Clinical Significance of Elevated Natriuretic Peptide Levels and Cardiopulmonary Parameters After Subarachnoid Hemorrhage

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Abstract

Daily changes in serum concentrations of natriuretic peptides and various cardiopulmonary parameters were measured after the onset of subarachnoid hemorrhage (SAH) to investigate the pathogenesis of the cardiac and pulmonary consequences in 15 patients with acute phase SAH, divided into the control group (n = 5) with consciousness continuously preserved from SAH onset to admission, and the consciousness disturbance group (n = 10). Daily changes in serum A-type and B-type natriuretic peptides (ANP and BNP, respectively) were measured for 10 days, and intrathoracic blood volume index and extravascular lung water index (EVLWI) were measured for 5 days by the single transpulmonary thermodilution method. Natriuretic peptides in the consciousness disturbance group showed significantly higher values during the 10-day period, with ANP 119.2 ± 12.4 pg/ml (mean ± standard error of the mean, p = 0.005) on day 2 and BNP 354.1 ± 80.3 pg/ml (p = 0.009) on day 1. EVLWI showed higher values in the consciousness disturbance group compared to the control group throughout the 5-day period. The increases in natriuretic peptide levels and increase in pulmonary extravascular water content found in SAH patients with consciousness disturbance show that load on the left ventricle or atrium as well as pulmonary capillary pressure are increased immediately after onset, supporting the contention that excessive release of catecholamines occurs at this time.

Key words: subarachnoid hemorrhage, B-type natriuretic peptide, A-type natriuretic peptide, transpulmonary thermodilution, pulmonary edema

Introduction

Subarachnoid hemorrhage (SAH) has been known to be associated with cardiopulmonary injury for over half a century. Patients with only slight hemorrhage may develop cardiopulmonary arrest, probably due to cardiopulmonary disorders such as arrhythmia, heart failure, and lung edema, rather than direct injury to the central nervous system. Various electrocardiography studies on rhythm disturbances have detected both minor abnormalities such as bradycardia, ST-T changes, and QTc prolongation, as well as less common but life-threatening arrhythmias such as ventricular tachycardia and ventricular fibrillation. Cardiac muscle injury associated with SAH has been confirmed by histological findings of myofibrillar degeneration, myocytolysis, and inflammatory cell infiltration, in addition to increased serum levels of myocardium-specific markers such as plasma phosphokinase myocardial fraction (CK-MB) and troponin I. Most patients also develop neurogenic pulmonary edema. However, the underlying pathophysiology of these injuries has not been adequately explained.

The present study measured the increase in serum natriuretic peptide levels after SAH and the changes occurring in cardiopulmonary parameters such as intrathoracic blood volume and extravascular lung water using the single transpulmonary thermodilution method.

Materials and Methods

Twenty consecutive SAH patients were evaluated who presented to the Emergency and Critical Care Center of Nara Medical University within 2 days of onset during the period from April 2001 to Decem-
ber 2003. The diagnosis of SAH was based on computed tomography or spinal tap on the day of presentation. Patients underwent cerebral angiography to determine the aneurysm location and then underwent surgical or intravascular coiling within 24 hours. Informed consent was obtained from the patient and/or family before enrollment in the study. Five of the 20 patients were excluded, one died within 1 week of entry, three because of a history of conditions such as acute myocardial infarction, arrhythmia, and congestive heart failure, and one because absence of consciousness loss after onset could not be determined. The remaining 15 patients, 5 males and 10 females (mean age ± standard deviation 64.6 ± 18.4 years), underwent the following procedures.

Screening for cardiopulmonary disorders was conducted in all patients prior to surgery using chest radiography, electrocardiography, and echocardiography. Sedation was achieved with midazolam, and the systemic systolic pressure controlled to ≤130 mmHg with a calcium antagonist, and preoperative rebleeding was prevented. Postoperatively, dehydration was corrected, and hypovolemia prevented for 3 days by administering about 3 l/day of fluid replacement consisting mainly of lactate saline and 5% albumin, with the volume of fluid replacement reduced after oral intake became feasible. To prevent any increase in blood viscosity, the hematocrit was maintained from 25% to 35% by adjusting the volume of postoperative transfusions. To detect cerebral vasospasm, transcranial Doppler sonography was used to measure the flow velocity in the middle cerebral artery.

Blood levels of atrial or A-type natriuretic peptide (ANP) and brain or B-type natriuretic peptide (BNP) were measured for 10 consecutive days after admission. Blood samples were collected in a tube containing ethylenediaminetetraacetic acid (1 mg/ml) and aprotinin (1000 kIU/ml), centrifuged at 4°C, and the plasma was freeze-preserved at −40°C. Immunoradiometric assay was performed using 2 types of monoclonal antibody to recognize the ring structure and carboxyterminal of natriuretic peptide (Shionogi Co., Ltd., Osaka). Serum sodium level was also measured using the same blood sample.

The cardiac index (CI), systemic vascular resistance index (SVRI), intrathoracic blood volume index (ITBVI), and extravascular lung water index (EVLWI) were measured for 5 consecutive days using a computer system (PICCO plus system; Pulsion Medical Systems AG, Munich, Germany). Intrathoracic blood volume and extravascular lung water were standardized using body surface area and body weight, respectively, as ITBVI and EV-LWI. These parameters were measured with a 4-Fr, 13 cm long flexible catheter (thermistor-tipped arterial thermodilution catheter) inserted into the femoral artery 1 or 3 times per day for 5 consecutive days in the intensive care unit by the single transpulmonary thermodilution method with 10 ml of 5% glucose chilled to 0°C infused from a central vein. The mean value was adopted as that day’s representative value.

The 15 patients were divided into the control group (n = 5), in whom consciousness was continuously maintained from SAH onset to admission with Hunt and Hess grade 1 or 2, and the consciousness disturbance group (n = 10), in whom consciousness was not preserved, including patients who suffered a short period of consciousness loss between onset and admission despite arriving with Hunt and Hess grade 1 or 2. Hunt and Hess grade was not used for patient classification, because the most minimally affected patients were included in the control group. All patients in the control group were ambulatory on arrival at the medical facility, despite the presence of headache and/or vomiting. Comparisons of clinical parameters between the two groups were performed using Mann-Whitney U-test, with p values < 0.05 considered significant.

Results

Table 1 compares the clinical characteristics of the patients in the control and consciousness disturbance groups. Only presenting Hunt and Hess grade showed a significant difference. Anterior communicating artery aneurysms were present in 8 patients, internal carotid artery aneurysms in 5, and middle cerebral artery aneurysms in 2, with no particular difference in the location of aneurysms between the groups. Hemostasis was accomplished by surgical neck clipping in 14 cases and coil embolization in a single case at 1.1 ± 1.2 days after onset. S-T segment abnormalities were noted in 2 patients in the consciousness disturbance group. QTc interval was slightly prolonged in both groups. Transcranial Doppler sonography indicated normal mean flow velocity values in both groups, so cerebral vasospasm was not thought to have occurred during the observation period.

The standard normal value for ANP with the measurement method used in this study is ≤43.0 pg/ml. Plasma ANP level showed a significant increase in the consciousness disturbance group compared to the control group on days 1 to 3, 7, 9, and 10, considering the day of admission as day 0. Plasma ANP level on day 2 peaked at 119.2 ± 12.4 pg/ml (mean ± standard error of the mean) in the con-
### Table 1 Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age (yrs)*</th>
<th>Sex (M/F)</th>
<th>Hunt and Hess grade*</th>
<th>Admission after onset (day)*</th>
<th>Hypertension (%)</th>
<th>QTc interval (sec)*</th>
<th>TCD mean flow velocity (cm/sec)*</th>
<th>GOS (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 5)</td>
<td>49.6 ± 22.5</td>
<td>1/4</td>
<td>1.6 ± 0.5</td>
<td>0.6 ± 0.9</td>
<td>20</td>
<td>0.46 ± 0.1</td>
<td>66.4 ± 19.9</td>
<td>GR 5</td>
</tr>
<tr>
<td>Consciousness disturbance group (n = 10)</td>
<td>70.6 ± 11.1</td>
<td>4/6</td>
<td>3.5 ± 1.1</td>
<td>1.1 ± 0.9</td>
<td>70</td>
<td>0.45 ± 0.1</td>
<td>81.1 ± 39.2</td>
<td>GR 3, MD 3, PVS 3, D 1</td>
</tr>
</tbody>
</table>

*p Values are mean ± standard deviation. D: dead, GOS: Glasgow Outcome Scale, GR: good recovery, MD: moderate disability, PVS: persistent vegetative state, TCD: transcranial Doppler.

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**Fig. 1** Daily changes in natriuretic factors. A: Plasma A-type natriuretic peptide (ANP) in the consciousness disturbance group (*) demonstrated peaks on day 2 to day 6, and all values were high compared to the control group (○) over the 10 days. The approximate line was convex shaped for the consciousness disturbance group (R² = 0.87). B: Peak value of B-type natriuretic peptide (BNP) in the consciousness disturbance group (*) was observed on day 1. Each value in the consciousness disturbance group was high compared to the control group (○) and the levels decreased linearly over the 10 days (R² = 0.86). Values are mean ± standard error of the mean. *p < 0.05, **p < 0.01.

**Fig. 2** Serum sodium decreased in the consciousness disturbance group (●) from day 3, with these low values persisting until day 10, whereas values in the control group (○) fluctuated around 140 mEq/l. Values are mean ± standard error of the mean. *p < 0.05.
Fig. 3 Daily changes in cardiopulmonary parameters. A: Intrathoracic blood volume index (ITBVI) showed higher values in the consciousness disturbance group (●) compared to the control group (□) without significance. B: Extravascular lung water index (EVLWI) showed higher values in the consciousness disturbance group (●) throughout the 5-day period, with the value increasing to 11.7 ± 2.8 ml/kg (p = 0.023) on day 3 and 11.0 ± 3.7 ml/kg (p = 0.042) on day 5. C, D: Systemic vascular resistance index (SVRI) were somewhat low in the consciousness disturbance group (●) on day 1 and gradually increased, but cardiac index (CI) and SVRI showed no significant differences with the control group (□). Values are mean ± standard error of the mean. *p < 0.05.

Serum sodium level fluctuated within the normal limits until day 2, then significantly decreased from day 3 to 135 ± 1.4 mEq/l on day 4 in the consciousness disturbance group (p = 0.017), and persisted until day 10. Serum sodium level fluctuated around 140 mEq/l in the control group, and no patient developed hyponatremia (Fig. 2).

The normal range for ITBVI is 850–1000 ml/m². ITBVI on days 1–4 was 1100–1200 ml/m² in the consciousness disturbance group, slightly higher compared to the control group. The upper normal limit was exceeded in both groups, but no significant difference was seen at any time during the measurement period (Fig. 3A). The normal range for EVLWI is 3.0–7.0 ml/kg. EVLWI was higher throughout the measurement period in the consciousness disturbance group compared to the control group, with a significant increase to 11.7 ± 2.8 ml/kg (p = 0.023) on day 3 and 11.0 ± 3.7 ml/kg (p = 0.042) on day 5 (Fig. 3B). CI was about 4.0 l/min/m² with no differences between the two groups (Fig. 3C). SVRI was about 2000 dyn·sec/cm²m², somewhat lower in the consciousness disturbance group on day 1 and then gradually increasing, but no significant differences were found between the two groups (Fig. 3D). All four parameters showed little change during the measurement period in the control group.

Discussion

Losses of water and sodium and the resultant hyponatremia associated with SAH are caused by 2 types of natriuretic peptides, ANP and BNP, which are humoral factors inducing natriuresis. In our cases, serum sodium level remained within normal limits until day 2, but decreased from day 3 and remained depressed until day 10 in the consciousness disturbance group. The delayed action of these natriuretic peptides is thought to have induced the decrease in serum sodium. ANP and BNP are formed by the cleavage of pro-ANP and pro-BNP. ANP is then stored in the atrial myocardium as a 28-amino acid peptide and released by stimulation, and BNP is a 32-amino acid peptide synthesized and released mainly in the ventricular myocardium.
Since the discovery of these natriuretic peptides, the heart has been widely recognized as an endocrine organ. These natriuretic peptides are secreted after cardiac dysfunction such as myocardial infarction and congestive heart failure, and are considered to be cardioprotective factors mediated by vascular smooth muscle relaxation and diuretic actions. A BNP cut-off value of 100 pg/ml for a diagnosis of heart failure in patients complaining of dyspnea has sensitivity and specificity of 90% and 73%, respectively. In our cases, an increase in BNP to above standard values but below 100 pg/ml was observed in the control group, but values exceeded 100 pg/ml throughout the 10-day measurement period in the consciousness disturbance group, indicating a state of mild heart failure.

Many reports have focused on the relationship between cerebral vasospasm and ANP or hyponatremia, whereas none have addressed the association between consciousness disturbance in the initial period and increased ANP. ANP was not measured on consecutive days, as in our study, but after dividing the period during 3 periods of 3 days after SAH onset. ANP was high immediately after onset and gradually decreased in cases without vasospasm, whereas high hyponatremia values were often seen in the second phase about 4–6 days after onset in cases with vasospasm. The overwhelming number of studies have focused on BNP since 1997. The plasma concentration of BNP after SAH ranges from 100 pg/ml to 300 pg/ml. In our study, the increase in BNP exceeded 200 pg/ml from day 1 to day 4 in the consciousness disturbance group. Since we measured ANP and BNP simultaneously in the same patients, we were able to detect differences in the daily fluctuation patterns of ANP and BNP. The increase in the BNP level peaked on day 1, whereas the increase in ANP level peaked on day 2, and the BNP level showed faster decrease. BNP is more rapidly secreted in response to secretory stimulation and more rapidly cleared from the circulation. This difference may be related to the more rapid expression of the BNP gene. Alternatively, BNP is chiefly synthesized from the ventricle and ANP chiefly from the atrium, so the atrium may be subjected to stress later than the ventricle.

Cardiac function after the onset of SAH can be evaluated with a Swan-Ganz catheter to monitor volume overload during the administration of hypertensive-hypervolemic-hemodilution (triple-H) therapy. Previously, we also used a Swan-Ganz catheter, but the usefulness of cardiopulmonary monitoring in the intensive care field has been recently demonstrated in European countries using the single transpulmonary thermodilution method. This method is based on the same basic principle as the thermodilution method using a traditional Swan-Ganz catheter, but differs in that a thermodilution curve is obtained in the iliac artery using a bolus of low temperature fluid, administered in a central vein, and passing through a long route via the pulmonary artery, pulmonary circulation, pulmonary vein, left heart, and aorta. Lung thermal capacity changes with differences in water content during passage through the pulmonary circulation, allowing evaluation of the lung extravascular water volume. Furthermore, the blood volume of the intrathoracic heart and large vessels can be measured. This method directly measures preload and afterload from the volume, whereas the Swan-Ganz catheter measures preload and afterload from the pulmonary artery pressure and pulmonary artery wedge pressure. EVLWI in the control group fluctuated around 8 ml/kg, but was elevated to 11–12 ml/kg throughout the 5 days of hospitalization in the consciousness disturbance group, showing a significant increase particularly on day 3. We interpret this finding to indicate that fluid volume in the lung interstitium increased resulting in sub-clinical lung edema in the consciousness disturbance group. Measurement of various parameters in patients with different cerebrovascular disease using a Swan-Ganz catheter and the double-indicator dilution method found that patients with neurogenic pulmonary edema showed no fluctuations in hemodynamic parameters, and only EVLWI was elevated. The theory of the ITBVI measurement method is basically the same as that of the PiCCO system used by us, and the results are very similar.

Increased ANP/BNP levels and EVLWI showed a slightly positive relationship, but not statistically significant (R = 0.3). Patients with high ANP/BNP levels do not always develop high values of EVLWI. Other factors increasing pulmonary arterial pressure, such as low reserve capacity of the systemic circulation and fluid overload, are also implicated in increasing extravascular lung water. Increased ANP/BNP levels indicate increased load on the left atrium and ventricle. Mean values exceeding 100 pg/ml in the consciousness disturbance group indicated mild heart failure. Patients with high ANP/BNP levels should not be subjected to too much fluid overload for triple-H therapy.

The developmental mechanisms of neurogenic pulmonary edema with markedly increased lung fluid have not yet been adequately explained. The present study suggests that the most convincing mechanism is an increase in catecholamine release induced by stimulation of the hypothalamus at the time of SAH onset. This study did not measure...
catecholamines, so no definitive statement can be made, but consciousness disturbance occurring early after SAH onset reflects the effect of stress to the hypothalamus and brainstem, which is thought to be related to the rapid increase in serum catecholamines. Several studies in relation to catecholamine release and cardiopulmonary compromise have been conducted in recent years. Naredi et al. has found evidence in SAH patients of prolonged and massive sympathetic nervous activation. A three-fold increase in norepinephrine spill-over into the plasma was detected, which was sustained for at least 10 days, but was normal at the 6-month follow up. This rise in catecholamine concentrations results in peripheral arteriole constriction and left heart failure, and in increased pulmonary vein pressure. The pulmonary capillary wall is extremely thin, and may be damaged at pressures exceeding 40 mmHg in the rabbit, causing enhanced permeability resulting in edema. However, it remains to be proved that short period consciousness loss after SAH can become enough stimuli associated with catecholamine secretion and increased pulmonary capillary pressure. Further investigations may need to be considered to resolve this issue.

The present study demonstrated that in patients sustaining hemorrhage of sufficient magnitude to cause loss of consciousness soon after SAH onset, ANP and BNP levels were increased for about 10 days and induced increased lung extravascular water content. In contrast, patients not losing consciousness soon after SAH onset suffered none of these events. The present findings indicate that the primary cause of natriuretic peptide secretion lies in the central nervous system, but support the idea that the site of secretion is not the central nervous system but the heart. The elevation of natriuretic peptides and increase in pulmonary extravascular water content in the acute period are thought to be attributable to the increased load to the left heart and increased pulmonary capillary pressure due to excessive release of catecholamines.

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**Commentary**

The team from Nara Medical University has carefully characterized the serum levels of type A and type B natriuretic peptides (ANP and BNP) after aneurysmal subarachnoid hemorrhage, including a strong and sustained difference in patients with and without early impaired consciousness (high grade versus low grade cases). The time course, including early elevation of both peptide levels, and some subtle difference in peaking time between them, is original and has not been described as carefully. The peptide levels do correlate, as expected, with clinical hyponatremia (which is of course also worse in the high grade patients).

Other clinical significance, including correlation with cardiopulmonary parameters, is more speculative, and may have been further confused by the aggressive volume resuscitation which was administered to all patients (more than 3 liters of intravenous fluids per day, including lactated saline and albumin). Such vigorous correction of hypovolemia may account, more than anything else, for the elevated ITBVI and CI in both high and low grade patients.

The slightly more elevated EVLWI in higher grade patients may indeed represent a trend or vulnerability to neurogenic pulmonary edema in those sicker patients, which is not altogether surprising. But any causative relationship to ANP or BNP levels cannot be established from the data at hand, and this vulnerability may be mediated by other mechanisms including direct cardiac injury.

It may be useful to articulate specific hypotheses about the potential clinical or scientific usefulness of...
monitoring ANP and BNP levels directly, beyond simple serum sodium levels, and how this may add prognostic significance or alter the management paradigm.

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In this interesting study, daily measurements of serum atrial and brain natriuretic peptides were done on SAH patients for the first 10 days. Significantly higher levels of both were found in patients whose conscious state had been disturbed at any time. Hyponatremia was present only in those with disturbed consciousness, who also showed an increase in extravascular lung water. It was felt likely that these changes correlated with excessive catecholamine release and increased load on the left heart.

As noted, disturbances of cardiac rhythm and function, and pulmonary edema, are common especially in severe SAH with conscious disturbance. This may be related to hypothalamic dysfunction due to the SAH. No correlation was found with an anterior communicating location of aneurysm, as has been suggested in the past, but the overall series is small.

The authors have also noted that fatal cardiac disturbance can follow an apparently minor SAH. I once experienced within a short period two patients whose SAH was misdiagnosed as myocardial infarction.1) One was submitted to an exercise test and the other treated with streptokinase, with disastrous results in each case.

Reference

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