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(Citation)
Journal of Clinical Neuroscience,103:131-140

(Issue Date)
2022-09

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/0100477804

The Impact of Hormonal Dynamics and Serum Sodium Fluctuations on Symptomatic Vasospasm after Subarachnoid Hemorrhage

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Article type: Clinical paper

Funding:

This work was supported in part by a Grant-in-Aid for Scientific Research <KAKENHI> from the Japan Society for the Promotion of Science (No. 19K09507, to Yoichi Uozumi).

Abstract

Background Symptomatic vasospasm (SVS) is a major cause of morbidity and mortality in aneurysmal subarachnoid hemorrhage (SAH), and serum sodium frequently decreases before SVS. Serum sodium changes might be regulated by sodium metabolism-related hormones. This multi-institutional prospective cohort study therefore investigated the measurement of sodium metabolism-related hormones to elucidate the pathophysiology of serum sodium changes in SAH. **Methods** SAH patients were treated with clipping or coiling from September 2017 to August 2020 at five hospitals. The laboratory data of 133 SAH patients were collected over 14 days and correlations between changes in serum sodium, sodium metabolism-related hormones (plasma adrenocorticotropic hormone (ACTH), serum cortisol, plasma arginine vasopressin (AVP)), and SVS were determined. Serum sodium concentrations were measured every day and serum sodium levels >135 mEq/L were maintained until day 14. **Results** Of the 133 patients, 18 developed SVS within 14 days of subarachnoid hemorrhage onset (SVS group) and 115 did not suffer from SVS (non-SVS group). Circulating AVP, ACTH, and cortisol concentrations were significantly higher on day 1 in the SVS group compared with the non-SVS group. Fluctuations in serum sodium in the SVS group were

significantly higher than those in the non-SVS group. There were antiparallel fluctuations in serum sodium and potassium from days 2 to 14. **Conclusions** Elevated levels of ACTH/cortisol and AVP on day 1 may be predictive markers for the occurrence of SVS. Multiple logistic regression analysis showed that serum sodium fluctuations were associated with SVS occurrence. Serum sodium fluctuations were associated with stress-related hormonal dynamics. (249 words)

Keywords: subarachnoid hemorrhage; symptomatic vasospasm; adrenocorticotropic hormone; cortisol; arginine vasopressin

1. Introduction

Symptomatic vasospasm (SVS) is a major cause of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (SAH) [1,2]. SVS prevention is preferred over controlling SVS symptoms or treating SVS because of its complex nature [2,3]. We previously reported that serum sodium concentrations progressively decrease prior to SVS, and this observation may help to predict symptomatic vasospasm [4].

Serum sodium concentrations vary with sodium and water intake and their renal excretion and are strictly regulated by the balance of sodium metabolism-related hormones. Therefore, measuring these hormones may predict SVS before serum sodium is decreased. In addition, elucidating the dynamics of these hormones in the acute phase of SAH will help reveal the pathophysiology of serum sodium decrease prior to SVS. Although cerebral salt-wasting syndrome, syndrome of inappropriate secretion of antidiuretic hormone and hypocortisolism have been proposed as causes of SAH-related hyponatremia [5-9], the underlying pathogenesis of serum sodium decrease preceding SVS is still unknown. Recently, fluctuations in serum sodium were reported to negatively affect the neurological outcomes of patients with SAH rather than hyponatremia or hypernatremia [10,11]. This might be related in part to the pathophysiology of dysnatremia in patients with SAH.

Considering these reports, we hypothesized that decreased serum sodium prior to SVS reflects the descending phase of serum sodium fluctuations, and that these fluctuations are caused by sodium metabolism-related hormonal dynamics. To test this hypothesis, we monitored laboratory data of aneurysmal subarachnoid hemorrhage patients for 14 days and assessed the relationship between serum sodium changes, sodium metabolism-related hormones and SVS.

2. Methods

This was a multi-institutional prospective cohort study. Among patients with acute SAH admitted from September 2017 to August 2020 at Kobe University Hospital, Hyogo Brain and Heart Center, Kita-Harima Medical Center, Steel Memorial Hirohata Hospital, and Toyooka Public Hospital, we enrolled patients treated by surgical clipping or endovascular coiling within 24 h of SAH onset. We did not include patients who suffered from dissecting aneurysms, died within 10 days after SAH onset, required dialysis, had a rebleed after an initial blood sampling, or suffered from chronic heart failure before SAH onset. Patients' data collected from medical records were compiled as case report forms after concealment of personal information at each hospital, and the case report forms were then collected at the Department of Neurosurgery, Kobe University Graduate School of Medicine, and registered in the database. This study was approved by the ethics committee of Kobe University Graduate School of Medicine (#180314) based on the Japanese Clinical Trails Act (Act No. 16, April 14, 2017) and by the respective ethics committees of the other four hospitals. Opt-out methods of consent were used.

2. 1. Data Collection

At admission, clinical severity was assessed using the World Federation of Neurological Surgeons (WFNS) grading scale. The Fisher group was determined from computed tomography (CT) images

at admission. Outcomes were assessed using the modified Rankin scale (mRS) one month after SAH onset. Blood cell counts and serum biochemical data were evaluated at least every 24 h. Daily urine volume, daily sodium intake, and 24-h urinary sodium and potassium excretion were measured. The mean fluctuation in serum sodium was calculated by averaging the difference between the highest and lowest sodium concentrations throughout the 14-day observation period in each case. In terms of sodium metabolism-related hormones, we monitored plasma adrenocorticotropic hormone (ACTH), serum cortisol, plasma arginine vasopressin (AVP), serum renin, aldosterone, and plasma brain natriuretic peptide (BNP) concentrations at 0700 h on days 1, 7, and 13. Additionally, to investigate the involvement of renin-aldosterone in sodium and potassium changes, the serum active renin and aldosterone concentrations of 34 cases (SVS, 5 cases; non-SVS, 29 cases) in which serum was cryopreserved, were measured.

Serum sodium and potassium concentrations were measured using ion-selective electrodes (sodium reference range: 138–145 mmol/L; potassium reference range: 3.6–4.8 mmol/L; Nihon Denshi, Co., Ltd., Tokyo, Japan). Plasma ACTH, serum cortisol, and plasma BNP concentrations were measured with a chemiluminescent enzyme immunoassay kit, CL AIA-PACK (Tosoh Bioscience, Tokyo, Japan) (ACTH reference range: 8.7–61.5 pg/mL; cortisol reference range: 4.4–21.1 μg/dL; plasma BNP reference range: <18.4 pg/mL; Tosoh Bioscience), with a chemiluminescent immunoassay kit (Abbott Japan, Tokyo, Japan) (cortisol reference range: 3.7–19.4 μg/dL; plasma BNP reference range: <18.4 pg/mL), or with an electro chemiluminescent immunoassay kit (Roche Diagnostics K.K. Tokyo, Japan) (ACTH reference range: 7.2–63.3 pg/mL). Plasma AVP concentrations were measured with a radioimmunoassay antibody kit (reference range: <2.8 pg/mL; Yamasa Shoyu Corp., Choshi, Japan). The AVP extraction rate of this kit is reportedly 0.74%, the lower limit of measurable plasma AVP is 0.4 pg/mL, and the intra- and inter-assay (n = 5) coefficients of variation were each <8% [12]. Serum active renin and aldosterone concentrations

were measured with a chemiluminescent enzyme immunoassay system using Lumipulse Presto (Fujirebio, Tokyo, Japan) (serum active renin reference range: 2.21–39.49 pg/mL; serum aldosterone reference range: 3.0–82.1 pg/mL). Most sample analyses were performed in the laboratory of each hospital where the patient was hospitalized, but active renin and aldosterone concentrations measurements were performed at Kobe University Hospital simultaneously. In terms of measurement of electrolytes and AVP, all measurements were performed with the identical devices and the identical reference ranges in the laboratories of each of the five hospitals. However, for ACTH, chemiluminescent enzyme immunoassay kits were used in four hospitals and chemiluminescent immunoassay kits were used in one hospital (Kita-Harima Medical Center). For BNP, chemiluminescent enzyme immunoassay kits were measured in 3 hospitals, chemiluminescent immunoassay kits were used in 2 hospitals (Kita-Harima Medical Center and Toyooka Public Hospital), chemiluminescent enzyme immunoassay kits were used for 4 in cortisol, and electro chemiluminescent immunoassay kit were used in 1 hospital (Kita-Harima Medical Center). The following investigations were conducted using the values corrected based on the method difference correction formula for ACTH* and BNP**, but there was no method difference correction formula for cortisol, therefore, raw data of cortisol were used in the following investigations.

*ACTH concentrations (pg/mL) = 1.07 × [Roche, ACTH pg/mL] − 3.92

** BNP concentrations (＜500 pg/mL) = 1.17 × [Abbott, NBP pg/mL] + 5

BNP concentrations (≧500 pg/mL, ＜2500 pg/mL) = 1.09 × [Abbott, NBP pg/mL] + 18

2. 2. Management Protocol

All patients with SAH were managed in the intensive care unit. To treat aneurysmal rupture, patients underwent surgical clipping or endovascular coiling within 24 h of SAH onset. After surgery, patients were maintained in a normotensive, normovolemic, normoglycemic, normothermic

state as much as possible. Water balance was calculated every 8 h. A negative water balance was corrected using normal saline infusion. From postoperative days 1 to 14, all patients were administered fasudil hydrochloride hydrate (Eril, Asahi Kasei Co., Tokyo, Japan) to prevent vasospasm [13].

We measured serum sodium concentrations every day and attempted to maintain serum sodium above 135 mEq/L until day 14 after SAH onset. The concentrations of sodium required for correction were calculated as body weight (kg) × 0.6 × (140 − serum sodium concentrations [mEq/L]).

According to Consensus 2009 [14], SVS was defined as a neurological deterioration in combination with radiographic findings with the exclusion of other possible causes, such as hydrocephalus, rebleeding, sepsis, or seizure. In terms of the imaging diagnosis of SVS, all patients underwent routine CT at admission, immediately after surgery, the day after surgery, and between days 13 and 15. Magnetic resonance imaging follow-up was performed at least between days 13 and 15. Most patients also underwent cerebral angiography between days 6 and 8, and patients who could not undergo cerebral angiography because of their general condition underwent magnetic resonance imaging or perfusion CT between days 6 and 8. In addition, perfusion CT was used to diagnose SVS, together with CT angiographic images created based on images taken in the arterial phase of perfusion CT. Transcranial Doppler was used as an additional method. When clinical deterioration could not be reliably determined in sedated or comatose patients, these consecutive imaging studies were compared to distinguish between vasospastic and treatment-associated infarction.

It would be ethically inappropriate not to treat patients with acute hypocortisolemia with steroids [8], and patients with a morning serum cortisol concentration of <10 μg/dL were administered intravenous hydrocortisone (50–100 mg) once or twice a day at 0800 h or 0800 h and 1800 h.

2. 3. Statistical Analysis

All data are presented as the mean ± standard deviation. The χ^2 and Fisher's exact tests were used for paired data to test for differences in distributions between groups. The Mann–Whitney *U*-test was used to compare continuous variables. To investigate potential predictor variables for SVS, significant variables among sodium metabolism-related hormones were evaluated by simple logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic power of sodium metabolism-related hormones to discriminate between the groups and to determine potential cut-off values to predict the SVS. A *p*-value of <0.05 was considered statistically significant. For multiple comparisons of hormonal changes, *p*-values were adjusted using Holm's procedure [15]. Finally, multivariable logistic regression analysis was used to examine the effects of the independent variables that showed significant differences in univariate analysis. All data were analyzed using GraphPad Prism 9.3.1 (GraphPad Software Inc., San Diego, CA, USA). All analyses were supported by biostatisticians at the Kobe University Clinical and Translational Research Center.

3. Results

3. 1. Patient Characteristics and Outcomes

We identified 142 SAH patients treated with surgical clipping or endovascular coiling from September 2017 to August 2020 at five hospitals. Among these, nine patients were excluded because they were treated >24 h after the onset of SAH (*n* = 5), died within 10 days after the onset of SAH (*n* = 2), suffered from chronic heart failure before SAH (*n* = 1), or had a rebleed while waiting for treatment (*n* = 1). There were no patients requiring dialysis in this study. Finally, 133 patients were included in this study, and of these, 115 (86.5%) did not suffer from SVS throughout the

postoperative period (defined as the non-SVS group), whereas 18 (13.5%) developed SVS within 14 days of SAH onset (defined as the SVS group). Among the SVS group, 14 patients were diagnosed with SVS with neurological deterioration and cerebral angiography, and three of four comatose patients were diagnosed with SVS with newly detected low-density lesions on CT scans, with confirmation of angiographic spasms on magnetic resonance angiography or cerebral angiography. Only one comatose patient was diagnosed with SVS alone with newly detected low-intensity lesions on CT scan. The mean time of SVS onset was 9.67 ± 2.01 days after SAH. No significant differences were observed in baseline characteristics between patients with and without SVS, including age, sex, WFNS grade, Fisher group, acute hydrocephalus requiring external ventricular drainage, renal function at admission, aneurysm location, treatment modality, and the number of patients with intubation managed for >2 days (Table 1). However, the number of patients who developed hyponatremia (≤ 135 mEq/L) for 14 days and the number of patients who took > 2 days to correct hyponatremia (treatment-resistant) were significantly higher in the SVS group ($p < 0.01$; Table 1). At the 1-month evaluation of outcomes, 58 patients (50.4%) had good outcomes (mRS score: 0–2). In comparison, four patients (22.2%) had good outcomes in the SVS group. SVS significantly affected outcomes ($p = 0.03$; Table 1). In the non-SVS group, nine patients with low serum cortisol (<10 μg/dL) were supplemented with hydrocortisone [8]. No patients with a cortisol concentration of <10 μg/dL were present in the SVS group. Additionally, none of the patients in the SVS group experienced an event that caused elevated cortisol concentrations, such as severe hypotension, cardiac respiratory arrest, or neurogenic lung before the onset of SVS. None of the patients in either group showed worsening of renal function during the postoperative period compared with that at admission. No patients received contentious mannitol, hypertonic saline, or barbiturate coma therapy to control intracranial pressure. One patient in the SVS group received 500 mL of mannitol only

once on day 9 when SVS caused global cerebral ischemia, and three patients in the non-SVS group were administered glycerol for several days.

3. 2. Sodium Metabolism-related Hormonal Dynamics, SVS and SAH Severity

To investigate the relationship between SVS and changes in sodium metabolism-related hormones, we examined the changes in hormonal levels between the SVS and non-SVS groups (SVS, 18 cases; non-SVS, 115 cases) at three time points—days 1, 7, and 13 (Fig. 1A–F). AVP, ACTH, and cortisol concentrations on day 1 were significantly higher in the SVS group compared with the non-SVS group (AVP: 46.0 ± 53.6 pg/mL vs 19.4 ± 23.7 pg/mL, Holm-adjusted $p = 0.042$; ACTH: 247.3 ± 325.1 pg/mL vs 77.7 ± 202.3 pg/mL, Holm-adjusted $p = 0.0018$; cortisol: 34.0 ± 14.5 µg/dL vs 25.1 ± 24.9 µg/dL, Holm-adjusted $p = 0.018$; Fig. 1A, B, and C, respectively). Following SAH, AVP and the hypothalamic-pituitary-adrenal (HPA) axis hormones were markedly elevated with parallel kinetics in the SVS group. Both AVP and ACTH concentrations showed similar changes over the 14-day period examined, showing an increase on day 1 and were reduced thereafter. Cortisol increased on day 1 and then declined gradually, compared with the decrease in AVP and ACTH. BNP concentrations were highest on day 7 (Fig. 1D). AVP concentrations on day 13 were significantly higher in the SVS group compared with the non-SVS group (AVP: 4.75 ± 3.06 pg/mL vs 3.39 ± 4.21 pg/mL, Holm-adjusted $p = 0.0135$). To investigate the involvement of renin and aldosterone in the changes of sodium and potassium, the active renin and aldosterone concentrations in 34 cases (SVS, 5 cases; non-SVS, 29 cases) in which serum was cryopreserved were measured at three time points—days 1, 7, and 12 (Fig. 1E, F). The concentrations of active renin and aldosterone were not increased above the physiological upper limit over the 14-day period examined. The active renin concentrations were stable in both groups, and the aldosterone

concentration changes were not related to changes in the serum sodium and potassium concentrations (Fig. 1E, F and Fig. 6A, B).

The above examinations revealed that, among the sodium metabolism-related hormones, levels of the stress-related hormones AVP, ACTH, and cortisol on day 1 were significantly higher in the SVS group compared with the non-SVS group. We therefore investigated the relationships between these hormones and SAH severity. We examined the changes in hormone levels between patients with WFNS grades I–III and grades IV, V (grades I–III, 85 cases; grades IV, V, 48 cases) (Fig. 2A–F), and with Fisher groups 3 and 4 (Fisher group 3, 116 cases; Fisher group 4, 17 cases) (Fig. 3A–F). When compared by WFNS grade, only cortisol on day 1 was significantly higher in patients with WFNS grades IV, V compared with patients with WFNS grades I–III (29.1 ± 10.7 μg/dL vs 22.1 ± 12.6 μg/dL, Holm-adjusted $p = 0.003$; Fig. 2C), while levels of the other five hormones on day 1 did not differ between the groups (Fig. 2A, B, D–F). BNP levels on days 7 and 13 were significantly higher in patients with WFNS grades IV, V compared with patients with WFNS grades I–III. In terms of Fisher group, there were no significant differences in any of the six tested hormones (Fig. 3A–F).

3. 3. The Onset of SVS and Timing of Serum Sodium Decrease in the SVS Group

To assess the relationship between the onset of SVS and the timing of the serum sodium decrease, we investigated changes in serum sodium in each of the eighteen SVS cases (Fig. 4). Of these, fourteen cases suffered from SVS during a period of reduced serum sodium (Fig. 4A). The other four cases suffered from SVS when the serum sodium was increasing, but in these cases, serum sodium dropped to its lowest concentration 2 – 3 days before the onset of SVS, and SVS occurred while correcting decreased serum sodium (Fig. 4B). Serum sodium concentrations decreased in every case in the SVS group a few days before the onset of SVS.

3. 4. Fluctuations in Serum Sodium

To investigate the relationship between fluctuations in serum sodium and SVS, fluctuations in serum sodium concentrations during the 14 days after SAH onset were compared between the SVS and non-SVS groups (Fig. 5). The mean serum sodium concentrations in both groups were within the normal range throughout the 14-day period (Fig. 5A). The mean fluctuation range of serum sodium was significantly greater in the SVS group compared with the non-SVS group (16.27 ± 4.81 mEq/L vs 9.31 ± 4.08 mEq/L, $p = 0.0059$; Fig. 5B).

3. 5. Correlation between Sodium and Potassium Kinetics

To clarify whether the kinetics of serum sodium were ADH-dependent or occurred through an alternative pathway, such as the mineralocorticoid receptor (MR), we examined the correlation between serum sodium and potassium fluctuations. Over the 14-day period in which serum sodium and potassium concentrations were measured, parallel increases in these elements were observed from days 1 to 2, and an antiparallel (inverse) fluctuation was observed from days 2 to 14 in both groups (Fig. 6A and B). Changes in urinary sodium and potassium excretion were not associated with fluctuations in serum sodium or potassium in either group (Fig. 6C and D).

3. 6. Effect of Hydrocortisone Supplementation on Serum Sodium and Potassium

In this study, nine patients in the non-SVS group showed low serum cortisol (<10 μg/mL) and were accordingly supplemented with hydrocortisone for ethical reasons (8). Hydrocortisone was first administered at 7.44 ± 3.13 days (median, day 7), and all cases received hydrocortisone after day 4. The mean administered dose was 144.4 ± 49.7 mg/day, and the average duration of cortisol replacement was 6.89 ± 3.35 days. To investigate the effect of hydrocortisone supplementation on electrolyte changes, serum sodium and potassium changes were compared between these nine

patients and the 106 patients not given hydrocortisone supplementation in the non-SVS group (Fig. 7). Serum sodium was more stable in the patients given hydrocortisone compared with those not given the steroid (Fig. 7 A); the decrease in serum sodium was suppressed. Additionally, serum potassium was maintained lower in the nine patients given hydrocortisone, compared with the other 106 patients (Fig. 7 B).

3. 7. Evaluation of SVS Predictive Power of Sodium Metabolism-related Hormones on Day 1

To evaluate the SVS predictive power of sodium metabolism-related hormones on day 1, simple logistic regression analysis was performed (Fig. 8A-F and Table 2). Among these six variables, cortisol on day 1 was the most suitable prognostic factor for SVS (Log-likelihood ratio; 11.95, p = 0.0005). According to ROC curve analysis, the hormones with significant differences were ACTH, cortisol, and AVP, and these areas under the curve (AUC) were 0.75, 0.72, and 0.67, respectively. (Fig. 9A-F and Table 3). Cut-off values to predict the SVS were ACTH > 139.7 pg/mL on day 1 (62.5% sensitivity and 82.1% specificity for SVS); cortisol >42.75 μg/dL on day 1 (41.2% sensitivity and 95.5% specificity for SVS); and AVP >13.75 pg/mL on day 1 (82.4% sensitivity and 52.8% specificity for SVS), respectively.

3.8. Evaluation by Multiple Logistic Regression Analysis

Variables that were significantly different in univariate analysis, including ACTH, cortisol, AVP on day 1, fluctuation of serum sodium concentrations, and hyponatremia (≤ 135 mEq/L) were evaluated with age and sex by multiple logistic regression analysis. The variance of inflation factor was 1.41, and ROC curve analysis revealed an AUC of 0.83 ($p < 0.0001$) for SVS occurrence. The model fit was assessed using the Hosmer-Lemeshow test. The p value for goodness-of-fit was 0.64.

Table 4 shows the odds ratio and 95% confidence intervals of each variable. Among these, fluctuations in serum sodium concentrations were associated with SVS occurrence.

4. Discussion

There were four major findings in this study. First, circulating AVP, ACTH, and cortisol concentrations on day 1 were significantly higher in the SVS group compared with the non-SVS group. Second, the fluctuations in serum sodium in the SVS group were significantly greater than those in the non-SVS group. Third, over the 14-day observation period, there were parallel increases in serum sodium and potassium from days 1 to 2, and antiparallel (inverse) fluctuations from days 2 to 14. Finally, multiple logistic regression analysis showed that fluctuations in serum sodium concentrations were the only factor associated with SVS occurrence.

4. 1. Sodium Metabolism-Related Hormones and SVS

We compared the temporal changes in endocrinological assessment between the SVS and non-SVS groups and SAH severity. AVP and ACTH concentrations on day 1 were significantly higher in the SVS group compared with the non-SVS group, and both hormones increased on day 1 and were reduced thereafter. Stressful conditions, such as cerebral aneurysm rupture, may lead to increases in AVP and ACTH, and elevated ACTH may cause excessive cortisol release from adrenal glands. Cortisol increased on day 1 and declined gradually, in contrast to the decrease in ACTH. This suggests that critically ill patients have reduced cortisol breakdown [16]. Several reports examined the activity of the HPA axis in patients with SAH in the acute phase [17-19]. Vergouwen et al. showed that increased cortisol concentrations after SAH onset were associated with delayed cerebral ischemia [18]. Their results are in line with our current findings. Several other previous studies have investigated the relationship between SAH and AVP [6,8,20]. However, no studies have investigated

the relationship between AVP and SVS. When compared by WFNS grade, only cortisol on day 1 was significantly higher in patients with WFNS grades IV, V compared with patients with WFNS grades I–III. However, when compared by Fisher group, there were no significant differences in any of the tested hormones. Although we could not rule out the possibility that the increase in stress-related hormones on day 1 might have been due to severe SAH, these results may indicate that the magnitude of stress at the onset of aneurysm rupture was more sensitive to stress-related hormone concentrations on day 1 than to the scale based on the consciousness level and imaging studies at admission. We accordingly demonstrated that elevated ACTH, cortisol, and AVP levels on the first day after SAH might be predictive markers for the development of SVS. Although, the highest AUC value was 0.75 for ACTH on day 1, the prediction by serum cortisol, which is readily available and the highest Log-Likelihood ratio, might be useful clinically. The AUC values of stress-related hormones were not particularly high, but were higher than other established delayed cerebral ischemia prediction scoring system such as VASOGRADE, a grading scale that combined WFNS grade and modified Fisher scale. The AUC of VASOGRADE was reported as 0.63 [21].

There was no correlation between changes in BNP concentration and changes in serum sodium in this study. Many studies have suggested a relationship between BNP concentrations and hyponatremia related to SAH [5,6,8,22]. However, most of these studies had small sample sizes [5,6,22]. Hannon et al. conducted a study of 100 patients with SAH [8]. No difference in plasma BNP concentrations was observed between any pathology of hyponatremia. Their results are in line with our current findings. Regarding active renin and aldosterone, all previous clinical studies investigating the relationship between SAH and aldosterone reported plasma aldosterone levels were not increased above the physiological upper limit [7,23,24]. Similarly, in the present study, the mean active renin and aldosterone concentrations were not increased above the physiological upper limit.

The effect of renin and aldosterone on the sodium and potassium kinetics of patients with SAH in the acute phase was limited.

4. 2. Potential Pathophysiology of Serum Sodium Fluctuations and the Decrease in Serum Sodium Prior to SVS

In this study, we showed that the magnitude of serum sodium fluctuations was related to SVS. The mean fluctuation range of serum sodium in the SVS group was significantly greater compared with the non-SVS group. In terms of the sodium and potassium kinetics, over the 14-day observation period, there were parallel increases in serum sodium and potassium from days 1 to 2, and antiparallel (inverse) fluctuations from days 2 to 14. AVP increased on day 1 and declined thereafter, whereas cortisol increased on day 1 and then gradually decreased. These findings suggest that the decrease after excessive secretion of AVP might lead to increase serum sodium and potassium concentrations initially. Subsequently, coupled with the decrease in AVP, serum sodium might continuously increase while MR activation by high serum cortisol continued , and serum sodium concentrations would begin to decrease when cortisol concentrations decreased to levels that did not activate MR. The greater the decrease in cortisol, the more sustained the decrease in serum sodium. A sequential decrease in serum sodium prior to SVS might reflect the descending phase of serum sodium fluctuations. And it is speculated that this serum sodium fluctuation is caused by a response to stress-related hormones associated with the onset of SAH. The difference in timing between the cortisol and serum sodium peaks may be caused by the prolonged high cortisol levels and the associated increase in MR activation. The finding that hydrocortisone supplementation suppressed the decrease in serum sodium and reduced serum potassium in nine patients in the non-SVS group indirectly supports this concept. Selective hydrocortisone supplementation based on serum cortisol and sodium concentrations may moderate the magnitude of serum sodium fluctuations.

Multiple logistic regression analysis showed that serum sodium fluctuations were associated with SVS occurrence. Although the number of patients with SVS was small, the Hosmer-Lemeshow test showed goodness-of-fit ($p = 0.64$). The results of this multiple logistic regression analysis suggest that the combined effect of AVP, ACTH, and cortisol dynamics might affect the magnitude of serum sodium fluctuations.

4. 3. Study Limitations

This study had some limitations. First, the number of patients with SVS was small. In our previous report of patients from 2007 to 2016, the incidence of SVS was 27.8% (27/97) [4], whereas in the present study, the incidence of SVS was 13.5% (18 of 133). Improvements in SAH management have decreased the incidence of SVS. Second, catecholamines were not measured in this study. Activation of the sympathetic nervous system occurs following SAH [23,25]. The catecholamine surge may have a role in the pathogenesis of hypokalemia in patients with SAH [26], but is unlikely to be the major cause of serum sodium fluctuations. Third, the roles of tissue necrosis and acid-base metabolism were not considered in this study. Furthermore, most measurements were taken at the respective hospitals, and the possible impact of variations in measurement results among facilities on the statistical analyses could not be ruled out. In particular, cortisol concentrations could not be corrected for differences between methods, which may have affected the results. Finally, active renin and aldosterone could only be measured in a limited number of cases for whom serum could be cryopreserved, which could limit the conclusions of the current study.

5. Conclusion

Circulating AVP, ACTH, and cortisol were elevated on day 1 after SAH in patients with SVS compared with those without SVS. Elevated levels of ACTH/cortisol and AVP on day 1 may be

predictive markers for the occurrence of SVS. Multiple logistic regression analysis revealed that fluctuations of serum sodium concentrations were associated with SVS occurrence. Serum sodium fluctuations were associated with stress-related hormonal dynamics.

Figure legends

Fig. 1. Comparison of hormonal changes between the SVS and non-SVS groups.

Comparison of hormonal changes between the SVS (n = 18) and non-SVS (n = 115) groups on days 1, 7, and 13. Mean plasma AVP (A), plasma ACTH (B), serum cortisol (C), and plasma BNP (D) concentrations. The active renin concentrations (E) and aldosterone concentrations (F) in 34 cases (SVS, 5 cases; non-SVS, 29 cases) in which serum was cryopreserved were measured at three time points (days 1, 7, and 12). *$p < 0.05$, **$p < 0.01$.

Fig. 2. Comparison of hormonal changes between patients with WFNS grades I–III and grades IV, V.

Comparison of hormonal changes between patients with WFNS grades I–III (85 cases) and with grades IV, V (48 cases) on days 1, 7, and 13. Mean plasma AVP (A), plasma ACTH (B), serum cortisol (C), and plasma BNP (D) concentrations. Active renin concentrations (E) and aldosterone concentrations (F) in 34 cases (grade I–III, 22 cases; grade IV, V, 12 cases) for whom serum was cryopreserved were measured at three time points (days 1, 7, and 12). **$p < 0.01$.

Fig. 3. Comparison of hormonal changes between patients with Fisher group 3 and Fisher Group 4.

Comparison of hormonal changes between patients with Fisher group 3 (116 cases) and Fisher group 4 (17 cases) on days 1, 7, and 13. Mean plasma AVP (A), plasma ACTH (B), serum cortisol (C), and plasma BNP (D) concentrations. Active renin concentrations (E) and aldosterone concentrations (F) in 34 cases (Fisher group 3, 32 cases; Fisher group 4, 2 cases) for whom serum was cryopreserved were measured at three time points (days 1, 7, and 12).

Fig. 4. **Serum sodium changes in each case of the SVS group.**

Fourteen cases suffered from SVS during a period of reduced serum sodium (A). Four cases suffered from SVS during a period of increased serum sodium, but in these cases, serum sodium was reduced to its lowest concentration 2 – 3 days before the onset of SVS, and SVS occurred while correcting for the decreased serum sodium (B). The rate of increase/decrease in each case was expressed as a percentage based on the serum sodium concentration 5 days before the onset of SVS.

Fig. 5. Fluctuations in serum sodium.

The mean serum sodium concentrations were within the normal range throughout the 14-day period in both groups (A). The mean fluctuation range in serum sodium concentration was significantly greater in the SVS group compared with the non-SVS group (B). $^{**}p < 0.01$.

Fig. 6. Comparison of changes in serum sodium and potassium concentrations between the SVS and non-SVS groups.

The 14-day time course of serum sodium and potassium concentration changes in the SVS group (n = 18) (A) or non-SVS group (n = 115) (B). Parallel increases were observed from days 1 to 2, and thereafter, antiparallel fluctuations were observed from days 2 to 14 in both groups. Changes in

urinary sodium and potassium excretion were not associated with fluctuations in serum sodium or potassium in either group (Fig. 6C and D).

Fig. 7. Comparison of changes in serum sodium and potassium concentrations between hydrocortisone-supplemented and non-supplemented patients in the non-SVS group

Changes in serum sodium (a) and potassium (b) concentrations were compared between nine patients supplemented with hydrocortisone and 106 patients not supplemented with hydrocortisone in the non-SVS group. Serum sodium was more stable in the nine patients given hydrocortisone supplementation than in the 106 patients not given hydrocortisone supplementation in the non-SVS group (a). The serum sodium decrease was suppressed. Serum potassium was maintained lower in the nine patients given hydrocortisone supplementation than in the 106 patients not given hydrocortisone supplementation in the non-SVS group (b).

Fig. 8. Simple logistic regression analysis of sodium metabolism-related hormones on day 1 to predict SVS.

The results of simple logistic regression analysis of AVP, ACTH, cortisol, BNP, active renin and aldosterone concentrations on day 1 are shown (A-F).

Fig. 9. ROC curve analysis of sodium metabolism-related hormones on day 1 to predict SVS.

(A–F) Results of ROC curve analyses of AVP, ACTH, cortisol, BNP, active renin, and aldosterone concentrations. Each circle indicates the selected cut-off points for the prediction of SVS (A–C).

Tables

Table 1. Patient characteristics

	SVS (−)	SVS (+)	*p*
Cases	115	18	
Mean age (years)	64.4	60	0.20
Female sex (%)	84 (74.3)	14 (77.8)	0.75
WFNS Grade			
Grade I	56	5	0.19
Grade II	14	6	
Grade III	7	1	
Grade IV	17	3	
Grade V	21	3	
Fisher Group 3	100	16	0.82
Fisher Group 4	15	2	
Acute hydrocephalus	3	2	0.08
Blood urea nitrogen (mg/dL)	14.53 ± 5.02	13.53 ± 3.27	0.63
Serum creatinine (mg/dL)	0.68 ± 0.23	0.61 ± 0.11	0.44
Location of An			
Anterior	108	17	0.93
Posterior	7	1	
Treatment modality			
Clip	76	11	0.68
Coil	39	7	
Intubation more than 2 days			
	12	3	0.44

Hyponatremia (≦ 135 mEq/L)				
Yes	Treatment responder*	33	7	＜0.01
	Treatment-resistant	8	6	
No		74	5	
Outcome				
	mRS 0–2	58	4	0.03
	mRS 3–6	57	14	

An = aneurysm, mRS = modified Rankin scale.

Treatment responder: hyponatremia corrected within 2 days

Treatment resistant: >2 days required to correct hyponatremia

Table 2. Simple logistic regression analysis of six hormones on day 1 for the prediction of SVS.

	Odds ratios (β1)	**95% CI**	**Log-Likelihood ratio**	***p***
AVP on day 1	1.019	1.006 to 1.034	8.04	0.0046
ACTH on day 1	1.004	1.002 to 1.007	10.36	0.0013
Cortisol on day 1	1.076	1.031 to 1.129	11.95	0.0005
BNP on Day 1	1.004	1.001 to 1.007	7.018	0.0081
Active renin on Day 1	0.798	0.314 to 1.027	1.70	0.1925
Aldosterone on Day1	0.858	0.471 to 1.008	3.14	0.0764

CI, confidence interval.

Table 3. ROC curve analysis of six hormones on day 1 for the prediction of SVS.

	Area under curve	95% CI	*p*
AVP on day 1	0.67	0.52 to 0.82	0.0218
ACTH on day 1	0.75	0.63 to 0.87	0.0013
Cortisol on day 1	0.72	0.58 to 0.86	0.0041
BNP on Day 1	0.57	0.44 to 0.71	0.1667
Active renin on Day 1	0.60	0.41 to 0.78	0.5930
Aldosterone on Day1	0.82	0.64 to 0.99	0.1320

CI, confidence interval.

Table 4. Multiple logistic regression analysis of AVP, ACTH, cortisol on day 1, fluctuation of serum sodium, and hyponatremia.

Variables	Odds ratio	95% CI (profile likelihood)
Age	0.985	0.938 to 1.033
Sex	0.701	0.109 to 3.559
AVP on day 1	1.013	0.994 to 1.034
ACTH on day 1	1.003	1.000 to 1.008
Cortisol on day 1	1.005	0.937 to 1.078
Hyponatremia (≦ 135 mEq/L)	1.354	0.347 to 5.718
Fluctuation of serum sodium	1.220	1.065 to 1.423

CI, confidence interval.

Acknowledgements

We would like to thank Mr. Kenichi Uto, Ms. Itsuko Sato, and Mr. Takamitsu Imanishi at the Department of Clinical Laboratory, Kobe University Hospital for measuring serum active renin and aldosterone concentrations. We are grateful for statistical advice from the members of the Kobe University Hospital Clinical and Translational Research Center. We thank J. Ludovic Croxford, PhD, and Susan Furness, PhD, from Edanz (https://jp.edanz.com/ac), for editing drafts of this manuscript.

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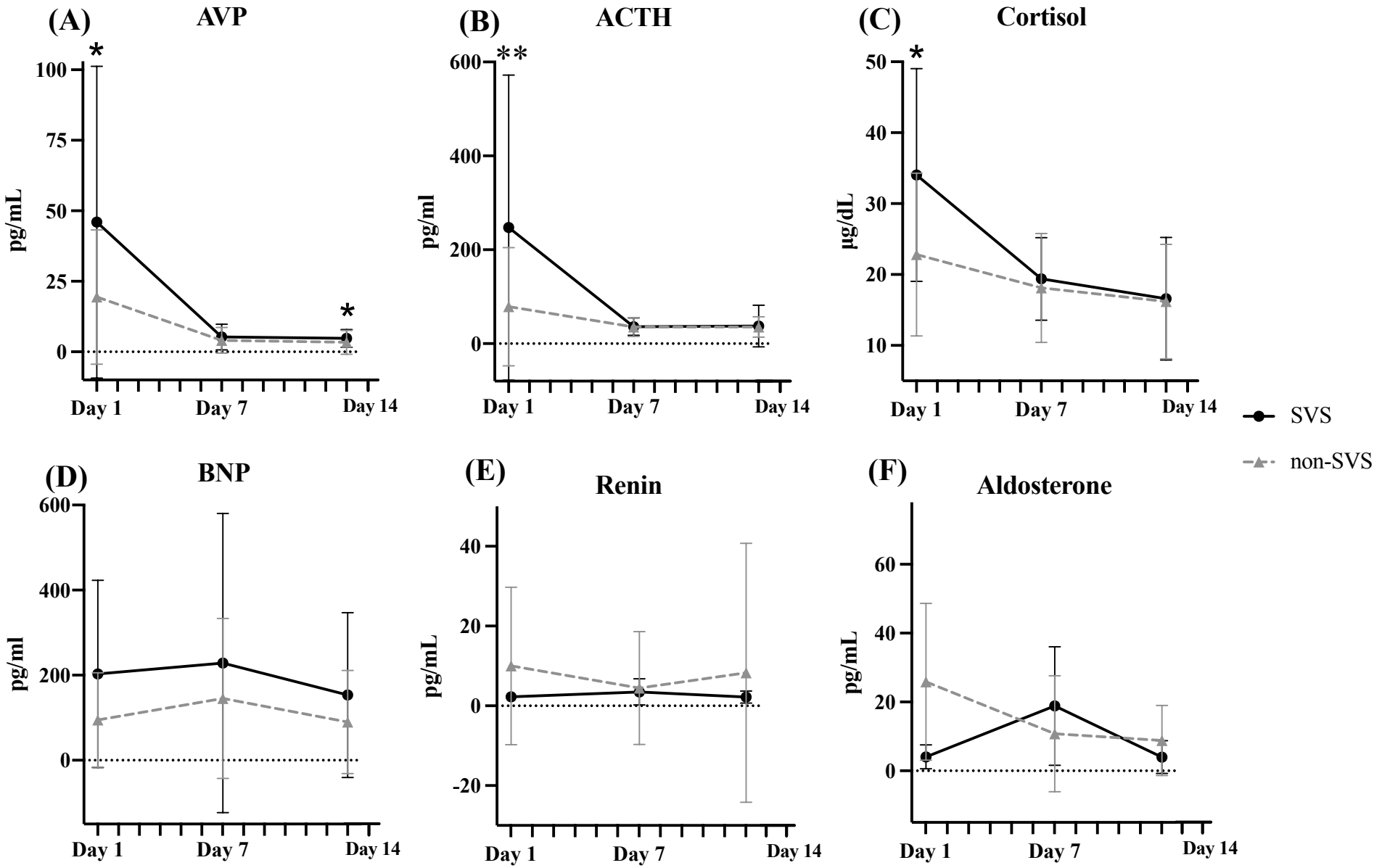
Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, YU. The data are not publicly available because they are containing information that could compromise the privacy of the research participants.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Day 1
Day 7
Day 14
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pg/ml
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400
200
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Day 1
Day 7
Day 14
(C)
Cortisol
μg/dL
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Day 1
Day 7
Day 14
SVS
non-SVS
(D)
BNP
pg/ml
600
400
200
0
Day 1
Day 7
Day 14
(E)
Renin
pg/mL
40
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Day 1
Day 7
Day 14
(F)
Aldosterone
pg/mL
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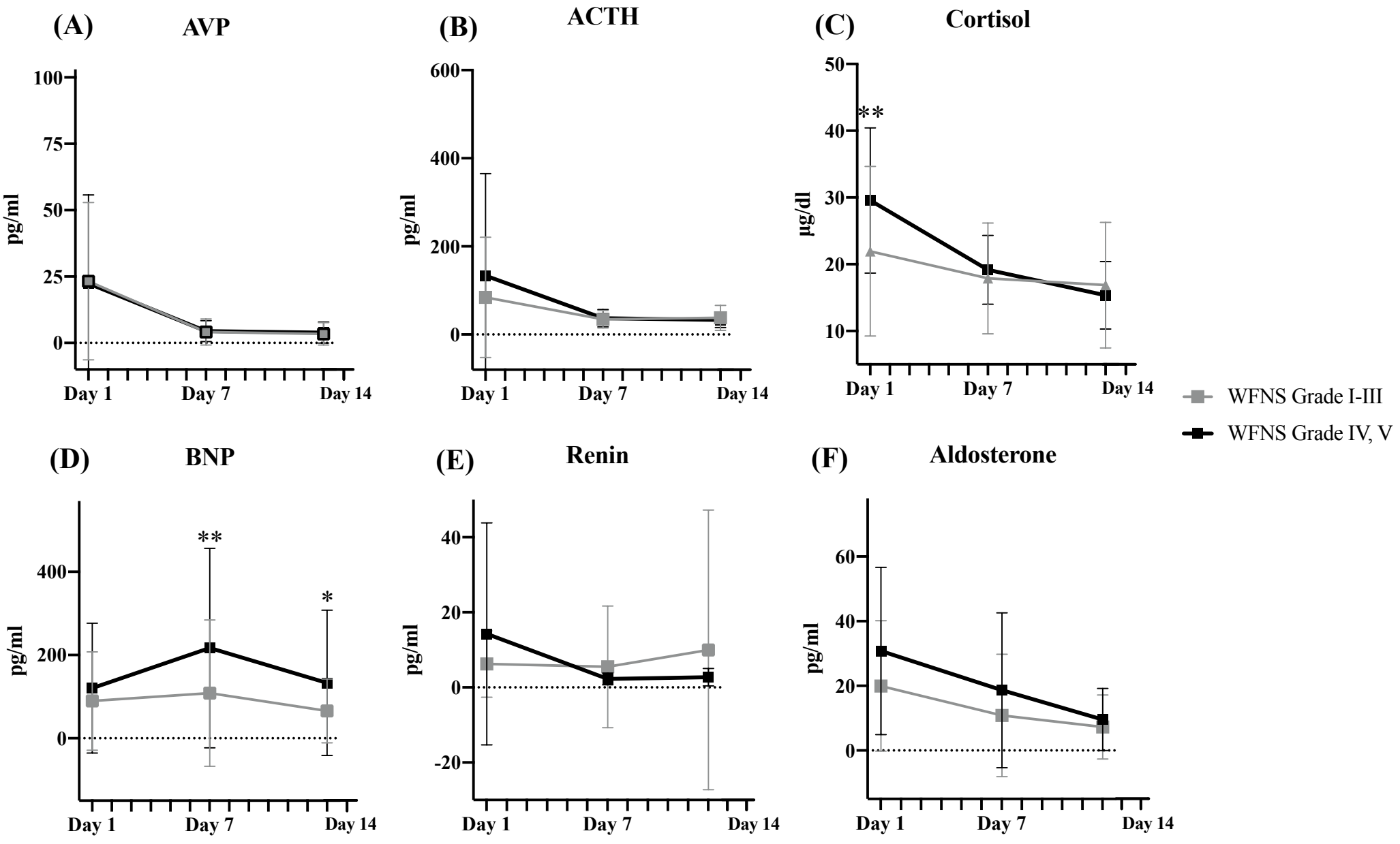
20
0
Day 1
Day 7
Day 14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0
Day 1
Day 7
Day 14
(C)
Cortisol
µg/dl
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40
30
20
10
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Day 1
Day 7
Day 14
WFNS Grade I-III
WFNS Grade IV, V
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pg/ml
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200
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Day 1
Day 7
Day 14
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Renin
pg/ml
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Day 7
Day 14
(F)
Aldosterone
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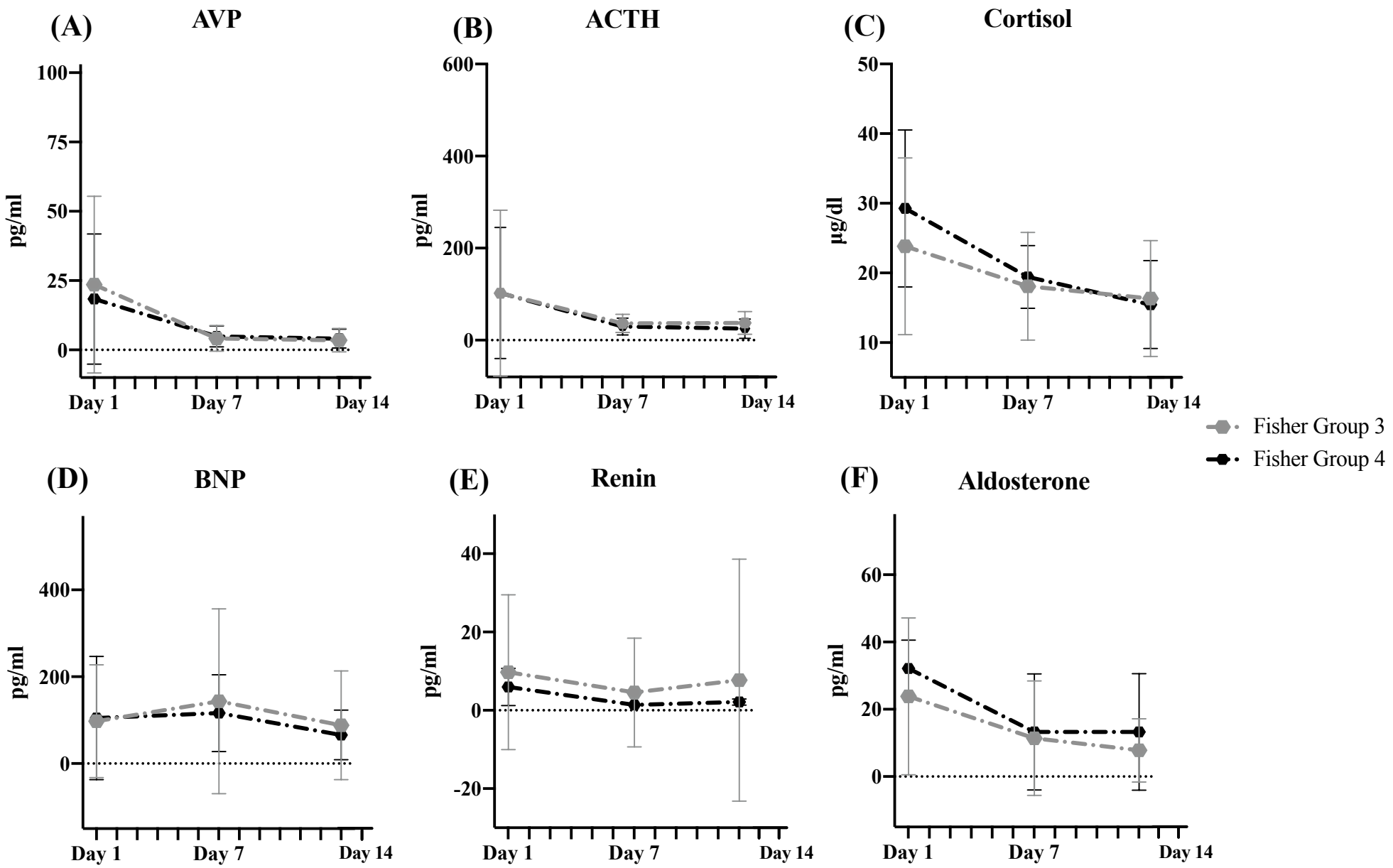
Day 1
Day 7
Day 14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Day 1
Day 7
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200
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Day 1
Day 7
Day 14
(C)
Cortisol
µg/dl
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Day 1
Day 7
Day 14
Fisher Group 3
Fisher Group 4
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Renin
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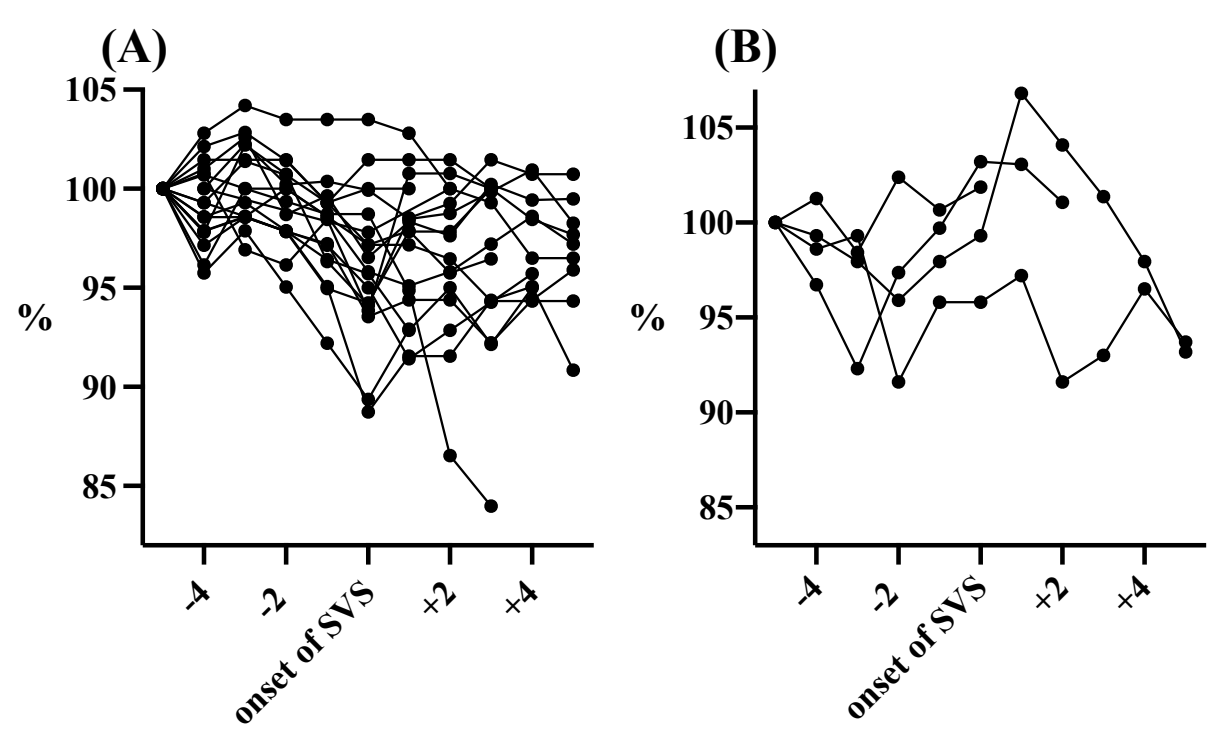
Day 7
Day 14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%
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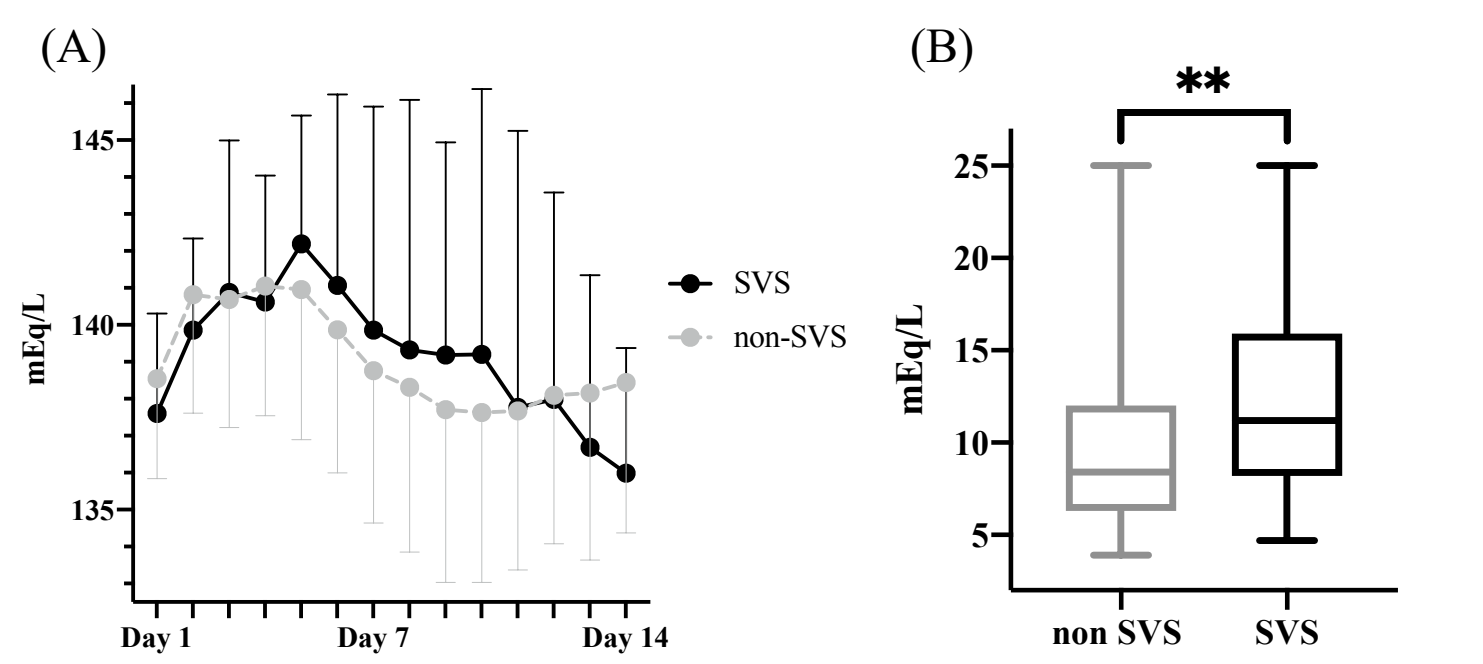
onset of SVS
+2
+4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Day 7
Day 14
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non-SVS
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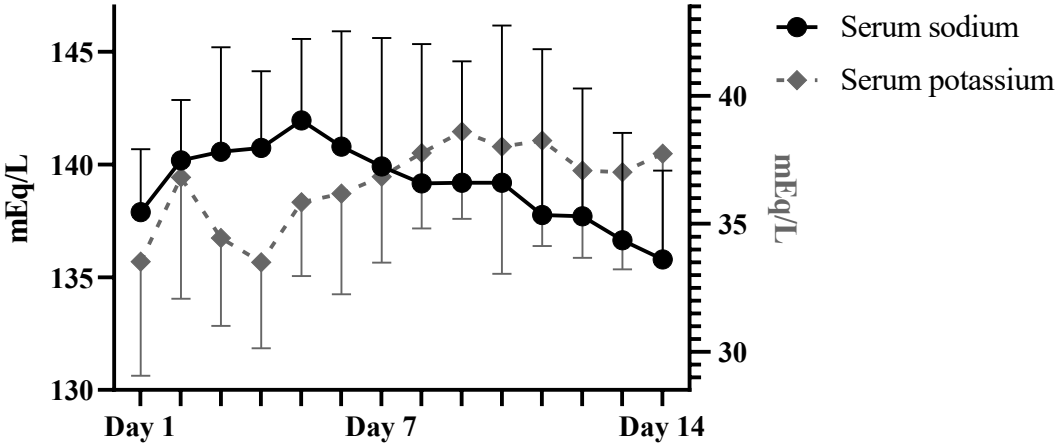
5
mEq/L
non SVS
SVS

(A) Serum sodium and potassium changes in the SVS group



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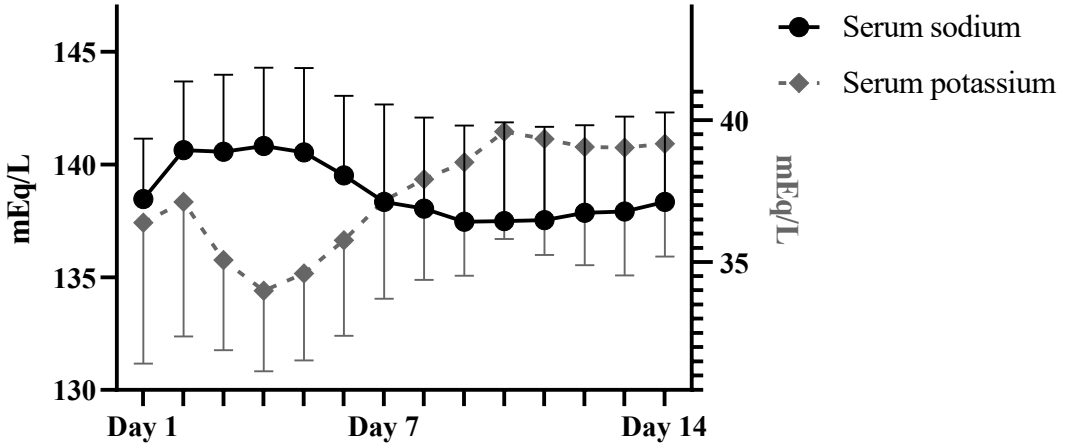

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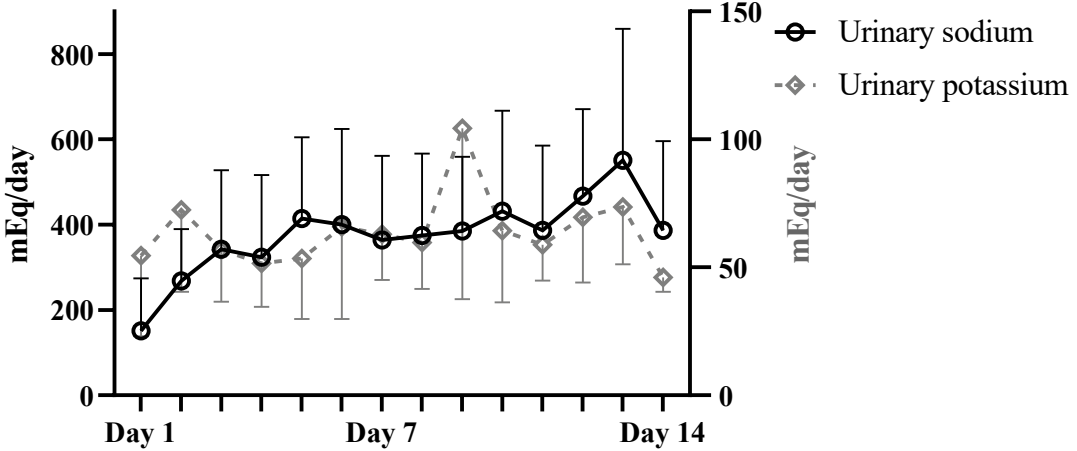
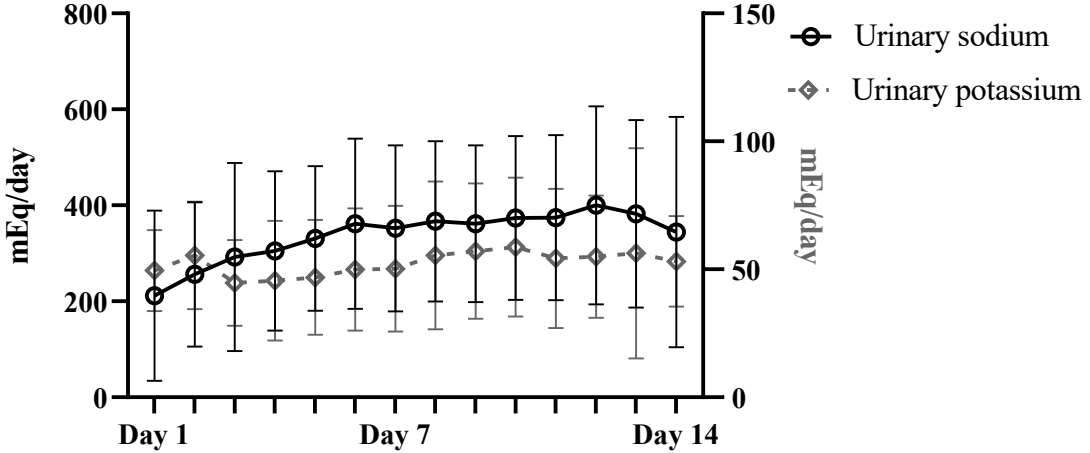
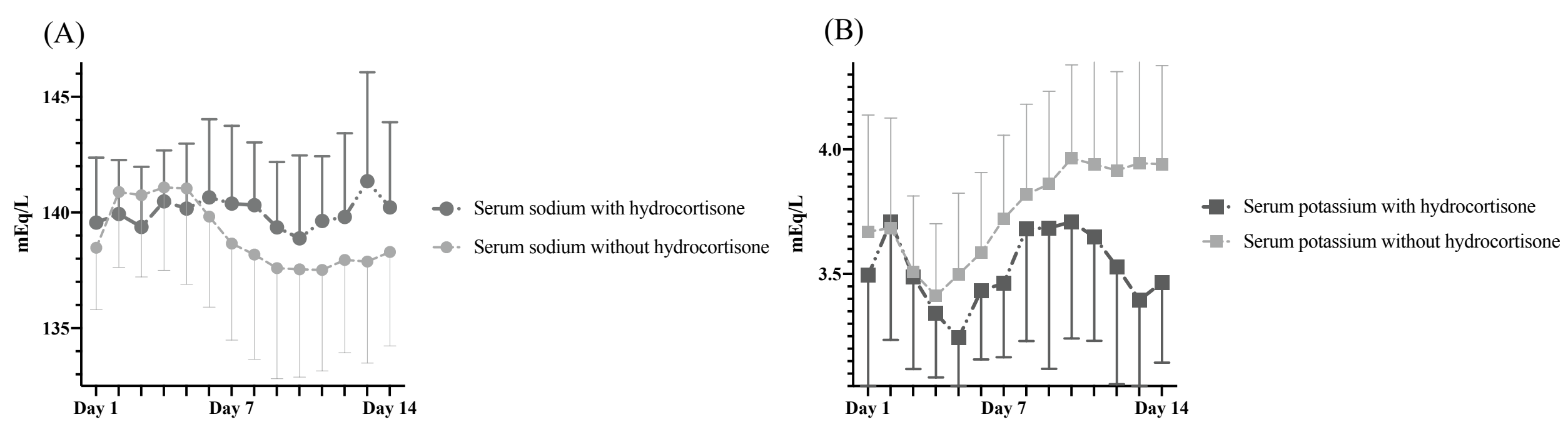


(D) Urinary sodium and potassium excretion in the non SVS group

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135
mEq/L
Day 1
Day 7
Day 14
Serum sodium with hydrocortisone
Serum sodium without hydrocortisone
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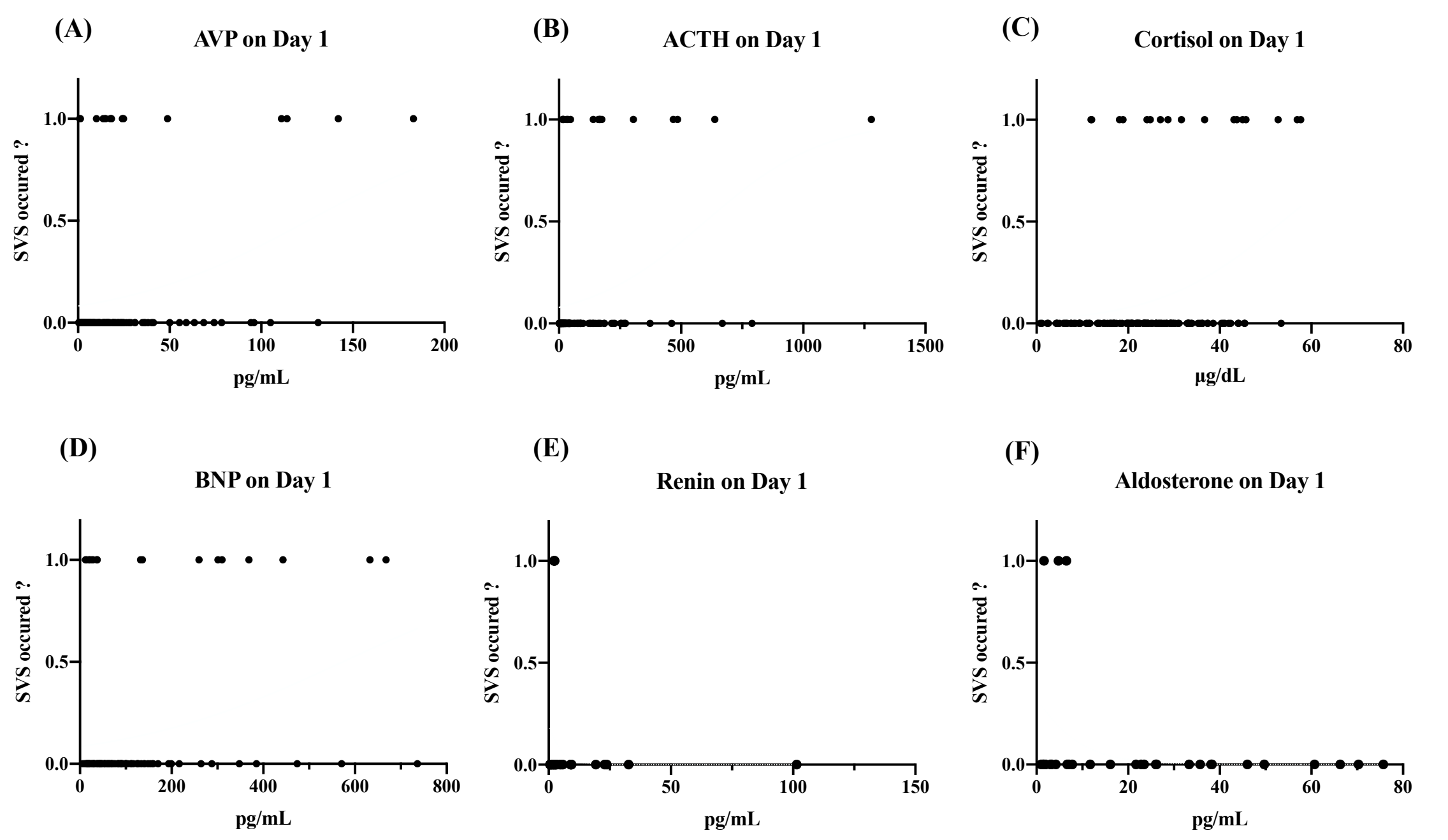
3.5
mEq/L
Day 1
Day 7
Day 14
Serum potassium with hydrocortisone
Serum potassium without hydrocortisone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150
200
pg/mL
(B)
ACTH on Day 1
SVS occured ?
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0.5
0.0
0
500
1000
1500
pg/mL
(C)
Cortisol on Day 1
SVS occured ?
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0.5
0.0
0
20
40
60
80
µg/dL
(D)
BNP on Day 1
SVS occured ?
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0.5
0.0
0
200
400
600
800
pg/mL
(E)
Renin on Day 1
SVS occured ?
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0.5
0.0
0
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100
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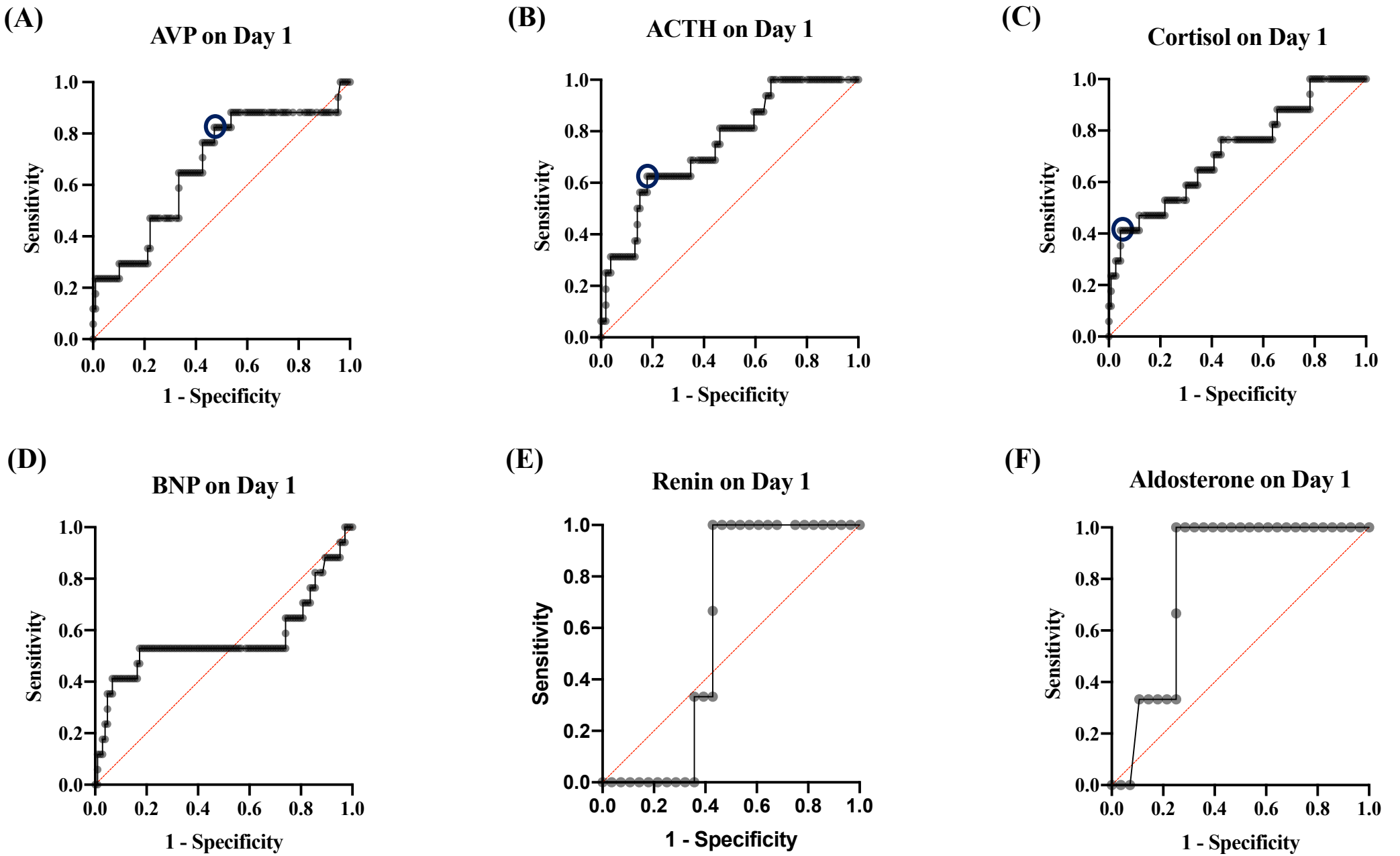
pg/mL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AVP on Day 1
Sensitivity
1 - Specificity
(B)
ACTH on Day 1
Sensitivity
1 - Specificity
(C)
Cortisol on Day 1
Sensitivity
1 - Specificity
(D)
BNP on Day 1
Sensitivity
1 - Specificity
(E)
Renin on Day 1
Sensitivity
1 - Specificity
(F)
Aldosterone on Day 1
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0