Predictors of increased cumulative serum levels of the N-terminal prohormone of brain natriuretic peptide 4 days after acute spontaneous subarachnoid hemorrhage

Clinical article

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Object. The rupture of an intracranial aneurysm is followed by increased intracranial pressure and decreased cerebral blood flow. A major systemic stress reaction follows, presumably to restore cerebral blood flow. However, this reaction can also cause adverse effects, including myocardial abnormalities, which are common and can be serious, and increased levels of natriuretic peptides, especially brain natriuretic peptide (BNP). The association of BNP with fluid and salt balance, vasospasm, brain ischemia, and cardiac injury has been studied but almost exclusively regarding events after admission. Brain natriuretic peptide has also been measured at various time points and analyzed in different ways statistically. The authors approached BNP measurement in a new way; they used the calculated area under the curve (AUC) for the first 4 days to quantitatively measure the BNP load during the first critical part of the disease state. Their rationale was a suspicion that early BNP load is a marker of the severity of the ictus and will influence the subsequent course of the disease by disturbing the fluid and salt balance.

Methods. The study included 156 patients with acute spontaneous subarachnoid hemorrhage (SAH). Mean patient age was 59.8 ± 11.2 years, and 105 (67%) of the patients were female. An aneurysm was found in 138 patients. A total of 82 aneurysms were treated by endovascular coiling, 50 were treated by surgery, and 6 were untreated. At the time of admission, serum samples were collected for troponin-I analysis and for the N-terminal prohormone of BNP (NT-proBNP); daily thereafter, samples were collected for the NT-proBNP analysis. The cumulative BNP load was calculated as the AUC for NT-proBNP during the first 4 days. The following variables were studied in terms of their influence on the AUC for NT-proBNP: sex, age, World Federation of Neurosurgical Societies grade of SAH, Fisher grade, angiographic result, treatment of aneurysm, clinical neurological deterioration, verified infections, vasospasm treatment, and 6-month outcome.

Results. The AUC for NT-proBNP was larger when variables indicated a more severe SAH. These variables were higher Fisher and World Federation of Neurosurgical Societies grades, high levels of troponin-I at admission, an aneurysm, neurological deficits, and infections. The AUC for NT-proBNP was also larger among women, older patients, and patients with poor outcomes. Linear regression showed that the best predicting model for large AUC for NT-proBNP was the combination of the following: female sex, high levels of troponin-I, an aneurysm, neurological deficits, and advanced age.

Conclusions. The cumulative BNP load during the first days after SAH can be predicted by variables describing the severity of the disease already known at the time of admission. This information can be used to identify patients at risk for an adverse course of the disease.

(http://thejns.org/doi/abs/10.3171/2013.8.JNS13625)

Key Words • subarachnoid hemorrhage • NT-proBNP • vascular disorders • brain natriuretic peptide • troponin-I

Rupture of an intracranial aneurysm is followed by an acute phase with a complex chain of events. Most obvious are the intracranial complications of clots, hydrocephalus, and brain ischemia in various degrees and combinations. Many patients also show serious systemic complications, probably as a result of the intracranial pathophysiology. It is generally thought that a main trigger for systemic changes is the increase in the intracranial pressure that occurs at the time of aneurysm rupture. The elevated intracranial pressure decreases cerebral blood flow and causes a transient or permanent global ischemia. A major stress reaction follows, including the release of adrenocorticotropic hormone, cortisol,
Few studies with a larger number of patients exist.22,28 According to a literature review on SAH and BNP, only a few studies compared BNP values with events during the intensive care phase.3,24,27 Later, BNP and vasospasm were studied. Results from these studies indicated that it was the clinically apparent brain ischemia, rather than the angiographic or transcranial Doppler defined vasospasm, that was associated with the BNP increase.13,19,20 This finding was later supported by Taub et al.,22 who showed in a larger study that high levels of BNP were associated with cerebral infarction detected on CT images. Brain natriuretic peptide has also been explored as a marker of cardiac injury in SAH patients, and high BNP at admission as well as high troponin-I on the 3rd day after admission has been found to be associated with increased inpatient deaths.28 Altogether, the studies so far suggest an association among SAH, complications in the heart and brain, and disturbances of fluid and salt balance. However, according to a literature review on SAH and BNP, only a few studies with a larger number of patients exist.22,28 Another problem is that BNP has been measured at different time points and the results have been statistically treated in various ways: median values, mean values, and single time points. Furthermore, earlier published studies almost exclusively compared BNP values with events during the intensive care phase.

We had a different scientific question: Can variables already known at admission, such as severity of the bleeding, sex, and age, predict the BNP load during the initial phase of the disease? Because BNP not only is a marker but has obvious biological effects, we also wanted to obtain a quantitative measurement of the BNP load. To do this, we used the calculated area under the curve (AUC) of the N-terminal prohormone of BNP (NT-proBNP) for the first 4 days after SAH. The NT-proBNP is the N-terminal part split from the prohormone during the synthesis of the biologically active BNP. It has no known biological effects and is therefore considered to be a more stable measure of BNP activity. The AUC for NT-proBNP was evaluated against clinical and demographic variables describing the severity of the disease and outcome with the aim of determining which variables could predict an increased BNP load.

Methods

Patients admitted to the Department of Neurosurgery at Uppsala University Hospital for acute spontaneous SAH from 2006 through 2011 were eligible. A total of 156 patients were included (Table 1). An aneurysm was found in 138 patients. Endovascular treatment was used for 82 patients, surgical clipping for 50, and no treatment for 6. The aneurysm was on the anterior communicating artery in 45 patients.

Table 1: Characteristics of the 156 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>female</td>
<td>105 (67)</td>
</tr>
<tr>
<td>WFNS grade</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>66 (42)</td>
</tr>
<tr>
<td>3–5</td>
<td>90 (59)</td>
</tr>
<tr>
<td>Fisher grade</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>90 (58)</td>
</tr>
<tr>
<td>3–4</td>
<td>66 (42)</td>
</tr>
<tr>
<td>high troponin-I†</td>
<td>79 (51)</td>
</tr>
<tr>
<td>angiographic result</td>
<td></td>
</tr>
<tr>
<td>aneurysm</td>
<td>138 (88)</td>
</tr>
<tr>
<td>normal</td>
<td>18 (12)</td>
</tr>
<tr>
<td>vasospasm treatment</td>
<td>31 (20)</td>
</tr>
<tr>
<td>any infection</td>
<td>97 (62)</td>
</tr>
<tr>
<td>neurological deficits</td>
<td>109 (70)</td>
</tr>
<tr>
<td>outcome</td>
<td></td>
</tr>
<tr>
<td>poor (GOS Score 1–3)</td>
<td>72 (46)</td>
</tr>
<tr>
<td>favorable (GOS Score 4–5)</td>
<td>84 (54)</td>
</tr>
</tbody>
</table>

* Mean (± SD) patient age was 59.8 ± 11.2 years. GOS = Glasgow Outcome Scale score; WFNS = World Federation of Neurosurgical Societies.
† Pathological plasma levels of troponin-I at admission.

Study Protocol

Patients were included if samples had been collected for serum NT-proBNP and troponin-I on Day 0 (day of ictus) and at least 4 daily samples of NT-proBNP had been collected altogether for Days 0–5. Data were recorded for sex, age, clinical condition at admission (using World Federation of Neurosurgical Societies [WFNS] grading of SAH),23 and the blood distribution according to the first CT image using the Fisher classification.6 Also recorded were the angiographic result, treatment of aneurysm, documented clinical neurological deterioration, any verified infection, and treatment of vasospasm. Outcomes after 6 months were measured with the Glasgow Outcome Scale.10

SAH Management

At the time of admission, angiography was performed to look for aneurysms. Ruptured aneurysms were generally treated as soon as possible, with either endovascular coiling or surgical clipping. The patients received nimodipine, were limited to bed rest for 10 days, and were kept normovolemic to avoid hypotension. Patients with hydrocephalus and/or decreased consciousness received a ventricular drain. Unconscious patients received mechanical ventilation. Vasospasm was considered to be present when neurological deterioration could not be explained by other factors such as hydrocephalus or an intracranial
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clot. Clinically suspected vasospasm was treated by increasing blood volume and blood pressure and improving blood rheology. Secondary insults (high intracranial pressure, low cerebral perfusion pressure, seizures, fever, hypoxia, and hypo/hyperglycemia) were treated according to the unit’s protocols for programmed care.16,18

Statistical Analyses

The NT-proBNP was quantified by using the trap-pezoidal method12 to calculate the AUC for each measurement on Days 0–4. If a measurement was missing, a value was interpolated by using previous and subsequent measurements. Statistica 10.0 (StatSoft, Inc.) was used for descriptive and analytical statistics. The clinical information was dichotomized as follows: male/female sex, presence/absence of high plasma troponin-I at admission, presence/absence of aneurysm, aneurysm on anterior communicating artery/on other location, endovascular/surgical treatment, presence/absence of verified infection, presence/absence of neurological deterioration, and treatment/no treatment of vasospasm. We also dichotomized WFNS, Fisher, and Glasgow Outcome Scale scores as follows: WFNS Grade 1–2 versus 3–5, Fisher Grade 1–2 versus 3–4, and Glasgow Outcome Scale Score 1–3 (poor) versus 4–5 (favorable). The AUC for NT-proBNP was compared between the aforementioned groups by using the Mann-Whitney U-test. Spearman’s rank-order correlation coefficient was used for analysis of correlation to age. The change of NT-proBNP over time was evaluated with 1-way ANOVA. A generalized linear model with a multinomial ordinal response and a logistic link function was used to calculate the best subset of variables predicting a large AUC for NT-proBNP. This was done by using Akaike information criterion.3 In this analysis, the natural logarithm of AUC for NT-proBNP was used, and treatment method and outcome were not included as input variables. A difference was considered statistically significant when p < 0.05.

Ethics

The Uppsala University Regional Ethical Review Board for clinical research granted ethical permission.

Results

At the time of patient admission, plasma troponin-I levels were increased (> 0.022 µg/L) in 51% of the patients. The highest value at admission was 8.2 µg/L. For 35 patients, troponin-I values were greater than 0.3 µg/L, indicating myocardial injury according to our hospital’s standard.

Results from the univariate analysis are shown in Table 2. The AUC for NT-proBNP was larger when variables indicated a more severe SAH. These variables were more blood as detected on CT images, worse clinical condition at admission, presence of an aneurysm, high plasma troponin-I at admission, neurological deficits either at admission or during the course of the disease, and presence of any infection. The AUC for NT-proBNP was also larger among women and patients with poor outcomes. The AUC for NT-proBNP did not differ between surgical and endovascular treatment of aneurysms or between groups that did or did not receive treatment for vasospasm. The AUC for NT-proBNP did not differ according to whether aneurysms were on the anterior communicating artery or in other locations. Using the Spearman’s rank-order correlation coefficient, we found that age was correlated with AUC for NT-proBNP; correlation coefficient was 0.41. We entered in the linear regression the variables that, according to univariate analysis, were significant. Results from linear regression showed that the best predicting model for a large AUC for NT-proBNP was the combination of the following variables: female sex, high plasma troponin-I, presence of an aneurysm, neurological deficits, and increasing age. A linear regression using the Glasgow Outcome Scale dichotomized to poor/favorable as the outcome parameter indicated that that the best predictive model consisted of the variables of age, clinical condition at admission, and amount of blood on the first CT scan. The AUC for NT-proBNP was included in the second best model, but AUC for NT-proBNP turned out to not be an independent predictor for clinical outcome.

The time course for the actual serum NT-proBNP values is shown in Fig. 1. Concentrations were low at the time of admission and increased during the next few days. The values peaked on Day 3 for patients with aneurysms and on Day 2 for those with normal angiography results. One-way ANOVA showed that the change was significant for patients with aneurysms (p < 0.025) but not for those with normal angiography results.

Discussion

The primary mission of neurointensive care is to prevent complications and to treat them effectively when they occur. It is therefore of interest to predict a complicated course of the disease as early as possible. Increased BNP has been shown to be involved in several complications frequently seen several days after SAH, not only as a biological marker but actually playing a causative role. The aim of this study was to determine whether high levels of BNP during the first 4 days after SAH could be predicted at the time of admission according to variables describing the severity of the disease, including troponin-I, as a sign of prehospitalization cardiac injury. A better understanding of the links between admission factors and subsequent complications may lead to more effective and better informed neurointensive care for these patients.

Our finding that NT-proBNP values increased over the first days after admission is in line with earlier results,5,14 but the difference we found between SAH with aneurysms and SAH with normal angiographic results has not, to our knowledge, been described. Furthermore, we found that troponin-I was elevated at admission in 51% of the patients, indicating prehospitalization cardiac injury. This finding is in line with those of earlier studies considering that measurements were taken on different days.26,28 The fact that the serum NT-proBNP levels were highest after 3 days in patients with SAH and aneurysms argues, though, that the initial cardiac injury is not solely responsible for the increased levels. Other events...
during these days probably also play a role. Earlier studies have indicated that brain ischemia is associated with the increase of BNP.\textsuperscript{13,19,20,22} Nakamura et al.\textsuperscript{15} described that BNP is higher in unconscious SAH patients than in awake patients. Brain ischemia appears several days after the bleeding as delayed ischemic neurological deficits, which could be associated with the BNP increase. The tendency to develop delayed ischemic neurological deficits is in turn associated with the severity of the SAH. Our results agree with this finding because signs of a more severe disease, which in turn could be expected to increase the risk for brain ischemia, predicted larger BNP load during the first days. Whether the BNP load causes the worse clinical conditions or results from them needs further study. Neurological deterioration and infection were not included in the best subset of variables predicting high BNP load in our study. It is possible that these events happened after our measurements were taken.

Univariate analysis indicated that AUC for NT-proBNP was significantly larger for patients with poor clinical outcomes. The linear regression indicated that AUC for NT-proBNP was included in the second-best model for predicting clinical outcome, but it was not an independent predictor. This finding is partly because BNP load is associated with severity of the disease. Another possible explanation is that during neurointensive care, suspected biological effects of BNP, such as hyponatremia and vasospasm, receive treatment. Because BNP is a mechanism and not just a marker of injury, these considerations do not detract from its clinical interest and importance.

The source of BNP in SAH patients has been discussed. BNP is expressed in cardiac myocytes as a result of mechanical stress\textsuperscript{8} or ischemia.\textsuperscript{17} More severe bleeding is probably associated with a stronger stress reaction, which in turn has a greater effect on the heart. Our results support this explanation because plasma troponin-I levels were high at admission in half of the patients in our study, and AUC for NT-proBNP was significantly larger for these patients. One study suggested that BNP expressed in the heart could reach the hypothalamus through the subfornical organ\textsuperscript{1} as a part of a stress response. There have also been indications that BNP is actually produced in the hypothalamus.\textsuperscript{21} Results of Tsubokawa et al.\textsuperscript{25} to some extent support the hypothalamic origin and the production of BNP in the brain.\textsuperscript{21} They described a series of 53 patients among whom BNP values were higher in those with anterior communicating artery aneurysms than in those with aneurysms in other locations. Similar results were found by Kawamura et al.\textsuperscript{11} We could not, however, verify these findings in our study. Intravenous administration of BNP mediated the pituitary-adrenal response to various types of stress.\textsuperscript{9} However, studies of

\begin{table}
\caption{Univariate analysis results showing AUC NT-proBNP values\textsuperscript{*}}
\begin{tabular}{|l|l|l|l|}
\hline
Patient Variable & Median Value (25th & 75th percentiles) & p Value \\
\hline
sex & male & female &  \\
\hline
Fisher grade & 3,610 (1,834 & 6,799) & 5,102 (2,716 & 15,339) & <0.006  \\
1–2 & 3–4 &  \\
\hline
WFNS grade & 2,041 (928 & 5,469) & 4,888 (2,438 & 12,447) & <0.007  \\
1–2 & 3–5 &  \\
\hline
angiographic finding & 3,570 (1,486 & 5,424) & 6,129 (2,995 & 16,817) & <0.00003  \\
normal & aneurysm &  \\
\hline
ACoA aneurysm & 1,632 (870 & 3,530) & 5,079 (2,690 & 12,447) & <0.00009  \\
yes & no &  \\
\hline
troponin-I at admission & 4,551 (2,458 & 10,009) & 5,102 (2,716 & 14,241) & NS  \\
normal & high &  \\
\hline
vasospasm treatment & 3,018 (1,348 & 5,781) & 6,402 (4,010 & 20,407) & <0.000001  \\
no & yes &  \\
\hline
neurological deficit & 4,401 (2,200 & 10,336) & 5,102 (2,355 & 13,909) & NS  \\
no & yes &  \\
\hline
any infection & 2,873 (1,246 & 5,652) & 5,132 (2,812 & 14,241) & <0.0002  \\
no & yes &  \\
\hline
aneurysm treatment & 3,630 (1,345 & 6,216) & 5,588 (2,758 & 12,783) & <0.003  \\
clip & coil &  \\
\hline
outcome & 4,517 (2,368 & 14,241) & 5,058 (2,758 & 12,352) & NS  \\
favorable & poor &  \\
\hline
\end{tabular}
\textsuperscript{*Parameters indicating a more severe SAH such as more blood detected by CT, worse clinical condition at admission, and the presence of an aneurysm had significantly larger values of AUC NT-proBNP. This finding is also true for female patients, patients with any infection, and patients with neurological deficits/deterioration. ACoA = anterior communicating artery; NS = not significant.}
\end{table}
NT-proBNP after subarachnoid hemorrhage

![Graph](image)

**Fig. 1.** Daily median concentrations (and 25th and 75th percentiles) of serum NT-proBNP for 138 patients with aneurysms and for 18 patients with normal angiographic results. Among patients with aneurysms, serum NT-proBNP changed significantly over time (p < 0.025).

BNP mRNA in the brain have so far had negative results, and immunoreactivity for BNP has been demonstrated in the periventricular nucleus and the subfornical organ.

We used the AUC for serum NT-proBNP concentrations to quantify the total load of BNP during the first days after acute spontaneous SAH. We found that AUC for NT-proBNP was significantly larger when the variables studied indicated more severe disease. Multiple factors probably contribute to the increased NT-proBNP levels over time, but the multivariate analysis indicated that the cumulative BNP load could be predicted on the basis of factors known at admission. Another thing to consider is that reference values of NT-proBNP are higher for female and older persons. The difference in reference values is, however, compensated for by using linear regression. Also, outcomes after SAH are worse for women and older persons; the possibility that different pre-SAH biology regarding BNP contributes to this should be considered.

The time window we decided to study can also be discussed; there are no standards in the literature. We chose the first 4 days because we believe that this time window is a very critical period for the pathophysiology after hemorrhage. It is after this period that complications such as vasospasm or hyponatremia occur. A better knowledge of the course of the disease in this initial phase could lead to interventions to avoid complications.

**Conclusions**

The findings in this series of patients demonstrated a temporal course with increasing levels of NT-proBNP over the first 4 days after SAH. The best subset of variables predicting high NT-proBNP load were female sex, high plasma troponin-I levels at admission, advanced age, and worse clinical condition at admission. This finding suggests that the initial injury is an important factor for increased NT-proBNP over the following days. Neurological deterioration and infection were associated with elevated NT-proBNP, but multivariate analysis did not find them to be independent predictors. The more detailed relations between SAH, BNP release, and brain and systemic complications need further study.

It seems that monitoring NT-proBNP during the acute phase of SAH would be of value. Brain natriuretic peptide is involved in the fluid and electrolyte disturbances that commonly occur after SAH. High BNP has also been found to be associated with increased long-term risk after stroke and with worse cardiac outcome after SAH.

**Acknowledgments**

We are grateful to the ever-enthusiastic staff of the neurointensive care and neurointensive care units.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ronne-Engström, Nyberg. Acquisition of data: Ronne-Engström, Nyberg. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critical reviewing the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ronne-Engström. Statistical analysis: Ronne-Engström, Nyberg.

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Manuscript submitted March 29, 2013. Accepted August 22, 2013. Please include this information when citing this paper: published online October 4, 2013; DOI: 10.3171/2013.8.JNS13625. Address correspondence to: Elisabeth Ronne-Engström, M.D., Ph.D., Department of Neurosurgery, Uppsala University Hospital, 751 85 Uppsala, Sweden. email: elisabeth.ronne.engstrom@akademiska.se.