 40% and a total blood volume of 5.5 L, the plasma volume is about 3.3 L. The proportions of red cell mass and plasma volume in the total blood is the same in the stressed and unstressed volumes. Thus, only about 1 liter of plasma contributes to stressed volume. This means that the normal plasma component of stressed volume is only about 1 liter. *A key point is that a volume bolus of more than 1 to 1.5 L is not likely to remain in the vascular space because the vessels do not have the capacity to hold it.*

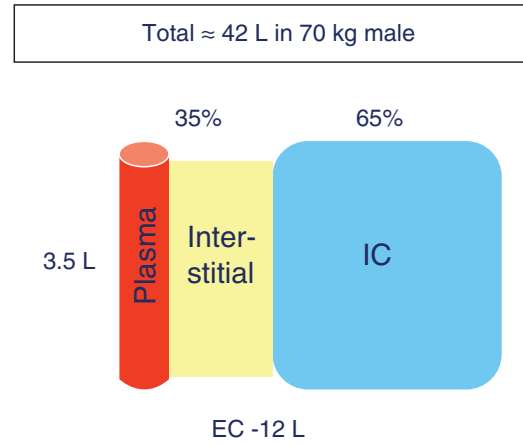

Fig. 10.1 Distribution of water in the body. See text for details. (*EC* extracellular volume, *IC* intracellular volume. The arrows indicate that plasma volume and the interstitial space are constantly interacting)

Compartments

Water makes up 60% of total body mass of an average male below the age of 40 and 50% in females and older males (West 1985; Mudge 1980). The differences between young males and females and older males are due to differences in the proportion of muscle mass relative to total body mass (Bhave and Neilson 2011b). In a 70 kg male, total body water is ~42 L. Of this total, approximately two-thirds of the water, i.e., ~ 28 L, are intracellular fluid (ICF) and 14 L are extracellular fluid (ECF) (Fig. 10.1). The ECF can be subdivided into five sub-compartments. These include plasma volume, interstitial and lymph fluid, dense connective tissue and bone fluids, transcellular fluids within cavities such as the pleural and peritoneal fluids, and the cerebrospinal fluid (Bhave and Neilson 2011a). Plasma volume accounts for 3–4 L of the ECF, and the other 10 to 12 L of the ECF, at least the exchangeable part, is primarily in the interstitial space. Adipose tissue can contain a large amount of water by weight. When body mass index is normal, and there is not a lot of fat, adipose tissue contributes a small amount to total ECF. However, it can account for a very large proportion of total body water in the morbidly obese (Bhave and Neilson 2011a). Interstitial volume as a percentage of total body water can increase dramatically when edema develops. Fluid that accumulates in body cavities, such as the pleural and peritoneal spaces, also freely communicates with the interstitial and plasma spaces, and they all should be considered as one compartment. This becomes very important for understanding the distribution of an infused crystalloid solution. As will be discussed below, the volume and electrolytes in all compartments must equilibrate with the vascular space. *A key point is that when considering volume therapy, the volume and composition of fluids in all extracellular compartments must be considered because they all are in equilibrium with the plasma space in the steady state.*

Regulation of the Distribution of Body Water and Electrolytes

Distribution of water between the extracellular (EC) and intracellular (IC) compartments is determined by hydrostatic pressure and osmosis. Steady state water distribution reflects the balance of these two forces across compartments:

$$P_{ic} - P_{ec} = \Pi_{ic} - \Pi_{ec} \qquad (10.1)$$

where P is the hydrostatic pressure and Π is the osmotic pressure inside (*ic*) and outside (*ec*) cells. Early life forms such as bacteria, fungi, and plants have rigid cell walls that are impermeable to water and produce hydrostatic pressure differences by pumping electrolytes into or outside of their intracellular compartment to maintain their volume. In contrast, animal species evolved non-rigid cell walls that are permeable. This gave these cells flexibility of movement, but it also meant that their intracellular volume needs to match the extracellular osmolality. Essentially, $P_{ic} - P_{ec}$ becomes zero and $\Pi_{ic} = \Pi_{ec}$. In this case, the whole organism is separated from the outside world by a surrounding barrier (i.e., skin) and all inner compartments have the same osmolality. This is expressed in the principle of iso-osmolality (West 1985; Freedman 1997) which states that all compartments of the body have essentially the same osmolality. This occurs because capillary endothelium, and almost all cell membranes, are freely permeable to water, which easily moves from areas of lower concentrations of osmoles to areas of higher concentrations of osmoles by osmosis. As will be discussed, there is a small exception to this; osmolality of the plasma is slight greater than that of the rest of the body.

What Are Osmoles?

Osmoles are discreet particles dissolved in a solution. They alter the properties of water such as its freezing and vaporization temperatures. Osmolality is the number of particles per mass (weight) of the solution; osmolarity is the number of particles per volume. The preferred term is osmolality because mass is a fixed property of a substance, whereas volume can vary with temperature and external pressure. However, volume is easier to measure and thus osmolarity is commonly used. The osmolality of a solution produces a pressure, which is defined by the Van't Hoff equation (West 1985; Freedman 1997):

$$\text{Osmotic pressure} = n\left(c / M\right)RT \quad (10.2)$$

where n is the number of particles, c is the concentration of the substances, M is the molecular weight of the substances, R is the ideal gas constant, and T is the absolute temperature. The expression c/M defines the molar concentration. One mOsmol generates 19.34 mmHg at 37 °C (Fig. 10.2). Of importance, the size of the particle does not matter so that the osmotic effect of a 69 kD albumin molecule is the same as that of a single Na^+ atom. Osmotic pressure from an electrolyte is modified by the valence (z) and the nonideality of the solution (φ),

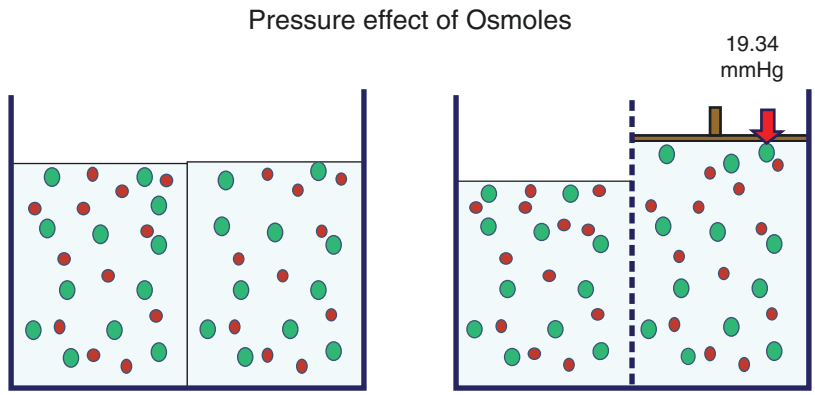

Fig. 10.2 Pressure effect of osmoles. In the panel on the left, the number of particles is equal on both sides of a semipermeable membrane that does not allow the particles to cross. On the right side, 1 mOsmol (one particle) was added and water moves from the left to make the concentrations equal. 19.34 mmHg of pressure would need to be added to make the heights of water equal on both sides of the membrane

which indicates the deviation of the effective osmolality of a substance in a solution from that predicted simply by its mass and particle number. The osmotic pressure from one osmole in the body is thus:

$$\prod_{ec}(37°, mmHg) = 19.34 * \varphi * Z * [c] \quad (10.3)$$

$$\text{Osmolatiy } (mOsm/kg) = \varphi * Z * [c] \quad (10.4)$$

Osmotic water movement is determined by how easily water can pass through a membrane, which is called hydraulic permeability (L_p) and the solute concentration gradient ($\Delta[c]$) between two solutions on either side of a membrane.

$$\text{Osmotic flux} = Lp \times 19.34 * \varphi * \Delta[c] \quad (10.5)$$

Most solutes are at least partially permeable across the cell membrane and undergo convective transport with water, but their ability to cross membranes varies. This is described by the reflection coefficient, σ, which is a dimensionless number between 0 and 1. When a solute has $\sigma = 1$, no particles move across the membrane, and the observed osmotic gradient produces the maximal osmotic force as predicted based on the difference in the number of particles on each side of the membrane. When there is a difference in the concentration of substances on the two sides of the membrane, the system is in a more "ordered" state and has a lower entropy. This attracts water to reduce the overall ordered state, thus increasing the overall entropy of the system in the same way as the energy in the form of heat moves from an area of higher temperature to an area of lower temperature. If some particles manage to cross the membrane, the osmotic force is reduced and σ is <1. When the particles easily cross the membrane, and σ is close to 0, there is no osmotic water movement (Bhave and Neilson 2011a). For a substance that has $\sigma < 1$, and is leaking across the membrane, another variable is that the gradient for osmosis requires that the concentration gradient develop faster than the solute flux across the membrane (Bhave and Neilson 2011a). For most of the discussion in this chapter, water movement between the extracellular and intracellular fluid (ICF) is primarily related to the concentrations of Na^+, K^+, and Cl^- which have σ close to 1 over short periods of time.

The compositions of plasma, interstitial, and extracellular fluid are shown in Fig. 10.3. Positive elements such as Na^+, K^+, Ca^{2+}, and Mg^{2+} and the negative element Cl^- play the major roles in regulating water balance by determining the osmolality of body fluids (West 1985; Freedman 1997). *A key point is that one must distinguish the concentration of elements from their actual amount in the body. The total amount of an element in the body is related to the total amount of the volume of water and the concentration of the element and the amount only can be regulated by absorption or excretion because elements cannot be created or*

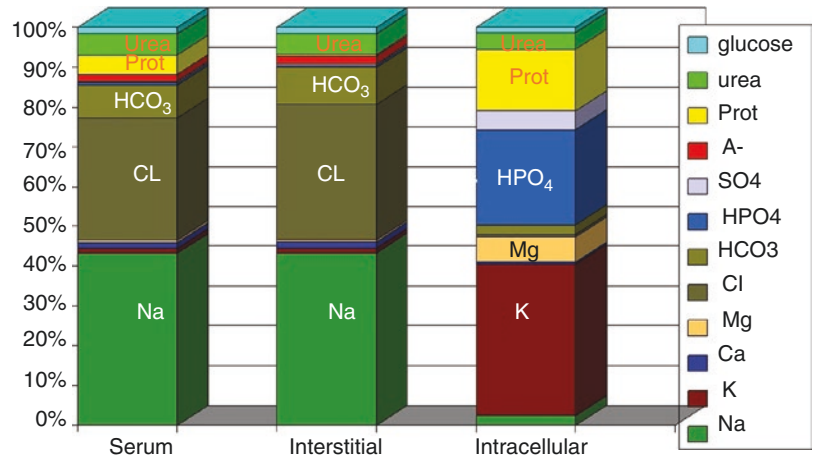

Fig. 10.3 Contents of serum and interstitial and intracellular spaces: Gamblegram

metabolized. Na^+ is by far the dominant cation in serum. Once mechanisms evolved to regulate Na^+ concentration (Stein 2002), the amount of negatively charged substances, such as Cl^-, had to follow Na^+ concentration to maintain electrical neutrality. Thus, by having Na^+ concentration controlled Cl^- concentration tends to be controlled, although there are some independent regulators of Cl^- concentration itself because of its importance in acid-base balance (Magder 2014; Magder and Emami 2015). To allow for independent control of intracellular volume from the extracellular space, there needed to be a another cation to replace Na^+ and K^+ filled this role. However, K^+ concentration must still follow the concentration of Na^+ in keeping with the principle of iso-osmolality because water can generally move in and out of cells. The presence of K^+ allowed the distribution of water to be controlled despite differences in the electrolyte compositions of the extracellular and intracellular spaces. The regulation of these differences in concentrations occur through the activity of selective channels and exchangers that control the influx or efflux of these key elements across membranes. Na^+ has the central role for the whole body regulation of osmolality because Na^+ ions are directly taken in or excreted from outside the organism (Hollenberg 1980; Manning Jr. and Guyton 1982). This sets the osmolality of plasma and the interstitial space. The concentration of K^+ inside cells, too, is dependent upon the osmolality of the surrounding interstitial space. The concentration of K^+ is regulated by the exchange with Na^+, gated channels in the membrane that allow influx and efflux of K^+ and the movement of water from the space outside cells, i.e., interstitial space. K^+ also has evolved with the important role of maintaining transmembrane potentials. Because of this, the concentration of K^+ across cell membranes must be controlled in a tight range to protect life-sustaining cell functions.

Water movement due to non-charged molecules is divided into a diffusive component down a concentration gradient that does not involve water movement and a convective component that occurs with water flux. The two factors for movement of a non-charged substance are the ease with which the substance can cross a membrane, which is called the diffusive permeability (P_D), and its refection coefficient, σ.

$$\underset{}{\text{Solute flux}\left(Js\right)} = \underset{\textit{Diffusive}}{Pd * \Delta\left[c\right]} + \underset{\textit{Convective}}{\left(1-\sigma\right) * Jv * \left[C\right]_m} \quad (10.6)$$

where Js is the solute flux, Jv is the volume flux, and Pd is the diffusive permeability. Pd can be high because a substance is lipophilic and can diffuse across membranes or because the substance is carried by active transport mechanisms.

Glucose is an example of a substance that can be osmotically active, i.e., has a σ close to 1, but normally does not create an osmotic gradient because of the many mechanisms that transport glucose into cells and its rapid metabolism. However, in type II diabetes, increases in glucose concentration can produce osmotic activity and water shifts. An important example is hyperosmolar hyperglycemia (Bear and Neil 1983). In this condition, a stress, such as an infection or myocardial infarction, triggers a rapid increase in plasma and interstitial glucose concentration because of uncontrolled glucose production, primarily by the liver, and decreased peripheral glucose uptake. Both of these are related to insulin resistance. The increase in extracellular osmolality pulls intracellular water out of cells and into the extracellular space. Plasma Na^+ concentration is diluted and there is a hyperosmolar plasma but hyponatremia. Most often, true total body Na^+ is reduced because Na^+ and water are lost by glucose-induced osmotic diuresis. When glucose is subsequently decreased, Na^+ concentration rises because there is a greater loss of water than Na^+ and the dehydration becomes obvious. It is clinically important to determine what the true Na^+ concentration will be when the hyperosmolar glucose state is dealt with because this predicts how much and what type of water is needed during resuscitation. This expected increase can be estimated in mMol by subtracting 5 from the measured glucose and dividing by 3.5 (Katz 1973). There are a number of assumptions in this calculation including that the extracellular osmolality does not completely equilibrate with intracellular osmolality, extracellular water is 14 L, the solute in cells does not change, there is no Na^+ in cells,

and the cells have no free glucose, all of which are not true but still allow an approximation.

Urea illustrates the difference between Pd and σ. Urea is hydrophobic. It normally has a σ close to 1 and a low Pd. However, along the inner medullary collecting ducts, there are urea transporters and aquaporin for the movement of water molecules. These allow independent urea and water movement under the control of antidiuretic hormone (Bhave and Neilson 2011a). Pd thus can be high and σ near 1, and urea then can create an osmotic gradient. An important variable for permeability is the surface area for the movement of a substance (Sands 1999). Although urea normally has a low Pd and σ near 1, the total area of cell membranes is large and urea production is relatively low, so that normally a concentration difference across cell membranes does not build up. In capillaries, σ also is <0.01, because urea can pass easily through inter-endothelial pores producing a high Pd. However, this is not true in the brain and this can produce an important clinical problem. Cerebral capillaries have a low diffusive permeability, i.e., low Pd, because they lack urea transporters. They also have a σ of 0.5. During dialysis, urea in the blood can fall rapidly and this can produce a sufficient concentration difference between the brain interstitial space and plasma which creates an osmotic force that makes the water move into the brain. The result can be what is called dialysis disequilibrium syndrome (Silver et al. 1996).

A special type of osmotic pressure is called colloid osmotic or oncotic pressure. This force is due to large molecules in the plasma space that cannot readily move across vascular walls. Their osmotic force thus is limited to the plasma space. The presence of colloids in the blood results in the osmotic pressure in the blood being slightly higher than that of the interstitial and intracellular spaces. The presence of this positive osmotic pressure gradient between the plasma and interstitial space creates an inward pressure difference that counteracts the outward hydrostatic pressure. The result is a reduction of fluid filtration out of capillaries and maintenance of plasma volume (Levick and Michel 2010; Adamson et al. 2004). The plasma oncotic pressure normally is approximately 25 mmHg, and 65 to 75% of this value is accounted for by albumin (Bhave and Neilson 2011a; Diem and Lentner 1970). Even though albumin is a large molecule with a concentration of ~40 g/L in the plasma, recall that osmotic pressure is dependent upon particle number and not mass. To calculate its osmotic effect, the total mass is converted to moles by dividing by the molecular weight of albumin which is 69 kDa. This gives the number of moles of albumin, which normally is around 0.58 mmol/kg. As a result, albumin produces an osmotic pressure of 11.2 mmHg. However, this value is less than the full effect of albumin in resisting the outward hydrostatic force.

Albumin molecules can dissociate and have a negative charge (Figge et al. 1992). The charge depends upon its isoelectric point (pKa), which for albumin is ~5, relative to normal plasma pH of 7.4. The negative charge creates an electrical force that attracts oppositely charged ions, which in plasma is primarily countered by Na^+. This results in a slightly higher concentration of Na^+ in plasma than in the interstitial space. By the same argument, Cl^- concentration is higher in the interstitial space than in plasma. The final concentrations of Na^+ and Cl^- in the plasma and interstitial spaces depend upon the equilibrium of their concentration gradients, the charge differences, the osmolality differences, and oncotic pressure, all of which affect water movement. The interaction of oncotic forces and charge forces is described by what is known as the Gibbs-Donnan relationship (West 1985; Sperelakis 1997; Overbeek 1956) (Kellum and Elbers 2009). The electrical component adds an inward force of 5.8 mmHg, which increases the net oncotic effect of albumin to 16 to 18 mmHg. In total, albumin accounts for 65 to 75% of the total plasma oncotic inward pressure. Although the same factors in the Gibbs-Donnan relationship exist across cell walls, the Na^+-K^+ adenosine triphosphate pump creates a much stronger force that easily overrides the Gibbs-Donnan relationship across cell walls (West 1985).

Albumin can be consumed rapidly during inflammatory states because it is part of the acute phase reaction. The fall in albumin con-

centration markedly reduces effective plasma oncotic pressure and allows increased fluid filtration. Other proteins in plasma are less osmotically effective because their molecular weights generally are even larger than albumin's, so that they have less particles per mass. Somewhat surprisingly, there is a condition called congenital analbuminemia in which sufferers have no albumin, yet these patients still survive without major edema (Koot et al. 2004; Kallee 1996). This occurs because the concentrations of smaller sized globulins increase. These smaller globulins also increase to some extent in inflammatory hypoalbuminemia because small α1 and α2 globulins are also part of the acute phase reaction, too, (Vavricka et al. 2009), although their effect is less efficient than in analbuminemia, because the large β fraction is unchanged and the larger γ fraction increases with chronicity of the inflammatory process (Kaysen 1993). Because of these changes in plasma protein concentration with hypoalbumnemia, the concentration of all plasma protein need to be assessed to predict the effect of the albumin loss on plasma oncotic pressure (Bhave and Neilson 2011a; Barclay and Bennett 1987).

A final determinant of plasma volume is the number of red cells and their size.

Large proteins, such as albumin, become part of the solution and create an effective osmotic force. This is not the case for red cells. They are not in solution, but rather act as a suspension in the plasma and do not contribute to plasma osmotic pressure. This means that an increase in the number of red cells does not "draw" water into the plasma space as occurs with the oncotic effect of proteins. Two simple considerations should make this obvious. In the initial stage of a large bleed, hemoglobin concentration does not change because plasma and red cells are lost equally. It is only when fluid is recruited from the interstitial space back into the plasma space, or a crystalloid solution is infused, that the loss of red cells and the decreas in the total amount of hemoglobin become obvious. On the other side, administration of packed red blood cells would not change the hemoglobin concentration if red cells had an osmotic drew water from the interstitial space into the plasma space. What red cells do is create a mass effect in vessels by taking up space. This mass still contributes to the hydrostatic pressure on the vascular wall and thus contributes to blood pressure. However, the effect of a transfusion is proportionally smaller than what occurs with an increase in the fluid component because red cell mass is a smaller fraction of the total blood volume than plasma volume. For example, if the initial blood volume is 5 L, a change in Hct from 20 to 25 would increase blood volume by 5%, whereas a change in plasma volume from 3 L to 3.5 L would change it by 10%.

Extracellular Fluid Dynamics

This is discussed in detail in Chap. 6 (Dr. Curry), but a few points relative to edema formation will be reviewed here. As indicated by Dr. Curry, the revised understanding of Starling's forces is that there is a net filtration of fluid from the capillaries under normal conditions (Levick and Michel 2010; Adamson et al. 2004). This is determined by the positive outward hydrostatic gradient across the capillaries which is produced by the intravascular capillary pressure of approximately 24 mmHg and hydrostatic pressure in the interstitial space of close to zero. This force is countered by the inward gradient in oncotic pressure of the intravascular space relative to the oncotic pressure in the ECF, which is primarily due to the presence of albumin. It was initially thought that the albumin concentration in the interstitial space is very low, but it now is evident that 10 g of albumin moves into the interstitial space and then the into the lymphatics per hour (Renkin 1986). The concentration of albumin in the ICF is 10 to 15 g/L and accounts for 25 to 50% of total body albumin (Renkin 1986). Based on these numbers, the interstitial albumin normally turns over approximately twice per day. However, the interstitial space is not a simple system and actually comprises three systems: a free flowing fluid that contains albumin, a gel phase that contains glycosaminoglycans (CAGs), and a collagen-based matrix. Water and small solutes move through all three compartments (Maroudas 1970), but albumin

only is found in the free flowing component (Reed et al. 1989). This produces an effective albumin concentration in the interstitial space of 20 to 30 g/L and an oncotic force that is 30 to 60% of that of the plasma (Bhave and Neilson 2011a).

The discovery that interstitial albumin is not close to zero, but rather almost 50% that of plasma, created a challenge to the classic Starling hypothesis for fluid filtration from capillaries. This has been resolved by the understanding the role of the glycocalyx on the vascular surface of endothelial cells. This region provides an area with a lower albumin concentration than the whole ECF and can alter filtration rates as discussed in detail in Chap. 6 (Dr. Curry) (Levick and Michel 2010).

A number of local counter-regulatory mechanisms prevent excessive volume loss by excessive filtration. When filtration is high, water flux outstrips albumin flux, and interstitial albumin concentration is diluted. This increases the net oncotic gradient across vascular walls, which reduces net filtration rate. By this mechanism, interstitial Π is kept at about 50% of plasma Π. Another feature of the interstitial space also helps. Normal hydrostatic pressure in the interstitial space is close to zero. However, the ISF space normally is very non-compliant (Wiig and Reed 1981; Reed and Wiig 1981; Guyton 1965). Thus, an increase in interstitial volume because of increased fluid filtration quickly increases the interstitial space hydrostatic pressure. This decreases the hydrostatic pressure gradient from the plasma to the interstitium and reduces capillary filtration rate (Reed et al. 1989). Unfortunately, the effect is limited. When interstitial volume increases by more than 20 to 50%, and the interstitial pressure rises above approximately 4 mmHg, the interstitial space becomes very compliant and edema can rapidly increase with little change in the interstitial hydrostatic pressure (Wiig and Reed 1981; Reed and Wiig 1981; Guyton and 1965). This increase in interstitial compliance occurs through the interaction of cell surface integrin receptors with the extracellular collagen matrix and force generating actin tension in the cytoskeleton (Berg et al. 2001; Lund et al. 1989; Lund et al. 1988; Reed et al. 2001; Reed and Rubin 2010; Pozzi and Zent 2003). The same increase in the interstitial compliance also occurs in inflammatory states or thermal injury by cytokine action and greatly increases capillary leak. *A key message from this section is that edema can produce further edema, and large volume resuscitation can makes things worse*.

Nephrotic syndrome demonstrates a number of challenges to vascular fluid balance. Aside from the presence of hypoalbuminemia, the proportion of high molecular weight proteins increases because small-sized proteins are preferentially lost. Thus, unlike what occurs in analbuminemic subjects, plasma oncotic pressure falls in proportion to the fall in albumin. The fall in plasma oncotic pressure leads to increased capillary filtration. As described above, the increased fluid flux increases interstitial Pi and lowers interstitial oncotic pressure so that the interstitial oncotic pressure remains at about 50% of the plasma oncotic pressure or about 12 mmHg (Koomans et al. 1986). However, when interstitial oncotic pressure falls to zero, it cannot be lowered further. When that happens, a further fall in plasma albumin cannot be defended by a further fall in interstitial oncotic pressure. The ratio of plasma to interstitial oncotic pressure falls and edema is inevitable. This can result in a rapid decrease in intravascular volume and is known as a nephrotic crisis in pediatrics (Van de Walle et al. 1996).

Movement and Distribution of Fluids

In this section, I will discuss the distribution of infused exogenous fluids among the different water compartments. So far in this chapter, the discussion of water movement largely has been based on osmotic forces, but as was evident in the discussion on colloids, not all osmoles have the same effect on cell volumes, which is a major homeostatic processes (Levick and

Michel 2010). In this regard, there are osmoles that are effective and others that are ineffective for the regulation of cell volume. At this time, it is necessary to introduce the term tonicity. This term is used to describe only effective osmolality across membranes (Gennari 1984; Mange et al. 1997). An isotonic solution can be defined pragmatically as one in which added red cells, with a normal intracellular osmolality, do not shrink or swell. When plasma osmolality is normal (~290 mOsm/kg), the terms iso-osmolar and isotonic are equivalent. However, a good example of the difference between isotonicity and iso-osmolarity is what happens when ethanol is added to plasma. Ethanol elevates osmolality but does not alter tonicity because it rapidly diffuses across cell membranes and increases intracellular osmolality to the same extent as in the extracellular space and cell volumes do not change (Bhave and Neilson 2011a). Iso-tonicity thus is more physiologically relevant than iso-osmotic.

The abundance of molecules inside cells that only poorly permeate to the outside, substances that interact with other molecules inside the cell, and the large K^+ concentration that acts as a counter ion to Na^+ outside cells, create a large Gibbs-Donnan effect. This produces an osmotic gradient that favors persistent water intake by cells. However, this does not happen because it is countered by the Na^+-K^+-ATPase, which actively extrudes Na^+ and, consequently, also draws Cl^- out of the cell to preserve electrical neutrality (Levick and Michel 2010). This process effectively makes the cell impermeable to Na^+, Cl^-, and K^+ ions because these ions are regulated by exchangers and gated channels (Bhave and Neilson 2011a). Water passively distributes between ECF and ICF based on Na^+ and K^+ concentrations and osmotic equilibrium (tonicity) to preserve cell volume.

An important assumption in the following discussion is that the patient's initial plasma osmolality is normal, but in clinical practice, this frequently is not the case. Thus, solutions considered to be iso-osmotic or iso-oncotic relative to normal plasma are often not so in relation to the patient's plasma.

Pure Water and Dextrose in Water

Water in the gastrointestinal tract is taken up by the intestinal walls and then is passed into the vasculature. This decreases the osmolality of plasma relative to that of the interstitial space so that the water moves to the higher osmolality in the interstitial space. This in turn lowers the osmolality of the interstitial space relative to the intracellular space and water moves into cells until osmolality is again equal in all compartments, except for the slightly higher plasma osmolality produced by the colloid oncotic pressure and Gibbs-Donnan effect (Bhave and Neilson 2011a; Overbeek 1956). The same occurs when 5% dextrose in water (D5W) is infused into the plasma space. Initially, the osmolality of D5W is the same as that of normal plasma and no movement of the water is expected. However, the dextrose moves into the interstitial space and cells and is metabolized. The plasma osmolality becomes diluted by the added water. The water then moves into the interstitial space and cells by osmosis just as with pure water coming from the gut. There also is some dilution of the concentration of Na^+ and Cl^- which will have transient effects on the charge and concentrations in different compartments until water is in equilibrium in all compartments.

Two other things happen when water is added to the plasma space. The increase in volume increases the hydrostatic pressure in the microcirculation and decreases plasma oncotic pressure by diluting the concentration of albumin and other proteins. Both of these processes increase filtration across the vascular walls (Levick and Michel 2010).

Normal Saline

Normal saline is a 0.9% solution and is made so that it is isotonic to normal plasma. Na^+ is 154 mEq/L in the normal saline rather the 140 mEq/L in normal plasma, because to make it isotonic to plasma, a higher concentration of Na^+ is needed to account for the other substances dissolved in plasma. Isotonic normal saline

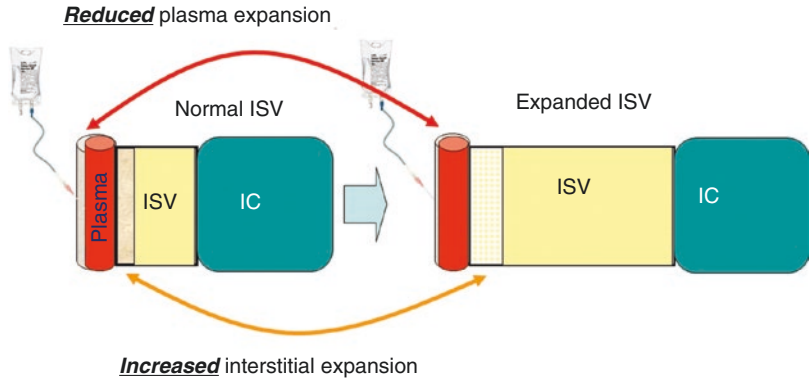

Fig. 10.4 Normal saline infusion with normal interstitial volume (ISV) (left) and expanded ISV (right). Plasma expansion is much less and ISV greater when ISV is expanded above normal values. *IC* intracellular volume

should primarily increase the plasma volume. However, the normal saline solution increases plasma Cl^- concentration which moves down its concentration gradient into the interstitial space. This drags some Na^+ with it for electrical neutrality and some water to maintain osmolality. The saline also dilutes plasma proteins and decreases oncotic pressure, which allows more filtration. In the end, the saline solution should distribute between the plasma and interstitial spaces based on their initial relative volumes and the Gibbs-Donnan equilibrium. The usual distribution based on the relative sizes of normal plasma and interstitial volumes is said to be one-third plasma and two-thirds interstitial (Fig. 10.1). Intracellular volume should not change because it has the same osmolality as the interstitial space, and the at equilibrium the osmolality of the interstitium will be the same as in plasma because the normal saline was isotonic. However, if the osmolality of the plasma and interstitial spaces is lower than normal, the normal saline will be hypertonic relative to the patient's plasma and cells, and some volume will be drawn out of cells. This effect should be small because the added Na^+ and Cl^- are distributed in the whole extracellular volume. If the extracellular space is greatly expanded because of retained fluid, the proportion of volume of the infused saline that remains in the vascular space is greatly decreased. For example, in a person who has 30 L of ascites and 12 L of interstitial volume, the total extracellular volume is 42 L, but the plasma volume likely still is only ~3 L. Thus, only about 70 ml of the 1 L of added normal saline will remain in the vascular space, and this amount gets smaller each time more crystalloid volume is added (Fig. 10.4).

Hypertonic Sodium Chloride Solutions

There has been a lot of interest in the use of hypertonic NaCl solutions because of their potential to expand intravascular volume faster and with less volume than normal saline (Santry and Alam 2010). These solutions have been especially studied for use in blunt and hemorrhagic trauma, but studies have failed to show a benefit (Bulger et al. 2011; Bulger et al. 2010). It is worth emphasizing again that volume balance really is about Na^+ balance. Consideration of the distribution of these solutions can help understand why they have failed to provide a benefit. The final effect of hypertonic saline depends upon the initial concentration of Na^+ in plasma, the plasma volume, the rate of bleeding, the renal function, and the amount given, for in the end what counts is how much the plasma concentration of Na^+ and osmolality change. The 7.5% solution of NaCl used in some of these studies (Bulger et al. 2011; Bulger et al. 2010) contains 129 mEq/100 ml of Na^+ compared to 15 mEq/100 ml in 0.9 saline. Thus, each 250 ml bolus adds 321 mEq of Na^+ to the plasma and also greatly increases Cl-, which will have a marked acidifying effect. If this solution stays in

the plasma space, it would increase the plasma Na^+ concentration to over 200 mEq/L, but instead the Na^+ and Cl^- rapidly move into the interstitial space. Typical Na^+ concentrations in the first 2 hours were in the 150 mEq/L range (Han et al. 2015), but very high concentrations were reached with repeated use (Wells et al. 2012). Initial values are not reported in the publications, but the very large Na^+ load on the system would likely have quickly drawn water out of the interstitial space, and Na^+ and Cl^- would rapidly move down their concentration gradients, increase interstitial osmolality, and pull water out of cells. As discussed above, this will induce intracellular transcriptional processes and the consequences cannot reliably be predicted because this is as much a pharmacological effect as a volume effect.

Iso-oncotic Colloids

A 5% solution of albumin is iso-oncotic and iso-osmotic compared to normal blood. Infusion of this solution expands the intravascular space and, theoretically, should not affect other compartments. The solvent for the solution is most often normal saline and distributes accordingly. If the patient's baseline albumin concentration is less than normal, the 5% solution is hyper-oncotic relative to that patient's plasma and behaves to some degree as a hyper-oncotic solution, which is discussed in the next section.

Starch solutions come in many different concentrations and molecular sizes (Treib et al. 1999). The precise oncotic value of a starch solution is difficult to assign because the oncotic effect is related to the number of particles, and serum amylase rapidly breaks starches into smaller particles. As the particle number goes up, so does the oncotic effect. When the particles are small enough, they are excreted by the kidney, which lowers the number of particles and the oncotic effect. The rate of breakdown of starch molecules can be changed by engineering the number of hydroxyethyl groups and where these are placed on glucose molecules (Treib et al. 1999). Starches therefore can function between iso-oncotic and hyperoncotic colloids, and the effect depends upon the initial concentration and size of the starch molecules, the rate of breakdown, which is dependent upon the substitution of the hydroxyethyl groups on the glucose molecules (Treib et al. 1999) and the plasma amylase activity.

Hyper-oncotic Solutions

A solution of 25% albumin is the prototypic example of a hyper-oncotic solution, i.e., one that has an oncontic effect greater than normal blood. The added volume expands the vascular space by a small amount, but because it also increases the oncotic pressure, it draws fluid from the interstitial space. As an example, an infusion of 100 ml of a 25% solution (25 g/100 ml) into someone with a plasma volume of 3.5 L and an albumin concentration of 25 g/L would theoretically increase the albumin concentration by 36% and the oncotic pressure by 25% (assuming albumin accounts for 70% of the total plasma oncotic pressure). This sudden increase in oncotic pressure likely transiently pulls water from the interstitial space into the plasma space, or at least significantly reduces filtration. Na^+ and Cl^- will follow the water, although not necessarily at the same rate, because initially the solutions have the same electrolyte composition, but a new Gibbs-Donnan equilibrium will ensue because of the higher albumin concentration. The shrinkage of the interstitial space and possible change in interstitial electrolyte composition could then result in loss of water from cells. Furthermore, the albumin is most often in a normal saline solution so that shifts associated with Na^+ and Cl^- also occur. Some leak of the albumin into the interstitial space should also be expected. This will increase the oncotic pressure in the interstitial space and could draw more water out of the intracellular space. The consequence of all these process is activation of intracellular stress signaling pathways and expression of stress molecules (O'Neill 1999; Shrode et al. 1970). Thus, 25% albumin does not act only as a volume expander, but it produces a "pharmacologic" effect by the associated fluid and elec-

trolyte shifts from cells (Magder and Lagonidis 1999). Hyper-oncotic hetastarches might act in a similar way (Potter et al. 2013). In addition, albumin binds many substances and can act as an antioxidant, which could further produce non-volume effects (Vincent et al. 2014). In support of this, 25% albumin has been show to produce an apparent increase in cardiac function independent of its volume expansion (Magder and Lagonidis 1999).

Sodium Bicarbonate Solution

As a way of giving Na^+ without Cl^-, a solution can be made by putting three ampoules containing 44 mEq of sodium bicarbonate ($NaHCO_3$) in D5W. The final concentration of Na^+ is 132 mEq/L which is slightly hypotonic. This Na+ of the solution should distribute between the plasma and interstitial space as occurs with Na^+ in normal saline, and the excess water will distribute in all fluid compartments. The HCO_3^- will be in equilibrium with H_2CO_3 and dissolved CO_2 in serum. PCO_2 is regulated by ventilation and so the added HCO_3^- is cleared by ventilation. However, if the patient is mechanically ventilated, and has no spontaneous efforts, CO_2 in the body will increase and be distributed in total body water with a consequent fall in pH (Jones 2008).

Summary

The major point covered in this chapter is that the total amount of Na^+ in the body dictates the amount of water in the body. Fluid balance thus is about Na^+ balance. Elements such as Na^+, K^+, and Cl^- only can be absorbed or excreted, and thus intake and output of Na^+ in particular needs to be followed carefully when managing critically ill patients. All fluid-filled compartments are connected in a dynamic equilibrium so that movement of fluids and electrolytes across all spaces needs to be considered when managing fluid balance. Finally, it is important to distinguish between the concentration and the total amount of substances.

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