Plasma Atrial Natriuretic Factor and Subarachnoid Hemorrhage

Michael Diringer, MD, Paul W. Ladenson, MD, Barney J. Stern, MD, Jonathan Schleimer, MD, and Daniel F. Hanley, MD

Hyponatremia is common following aneurysmal subarachnoid hemorrhage and has been linked to the syndrome of inappropriate secretion of antidiuretic hormone. However, the demonstration of volume depletion and natriuresis in some patients has suggested that salt wasting is a more likely etiology. Atrial natriuretic factor appears to play a role in both central and peripheral regulation of sodium homeostasis. To investigate the behavior of circulating atrial natriuretic factor following subarachnoid hemorrhage, we studied 25 patients with intracranial aneurysms: 21 after acute subarachnoid hemorrhage and four without evidence of recent rupture. Atrial natriuretic factor was measured by radioimmunoassay of extracted plasma (normal value, 20.8 ± 24.6, mean ± 3 SD). Mean ± SEM plasma atrial natriuretic factor concentration was elevated to 84 ± 25 pg/ml on Day 1, rose to 134 ± 29 pg/ml on Day 3, and fell to 86 ± 17 pg/ml by Day 7 after subarachnoid hemorrhage (p < 0.01). In two patients (9.5%) who developed hyponatremia after aneurysm rupture, plasma concentrations were no different from that in the group as a whole; concentrations in patients with no evidence of recent subarachnoid hemorrhage were not elevated. Neither fluid administration nor timing of surgery could account for the elevated concentrations. We conclude that concentrations of circulating atrial natriuretic factor are elevated after subarachnoid hemorrhage but do not solely account for the accompanying hyponatremia. (Stroke 1988;19:1119-1124)

Disorders of serum sodium concentration are well recognized in neurologic patients and are frequently associated with worsening of the patients' neurologic condition. Hyponatremia has been reported to occur in 9-33% of patients after aneurysmal subarachnoid hemorrhage (SAH)1,2 and has often been attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH),3-6 in which elevated concentrations of circulating antidiuretic hormone (ADH) produce free water retention7 and dilutional hyponatremia. Indeed, patients with SAH often meet the diagnostic criteria for SIADH3-5; hyponatremia with hyposmolar serum, hyperosmolar urine, urinary sodium concentration of >25 meq/l, and apparent euvolemia in the absence of renal, adrenal, or thyroid disease. In some patients the diagnosis of SIADH has been supported by the finding of elevated ADH concentrations in blood and cerebrospinal fluid8 and by the correction of hyponatremia with fluid restriction.6

However, other patients with hyponatremia after SAH exhibit progressive weight loss and volume contraction, findings that are inconsistent with SIADH. Nelson et al9 studied 12 unselected neurosurgical patients (10 with aneurysms and two with head trauma) who fulfilled the laboratory criteria for SIADH and found that, in fact, 10 had significantly reduced blood volumes. Wijdicks et al10 also observed this pattern of hyponatremia, volume contraction, and negative sodium balance in a group of patients with SAH. In a primate model of SAH,11 hyponatremia was associated with a negative sodium balance without altered concentrations of circulating ADH or aldosterone. The presence of hyponatremia and its precise underlying pathophysiology has important clinical consequences. In a large retrospective study,12 hyponatremia was associated with an increased incidence of cerebral infarctions. Furthermore, hyponatremic patients who were fluid-restricted, the accepted treatment for SIADH, suffered a higher incidence of cerebral infarctions.

It has been proposed that the hyponatremia, volume contraction, and negative sodium balance...
found in some patients after SAH might be due to a brain natriuretic hormone or to altered neural input to the kidneys. The natriuretic peptide atrial natriuretic factor (ANF) is produced in and released from the atrial myocardium. ANF has also been identified in areas of the central nervous system (CNS) involved in cardiovascular, sodium, and fluid regulation. We tested the hypothesis that the concentration of circulating ANF is elevated after acute SAH. We also investigated the relation between serum sodium and circulating ANF concentrations in this setting.

**Subjects and Methods**

Informed consent was obtained from 25 study patients or family members, 21 patients after acute rupture of an intracranial aneurysm, three with unruptured aneurysms before and after elective surgery, and one perioperatively 30 days after SAH. No patient had a recent history of head trauma, mycotic aneurysm, congestive heart failure, arrhythmias, or renal or endocrine disease. Computed tomography and cerebral angiography were performed on all patients. No patient received diuretics, and all were given supraphysiologic doses of dexamethasone (16–40 mg/day) in the perioperative period. Preoperative intravenous fluids consisted of 2–3 L/day of normal saline. Postoperative fluid and sodium administration were adjusted to maintain normal intravascular volume and to avoid negative sodium balance. During this period, fluid administration was always >2 L/day. Aneurysms were clipped in 19 patients within 2 days of presentation. Five patients were treated for vasospasm with volume expansion using normal saline and colloids (5% human plasma protein fraction), and inotropic agents (dopamine) and vasopressors (phenylephrine) were added when necessary in an attempt to resolve neurologic deficits and to maintain neurologic function. The time of clinical onset of SAH, the Hunt and Hess grade on presentation, the aneurysm location, and the patient’s sex and age were recorded. Serum sodium, serum creatinine, and plasma ANF concentrations were determined each morning. In patients with ruptured aneurysms, these determinations were continued for 7–14 days; patients with unruptured or remotely ruptured aneurysms were assessed before and for 6 days after surgery. Heart rate and rhythm, blood pressure, and when available, central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) were recorded when blood samples were collected. Neurologic function was monitored using the Glasgow Coma Scale.

Plasma samples were collected in tubes containing EDTA and 1 µg/ml peptatin A, were cooled immediately to 4°C, were separated by centrifugation at 2,000 g for 10 minutes at 5°C, and were stored at −70°C. Before assay, 2.5-ml plasma samples were acidified with 2.5 ml 0.1% trifluoroacetic acid (TFA) and centrifuged at 2,000 g for 45 minutes at 5°C. ANF was extracted by loading the supernatant onto preactivated (5 ml 60% acetonitrile, 0.1% TFA) C_{18} octadecyl silica cartridges (Sep-Pak C_{18}, Waters Associates, Milford, Massachusetts), which were then washed with 20 ml 0.1% TFA and eluted with 3 ml 60% acetonitrile, 0.1% TFA solution. Recovery of [125I]human ANF was 90%; reported values are not corrected. Extracted samples were then dried in a centrifugal concentrator (Spin-Vac, Farmingdale, New York) with a liquid nitrogen coolant and were resuspended in 250 µL assay buffer for analysis in duplicate. ANF was quantified by specific radioimmunoassay for human α-ANF (Peninsula Laboratories, Belmont, California). Assay sensitivity was 4–8 pg/tube; intra-assay and interassay coefficients of variation were 5% and 16%, respectively. All of an individual patient’s samples were assayed in the same run. The normal mean ± 3 SD ANF concentration was 20.8 ± 24.6 pg/ml (n = 38).

Serial plasma ANF concentrations were analyzed independently for patients with ruptured and unruptured aneurysms using one-way analysis of variance (ANOVA) for repeated measures. For patients with ruptured aneurysms, data were evaluated for three periods: an initial value 1 or 2 days after acute SAH, the peak value on Day 3 or 4, and a subsequent value on Day 6 or 7. In each patient with an unruptured aneurysm, seven sequential daily values were analyzed; one patient with a remotely ruptured aneurysm was included in the unruptured group. Comparisons of patients with ruptured and unruptured aneurysms, comparisons of Hunt and Hess grades and aneurysm locations in patients with ruptured aneurysms, and comparisons of patients who were and were not treated for vasospasm employed a two-way ANOVA. Results are expressed as mean ± standard error of the mean; p<0.05 was considered significant. When appropriate, the level of significance was corrected for multiple comparisons using the Bonferroni correction.

**Results**

The patients’ Hunt and Hess grade, aneurysm location, sex, and age are presented in Table 1. The majority of the patients with ruptured aneurysms (72%) were Grades 1 or 2, and the most common location of ruptured aneurysm was the anterior communicating artery (50%); overall there were 18 women and seven men, and they ranged in age from 21 to 85 years. Throughout the study no patient experienced significant cardiac arrhythmia, congestive heart failure, or change in serum creatinine concentration.

Daily serum sodium and plasma ANF concentrations in patients after acute aneurysm rupture are depicted in Figure 1. Whereas the mean serum sodium concentrations remained normal, plasma ANF concentrations were elevated during the entire study. Plasma ANF concentrations on Day 1 were...
TABLE 1. Distribution of Patients by Hunt and Hess Grade, Aneurysm location, Sex, and Age

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>Ruptured</th>
<th>Unruptured</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Hunt and Hess grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACoA</td>
<td>10</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>PCoA</td>
<td>4</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>MCA</td>
<td>4</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>3</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>30–39</td>
<td>4</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>40–49</td>
<td>4</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>50–59</td>
<td>4</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>60–69</td>
<td>4</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>70+</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

ACoA, anterior communicating artery; PCoA, posterior communicating artery; MCA, middle cerebral artery.

84 ± 25 pg/ml, peaked at 134 ± 29 pg/ml on Day 3, and subsequently fell to 86 ± 17 pg/ml on Day 7 (p < 0.01). In two patients studied for a prolonged period, ANF concentrations returned to normal after 2 weeks. Concentrations of circulating ANF tended to be lower for patients of Hunt and Hess Grade 1 than for patients of other grades (initial value of 59 pg/ml, value of 55 pg/ml on Day 3–4), but these differences were not significant. Aneurysm location had no effect on ANF concentrations. There was no relation between mean arterial blood pressure and ANF concentrations. In nine patients in whom CVP was measured, there was no relation with circulating ANF (Figure 2). ANF concentrations were not different in the subgroup treated for vasospasm.

Following aneurysm rupture two patients (9.5% of 21) became hyponatremic, with serum sodium concentration falling to 123 meq/l on Day 9 and 126 meq/l on Day 12 for Patients 1 and 2, respectively (Table 2). Both patients were Hunt and Hess Grade 3 and had significant hydrocephalus requiring ventricular drainage. Patient 1 had diffuse vasospasm on angiography, and Patient 2 was treated for clinical vasospasm with hypervolemic hypertensive therapy. Urinary sodium concentrations were unavailable in Patient 1 and in Patient 2 ranged from 65 to 178 meq/l. The serial plasma ANF concentrations in these two patients were not significantly different from that of the remainder of the group; the highest levels reached were 167 pg/ml on Day 8 and 182 pg/ml on Day 3 in Patients 1 and 2, respectively. There was no relation between plasma ANF and serum sodium concentrations in normonatremic or hyponatremic patients.

Daily ANF and sodium concentrations for patients with unruptured aneurysms are presented in Figure 3. ANF values were normal (41 ± 7.6 pg/ml) preoperatively and did not change significantly after surgery. Plasma ANF concentrations in patients with unruptured aneurysms were significantly lower than in patients after acute SAH (p < 0.02). Sodium concentrations were normal preoperatively and did not change after surgery.

The data were sorted for time elapsed from SAH to surgery to determine if there was any increase in circulating ANF concentrations after surgery. The concentrations did not rise significantly postoperatively in either group.

Discussion

We investigated the relation between circulating ANF concentration and hyponatremia in 25 patients with ruptured or unruptured intracranial aneurysms. Serial measurements of circulating ANF concentrations revealed abnormally high levels only in patients whose aneurysms acutely ruptured; however, a relation between plasma ANF and serum sodium concentrations was not present in patients with ruptured aneurysms.

Hyponatremia is frequently associated with intracranial disease. In the early 1950s it was referred to as "cerebral salt wasting" because it was associated with natriuresis and volume contraction. Following the description of SIADH, hyponatremia after SAH was generally attributed to SIADH. This impression was supported by reports of elevated concentrations of ADH and corrected hyponatremia with fluid restriction. However, the observation that some patients with SAH actually had...
reduced blood volumes and negative sodium balances suggested that the pathogenesis of hyponatremia was increased sodium excretion rather than free water retention. Furthermore, fluid restriction in hyponatremic patients with SAH was correlated with an increased rate of cerebral infarction. Thus, while in some cases hyponatremia after SAH may be due to SIADH, in the majority of patients other mechanisms appear to be involved. These observations underscored the need for a better understanding of the underlying pathophysiologic process so that more appropriate therapy could be designed. Previous studies that have addressed this issue could not account for the negative sodium balance by changes in circulating ADH or aldosterone concentrations. Alternate hypotheses have attributed sodium wasting to increased concentrations of a circulating natriuretic factor or altered renal responsiveness to the normal sodium regulatory systems, perhaps by a neural mechanism. Therefore, we hypothesized that the concentration of ANF, with its natriuretic properties and its localization to brain centers involved in fluid and sodium regulation, would be elevated following aneurysmal SAH and would be correlated with hyponatremia.

Plasma concentrations of ANF were initially elevated following aneurysm rupture, rose to four to seven times normal, and then slowly declined. Several factors including vigorous fluid administration, effects of surgery, or aneurysm rupture per se could potentially have contributed to elevated ANF concentrations in these patients with ruptured aneurysms. Although it is possible that parenteral fluid administration accounted for some of the subsequent rise in ANF concentrations, the average admission plasma levels were already abnormally high and were different from controls and from patients with unruptured aneurysms. Since the patients had not received significant volumes of fluid before admission and, in fact, many were fluid-restricted, fluid administration cannot account for these initially elevated ANF concentrations. While the relation between circulating ANF concentrations and surgery was not a priori investigated, two lines of evidence in our study suggest that surgery itself did not solely account for the high concentrations seen: ANF levels in patients with ruptured aneurysms were elevated before surgery, and ANF concentrations did not rise significantly in either group after surgery. For the entire study, ANF concentrations were abnormally elevated in patients with ruptured aneurysms, and these elevations were significantly different from those in patients with unruptured aneurysms. Thus, the elevation in circulating ANF concentrations reported here is most closely associated with the acute hemorrhage itself and not with fluid administration or with surgery.

Circulating ANF concentrations after SAH were initially elevated, continued to rise for several days, and then gradually declined to initial values over approximately 1 week. In two patients studied for a prolonged period, plasma ANF concentrations returned to normal after 2 weeks. This temporal pattern is similar to that seen for the peak incidence of hyponatremia1 and vasospasm21-22 and suggests that the primary cerebral pathology may account for all three phenomena. Evidence for a CNS role in the control of circulating ANF concentrations is inconclusive. The principal mechanism for controlling cardiac ANF release is believed to be atrial stretch2; whether neural influences modulate cardiac ANF release has not been resolved. Adrenergic and cholinergic agents cause ANF release, which is blocked by appropriate antagonists. On the other hand, in some studies vagotomy does not alter release of ANF stimulated by atrial distention. However, these findings do not exclude the possi-

![Graph](image-url)

**TABLE 2.** Daily Sodium and ANF Concentrations for Two Patients Who Developed Hyponatremia After Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Day after hemorrhage</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (meq/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>136</td>
<td>137</td>
<td>138</td>
<td>139</td>
<td>141</td>
<td>130</td>
<td>130</td>
<td>126</td>
<td>125</td>
<td>123</td>
<td>124</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>70</td>
<td>107</td>
<td>142</td>
<td>123</td>
<td>167</td>
<td>146</td>
<td>139</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>136</td>
<td>136</td>
<td>142</td>
<td>143</td>
<td>136</td>
<td>134</td>
<td>134</td>
<td>132</td>
<td>137</td>
<td>135</td>
<td>133</td>
<td>128</td>
<td>126</td>
<td>126</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>54</td>
<td>68</td>
<td>182</td>
<td>150</td>
<td>135</td>
<td>78</td>
<td>104</td>
<td>144</td>
<td>136</td>
<td>164</td>
<td>100</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANF, atrial natriuretic factor.
bility that the CNS may modulate ANF release. We describe a group of patients with persistently elevated concentrations of circulating ANF in association with an acute intracranial event. In these patients disturbed atrial release is suggested by the absence of any correlation between plasma ANF concentrations and CVP.

It is not clear that elevated ANF concentrations alone account for the hyponatremia, volume contraction, and negative sodium balance that occur in patients with SAH. Despite therapy designed to prevent hyponatremia and volume contraction, two of our patients developed hyponatremia. Their plasma ANF concentrations were not significantly higher than that in the remainder of the group, thus it is unlikely that circulating ANF levels alone accounted for their hyponatremia. Sodium balance studies would detect a more subtle relation between renal sodium wasting and circulating ANF concentration in such patients since a significant and prolonged natriuresis would be required to produce hyponatremia. Furthermore, it is not clear that elevated concentrations of circulating ANF can independently produce natriuresis; it appears that neural input is also required. For example, atrial distention produces a rise in ANF concentration and natriuresis; however, the natriuresis but not the rise in ANF concentration is blocked by cardiac denervation. On the other hand, volume infusion produces a rise in ANF concentration and natriuresis, and neither is blocked by cardiac denervation. Thus, neural input can originate in the heart as following atrial distention or it can be widely distributed as occurs after volume expansion. Taken together, these data suggest that a rise in ANF concentration does not produce diuresis unless there is also neural input regarding increased intravascular volume. Studies in humans also suggest that there is not a direct relation between circulating ANF concentration and natriuresis. Although ANF concentrations in patients with congestive heart failure are elevated in proportion to cardiac filling pressures, these patients are typically volume-overloaded and have low urinary sodium concentrations. Pharmacologic doses (50–100 μg) of ANF produce natriuresis in humans; however, it seems that elevations in the physiologic range without concomitant increases in intravascular volume and concurrent neural input do not have this same effect.

The CNS plays a well-known role in the regulation of sodium balance, and it mediates its effects through both neural and humoral mechanisms. Neural mechanisms include renal nerve regulation of renin release and modulation of sodium reabsorption from the proximal tubule of the kidney. Humoral mechanisms include CNS regulation of ADH release and systemic hormonal alteration of behaviors such as drinking in response to angiotensin II. The renin-angiotensin-aldosterone axis is the best example of the interactions between neural and humoral mechanisms of sodium and volume regulation. It may be that such a relation exists for ANF, that is, that there is neural modulation of ANF release and its renal effects.

In summary, we have found that circulating ANF concentrations are elevated after aneurysm rupture and return to normal over 2 weeks. However, high plasma ANF concentrations alone do not appear to account for the hyponatremia seen in our patients. Further investigation into hyponatremia following SAH requires assessment of sodium and fluid balance as well as both neural and humoral aspects of sodium and volume homeostasis.

Acknowledgments

The authors gratefully acknowledge Graeme Hart and Jeffrey Kirsch for their help with data collection and the preparation of this manuscript and Ned Kaufman for his technical assistance with the ANF assay.

References


KEY WORDS • hyponatremia • natriuretic peptides, atrial • subarachnoid hemorrhage
Plasma atrial natriuretic factor and subarachnoid hemorrhage.
M Diringer, P W Ladenson, B J Stern, J Schleimer and D F Hanley

Stroke. 1988;19:1119-1124
doi: 10.1161/01.STR.19.9.1119

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/19/9/1119