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Elevated BNP is Associated with Vasospasm-Independent Cerebral Infarction Following Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background—Elevated levels of B-type natriuretic peptide (BNP) have been associated with cardiac dysfunction and adverse neurological outcomes after subarachnoid hemorrhage (SAH). We sought to determine whether elevated levels of BNP are independently associated with radiographic cerebral infarction after SAH.

Methods—Plasma BNP levels were measured after admission, a mean of 5.5 ± 3.0 days after SAH onset. Cerebral infarction was determined by retrospective review of computerized tomography (CT) scans. Cerebral vasospasm was confirmed by the presence of vascular narrowing on cerebral angiogram. The association between BNP and cerebral infarction was quantified using multivariable logistic regression and reverse stepwise elimination of clinical covariates. A stratified analysis was performed to quantify the association between BNP levels and infarction in patients with and without angiographic vasospasm.

Results—BNP levels were measured from 119 subjects. The median BNP level was 105 pg/ml (interquartile range 37–275 pg/ml). In our multivariable model, the top quartile of BNP levels (≥ 276 pg/ml) were associated with an increased odds of cerebral infarction (OR 4.2, $P = 0.009$). The stratified analysis showed that the association between BNP and infarction was strongest in patients without angiographic vasospasm (OR 7.8, $P = 0.006$).

Conclusions—Elevated levels of BNP are strongly and independently associated with cerebral infarction, and the association is most pronounced in patients without angiographic vasospasm. These results provide further evidence that other mechanisms can contribute to infarction, and BNP may be a useful biomarker in detecting patients at risk for adverse outcomes without large vessel vasospasm.

Keywords

Subarachnoid hemorrhage; Cerebral infarction; Cerebral vasospasm; B-type natriuretic peptide

Background

Radiographic infarction following aneurysmal subarachnoid hemorrhage (SAH) is one of the most powerful predictors of long-term outcome [1–4]. The presence of cerebral infarction on CT scan is associated with more than a fivefold increase in the likelihood of death or dependency [1, 2]. Mounting evidence suggests that cerebral infarction following SAH results from both vasospasm-mediated and vasospasm-independent processes [5–7] yet little is known about the pathway to cerebral infarction that appears to occur in the absence of angiographic vasospasm.

Cardiac dysfunction, likely the result of catecholamine toxicity [8], occurs commonly after SAH and is related to the severity of initial neurologic injury [9, 10] but may also play a role in the complications of SAH. B-type natriuretic peptide (BNP) release from the heart has been shown to be a surrogate for cardiac dysfunction in SAH as BNP levels are increased in a subset of patients with SAH [11, 12]. Elevated BNP levels have been independently associated with cerebral vasospasm, delayed ischemic neurological deficits (DIND), and increased inpatient mortality [13–15]. The relationship between BNP and cerebral infarction, however, has not been investigated. The aim of this study was therefore to examine the association between BNP levels and radiographic cerebral infarction, both in the presence and absence of angiographic vasospasm.

Materials and Methods

Subjects

This is a sub-study from a cohort of patients with confirmed aneurysmal SAH admitted between 1999 and 2003 to a tertiary care referral center. SAH was confirmed by head CT or lumbar puncture in cases with negative head CT but high clinical suspicion of SAH. All patients had cerebral aneurysm identified as the source of hemorrhage primarily by cerebral angiogram. Patients were excluded if they had a history of antecedent head trauma or nonaneurysmal source of hemorrhage. Additional exclusion criteria were previous history of

myocardial infarction or cardiomyopathy, early mortality before vasospasm onset (typically 3–14 days after SAH), and delayed imaging of insufficient quality to detect cerebral infarction. Blood samples were collected in EDTA tubes, centrifuged, and stored at -70°C . Plasma BNP levels were measured using the Bayer Centaur BNP assay (Bayer Diagnostics, Tarrytown, NY). The study protocol was approved by the University of California Institutional Review Board and informed consent was obtained from each patient or an appropriate surrogate.

SAH Management

Ruptured aneurysms were typically treated with either surgical clipping or endovascular coiling within the first 48 h of admission. All patients were managed in the Neurointensive Care unit. Patients were monitored with daily transcranial Doppler (TCD) screening for vasospasm and frequent neurological examination. Standard medical management for vasospasm included volume resuscitation, induced hypertension, and oral nimodipine (30 mg every 2 h). Follow-up head CT and cerebral angiograms were obtained if vasospasm was suspected by elevated TCD velocities and ratios or clinical neurologic deterioration not explained by other causes (rebleeding, hydrocephalus, seizures, or metabolic disturbances). Patients who had evidence of angiographic spasm and were failing standard medical therapy were considered for endovascular treatment with intraarterial verapamil or transluminal angioplasty. Angiographic vasospasm was determined by the neurointerventional radiologist if there was evidence of arterial narrowing compared to the normal vessel caliber (mild <30%, moderate 30–60%, severe 61–99%).

Cerebral Infarction

All patients had an initial admission head CT scan. Follow-up CT scans were obtained by the treating physicians for clinical care and were typically used to evaluate unexplained declines in neurological status. Presence of cerebral infarct was initially determined by a neuroradiologist based on any new hypodensity in a vascular distribution not present on the initial admission scan. All CT scans were also retrospectively reviewed by a stroke neurologist blinded to BNP levels. Any new hypodensities that may have been related to post-operative edema or documented procedural complications were excluded from the infarct group.

Statistical Analysis

Presence of any new cerebral infarction on follow-up head CT was treated as a dichotomous outcome variable. BNP levels were not normally distributed and were divided into four quartiles for analysis purposes: <46, 46–105, 106–275, and 276–3504 pg/ml.

The covariates included in the initial model included five factors which modulate BNP levels (age, gender, serum creatinine, body surface area, and time from SAH symptom onset to BNP measurement) [16], SAH-specific factors (initial Hunt–Hess grade, Fisher group, aneurysm position, and aneurysm treatment), and other variables reflective of co-morbid conditions (history of smoking, hypertension, and stimulant use, intubation during the ICU stay, pulmonary edema on chest X-ray during the hospitalization). Based on prior studies [8], we also included variables associated with vasospasm outcomes, such as the peak phenylephrine dose (to induce hypertension for vasospasm), endovascular vasospasm treatment, and cardiovascular variables (left ventricular ejection fraction, systolic blood pressure, heart rate).

Multivariable logistic regression was performed using reverse, stepwise elimination of variables until all remaining variables had a P value < 0.10. We also tested for interactions between the five covariates known to modulate BNP and there was no significant interaction

between these variables and BNP levels. Finally, we performed a stratified analysis to quantify the associations between BNP and cerebral infarction in patients with angiographic spasm (severe enough to require endovascular therapy) and without angiographic vasospasm (mild or absent requiring medical therapy only). The models reported odds ratios (OR) and 95% confidence intervals (CI). Because BNP levels were not normally distributed and the association between BNP and cerebral infarction was non-linear, an analysis using log BNP level as the predictor variable was also performed.

All statistical analyses were performed using commercially available software (STATA, College Station, TX) and a P value < 0.05 was considered significant.

Results

The study included 119 patients. The average age of the entire cohort was 58 years, and 90 patients were female. BNP was measured at a mean of 5.5 ± 3.0 days after SAH symptom onset. The median BNP level was 105 pg/ml (interquartile range of 37–275 pg/ml). A total of 46 patients (39%) had cerebral infarction on delayed head CT.

The cohort was divided into two groups based on presence of cerebral infarction (Table 1). The infarct group had significantly more patients with higher Hunt–Hess grade, any vasospasm on angiogram, higher phenylephrine dose, and higher mortality.

As shown in Fig. 1, there was a significant difference in the infarction rate between patients in the top quartile (BNP ≥ 276 pg/ml) versus the lower three quartiles. The univariate OR for infarction was 5.0 for BNP ≥ 276 pg/ml compared to BNP levels less than < 276 pg/ml (95% CI 2.0–12.5, $P = 0.001$). The final multivariable model results are shown in Table 2. There was a significant, independent association between a BNP level ≥ 276 pg/ml and cerebral infarction (OR 4.2, 95% CI 1.4–12.4, $P = 0.009$). Similar univariate ($P = 0.001$) and multivariate ($P = 0.02$) associations were observed when the log BNP level was used as the primary predictor, instead of BNP quartiles. In addition, intubation in the ICU (excluding intubation for procedures), peak phenylephrine dose, serum creatinine on admission, and anterior circulation aneurysm location were significant predictors of infarction (Table 2). There was no significant association between BNP levels and markers of cardiac dysfunction such as troponin level, ejection fraction, and presence of cardiogenic pulmonary edema.

Among patients with ($N = 46$) and without ($N = 68$) angiographic vasospasm (as previously described), the infarction rates were 50 and 29%, respectively. As shown in Fig. 2, the stratified analysis revealed that the association between BNP and infarction was strongest in patients with mild to absent vasospasm (OR 7.8, 95% CI 1.8–33.7, $P = 0.006$) and not significant in patients with moderate to severe vasospasm (OR 1.5, 95% CI 0.2–10.3, $P = 0.7$).

Discussion

The present study is the first to our knowledge to consider BNP in relation to radiographic cerebral infarction after SAH. The results of this study provide further confirmation that elevated BNP levels after SAH are independently associated with brain injury. Prior smaller investigations ($n \leq 40$) have reported associations between elevated BNP levels and cerebral vasospasm, delayed ischemic neurologic deficit, and early in-hospital mortality [13, 14, 17]. This study includes both a larger sample size ($n = 119$) and adjustment for clinical covariates. In multivariable analysis, we found that patients with a serum BNP level in the top quartile had a fourfold increased odds of developing a radiographic cerebral infarction compared to those with BNP in the bottom three quartiles.

To determine if BNP levels were associated with vasospasm-mediated cerebral infarction, we stratified our study population into two groups—one with severe angiographic vasospasm (requiring endovascular therapy) and a second with mild or absent vasospasm (requiring medical therapy only). We found that elevated BNP was significantly associated with infarction only in those patients with mild or absent angiographic vasospasm, with an odds ratio for infarction of 7.8 (CI 1.8–33.7, $P = 0.006$), suggesting that BNP may be related to other mechanisms other than large vessel spasm.

Several lines of evidence suggest that cerebral infarction after SAH is not due exclusively to large vessel spasm. The clazosentan Phase II trial, despite a marked reduction in the burden of angiographic vasospasm, did not significantly decrease infarct on CT or improve neurological outcomes following SAH [18]. A number of inter-related hypotheses for the cause of cerebral infarction after SAH distinct from angiographically detectable vasospasm have been proposed, including systemic inflammation, microcirculatory spasm, and release of microemboli [5, 19].

BNP may be a marker for a more generalized process of microcirculatory dysfunction involving multiple vascular beds. BNP is elevated in a number of non-cardiac diseases—such as sepsis, acute respiratory distress syndrome (ARDS), and cirrhosis—that are characterized by systemic inflammation, generalized microcirculatory dysfunction, and localized thrombosis [20]. In addition, recent evidence links BNP release to pro-inflammatory cytokines [21]. In multivariable analysis, we also detected an association between higher creatinine levels and the risk of cerebral infarction that may result from a similar mechanism within the vasculature of the kidney. Small decreases in creatinine clearance have been associated with poor outcomes in SAH [22], although to our knowledge, changes in creatinine or creatinine clearance have not been correlated with radiographic infarction specifically in prior studies. Similarly, intubation in the ICU and peak phenylephrine dose also proved to be significant predictors of radiographic infarction. Although these factors likely represent markers for severity of SAH injury, they may also reflect severity of a systemic inflammatory response.

BNP is also biologically active and could increase the risk of cerebral infarction through its direct effects on the kidney and systemic vasculature, resulting in natriuresis, hypovolemia, and vasodilatation [20, 21]. More recent evidence suggests that elevated BNP levels are seen in acute ischemic stroke, may correlate with stroke severity independent of cardiac disease, and may represent underlying cardiac disease as the etiology [23–25]. In SAH, these direct effects, could lead to relative hypotension and decreased cerebral perfusion pressure, particularly during periods of cerebral vasospasm. In addition, BNP has been associated with left ventricular dysfunction after SAH [11], which could further decrease cerebral blood flow. In general, the standard medical management of vasospasm with salt repletion, vasopressors, and volume resuscitation would tend to counteract the direct effects of BNP.

This study has several limitations. First, BNP was not measured serially, although peak BNP levels in SAH patients with vasospasm have been determined to occur 4–9 days after SAH [13], a time frame consistent with the collection of BNP samples for our study. Second, both cerebral angiography and follow-up CT scans were performed based on clinical need determined by treating physicians. Additional diagnostic testing was generally in response to changes in clinical neurological exam or concern for medically refractory vasospasm. Delayed imaging likely occurred in more symptomatic patients, and may have excluded mild or asymptomatic patients. Similarly, patients selected for angiography may have biased the results to having more endovascular treatments for vasospasm and decreasing the infarction rate in this subgroup. However, BNP levels measured prior to endovascular treatment would likely not be affected.

The results of our investigation, if confirmed by other studies, suggest that BNP measured in the first few days after SAH may be useful in the risk stratification of patients for subsequent cerebral infarction. Several risk factors have been identified as predictors of radiographic infarction following SAH. Analysis of pooled data from studies evaluating the use of trilizad identified the following risk factors as significant predictors of radiographic infarction: increasing age, World Federation of Neurological Surgeons (WFNS) grade, a history of hypertension or diabetes, increasing aneurysm size, induced hypertension, symptomatic vasospasm, and elevated temperature 8 days after SAH [1]. A recent substudy of the CONSCIOUS 1 trial (a randomized trial of clazosentan for the prevention of vasospasm) identified only angiographic vasospasm, WFNS grade, and larger aneurysm size as significant predictors of infarction in multivariate analysis [26]. In these two studies, the overall risk of infarction on follow-up CT scan was 26% in the first study and 11% in the second. Many, though not all, of these putative risk factors were controlled for in our study, yet BNP provided substantial additional discriminative power in identifying patients at risk for stroke (especially those without angiographic vasospasm) following SAH. Because of the limitations of our study—including the lack of routine CT scans and the absence of a standardized approach to sampling BNP—the findings of our study must be interpreted as hypothesis-generating.

Summary

In conclusion, we found that elevated BNP levels are independently associated with cerebral infarction after SAH, particularly in the subgroup of patients without severe angiographic vasospasm. These results suggest that cerebral infarction occurs in the absence of the large vessel vasospasm typically seen on angiogram and treated with endovascular therapy. Prospective studies with serial BNP measurements and standardized imaging studies will be required to determine whether the association between BNP and cerebral infarction is causal or whether BNP is a marker for another process, such as microcirculatory dysfunction and systemic inflammation after SAH.

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Fig. 1.

The rates of cerebral infarction for each quartile of BNP level are shown. The numbers within the columns indicate the absolute number of cerebral infarctions within each quartile.

* $P = 0.001$, see Table 2

Fig. 2.

Association of radiographic infarction with elevated BNP stratified by angiographic vasospasm. Odds ratio (OR) of radiographic infarction for top quartile BNP relative to bottom three quartiles in the entire study population and for the study population stratified by vasospasm severity

Table 1

Clinical characteristics and outcomes

	Infarct	No infarct	P value
Patients, <i>N</i>	46	73	
Age, mean $\pm$ SD	59 $\pm$ 12	56 $\pm$ 11	0.14
Female, <i>n</i> (%)	35 (76%)	55 (75%)	0.927 [†]
Admission serum creatinine, mean $\pm$ SD	0.8 $\pm$ 0.47	0.68 $\pm$ 0.16	0.5
Body surface area	1.8 $\pm$ 0.2	1.8 $\pm$ 0.2	0.6 [*]
Admission Hunt–Hess grade, <i>N</i> (%)			0.007[†]
I	15 (33%)	28 (39%)	
II	1 (2%)	14 (19%)	
III	17 (37%)	25 (34%)	
IV	12 (26%)	5 (7%)	
V	1 (2%)	1 (1%)	
Fisher score			0.553
I	1 (2.3%)	0 (0%)	
II	22 (51%)	41 (59%)	
III	17 (40%)	24 (34%)	
IV	3 (7%)	5 (7%)	
Posterior aneurysm location, <i>N</i> (%)	30 (42%)	41 (58%)	0.33 [†]
Anterior aneurysm location, <i>N</i> (%)	16 (33%)	32 (67%)	
Aneurysm treatment			0.20 [†]
Neurosurgical clipping, <i>N</i> (%)	30 (65%)	37 (51%)	
Percutaneous coiling, <i>N</i> (%)	16 (35%)	31 (42%)	
Clipping and coiling, <i>N</i> (%)	0 (0%)	3 (4%)	
No treatment, <i>N</i> (%)	0 (0%)	2 (3%)	
Vasospasm requiring treatment <i>N</i> (%)	23 (50%)	23 (32%)	0.026[†]
Peak dose of phenylephrine, mean $\pm$ SD	166 $\pm$ 180	60 $\pm$ 165	0.0014[‡]
Inpatient mortality	8 (17%)	1 (1%)	0.001[†]

* *T* test;[†] Pearson chi-square;[‡] Wilcoxon rank sum testBold values are statistically significant ($P > 0.05$)

Table 2

Final multivariable association model between BNP level and cerebral infarction

Variable	Odds ratio	95% CI	P value
Top quartile BNP level (vs. lower three)	4.2	1.4–12.4	0.009
Creatinine (per 1 mg/dl ↑)	6.7	1.0–45.0	0.049
Time from SAH to BNP measurement (per 1 day ↑)	1.2	1.0–1.4	0.018
Intubation during the ICU stay	4.1	1.6–10.4	0.003
Neosynephrine maximum dose	1.2	1.1–1.5	0.01