Here is compelling evidence that body fluid homeostasis is perturbed after aneurysmal subarachnoid hemorrhage (SAH). Hypovolemia is frequently associated with SAH and has been found to result from a marked natriuresis and diuresis (ANP and BNP), and regulates vascular tone (CNP). A reciprocal relationship between ANP and endothelin (ET) has been suggested, and earlier studies have documented a possible role of ET in cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH).

The authors studied plasma ANP, BNP, CNP, and ET for 6 consecutive days in 13 patients with SAH by using radioimmunoassay. The median admission values for ANP were 31.5 pg/ml (range 16.8–323 pg/ml [normal 15 ± 7 pg/ml]); for BNP, 45.3 pg/ml (range 2.2–80.2 pg/ml [normal 12 ± 9 pg/ml]); for CNP, 7.7 pg/ml (range 2–20 pg/ml [normal 5.2 ± 3 pg/ml]); and for ET, 11 pg/ml (range 6.5–25.1 pg/ml [normal 7.2 ± 4 pg/ml]). Additional increases (defined as 100% increase on two consecutive measurements) were noted in ANP (11 patients), BNP (10 patients), and CNP (three patients), and resulted in a negative fluid balance in 10 of the 13 patients. The CNP increased in three of four patients with cerebral vasospasm and in one of nine patients without cerebral vasospasm (Fisher’s exact test, p = 0.2). No major fluctuations in plasma ET were noted. In seven patients, the plasma ET level did not increase beyond 10 pg/ml during the days of measurement. In six patients, only an occasional sample showed an increase to a maximum of 25 pg/ml. Changes in BNP, ANP, and CNP were independent of each other.

The authors conclude that both plasma ANP and BNP increase after SAH and often result in a negative fluid balance. Plasma ANP and BNP seem differentially regulated in the presence of SAH but not by the level of the plasma ET. The possible role of CNP as a regulatory response to cerebral vasospasm needs further exploration.

KEY WORDS • atrial natriuretic peptide • subarachnoid hemorrhage • endothelin • diuresis
delayed cerebral ischemia; and 3) whether plasma ET is elevated in patients who develop cerebral vasospasm after SAH.

Materials and Methods

Monitoring of Patients

Thirteen patients with an aneurysmal SAH evidenced by blood clots in the basilar cisterns on computerized tomography (CT) scanning were admitted to the neurological–neurosurgical intensive care unit at St. Mary’s Hospital, Mayo Medical Center. All patients were admitted within 24 hours after ictus and studied for a minimum of 6 days. During the study, fluid balance and Swan–Ganz catheter parameters, if available, were recorded daily. All patients were graded using the World Federation of Neurological Surgeons (WFNS) grading system.2 Transcranial Doppler (TCD) studies were performed in patients who deteriorated as a result of vasospasm in concentrations ranging from 2 to 500 pg/tube. There was no detectable immunoreactivity to ANP, demonstrating a cross-reactivity of less than 1%. The CNP immunoreactivity was determined using a double-antibody RIA. A specific antibody to human CNP-22 was used in the assay. Recovery of CNP was 72 ± 6% as determined by addition of synthetic CNP-53 to the CNP-22 assay at concentrations ranging from 2 to 500 pg/tube. The crossreactivity of the CNP-22 antibody with CNP-53 was established by addition of synthetic CNP-53 to the CNP-22 assay at concentrations ranging from 0.5 to 500 pg/tube with no detectable immunoreactivity, demonstrating a cross-reactivity of less than 1%.

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pro-ET. Additional details on the methodology of the RIAs have been published previously.9,10

Sources of Supplies and Equipment

Peninsula Laboratory, Inc. (Belmont, CA) provided the synthetic peptide of human α-ANP and the rabbit antiserum to human α-ANP (RAS 8798); the BNP RIA kit; synthetic ANP, BNP, and ET; synthetic ANP-28, BNP-32, and CNP-53; and the antibody to human CNP-22. Amersham International (Amersham, England) provided the antibody to ET-1. Bio-Rad (Hercules, CA) provided the P-2 column, and the Bond Elut cartridges used in the RIAs were obtained from Varian (Harbor City, CA).

Results

Clinical Features

Thirteen patients with aneurysmal SAH were evaluated in the neurological–neurosurgical intensive care unit. The age of the patients ranged from 39 to 73 years (median 56 years). There were eight patients with WFNS Grade I, two patients with WFNS Grade II, and three patients with WFNS Grades III or IV SAH. Admission CT scans demonstrated SAH in the basal cisterns in all patients, with additional presence of significant intraventricular hemorrhage in two patients (excluding patients with sedimentation in the posterior horns of the ventricular system). Acute hydrocephalus developed in three patients. Five patients had an anterior communicating artery aneurysm, four patients had a posterior communicating artery aneurysm, three patients had a middle cerebral artery aneurysm, and one patient had a carotid aneurysm. Within 48 hours after presentation, 11 patients underwent clipping of the aneurysm, and in two patients several platinum detachable coils were placed to obliterate the aneurysm.

Four patients developed delayed cerebral ischemia. Delayed cerebral ischemia was diagnosed on the basis of progressive drowsiness and either increased velocities on TCD ultrasonography or the presence of cerebral vasospasm on angiography. In three patients, no improvement was noted after hypertensive–hypervolemic treatment, and papaverine was infused intraarterially, which resulted in a significant decrease in the severity of cerebral vasospasm. Additional angioplasty of the M1 segment of the middle cerebral artery was performed with success in one patient.

Plasma ANP, BNP, CNP, and ET Concentrations

The median admission values for ANP were 31.5 pg/ml (range 16.8–323 pg/ml); for BNP, 45.3 pg/ml (range 2.2–80.2 pg/ml); for CNP, 7.7 pg/ml (range <2–20 pg/ml); and for ET, 11 pg/ml (range 6.5–25.1 pg/ml). The values for ANP and BNP were twofold higher than normal controls (normal ANP value 15 ± 7 pg/ml; normal BNP value 12 ± 9 pg/ml). Admission values for CNP and ET were not significantly different from controls (normal CNP value 5.2 ± 3 pg/ml; normal ET value 7.2 ± 4 pg/ml).

Interrelationship of Natriuretic System Peptides and Their Relationship With ET

The fluctuations in daily values of plasma ANP and plasma BNP are portrayed in Fig. 2. The ANP and BNP profiles were similar in three patients (Cases 1, 3, and 8); however, plasma ANP and BNP changes appeared independent of each other in the remaining patients. No major fluctuations in ET (>100% from baseline) were noted. In seven patients the plasma ET levels did not increase beyond 10 pg/ml during the days of measurement. In six patients only occasional samples showed an increase to a maximum of 25 pg/ml. No reciprocal profiles were found when ET was compared with ANP and BNP (data not shown).

Relationship Between the Natriuretic Peptide System and Fluid Balance

The cumulative fluid balance over 6 consecutive days ranged from −3.2 to 10.6 L (median 3.2 L). Of the 13 patients, three patients had a negative cumulative fluid balance: −2.1, −1.6, and −3.2 L, respectively. When a sensible loss of 750 ml daily was taken into account, eight of 13 patients had a negative fluid balance over 6 days.

Secondary increases (2nd and 3rd day) were noted over elevated baseline values in 11 patients for ANP, in 10 patients for BNP, and in three patients for CNP. (A secondary increase was defined as ≥100% increase on two consecutive measurements.) No correlation between an increase in ANP, BNP, or CNP and a cumulative negative fluid balance was found, but increases in ANP or BNP were correlated with the development of a negative fluid balance the same day or 1 day thereafter in 10 patients. Frank hyponatremia (plasma sodium level of ≤130 mmol/L) was found in only one patient. In five patients Swan–Ganz catheters were placed to monitor hypervolemic therapy. Pulmonary artery wedge pressure values ranged from 10 to 24 mm Hg in all instances.

Electrocardiographic abnormalities were documented in nine of 13 patients. In seven patients inverted T waves were found and in two patients a prolonged QT interval (normal QT interval is 0.41 seconds for women and 0.39 seconds for men). In two patients mild ventricular segmental hypokinesis was demonstrated on echocardiography, but without evidence of a left ventricular dysfunction, using pulmonary artery balloon catheter parameters.

Relationship Among Natriuretic System Peptides, ET, and Delayed Cerebral Ischemia

Four patients (Cases 1, 7, 12, and 13) (Fig. 2) developed delayed cerebral ischemia. In one additional patient (Case 3), abnormal TCD patterns were found but without any clinical manifestation of delayed cerebral ischemia. The plasma concentrations of the natriuretic peptides ANP and BNP, and of ET in these patients did not differ from the plasma concentrations in patients who did not develop cerebral ischemia (Fig. 2). In four patients an elevation of CNP was noted (>100% above baseline). Three of the four patients with delayed cerebral ischemia developed increases in CNP (the highest attained values were 17, 25, and 150 pg/ml) as opposed to one of the nine patients without delayed cerebral ischemia (highest value 145 pg/ml). However, this trend was not statistically significant (Fisher’s exact test, p = 0.2). In one of the four patients with delayed cerebral ischemia, an increase in ET (maximum level 33 pg/ml) was observed, as opposed to increases in ET (maximum level 40 pg/ml) in five of nine patients without cerebral vasospasm.
**Patient Outcome**

In two patients a ventriculostomy was placed. Ten patients achieved an independent state or had a full recovery, two patients remained in a severely disabled state, and one patient died from massive bihemispheric infarction.

**Discussion**

To our knowledge, our study is the first to measure the entire natriuretic peptide system and its relationship with ET in patients with aneurysmal SAH. Several novel observations are apparent. First, plasma ANP and BNP increase...
above baseline value at ictus. These increases are mostly visible on the 2nd and 3rd day and although both peptides may increase, they do not seem to parallel each other in all instances. This indicates that these peptides seem to be differentially regulated; however, we cannot exclude an interaction. Second, the increases in ANP and BNP are associated with the development of a negative fluid balance on the same or the following day, suggesting that these natriuretic peptides are not a consequence of volume expansion and atrial stretch, but rather are implicated in natriuresis and diuresis. In fact, most of our patients exhibited a marginal fluid balance despite attention to fluid intake. Third, plasma ET levels were seldom elevated during SAH and no major fluctuations in these levels were noted during the period of observation. In addition, no reciprocal relationship between the ANP system and ET was found. This is in contrast to preliminary studies on plasma ET levels in patients with aneurysmal SAH. The role of ET in the pathogenesis of delayed cerebral ischemia seems established, and research is focusing on the development of ET receptor antagonists. However, measurement of plasma ET is not a clear reflection of its presence after SAH. Fourth, CNP was elevated in three patients, two of whom developed delayed cerebral vasospasm, although this trend was not statistically significant. This suggests that CNP has a regulatory vasodilator role. This conclusion, however, remains preliminary because of the small number of patients. A possible clinical application of this finding is that CNP or similar compounds may be capable of inhibiting the action of vasospastic substances. An observational study such as this cannot establish any causal link, but a recent study using CNP infusions found that CNP indeed can inhibit the vasoconstrictive effect of the renin–angiotensin system.

Brain natriuretic peptide clearly was elevated in all patients with aneurysmal SAH. What are the possible explanations for the apparent discrepancy between the results of our study and that of Isotani et al.? One explanation is that sampling in their study was performed every 2 to 4 days, raising the possibility that elevations in BNP may not have been detected. Another explanation may be a comparatively higher incidence of aneurysm in the anterior communicating artery complex with closer proximity to the hypothalamus in our study. Lesions in the hypothalamus may result in cardiac lesions with subsequent release of these peptides. Indeed, a previous study on digoxin-in immunoreactive substance, another recently identified natriuretic factor, in SAH confirmed such a relationship.

The mechanisms involved in the release of natriuretic peptides and recently discovered digoxinlike substances during SAH are not known. It would appear that an SAH produces the cardiac release of these natriuretic substances located in the atrium or ventricle. Cardiac release of these natriuretic substances does not necessarily correlate with electrocardiographic abnormalities pertaining to ventricular dysfunction, but this area needs further study. None of our patients had electrocardiographic abnormalities or significant cardiac arrhythmias and only two patients had hypokinesis of the left ventricular wall.

Although the chemistry of natriuretic peptides and their receptors has been outlined, the physiological regulation of these agents needs further refinement. However, plasma values as low as 50 pmol/L result in a significant increase in urine volume and sodium. Therefore, the plasma values of ANP and BNP measured in our cohort of patients with aneurysmal SAH should account for the development of a negative fluid balance. The regulation and physiological properties of CNP remain largely speculative. Whether the increase in CNP measured in some of our patients, results in a vasodilation is unknown. Nonetheless, it has been demonstrated that prolonged infusion of CNP significantly reduced lumen stenosis after injury to the arterial vessel wall.

On a practical level, our results demonstrate that plasma ANP and BNP are significantly elevated in aneurysmal SAH. The presence of two potent natriuretic substances should explain the overall difficulty of keeping these patients in adequate homeostasis. Hypervolemic therapy is often required to prevent volume contraction. Aggressive fluid management should begin promptly and may reduce the rates of mortality and morbidity from delayed cerebral ischemia. Manipulation of the natriuretic peptide system and extension of the possible role of CNP in cerebral vasospasm warrants further investigation.

References


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