Clinical Study

Plasma brain natriuretic peptide is elevated in the acute phase of intracerebral hemorrhage

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1. Introduction

Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload. Previous studies have shown that the BNP level is related to cardiac function and it has been used as a biochemical marker for congestive heart failure.

In addition, plasma BNP levels have also been shown to be elevated in the acute phase of subarachnoid hemorrhage and in acute ischemic stroke patients. However the relationship between plasma BNP and intracerebral hemorrhage (ICH) has not been fully examined.

Hypertension is the main risk factor for ICH and induces an increased load on the cardiac ventricles. Thus, hypertension causes left ventricular hypertrophy and systolic or diastolic dysfunction. In addition, early elevation of blood pressure after ICH is well documented. Therefore, we suspected that the plasma BNP level may be elevated in patients with ICH because of the increased load on the cardiac ventricles seen in the acute phase of ICH. We investigated this hypothesis and the presence of associated factors.

2. Patients and methods

We prospectively enrolled consecutive acute spontaneous ICH patients within 24 hours of onset who were admitted to our Stroke Center between June 2006 and February 2010. Patients with underlying aneurysm, vascular malformation, dissection, hemorrhagic transformation of ischemic stroke, traumatic ICH, or those who underwent emergency surgery were excluded. In addition, patients with atrial fibrillation, dialysis-dependent chronic renal failure, or a history of myocardial infarction or chronic pulmonary disease were excluded from the present study, because plasma BNP levels are increased in these patients.

The plasma BNP level was measured on admission. The study was conducted in compliance with the Declaration of Helsinki with regard to investigations in human subjects. The ethics committee of Kawasaki Medical School Hospital approved the study protocol.

A diagnosis of acute ICH was made by stroke neurologists, and confirmed by CT scans or MRI. The following factors were assessed: age, sex, prior ICH, vascular risk factors, left ventricular hypertrophy, creatinine, cardio–thoracic ratio (CTR) on chest radiograph, systolic and diastolic blood pressure on admission, National Institutes of Health Stroke Scale (NIHSS) score on admission, ICH location, ICH volume on admission, ICH volume enlargement, subarachnoid extension, intraventricular extension, hydrocephalus, ICH score, and in-hospital death.

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We also evaluated the following vascular risk factors: hypertension (defined as the use of antihypertensive agents, systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg before stroke onset or 2 weeks after stroke onset), diabetes mellitus (defined as the use of oral hypoglycemic agents or insulin, fasting blood glucose level $\geq 126$ mg/dL, or a glycosylated hemoglobin level $\geq 6.4\%$), and hyperlipidemia (defined as the use of antihyperlipidemic agents or a serum cholesterol level $\geq 220$ mg/dL). Electrocardiographic left ventricular hypertrophy was defined as $S_{V_1} + R_{V_5}$ or $V_6 \geq 3.5$ mV.\textsuperscript{26}

Cranial CT scanning was carried out twice, at the baseline visit (<24 hours after onset) and on follow-up (24–48 hours after onset). All cranial CT scans were performed according to our radiology department protocol, with an image matrix of $340 \times 340$ and a slice width of 8–10 mm. The investigators who read the CT scans had no prior knowledge of the clinical data. ICH volume was measured using the $A \times B \times C/2$ method, as described previously.\textsuperscript{26}

The site of the ICH was classified according to the location of the largest amount of hematoma, and categorized as the putamen, thalamus, lobar, brainstem, or cerebellum.\textsuperscript{22} ICH enlargement was defined as a hematoma that grew by more than 33% of its initial volume.\textsuperscript{28} The ICH score is a clinical grading scale that is composed of five components related to outcome after nontraumatic ICH: the Glasgow Coma Scale score, ICH volume, presence of intraventricular hemorrhage, infratentorial origin, and age.\textsuperscript{29} All patients had baseline blood samples drawn on admission. Serum creatinine and plasma BNP were assessed.

### 2.1. Measurement of plasma BNP levels

The plasma BNP level was measured twice, on admission and 4 weeks after ICH onset or at discharge. Samples were collected from a peripheral vein into tubes containing aprotinin and ethylenediamine tetra acetic acid (EDTA), and the plasma was isolated and then stored at -80 °C until analysis. The plasma BNP concentration was measured using a chemiluminescence enzyme immunoassay for human BNP (Shionogi & Co., Osaka, Japan). Briefly, this assay uses two monoclonal antibodies against human BNP, one recognizing a carboxyl-terminal sequence and the other the ring structure of BNP, and measures BNP by sandwiching it between the two antibodies. At our hospital the normal value of BNP is $<18.4$ pg/mL. The minimum detectable quantity of BNP is 3.9 pg/mL. Investigators were blinded to the BNP results, and evaluated the clinical and radiographic findings.

### 3. Statistical analysis

The Mann–Whitney U test was used to examine factors associated with plasma BNP level on admission. Linear regression analysis was performed to assess factors related to log BNP. Because the plasma BNP level had skewed distributions, it was log-transformed. The BNP level of patients with cerebellar hemorrhage was significantly higher in patients with intraventricular extension than in patients without intraventricular extension (77.9 ± 79.4 versus 66.6 ± 117.8 pg/mL, $p = 0.0039$) and was significantly higher in patients with hydrocephalus than in those without hydrocephalus (113.5 ± 159.7 versus 62.6 ± 86.9 pg/mL, $p = 0.0046$). The plasma BNP level of deceased patients was significantly higher than that of surviving patients (99.9 ± 101.6 versus 67.4 ± 104.1 pg/mL, $p = 0.0030$). There were no differences in other variables such as NIHSS score on admission ($r = 0.081$, $p = 0.2034$), or ICH enlargement ($p = 0.2114$). The BNP level of patients with cerebellar hemorrhage was the highest (130.2 ± 152.0 pg/mL), followed by brainstem (84.5 ± 170.6 pg/mL), lobar (72.4 ± 148.1 pg/mL), thalamus (64.8 ± 72.1 pg/mL), and putamen (59.9 ± 62.6 pg/mL) hemorrhage (Fig. 1). The plasma BNP level of patients with cerebellar hemorrhage was significantly higher than that of patients with putamen ($p = 0.0064$), thalamus ($p = 0.0098$), and lobar hemorrhage ($p = 0.0500$). The differences in BNP level between brainstem and cerebellum hemorrhage did not reach statistical significance ($p = 0.1204$). Table 1 shows the clinical characteristics in each ICH location. Older age, higher CTR, higher ICH score and intraventricular extension were more frequent in patients with cerebellar hemorrhage than in those with other ICH locations.

![Fig. 1](image-url)
Follow-up BNP was measured at 25 ± 10 days after ICH onset. In 65 of the 250 patients, plasma BNP could not be measured in the subacute phase of stroke because of death (n = 29), transfer to another department (n = 5), and not being measured (n = 31). The plasma BNP level in the acute phase of ICH was significantly higher than that in the subacute phase of ICH (69.3 ± 108.1 pg/mL versus 21.7 ± 23.5 pg/mL, p < 0.0001). The BNP level reduced during the subacute phase of ICH in each location of ICH (Fig. 2). There was no difference in BNP level among the different locations of ICH in the subacute phase.

### Table 1

<table>
<thead>
<tr>
<th>Location</th>
<th>Putamen (n = 78)</th>
<th>Thalamus (n = 96)</th>
<th>Lobar (n = 29)</th>
<th>Brainstem (n = 29)</th>
<th>Cerebellum (n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 (14)</td>
<td>71 (12)</td>
<td>70 (14)</td>
<td>60 (11)</td>
<td>74 (8)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Male</td>
<td>49 (63)</td>
<td>63 (66)</td>
<td>15 (52)</td>
<td>23 (79)</td>
<td>14 (78)</td>
<td>0.1752</td>
</tr>
<tr>
<td>Prior ICH</td>
<td>4 (5)</td>
<td>5 (5)</td>
<td>9 (31)</td>
<td>2 (7)</td>
<td>2 (11)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 (73)</td>
<td>68 (71)</td>
<td>14 (48)</td>
<td>20 (69)</td>
<td>15 (83)</td>
<td>0.0793</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (14)</td>
<td>14 (15)</td>
<td>7 (24)</td>
<td>7 (24)</td>
<td>3 (17)</td>
<td>0.5615</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11 (14)</td>
<td>19 (20)</td>
<td>9 (31)</td>
<td>4 (14)</td>
<td>2 (11)</td>
<td>0.2601</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>21 (27)</td>
<td>20 (21)</td>
<td>3 (10)</td>
<td>8 (28)</td>
<td>3 (17)</td>
<td>0.3670</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.67 (0.20)</td>
<td>0.69 (0.26)</td>
<td>0.68 (0.26)</td>
<td>0.72 (0.28)</td>
<td>0.68 (0.22)</td>
<td>0.8019</td>
</tr>
<tr>
<td>Cardio–thoracic ratio</td>
<td>54.6 (4.6)</td>
<td>55.1 (5.5)</td>
<td>52.3 (5.5)</td>
<td>55.0 (5.8)</td>
<td>56.7 (9.2)</td>
<td>0.2466</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>179 (34)</td>
<td>183 (25)</td>
<td>154 (19)</td>
<td>171 (30)</td>
<td>169 (23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>98 (23)</td>
<td>102 (18)</td>
<td>87 (17)</td>
<td>95 (22)</td>
<td>94 (18)</td>
<td>0.0050</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>14 (8)</td>
<td>13 (6)</td>
<td>11 (9)</td>
<td>18 (12)</td>
<td>11 (10)</td>
<td>0.0931</td>
</tr>
<tr>
<td>ICH volume, mL</td>
<td>3.7 (49.2)</td>
<td>9.9 (8.1)</td>
<td>35.0 (38.6)</td>
<td>4.7 (4.8)</td>
<td>13.7 (20.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICH volume enlargement</td>
<td>0.070 (9)</td>
<td>6/95 (6)</td>
<td>1/27 (3)</td>
<td>0/27 (17)</td>
<td>2/16 (11)</td>
<td>0.2768</td>
</tr>
<tr>
<td>Subarachnoid extension</td>
<td>12 (15)</td>
<td>8 (8)</td>
<td>13 (42)</td>
<td>1 (3)</td>
<td>3 (17)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>17 (22)</td>
<td>60 (63)</td>
<td>5 (17)</td>
<td>7 (24)</td>
<td>9 (50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>13 (17)</td>
<td>13 (14)</td>
<td>3 (10)</td>
<td>8 (28)</td>
<td>5 (28)</td>
<td>0.2345</td>
</tr>
<tr>
<td>ICH score</td>
<td>1.1 (1.0)</td>
<td>1.2 (0.9)</td>
<td>1.2 (1.2)</td>
<td>2.1 (1.3)</td>
<td>2.5 (1.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>14 (18)</td>
<td>7 (3)</td>
<td>3 (10)</td>
<td>5 (17)</td>
<td>4 (22)</td>
<td>0.0128</td>
</tr>
</tbody>
</table>

Data are presented as number (%).  
ICH = intracerebral hemorrhage, NIHSS = National Institutes of Health Stroke Scale.

5. Discussion

We have demonstrated that plasma BNP is elevated in the acute phase of ICH and reduced in the subacute phase of ICH. Furthermore, plasma BNP is significantly associated with the presence of intraventricular extension and hydrocephalus.

There are a few possible explanations for the increase in plasma BNP level in patients with ICH. First, a previous study assumed that BNP production may be induced by a lesion to the hypothalamus caused by SAH. Interestingly, the plasma BNP level was significantly higher than that in the subacute phase of ICH (Fig. 2).
significantly associated with the presence of intraventricular extension and hydrocephalus, and was high in patients with cerebellar or brainstem hemorrhage in the present study. Intraventricular extension or hydrocephalus due to infratentorial lesions might influence the hypothalamus and trigger BNP secretion. Further study is necessary to evaluate this hypothesis. Second, neuroendocrine changes, including of catecholamine levels, due to ICH induce an increased load on the cardiac ventricles. Takotsubo-like cardiomyopathy is occasionally a complication of ICH. Third, patients with a high levels of BNP have already suffered cardiac dysfunction prior to ICH onset. Hypertension is the main risk factor for ICH, and induces hypertensive heart disease. Furthermore, marked elevation of blood pressure in the acute phase of ICH might induce the increased load on the cardiac ventricle. The present results demonstrate a relationship between the plasma BNP level and the CTR. Thus, the plasma BNP level, being a marker of cardiac dysfunction, would be elevated in ICH patients. Little is known regarding the association between plasma BNP and ICH. In a previous small study (n = 44), a comparison of BNP levels between ICH and essential hypertension patients did not show a statistically significant relationship. In contrast, another small study (n = 25) found that the plasma BNP levels of ICH patients with hypertension were significantly higher than that of normotensive controls (15.9 ± 13.6 versus 7.4 ± 3.7 pg/mL, p < 0.05). To our knowledge, there has been no previous large study of the relationship between plasma BNP and ICH. Intravenous glycerol reduces cerebral edema and intracranial pressure in the acute phase of ICH. However, glycerol induces an increased load on the cardiac ventricles in patients with cardiac dysfunction. If the plasma BNP level in ICH is high, the increased load on the cardiac ventricle should be considered and a diagnostic workup performed, and the volume of intravenous fluids, including glycerol, and urine volume should be carefully monitored to avoid heart failure. Therefore, we propose routine measurement of plasma BNP to evaluate the load on the cardiac ventricle in patients with ICH.

This study has several limitations. First, we did not evaluate cardiac function. Further detailed investigation of cardiac function, such as ejection fraction, ventricular septal thickness, and posterior wall thickness should be performed in a similar study. Second, the number of patients with cerebellar hemorrhage was relatively small. Third, follow-up BNP measurement was not performed in all patients. In conclusion, plasma BNP appears to be elevated in the acute phase of ICH, possibly due to the increased load on the heart. Further investigation is required to clarify this issue.

Conflicts of interest/disclosure
The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References
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