CHAPTER 1

DISORDERS OF EXTRACELLULAR FLUID VOLUME

As tough as it may seem, the human body is made mainly with water. The fraction that is represented by water ranges from 60% to 70% and depends on age, sex and body fat amount. Children are more "watery" than adults, and body water decreases in the elderly. Females have more fat and less water than males but pregnancy is a very unique condition in which extracellular fluid volume increases by 15% (see Chapter 11).

Two thirds of body water are inside the cells (Intracellular Fluid, ICF), one third is outside of the cells (Extracellular Fluid, ECF). In turn, ECF is distributed in different compartments. Its major fraction is in the interstice, and most of the remaining part is inside the circulatory system. Small volumes of ECF are contained in joints (synovial fluid), brain (liquor), and eye. In pathological conditions ECF accumulates in the pleural or peritoneal cavity and in the pericardium.

The most "important" part of ECF is that contained in the circulation, on which depends the delivery of nutrients and oxygen to peripheral tissues. Indeed, the systems that regulate ECF volume utilize blood volume both as the index of ECF status and as the target of regulation. One important concept is that the volume of blood perceived by the regulatory systems is not the total volume of blood that is contained in vessels, but the volume of blood that is actually

circulating (Effective Blood Volume, EBV). The difference between total blood volume and EBV is accounted for by the "capacitance vessels", i.e. the venous vessels that behave like an elastic tank that expands and collapses thereby changing the blood that is distributed to the peripheral tissue.

BODY SODIUM CONTENT IS THE DETERMINANT OF ECF VOLUME

All cells have in their plasma membrane the Na^+/K^+ adenosine triphosphatase (ATPase) pump that drives sodium out and potassium into the cell. The sodium concentration gradient generated by the pump is steep, approximately 140 (out) vs. 10 (in) mmol/L, and characterizes the ECF as a "sodium space". Sodium is present in body water in ion form and its cumulative electric positive charge is neutralized by an equivalent mass of anions, the main ones being chloride and bicarbonate.

In view of the almost total distribution of sodium in the extracellular space the osmotic attraction generated by sodium retains water out of the cells and the more sodium is present in the body, the more expanded is its ECF volume. Normal sodium concentration averages 140 mmol/L (range 135-145 mmol/L), so that in clinical practice it can be assumed that the addition of 140 mmol of sodium to body sodium mass expands ECF volume by 1 L and the opposite holds for the loss of 140 mmol.

It must be stressed that ECF volume depends on the content, i.e. the mass of sodium present in the body, that is expressed in weight units. The mass of sodium must not be confused with serum sodium concentration that is expressed in weight/volume units. Misunderstanding mass for concentration is a gross mistake and the difference between the two concepts seems obvious, but in clinical practice the distinction is often obscured by tricky circumstances that deviate rational thinking to wrong conclusions.

ESTIMATE OF ECF VOLUME IN CLINICAL PRACTICE

A pathological depletion/expansion of ECF volume is one of the most common clinical problems met in daily practice. Unfortunately, there is no laboratory, radiological, or instrumental way to measure ECF volume and understanding its state rests on clinical experience and physical examination. Observing the patient for some consecutive days is often the clue to understand the dynamics of ECF volume. In particular a very simple way to detect changes in body fluid is to weigh regularly the patient, assuming that in the short term of a few days weight changes of 0.5 kg or more are not caused by fat or muscle mass variation.

SIGNS OF DEPLETION

Blood pressure (BP) measured in the supine position and soon after the patient stood up is a way to check volume depletion, that is suggested by a decrease in diastolic blood pressure. A decline of 3 or more mm Hg is considered in some textbooks as diagnostic. But at least 5 mm Hg are realistic, considering the confounding factors that are associated with the maneuver. The test is biased by conditions that block the reflex vasoconstriction such as autonomic nervous insufficiency or antihypertensive drugs.

Normally in a subject laying supine jugular vein is visible up to the mandibular angle, finding it collapsed at a lower level indicates volume depletion.

Additional physical findings suggesting volume depletion involve the tongue and skin. The tongue may show transversal furrows and may appear dry; sometimes, however, the tongue is dry because the patient is breathing with the mouth open; in these cases it should be checked whether the oral mucosa is dry under the tongue. The skin may have lost its elasticity, which can be detected by pinching it to form a fold and observing how fast it flattens.

Thirst is a subjective sign of volume depletion, that depends on stimulation of brain thirst centers by angiotensin II, produced by

activation of the renin-angiotensin system (RAS). On evaluating thirst as indicator of volume depletion the alternative possibility of a rise in plasma osmolality has to be considered.

A rise in hematocrit and serum protein concentration detected by serial measurements in a time of some days indicates volume depletion. Note that hematocrit does not change when the loss of fluid is limited to pure water because water is lost in the same proportion from the intra- and extracellular volume, so that the ratio of red blood cell volume over plasma volume remains the same.

Finally, volume depletion activates humoral, hemodynamic and nervous signals that reduce renal sodium excretion (in a urine sample the sodium concentration will be low), mainly by increasing tubular sodium reabsorption. This sign, however, must be interpreted in single cases because urinary sodium retention can be the response to a decrease in EBV, that does not depend on sodium depletion, but is rather associated with excess ECF volume, e.g. congestive heart failure (see later).

SIGNS OF EXPANSION

Peripheral edema, i.e. swelling due to accumulation of fluid in the interstice, is the paradigm of ECF excess. Usually edema is localized in the legs where fluid is drained by gravity, but in bedridden people it distributes throughout the lower part of the body and it is particularly visible in the sacral region. A popular diagnostic maneuver consists of pressing fingers on the tibial plate and observing the formation of a deep pit. A common mistake made by beginners checking for pitting edema is to press the leg too lightly to displace interstitial fluid.

Pitting edema indicates a fluid retention of around 5 kg in a 70 kg body weight person.

Hypertension, dilution of hematocrit and serum protein concentration are accessory signs of expansion, but they are affordable only if their change is documented in a quick follow up after a few days.

Excess ECF can accumulate in the lung, usually as pleural effusion or in the tissue. In the latter case, rales can be detected

by auscultation, but sometimes the fluid is interstitial and physical examination fails to detect it, a case that is particularly frequent in uremic patients.

Causes of ECF volume depletion

Gastrointestinal disorders that cause diarrhea or vomiting and stop or reduce eating and drinking are the most frequent cause of ECF volume depletion. Diuretics are common culprits, usually when their assumption is continued in a condition in which feeding and drinking ability is decreased, e.g. in patients with low consciousness or elderly subjects in rest homes.

Skin is a source of fluid loss, either as *perspiratio insensibilis* or as sweat. Note that sweating and *perspiratio insensibilis*, however, contain a low sodium amount (sweat) or no sodium at all (*perspiratio insensibilis*), therefore they cause a loss of water rather than of sodium and have the major effect on plasma osmolality (see later). However, profuse sweating may cause severe ECF volume depletion.

Also burns and severe inflammatory disease of the skin cause loss of fluid with protein concentration similar to that of plasma with a dramatic effect on plasma volume.

"Salt-losing nephropathies" are renal disorders that decrease the tubular ability to reabsorb sodium such as chronic pyelonephritis and adult polycystic kidney disease.

Pressure diuresis is an experimental natriuresis caused by a steep rise in renal arterial perfusion pressure. It occurs when perfusion pressure rises beyond the limit of renal autoregulation. Renal autoregulation is the phenomenon by which renal blood flow and the glomerular filtration rate (GFR) remain constant at variations of perfusion pressure between 180 and 80 mm Hg.

"Exaggerated natriuresis" consists of the very prompt and massive elimination of an intravenous sodium load that occurs in hypertensive patients. The phenomenon depends on renal vasodilation induced by ECF volume expansion that blocks the vasoconstrictive response of autoregulation. On their own, "pressure natriuresis" and "exaggerated natriuresis" are experimental models that do not reproduce clinical conditions. However, they are a clue

to understanding the mechanisms that account for renal sodium loss in malignant hypertension and hypertension in pregnancy (see Chapter 11).

Hypercalcemia, especially when associated with malignancy, affects sodium reabsorption by inhibiting tubular Na/K exchanger an Na/H cotransporter, and can induce massive saline diuresis.

Major surgery, especially when requiring laparotomy, is at risk for volume depletion, because of the loss of blood, drying of peritoneal surface, wound leakage, post-surgery bowel palsy with luminal fluid sequestration, and post-surgery fasting. The amount of fluid that is lost in this setting is often underestimated and the infusion program is often not adequate to maintain or recover fluid balance, a failure that can depend on the method by which patient fluid need is calculated (see later).

Causes of ECF volume expansion

Two distinct pathogenic mechanisms can account for sodium and water retention, one resulting from the response of functioning kidneys to deceiving information on body sodium content, the other one dependent on kidney failure.

It is intriguing that in most cases peripheral edema occurs because the kidneys comply correctly with an incorrect order. In fact, the salt retaining sequence is turned on by a defect of EBV that is perceived by regulatory systems as a loss of ECF volume, i.e. of body sodium mass. The kidney is forced to recover sodium that does not improve EBV but accumulates out of the circulation.

The most common condition of peripheral edema is congestive heart failure. In the past, two pathogenic mechanisms were in competition to explain fluid retention in heart failure, the so-called "anterograde" and "retrograde" theories. The former pointed to low cardiac output that evoked renal avidity for sodium. The retrograde theory pointed to the difficulty of the failing heart to receive blood preload and to the consequent rise in venous pressure transmitted to the peripheral capillary circulation. Here, the rise in hydrostatic pressure prevails over oncotic pressure and the imbalance between the two Starling forces shifts fluid in the interstice.

The simple consideration that the amount of fluid that generates a pitting edema is about 5 L, and that the total volume of plasma is about 2-3 L, makes the retrograde theory unrealistic.

What really occurs is that fluid is retained by the kidney to restore circulating blood volume, but the kidney's effort cannot be successful because the problem is pump failure, not lack of fluid.

Low EBV is the pathogenic mechanism of edema also in nephrotic syndrome. Nephrotic syndrome is a cluster of symptoms that are edema, high grade proteinuria (>3 g/24 h), low plasma protein with altered protein fractions, and hypercholesterolemia. The symptoms start with proteinuria. Note that proteinuria indicates an abnormal permeability of glomerular capillaries that can be caused by diverse diseases with different pathogenic mechanisms (see Chapter 5). Protein loss is followed by a decrease in plasma protein concentration with a prevalent effect on low molecular weight albumin. The albumin fraction of plasma proteins falls below 50% while large proteins, namely alpha-2 globulins rise from about 10-12% up to 30%.

As part of its response to protein loss the liver increases protein synthesis including lipoproteins that, like alpha-2 globulin, are big and accumulate in serum where they bind lipids, increasing circulating lipid levels. Formation of edema starts with the imbalance of Starling forces due to low oncotic pressure that shifts fluid from the intravascular compartment to the interstice. The ensuing hypovolemia triggers sodium retention through neural, hemodynamic and humoral effectors. A main effector is the renin-angiotensin system that is strongly activated and stimulates aldosterone release. In fact, aldosterone was discovered in a patient with nephrotic syndrome in which plasma levels of aldosterone were so high as to be detectable with the rudimentary biochemistry means available in the 1930s.

Liver cirrhosis is associated with fluid retention that mostly accumulates as ascites, but in a minority of patients also causes peripheral edema. Ascites results from increased pressure in the portal circulation and low serum albumin. Both of these phenomena contribute to generate an imbalance in Starling forces and the

prevalence of hydrostatic over oncotic pressure moves fluid out of the capillary.

Quite surprisingly, chronic renal failure is not as frequently the cause of peripheral edema. In fact, in chronic renal failure the decrease in the amount of filtered sodium causes sodium retention, but to a limited extent because ECF volume and effective blood volume rise proportionally and hypervolemia inhibits tubular sodium reabsorption. Also in acute renal failure oliguria is rarely associated with edema. In cases treated with dialysis fluid is removed by ultrafiltration (see Chapter 9), while in patients on conservative treatment, restriction of salt is often sufficient to limit ECF volume expansion till GFR is recovered.

HOW TO TREAT DISORDERS OF ECF VOLUME

The disorders of ECF volume are treated as disorders of sodium mass, i.e. by adding sodium to the body or subtracting it, in cases of ECF volume depletion or expansion, respectively. Sodium is delivered orally or intravenously, as sodium chloride or sodium bicarbonate. We do not recommend solutions of sodium lactate or citrate that are available as substitutes for bicarbonate, because they need metabolic transformation to generate bicarbonate and the rate of the metabolic process is not predictable. Their use can be advantageous in patients that need calcium because calcium can be mixed with them remaining soluble, while it precipitates as carbonate in a bicarbonate solution.

Sodium chloride has a molecular weight of 58 daltons, and 1 g delivers 17 mmol of sodium, while sodium bicarbonate weights 84 daltons and 1 g delivers 12 mmol of sodium.

Excess ECF volume is treated by reducing dietary sodium intake or by using diuretics. In fact, currently used diuretics are natriuretic drugs, that reduce tubular sodium reabsorption and drag water to urine by osmotic drive. Diuretic drugs that are currently used are thiazides (chlortalidone and hydrochlorothiazide) and high-ceiling diuretics (furosemide, ethacrynic acid, bumetanide). The first ones inhibit sodium reabsorption in the early tract of distal tubule, the

second group in the thick portion of Henle's ascending limb. The two classes differ in their range of power. Thiazides have a restricted possibility to increase sodium loss by increasing their dose. A rise in sodium excretion can be expected by doubling the dose of chlortalidone from 25 to 50 mg, but further dose increments are not effective. For thiazides to work the GFR has to be normal or at least higher than 50 mL/min. High-ceiling diuretics, furosemide for example, can be used in a range of 20 mg to 1 g, and high doses are effective also in patients with low GFR. Chlortalidone differs from furosemide also for its long-lasting effect, continuing for 24 h, while furosemide has a brisk action, peaking in a few hours.

The simplest way to estimate short term (days) ECF volume changes is to monitor body weight. The amount of sodium gained or lost that corresponds to 1 kg, i.e. 1 L of ECF volume is nominally 140 mmol.

Programming infusion to maintain fluid balance

There are clinical conditions in which the patient is not able to maintain fluid balance, i.e. to introduce water and electrolytes in the amount that he/she is losing, e.g. in a neurologic coma or after abdominal surgery. In such cases the physician is faced with the challenge of programming an infusive or enteral replacement that targets the balance.

The task is not easy because of the many sources of fluid loss: the skin, ventilation, surgical procedures, wound drainage, diuretic treatment and the variable circumstances pertaining the single case (environmental impact, fever, blood pH, diabetes, cerebral injury…). An estimate of fluid and electrolyte loss from skin, gastrointestinal apparatus, breathing, is reported in **Table 1**.

On planning a program of water and electrolyte infusion tailored to replace losses, a preliminary step is to distinguish the patient with normal renal function from that with renal failure. Functioning kidneys are internal detectors of fluid balance that can be used to understand whether the fluid delivery is correct.

Here following are the operative instructions for the two conditions, i.e. normal renal function and renal failure:

Table 1 Approximate concentrations of electrolytes in transcellular fluids

FLUID	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3 (mEq/L)
Saliva	33-40	5-20	34-40	40
Gastric juice	60-120	5-10	100-150	0
Bile	120-140	5-15	100-120	45
Pancreatic juice	120-140	5-15	90-120	90
Small bowel	110-120	5-10	90-120	90
Diarrhoea (adult)	80-120	20-100	90-110	90
Sweat	30-70	0-5	30-70	0
Burns	140	5	110	20

Patient with normal renal function

(i) Try to define the present state of ECF volume, i.e. if it is normal, expanded or depleted. To that purpose collect precise information on recent fluid losses and gains, check for recent recordings of body weight and blood pressure, get updated measurement of serum electrolyte concentration and blood pH and of urinary sodium concentration. Make a careful physical examination and evaluate physical signs of expansion/depletion of ECF volume. Try to quantify excess/defect, expressing it as mMol Na^+.

(ii) Consider sources of fluid and electrolyte loss and list separately the loss of water (mL/24 h), sodium (mEq/24 h), potassium (mEq/24 h). Do not include in loss urinary volume and urinary electrolytes. As discussed soon later, it is YOUR task to decide the amount of water, sodium and potassium that will be eliminated in urine in 24 h after the start of the infusion program.

(iii) Sum the loss of water, sodium, potassium from all sources but urine. Distinguish the fraction of sodium lost as chloride or bicarbonate.

(iv) Add to the losses calculated in (iii) the amount of water and electrolytes that you wish to eliminate in the urine (urinary sodium is eliminated as chloride). The resulting sum is the amount of water and electrolyte to be delivered during the next 24 h, timing the sequence and rate of infusion of different solutions with a priority determined by clinical risk, e.g. consider whether to address first a volume or a pH problem.

(v) Twenty-four hours after the start of IV infusion program compare the amount of water and electrolytes eliminated in urine with that wished by you as your target. The difference estimates your precision in evaluating losses. Correct the infusion program and repeat the procedure until the amounts (actual and programmed) coincide.

Patient with renal failure

In the patient with renal failure the kidney is not able to adjust water and electrolyte excretion and attain water and electrolyte balance obviating the gap between actual and calculated losses. The diagnosis of body fluid disorders is based on history, evaluation of losses, physical examination and plasma electrolyte concentration. From the information thus obtained state if ECF volume is depleted, normal or expanded. Now calculate an infusion program that includes urine in losses. Monitoring is essential to be prompt in modulating fluid therapy. Careful recording of body weight, blood pressure and urine volume and physical examination, in particular lung and heart auscultation are essential support to decision making. Avoid contradictions or misunderstanding, e.g. do not deliver a saline load associated with diuretic drugs. The two treatments conflict, one increasing sodium gain the other one increasing sodium loss. One of the two treatments is obviously wrong, but the mistake is much more common than expected mainly when protocol infusions are not cross-checked vs. individual prescriptions.

A major mistake is misinterpreting natremia (i.e. the serum concentration of sodium. Sodium symbol is Na from the Latin *natrium*) as an indicator of sodium content in the body, i.e. of ECF volume. In fact, natremia is an indicator of plasma osmolality.

Note: in general the combined administration of saline and diuretics makes no sense. Exceptions are rare, for example to increase urinary calcium excretion in cases of severe hypercalcemia.