

Fluid and Electrolytes

CHAPTER 54

Blood Biochemistry: Measuring Major Plasma Electrolytes

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OBJECTIVES

This chapter will:

1. Outline relevant principles of physical chemistry.
2. Describe the assays used to measure sodium chloride and potassium in blood.
3. Examine the reliability of such assays.

In clinical work, the most commonly measured electrolytes in plasma are sodium, potassium, and chloride. These variables are assessed in their own right and are used to derive other variables, such as tonicity, water balance, anion gap, strong ion difference, and strong ion gap.¹ To measure electrolytes, flame photometry² remains one of the oldest direct potentiometric methods³: a sample diluted with a known concentration of a reference ion (usually lithium or cesium) is aerosolized and passed through a flame, which excites the cations. They reemit the energy as light of different frequencies; the amplitude of this emission is proportional to the ion concentration in the sample. Nevertheless, this method has drawbacks, such as having a low throughput, requiring manual operation, and being a time-consuming procedure. Recently, inductively coupled plasma (isotope dilution) sector field mass spectrometry (ICP [ID] SFMS) has been proposed as a new reference method.⁴

However, ion-selective potentiometry remains the currently used method in clinical medicine for the determination of electrolytes in various body fluids. With regard to potassium, sodium and chloride, this technique has almost completely displaced flame photometry and other previously proposed techniques, such as atomic absorption spectrophotometry and coulometry. Sodium and potassium are positive ions (*cations*), whereas chloride is a negative ion (*anion*).^{5,6} An ideal ion-selective electrode (ISE) consists of a thin membrane across which only the intended ion can be transported. The transport of ions from a high concentration to a low one through a selective binding with some sites within the membrane creates a potential difference that is proportional to the concentration. The results for

these electrodes are reported as mmol/L of total plasma, although the electrodes actually measure a different quantity, known as the activity.⁶ To understand the fundamentals of these electrodes and some of their shortcomings requires an understanding of some of the underlying physical chemistry. The electrolytes are present in the plasma water only, and the body is responding to that. Thereby, it is actually only the plasma water that is of interest for the measurement of electrolytes. Moreover, ISEs are involved with electrochemical reactions with their designated ions—for this discussion, one of sodium, potassium, or chloride. When an ion interacts with its ISE, not all of the ions present can take part. The reason is the interactions between the measured ion and other ions in the solution; in the clinical situation, the solution is plasma.⁶ These interactions depend on the types of other ions present and their concentrations. For example, less sodium interacts with a sodium ion-specific electrode if more chloride is present.⁷

This type of interaction results in an effective concentration known as the *activity*. The electrical potential of the ion-specific electrode is related directly to the activity (effective concentration) of the electrolyte rather than to the actual concentration.

To estimate the total plasma concentration of an electrolyte, the first step is to convert the measured activity to the concentration in plasma water.⁸ The activity is related to the molar concentration of the electrolyte by means of the activity coefficient of that electrolyte, as follows:

$$\text{Activity} = \text{Concentration} \times \text{Activity coefficient}$$

The activity represents the effective concentration of a solute in the solution, that is, the actual number of particles that take active part in a given phenomenon. The value of the activity coefficient depends on several factors, including the specific ion, the chemistry of the surrounding solution, and the temperature. Clinical assays measure at 37°C. One variable for the activity coefficient is the *ionic strength*, the sum of the charge effects of the electrolytes in the solution. Plasma has particularly complex chemistry with many types of ions, fully dissociated ions and partly dissociated ions such as phosphate.⁹ In addition are other very

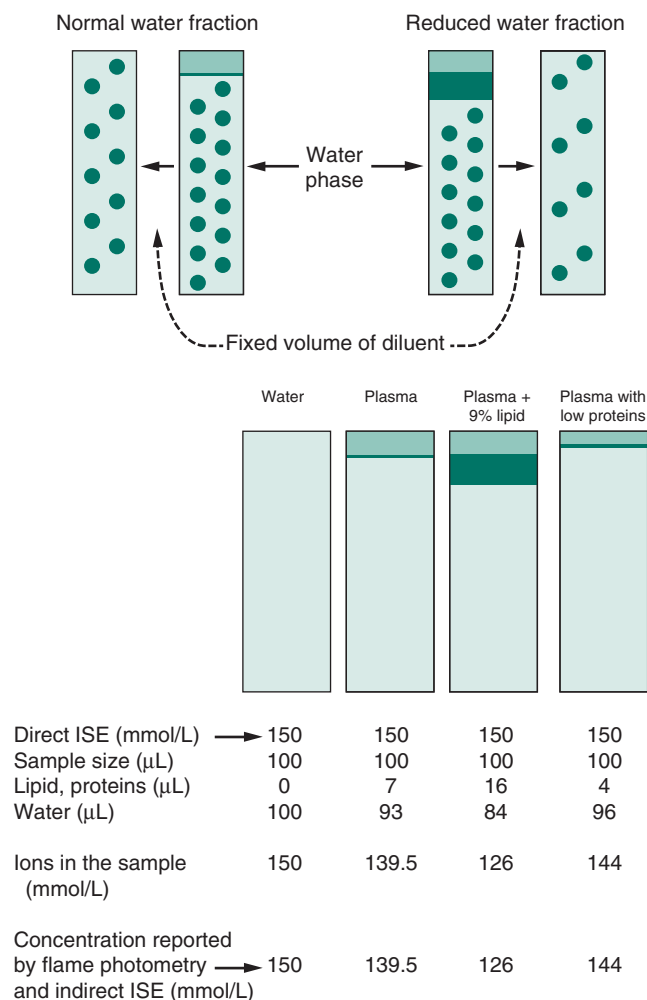


FIGURE 54.1 Effects of the predilution and calculation performed by the indirect estimation of sodium. ISE, ion-selective electrode. (Modified from Fortgens P, Pillay TS. Pseudohyponatremia revisited: a modern-day pitfall. *Arch Pathol Lab Med*. 2011;135:516, with permission. Copyright 2011 College of American Pathologists.)

complex charged molecules, such as albumin.¹⁰ Furthermore, particularly in critical illness, the concentrations of many of these constituents may change. Because of these factors, the variation of activity coefficients for electrolytes in plasma is unclear. The final step in converting the activity to the concentration in total plasma is to account for the proportion of plasma volume that is solid rather than water. The solid phase, usually about 7% of plasma volume, is a combination of lipids and proteins, with much of the protein being albumin.^{5,6} Therefore 93% of plasma volume is usually water (Fig. 54.1). Unlike calcium and magnesium, sodium, potassium, and chloride do not form significant bonds with plasma proteins.^{6,9,11} Therefore the solid phase is assumed not to contain sodium, potassium, or chloride.⁶ It follows that the total plasma concentration of an electrolyte is about 93% of the plasma water concentration.

For example, the measured activity for sodium is 112 (no units). The activity coefficient for sodium in plasma at 37°C is 0.737. The plasma concentration is calculated as follows:

$$\text{Concentration} = \text{Activity} \div \text{Activity coefficient}$$

Therefore the plasma water concentration is $112 \div 0.737$, or 150 mmol/L. Multiplying the plasma water concentration by the proportion of plasma that is water ($93\% \times 150$ mmol/L) yields the total sodium plasma concentration, 140 mmol/L.

When a blood sample is processed by a blood gas machine, such as those in intensive care unit (ICU) laboratories, the software process is identical to the calculations just described.⁶ The ISE are known as *direct electrodes* because there is no predilution of the sample. Direct ISE actually measures the electrolyte activity in the plasma water (mmol/kg H₂O) rather than concentration in the plasma (mmol/L). The electrochemical activity of the ions in the water is converted to the readout concentration by a fixed (ion-specific) multiplier, the activity coefficient. This is accurate only for a given ionic strength, usually chosen to equal 160 mmol/L for plasma. The use of this fixed factor ensures that direct ISE reflects the actual, clinically relevant activity, regardless of the level of proteins and/or lipids. This is not changed by the fact that the result traditionally is termed concentration. This conversion is based on recommendations from the IFCC Expert Panel on pH and blood gases.¹¹

However, central laboratories often use *indirect assays*.⁶ The indirect assays use ISE, but before analysis the sample is diluted with a solution with high ionic strength. The high ionic strength means that the activity coefficient for each electrolyte is 1. Therefore the measured activity effectively equals the concentration of the electrolyte (Concentration = Activity/Activity coefficient) in total plasma. The indirect assays use smaller volumes of plasma than direct assays, allowing more assays per sample in multicomponent analyzers and faster automated processing of multiple samples. Although direct ISEs respond to the electrolyte content in the plasma water, the indirect ISEs respond to the electrolyte content in the volume of total plasma.

A safe and unambiguous medical interpretation of sodium and chloride ion concentration in serum is not possible without knowledge of the water concentration or of the lipid and protein concentration of the individual sample. The use of undiluted samples and a fixed factor ensures that direct ISE reflects the actual, clinically relevant activity, irrespective of the level of proteins and/or lipids. The use of undiluted samples is preferred, because changes in plasma solids may lead clinicians to misinterpret changes in total plasma concentration for parallel changes in the plasma water concentration. The plasma water concentration of an ion has a stronger relationship with its physiologic effect than the total plasma concentration.⁶

For the clinician, it is possible that electrolyte measurements in plasma could be derived from either direct or indirect assays, or both, depending on the equipment used at a given site in a given hospital. Usually, point-of-care testing (POCT) instruments, such as blood gas analyzers, use direct ISE, whereas results produced by big autoanalyzers from central laboratories derive from indirect ISE. Because of differences in the methodology between direct and indirect ISE, the reported electrolyte concentrations in total plasma can differ considerably even with paired samples from the same patient.¹² The desirable and maximum acceptable errors in the assays are related to biologic variation and instrument error.^{13,14}

However, there is a great discussion about the definition of analytic performance specifications.¹⁵ Particularly, biologic variation and instrument error for sodium, potassium, and chloride are so little that desirable total error and acceptable maximum error would be too narrow. Other references usually are used by laboratories to define their analytic

TABLE 54.1

Plasma Electrolytes and Analytic Goals

ANALYTE	REFERENCE RANGE	CLIA	DESIRABLE BIOLOGIC GOAL	RCPA	RiliBAK
Sodium	136–145 mmol/L	± 4 mmol/L	± 0.73 mmol/L	± 3 mmol/L ≤ 150 mmol/L; ± 2% > 150 mmol/L	± 5.0%
Potassium	3.5–4.5 mmol/L	± 0.5 mmol/L	± 5.61%	± 0.2 mmol/L ≤ 4.0 mmol/L; ± 5% > 4.0 mmol/L	± 8.0%
Chloride	98–107 mmol/L	± 5 %	± 1.5%	± 3.0 mmol/L < 100 mmol/L; ± 3% > 100 mmol/L	± 4.5%

CLIA, Clinical Laboratory Improvement Amendments (USA); RCPA, Royal College of Pathologists of Australasia; RiliBÄK (Richtlinien der Bundesärztekammer), literally, the guidelines (“Rili”) of the German Federal Medical Council (BÄK).

goal, such as peer specification from proficiency testings (PT), manufacturer claims, predefined specification from regulatory institutions, such as Clinical Laboratory Improvement Amendments (CLIA) PT goals from the United States,¹⁶ German RiliBÄK specifications,¹⁷ and Royal College of Pathologists of Australasia (RCPA) allowable limits of performance¹⁸ (Table 54.1).

Previous and more recent studies have examined the agreement for plasma electrolyte measurements between indirect hospital (central laboratory) assays and direct ICU laboratory blood gas machine (ICU) assays, finding differences between the two methods that exceeded some of the proposed analytic goals^{12,19,20} (see Table 54.1).

One phenomenon associated with the disagreement between direct and indirect sodium assays is pseudohyponatremia.²¹ In this situation, increased plasma solids (see Fig. 54.1) lead to a decreased total plasma sodium estimate from the indirect sodium assay (central laboratory) when plasma water sodium is unchanged.²¹ This is called pseudohyponatremia because there is hyponatremia without hypotonicity.¹⁴ In contrast, because direct assays use a fixed value for plasma solids, the direct assays maintain a fixed relationship with plasma water concentration in the presence of increased plasma solids (see Fig. 54.1). What is little recognized is that decreases in plasma solids also should alter the relationship between the total plasma concentration and plasma water concentration of sodium with indirect assays, leading to possible pseudonormonatremia and pseudohypernatremia.²² Because of reported morbidity with pseudohyponatremia,¹⁴ much of the published research and commentary has focused on sodium assays, with far less attention on other ion assays.

The effect of protein concentration on plasma sodium and chloride measurements in critically ill patients was investigated by Story et al.¹ in 2007 and more recently by Goldwasser et al.²³ They found that as the plasma albumin (a plasma solid) value fell, the direct estimate for sodium was increasingly greater than the indirect estimate, and for each 10 g/L rise or fall in total protein, clinicians may find it useful to adjust indirect ISE by 0.7–1.6 mmol/L in the same direction, to correct indirect ISE for nonwater bias. Importantly, changes in proteins are likely to be only one of several causes for the differences between direct and indirect sodium assay results. These findings also highlight the complexity of plasma chemistry and its measurement.

When a clinician assesses plasma chemistry, it is important to know what kind of assay has been used. The frequently used indirect assays for sodium represent plasma water sodium concentration in critically ill patients less reliably than the direct assay. Previously, clinical chemists

have recommended that direct assays should be used to measure plasma sodium in patients with increased plasma solids to avoid the risk of pseudohyponatremia, pseudonormonatremia, and pseudohypernatremia.^{6,21} These differences could be not significant, according to some analytic goals, but it should be taken into account in the management of the patients. In critically ill patients, decreased plasma albumin is almost universal^{24,25}; therefore direct sodium assays are preferred. The situation for potassium and chloride is less clear, but purely for convenience, the easiest path is to use the direct assay results available with sodium.

Key Points

1. Plasma physical chemistry of ions is complex.
2. Assays measure activities but report concentration in total plasma.
3. Direct and indirect assays can have important differences.
4. Actual analytic goals for ions measurement based on biologic variability could be too narrow.
5. Direct assays are preferable to indirect assays.

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A complete reference list can be found online at ExpertConsult.com.

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