Brain Natriuretic Peptide and Cerebral Vasospasm in Subarachnoid Hemorrhage
Clinical and TCD Correlations
Gil E. Sviri, MD; Moshe Feinsod, MD; Jean F. Soustiel, MD

Background and Purpose—Hyponatremia has been shown in association with cerebral vasospasm (CVS) following aneurysmal subarachnoid hemorrhage (SAH). In the past few years there has been increasing evidence that brain natriuretic peptide (BNP) is responsible for natriuresis after SAH. The purpose of the present study was to investigate the relationship between BNP plasma concentrations and CVS after aneurysmal SAH.

Methods—BNP plasma concentrations were assessed at 4 different time periods (1 to 3 days, 4 to 6 days, 7 to 9 days, and 10 to 12 days) in 19 patients with spontaneous SAH. BNP plasma levels were investigated with respect to neurological condition, SAH severity on CT, and flow velocities measured by means of transcranial Doppler.

Results—Thirteen patients had Doppler evidence of CVS; 7 of these had nonsymptomatic CVS. In 6 patients, CVS was severe and symptomatic, with delayed ischemic lesion on CT in 5 of these. CVS was severe and symptomatic in 6 patients, and delayed ischemic lesions were revealed on CT in 5 of these. BNP levels were found to be significantly elevated in SAH patients compared with control subjects (P = 0.024). However, in patients without CVS or with nonsymptomatic CVS, BNP concentrations decreased throughout the 4 time periods, whereas a 6-fold increase was observed in patients with severe symptomatic CVS between the first and the third periods (P = 0.0096). A similar trend in BNP plasma levels was found in patients with severe SAH compared with those with nonvisible or moderate SAH (P = 0.015).

Conclusions—In conclusion, our results show that BNP plasma levels are elevated shortly after SAH, although they increase markedly during the first week in patients with symptomatic CVS. The present findings suggest that secretion of BNP secretion after spontaneous SAH may exacerbate blood flow reduction due to arterial vasospasm. (Stroke. 2000;31:118-122.)

Key Words: hyponatremia • natriuretic peptide, brain • subarachnoid hemorrhage • ultrasonography, Doppler • vasospasm

Cerebral vasospasm (CVS) is a major case of morbidity and mortality after subarachnoid hemorrhage (SAH), due to rupture of aneurysm.1,2 Despite intensive efforts to understand the pathogenesis of CVS, the biological processes leading to arterial narrowing remain unclear. In the past few years, increasing evidence has shown that natriuretic peptides (NPs), very potent vasodilators, are responsible for diuresis, natriuresis, and hyponatremia in patients with SAH.3-5 It was first speculated that atrial natriuretic peptide (ANP), which was found to be elevated in the cerebrospinal fluid and plasma of patients with SAH, might be responsible for profound diuresis and natriuresis.6 ANP plasma concentration, however, did not show significant correlation with hyponatremia, which therefore suggested the existence of an additional factor.7,8 Okunchi et al9 speculated that another potent natriuretic factor, similar to ANP, may induce rapid natriuresis. These authors reported that such a profound natriuresis precedes the development of ischemic symptoms and therefore acts as a potential trigger for symptomatic CVS after SAH. Later, Berendes et al4 and Wijdicks et al9 provided convincing evidence that the brain natriuretic peptide (BNP) may be related to hyponatremia associated with natriuresis after SAH. Furthermore, Tomida et al5 reported that patients with hyponatremia after SAH have high BNP plasma levels during the first 2 weeks after SAH, although they did not investigate the correlation between BNP plasma concentrations and CVS.

The present study was designed to examine the correlation between plasma levels of BNP and CVS after spontaneous SAH.

Subjects and Methods
Clinical Material
Between October 1997 and December 1998, 19 patients admitted because of spontaneous SAH to the neurosurgical department at Rambam Medical Center in Haifa, Israel, were recruited for the
present study. All patients were admitted within 48 hours after the onset of the SAH. There were 7 men and 12 women. The mean age was 49.1 years (SD 13.3 years), with a range of 22 to 69 years. To exclude the possibility of bias due to cardiovascular or systemic disease, patients with ischemic heart disease, congestive heart failure, hypertension, and chronic renal failure, as well as those <16 or >70 years, were deliberately excluded. Informed consent was obtained from all patients.

**Clinical Evaluation**

Neurological status was assessed every 6 hours, and level of consciousness was scored according to the Hunt & Hess classification.10 Delayed neurological deterioration was defined as a negative neurological trend that could not be attributed to rebleeding, systemic, or postoperative complications. Final neurological outcome was assessed by Glasgow Outcome Scale score11 for all patients after 6 months.

**Management Protocol**

Conscious and neurological stable patients were managed with bed rest, intravenous 0.9% saline and continuous drip of nimodipine at a rate of 2 mg/h. Fluid management aimed at the maintenance of normovolemic normal blood pressure. Comatose patients were sedated and ventilated. Delayed neurological deterioration due to CVS was managed by moderate hypervolemic hypertension, with use of fluid administration and catecholamines as indicated.

**CT Findings**

**SAH Severity**

All patients underwent CT scan on admission and then later as clinically indicated. Intensity of SAH was determined according to amount and location of blood on the initial CT scan, with the grading system proposed by Fisher et al12: grade 1, normal CT scan; grade 2, diffused SAH or thin vertical layer <1 mm thick; grade 3, localized clots or vertical layer of subarachnoid blood >1 mm thick; and grade 4, intraventricular or intracerebral hemorrhage.

**Delayed Ischemic Deficit**

Delayed brain infarction was defined by the presence of new hypodense lesions circumscribed to arterial supply territory and compatible with brain infarction.

**Transcranial Doppler Recording**

**Technique**

Mean flow velocities (FVs) were evaluated with an Intraview system (Rimed) with a 2-MHz pulse-wave and range-gated transducer, according to the technique described by Aaslid et al.13 Initial transcranial Doppler (TCD) evaluation was performed within the first 48 hours after the onset of the SAH and repeated daily until patient’s stabilization or discharge from the department. Middle (MCA) and anterior (ACA) cerebral arteries were insonated through the temporal acoustic window, whereas the vertebral and basilar arteries were assessed through the foramen magnum. Basilar artery location was defined at an insonation depth of >80 mm, according to the technique described by Fujioka and Douville.14 Internal carotid flow velocity measurements were performed extracranially below the mandible.

**Vasospasm**

Mean FVs of >120 cm/s and higher than the FV in the internal carotid artery by 3-fold were selected as a criterion of vasospasm in the MCA and ACA according to Aaslid et al15 and Lindegaard et al.16 Verteobasilar vasospasm was defined by mean FVs >85 cm/s in the vertebral or basilar arteries, according to TCD criteria suggested by Sloan et al.17 These authors showed through comparison of angiographic and sonographic findings that a 60 cm/s threshold criteria for the diagnosis of vertebrobasilar vasospasm would yield a sensitivity of 76.9% and a specificity of 79.3%, whereas a threshold criteria of 95 cm/s would be associated with vasospasm in all instances.

Patients with TCD evidence of vasospasm were further divided into 2 clinical subsets: patients with symptomatic and those with nonsymptomatic vasospasm. Nonsymptomatic vasospasm was defined by transient elevation of FVs without neurological deterioration. Intense and prolonged FV elevation associated with delayed neurological and/or ischemic deficit indicated symptomatic vasospasm.

**Blood Tests**

Phlebotomy was performed for plasma sampling of BNP 4 times during the first 2 weeks of hospitalization, defining 4 periods within the clinical course: period 1, between days 1 and 3 (day 1 being regarded as the day of SAH onset); period 2, between days 4 and 6; period 3, between days 7 and 9; and period 4, between days 10 and 12. Blood samples were collected in chilled syringe and transferred into polypropylene tubes containing 7.5 mg EDTA and 1000 kIU/mL aprotinin at 4°C, and centrifuged at 4000 rpm for 15 minutes at 4°C. Plasma was stored at −70°C and assayed within 6 months. The plasma BNP levels were determined by means of a specific immunoradiometric assay (SHIONORIA BNP, Shionogi & Co, Ltd). For statistical purposes, trends in BNP plasma levels were analyzed by means of the ratio between BNP plasma levels at the third and first periods. Blood samples were also collected from 10 healthy volunteers to determine the normal BNP plasma concentration.

**Statistical Analysis**

BNP levels in the different groups were compared by means of ANOVA. Differences were considered significant when they reached a value of P<0.05.

**Results**

**Clinical Features**

The clinical features are summarized in Table 1. Thirteen patients had TCD evidence of CVS. In 7 patients, CVS was nonsymptomatic and limited to the anterior circulation vessels, whereas CVS was symptomatic and involved both anterior and posterior vessels in 6 patients. None of the patients without CVS or with nonsymptomatic CVS presented with delayed neurological deterioration or brain infarction. On the contrary, delayed neurological deterioration occurred in all 6 patients of the severe CVS group. In 5 of these, follow-up CT scan showed brain infarction. There was no significant difference, however, in the neurological condition on admission between the different clinical subsets.

**Plasma BNP Concentrations and SAH Severity**

BNP plasma levels are summarized in Table 2. As a group, SAH patients had initial BNP plasma levels significantly higher than those found in the control group (76.09±106.93 pg/mL versus 5.78±1.91 pg/mL, P=0.024). BNP levels increased markedly between the first and third periods in patients who sustained severe SAH (Fisher grade 3) compared with those with moderate or cryptic SAH (Fisher grades 1 and 2, P=0.015). Conversely, in patients with intraparenchymal or intraventricular hemorrhage (Fisher grade 4), BNP elevation did not have the same magnitude and therefore did not reach statistical significance (Figure 1, Table 2). It should be noted, however, that initial BNP levels in this group of patients were significantly higher (Table 2).
In patients with symptomatic vasospasm, BNP plasma levels showed a continuous elevation between the first and third periods. This trend in BNP levels, however, was significant only at the third period, at which time BNP levels were about 6 times their initial value in this group (Figure 2, Table 2, \(P = 0.0096\)). In patients without CVS or with nonsymptomatic CVS, BNP plasma levels showed an opposite trend and decreased progressively between period 1 and period 3 (Figure 2, Table 2). By the end of the fourth period, however, BNP levels decreased in all patients (Figure 2). Because elevated flow velocities were associated with increasing BNP levels only in the patients who presented with neurological deterioration, there was no correlation between flow velocities in the MCA alone and BNP plasma levels or their trends throughout the 4 periods. Moreover, neurological status on

**TABLE 1. Clinical Features in 19 Patients with SAH**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Hunt &amp; Hess Score</th>
<th>Fisher Grade</th>
<th>MCA FV, cm/s</th>
<th>DND</th>
<th>DBI</th>
<th>BNP Ratio Period 3:1</th>
<th>CVS</th>
<th>GOS Score</th>
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<td>3</td>
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<td>0.46</td>
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<td>4</td>
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<td>3</td>
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<td>22/M</td>
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<td>3.68</td>
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</tbody>
</table>

DND indicates delayed neurological deficit; DBI, delayed brain infarction.

*Ratio between BNP levels at days 7–9 and days 1–3.*

**TABLE 2. BNP Concentration Levels by Clinical Subset**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Days 1–3</th>
<th>Days 4–6</th>
<th>Days 7–9</th>
<th>Days 10–12</th>
<th>Period 3:1</th>
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<tr>
<td>Vasospasm</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>6</td>
<td>102.2±59.5</td>
<td>52.6±42.8</td>
<td>46.8±27.7</td>
<td>8±7</td>
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<tr>
<td>Non symptomatic</td>
<td>7</td>
<td>91.2±167.2</td>
<td>19.88±20.9</td>
<td>7.4±5</td>
<td>6.3±6.1</td>
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<tr>
<td>Symptomatic</td>
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<td>32.4±25.7</td>
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<td>132.4±97.7</td>
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<td>Fisher grade</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>100.6±130</td>
<td>31±24.9</td>
<td>96.1±60.7</td>
<td>17±19.8</td>
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<tr>
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<td>7</td>
<td>52.6±40.9</td>
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<tr>
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<td>Hunt &amp; Hess score</td>
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<td>60.1±138.1</td>
<td>100.1±141.6</td>
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Period 3:1 indicates the ratio between BNP levels at days 7–9 and days 1–3.

*P=0.0096; †P=0.015.

Plasma BNP Concentrations and Vasospasm

In patients with symptomatic vasospasm, BNP plasma levels showed a continuous elevation between the first and third periods. This trend in BNP levels, however, was significant only at the third period, at which time BNP levels were about 6 times their initial value in this group (Figure 2, Table 2). By the end of the fourth period, however, BNP levels decreased in all patients (Figure 2). Because elevated flow velocities were associated with increasing BNP levels only in the patients who presented with neurological deterioration, there was no correlation between flow velocities in the MCA alone and BNP plasma levels or their trends throughout the 4 periods. Moreover, neurological status on
Discussion

Homeostatic disorders after SAH due to aneurysmal rupture and involving increased natriuresis have long been identified and recognized as a predictor of cerebral ischemia in patients suffering from CVS. In the present study, it is demonstrated for the first time that BNP plasma levels increase progressively and significantly during the first 2 weeks in patients with severe CVS after aneurysmal SAH compared with patients with nonsymptomatic CVS or without vasospasm.

These findings raise the question of the role of natriuretic peptides (NPs), particularly the BNP, in the pathogenesis of CVS. Three types of NPs have been described to date. The ANP, first discovered, is mainly produced in the right atrium in response to hypervolemia and increase in the cardiac preload. The BNP is produced mainly in the cardiac ventricles and the C type of natriuretic peptide is mainly released from the vascular endothelium in response to injury and inflammation. All types of natriuretic peptide have been demonstrated to be very potent vasodilators and natriuretic.

They also demonstrate direct effects on blood vessels, which leads to vasodilation directly or through inhibition of vasoconstrictor signals, such as endothelin. Although primarily of cardiac origin, the BNP has been shown to be produced also in the hypothalamus, so its release may be induced by pathological processes involving this region.

Early studies have drawn attention to the frequent occurrence of hyponatremia in CVS as a cause of neurological deterioration following aneurysmal SAH. These studies speculated that natriuresis and secondary salt-wasting syndrome account for hyponatremia rather than inappropriate secretion of antidiuretic hormone. Both the ANP and BNP have been proposed as a plausible origin for the occurrence of this cerebral salt wasting syndrome. Several reports involving the investigation of cerebral salt-wasting syndrome, however, have shown that the ANP alone is unlikely to be responsible for hyponatremia in patients with SAH. BNP plasma levels, in contrast, were found to be consistently elevated in patients with aneurysmal SAH.

Our results further support the theory that BNP release is indeed induced by SAH and may therefore be responsible for the hyponatremia reported after rupture of aneurysm. In the present series, however, BNP levels showed a continuous trend of elevation only in patients with symptomatic vasospasm. Moreover, 5 of 6 patients with symptomatic vasospasm developed delayed brain infarction evidenced by CT scan. These findings are compatible with those reported by Morinaga et al in their series of 121 patients with aneurysmal SAH. These authors reported hyponatremia in 19 patients (16 of whom had symptomatic vasospasm), with CT scan evidence of ischemic lesion in 8 patients. Their results as well as ours suggest that increasing release of BNP may exacerbate in some patients the hemodynamic consequences of vasospasm and lead to cerebral ischemia. Interestingly, the time course of BNP elevation in this series is closely related to that of CVS, reaching a maximum intensity between days 7 and 9 and decreasing by the end of the second week. This observation is compatible with the results of Tomida et al and the clinical findings of Morinaga et al.

Nevertheless, the relationship between BNP release in SAH patients and vasospasm remains poorly defined, and several mechanisms should be considered. Tomida et al relate this increase in BNP levels to an augmented cardiac production triggered by stress-induced noradrenaline release. Wijdicks et al assume that expanded cardiac BNP production may be induced by lesion to the hypothalamus caused by SAH, especially in patients with ruptured anterior communicating artery aneurysm. This assumption is partially supported by our findings showing a 6-fold increase in BNP levels between the first and third period in patients with severe SAH (Fisher grade 3). Patients with intraventricular and intraparenchymal hemorrhage also showed an elevation of BNP levels during the clinical course, although high initial levels in this group might have tapered the magnitude of subsequent changes. On the contrary, patients with no visible or only mild SAH (Fisher grade 1 and 2) presented with merely limited changes in BNP levels. Because in most of our patients severe SAH was related to anterior circulation aneurysm, we may speculate that rupture of the aneurysm
may have caused damage to hypothalamic perforating vessels, secondarily aggravated by vasospasm. It seems unlikely, however, that either initial microcirculation damage or vasospasm alone are responsible for such a hypothalamic response, since BNP concentrations did not correlate with flow velocities in anterior cerebral vessels or with neurological condition on admission. A second plausible hypothesis is that the vasospasm itself may be responsible for hypothalamic ischemia, especially in patients with ruptured anterior circulation aneurysms. This hypothalamic ischemic insult may in turn induce BNP secretion. In that case, only when hemodynamically significant should vasospasm explain both neurological deterioration and BNP secretion. Another possibility is that both vasospasm and BNP secretion may be an epiphenomenon of the same underlying mechanism, such as the release of endothelin. Indeed, several studies have shown that endothelin, a potent and long-lasting vasoconstrictor, may contribute significantly to CVS. In addition, endothelin has been identified in hypothalamic neurons involved in water and electrolyte metabolism and has been proved to induce natriuresis. It is therefore plausible that the release of endothelin induced by the initial vascular damage may account for both BNP secretion and vasospasm.

In conclusion, our results show that BNP plasma levels are elevated shortly after SAH, although they increase markedly during the clinical course only in patients with symptomatic CVS. The underlying mechanism of BNP secretion in SAH and its relation to the occurrence of vasospasm remains to be clarified. Nevertheless, the present findings suggest that despite some protective effects, such as vasodilatation, BNP secretion may exacerbate blood flow reduction due to arterial vasospasm and eventually result in ischemic brain damage. Further experimental and clinical studies should be conducted to investigate the pathophysiological mechanisms leading to BNP secretion in patients who eventually suffer from brain ischemia.

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References

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