Body and Brain Fluid and Volume Kinetics

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Abstract

The capillary and cell membranes are important barriers to the distribution of fluid in the body. The former separates the plasma from the interstitial fluid, and the latter separates the extracellular fluid (ECF) from the intracellular fluid (ICF). The volumes of these body fluid spaces are tightly controlled by nervous and hormonal mechanisms.

Infusion fluids can be tailored to distribute on either or both sides of these barriers. In general, iso-oncotic fluid accumulates in the plasma and isotonic fluid in the ECF space. For scientific purposes, translocation of fluid across the capillary and cell membranes can be estimated by means of mass balance calculations, while the disposition of an infusion fluid over time is best studied with volume kinetic analysis.

The capillary walls of the brain control the chemical environment by pumping mechanisms and are not permeable for diffusion of substances other than water ("blood-brain barrier"). However, low osmolality allows more water to enter the brain and quickly increases the hydration of the neurons. The sensitivity of the brain volume to changes in serum osmolality has important implications for the choice of infusion fluid when caring for patients with neurotrauma who are undergoing neurosurgery. The brain lacks lymphatic vessels, so the filtered fluid is returned to the plasma via the cerebrospinal fluid. The cerebral fluid pressure is maintained at approximately 10 mmHg by absorption of fluid into the cerebrospinal fluid system. At high pressures, filtered fluid can also pass directly into venous sinuses.

Keywords

Body water · Physiology · Crystalloid solutions · Pharmacokinetics · Extracellular space · Physiology · Intracellular space Pharmacokinetics · Saline solution Hypertonic

Barriers to Water Distribution

The human body consists of billions of cells bathing in an aqueous solution with a salt concentration similar to that of prehistoric seawater. The water volumes outside and inside the cells are tightly controlled by a combination of semipermeable membranes and pumping functions.

Two main barriers regulate fluid distribution. The first one is the *capillary membrane* that separates the blood from the interstitial fluid. This

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membrane is highly permeable to water and electrolytes, while larger elements, like blood cells and plasma proteins, do not pass at all or they pass very slowly. Elements dissolved in body water attract water by virtue of their *osmolality.* The osmotic pressure exerted by these large intravascular molecules maintains the plasma volume and is termed *oncotic* or *colloid osmotic* pressure.

The second barrier for fluid distribution is the *cell membrane* that surrounds all body cells. The distribution of electrolytes across this membrane determines how much water will be located on either side. The distribution of electrolytes, in turn, depends on active pumping mechanisms located in the cell membrane itself.

Translocation of water across the cell membrane can be achieved deliberately by the clinician. Infusing sodium chloride at a concentration higher than 0.9%, which corresponds to the normal body osmolality of 295 mosmol/kg, withdraws water from the cells and shrinks them. Conversely, infusing a solution with a sodium concentration lower than 0.9% increases the volume of the cells.

Not all substances in an infusion fluid remain outside the cells; some enter the cells sooner or later. Therefore, the osmolality of a solution does not always determine the distribution of fluid across the cell membrane. Examples of penetrating substances are ethanol and amino acids. Therefore, one often uses the *tonicity* to describe the ability of an infusion fluid to redistribute water across the cell membrane. An *isotonic* fluid remains in the outside the cells only. Hence, ethanol and amino acids in isoosmotic solutions are considered hypotonic.

Nevertheless, even here the nomenclature can be misleading. One example is when fluids contain glucose. A 5% glucose solution is initially isotonic, but water slowly enters the cells anyway, along with the uptake of glucose. The end products of glucose metabolism are carbon dioxide and water, which have tonicities of zero.

The capillaries of the brain have a much lower permeability than the remainder of the body. Electrolytes and proteins are stopped (by the "blood-brain barrier"), while those that finally enter require pumping mechanisms. By contrast, water passes freely. The brain cells are therefore susceptible to changes in osmolality [1]. Metabolic and physical damages are other factors that cause brain cells to swell—one of the feared complications of neurotrauma. These concerns are important because the brain is encased within a bony structure (the skull) and cannot undergo much expansion before the intracranial pressure increases sharply.

Body Fluid Volumes and Their Control

The body fluid compartments consist of extracellular fluid (ECF) and intracellular fluid (ICF), which make up 20% and 40% of the body weight, respectively, in an adult male. The fractions are higher in children and lower in the elderly. The ECF is, in turn, divided into plasma and interstitial fluid, which are located on either side of the capillary membrane (Fig. 1). The cellular components of the blood (erythrocytes, leukocytes) belong to the ICF space.

The body fluids circulate constantly. The entire blood volume is pumped around the cardiovascular system within 1 min. Plasma is filtered in the capillaries and hydrates the interstitial fluid space, where the exchange of gases and nutrients with the cells takes place. The interstitial fluid is slowly directed to lymphatic vessels and then passes to the lymph nodes, where antibody reactions take place, and is then returned to the plasma. This circuit is accelerated by the infusion of crystalloid fluid.

The osmolality and the volumes of the body fluids are maintained within narrow limits by a multitude of hormonal and neurological mechanisms. *Vasopressin* (AVP) is secreted in small amounts from the neurohypophysis in response to slight hyperosmolality and in large amounts in response to hypotensive hemorrhage. *Atrial natriuretic peptide* (ANP) and *brain natriuretic peptide* (BNP) are secreted from the cardiac atrium and ventricle, respectively, in response to locally elevated fluid pressures. Both hormones increase the capillary filtration of albumin, as well as urinary excretion. The cardiac hormone

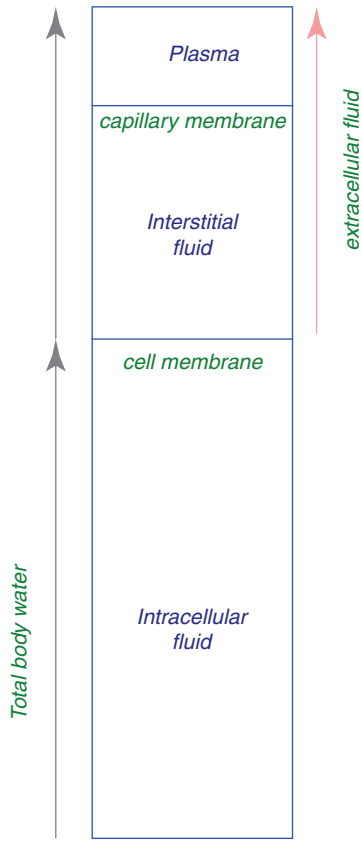

Fig. 1 Schematic drawing of the body fluid spaces

levels may increase in response to vigorous fluid therapy. *Cortisol* and *aldosterone* are steroid hormones that are secreted in greater amounts in response to trauma, and they increase the ECF volume.

Nervous system activity also affects the fluid balance. The vascular tone is governed by the sympathetic nervous system, which maintains the size of the "vascular costume." Specific receptors also have an impact on the fluid balance; for example, β_1-adrenergic stimulation (isoprenaline) retains fluid, and α_1-stimulation (phenylephrine) increases the urinary excretion, even in the anesthetized state [2].

Water Turnover

The minimal recommended intake of water in humans is 1.0 mL/kg/h. The limit is often set 25% higher to obtain a "safety margin" for sweating and unforeseen losses. Children have a greater metabolic activity and therefore require more fluid. Naturally, the fluid requirement also increases greatly in many disease states, like burn injuries and diarrhea. The body also creates approximately 300 mL of water per day from its energy metabolism. The water intake is needed to compensate for evaporation from the skin and lungs (*insensible water losses*), as well as for maintaining a baseline urine flow that is sufficient for the excretion of metabolic end products (such as creatinine).

The need for a fluid volume is markedly increased during anesthesia, for several reasons. One is that anesthesia causes vasodilatation, which increases the "unstressed" blood volume. The plasma volume should then be expanded to maintain adequate venous return to the heart; otherwise, the hemodynamics needs to be supported by administration of a vasoconstrictor. Moreover, the general depression of the autonomous system during anesthesia redirects blood flows between vascular beds, which might induce local disturbances of tissue perfusion. The aim of expansion of the plasma volume at the initiation of anesthesia is combat these disturbances. Moreover, blood loss during the surgery, and the fact that oral fluid intake has been temporarily stopped, also increases the need for fluid. Contrary to common belief, the loss of water by evaporation from surgical wounds is not particularly impressive. As a rule, open abdominal surgery with wide exposure of the intestines doubles the insensible fluid losses.

Derangement of the Body Fluid Volumes

The physiological tolerance to derangement of the body fluid volumes varies greatly. Most delicate is a loss of blood volume (hypovolemia), which initially is compensated by an increased stroke volume and sometimes by an accelerated heart rate. When approximately 1 L has been lost, the arterial pressure falls and the patient exhibits signs of *shock*. This situation is directly life-

threatening within minutes if combined with neurotrauma that has raised the intracranial pressure.

Tolerance is greater for a loss of ECF volume (*volume depletion*), which occurs in diarrhea, ileus, and diabetic ketoacidosis. Here, 3–4 L, or even more, can be lost before shock ensues.

The tolerance for losses of ICF is poorly known, but it is far greater than for volume depletion. Dehydration of the ICF is associated with poor intake of water in the elderly. The chief compensation is to increase the renal water conservation by concentrating the urine. If the capacity of the kidney is not sufficient, the plasma osmolality increases. A value exceeding 300 mosmol/kg is a frequently used criterion for dehydration of the ICF space [3].

The Starling Equation

The forces involved in the distribution of fluid across the capillary membrane are summarized as follows in the classical *Starling equation*:

$$\text{Fluid exchange} = K_f \left[\left(P_c - P_i \right) - \sigma \left(\pi_p - \pi_i \right) \right]$$

where K_f is a proportionality constant; P_c and P_i are the hydrostatic fluid pressures in the capillary and interstitium, respectively; and π_p and π_i are the colloid osmotic pressures in the plasma and interstitial fluid, respectively. The symbol σ is the reflection coefficient, which explains how easily macromolecules pass through the capillary wall. A reflection coefficient of 1.0 means that the membrane is impermeable, while 0 means that the molecule passes without any difficulty. The value of σ varies greatly between vascular beds. In a normal man, P_c is 17–25 mmHg, P_i is −3 mmHg, and π_p is 25 mmHg. In typical tissues, π_i amounts to only 5 mmHg.

The Starling equation summarizes our possibilities for infusing fluid that translocates a volume across the capillary membrane. Infusing a crystalloid fluid increases P_c and dilutes π_p, both of which promote a distribution of volume from the plasma to the interstitial fluid space. Infusing a colloid with a π_p higher than 25 mmHg recruits fluid from the interstitial fluid space to the plasma. Modern microcirculatory research holds that this type of recruitment cannot occur across the capillary wall. However, this is an academic issue, as recruitment does occur either by the lymph or by transcapillary flow.

The sensitivity of the brain to changes in serum osmolality has implications for the choice of infusion fluid in neurotrauma and neurosurgery. Isotonic infusion fluids should be used when providing volume expansion to compensate for anesthesia and/or hemorrhage due to the sensitivity of the brain to changes in osmolality. Hypotonic infusion fluids should be avoided, whereas hypertonic fluid has a place in the clinical handling of cerebral edema.

Cerebral Circulation

The brain has a more delicate system for regulating its fluid content than is found in the rest of the body. The "blood-brain barrier" prevents fluid shifts from the plasma to interstitial fluid by restricting passive diffusion of even small molecules. Therefore, the capillaries of the brain are much less "leaky" than are capillaries elsewhere. However, changes in hydrostatic and oncotic forces in the plasma may still, to some degree, change the water content of the brain, as water is freely diffusible [4].

Filtered water is circulated by means of the cerebrospinal fluid system, as the brain lacks lymphatic vessels. The cerebrospinal fluid volume amounts to approximately 150 mL of the total volume of 1.7 L contained in the brain and spinal cord. The turnover rate is approximately 500 mL per day.

Most tissues have autoregulated blood flow governed by factors such as metabolic rate and the availability of oxygen. Increases in the local blood flow and hydrostatic pressure also stimulate the glycocalyx to release nitric oxide, which causes vasodilatation and makes room for more blood.

The blood flow to the brain, which amounts to 15% of the cardiac output, follows these general principles, but it is also regulated by carbon dioxide and pH. Increases in any of these dilate the cerebral vessels, thereby allowing a more efficient washout of metabolic end products from the brain. This is considered important as neuronal activity strongly depends on both the carbon dioxide pressure and on pH.

Autoregulation protects the brain from being affected by variations in arterial pressure and operates in a mean arterial pressure range between 60 and 140 mmHg. If the pressure becomes excessive, the sympathetic nervous system constricts the cerebral arteries to limit the capillary filtration. The cerebral fluid pressure is maintained at approximately 10 mmHg by absorption of filtered fluid into the cerebrospinal fluid that then circulates around the brain and the spinal cord. The arachnoid villi also have a valve function that allows direct entry of fluid into the venous sinuses in cases where the intracranial pressure exceeds the venous pressure.

Brain edema is most often caused by trauma that damages the blood-brain barrier and causes inflammatory swelling in the injured areas. The edema compresses the blood vessels, thereby decreasing the perfusion. Elevation of the carbon dioxide pressure might not be sufficient to restore the blood flow, and ischemia develops. This is a situation where the clinician must take prompt action to limit cell death and even to save the brain. For this purpose, fluid therapy with hypertonic fluid that reduces the edema is of paramount importance.

Head trauma that is combined with circulatory shock from hemorrhage poses an even more complicated problem. Here, the mean arterial pressure (MAP) must be restored sufficiently to allow perfusion of the brain. The cerebral perfusion pressure is given by the difference between the MAP and the intracranial pressure, which is approximately 10 mmHg. In neurotrauma, where the intracranial pressure is markedly elevated, the MAP may become a crucial parameter for the survival of the brain. High venous pressure might also be a problem, as the filtered fluid enters the venous system directly in cases where the intracranial pressure is high. The cerebral perfusion pressure is then determined as the difference between the MAP and the pressure in the jugular vein.

Fluid Translocation Across the Cell Membrane

The brain is susceptible to changes in osmotic pressure, which governs the fluid distribution between the ECF and ICF.

The equation below shows the equilibrium that always persists between the ECF and ICF. Assuming that the ECF and ICF volumes are 20% and 40% of the body weight, respectively, and that normal body osmolality is 295 mosmol/kg, we obtain the following [5]:

$$\frac{\text{ECF} \cdot 295 + \text{infused osmoles}}{\text{ECF} + \text{fluid exchange} + \text{infused volume}} = \frac{\text{ICF} \cdot 295}{\text{ICF} - \text{fluid exchange}}$$

The idea behind this mass balance equation is that the amount of solutes divided by the fluid volume must remain the same after manipulation of any of involved factors. The reason is that the osmolality is the same in all body fluid compartments. The only unknown factor in this equation is "fluid exchange," which can change in any direction, although positive values denote translocation from the ICF to the ECF.

This equation can be applied to sodium chloride and mannitol solutions. However, glucose is not pertinent because glucose only remains temporarily outside the cells.

A single extracellular solute can also be used for this calculation. The simplest solute to monitor is plasma sodium, which is the electrolyte that is most often manipulated by fluid therapy intended to control the intracranial pressure. The plasma concentrations before the intervention, Na_o, and at any time t after it has occurred, Na_t, are then connected in the following equation [6]:

$$\text{Fluid exchange} = \text{ECF}_o + \text{infused volume} - \left[\left(\text{Na}_o\text{ECF}_o + \text{infused Na}\right) / \text{Na}_t\right]$$

If urinary excretion has occurred, the voided volume should be subtracted from the infused fluid volume. Similarly, the sodium ions excreted in the urine should be subtracted from the infused amount of sodium.

Fluid Kinetics

Tracers

The volumes of the physiological body fluids spaces can be measured with tracers that distribute in one single physiological fluid space only. The *dilution principle* is then employed to estimate the size of the compartment. This principle means that the volume of distribution of a molecule is the dose divided by the plasma concentration after adequate equilibration. Examples of tracers include radioactive albumin and indocyanine green for the plasma volume, iohexol and bromide for the ECF volume, and deuterium for the total body water.

The benefit of using a tracer is that it yields (presumably) precise information about the size of a body fluid space. Downsides include the abundant potential methodological errors and the ability to obtain (usually) only one measurement. Tracer methods require a reasonable steady state during the mixing period; therefore, capturing the distribution phase of a crystalloid fluid, for example, is not possible with these methods.

Mass Balance

Several methods are available to calculate the distribution of infused fluid between the plasma, the interstitial fluid, and the ICF. The most widely applied protocol is to use a set of mass balance equations, where the blood volume at baseline (BV_o) is estimated based on anthropometric equations and the BV changes are estimated from measurements of the blood Hb concentration at time 0 and at a later time t [7].

$$\text{Hbmass}_o = \text{BV}_o\,\text{Hb}_o$$

$$\text{BV}_t = \text{Hbmass}_o - \text{bled volume}\left(\left(\text{Hb}_o + \text{Hb}_t\right)/2\right)$$

$$\Delta BV_{t-0} = \text{BV}_t - \text{BV}_o$$

$$\text{Clinical efficacy} = \Delta BV_{t-0} / \text{Infused volume}$$

$$\text{Interstitial fluid volume} = \text{infused volume} - \text{urine} - \Delta BV_{t-0}$$

The weaknesses of this approach are that the BV is assumed and that the distribution of Hb molecules must be even throughout the blood volume. No simulation can be performed that predicts the outcome of experiments not performed. One should note that the equation reflects the distribution of the infused fluid volume and not of the Hb molecules. The glycocalyx volume is included when crystalloid fluid is infused, as the glycocalyx is hydrated as well. Whether the

glycocalyx volume is included when colloid fluid is studied is not known.

Volume Kinetics

A more complete approach for the description of fluid distribution and elimination is offered by a research method called *volume kinetics*, which has similarities to pharmacokinetics [8]. The studied fluid is administered over 30 min, and the Hb concentration and the urinary excretion are measured repeatedly over 3–4 h. A kinetic model with (usually) two expandable compartments is fitted to these data, thereby allowing the estimation of a number of parameters in the kinetic model using complex mathematics. A second step is to test for the potential influence of various individual-specific covariates on these parameters. These covariates can be factors such as body weight, gender, age, or arterial pressure (Fig. 2). Many studies have demonstrated that the obtained values correspond reasonably well to the known volumes of the major physiological body fluid spaces.

Volume kinetic analysis of crystalloid fluid shows an initial distribution over the plasma volume. Diffusion across the capillary membrane to the interstitial fluid space occurs with a half-life of approximately 8 min. Complete distribution is finally achieved after 30 min (four half-lives). Iso-oncotic colloid fluid does not have a distribution phase, and hyperoncotic solutions recruit fluid from the interstitial fluid space and, to some degree, from the ICF as well.

The distribution phase for crystalloids makes short bolus infusions a risky practice in neu-

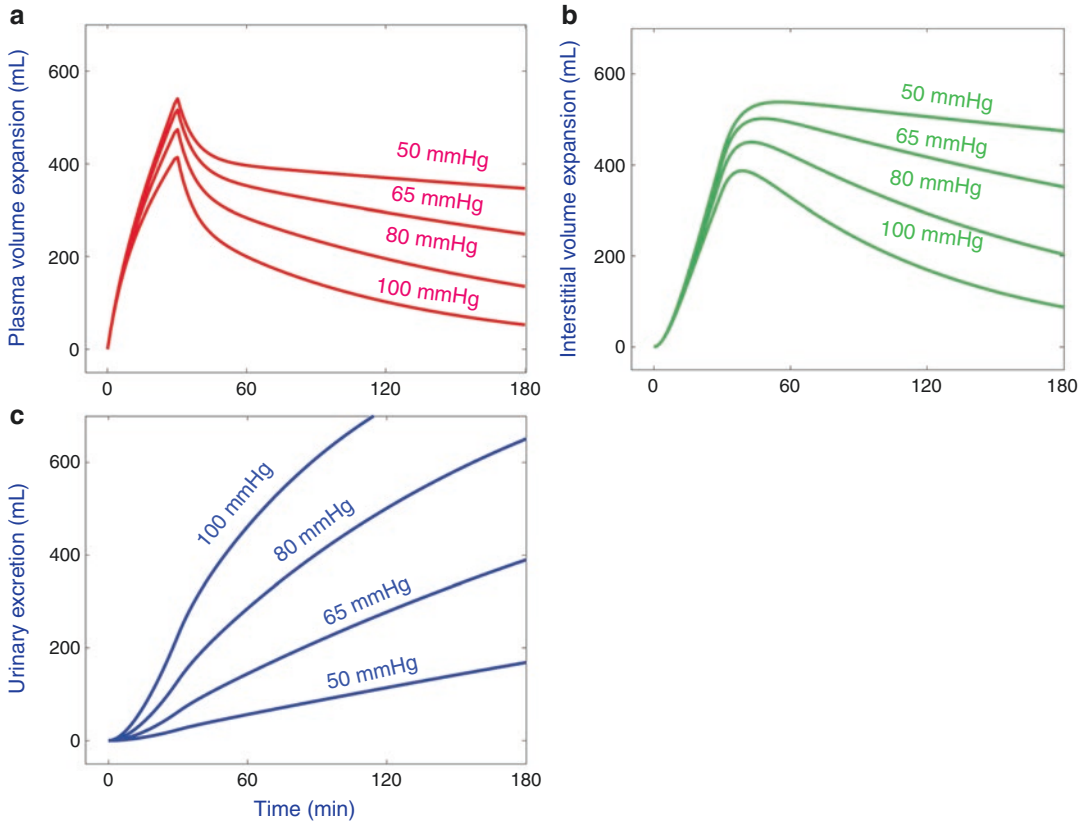

Fig. 2 Volume kinetic plots showing (**a**) plasma volume, (**b**) interstitial volume, and (**c**) urinary excretion, all resulting from covariance between the mean arterial pressure (MAP) and urinary excretion during 78 infusion experiments. Computer simulation of an infusion of 1 L of Ringer's solution over 30 min, based on kinetic data published in *Anesthesia and Analgesia* 2017; 124: 1824–1833

rotrauma patients, as the intravascular hydrostatic pressure might suddenly become very high. By contrast, the rate of infusion does not matter much for colloid infusions. However, colloids expand the plasma volume more than the crystalloid fluids do (iso-oncotic fluids 1:1, 20% albumin 2:1), and the plasma remains expanded for a longer time.

The intravascular persistence of colloid fluid is not greatly dependent on the arterial pressure, but the excretion of crystalloid fluid becomes markedly retarded by a reduction in the arterial pressure, such as occurs during general anesthesia (Fig. 2). In the intensive care setting, this slow excretion can create a similar plasma volume expansion for either colloid or crystalloid fluids from 6–8 h after an infusion and onward.

Urinary Excretion

The diuretic response to infusion fluids may affect their distribution. For example, the urinary sodium concentration in everyday life is approximately 60 mmol/L, and a number of hours are required for the kidneys to increase the excretion to match the concentration of an infused isoosmotic crystalloid fluid. Therefore, serum sodium will remain largely unchanged, and water will be recruited from the cells during the first 1–2 h after initiating an infusion of Ringer's lactate solution, despite the fact that Ringer's has an osmolality of 273 mosmol/kg (plasma has 295 mosmol/kg) [6].

Another example is hypertonic (15%) mannitol, which is marketed as a solution devoid of electrolytes. Mannitol distributes over the entire ECF volume and recruits fluid from the cells by virtue of its hyperosmotic nature (iso-osmotic mannitol is 5%). The induced osmotic diuresis removes the recruited fluid from the body. However, osmotic diuresis brings along extracellular electrolytes and amino acids in an uncontrolled fashion. The loss of electrolytes makes the ECF hypo-osmotic, thereby creating a "rebound" flow of fluid in the opposite direction. This phenomenon would not occur if electrolytes were added to the fluid or supplemented by a separate infusion.

In conclusion, the distribution of an infusion fluid is fairly well predictable from its composition. However, modifications exist due to distribution effects, arterial pressure, and kidney function.

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