Hyponatremia in patients with central nervous system disease: SIADH versus CSW

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The syndromes of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW) are two potential causes of hyponatremia is patients with disorders of the central nervous system. Distinguishing between these two causes can be challenging because there is considerable overlap in the clinical presentation. The primary distinction lies in the assessment of the effective arterial blood volume (EABV). SIADH is a volume-expanded state because of antidiuretic hormone-mediated renal water retention. CSW is characterized by a contracted EABV resulting from renal salt wasting. Making an accurate diagnosis is important because the treatment of each condition is quite different. Vigorous salt replacement is required in patients with CSW, whereas fluid restriction is the treatment of choice in patients with SIADH. Although most physicians are familiar with SIADH, they are much less familiar with CSW. This review emphasizes the need for CSW to be included in the differential diagnosis of hyponatremia in a patient with central nervous system disease. Distinguishing between these two disorders is of crucial importance because therapy indicated for one disorder but used in the other can result in negative clinical consequences.

Hyponatremia is a common electrolyte disorder in the setting of central nervous system (CNS) disease and is often attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This syndrome is characterized by hyponatremia in the setting of an inappropriately concentrated urine, increased urine Na^+ concentration and evidence of normal or slightly increased intravascular volume. By contrast, there are patients with intracranial disease who develop hyponatremia with similar characteristics, but differ in that there is clinical evidence of a contracted extracellular fluid (ECF) volume. This form of hyponatremia is caused by excessive renal Na^+ excretion, resulting from a centrally mediated process, and is termed cerebral salt wasting (CSW).

The concept of a CSW syndrome was first introduced by Peters and colleagues in 1950 in a report describing three patients with neurological disorders who presented with hyponatremia, clinical evidence of volume depletion and renal Na^+ wasting, without an obvious disturbance in the pituitary–adrenal axis [1]. These findings were subsequently confirmed in additional patients with widely varying forms of cerebral disease [2,3]. In these initial reports it was theorized that cerebral disease could lead to renal salt wastage and subsequent depletion of ECF volume by directly influencing nervous input into the kidneys. However, with the subsequent description of SIADH by Schwartz *et al.* [4], the clinical entity of CSW became viewed as either an extremely rare disorder or a misnomer for what was truly SIADH. Only in recent years has CSW been thought of as a distinct entity. This recognition has been particularly striking in the field of neurosurgery, where it is viewed by some as a more common disorder than SIADH [5,6].

The distinction between these two disorders is of considerable clinical importance given the divergent nature of the treatments. Fluid restriction is the treatment of choice in SIADH, whereas the treatment of CSW comprises vigorous Na^+ and volume replacement. Figure 1 illustrates how CSW and SIADH fit into the differential diagnosis of hyponatremia.

SIADH is a volume-expanded state

The primary pathogenic mechanism underlying SIADH is excessive antidiuretic hormone (ADH) release causing renal water reabsorption and resulting in expansion of the ECF volume. Evidence for a volume-expanded state in SIADH initially came from studies of normal individuals given exogenous pitressin [7]. In these experiments, administration of pitressin resulted in an abrupt decrease in urine volume and increase in urine osmolality. The water retention produced by this antidiuretic effect resulted in an increase in body weight and a reduction in the serum Na^+ concentration. After several days of pitressin administration, a large increase in urine Na^+ and Cl^- excretion was noted, which was triggered by the progressive expansion of total ECF volume, as reflected by the increase in body weight. If fluid intake was kept low during the administration of pitressin, body weight remained unchanged and urine electrolyte excretion did not increase. These findings were reproduced when the first clinical cases of SIADH were described in two patients with bronchogenic carcinoma [4].

During administration of vasopressin, when water

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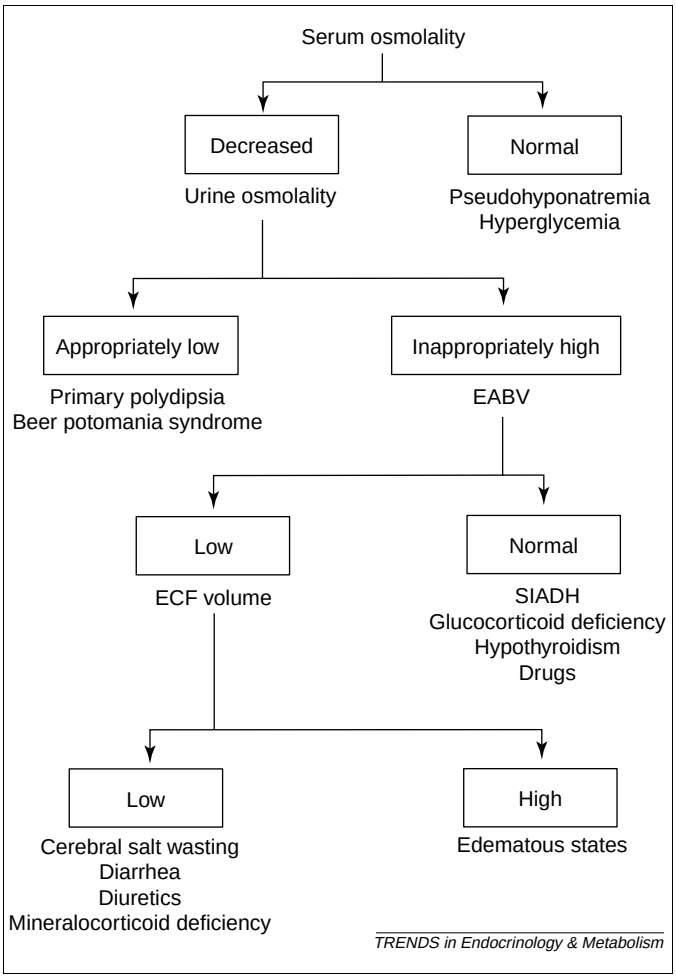

Fig. 1. The general approach to the hyponatremic patient. Cerebral salt wasting (CSW) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) can be differentiated most effectively by assessment of the volume status of the patient. Abbreviations: ECF, extracellular fluid volume; EABV, effective arterial blood volume.

intake is not limited and body weight is allowed to increase, a steady state is eventually reached in which urine Na^+ excretion stabilizes and is equal to dietary Na^+ intake. At this time, severe dietary Na^+ restriction will lead to excretion of a urine that is essentially Na^+ free, whereas administration of a large isotonic Na^+ load is followed by rapid and almost quantitative urinary excretion of the infused solute [8]. The establishment of normal renal Na^+ handling in spite of a decreased serum Na^+ concentration is a characteristic feature of SIADH.

In SIADH, expansion of ECF volume is not typically accompanied by overt signs of hypervolemia, such as edema or distended neck veins, because only one-third of retained water is distributed in the ECF space. Nevertheless, modest expansion of the intravascular volume results in increased glomerular filtration rate (GFR) and increased renal plasma flow. In addition, the volume expansion leads to decreased proximal Na^+ reabsorption and urinary Na^+ excretion is increased and equal to dietary Na^+ intake. Substances such as uric acid and urea nitrogen, which are reabsorbed proximally in concert with Na^+, also tend to be reduced because of diminished proximal reabsorption.

CSW is a volume-depleted state

The newly found appreciation for the diagnosis of CSW can be traced to reports in which blood and plasma volume were found to be decreased in patients who met the traditional laboratory criteria for SIADH. Nelson *et al.* [9] studied 12 unselected hyponatremic neurosurgical patients with subarachnoid hemorrhage, intracranial aneurysm and head injury. On an average, hyponatremia developed on the tenth day of illness and was associated with increased urine Na^+ concentrations ($>25\ mEq\ l^{-1}$) and an inappropriately concentrated urine. As compared with neurosurgical patients without intracranial disease, ten of the 12 patients had significant reductions in plasma volume and total blood volume. These same investigators then examined Na^+ balance in a monkey model of subarachnoid hemorrhage [10]. Following the hemorrhage, seven of nine animals developed hyponatremia in association with natriuresis and negative salt balance. There was a slight decline in plasma volume, although it was not statistically significant. By contrast, sham-operated control animals did not become hyponatremic or natriuretic and plasma volume did not change.

Wijdicks *et al.* [11] determined Na^+ balance and measured plasma volume in 21 patients with subarachnoid hemorrhage. On an average of seven days after the event, nine patients developed hyponatremia that met the criteria for a diagnosis of SIADH. Eight of nine patients were found to have a negative Na^+ balance, which preceded the development of hyponatremia. Body weight declined in all of the hyponatremic patients, with six demonstrating a $>10\%$ decrease in plasma volume. Interestingly, of the 12 patients without hyponatremia, negative Na^+ balance developed in four patients and plasma volume decreased in eight. Levine *et al.* [12] studied ten consecutive patients during the postoperative period after they had undergone cranial vault remodeling for correction of craniosynostosis. All patients were given normal saline in an amount to match urine output. In spite of the administration of fluids, all patients developed some degree of hyponatremia and had clinical evidence of volume depletion. In one additional report of 21 neurosurgical patients with hyponatremia associated with increased urine Na^+ concentration and an inappropriately concentrated urine, volume status was assessed by measurement of total blood volume and central venous pressure and determining the response to volume supplementation [13]. In spite of fulfilling the laboratory criteria for SIADH, these patients all showed evidence of a contracted ECF volume.

In summary, many neurosurgical patients who develop hyponatremia and otherwise meet the clinical criteria for a diagnosis of SIADH have a volume status that is inconsistent with that diagnosis. Rather, the evidence of negative salt balance and reductions in both plasma and total blood volume in these patients is more consistent with a diagnosis of CSW. The onset of this disorder is typically seen within the first ten days following a neurosurgical procedure or after a definable event, such as a subarachnoid hemorrhage or stroke. A very delayed onset of the disorder (postoperative day 35) has been described in one patient who underwent transphenoidal

surgery for treatment of a pituitary macroadenoma [14]. CSW has also been described in other intracranial disorders, such as carcinomatous or infectious meningitis and metastatic carcinoma [15–18]. The occurrence of CSW in these disorders emphasizes that CSW must be included in the differential diagnosis of hyponatremia in any patient with CNS disease.

Pathophysiology of CSW

The mechanism by which cerebral disease leads to renal salt wasting is poorly understood. The most probable process involves disruption of neural input into the kidney and/or central elaboration of a circulating natriuretic factor (Fig. 2). By either or both mechanisms, increased urinary Na^+ excretion would lead to a decrease in effective arterial blood volume (EABV), and thus provide a baroreceptor stimulus for the release of arginine vasopressin (AVP). In turn, increased AVP levels would impair the ability of the kidney to elaborate a dilute urine. In this setting, the release of AVP is an appropriate response to the volume depletion. By contrast, release of AVP in SIADH is truly inappropriate, because EABV is expanded.

A probable site for depressed renal Na^+ absorption in CSW is the proximal nephron. Because this segment normally reabsorbs the bulk of filtered Na^+, a small decrease in its efficiency would result in the delivery of large amounts of Na^+ to the distal nephron and, ultimately, into the final urine. Decreased sympathetic input to the kidney could be an explanation for impaired proximal reabsorption, because the sympathetic nervous system (SNS) has been shown to alter salt and water handling in this segment through various indirect and direct mechanisms. Because the SNS also plays an important role in the control of renin release, decreased sympathetic tone could explain the failure of circulating renin and aldosterone levels to rise in patients with CSW [19,20]. The failure of serum aldosterone levels to rise in response to a decreased EABV can account for the lack of renal K^+ wasting, despite a large increase in distal delivery of Na^+. In this regard, hypokalemia has not been a feature of CSW.

In addition to decreased neural input to the kidney, release of one or more natriuretic factors could also play a role in the renal salt wasting seen in CSW [20,21]. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have several effects that could lead to the clinical syndrome of CSW. For example, infusion of either of these peptides into normal human subjects results in a natriuretic response that is unrelated to changes in blood pressure [22]. The ability of these compounds to increase GFR accounts for some of the natriuresis; however, even in the absence of a change in GFR, urinary Na^+ excretion increases because of a direct inhibitory effect on Na^+ transport in the inner medullary collecting duct [22]. These peptides can also increase urinary Na^+ excretion without causing hypokalemia. For example, ANP and BNP are associated with decreased circulating levels of aldosterone because of direct inhibitory effects on renin release in the juxtaglomerular

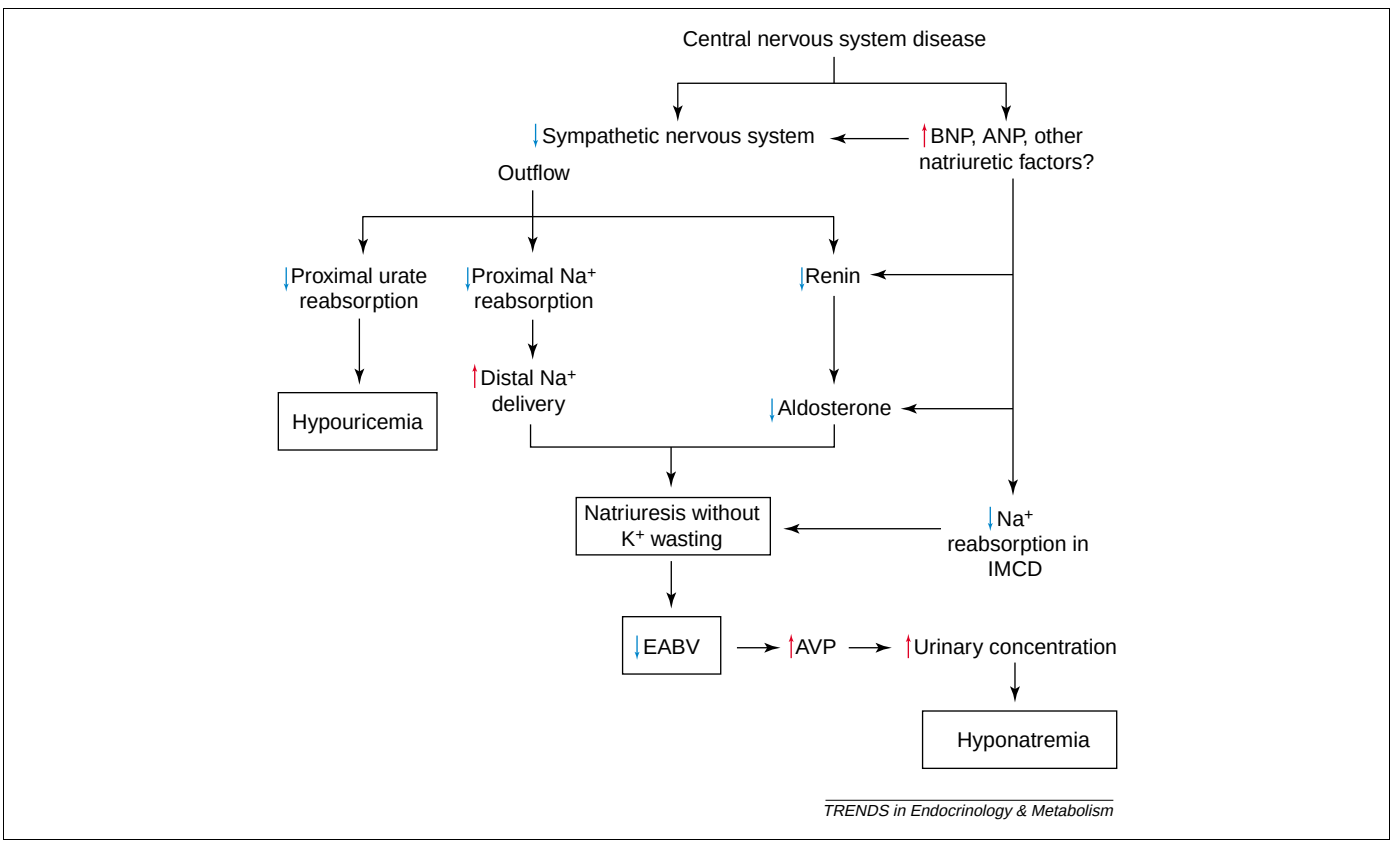

Fig. 2. The pathophysiology of cerebral salt wasting (CSW). Conditions associated with increased urinary Na^+ excretion in the setting of volume contraction would be expected to result in renal K^+ wasting because of increased delivery of Na^+ to the cortical collecting duct in the setting of increased aldosterone levels. The lack of renal K^+ wasting in CSW can be accounted for by the failure of aldosterone to increase in spite of the low extracellular fluid volume. Abbreviations: ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide; EABV, effective arterial blood volume; IMCD, inner medullary collecting duct.

cells of the kidney and direct inhibitory effects on aldosterone release in the adrenal gland. In addition, inhibition of Na^+ reabsorption in the inner medullary collecting duct would not be expected to cause renal K^+ wasting, because this segment is distal to the predominant K^+ secretory site in the cortical collecting duct. As ECF volume becomes contracted, proximal Na^+ reabsorption would increase, resulting in less distal delivery of Na^+ to the collecting duct. Decreased Na^+ delivery protects against K^+ wasting in the setting of high circulating levels of aldosterone.

ANP and BNP can also directly decrease autonomic outflow through effects at the level of the brain stem [22,23]. In this manner, natriuretic peptides can act synergistically with CNS disease to decrease neural input to the kidney. The evidence both for and against ANP and a circulating ouabain-like factor as important factors in the development of CSW has recently been reviewed [24].

For the various natriuretic compounds, Berendes *et al.* [20] have provided evidence that BNP might be the more probable candidate to mediate renal salt wasting. The authors compared ten patients with subarachnoid hemorrhage who underwent clipping of an aneurysm with a control group comprising ten patients who underwent craniotomy for resection of cerebral tumors. All of the patients with subarachnoid hemorrhage and none of the control group showed an increase in urine output accompanied by increased urinary Na^+ excretion, which tended to peak three to four days following the procedure. Sodium and fluid loss in the urine were matched by intravenous replacement, thus preventing the development of hyponatremia. Compared with the control group, significantly greater levels of BNP were found in the subarachnoid hemorrhage patients, both before surgery and up to postoperative day eight. The BNP concentration was significantly correlated with both urinary Na^+ excretion and intracranial pressure. By contrast, there were no differences in the circulating concentration of ANP or digoxin-like immunoreactive substances between the two groups. Plasma renin concentration was the same in both groups, but plasma aldosterone concentrations were suppressed and varied in an opposite direction to that of BNP in the subarachnoid hemorrhage group.

BNP in humans is found primarily in the cardiac ventricles, but also in the brain [22,25]. It is not known whether either brain or cardiac tissue or both contribute to the increased BNP concentrations found in these patients with subarachnoid hemorrhage. Increased release of cardiac BNP could be part of a generalized stress response to the underlying illness, whereas increased intracranial pressure could provide a signal for brain BNP release. In this regard, one could speculate that the development of renal salt wasting and resultant volume depletion in the setting of intracranial disease is a protective measure, limiting extreme rises in intracranial pressure. In addition, the vasodilatory properties of these natriuretic peptides might decrease the tendency for vasospasm in disorders such as subarachnoid hemorrhage.

Differentiation of SIADH and CSW

Distinguishing between CSW and SIADH in clinical practice can be difficult, given the similarity in laboratory values and the overlap in associated intracranial diseases. Determination of ECF volume remains the primary means of distinguishing these disorders (Table 1). ECF volume is increased in SIADH, whereas it is low in CSW. Physical findings that support a diagnosis of CSW include orthostatic changes in blood pressure and pulse, dry mucous membranes and flat neck veins. Weight loss or negative fluid balance as determined by a review of hospital flow sheets are particularly good pieces of evidence in support of a declining ECF volume. Laboratory findings that are useful include evidence of hemoconcentration, as reflected by an increased hematocrit and increased serum albumin concentration, and the finding of a raised serum bicarbonate concentration, because decreased ECF volume is an important factor in the maintenance of metabolic alkalosis.

Normally, the serum level of uric acid would be a useful tool in this situation. As previously mentioned, uric acid levels are depressed in patients with SIADH, which reflects the slight increase in ECF volume. By contrast, uric acid levels in patients with hyponatremia occurring in the setting of decreased ECF volume are either normal or slightly increased. Although not well studied, serum uric acid levels in CSW tend to be unexpectedly low [26]. In fact, hypouricemia and increased fractional urate excretion might be a common feature of intracranial disease in general [26,27]. Maesaka *et al.* [28] studied 29 consecutive neurosurgical patients with a variety of intracranial diseases. Eighteen of the patients had fractional excretion of urate values $>10\%$ of normal and 16 of the patients had a serum urate concentration ≤ 4 mg dl^{-1}. Only one patient in the series had coexistent hyponatremia. In this patient, the hypouricemia and increased fractional urate excretion persisted after correction of the serum Na^+ concentration. Although not always accompanied by hyponatremia, hypouricemia and increased renal uric acid excretion have also been noted in patients with Alzheimer's disease and in patients with AIDS [27,29]. Although correction of the serum Na^+ concentration in SIADH leads to a

Table 1. Clinical features of CSW and SIADH[a]

	CSW	SIADH
Extracellular fluid volume[b]	Decreased	Increased
Hematocrit	Increased	Normal
Plasma albumin concentration	Increased	Normal
Plasma BUN/creatinine	Increased	Decreased
Plasma K^+	Normal or increased	Normal
Plasma uric acid	Normal or decreased	Decreased
Treatment	Normal saline	Fluid restriction

[a]Abbreviations: BUN, blood urea nitrogen; CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
[b]Determination of extracellular fluid volume is the primary way to differentiate CSW from SIADH.

normalization of uric acid handling by the kidney [30], hypouricemia and increased renal uric acid excretion remain persistent findings following the correction of the serum sodium concentration in CSW [26].

Treatment of CSW and SIADH

Making the distinction between CSW and SIADH is of particular importance with regard to treatment [31]. Fluid restriction is employed in SIADH because the primary abnormality is expansion of the ECF volume with water. Administration of NaCl is indicated in CSW because ECF volume is decreased as a result of renal salt wasting. Failure to distinguish properly between these disorders so that treatment indicated for one disorder is inappropriately used for the other can potentially result in an adverse outcome.

The potential for fluid restriction to worsen the underlying neurological condition in the setting of CSW was suggested by Wijdicks *et al.* [32]. In a retrospective study of patients with subarachnoid hemorrhage, 44 of 134 patients developed hyponatremia between two and ten days after the hemorrhage. Of 44 patients treated with fluid restriction, 21 developed a cerebral infarction, including 15 of 17 patients who clinically met the criteria for SIADH. Although the volume status of the patients was not defined, the authors suggested that many of these patients might have had CSW as a cause of the hyponatremia. If so, fluid restriction would tend to aggravate an already decreased plasma volume. Maintenance of an adequate intravascular volume is important in the management of subarachnoid hemorrhage to minimize cerebral ischemia induced by vasospasm. A decrease in plasma volume could potentially worsen cerebral blood flow by increasing blood viscosity and decreasing cardiac output.

In patients with CSW, intravascular volume must be vigorously maintained with intravenous saline. Once patients are capable of taking oral medications, salt tablets can be utilized. Administration of an agent with mineralocorticoid activity, such as fludrocortisone, can also be used [33,34]. Although not well studied, CSW tends to be transient in nature, with evidence of renal salt wasting usually resolving after three to four weeks.

Just as fluid restriction can potentially worsen the underlying condition in CSW, intravenous saline given to patients with SIADH can cause a further lowering of the serum Na^+ concentration and result in symptomatic hyponatremia. This potentially deleterious response is the result of SIADH being a disorder in which renal water handling is impaired but renal Na^+ handling is normal. Consider the response of a patient with SIADH given one liter of normal saline (308 mOsm). Assuming a urine osmolality of 616 mOsm l^{-1}, all the NaCl will be excreted in 500 ml of fluid. The remaining 500 ml of administered fluid will remain within the body and cause a further lowering of the serum Na^+ concentration. To avoid worsening hyponatremia in this setting the osmolality of the fluid given must exceed the osmolality of the urine.

In summary, a great deal of evidence suggests that CSW needs to be included in the differential diagnosis of hyponatremia in patients with diseases of the CNS. Distinguishing between SIADH and CSW is of crucial importance given the divergent nature of therapy. Still lacking is an understanding of the pathophysiology of CSW and a complicating factor is that components of SIADH and CSW could both be present in any given patient. Changes in circulating natriuretic factors and alterations in autonomic input to the kidney are attractive possibilities but need to be better documented. Future studies should only include CSW patients in whom volume contraction and ongoing salt wasting is rigorously supported.

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