Relation between admission serum sodium concentration and clinical outcomes in patients hospitalized for ischemic heart failure And short term follow up (3 months)

Protocol of thesis

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Introduction

Heart failure is pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues.

There are a number of diseases, medical conditions and other factors that put people at higher-than-average risk for heart failure as coronary heart disease, heart rhythm disorders, diabetes mellitus, hypertension, alcohol, smoking, abnormal heart valves, cardiomypathy, anaemia, hyperthyroidism and electrolytes disturbances as hyponatraemia ***(Felker et al., 2004)***.

Hyponatraemia, is a relatively common finding in patients admitted to the hospital with heart failure. Hyponatraemia is defined as a serum sodium concentration less than ١٣٥mmol/L ***(Kumar and Berl, 1998; Adrogue and Madias, 2000)***.

The mechanism of hyponatraemia in heart failure remains unclear. Water retention in excess of Sodium retentions appears to the principle mechanism ***(Leir et al., 1994)***.

Increased sodium retention results from: decreased renal perfusion, activation of rennin-angiotension- aldosterone system and impaired natriuretic peptide response.

Water retention results from increased reabsorption at proximal renal tubules, increased release of arginine vasopressin by the posterior pituitary and enhanced angiotensin mediated thirst. Thus, there is both increased total body sodium and water retention, but the total body water retention exceeds that of sodium retention resulting in Hyponatraemia ***(Chatterjee, 2008)***.

Serum sodium is a known predictor of outcome in patients with heart failure. Patients with hyponatraemia had significantly higher rates of in-hospital and follow-up mortality and longer hospital stays.

Patients admitted with hyponatraemia were clinically similar to patients with normonatraemia in terms of age, gender, heart failure etiology, diabetes, heart rate, ejection fraction, and symptoms of congestion. However they have lower admission systolic blood pressure and an atrial arrhythmia ***(Gheorghiade et al., 2006)***.

The therapeutic approach to the treatment of hyponatraemia in heart failure has traditionally relied on attempts to improve cardiac function and at the same time limit fluid intake. However, this approach is not likely to improve or normalize serum sodium concentration. Recently, agents that selectively block the type ٢

vasopressin receptor and increase free water excretion without any of the adverse consequences of other therapies, such as loop diuretics, have been shown to improve or normalize serum sodium in patients with mild, moderate, or severe heart failure without affecting heart rate, blood pressure, or renal function ***(Gheorghiade et al., 2004)***.

Aim of the Work

The aim of work is to determine serum sodium concentration in patients with heart failure and detect the relation between admission serum sodium concentration and clinical outcomes (in hospital mortality, length of hospital stay and short term follow up for ٣ months) in patients hospitalized for ischemic heart failure EF<٤٥٪

Sodium Metabolism

١- Introduction:

Body fluid balance is meticulously regulated by neuroendocrine control systems. After a change in the volume or content of the extracellular fluid (ECF; which includes blood plasma), these control systems enact appropriate compensations to bring it back within narrow limits. In the equations of body fluid balance, the two primary variables are water and sodium. Balance is maintained through complementary adjustments in their ingestion and excretion.

The control systems that regulate the intake and excretion of water are the primary means for adjusting the concentration of solutes in the extracellular fluid, whereas control of both water and sodium is necessary for maintaining a volume of blood sufficient for optimal tissue perfusion by the heart ***(Verbalis, ٢٠٠٣)***. The basic regulatory mechanisms for controlling water intake (thirst), water excretion and sodium excretion are fairly well characterized and widely appreciated ***(Andersson, 1978; Stricker and Sved, 2002; McKinley et al., 2004)***, but less is understood about the regulation of sodium intake.

Sodium is, by far, the most abundant extracellular solute. The osmolarity of the extracellular fluid (including blood plasma) is dictated primarily by the concentration of sodium and its attendant anions ***(Verbalis, 2003)***. Extracellular osmolarity is meticulously maintained near a set point of roughly ٢٩٠ mosmol $l^{-١}$ (the vast majority of which is composed of ~١٤٠ mM Na^{+}, plus its attendant anions, primarily chloride).

In order to appreciate the role of sodium in body fluid homeostasis, it is critical to understand that extracellular osmolarity is regulated primarily by the ingestion and excretion of water, whereas the volume of extracellular fluid is directly proportional to the total body content of sodium ***(Verbalis, 2003)***. That is, the total volume of extracellular fluid in the body depends largely upon the amount of sodium present in the extracellular space, around which water input and output are tailored to tightly control osmotic pressure. This regulatory arrangement is the reason that sodium must be excreted to reduce plasma volume, and it must be ingested and retained to increase plasma volume.

Expansion of the ECF volume (a requirement for growth and for replacing fluid losses) is therefore absolutely limited by dietary sodium intake. Water intake alone is adequate to replace

volume losses only when the sodium concentration is elevated owing to a loss of water greater than the loss of sodium. In contrast, as shown in **Fig. ١**, fluid losses involving large amounts of sodium (prolonged sweating or bleeding, for example) cannot be adequately replaced by water intake alone ***(Stricker and Jalowiec, 1970; Nose et al., 1988)***.

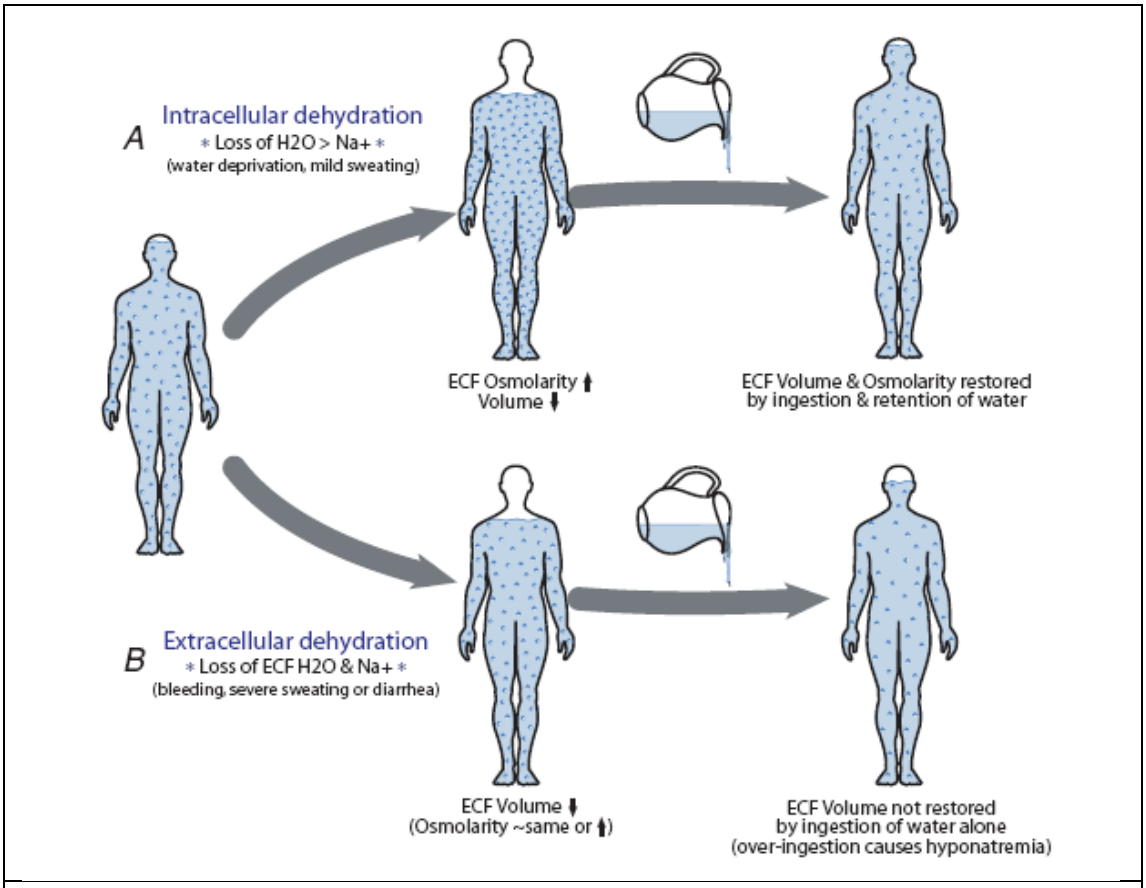

Figure ١: Intracellular and extracellular dehydration.
A, after body water is lost, the extracellular fluid (ECF) volume decreases, its solute concentration (osmolarity) increases, and cells shrink because water moves out into the now-hypertonic extracellular space, a condition referred to as 'intracellular dehydration.' This situation stimulates antidiuresis and thirst, and the resulting ingestion and retention of water can restore ECF volume and osmolarity to normal (note that for simplicity, this figure does not include the renal natriuresis that can occur during more prolonged dehydration, which does not restore ECF osmolarity, but does result in a minor additional loss of ECF volume, providing a minor stimulus for sodium appetite in addition to thirst). B, in contrast, 'extracellular dehydration' is a

more significant reduction in ECF volume (with or without a change in osmolarity) due to a loss of sodium-containing fluids. In this case, the ingestion of water alone is not adequate to restore the ECF to normal. In fact, excess water ingestion will cause a decrease in ECF osmolarity (hyponatraemia), which inhibits additional intake and retention of fluids until an adequate amount of solute (sodium) is restored.

In such situations, consuming too much fluid without salt will produce hyponatraemia, which typically inhibits further drinking ***(Stricker, 1969)***. Overdrinking water, known as 'water intoxication', can be fatal, as in the case of a woman who died after ingesting two gallons of water as part of a radio station contest ***(Associated Press, 2007)***. Occasionally, this problem is encountered by endurance athletes, such as marathon runners, who can become dangerously hyponatraemic after drinking large volumes of fluid in excess of their sweat losses ***(Almond et al., ٢٠٠٥)***. If salt is consumed in addition to water, however, the body can retain an isotonic mixture of ingested sodium and water to more effectively restore blood volume ***(Stricker and Jalowiec, ١٩٧٠; Nose et al., ١٩٨٨; Twerenbold et al., ٢٠٠٣)***.

Since sodium represents less than ١٪ of the extracellular fluid by weight, the mass of sodium required for volume restoration is quite small relative to the amount of water that must be consumed. Accordingly, antidiuresis and thirst are the primary homeostatic drives stimulated in response to fluid loss and,

initially, the most critical aspect of sodium regulation is retention by the kidney.

When the ECF volume expands, the blood pressure rises, and the increased perfusion pressure causes the kidneys to excrete more sodium ***(Guyton, 1991)***. Conversely, when the ECF volume is reduced, sodium is retained. This retention is primarily mediated by the steroid hormone aldosterone. Elevated levels of aldosterone, which is produced in the adrenal glands, can stimulate near-total conservation of sodium from the urine. This remarkable regulatory mechanism is critical for survival. Removal or gross dysfunction of the adrenal glands is invariably lethal without either exogenous replacement of aldosterone or continuous dietary supplementation of sodium ***(Richter, 1936; Wilkins and Richter, 1940)***.

Eventually, however, sodium conservation is only half the battle; the kidneys can retain only what is already present in the body. The other important aspect of this control system is the regulation of salt intake. Under normal conditions, obligatory sodium losses are small and, when necessary, the kidneys can maintain near-total urinary sodium conservation for extended periods of time. This allows animals to survive for many weeks on

a sodium-free diet ***(Orent-Keiles et al., 1937; Fine et al., 1987a)***. Ultimately, however, ECF volume can be neither increased nor restored without the consumption of sodium. The chronic volume deficit and the secondary increase in plasma potassium that result from sodium deprivation lead insidiously to severe health consequences. Chronic sodium deprivation causes growth retardation, reproductive deficits, reduced muscle mass, alterations in bone composition and various other pathologies, which are eventually lethal ***(Orent-Keiles et al., 1937; Bursey and Watson, 1983; Fine et al., 1987a)***.

Put simply, normal growth requires the ingestion and retention of sodium. Without dietary salt, growth slows, reproduction fails, and animals die prematurely ***(Orent-Keiles et al., 1937; Fine et al., 1987a,b)***. In humans sustained on sodium-free nutrient infusions, bone mineralization ceases and growth stops in all tissues except fat ***(Rudman et al., 1975)***. Even short-term sodium deficiency in humans causes severe muscle cramps, loss of appetite, nausea, fatigue and considerable weight loss ***(McCance, 1936)***.

Given these severe health consequences, particularly the deficits in growth and reproduction, it should come as no surprise

that a hard-wired behavioral mechanism has evolved to promote salt intake in response to a prolonged sodium deficiency.

١-What is sodium appetite?

Sodium appetite (also known as salt appetite) is a motivated behavioural state that arises in a number of species specifically as a response to sodium deficiency. As the name indicates, it drives an animal to seek and ingest foods and fluids that contain sodium. Sodium appetite is a hard-wired regulatory mechanism and, like thirst, it is vital for restoring extracellular fluid.

It is important to note that when salty foods or fluids are freely available, animals (including humans) spontaneously exhibit a baseline or 'need-free' level of intake in excess of any immediate need or growth requirement. This baseline ingestion of salt (and water) is more than adequate for maintaining fluid balance in the absence of significant fluid loss, and any excess sodium or water is simply excreted in the urine. The magnitude of 'need-free' salt intake can be influenced by prior episodes of sodium deficiency ***(Sakai et al., 1989)***, especially prenatal experience with maternal illness during pregnancy ***(Nicolaidis et al., 1990; Crystal and Bernstein, 1995, 1998)***. It remains unclear,

however, to what extent spontaneous salt-ingestive behaviours engage the same brain circuits that are responsible for sodium appetite, which is operationally defined as a specific response to sodium deficiency.

Abundant anecdotal evidence for sodium appetite existed for centuries ***(Kare et al., 1980; Denton, 1982)***, but a direct experimental demonstration awaited the seminal work of ***Curt Richter (1936)***. At this time, it was recognized that removal of the adrenal glands rendered animals unable to conserve urinary sodium owing to the loss of a vital 'mineralocorticoid' hormone (aldosterone) produced in the adrenal cortex. Unless their diet was continually supplemented with sodium, adrenalectomized animals deteriorated rapidly and died after roughly ١ week. Richter wanted to know whether animals possess an innate behavioural mechanism that would compel them to seek and ingest extra salt if it suddenly became necessary for their survival. When he gave adrenalectomized rats access to saline, they drank greatly increased amounts, even at a high concentration (٣٪ NaCl; roughly the concentration of seawater), which they had only sampled in small amounts prior to surgery. The voluntary increase

in salt intake by these rats was more than sufficient to compensate for their urinary sodium losses, allowing their continued survival.

That this change in ingestive behaviour occurred specifically in response to sodium deficiency was confirmed by the demonstration that saline intake returned to normal when functional adrenal tissue was transplanted back into adrenalectomized rats ***(Richter and Eckert, 1938)***. Likewise, their increased saline intake vanished when sodium conservation was re-instated using replacement-dose mineralocorticoid injections ***(Wolf, 1965; Fregly and Waters, 1966)***, but promptly reappeared when hormone replacement was withdrawn ***(McEwen et al., ١٩٨٦; Tordoff et al., ١٩٩٣)***.

Subsequent investigators identified a number of other experimental methods that produce a sustained sodium deficit (hypovolaemia) to stimulate sodium appetite without removing the adrenal glands. These methods include chronic dietary sodium deprivation ***(Nachman and Pfaffmann, 1963; Wagman, 1963; Contreras and Hatton, 1975; Stricker et al., 1991)***, peritoneal dialysis ***(Falk and Lipton, 1967; Toth et al., 1987)***, colloid-induced hypovolaemia ***(Stricker and Jalowiec, 1970; Stricker,***

۱۹۸۱), and furosemide diuresis combined with short-term dietary sodium deprivation ***(Jalowiec, 1974; Wolf, 1982)***.

Appropriately, the appetite stimulated by sodium deficiency is highly specific for the taste of sodium salts ***(Richter and Eckert, 1938)***. Sodium-deficient rats consistently choose sodium over non-sodium salts (potassium, calcium, etc.), and the paired anion (chloride, acetate, etc.) has little or no effect on this preference ***(Nachman, 1962)***.

Sodium appetite is a highly motivated behavioural state. Sodium-deprived rats will perform increased amounts of work (bar pressing) for a salty reward ***(Wagman, 1963; Quartermain et al., 1967; McCutcheon and Levy, 1972)***. They will also sprint significantly faster down a runway leading to a tube of saline when they are salt-hungry ***(Zhang et al., 1984; Schulkin et al., ۱۹۸۵)***. Interestingly, the hedonic values of other, normally rewarding stimuli, such as sugar, appear to decrease in concert with the increasing appeal of sodium ***(McCance, 1936; Grippo et al., 2006; Morris et al., 2006)***. In fact, the normal preference for sugar over salt reverses during sodium deficiency, such that rats will ingest more saline than glucose or other sugary solutions ***(Smith et al., 1968; Nozaki et al., 2002)***. When given the choice,