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Bioreactance and Apelin in the Management of Severe Hyponatremia

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Abstract

Hyponatremia is a severe electrolyte disturbance associated with substantial morbidity and mortality. It often poses a diagnostic and therapeutic challenge. Accurate assessment of patient fluid-volume status is central to effective management. This pilot study aimed to evaluate the usefulness of the Cheetah NICOM bioreactance system and apelin in early differentiation between hypo- and euvolemia in patients with severe hyponatremia. **Methods:** Patients > 50 years of age with a serum sodium ≤ 125 mmol/L were eligible for inclusion after written informed consent. Blood- and urine analyses of cardiovascular load (NT-proBNP), osmotic stress (copeptin, apelin, osmolality, sodium), mineralocorticoid status (aldosterone, renin) and sympathetic activity (methoxycathecholamines) were analysed at baseline and after isotonic sodium chloride infusion. Bedside bioreactance examination was used to visualise parameters, including stroke volume before and after passive leg raise test. Classification of volume status was made retrospectively blinded for biomarker and bioreactance results. **Results:** 8 patients (4 hypovolemic and 4 euvolemic), 79 years old, median plasma sodium 120 mmol/L were included. At the Emergency Department volume status was misclassified in all hypo- and in 2 of 4 euvolemic patients. Apelin was significantly higher in hypovolemic patients ((299 vs. 175 ng/ml), p = 0.021). All hypovolemic, but none of the euvolemic, patients had a level above 250 ng/ml. Copeptin did not differ between groups. All patients in the hypovolemic group increased their stroke volume after passive leg raise. **Conclusions:** Apelin seems to be a promising future biomarker in the early management of severe hyponatremia. Bioreactance measurements may offer a supplement to bedside evaluation of volume status.

1. Introduction

Hyponatremia is a severe electrolyte disturbance with multifactorial aetiology, associated with substantial morbidity and mortality [1] [2]. However, despite being the most common water balance disorder, it often poses a diagnostic and therapeutic challenge, and the clinical management of hyponatremia is still not optimal [3] [4]. After excluding non-hypotonic causes of hyponatremia, diagnosis at the emergency department is usually guided by assessed patient volume status or urinary sodium (U-sodium) concentration. Patient volume status is difficult to determine accurately even for experienced doctors and urinary sodium might be challenging to obtain and is affected by renal function and use of diuretics. At the same time the determination of volume status in hyponatremia is crucial for choosing the correct treatment regime. This study examines bioreactance measurement and plasma apelin levels for accurate, objective differentiation between hypo- and euvolemia in patients with severe hyponatremia.

Vasopressin is a key hormone in the regulation of plasma osmolality and fluid volume status but is difficult to measure. Copeptin, the C-terminal part of the prohormone, can be used as a surrogate for vasopressin levels [5]. Previous studies have indicated that the analysis of copeptin can be useful in the diagnosis of primary polydipsia but cannot reliably differentiate between other causes of hyponatremia [6]. Even though copeptin levels are lowest in primary polydipsia and highest in hypovolemic hyponatremia the large overlap in copeptin levels prevents use in differential diagnosis of hyponatremia. It cannot distinguish between hypo- and euvolemic patients [7].

Apelin, an endogenous peptide, is also involved in the regulation of plasma osmolality and fluid volume status. It regulates vascular tone, cardiac contractile function and fluid balance [8] [9]. Apelin counteracts vasopressin by inhibiting the phasic electric activity of arginine vasopressin neurons, reducing vasopressin blood levels and increasing free water renal excretion. Increased plasma osmolality simultaneously raises plasma vasopressin levels and decreases plasma apelin levels in control subjects. Conversely, decreased plasma osmolality reduced plasma vasopressin levels and rapidly increased plasma apelin levels [10] [11]. Apelin has not previously been evaluated in the differential diagnosis of hyponatremia.

The Cheetah NICOM system is a bedside bioreactance measurement device designed to visualise the hemodynamic status [12]. It has been used in intensive care units for non-invasive monitoring of sepsis patients for early differentiation between hypotension that will respond to aggressive fluid infusion versus the need for inotropic drugs [13].

The aims of this pilot study were to evaluate the usefulness of bioreactance

measurement and plasma apelin levels in early differentiation between hypo- and euvolemia in patients with severe hyponatremia.

2. Methods

2.1. Participants

This single-centre pilot study was performed at Skane University Hospital, Sweden (June 2015-Dec 2016). Patients were recruited from the Department of Emergency Medicine. The study was approved by the Regional Ethics Committee, Lund, Sweden and was performed according to the Declaration of Helsinki.

Patients admitted to the Emergency Department at Skane University Hospital, Lund, Sweden, older than 50 years of age with a serum sodium concentration of ≤ 125 mmol/L and able to give a written informed consent were eligible for inclusion. Patients with seizures, uncompensated heart failure, eGFR < 30 ml/min, systolic blood pressure < 90 mmHg, ongoing gastrointestinal losses, or a haemoglobin concentration below 100 g/L were excluded, as were patients who had received an intravenous infusion of sodium chloride before inclusion.

2.2. Procedure

After examination in the Emergency Room, blood- and spot urine analyses were taken according to standard clinical practice [14]. If hyponatremia was detected, eligible patients were informed about the study by the principal investigator and written informed consent was obtained before any study-related procedure was done. Before transferral to an intermediary care ward, blood- and spot urinary samples were taken and stored for later analysis, the physician at the Emergency Department assessed patient volume status, and the principal investigator evaluated volume status with the Cheetah NICOM system. Routine treatment was then initiated with 1000 ml of isotonic sodium chloride over 10 hours, and drugs suspected of causing or aggravating hyponatremia were withheld. Plasma sodium, osmolality levels and biomarkers were analysed at 4 h, 12 h, 24 h and daily until discharge.

Classification of volume status was made retrospectively after patient discharge based on available information in patient records, routine blood- and urine analyses as well as response to treatment [14]. Bioreactance measurements, as well as biomarkers measured in stored samples, were not available for the expert.

Plasma and urine samples were immediately frozen and stored at −80˚C until analysis, including biomarkers of cardiovascular load (NT-proBNP, osmotic stress (copeptin, apelin), and mineralocorticoid status (aldosterone, renin). The sympathetic activity was elucidated in urine collected in 4 - 12-hour fractions using methoxycatecholamine to creatinine ratio. NT-proBNP was determined using the Dimension RxL N-BNP (Dade-Behring, Marburg, Germany) [15]. The reference range for the NT-proBNP assay is < 300 ng/L in patients > 60 years, with an interassay CV of 4.6% [16]. Copeptin was measured using a fully automated immunoassay system (Kryptor, Thermo Fisher, Henningsdorf, Germany)

[5]. Median copeptin in 359 healthy individuals in previous investigations was 4.2 pmol/L, with 2.5th and 97.5th percentiles being 1.7 and 11.3 pmol/L, respectively. The interassay CV at 4.2 pmol/L is 14% and 9% at 11.25 pmol/L [6]. Apelin were analysed using ELISA (Ray Biotech Inc, Norcross GA, USA.) The interassay CV is < 15%. Median Apelin in 35 healthy individuals with a median age of 55 years was 325 ± 152 pg/ml [17] [18]. Blood and urine samples for evaluation of electrolytes, creatinine, osmolality, thyroid hormones, cortisol, and ACTH were analysed using standard procedures at our clinical laboratory (Fiske model 210, Micro-Osmometer. Cobas 6000/8000 ROCHE, Basel, Switzerland). Methoxycatecholamines were analysed using liquid chromatography-tandem mass spectrometry method [19] [20].

Bioreactance measurements were performed using the NICOM system (Cheetah Medical, Portland, OR, USA). The device is connected to the patient with four double-electrodes on the chest wall. An alternating electric current pass between the outer electrodes and the inner electrodes senses the resulting voltage signal. Comparison of the phase shift is proportional to aortic flow. The first examination was undertaken at the Emergency Department, and these baseline values, including heart rate, stroke volume, mean arterial pressure and blood pressure, were registered with patients in a 45˚ semi-recumbent position. The device then calculated cardiac output and total peripheral resistance. A passive leg raise test was performed by lowering the head to a flat position and elevating the legs to 45˚. An increase in stroke volume index (SVI = SV/body surface area) ≥ 10% was considered a sign of fluid responsiveness *i.e.* hypovolemia [12].

Since the hallmark of SIADH is an inappropriate secretion of vasopressin related the sodium level, we calculated a ratio for this inappropriate response by dividing copeptin with plasma sodium.

2.3. Statistics

Data were analysed using SPSS statistical software (version 25, SPSS Inc, Chicago Ill, USA).

Data are given as median (range) and percentages. Mann-Whitney U-test was used to compare continuous variables between groups, and Fisher's exact test to compare categorical variables. A p-value < 0.05 was considered as statistically significant.

3. Results

In total, 8 participants, six women, and two men, with a median age of 79 (63 - 88) years, were included in this pilot study. Their baseline sodium level was 120 (107 - 123) mmol/L, and all but one was taking drugs tentatively associated with hyponatremia, beta-blockers (n = 4), diuretics (n = 3), antiepileptic drugs (n = 1), and selective serotonin uptake inhibitors (n = 1) (Table 1).

Four of the patients were classified bedside at admission as hypovolemic, and four euvolemic.

Table 1. Patient baseline characteristics.

	Median, % (n = 8)
Age (yrs)	
Gender (female)	75%
Morbidities:	
Heart failure	38%
Hypertension	63%
Cerebrovascular disease	25%
Epilepsy	13%
Depression	13%
Diabetes mellitus	25%
Previous cancer	13%
Drug treatment:	
Diuretics	38%
SSRI	13%
Antiepileptic drugs	13%
Betablockers	50%

The emergency physicians' determinations, based on all available information at the time of patient transferral to an intermediary care ward, were incorrect in all four cases in the hypovolemic group, and in two of the four cases in the euvolemic group.

Comparisons of biochemical and bioreactance measures between hypovolemic and euvolemic patients are shown in Figure 1. Urine osmolality and urine sodium concentration were higher in the euvolemic group (U-Osm 537 mOsm/kg (290 - 600) versus 236 mOsm/kg (204 - 269), $p = 0.317$ and U-Na 82 mmol/L (44 - 149) vs. 24 mmol/L (20 - 34), $p = 0.180$, respectively) (Table 2).

Stroke volume, stroke volume index, cardiac output, mean atrial pressure and thoracic fluid content were similar and not statistically different between the two groups (data not shown). All patients in the hypovolemic group increased their stroke volume after passive leg raise. Compared to the euvolemic group, total peripheral resistance index (TPRI) decreased more after passive leg raise in the hypovolemic than the euvolemic group (-20 (-28 - (-7)) vs. -1 (15 - 46), $p = 0.043$).

At baseline, apelin was significantly higher in the hypovolemic group (299 (265 - 433) vs. 175 (147 - 228), $p = 0.021$), and apelin concentration was > 250 ng/ml in all hypovolemic patients. In all euvolemic patients, the apelin concentration was below this level (Figure 1).

Copeptin was similar between groups, but the apelin/copeptin ratio significantly differed (48.8 (22.1 - 217.1) vs. 18.5 (14.9 - 24.4), $p = 0.043$).

Copeptin to plasma sodium ratios at admission did not statistically significantly differ between the hypovolemic and euvolemic groups.
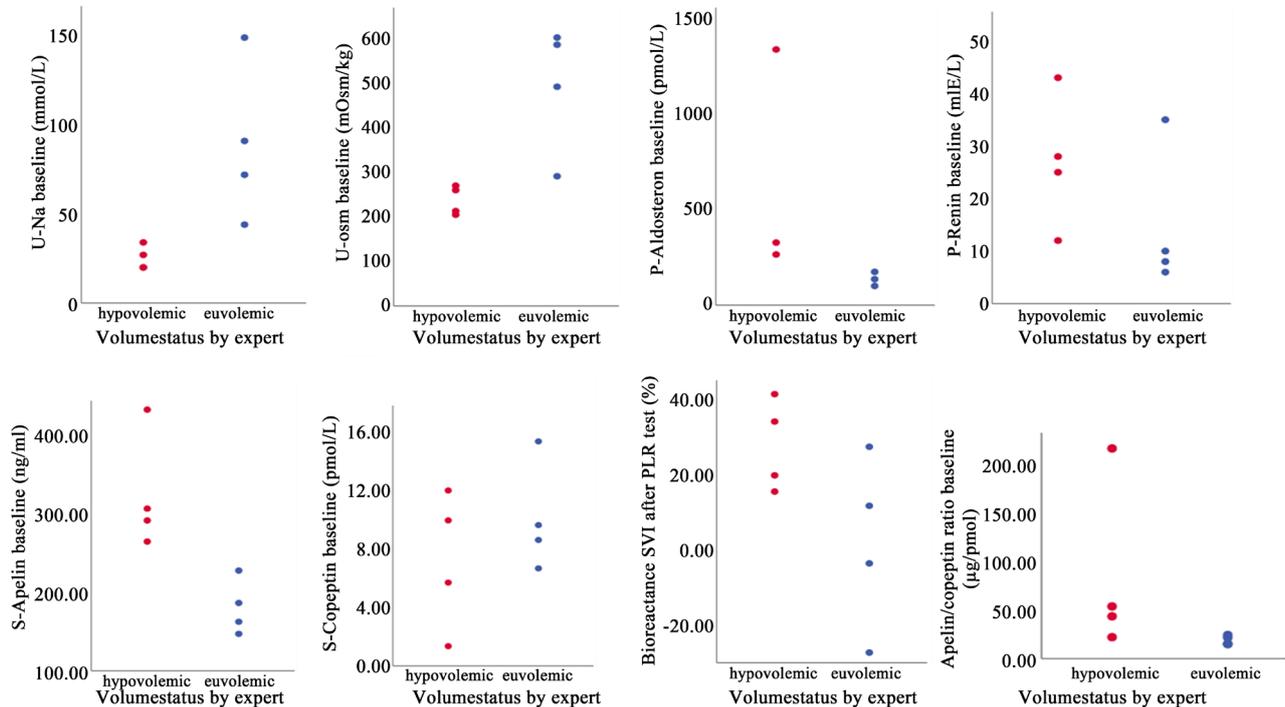
Figure 1. Baseline biomarker levels in patients with hypo- versus euvolemic hyponatremia. Bioreactance analysis of stroke volume index after passive leg raise test.

Table 2. Hypovolemia vs Euvolemia.

	Hypovolemia (n = 4) Value (range min-max)	Euvolemia (n = 4) Value (range min-max)	p-value
Age (years)	76 (63 - 88)	80 (70 - 86)	0.564
Gender (female)	4	2	0.105
BP systolic (mmHg)	145 (130 - 169)	158 (150 - 200)	0.191
BP diastolic (mmHg)	76 (70 - 80)	103 (74 - 110)	0.081
Heart rate (beats/min)	79 (60 - 92)	79 (70 - 87)	1.000
TSH (mU/L)	1.3 (1 - 4)	1.4 (1.0 - 37.0)	0.663
T4 (mU/L)	15 (12 - 18)	20 (2 - 27)	0.309
T3 (mU/L)	3.7 (3 - 5)	3.4 (1 - 4)	0.564
Cortisol (mmol/L)	421 (191 - 821)	540 (283 - 582)	0.564
ACTH (pmol/L)	3.6 (2 - 12)	5.1 (3 - 15)	0.289
Hb (g/L)	122 (102 - 164)	140 (128 - 142)	0.386
Potassium (mmol/L)	3.9 (2.9 - 4.5)	4.2 (4.0 - 4.5)	0.189
Creatinine (μmol/L)	101 (52 - 153)	69 (45 - 92)	0.248
Glucose (mmol/L)	6.0 (5 - 13)	6.5 (5.8 - 8.0)	0.564
CRP (mg/L)	3 (1 - 6)	2 (1 - 5)	0.663
P-osm (mOsm/kg)	263 (261 - 288)	251 (237 - 277)	0.146
U-osm (mOsm/kg)	236 (204 - 269)	537 (290 - 600)	0.021
U-Na (mmol/L)	24 (20 - 34)	82 (44 - 149)	0.020
U-K (mmol/L)	24 (23 - 36)	31 (19 - 46)	0.724
U-Methoxynorepinephrine/creatinine	291 (191 - 430)	199 (168 - 674)	0.386
U-Methoxyepinephrine/creatinine	104 (54 - 219)	141 (111 - 211)	0.564

Cortisol, ACTH, TSH, T4, T3, glucose, CRP, metoxycatecholamines and base-excess did not differ between groups, and all values were within the reference ranges. Pro-BNP did not differ between groups (451 (140 - 889) vs. 528 (174 - 1109), n.s.).

A trend towards shorter hospital stay in the hypovolemic group was seen (3 (2 - 10) vs. 7 (3 - 17) days, n.s.).

4. Discussion

Optimal management of hyponatremia is fundamentally based on the patient's volume status [14]. However, at the emergency, clinical examination, as well as routine blood and urine samples, seem to be of unpredictable value, which has been confirmed in our as well as previous studies [1] [3] [4]. Accordingly, the present golden standard of volume status at admission is usually done in retrospect by experienced clinicians, based on analysis of clinical and laboratory findings before and following treatment [14] [21].

In the present study, we aimed to improve early bedside evaluation of volume status using biomarkers and a simple test of bioreactance, which mirrors stroke volume before and after "self transfusion" of fluid following passive leg raise [12]. Our findings following this test were in concert with expert opinion in six of the eight patients. To our knowledge, this method has not previously been studied in severe hyponatremic patients, and our outcome suggests further studies to validate our findings. Bioreactance may aid in determination of volume status in hyponatremic patients and perhaps also be an instrument to further understanding of the complex relationship between volume status and sodium in multifactorial hyponatremia.

Apelin levels were significantly higher in hypo- than euvolemic, hyponatremic patients, and none of our studied hypovolemic patients displayed a value below 250 nmol/l. This may mirror that a normal physiological response to hyponatremia or hypovolemia requires crosstalk between vasopressin and apelin, not present in SIADH patients [11].

Vasopressin levels, evaluated by analysing copeptin were similar in hypo- and euvolemic hyponatremia, confirming findings in previous studies [6] [7].

Regarding hypovolemia, our findings are in concert with those of a previous study, where Urwyler *et al*. found higher plasma apelin levels in patients with nephrogenic diabetes insipidus, however, no previous study has found differences in apelin between hypo- and euvolemic hyponatremia [22]. The outcome of our small pilot study, thus indicates that apelin could be a useful marker for differentiating between hypo- and euvolemia in the early management of hyponatremia.

In a routine clinical management perspective, differentiation based on apelin concentration may be preferable to bioreactance measurements, as the former is easily accessible by a single blood sample. In contrast, a bioreactance measurement not only is more time-consuming but also requires a device and individual

skills to handle it.

The main limitation of our study is the number of patients included. However, a positive outcome of the hypothesis in a small prospective study might indicate a high clinical relevance, which should be confirmed in further studies.

In conclusion, our small pilot study indicates that apelin seems to be a promising future tool in the early management of severe hyponatremia. Bioreactance measurements may offer a supplement to bedside evaluation of volume status.

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Disclosure Summary

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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