Recognition and Treatment of Hyponatremia in Critically Ill Patients

An essay
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List of abbreviations

AA/EA	Afferent and efferent arterioles
ADH	Antidiuretic hormone
aLOH	Ascending part of loop of Henle
ANP	Atrial natriuretic peptide
AT II	Angiotensin II
AVP	Arginine vasopressin
BNP	Brain natriuretic peptide
CCF	Congestive cardiac failure
CD	Collecting duct
CNS	Central nervous system
CPM	Central pontine mylenosis
CSW	Cerebral salt wasting
DT	Distal tubule
ECBV	Effective circulatory blood volume
ECF	Extracellular fluid
FDA	Food and drug administration
FeNa	Fractional excretion of sodium
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
HF	Heart failure
ICU	Intensive care unit
MBF	Medullary blood flow
MELD	Model for End-stage Liver Disease
NHANES	The National Health and Nutrition Examination Survey
NO	Nitric Oxide
OR	Osmo-receptors
PGs	Prostaglandins
PT	Proximal tubule
PTC	Peritubular capillaries
PV	Paraventricular
RAAS	Renin–angiotensin–aldosterone system
SF	starling force
SIADH	Syndrome of inappropriate ADH secretion
SNS	Sympathetic nervous sytem
SO	Supraoptic
SSRIs	Selective serotonin reuptake inhibitors
TBW	Total body water
USA	United States of America
V1A	Vasopressin receptor subtype 1A

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Introduction

Hyponatremia is a common electrolyte abnormality in critically ill patients, reflecting serum sodium level of <135 mEq/L (Normal serum sodium 135-145 mEq/L) **(Oh et al., 2002).**

Hyponatremia is occurring in up to 15% to 30%of both acutely and chronically hospitalized patients **(Upadhyay et al., 2006).**

Hyponatremia is characterized by either solute depletion (decreased total body solute and water retention) or solute dilution (increased total body water [TBW] with or without solute depletion) **(Verbalis et al., 2003)**.

For hyponatremia to develop, a relative excess of water in conjunction with an underlying condition that impairs the kidney's ability to excrete water is required. Stimuli for the release of arginine vasopressin (AVP) and hence the impairment of water excretion are so frequent in hospitalized patients, especially those in the ICU, that virtually all patients are at risk of hyponatremia. Thus, the most important factor resulting in hospital-acquired hyponatremia is the administration of hypotonic fluids to a patient with impaired urine-diluting capacity (**Ayus et al., 2008**).

Despite knowledge of hyponatremia since the mid-20thcentury, this common disorder remains incompletely understood in many basic areas because of its association with a plethora of underlying disease states, and its multiple etiologies with differing pathophysiologic mechanisms **(Verbalis et al., 2007).**

Optimal treatment strategies have not been well defined, both for these reasons and because of marked differences in symptomatology and clinical outcomes based on the acuteness or chronicity of the hyponatremia **(Sterns and Silver, 2006).**

Symptoms of hyponatremia include nausea and vomiting, headache, confusion, lethargy, fatigue, appetite loss, restlessness and irritability, muscle weakness, spasms, or cramps, seizures, and decreased consciousness or coma, The presence and severity of symptoms are associated with the level of serum sodium, with the lowest levels of serum sodium associated with the more prominent and serious symptoms **(Schrier et al., 2010)**.

The treatment of hyponatremia will depend on the underlying cause and whether the patient's volume status is hypervolemic, euvolemic or hypovolemic (**Bernsen and Prick, 1999)**.

Hyponatremia must be corrected slowly in order to lessen the chance of the development of central pontine mylenosis (CPM), a severe neurological disease. In fact, overly rapid correction of hyponatremia is the most common cause of that potentially devastating disorder (**Bernsen and Prick, 1999).**

Aim of the Work:

To shed the light on the frequency of hyponatremia in critically ill patients admitted to the ICU and to determine its complications and management.

Physiology of Sodium and water balance

Body fluid compartments

Water makes up 50-75 percent of the body mass. The most important determinants of the wide range in water content are age and gender: a. the water content of a newborn, an adolescent and an elderly man are approximately 75, 60 and 50 percent; b. after puberty males generally have 2 to 10 percent higher water content than females **(Bianchetti et al., 2009).**

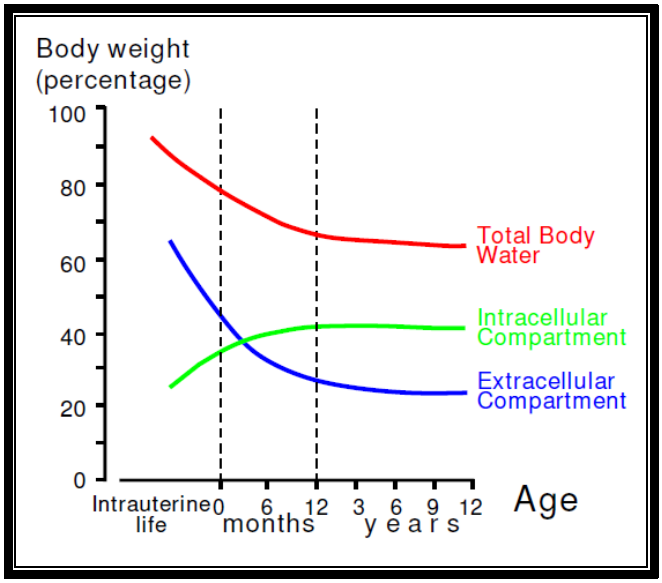

Figure (1): Winters diagram with the subdivision of total body water, intracellular fluid and extracellular fluid as a function of age. For clinical purpose the use of "the rule of 3" is recommended: 1. total body water makes up 2/3 of the body mass; 2. the intracellular compartment contains 2/3 of the total body water and the remaining (= 1/3) is held in the extracellular compartment; 3. the extracellular compartment is further subdivided into the interstitial and the intravascular compartments (blood volume), which contain 2/3 and 1/3 of the extracellular fluid, respectively. After puberty males generally have 2 to 10 percent higher water content than females **(Bianchetti et al., 2009).**

The intracellular compartment contains about two-third of the total body water and the remaining is held in the extracellular compartment. The solute composition of the intracellular and extracellular fluid differs considerably because the sodium pump maintains potassium in a primarily intracellular and

sodium in a primarily extracellular location. Consequently potassium largely determines the intracellular and sodium the extracellular compartment **(Ruth and Wassner, 2006).**

The extracellular compartment is further subdivided into the interstitial and the intravascular compartments (blood volume), which contain two-thirds and one-third of the extracellular fluid, respectively. Finally, the transcellular fluid compartment comprises the digestive, cerebrospinal, intraocular, pleural, peritoneal and synovial fluids. The size of the intravascular compartment is determined by the overall size of the extracellular fluid compartment and by the Starling forces: they control the partition of fluids between intravascular and interstitial compartments across the capillary membrane that is crossed by salts like sodium chloride and by glucose but not by blood proteins (especially albumin) **(Bianchetti et al., 2009).**

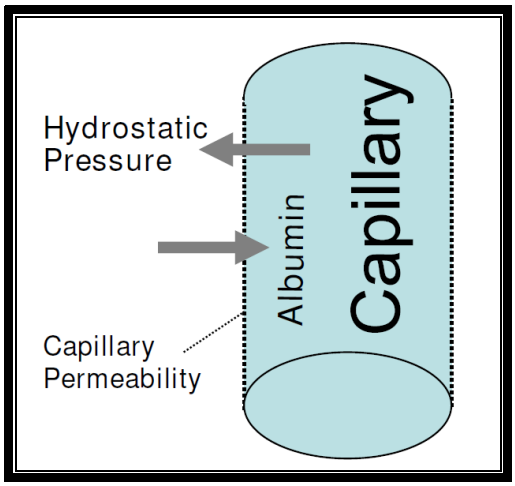

Figure (2): Distribution of ultrafiltrate across the capillary membrane. The barrel-shaped structure represents a capillary. A high hydrostatic pressure or an increased capillary permeability causes fluid to leave the vascular space. On the contrary an increased intravascular albumin concentration and, therefore, an increased oncotic pressure causes fluid to enter the vascular space **(Bianchetti et al., 2009).**

Three major forces control the distribution of fluids across the capillary membrane: a. the hydrostatic pressure causes fluids to leave the vascular

space, and; b. the higher concentration of proteins in the intravascular compartment as compared with that in interstitial fluid, which causes fluids to enter the vascular space. This force, which is called oncotic pressure, is due both to the concentration gradient of albumin (blood proteins other than albumin account for 50 percent of the weight of proteins in g in blood but only for 25 percent of the oncotic pressure) as well to the fact that albumin is anionic and therefore attracts cations (largely sodium) into the vascular compartment (Gibbs-Donnan effects). c. Capillary permeability is a further major mechanism that modulates the distribution of fluids across the capillary membrane **(Bianchetti et al., 2009).**

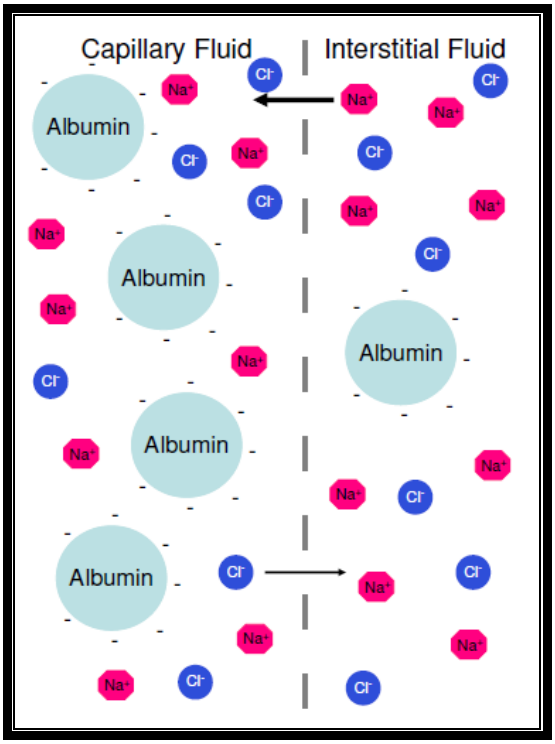

Figure (3): The Gibbs-Donnan effect. There is a different concentration in the concentration of anionic albumin, which is impermeant, between the vascular (albumin approximately 40 g/L) and the interstitial (albumin approximately 10 g/L) compartments. The negative charges of albumin "attract" cations (largely Na+) into the vascular compartment and "repell" anions (Cl- and HCO3-) out. Because the concentration of Na+exceeds that of Cl- and HCO3 -, "attraction" outweighs "repulsion". Consequently the Gibbs-Donnan effect increases the vascular compartment. The dashed line represents the capillary bed separating the intravascular and interstitial spaces is freely permeable to Na+, K+, Cl-, and glucose **(Bianchetti et al., 2009).**

Effective circulating volume

Effective circulating volume denotes the part of the intravascular compartment that is in the arterial system and is effectively perfusing the tissues. The effective circulating volume is biologically more relevant than the intravascular compartment and usually varies directly with the extracellular fluid volume **(Schrier, 2007).**

As a result, the regulation of extracellular fluid balance (by alterations in urinary sodium excretion) and the maintenance of the effective circulating volume are intimately related. Sodium loading will tend to produce volume expansion, whereas sodium loss (e.g., due to vomiting, diarrhea, or drug management with diuretics) will lead to volume depletion. The body responds to changes in effective circulating volume in two steps: 1. The change is sensed by the volume receptors, which are located in the cardiopulmonary circulation, the carotid sinuses and aortic arch, and in the kidney; 2. These receptors activate effectors that restore normovolemia by varying vascular resistance, cardiac output, and renal water and salt excretion. Briefly, the extrarenal receptors primarily govern the activity of the sympathetic nervous system and natriuretic peptides. On the other side the renal receptors affect volume balance by modulating the renin-angiotensin II-aldosterone system. In some settings the effective circulating volume is independent of the extracellular fluid volume. Among patients with heart failure the extracellular fluid volume is increased but the patient is effectively volume depleted due to the low cardiac output **(Bianchetti et al., 2009).**

Blood osmolality - measurement of sodium

Osmolality is the concentration of all of the solutes in a given weight of water. The total (or true) blood osmolality is equal to the sum of the osmolalities of the individual solutes in blood. Most of the osmoles in blood are sodium salts, with lesser contributions from other ions, glucose, and urea. However, under normal circumstances, the osmotic effect of the ions in blood can usually be estimated from two times the sodium concentration. Blood osmolality (in mosm/kg H_2O) can be measured directly (via determination of freezing point depression) or estimated from circulating sodium, glucose and urea (in mmol/L [To obtain glucose in mmol/L divide glucose in mg/dL by 18. To obtain urea in mmol/L divide urea nitrogen in mg/dL by 2.8 or urea in mg/dL by 6.0.]) as **(Haycock, 2006).**

The effective blood osmolality, known colloquially as blood tonicity, is a further clinically significant entity, which denotes the concentration of solutes impermeable to cell membranes (sodium, glucose [Glucose is a unique solute because, at normal concentrations in blood, it is actively taken up by cells and therefore acts as an ineffective solute, but under conditions of impaired cellular uptake (like diabetes mellitus) it becomes an effective extracellular solute.], mannitol) and are therefore restricted to the extracellular compartment (osmoreceptors sense effective blood osmolality rather than the total blood osmolality). These solutes are effective because they create osmotic pressure gradients across cell membranes leading to movement of water from the intracellular to the extracellular compartment. Solutes that are permeable to cell membranes (urea, ethanol, methanol) are ineffective solutes because they do not create osmotic pressure gradients across cell

membranes and therefore are not associated with such water shifts. Since no direct measurement of effective blood osmolality (which is biologically more important than the total or true blood osmolality) is possible, following equations are used to calculate this entity **(Burnettet al., 2000)**

Flame photometry, the traditional assay for circulating sodium, measures the concentration of sodium per unit volume of solution, with a normal range between 135 and 145 mmol/L. In fact, sodium is dissolved in plasma water, which normally accounts for 93% of the total volume of plasma, the remaining 7% consisting of protein and lipid. Ion selective electrodes, that have replaced flame photometry in most laboratories, determine the activity of sodium in plasma water, which ranges between 145 and 155 mmol/L. For convenience, laboratories routinely apply a correction factor so that the reported values still correspond to the traditional normal range of 135-145 mmol/ L **(Haycock, 2006).**

A kind of "pseudohyponatraemia" caused by expansion of the non-aqueous phase of plasma – for example, due to hyperlipidaemia or paraproteinemia – is no longer seen because determination by selective electrodes in undiluted serum, plasma or whole blood is unaffected by this [The recommended name for this quantity is ionized sodium] **(Burnett et al., 2000).**

Although, strictly speaking, a sodium concentration outside the range of 135-145 mmol/L denotes dysnatremia, clinically relevant hypo- or hypernatremia is mostly defined as a sodium concentration outside the extended normal range of 130-150 mmol/L **(Haycock, 2006a).**

Cellular water and sodium control

Steady intracellular water and osmolality are necessary to ensure normal cell membrane integrity and cellular processes. In health IC osmolality is constant so IC water movement is usually due to changes in EC osmolality. water redistribution occurs if there is an osmotic disequilibrium across the cell membrane, i.e. an increase or decrease in Na+ concentration in ECF. As a result, cells shrink or swell in order to adapt to changes in osmolality of the environment **(McManus et al., 1995).**

On the other hand, if osmolality is increased equally in all body fluids due to urea, cellular volume does not change because an osmotic gradient does not develop **(Patel, 2009).**

Acute osmolar stresses elicit electrolytes transportation across the cell membrane and return the cell volume back to normal within minutes. Cells adapt to chronic changes in tonicity by altering their osmolal constituents. Chronic ECF tonicity causes the accumulation or loss of small IC organic molecules termed osmolytes (ex. sorbitol) and amino acids. Both compensatory mechanisms occur over a different time scale. Clinically, correction of Na+ imbalance should be carried out gradually to allow time for reversal of these compensatory processes. Rapid reversal of serum Na+ level back to normal can cause serious cellular water, and volume changes particularly in the neuronal cells of the brain **(Reddy and Mooradian, 2009).**

Role of Na+-K+-ATPase pump

The Na+-K+-ATPase pump is a membrane bound enzyme that carries

out the active electrogenic translocation of Na+ and K ions across the plasma membrane of most cells. In a normal isoosmolar environment, the cellular volume is maintained by Na+-K+-ATPase **(Koko, 2004).**

It indirectly controls ionic balance and epithelial transport. There are hundreds to thousands of Na+-K+- ATPase pumps per cell bound to its membrane. Na+-K+-ATPase pumps indirectly control the cell water at a "local" level. The activity of this enzyme is under multifactorial control. At the cellular level, changes in cytoplasmic concentration of Na+, K and calcium can modulate the activity of the pumps. Various hormones, notably aldosterone, increase the activity and numbers of these pumps. Their function is also affected by diseases and drugs. One of the main functional activities of the Na+-K+-ATPase pumps is to create an electrochemical gradient in luminal cells of the intestine and nephron **(Patel, 2009).**

Role of the cardiovascular system

Body fluids protect circulatory blood volume by altering Na+ and water balance. This is the most vital homeostatic function of the body. Changes in ECF volume are sensed by various cardinal sensors. These sensors in turn send signals, which lead to various effective changes via neural, hormonal and physical responses. In fact, as mentioned earlier, the mean arterial blood pressure is a major determinant of Na+ output **(Brown et al., 2005).**

Starling forces

Plasma and ISF are continuously interchanged because of starling forces (SF) operating at the capillary level. These forces are hydrostatic and osmotic within the vascular and interstitial compartments. Dynamically, the