Suprasellar and Intraventricular Blood Predict Elevated Plasma Atrial Natriuretic Factor in Subarachnoid Hemorrhage

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Following subarachnoid hemorrhage, the plasma concentration of atrial natriuretic factor is elevated and appears to be independent of atrial stretch. While the hypothalamus and circumventricular organs contribute to sodium and intravascular volume regulation, their influence on atrial natriuretic factor is not known. We tested the hypothesis that, following subarachnoid hemorrhage, suprasellar cisternal blood, intraventricular blood, or ventricular enlargement would be associated with elevated plasma levels of atrial natriuretic factor. Computed tomograms of 26 patients performed ≤3 days after hemorrhage were analyzed to determine the presence of suprasellar or intraventricular blood and enlargement of the third or lateral ventricle. These results were correlated with the plasma atrial natriuretic factor and serum sodium concentrations. The initial atrial natriuretic factor concentration was elevated and was higher in patients with suprasellar or intraventricular blood than in those without (suprasellar: 131 ±20 and 54±10 pg/ml, respectively; intraventricular: 137±25 and 84±31 pg/ml, respectively). The atrial natriuretic factor concentration remained higher over the week following hemorrhage in patients with suprasellar blood than in those without (127 ±16 and 68±12 pg/ml, respectively). The atrial natriuretic factor concentration was not correlated with hyponatremia (125-134 meq/l) or age-corrected ventricular size. Hyponatremia did not correlate with the presence of intraventricular or suprasellar blood. Our data suggest that suprasellar and intraventricular blood disturb hypothalamic function, resulting in an elevated plasma atrial natriuretic factor concentration. The presence of a direct relation between atrial natriuretic factor and hyponatremia remains unclear. (Stroke 1991;22:577-581)

Hyponatremia develops in up to one third of patients following aneurysmal subarachnoid hemorrhage (SAH).1,2 While initially attributed to the syndrome of inappropriate secretion of antidiuretic hormone,3-5 hyponatremia following SAH has more recently been associated with a disturbance of sodium and volume regulation, manifest by salt wasting and hypovolemia.6-8 The precise nature of this disturbance has not been determined. Recent attempts to further define the etiology of the disturbance have investigated the role of atrial natriuretic factor (ANF).9-11 The plasma ANF (pANF) concentration is elevated following acute SAH; however, a clear link between pANF concentration and hyponatremia remains to be established.9-11

The ANF is released into the circulation from granules in the cardiac atrium.12 The primary stimulus for release is atrial distension.13 A potential role for central neural modulation of cardiac ANF release has not been resolved. However, the marked elevation of the pANF concentration following an acute intracranial event, such as SAH, suggests central nervous system (CNS) modulation of peripheral release.9-11

The CNS regulates intravascular volume and sodium balance through both neural and humoral mechanisms. A network of circumventricular organs that surrounds the third ventricle contributes to the regulation of sodium and volume homeostasis.14 Given the proximity of many berry aneurysms to these, it seems likely that their regulatory functions could be disturbed following SAH. This could result from a direct effect of the initial hemorrhage, prolonged exposure to subarachnoid blood, or increased

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pressure due to ventricular enlargement. The presence of intraventricular blood and enlargement of the third ventricle have been associated with hyponatremia following SAH. These factors may also be associated with elevated pANF levels following SAH. We investigated the relations between pANF concentration and the presence of subarachnoid blood in the suprasellar cistern and intraventricular space and enlargement of the third and lateral ventricles following SAH. We tested the hypotheses that the presence of blood in the suprasellar cistern, the presence of intraventricular blood, or the enlargement of the ventricles were associated with high pANF concentrations and hyponatremia.

Subjects and Methods

We reviewed the computed tomograms (CT scans) of 26 unselected patients in whom we had measured pANF concentrations following acute SAH. The pANF concentrations of 15 of these patients have been reported. Data collection began ≤3 days after SAH, and no patient with a history of head trauma, mycotic aneurysm, congestive heart failure, arrhythmias, or renal or endocrine disease was included. The CT scans and cerebral angiograms confirmed aneurysmal SAH in all patients, and the Hunt and Hess score on admission was recorded. Preoperative intravenous fluids consisted of 2–3 l/day of normal (0.9%) saline. Postoperative fluid and sodium administration were adjusted to maintain a normal intravascular volume and avoid a negative sodium balance. Additional fluids were administered in patients with clinical vasospasm in an attempt to maintain central venous pressure at 7–10 mm Hg or pulmonary capillary wedge pressure at 15–18 mm Hg. During the postoperative period, fluid administration always exceeded 2 l/day. A good outcome was defined as being able to carry out the activities of daily living.

All patients had their initial CT scan performed ≤36 hours after SAH. Subsequent CT scans were performed when clinically indicated. The CT scans were analyzed by a neuroradiologist who was unaware of the patient's serum sodium or pANF concentrations. The CT image that best demonstrated the suprasellar cistern was chosen to determine if subarachnoid blood was present within it. The width of the third ventricle was determined from the CT image that demonstrated its maximal diameter; ventricular width was normalized for age by dividing the measured width by the upper limit of normal (90th percentile) for the patient's age. Thus, the upper limit of normal was defined as 5 mm for patients aged ≤40 years, 6 mm for those aged 41–50 years, 7 mm for those aged 51–60 years, and 9 mm for those aged 61–80 years. A value of ≥1 was considered enlarged. The size of the lateral ventricles was ascertained by determination of the bicaudate index, which was defined as the width of the frontal horns at the level of the head of the caudate nucleus divided by the corresponding diameter of the brain at the same level. The bicaudate index was normalized for age by dividing the measured index by the upper limit of normal for the patient's age. The upper limit of normal (95th percentile) was defined as 0.16 for patients aged ≤30 years, 0.18 for those aged 31–50 years, 0.19 for those aged 51–60 years, 0.21 for those aged 61–80 years, and 0.25 for those aged >80 years. The serum sodium concentration was measured daily, and hyponatremia was defined as a serum sodium concentration of <135 meq/l on at least two consecutive days.

Plasma samples for the determination of pANF concentration were drawn on the day of admission and either daily or every other day for at least 1 week. Mean concentration for the week following SAH was calculated. Heart rate, blood pressure, and, when available, central venous pressure and pulmonary capillary wedge pressure were recorded at the time of plasma sampling. The presence of clinical vasospasm and its treatment and the volume of daily fluid administration were recorded.

Plasma was collected and assayed using the same techniques we have previously employed. In our laboratory, mean ±2 SD pANF concentration in 38 normal volunteers was 21 ± 16 pg/ml.

Based on the initial CT scan, patients were grouped according to 1) the presence or absence of blood in the suprasellar cistern; 2) the presence or absence of intraventricular blood; 3) a normal or enlarged third ventricle; and 4) a normal or enlarged lateral ventricle. Each grouping was then analyzed to determine if there was a difference between groups in the initial and weekly mean pANF concentrations (Kruskal-Wallis test), incidences of hyponatremia and clinical vasospasm, and Hunt and Hess grade (χ² test or Fisher's exact test). Individual pANF concentrations were correlated with central venous pressure, pulmonary capillary wedge pressure, blood pressure, and fluid administration using Pearson's correlation. All values are presented as mean ± standard error of the mean; p ≤ 0.05 was considered significant.

Results

The patient population consisted of six men and 20 women aged 23–83 years. On admission, two patients were Hunt and Hess grade I, five were grade II, 14 were grade III, four were grade IV, and one was grade V. Seven aneurysms were found in the anterior communicating artery, 13 in the posterior communicating artery/internal carotid artery, two in the middle cerebral artery, two in the basilar artery tip, one in the pericallosal artery, and one in the posterior cerebral artery. All patients underwent early surgery with clipping of the aneurysm ≤3 days after SAH. Thirteen patients (50%) were treated with hypervolemic hypertensive therapy for clinical vasospasm. Fluid administration in those patients ranged from 3 to 18 l/day of normal saline and plasma protein fraction (5% albumin). In those patients unresponsive to hypervolemic therapy, mean blood pressure...
was elevated 10–20% above baseline with dopamine and phenylephrine. Outcome was considered good in 19 patients and poor in six; one patient died. Blood was present in the suprasellar cistern in 19 patients (73%) and absent in the other seven. Intraventricular blood was present in 13 patients (50%).

The third ventricle was enlarged in 18 patients (69%), whereas the bicaudate index was increased in eight (31%). Every patient with an increased bicaudate index had an enlarged third ventricle; however, 10 patients with an enlarged third ventricle had a normal bicaudate index. There was no relation between the width of the third ventricle or the bicaudate index and the presence or absence of intraventricular or suprasellar blood.

The initial pANF concentration was elevated in 19 patients (73%). Values for the entire population ranged from 12 to 209 pg/ml, with the mean of the initial values being 110 pg/ml (normal <45 pg/ml). The daily mean pANF concentration rose to 141 pg/ml on day 2 and remained between 98 and 116 pg/ml for the remainder of the week. For individual patients, pANF levels did not change during the first week. In patients without blood in the suprasellar cistern, the initial pANF concentration was 54±10 pg/ml; a significantly higher level was found in those with blood in the suprasellar cistern (131±20 pg/ml; Figure 1, top). In addition, the mean pANF concentration during the week following SAH was higher in patients with suprasellar blood than in those without blood (127±16 versus 68±12 pg/ml, respectively). Similarly, patients with intraventricular blood had a significantly higher initial pANF concentration (84±31 pg/ml) than those without (137±25 pg/ml; Figure 1, top), but this difference did not persist for the week following SAH. The pANF concentration was elevated in all four ventricular size groups (Figure 1, bottom). However, there was no difference between patients with normal or enlarged third or lateral ventricles. The mean pANF concentration for the week following SAH also did not differ between groups with normal and enlarged third ventricles (113±22 and 110±17 pg/ml, respectively) or normal and enlarged lateral ventricles (112±15 and 109±29 pg/ml, respectively). The ANF concentration did not correlate with central venous pressure or pulmonary capillary wedge pressure (data not shown) and did not differ between patients treated for clinical vasospasm with hypervolemic therapy and those not (117±16 and 105±26 pg/ml, respectively). Clinical vasospasm was more frequent in patients with suprasellar blood than in those without (63% [12] versus 14% [1]).

Hyponatremia developed in seven patients (27%). In six it was mild (130–134 meq/l) and in the other sodium concentration reached a nadir of 125 meq/l. The initial pANF concentration and the mean concentration over the week following SAH did not differ between patients who developed hyponatremia and those who did not (data not shown). Hyponatremia was more frequent in patients with intraventricular blood and enlarged lateral ventricles (Table 1), but these differences were not significant (p<0.068 and p<0.09, respectively). There was no difference in the incidence of hyponatremia between patients with and without blood in the suprasellar cistern.

**Discussion**

The pANF concentration is elevated following SAH and appears to be independent of atrial stretch. The mechanisms by which SAH produces this elevation in pANF concentration are not known. We report a relation between an elevated pANF concentration and the presence of suprasellar cisternal or intraventricular blood. Hyponatremia tended to be more frequent in patients with intraventricular blood but did not correlate with the presence of suprasellar blood. The presence of suprasellar subarachnoid blood was also associated with a higher incidence of clinical vasospasm. The ANF concentration did not
correlate with enlargement of the third or lateral ventricles, presence of clinical vasospasm treated with hypervolemic hypertensive therapy, or hyponatremia.

The primary stimulus for ANF release from the heart is atrial distention. In humans there is a linear relation between pulmonary capillary wedge pressure and pANF concentration. However, several lines of evidence suggest that the CNS influences the pANF concentration. Intracerebroventricular infusion of hypertonic saline raises the pANF concentration and infusion of hypertonic urea lowers it in rats. Electrical stimulation of the rostral nucleus tractus solitarius raises the pANF concentration and stimulation of the region anteroventral to the third ventricle (AV3V) with carbachol produces a dramatic rise in circulating ANF levels. In humans, the pANF concentration is elevated following SAH and intracerebral hematoma.

While local neural mechanisms play a role in the release of ANF in response to hypoxia and pulmonary hypertension, there is conflicting evidence regarding a central mechanism influencing release. In isolated cardiac preparations, adrenergic and cholinergic agents stimulate ANF release and these responses are blocked by appropriate antagonists. However, the response to increases in atrial pressure was not altered by vagotomy and cardiac β-adrenoceptor blockade or by intrapericardial cardiac denervation. This, however, does not preclude the possibility that neural stimulation promotes the release of ANF from the heart. On the other hand, neurohumoral factors may influence the circulating levels of ANF. Hypophysectomy reduces basal and stimulated pANF levels, and these changes are reversed when the anterior pituitary is reimplanted.

Thus, SAH could alter the CNS regulation of pANF concentrations by interfering with hypothalamic peripheral autonomic and/or anterior pituitary function. Hypothalamic damage is known to occur following SAH. In a consecutive series of autopsies on patients dying following SAH, 61% of 105 patients were found to have hypothalamic lesions. Doshi and Neil-Dwyer noted a correlation between hypothalamic damage and myocardial lesions and suggested that hypothalamic dysfunction leads to myocardial damage. Impaired pituitary function may also be common. Yoshimoto and Uozumi found evidence of impaired anterior pituitary secretion in 77% of 53 patients following acute SAH. Our findings are consistent with either hypothalamic or anterior pituitary dysfunction being an important part of the mechanism responsible for elevated pANF levels following SAH. Investigation of the relation between pANF concentration and levels of anterior pituitary hormones or other indicators of hypothalamic dysfunction could help clarify this question.

The relation between pANF concentration and disturbed sodium or volume regulation or hyponatremia following SAH remains unclear. ANF may act in conjunction with other neural and humoral regulators of sodium and intravascular volume to produce the picture seen after SAH. Alternatively, the pANF level may be a nonspecific indicator of CNS injury as ANF appears to be in the cerebrospinal fluid. Our findings suggest a possible mechanism to explain the rise in pANF levels after brain injury.

Hyponatremia has been reported to be more frequent in patients with intraventricular blood and enlarged third ventricles. While we did not confirm these findings in our study, similar trends were evident. The lack of statistical significance may reflect our small sample size.

In summary, we found that the presence of intraventricular or suprasellar cisternal blood was associated with elevated pANF concentrations following SAH. Hydrocephalus, intraventricular blood, and pANF concentration were not associated with hyponatremia. The relation of the pANF level to hyponatremia remains unclear. We speculate that elevated pANF concentrations following SAH may result from disturbed hypothalamic and/or anterior pituitary function.

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