THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 4

RESEARCH ARTICLE

Fractional Urate Excretion in Hyponatremia Differentiates Cerebral Renal Salt Wasting from Inappropriate Secretion of Antidiuretic Hormone

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OPEN ACCESS

PUBLISHED
30 April 2026

CITATION
Maesaka, JK., Imbriano, LJ., et al., 2026. Fractional Urate Excretion in Hyponatremia Differentiates Cerebral Renal Salt Wasting from Inappropriate Secretion of Antidiuretic Hormone. Medical Research Archives, [online] 14(4).

ISSN
2375-1924

ABSTRACT

Hyponatremia, defined as a serum sodium < 135 mmol/L, is the most common electrolyte abnormality in hospitalized patients. There has been an unresolved controversy over the prevalence of cerebral renal salt-wasting (CRSW). Internists consider the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) dominates the field of hyponatremia and cerebral renal salt wasting to be rare, while neurologists, neurosurgeons and critical physicians consider cerebral renal salt wasting to be common. Differentiating the two hyponatremic syndromes is difficult because of identical essential blood and urinary parameters and cannot be resolved by the ineffectual volume approach. We developed a pathophysiologic approach by determining fractional excretion of urate and response to isotonic saine infusions that not only simplified differentiating SIADH from CRSW but also simplified identification of other causes of hyponatremia such as a reset osmostat, psychogenic polydipsia, Addison's disease, prerenal azotemia with normal kidney function, heart failure, nephrosis, and cirrhosis. We also identified CRSW in 38% of hyponatremic patients in the general medical wards of the hospital, induced salt wasting in rats by infusing plasma of neurosurgical and Alzheimer patients, identified haptoglobin related protein without signal peptide (HPRWSP) from a normonatremic patient with subarachnoid hemorrhage and another with Alzheimer disease (AD) as the protein that causes cerebral renal salt wasting and possibly in patients with Alzheimer disease. We intend to develop HPRSWP as a biomarker of CRSW to simplify diagnosis of CRSW in hyponatremic and a growing list of normonatremic patients on first encounter to improve therapeutic outcomes.

Introduction

The assessment of patients with hyponatremia appears to have reached a state of unresolved controversies that are in part due to the inadequacy of the method used to evaluate patients with hyponatremia and errors and misconceptions that require clarification. Addressing the state of unresolved controversies might benefit from a brief comment on how conclusions are derived from variable degrees of credible data. A basic tenet of science is to generate data that will hopefully lead to worthy conclusions as typified by the frequent demand to "show me the data." However, it has become increasingly evident that the validity of conclusions depends on the validity of the data that generated the conclusions. Medical publications are filled with conclusions that are based on variable degrees of credible data. The evaluation of patients with hyponatremia has been handicapped by the volume approach, which has been in existence for over 50 years despite our awareness that we are unable to assess accurately the volume status of patients by usual clinical criteria.[1] Conclusions derived from the volume approach are, therefore, based on data of low credibility. When we came to this realization more than 40 years ago, we sought to generate pathophysiologic data of high credibility that will strengthen our conclusions.

Status of controversy over existence of cerebral renal salt-wasting

The longstanding controversy over the existence and prevalence of cerebral renal salt-wasting (CRSW) can be generalized to internists advocating the rarity of CRSW and neurosurgeons, neurologists and critical care physicians advocating a high prevalence of CRSW. The term cerebral salt-wasting appeared to be appropriate at that time because most studies were performed in patients with a variety of cerebral diseases. A major problem in identifying patients with CRSW is to differentiate them from those with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Both syndromes present with identical key clinical parameters such as the presence of cerebral disease, normal renal, adrenal and thyroid function, hyponatremia, hypouricemia, concentrated urine where urine osmolality (Uosm) is greater than plasma osmolality (Posm), usually high urinary sodium concentration (UNa) exceeding 30 mmol/L and high fractional excretion of urate (FEurate) exceeding 11%, table 1.

Clinical and laboratory findings common to SIADH and CRSW.

- Association with intracranial diseases
- Hyponatremia
- Concentrated urine
- Urinary [Na] usually> 30 mmol/l
- Normal renal/adrenal/thyroid function
- Non-edematous
- Hypouricemia, Increased fractional excretion of urate
- Only difference is volume status

Table 1. Table showing identical clinical and key laboratory findings that ate identical in SIADH and CRSW. A key difference is the volume expansion in SIADH and volume depletion in CRSW, It is essential to differentiate SIADH from CRSW patient from a volume depleted CRSW patient is essential to determine whether to water-restrict or administer salt and water , respectively

The volume approach could never determine whether the patient was volume expanded as in SIADH or volume depleted from CRSW. It is, therefore, extremely important to differentiate SIADH from CRSW because of diametrically opposite therapeutic goals of water-restricting water-loaded patients with SIADH or administering salt and water to volume depleted patients with CRSW. Internists cite retrospective and prospective studies of hyponatremic patients with subarachnoid hemorrhage from the same group which proposed the unlikely and undefined combination of SIADH and salt wasting in the same patient in retrospective studies and misdiagnosis of 49 hyponatremic patients as having SIADH when they actually had CRSW.[2-6] Those advocating a high prevalence of CRSW cite studies that resolved the single most important difference between SIADH and CRSW by determining blood volume by gold standard radioisotope dilution methods that utilized radio iodinated serum albumin and/or chromium 51 labeled red blood cells, tables 1 and 2.[7-9]

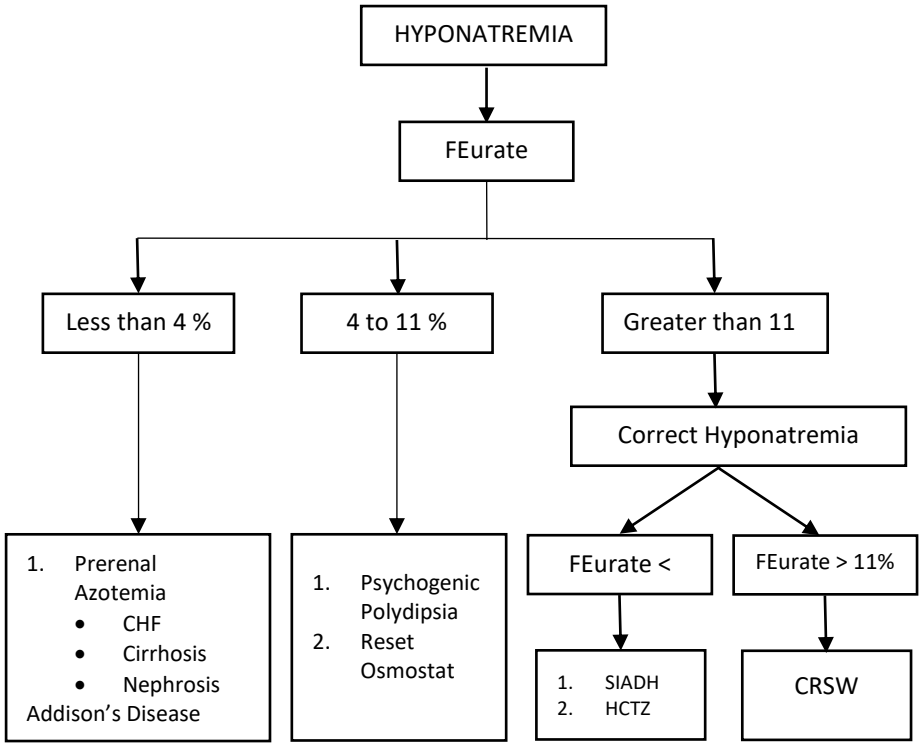
	Blood Volume ↓	Blood Volume ↑	UNa mmol/L
Nelson	10 (83 %)	2	41-203
Wijdicks	8 (89 %)	1	
Normonatremic	8 (67 %)	4	
Sivakumar	17 (100 %)	0	43-210

Table 2. Three studies in neurosurgical patients with hyponatremia and normonatremia where blood volumes were determined by radio isotope dilution methods. Note high percentage of volume depleted CRSW patients as compared to volume expanded SIADH patients and CRSW can occur in normonatremic patients.

As noted in table 2, three studies of hyponatremic and normonatremic neurosurgical patients report decreased blood volume in 10 (83 %), 8 (89 %), and 17 (100 %) as compared to increased blood volume in 2, 1 and 0 patients, respectively with 8 (67 %) decreased and 4 increased in normonatremic patients. UNa ranged from 41 to 203 and 43 to 210 mmol/L in 2 studies that were consistent with CRSW and SIADH. CRSW appears to be more common than SIADH in neurosurgical patients, table 2.[7-9]

How the Pathophysiologic Approach to Hyponatremia Was Conceived And Evolved

In 1980 we encountered a hyponatremic patient who presented with postural dizziness weakness and hilar adenopathy diagnosed to be adenocarcinoma. His blood pressures and pulses were 110/70 mmHg and 90 beats/min lying and 94/70 mmHg and 110 beats/min standing. His serum sodium was 120 mmol/L, uric acid 2.0 mg/dL, Uosm 323 mOsm/Kg, UNa 42 mmol/L, FEurate 26.5% (normal 4-11%) and normal renal, adrenal, and thyroid function. The postural hypotension and reflex tachycardia that brought on postural dizziness and weakness prompted the administration of 4,100 ml of isotonic saline on the first day and 3,700 ml on the second day which eliminated the postural hypotension and dizziness and increased serum sodium from 110 to 131 mmol/L while generating a dilute urine with a Uosm of 120 mOsm/kg.[10] A greater than 6 mmol/L increase in serum sodium and excretion of a dilute urine in a hyponatremic patient receiving isotonic saline were consistent with a volume depleted state such as CRSW that will be discussed later.[11] At this time, the staff began water- restricting the patient because the diagnosis of SIADH was made on the basis of an article which proposed that the coexistence of hypouricemia and hyponatremia was consistent with SIADH and differentiated SIADH from most other causes of hyponatremia.[12] The patient was water-restricted to <1000 ml per day for a diagnosis of SIADH. We felt that the postural hypotension and reflex tachycardia were very consistent with a volume depleted state that justified the liberal administration of isotonic saline. Moreover, the high UNa of 42 mmol/L was consistent with CRSW because a volume depleted patient with normal kidney function would be expected to conserve sodium where UNa would be around 10 mmol/L or less and FEurate to be < 4%, table 3.[1, 13]



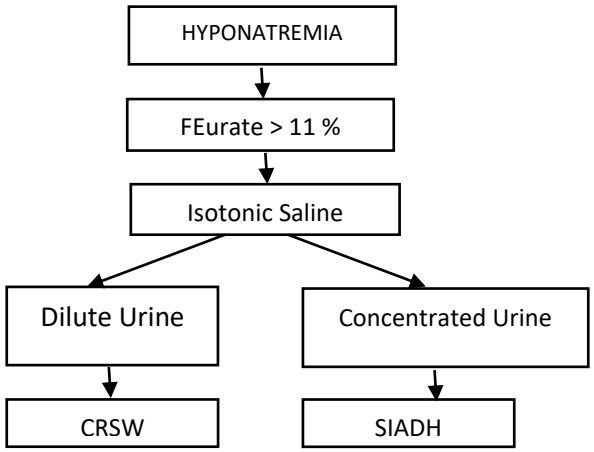


Table 3. Table showing low (< 4 %), normal (4-11%) and high (>11 %) FEurate in diseases causing hyponatremia. It also differentiates SIADH from CRSW by correcting the hyponatremia and seeing whether FEurate normalizes as in SIADH or remains increased as in CRSW and by infusing isotonic saline to see if it does not dilute the urine or correct the hyponatremia as in SIADH or dilute the urine and correct the hyponatremia as in CRSW

The diagnosis of renal salt-wasting was also difficult to entertain because it was called cerebral salt-wasting and the patient had no evidence of cerebral disease, including a normal CT scan of brain. We were unwilling to accept the diagnosis of SIADH because we were convinced, he was notably volume-depleted by being very symptomatic from the postural hypotension and reflex tachycardia that was not due to autonomic failure which would not have an increase in pulse rate on standing. We proposed continuing the water-restriction to correct the hyponatremia and show that FEurate will differentiate CRSW from SIADH by remaining persistently increased instead of normalizing as several publications had shown in SIADH, figure 1.[10,12,14-18]

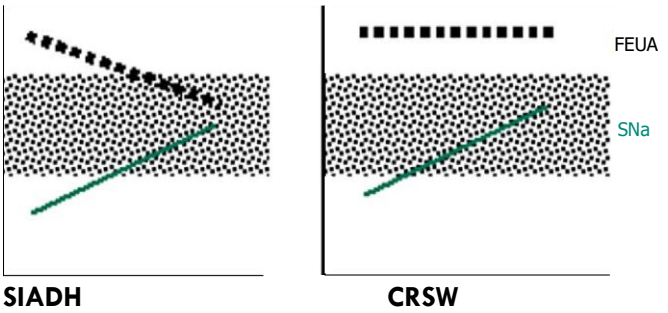


Figure 1. Figure showing increased FEurate in dotted lines being increased when hyponatremic in both SIADH and CRSW but normalizes FEurate in SIADH and remains increased in CRSW when serum sodium normalizes. Shaded rectangles represent normal values.

Water-restriction led to a weight loss of 6.8 kg with return of his postural hypotension with reflex tachycardia with dizziness, weakness, staggered gait, slurred speech, and somnolence. On this regimen serum sodium increased to 138 mmol/L when his Uosm was 980 mOsm/kg, which reflected maximum ADH stimulation due to the extreme volume depletion, and unexpectedly very high UNa of 181 mmol/L, FENa 0.70 % and FEurate 14.7 % that were dramatically higher than expected from a normal functioning kidney. It was consistent with renal salt-wasting. We felt that the persistently high FEurate after correction of hyponatremia might be a way to differentiate CRSW from SIADH. We demonstrated persistently high FEurate after correction of hyponatremia by water restriction in 4 other hyponatremic patients, one each with metastatic pancreatic carcinoma with ascites and peripheral edema, bronchogenic carcinoma of lung metastatic to brain, cryptococcal meningitis, and uncomplicated Hodgkin's disease. Of note is that 3 patients had no clinical evidence of cerebral disease, which was not used to advocate changing cerebral to renal salt wasting until a later date as the data to prove renal salt-wasting were not strong enough to advocate changing the term cerebral to renal salt wasting. [10]

FEurate determines the percentage excretion of the urate that is filtered at the glomerulus. Urate is transported exclusively in the proximal tubule by reabsorbing and secretory transporters before being excreted in the final urine. FEurate can be determined by collecting blood and urine at the same time and calculating FEurate by the following formulae:

$$FE\ urate\ in\ \% = \frac{urine\ urate}{serum\ urate} \div \frac{urine\ creatinine}{serum\ creatinine} \times 100$$

Acquired immunodeficiency syndrome (AIDS)

We initiated studies on hyponatremia at a time when hypouricemia and its relationship with hyponatremia was being investigated.[12] We performed a chart review of 93 patients and prospectively studied 23 patients with AIDS. Hypouricemia, defined as a serum urate < 3 mg/dL, was found in 11 of the 93 and 10 of the 23 patients. Eight of the 23 patients had central venous pressures (CVP) < 1 cm with postural hypotension and reflex tachycardia, 6 were hypouricemic and all 8 had increased FEurate at a mean of 18.9 %. The presence of low CVPs, postural hypotension with reflex tachycardia and high UNa were highly consistent with an underlying renal salt-wasting as volume depleted patients with normal kidney function would be expected to have lower UNa around 10 mmol/L or less and FEurate < 4 % as noted in our insight case above, table 3.[13]

Demonstration of natriuretic activity in plasma of patients with neurosurgical and Alzheimer diseases

One of us, JM, spent 5 years exclusively in a renal micropuncture laboratory where cause and effect relationships were under constant consideration. We were aware that CRSW was considered to be a common syndrome among neurosurgeons, neurologists, and critical care physicians. Many neurosurgical patients with or without hyponatremia and high UNa were found to be volume depleted as reviewed earlier, table 2.[7-9] We proposed that a circulating natriuretic factor might be inducing CRSW in these patients. We injected mainly normonatremic plasma of 21 patients with different neurosurgical diseases and 19 patients with Alzheimer disease (AD) because they were hypouricemic with increased FEurate.[19, 20] We decided to investigate those with advanced AD with mini mental state examination scores (MMSE) less than 12. Hyponatremia was never a prerequisite to study patients with suspected CRSW, although the high FEurate and normonatremia were highly consistent with CRSW. We did not expect patients with AD to have hyponatremia because of their reduced water intake due to age-related loss of thirst and dementia. Because urate is transported exclusively in the proximal tubule, we hypothesized that a circulating plasma natriuretic factor will have its major effect in the proximal tubule.[21,22] We determined FELithium because lithium was known to be transported on a 1 to 1 basis with sodium in the proximal tubule and was thus used as a marker of sodium transport in the proximal tubule.[23] Mean FEurate was significantly higher in the patients with Alzheimer and neurosurgical diseases as compared to age and gender-matched controls, being 6.6 % and 6.9 % in controls and 9.7 % and 14.0 %, respectively.[19,20] The infusion of plasma from patients with AD and neurosurgical diseases increased FENa from age and gender-matched controls of 0.33 to 0.63 % and 0.30 to 0.59 % and FELithium from 27.2 to 41.7 % and 22.3 to 36.6 %, respectively. There were no changes in blood pressure or glomerular filtration rates (GFR).[19,20] These studies provided convincing evidence for the existence of a natriuretic factor that might be inducing CRSW in patients with AD and neurosurgical diseases. Only 1 patient with AD had hyponatremia, suggesting that CRSW probably occurs in many patients without hyponatremia. We studied patients with advanced AD with MMSE that ranged from 0 to 12 and as noted in figure 2, an already increased FELithium increased progressively as MMSE decreased from 12 to 0. Because there was a dose-depending increase in FELithium, blood levels of the natriuretic Factor must have been increasing as the patient became demented or becoming more volume depleted, figure 2.[20] Protein analysis in 1993 had not developed sufficiently for us to identify the factor.

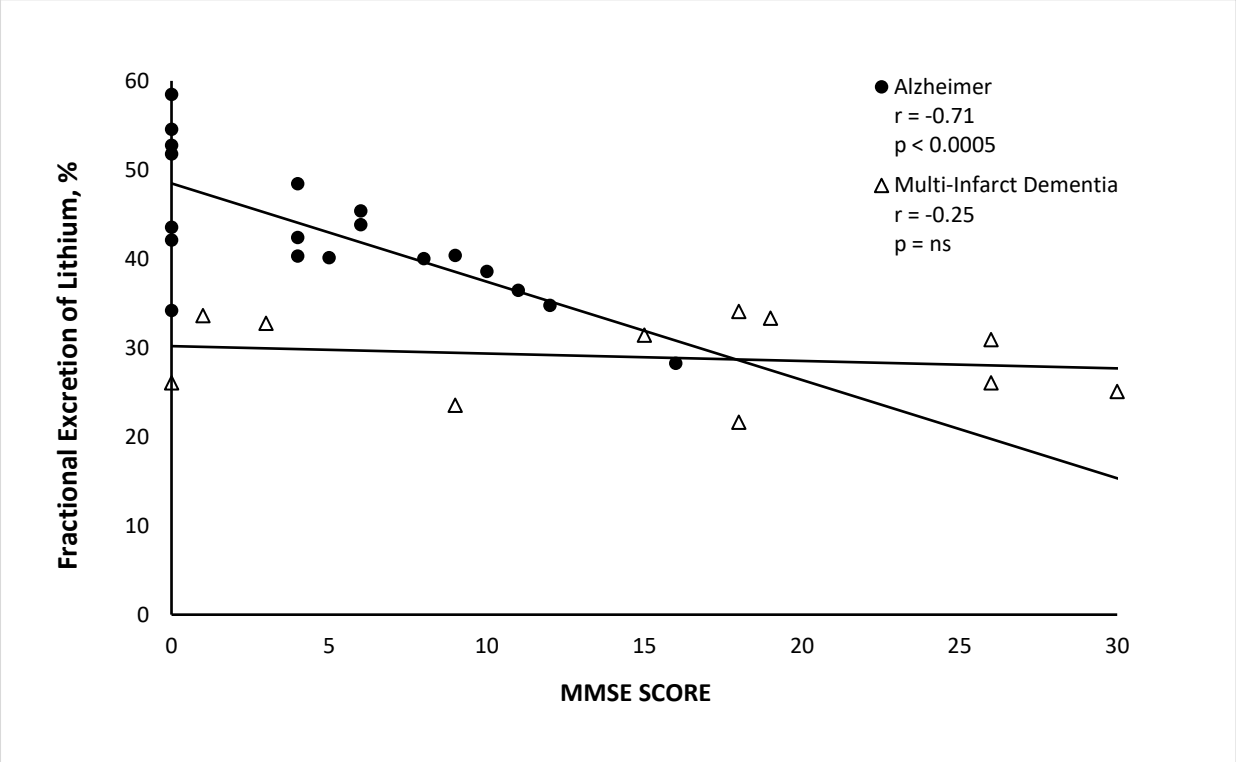


Figure 2. Graph showing increasing FELithium as MMSE decreases from 12 to 0. Because FELithium increases with increasing dose of HPRWSP, the increasing FELithium below an MMSE of 12 suggests that the patients are getting more volume depleted as they become more demented.

Pathophysiology of CRSW

Initiation Phase

There are many comorbidities that activate cytokine production such as IL 6 that increase production of acute phase reactants such as haptoglobin related protein without signal peptide (HPRWSP) as well ADH.[24-26] During the initiation phase, the amount of sodium and water excretion increases abruptly to a point where sodium and water excretion is greater than input to place the subject in a negative sodium balance to decrease extracellular volume. The volume depletion can be significant enough to decrease blood pressure and induce hemodynamic instability to a point where they will require infusions of isotonic saline. Under most conditions the volume depletion is mild without inducing hemodynamic instability but may be associated with subtle symptoms such as fatigue and weakness as they move into the equilibrated stage where sodium input matches sodium output at a lower blood volume.

Equilibrated Phase

The patient cannot remain in a continuous state of negative sodium balance because it would eliminate all the available sodium from the body. This would not be physiologically possible because there is an escape from the salt-wasting which we termed salt-wasting escape.[27] During the equilibrated phase, the volume depletion induces hemodynamic, humoral, and neural mechanisms that reduce GFR, stimulate renin, angiotensin, aldosterone, and ADH production and increase sodium and water reabsorption to counteract the salt wasting and sodium imbalance and reach an equilibrated state where sodium and water input matches output. The concept of escape has been noted as mineralocorticoid escape, pitressin escape in SIADH, diuretic escape, idiopathic edema escape that has been recently reviewed.[27-30] In this volume-depleted and equilibrated state the patient will have symptoms that depend on the magnitude of the salt-wasting and sufficient salt intake to maintain an equilibrated state at an acceptable extracellular volume. The increase in salt and water intake can only be estimated and is probably incomplete as the increase in urinary output, especially nocturia, reduces quality of life. The goal is to develop an inhibitor to the natriuretic factor that will eliminate salt-wasting.

Utilization of FEurate to identify other causes of hyponatremia

Reset Osmostat

While determining FEurate in hyponatremic patients, we encountered a puzzling patient with a normal FEurate of 4-11%, who spontaneously excreted a dilute urine that was highly consistent with a reset osmostat (RO). We investigated 14 hyponatremic patients with a normal FEurate between the ages 50-89 years. All had normal kidney function with creatinine ranging from 0.3 to 1.09 mg/dL, UNa exceeding 30 mmol/L except for 2 patients with UNa <20 mmol/L, the duration of RO was usually <1 year but 3 had it for 3 years and 3 had it for 9-12 years. Five had spontaneously excreted dilute urines where Uosm was < Posm and 6 had a normal water loading test to support the diagnosis of RO.[31] RO appears to be a commonly encountered syndrome which can be diagnosed simply by demonstrating a normal FEurate and spontaneously excrete a dilute urine. There is no need to perform a water-loading test. RO appears

to be a common syndrome that makes up about 30% of hyponatremic patients.[32,33] The normal FEurate in psychogenic polydipsia can be simply differentiated from RO by the voluminous water intake and urine production.[34] RO should not be considered a subtype of SIADH but a separate syndrome where ADH responds appropriately to volume and osmolar stimuli, but at a lower osmolality. RO is initiated by multiple comorbidities and are of short duration after resolution of the comorbid condition but may have unidentified comorbidities that can exceed 10 years. Because the extent of the hyponatremia in patients with RO is dependent on how low the osmostat has been reset, these patients are protected from severe, symptomatic hyponatremic episodes. Treatment is to water-restrict these patients as in SIADH.[31]

Addison's disease

A 51-year-old female presented with malaise, anorexia and weight loss with a serum sodium of 119 mmol/L, potassium 5.4 mmol/L, blood urea nitrogen 19 mg/dL, creatinine 0.6 mg/dL, uric acid 4.1 mg/dL, Uosm 621 mOsm/kg, UNa 140 mmol/L, and FEurate very low at 1.4 %. She was hyperpigmented, blood pressure 95/60 mmHg with postural hypotension and reflex tachycardia suggestive of significant volume depletion. The diagnosis of Addison's disease was confirmed by a low cortisol level of 2.8 ug/dL and increased adrenocorticotrophic hormone of 865 pg./mL. She received large volumes of isotonic saline which led to dilution of the urine with a Uosm of 140 mOsm/kg with undetectable levels of ADH that is seen in patients with CRSW but not SIADH. Her hyponatremia corrected and she was discharged on fludrocortisone and hydrocortisone.[35] The diagnosis of Addison's disease is difficult to make because of the vague presentations which often lead to a diagnosis being frequently made at a time of adrenal crisis.[36] They are more frequently hyponatremic than being hyperkalemic where the reduced mineralocorticoid decreases distal tubular sodium transport to increase urinary sodium and water excretion to induce volume depletion. This is distinctly different from CRSW where sodium transport is reduced in the proximal tubule to account for the differences in FEurate. The intact proximal tubule in Addison's disease will increase solute reabsorption in the proximal tubule to reduce FEurate that is similar to patients who become volume depleted from vomiting or diarrhea with intact kidney function that leads to a similar prerenal state with decreased FEurate as in Addisons's disease, Table 3. The low FEurate in any hyponatremic patient must consider Addisons's disease that will facilitate identifying patients with Addison's disease.

Psychogenic polydipsia

Psychogenic polydipsia is an uncommon cause of hyponatremia that can be readily identified by the voluminous intake of water and excretion of large volumes of dilute urine. It causes hyponatremia when water intake exceeds the ability of the kidneys to excrete free water. The normal FEurate can be readily differentiated from RO by the large volumes of ingested water and excretion of urine. Treatment is to seek psychiatric assistance and limit water intake.[34]

Value of determining FEurate in a complicated case

A 71-year-old male with advanced large B-cell lymphoma presented with bilateral leg edema over a 6-week period, 9.1 kg weight gain, postural hypotension with reflex tachycardia with lying blood pressure of 95/65 mmHg and pulse rate of 109 beats/min that decreased to 76/56 mmHg and pulse rate 138 beats/min on standing. He was also noted to have ascites and pleural effusion. His serum sodium was 115 mmol/L, creatinine 0.9 mg/dL, blood urea nitrogen 22 mg/dL, uric acid 6.8 mg/dL, Uosm 308 mOsm/kg, UNa 10 mmol/L and FEurate increased at 22.7%. There was no evidence of cerebral disease. The most important findings of this complicated case were the high FEurate of 22.7 % (normal 5-11 %) and postural hypotension with reflex tachycardia that were consistent with a volume depleted state due to CRSW despite the absence of cerebral disease. The low UNa of 10 mmol/L was consistent with a low salt intake and not due to heart failure where FEurate would be much lower at < 4 %. The volume depleted state was possible because the edema of both lower extremities was diagnosed and later proven by computed tomography to be due to complete obstruction of the inferior vena cava. Isotonic saline infusions diluted the urine to 140 mOsm/kg 14 hours later when plasma ADH was undetectable as expected in hyponatremic CRSW patients receiving isotonic saline.[37] On this regimen his serum sodium increased by 5 mmol/L over a 5-hour period which required 5 % dextrose in water to slow the rate of sodium correction to less than 8 mmol/L/24 hours to prevent osmotic demyelination.[38] The presence of bilateral lower extremity edema, ascites, pleural effusion, decreased cardiac output and UNa of only 10 mmol/L were construed by physicians caring for the patient to be due to heart failure that would create a prerenal azotemia where there is significant renal conservation of solutes as evidenced by a UNa of 10 mmol/L but not the high FEurate. We cautioned the use of a diuretic such as furosemide because the natriuretic protein that we demonstrated in the plasma of patients with CRSW had a significant increase in lithium excretion which estimates the amount of sodium being presented to the distal tubule which was reabsorbed by the distal nephron as noted in our rat studies.[19,20] The patient was given intravenous furosemide which induced a profound diuresis that required large volumes of isotonic saline to maintain hemodynamic stability. This case illustrates the inadequacy of the volume approach to hyponatremia. This difficult case required a pathophysiological approach that identified the importance of the postural hypotension with reflex tachycardia that indicated the presence of a volume depleted state and increased FEurate that were consistent with CRSW and not heart failure. The reduction in cardiac output with ascites, pleural effusion and UNa of 10 mmol/L would reduce FEurate to < 4% and isotonic saline infusion would not have diluted the urine in heart failure.[13] The UNa of 10 mmol/L was misleading and was pathophysiologically consistent with a reduction in appetite and a diet that was low in sodium. As will be discussed later, determinations

of UNa in hyponatremic patients have much less value than previously espoused.

Clarification of the effect of saline Infusions on FEurate

There is some controversy over the effects of saline infusion on FEurate that needs clarification. As noted in table 4, infusion of isotonic saline only modestly increased FEurate from a baseline of 7.98 and 5.0 % to 9.76 and 5.8 % when FENa increased from a baseline of 1.04 and 1.6 to 4.43 and 8.2 %, respectively. The FEurate of 9.76 and 5.8 % fall within accepted normal ranges for FEurate after reaching very high FENa that are rarely seen clinically, suggesting that saline has a meager effect on FEurate.[39,40] This was contested by others who cited a study where massive doses of hypertonic saline increased FENa to a clinically unseen level of 14.5 % and FEurate of 18.7 %, table 4. (41,42) The mean FENa was only 0.68 when the mean FEurate was 18.7 % in our salt-wasting patient.[37]

	FE Na (%)		FE Urate (%)	
	Control	**Exp**	**Control**	**Exp**
Isotonic	1.04	4.43	7.98	9.76
	1.6	8.2	5.0.	5.8
Hypertonic	2.9	18.6	5.4	12.1
	1.4	14.5	12.5	18.7
Hypotonic	1.1	6.1	4.0	7.3

Table 4. Effect of Isotonic, Hypertonic, and Hypotonic saline infusions on FENa and FEurate in normal human subjects

There are other credible data that add additional insights into the effect of saline infusions on FEurate. While the infusion of isotonic saline leads to small increases in FEurate that remain within established normal levels in normal humans, FEurate in a volume depleted renal salt-waster has been shown to increase to abnormally remarkably high levels.[39,40] Isotonic saline infusion at a rate of 120 ml/hour in a patient with unequivocal evidence of CRSW has shown significant increases in FEurate from a baseline elevated level of 27.5 to 42, 43, 46.5, 63, 58 and 49 % when FENa was 0.68, 0.65, 0.78, 1,35, 1,60 and 1.80 %, respectively over a 45-hour period, figure 3a. [37] Comparing the FENa attained by isotonic saline infusions in a salt-wasting patient exemplifies the extent to which normal subjects were extensively volume expanded with FENa reaching 8.3, 14.5 and 18.6 % in the saline infusion studies listed in table 4.[39-41] These data also suggest that in contrast to a patient with SIADH where isotonic saline infusion did not increase FEurate even after infusing hypertonic saline to correct the hyponatremia (figure 3b) isotonic saline infusion in a renal salt-waster will not only increase FENa and FELithium but significantly increase FEurate to a point where it might be an additional method to differentiate SIADH from CRSW.[35]

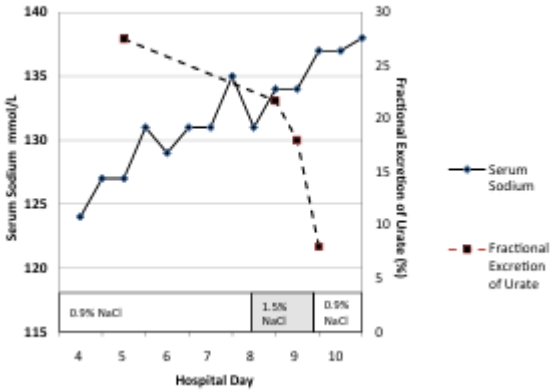


Figure 3a. Graph showing how isotonic failed to correct the hyponatremia in SIADH. Infusing hypertonic saline gradually increased serum sodium and decreased FEurate to normal.

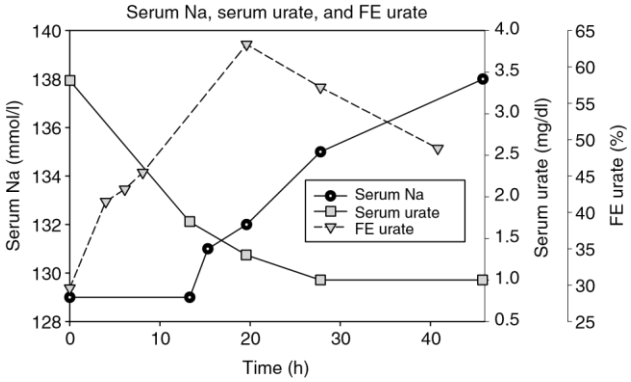


Figure 3b. Graph shows how infusion of isotonic saline gradually corrected the hyponatremia in closed circles while dramatically increasing FEurate in open triangles from a high of 31 % to a maximum of 64 % in a patient with CRSW.

Differentiating SIADH from CRSW by differences in response to isotonic saline infusions

We accumulated sufficient data to utilize FEurate to identify many causes of hyponatremia that was dominated by being able to differentiate SIADH from CRSW, table 3. [10,31,34,35,37,45] CRSW was called cerebral salt-wasting and was held in some disrepute, especially among internists. There is some justification for this sentiment because the original publication of cerebral salt wasting in 1950 failed to prove salt-wasting in 3 patients with cerebral diseases that included acute encephalitis, subarachnoid hemorrhage, and bulbar poliomyelitis as previously reviewed.[43,44]

We encountered a patient with a pneumonia and normal cerebral function who presented with hyponatremia. Increased FEurate and increased aldosterone who received isotonic saline infusion for 48 hours. His urine diluted to 178 mOsm/kg 26 hours after initiation of isotonic saline infusion with correction of hyponatremia to 138 mmol/L at 48 hours when the FEurate remained increased to confirm the diagnosis of CRSW. He had a normal water-loading test after being volume-repleted with isotonic saline to confirm further the absence of SIADH.[45]

This pivotal case reminded us of comments made by Bartter in 1957 and later by others that large volumes of isotonic saline infusions do not correct the hyponatremia of SIADH.[45] We decided to add another pathophysiologic phenomenon to differentiate SIADH from CRSW. Because SIADH and CRSW have identical blood and urine findings as noted in table 1, we determined blood volume by radioisotope dilution methods in addition to plasma renin and aldosterone levels to differentiate SIADH from CRSW with greater certainty. The patient was a 76-year-old female with a hip fracture and no evidence of cerebral disease who was hyponatremic, increased FEurate of 29.6 % UNa of 6 mmol/L, decreased blood volume, and increased renin, aldosterone and ADH levels that confirmed the diagnosis of CRSW. As noted in figure 4, Isotonic saline infused at a rate of 125 ml/h progressively diluted the urine to 152 mOsm/kg at 13 hours when plasma ADH was undetectable. Serum sodium increased to 138 mmol/L at 48 hours when the FEurate of 48 % was consistent with CRSW and not SIADH, figure 3a, 3b.[37] Interestingly the puzzling UNa of 6 mmol/L was explained by being water-restricted for an erroneous diagnosis of SIADH for 10 days when she lost her appetite and reduced salt intake to decrease UNa. Of note is the low atrial natriuretic peptide of 35 pg./ml that is often cited as a possible cause of CRSW.[37]

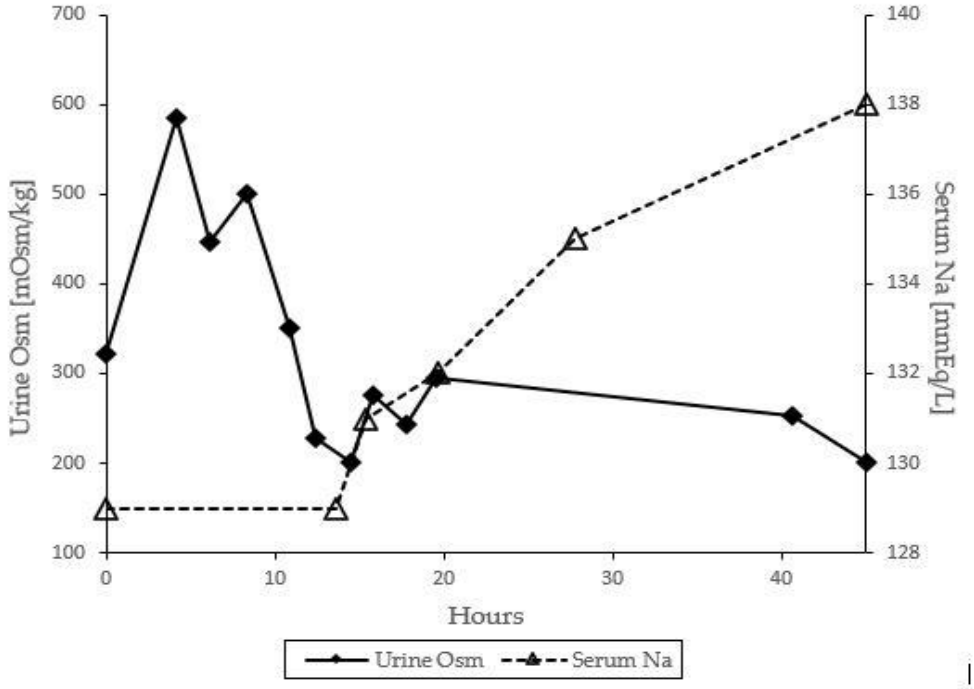


Figure 4. Graph showing isotonic saline infusion inducing excretion of dilute urines or removing pure water from body to correct the hyponatremia in a hyponatremic patient with low blood volume and increased plasma renin, aldosterone and ADH levels to prove CRSW. Plasma ADH was undetectable when urine was dilute 13 hours after initiation of isotonic saline infusions to prove how the infusion of isotonic saline removed the more potent volume stimulus to ADH secretion and allowed the coexistent hypoosmolality of plasma to inhibit ADH secretion and dilute the urine.

The second patient was a 76-year-old male who was admitted for a recurrence of his glioblastoma. His serum sodium was 122 mmol/L, creatinine 0.7 mg/dL, UNa 161 mmol/L, FEurate increased at 21.2 %, Uosm 534 mOsm/kg, increased blood volume and low renin and aldosterone levels that were consistent with a diagnosis of SIADH. He received Isotonic saline infusion at a rate of 75 ml/hour for 110 hours. The Uosm never reached dilute levels throughout this period with no correction of his hyponatremia figure 5.[45]

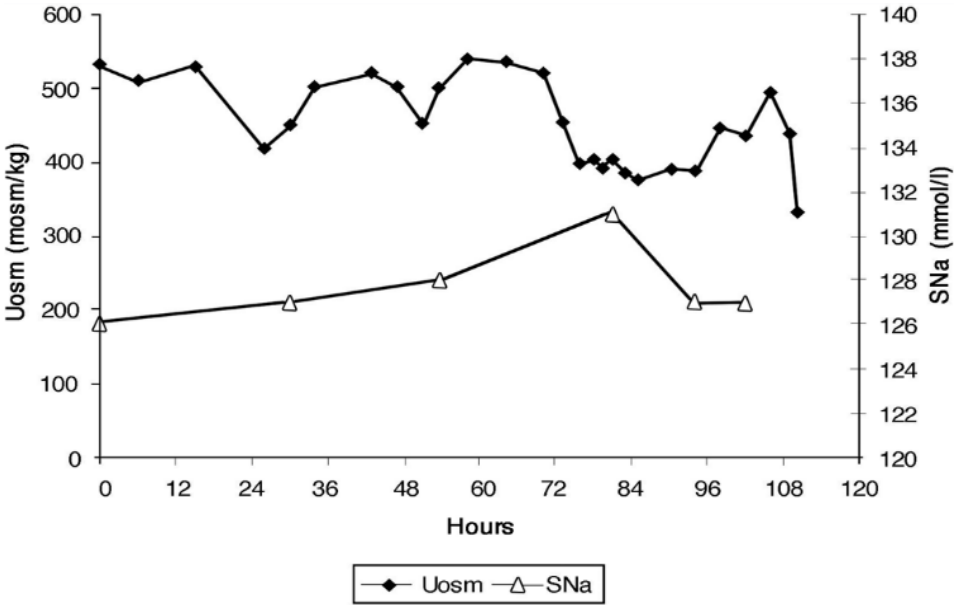


Figure 5. Graph demonstrating the failure of isotonic saline infusion failing to dilute the urine or correct the hyponatremia in an SIADH patient with increased blood volume and decrease aldosterone. Identical findings were demonstrated in a second SIADH patient with increased blood volume and decreased aldosterone levels, data not shown. Note distinct difference in response to patient with proven CRSW in figure 4.

A second patient with SIADH was a 75-year-old female with autonomic failure who was admitted with a bad flu and hyponatremia with a serum sodium of 131 mmol/L creatinine 0.6 mg/dL, Uosm 303 mOsm/kg, UNa 99 mmol/L, FEurate 16.7 %. Plasma renin 0.29 ng/ml/h, aldosterone 4.3 pg./dL and a 3% increase in blood volume. She also failed to dilute the urine or correct the hyponatremia after 48 hours of isotonic saline infusion.[45] These infusion studies demonstrate the appropriate and inappropriate response to ADH secretion in CRSW and SIADH, respectively. In CRSW, ADH secretion is controlled by the more potent volume stimulus as compared to the less potent osmolar stimulus of ADH secretion.[47] ADH levels will, thus, remain increased to maintain the hyponatremic hypo-osmolar state as long as the subject is hypovolemic.[46] Isotonic saline infusions will remove the more potent volume stimulus to ADH secretion and permit the coexisting hypo-osmolality to inhibit ADH secretion to increase free water excretion and ultimate correction of the hyponatremia, figure 4. In contrast, because ADH levels are unresponsive to the volume and osmolar stimuli in SIADH, ADH levels remain increased during the period of isotonic saline infusions that maintain the hypertonic urine and hyponatremia, figure 5.[45]

High prevalence of RSW in hyponatremic patients from general medical wards of hospital: Value of determining FEurate and response to isotonic saline infusions

We have accumulated sufficient data on studying a broad range of patients with hyponatremia as noted by the algorithm, table 3. We decided to perform a labor-intensive funded study of hyponatremic patients from the general medical wards of the hospital. Patients with serum sodium < 134 mmol/L were included in the study and those with serum creatinine > 1.5 mg/dL and those with cirrhosis of liver, congestive heart failure and nephrosis were excluded from the study.[33] The protocol emphasized determinations of FEurate to determine the cause of hyponatremia and to correct the hyponatremia of those with increased FEurate > 11% to see if FEurate normalizes or remains increased as seen in SIADH and CRSW, respectively. Patients with baseline high FEurate of >11% were administered isotonic saline to determine whether they diluted their urine or not. Those who diluted their urine were considered to have CRSW and those who failed to excrete dilute urines were considered to have SIADH. Of the 62 hyponatremic patients 17 (27%) had SIADH, 5 normalized FEurate after correcting their hyponatremia and 11 failed to dilute their urine while receiving isotonic saline infusions. Nineteen (31%) had a reset osmostat based on all having normal FEurate that ranged between 4 and 11% and 8 had spontaneously excreted dilute urines to meet the criteria for RO. It is interesting to note that the prevalence of RO matches that reported by others.[32] Twenty-four (38%) had CRSW based on 11 demonstrating persistence of an elevated FEurate that exceeded 11% after correcting their hyponatremia, 19 had saline-induced dilution of urine where Uosm was lower than Posm with 2 showing undetectable levels of plasma ADH when the urine was dilute. Ten required replacements of isotonic saline with 5% dextrose in water to prevent increasing serum sodium by more than 8 mmol/L over 24 hours to prevent osmotic demyelination.[38] Of great interest was the 21 of 24 patients who had no evidence of clinical cerebral disease that supported our proposal to change the term cerebral to renal salt-wasting.[48] Baseline UNa of <20 mmol/L was noted in 10 of the 24 patients with CRSW as compared to 5 of the 19 patients with RO and 2 of the 17 patients with SIADH. These data provide very credible data to reduce the importance of UNa in making the diagnosis of RSW or SIADH.[33] Because most or all the patients included in this report were in an equilibrated state where input of sodium matches sodium excretion, the lower UNa in so many patients with CRSW suggest that the degree of volume depletion had reduced appetite and decreased salt intake in these patients.[33]

Haptoglobin related protein without signal peptide as natriuretic factor in CRSW

We demonstrated natriuretic activity in mainly normonatremic plasma of 21 patients with different neurosurgical diseases and 19 patients with advanced Alzheimer's disease (AD) with MMSE of 0 to 12 in 1993.[19,20] The limitations of protein analysis at that time prevented us from identifying the protein until 2024 when protein analysis readily identified the protein as HPRWSP. The physiological effects of HPRWSP were identical to the studies performed in 1993 with increases in FENa and FELithium. HPRWSP was identified in normonatremic serum from 2 salt-wasting patients, one with a subarachnoid hemorrhage and another with AD.[49] It is interesting to note that HPR with signal peptide had no natriuretic activity. We are in the process of developing an assay that will be able to determine HPR levels with and without the signal peptide since HPR with an attached signal peptide has been reported in the blood of patients.[50] Based on the demonstration of natriuretic activity in the plasma of patients with neurosurgical diseases and AD in rats, HPRWSP should eventually develop into a reliable biomarker of CRSW in hyponatremic and a potentially large list of normonatremic patients. Since there appears to be a parallel relationship between haptoglobin and HPRWSP in blood, the report of haptoglobin 2-2 to be increased in the plasma of salt wasting patients associated with a subarachnoid hemorrhage would support such a conclusion.[51]

Conclusion

The goal of this manuscript was to review the transition from an ineffective volume approach to a pathophysiologic one that identified many of the causes of hyponatremia. We point out the major overlapping findings in SIADH and CRSW created a diagnostic dilemma that required solutions to its differentiation because of diametrically opposite therapeutic goals. We encountered a hyponatremic patient with all the features of SIADH except for significant postural hypotension and reflex tachycardia that was consistent with CRSW. We utilized a persistent increase in FEurate after correction of hyponatremia that contrasted to SIADH where FEurate normalized after correction of hyponatremia. We duplicated this persistent increase in FEurate in other hyponatremic patients that suggested CRSW. We also differentiated SIADH from patients with CRSW by differences in response to isotonic saline infusions. We used FEurate determinations and responses to isotonic saline infusions in a study of 62 hyponatremic patients in the general medical wards of the hospital and unexpectedly found a high prevalence of CRSW in 24 (38%) patients. Twenty-one of the 24 patients had no clinical evidence of cerebral disease which supported our proposal to change cerebral to renal salt-wasting. Ten patients had baseline urine sodium concentrations of < 20 mmol/L which undervalued determinations of urinary sodium concentration in the work up of hyponatremic patients. The high morbidity and mortality associated with hyponatremia may in part be iatrogenic these dehydrated patients were water-restricted for an erroneous diagnosis of SIADH.

We then injected rats with the plasma of patients with different neurosurgical diseases and Alzheimer's disease and found identical natriuretic activity that was identified as HPRWSP. Future studies intend to identify a new syndrome of CRSW in Alzheimer's disease, develop HPRWSP as a biomarker of CRSW in hyponatremic and a growing list of normonatremic patients with CRSW. Successful development of HPRWSP as a biomarker of CRSW will permit us to identify patients with CRSW on first encounter when appropriate therapeutic intervention will improve clinical outcomes. HPRWSP can also serve as a potent proximal diuretic when combined with a distal diuretic to more effectively mobilize the edema in heart failure. There are many misconceptions in the literature that was only partially covered in this manuscript.

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