THE RELATIONSHIP BETWEEN BNP, NEUROCARDIAC INJURY SEVERITY, NONINVASIVE CARDIAC OUTPUT, AND OUTCOMES AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

by

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BACKGROUND: Neurocardiac injury is a type of myocardial dysfunction associated with neurological insult to the brain and occurs in 31-48% of aneurysmal subarachnoid hemorrhage (aSAH) patients. Elevated cardiac troponin I (cTnI) is commonly used to diagnose neurocardiac injury and has been associated with poor outcomes after aSAH. Brain natriuretic peptide (BNP) is another marker of cardiac dysfunction, but is more often used to evaluate varying degrees of heart failure. The purpose of this study was to examine the relationship between BNP and a) neurocardiac injury severity as defined by cTnI level, b) noninvasive continuous cardiac output (NCCO) monitoring parameters, and c) outcomes in aSAH patients.

METHODS: This descriptive longitudinal study enrolled 30 adult patients age < 75 years diagnosed with aSAH. Data collected for 14 days included BNP and cTnI levels, NCCO monitoring parameters, and outcomes (modified Rankin scale [mRS] and mortality) at hospital discharge and three months. Generalized estimating equations (GEE) were used to evaluate the longitudinal associations between BNP and cTnI, BNP and NCCO monitoring parameters within 30 minutes of BNP determination, and BNP and outcomes. BNP and NCCO variables required log transformation due to non-normal distribution.

RESULTS: Elevated BNP was significantly associated with cTnI. For every 1 unit increase in *log* BNP, cTnI increased by 0.05 ng/ml ($p = .001$). BNP was also significantly associated with thoracic fluid content ($p = .0003$) but no other NCCO parameters. On multivariable analyses, significant associations were found between BNP and poor mRS. For every 1 unit *log* BNP, patients were 3.16 times more likely to have a poor mRS at discharge ($p = .021$) and 5.40 times more likely to have poor mRS at 3 months ($p < .0001$).

CONCLUSIONS: There is a significant relationship between BNP, cTnI, and poor outcomes after aSAH. BNP may have utility as a marker of neurocardiac injury and outcomes after aSAH.

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1.0 INTRODUCTION AND BACKGROUND

Neurocardiac injury is a type of myocardial dysfunction associated with neurological insult to the brain. After aneurysmal subarachnoid hemorrhage (aSAH), neurocardiac injury occurs in 31–48% of patients [1–3]. It is widely accepted that neurocardiac injury is caused by an acute release of catecholamines that results from elevated intracranial pressure post-hemorrhage [4–6]. Manifestations of neurocardiac injury often include cardiac arrhythmias, widened QT intervals, depressed cardiac output and ejection fraction on echocardiogram, and elevated serum cardiac troponin I (cTnI) [2]. Neurocardiac injury is typically diagnosed with elevated cTnI ($\geq$ 0.3 ng/mL) and myocardial wall motion abnormalities on echocardiogram within the first five days following aneurysm rupture [2, 3]. Elevated cTnI levels are seen in 20-68% of aSAH patients who have no prior history of cardiac disease or myocardial infarction [7–9]. In addition, elevated cTnI has been associated with poorer Hunt and Hess (HH) grade, Fisher grade, and neurological status on hospital admission [7–9]. Furthermore, elevated cTnI has been associated with increased risk for developing cardiopulmonary complications and delayed cerebral ischemia [7, 10]. Therefore, it can be suggested that the degree of neurological insult is implicated in neurocardiac injury development.

Demographic and prior comorbidity risk factors for neurocardiac injury include advanced age, coronary artery disease, hypertension, and other cardiovascular disorders [11]. Although neurocardiac injury after aSAH is often transient [4], evidence suggests that it is associated with

increased mortality [12]. In addition, neurocardiac injury is independently associated with poorer functional outcomes in aSAH patients [2, 13]. The reason for this association may be related to the impact of hypotension, arrhythmias, and depressed ejection fraction and stroke volume on cerebral blood flow [2, 14].

Brain natriuretic peptide (BNP) is a 32-amino acid peptide that is released in response to cardiac myocyte stretch due to elevated filling pressures [15], in order to regulate blood pressure and fluid balance [16]. BNP is produced by cardiac ventricular cardiomyocytes, as well as in the hypothalamus [17–19]. BNP is often used diagnostically during the evaluation of patients presenting with symptoms of acute dyspnea to determine whether their etiology is of a cardiac or pulmonary origin [20]. Meaudre et al reported that 25 patients (80%) diagnosed with aSAH had a BNP level greater than 100 ng/L during the first three days after aneurysm rupture, whereas by the seventh day, only 4 patients (13%) remained elevated above 100 ng/L [15]. A significant association has also been reported between BNP, cTnI, cardiac dysfunction measured by transthoracic echocardiogram (regional wall motion abnormalities, reduced left ventricular function, and diastolic dysfunction) and the development of pulmonary edema after aSAH [20]. Tung et al also found increased BNP levels to be significantly associated with increased inpatient mortality in aSAH patients who had no prior history of myocardial infarction or congestive heart failure [21].

Based on the current literature, the degree to which BNP level correlates with the severity of neurocardiac injury, cardiac output, and functional outcomes after aSAH is not well established. It also remains unclear if BNP level can be used as an independent predictor of neurocardiac injury in this population. Although BNP is known to be associated with cardiac dysfunction according to echocardiogram, it would also be helpful to determine if there is a

relationship between BNP and noninvasive continuous cardiac output (NCCO) parameters. Determining the relationship between BNP, NCCO, and functional outcomes could potentially help to determine whether BNP could be used as a biomarker for neurocardiac injury and poor outcomes after aSAH.

2.0 PURPOSE AND AIMS

The overarching purpose of this study is to examine the relationship between BNP and a) neurocardiac injury severity, b) noninvasive continuous cardiac output, and c) outcomes in aSAH patients. The specific aims of this study are to:

Specific aim #1: Determine the relationship between BNP level and the degree of neurocardiac injury as defined by cTnI level.

Specific aim #2: Examine the relationship between BNP level and noninvasive continuous cardiac output monitoring parameters.

Specific aim #3: Assess the relationship between BNP level and outcomes (mortality, modified Rankin Scale [mRS]) at hospital discharge and 3 months after aSAH.

3.0 METHODS

3.1 SAMPLE AND SETTING

This is a descriptive longitudinal study of data collected prospectively on aSAH patients enrolled in an NIH funded study (R01NR014221). Patients between the ages of 21 and 75 years, admitted to the neurological intensive care unit (NICU) after being diagnosed with aSAH by computed tomography (CT) and/or cerebral angiogram and assigned a Fisher grade > 1 by the attending neurosurgeon were eligible. Patients were excluded if they had preexisting chronic neurological disease, traumatic subarachnoid hemorrhage, mycotic aneurysms, or myocardial infarction within the past year. Informed consent was obtained from all eligible patients based on an IRB approved protocol (021039). All aSAH inpatients received standard nursing and medical care in the NICU.

3.2 STUDY VARIABLES

3.2.1 Demographic and Clinical Characteristics

Basic demographic information including severity of injury, aneurysm information, age, race, gender, and past medical history were obtained from the patient, family, or medical record.

Severity of injury (HH grade and Fisher grade) was obtained from the neurosurgical notes in the patient's clinical record. The Hunt and Hess scale is used to grade the severity of non-traumatic SAH based on symptoms at presentation to the emergency department [22]. A higher score corresponds to a higher severity, and the scale has five grades; 1 = asymptomatic, or minimal headache and slight nuchal rigidity; 2 = moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy; 3 = drowsiness, confusion, or mild focal deficit; 4 = stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances; and 5 = deep coma, decerebrate rigidity, moribund appearance [22]. The Fisher grade is used to classify the initial appearance of SAH based on CT scan findings [23]. The scale has four grades; 1 = no blood or hemorrhage evident; 2 = diffuse or thin layer of blood less than 1 mm thick (interhemispheric, insular, or ambient cisterns); 3 = localized clots and/or layers of blood greater than 1 mm thick in the vertical plane; 4 = intracerebral or intraventricular clots with diffuse or absent blood in basal cisterns [23].

3.2.2 BNP

Blood samples were collected daily. BNP was measured by chemiluminescence on a Beckman Coulter Access analyzer (Beckman Instruments Inc., Chaska, MN) using the Lumi-Phos 530 ready-to-use chemiluminescent reagent formulation containing alkaline phosphatase substrate, Lumigen PPD, at the hospital laboratory. The lower limit of analytical range for BNP was 1 pg/ml; and the upper limit was 5000 pg/ml.

3.2.3 Neurocardiac Injury

Neurocardiac injury was defined by cTnI level. cTnI was extracted from serum at least daily and quantified by a Beckman Coulter Access AccuTnI assay (Beckman Instruments Inc., Chaska, MN), a two-site immunoenzymatic assay that uses the chemiluminescent substrate Lumi-Phos 530, at the hospital laboratory. The lower analytical limit for cTnI was 0.001 ng/ml, and the upper limit was 75 ng/ml. cTnI was used as a continuous variable.

3.2.4 Cardiac Output Monitoring

An FDA-approved NCCO device was used (NICOM®, Cheetah Medical, Wilmington, DE) to continuously record cardiac output measurements. The device's function is based on transthoracic Bioreactance® monitoring that analyzes relative phase shifts of an oscillating current traversing the thorax surface. Continuously obtained data were downloaded on each patient at a minimum frequency of one data point every 30 seconds. In the analyses, NCCO data were averaged on 5-minute intervals. Variables collected through NCCO included cardiac output (CO), cardiac index (CI), stroke volume index (SVI), stroke volume variation (SVV), thoracic fluid content (TFC), ventricular ejection time (VET), cardiac contractility (dx/dt), and heart rate (HR).

3.2.5 Outcomes

Patient outcomes were assessed at discharge and at three months post-aSAH using the modified Rankin Scale (mRS). The mRS is a self-appraisal of functional disability containing mental and

physical adaptations [24]. It is widely used in stroke populations and contains seven levels; 0 = no symptoms at all; 1 = no significant disability despite symptoms; 2 = slight disability (unable to perform all activities); 3 = moderate disability (able to walk without assistance); 4 = moderately severe disability (unable to walk without assistance); 5 = severe disability (bedridden, incontinent, in nursing home) and 6 = death [24]. mRS at discharge was based on medical record information, while 3-month mRS was based on patient interviews. If subjects were unable to complete the interview, a family member or caregiver answered the questions. mRS was dichotomized as good (mRS 0-2) and poor (mRS 3-6). Inpatient records or family members provided information regarding patient mortality.

3.3 ANALYTIC APPROACH

To describe the sample, we used frequency distributions for categorical variables and mean and standard deviations for normally distributed continuous variables, or median and interquartile ranges for non-normally distributed continuous variables. IBM SPSS 22 and SAS 9.3 were used with a p-value of 0.05 or less indicating significance. Due to non-normal distribution of the data, logarithmic transformation was used for BNP in each analysis and for certain NCCO variables. The analysis plan for each specific aim is listed below.

Specific aim #1: Determine the relationship between BNP level and degree of neurocardiac injury as defined by cTnI level.

The levels of BNP and cTnI collected over the study period were included, and the daily peak values of each were used in the analysis as time-varying variables. Generalized estimating equation (GEE) was used to evaluate the longitudinal association between BNP and cTnI where

BNP was used as the independent variable and cTnI as the dependent variable without covariate adjustment. Logarithmic transformation of BNP was used.

Specific aim #2: Examine the relationship between BNP level and continuous non-invasive cardiac output monitoring parameters.

The relationship between BNP and NCCO was analyzed using GEE. BNP was used as the independent variable. NCCO values were averaged over 5 minutes. For each BNP level (all data points used) the NCCO data for the 30 minutes before and after BNP determination (1 hour total) were used. Logarithmic transformation was used for BNP as well as for cardiac output, cardiac index, stroke volume, stroke volume index, thoracic fluid content, dx/dt, and ventricular ejection time. Therefore, the only two NCCO variables that were not *log* transformed were heart rate and stroke volume variation.

Specific aim #3: Assess the relationship between BNP level and outcomes (mortality and mRS) at hospital discharge and at 3 months post-aSAH.

In order to assess the relationship between BNP and outcomes, GEE was conducted. All BNP levels collected over the study period were included in the model as the independent variable, and mRS was treated as a categorical variable dichotomized as good and poor, as described. Mortality was included in the analysis as a dichotomous variable. Logarithmic transformation of BNP was used.

4.0 RESULTS

A total of 30 patients were recruited in this study. As shown in Table 1, patients were predominantly female, middle aged, and Caucasian. The majority of patients had an admission HH grade of 2 (43%) or 3 (33%). Fourteen (53.3%) had poor mRS at discharge and similarly fourteen (48.3%) had poor mRS at 3 months post-hemorrhage. Four patients died by hospital discharge and one additional patient died by the follow-up at 3 months. One patient was lost to the 3-month follow-up. The daily mean cTnI was 0.20 ng/ml, with a minimum value of 0.04 ng/ml and maximum value of 10.36 ng/ml. The daily mean BNP level was 322.99 pg/ml, and the minimum and maximum values ranged from 5.00 pg/ml to 2676.00 pg/ml respectively. The mean time of NCCO monitoring was 8.89 days, ranging from 1.05 to 13.70 days.

Finding related to specific aim #1: *Determine the relationship between BNP levels and the degree of neurocardiac injury as defined by cTnI level*.

GEE modeling on daily peak cTnI and daily peak BNP showed statistically significant association between cTnI and BNP. For every 1 unit increase in *log* BNP, cTnI increased by 0.05 ng/ml ($p = .001$).

Findings related to specific aim #2: *Examine the relationship between BNP and continuous non-invasive cardiac output monitoring parameters.*

Table 2 shows the relationship between BNP and NCCO parameters without covariate adjustment. The results show that BNP increases by 0.09 pg/ml for every 1 unit increase in *log*

TFC (p = .0003). There was no statistically significant relationship between BNP and any other NCCO-derived variable.

Finding related to specific aim #3: Assess the relationship between BNP and outcomes (mortality and mRS) at hospital discharge and at 3 months post-aSAH.

On univariable analyses, there were significant association between *log* BNP and poor mRS at 3 months, mortality at 3 months, and mortality at discharge. There was a trend toward significance for the association between *log* BNP and poor mRS at discharge. For every 1 unit increase in *log* BNP, patient were 1.26 and 4.90 times more likely to have poor mRS at discharge (p = .069) and at 3 months (p < .0001) respectively. Furthermore, for every 1 unit increase in *log* BNP, patients were 1.42 and 1.43 times more likely to die at discharge (p = .032) and at 3 months (p = .031) respectively. Similar results were found on multivariable analyses (Table 3). BNP remained a significant predictor for poor outcome even after controlling for age and HH grade. For every 1 unit increase in *log* BNP, patients were 3.16 times more likely to have a poor outcome at discharge (p = .021) and 5.40 times more likely to have poor mRS at 3 months (p < .0001). For every 1 unit increase in age, patients were 3.18 times more likely to have a poor outcome at discharge (p < .0001), and 0.96 times more likely to have a poor outcome at 3 months post-hemorrhage (p = .573). For every 1 unit increase in HH grade, patients were 86.29 times more likely to have a poor outcome at discharge (p = .019) and 6.53 times more likely to have a poor outcome at 3 months post-hemorrhage (p = .052).

5.0 DISCUSSION

Our main finding corroborates that BNP increases as cTnI increases and, therefore, supports the use of BNP as a marker of neurocardiac injury. This relationship may be mediated by the known catecholamine surge that occurs after aneurysm rupture and that often results in myocardial dysfunction and subsequent neurocardiac injury [2]. In response to the injury, inflammation, and cardiac myocyte stretch, BNP is secreted and its levels gradually increase [15].

We also sought to assess the relationship between BNP and cardiac function based on a novel approach using NCCO. We were able to demonstrate that BNP increases as thoracic fluid content, a marker of pulmonary edema, increases. This finding is not surprising given the known relationship between BNP and increased myocardial stretch and wall tension [25]. Thoracic fluid content, as measured by NCCO, is a qualitative measure of directional changes in total thoracic fluid content [26, 27]. Therefore, as thoracic fluid volume increases, theoretically both myocardial stretch and wall tension will increase. Subsequently, BNP will be secreted, and BNP levels will continue to rise.

Tung et al [8] found that elevated BNP levels are associated with myocardial necrosis, pulmonary edema, and left ventricular systolic and diastolic dysfunction early after SAH. However, we were unable to demonstrate that elevated BNP was significantly associated with depressed myocardial function by any variable measured with NCCO, with the exception of elevated thoracic fluid content. Possibly our sample size was too small to detect such a change,

and this is a study limitation. It is also possible that the use of vasopressors for blood pressure support in this population may have affected the NCCO parameters, which is also a significant limitation of the study.

Yarlagadda et al [28] found BNP levels greater than 600 pg/ml to be a significant indicator of mortality after aSAH, while Duello et al [29] did not find any significant relationship between BNP elevation and increased mortality. We also were not able to demonstrate a relationship between BNP and mortality. We did find, however, that elevated BNP was associated with poorer mRS at discharge and 3 months later, and that this association was independent of age and HH grade. No other study to our knowledge has investigated the relationship between BNP and poor mRS in the aSAH population. Taub et al [30] found that elevated BNP levels are independently associated with cerebral infarction following aSAH. Sviri et al [31] reported that elevated BNP levels are related to severity of bleeding and vasospasm following aSAH. However, the mechanistic underpinning explaining these poorer outcomes for aSAH patients with elevated BNP is still unclear. McGirt et al [32] found that elevated BNP was independently associated with hyponatremia and predicted the 2-week Glasgow Coma Scale score. Thus, the pathophysiological mechanism linking elevated BNP and poorer functional outcomes remains unclear. Whether poor outcomes are an indirect result of elevated BNP levels or a direct result of alternative mechanisms still requires further investigation. Future studies must involve larger sample sizes and analysis of other potential variables. Once this further investigation is conducted, BNP may prove to be a valuable independent marker of neurocardiac injury.

6.0 CONCLUSION

The clinical implications of this study relate to the significant relationship between BNP and cTnI, and that elevated BNP is associated with poor mRS in aSAH patients, even after age and injury severity are taken into account. If BNP levels are routinely monitored in aSAH patients, healthcare providers will be more aware of any increased likelihood of adverse outcomes that these patients may have. Therefore, the healthcare providers may be able to more promptly incorporate strategies into the patient's plan of care that may help to prepare for or prevent such potential adverse outcomes. Overall, the establishment of BNP as a potential predictor of poor outcomes may promote a more effective, therapeutic approach to treating patients who have experienced aSAH.

Table 1 - Characteristics of patients in the sample (*n*=30)

Characteristics	Statistics
Age in years (mean±SD)	54.5 ± 11.1
Admission GCS (mean±SD)	12.3 ± 4.1
Gender [n (%)]	
Male	2 (6.7%)
Female	28 (93.3%)
Race [n (%)]	
White	28 (93.3%)
Black	2 (6.7%)
Admission Hunt and Hess [n (%)]	
Grade 1	1 (3.3%)
Grade 2	13 (43.3%)
Grade 3	10 (33.3%)
Grade 4	4 (13.3%)
Grade 5	2 (6.7%)
mRS at discharge [n (%)]	
Poor (mRS 3-6)	16 (53.3%)
Good (mRS 0-2)	14 (46.7%)
mRS at 3 months [n (%)]	
Poor (mRS 3-6)	14 (48.3%)
Good (mRS 0-2)	15 (51.7%)
Mortality at discharge [n (%)]	
Dead	4 (13.3%)
Alive	26 (86.7%)
Mortality at 3 months [n (%)]	
Dead	5 (17.24%)
Alive	24 (82.76%)

Key: GCS = Glasgow Coma Scale, mRS = modified Rankin Scale, SD = standard deviation

Table 2 - Relationship between patients (*n*=30) brain natriuretic peptide (BNP) levels and noninvasive continuous cardiac output monitoring (NCCO) parameters for 30 minutes before and after each BNP measurement.

NCCO	Estimate	Standard Error	p-value
log Cardiac Output	0.02	0.04	0.578
log Cardiac Index	0.03	0.04	0.572
Heart Rate	-0.16	0.16	0.317
log Stroke Volume	0.05	0.03	0.106
log Stroke Volume Index	0.05	0.03	0.098
Stroke Volume Variation	-0.24	0.37	0.515
log Thoracic Fluid Content	0.09	0.02	0.0003*
log dx/dt	0.05	0.04	0.192
log Ventricular Ejection Time	0.00	0.03	0.871

Key: dx/dt = maximum aortic flow (indirect measure of contractility)

Table 3 - Multivariable analysis of the relationship between brain natriuretic peptide (BNP) and outcomes at hospital discharge and 3 months.

Variable	mRS at discharge *n*=30			mRS at 3 months *n*=29			Mortality at discharge *n*=30			Mortality at 3 months *n*=29		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Log BNP	3.16	(1.19, 8.39)	.021*	5.40	(3.24, 8.99)	<.0001*	1.30	(0.92, 1.84)	.130	1.28	(0.90, 1.82)	.175
Age	3.18	(1.84, 5.51)	<.0001*	.96	(0.84, 1.10)	.573	--		--	--		--
HH grade	86.29	(2.11, 3526.99)	.019*	6.53	(0.98, 43.27)	.052	1.69	(0.35, 8.24)	.518	2.05	(0.45, 9.28)	.352

Key: mRS = modified Rankin Scale, HH = Hunt and Hess, OR = odds ratio, CI = confidence interval

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