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**Original Article**

# Cardiovascular Predictors of In-Patient Mortality After Subarachnoid Hemorrhage

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## Abstract

***Background and Purpose:*** Whether cardiac dysfunction contributes to morbidity and mortality after subarachnoid hemorrhage (SAH) remains controversial. The objective of this study was to test the hypothesis that cardiovascular abnormalities are independently related to in-patient mortality after SAH.

***Methods:*** This was a prospective cohort study of patients with aneurysmal SAH. Heart rate and blood pressure were measured, a blood sample was obtained, and echocardiography was performed on three study days, starting as soon after admission as possible. The cardiovascular predictor variables were heart rate, systolic blood pressure (SBP), cardiac troponin I (cTi) level, B-type natriuretic peptide (BNP) level, and left ventricular ejection fraction. The primary outcome measure was in-patient mortality. The association between each predictor variable and mortality was quantified by multivariate logistic regression, including relevant covariates and reporting odds ratios (OR) and 95% confidence intervals (CI).

***Results:*** The study included 300 patients. An initial BNP level greater than 600 pg/mL was markedly associated with death (OR 37.7, $p < 0.001$). On the third study day (9.1 ± 4.1 days after SAH symptom onset), a cTi level greater than 0.3 mg/L (OR 7.6, $p = 0.002$), a heart rate of 100 bpm or greater (OR 4.9, $p = 0.009$), and a SBP less than 130 mmHg (OR 6.7, $p = 0.007$) were significantly associated with death.

***Conclusions:*** Cardiovascular abnormalities are independent predictors of in-patient mortality after SAH. Though these effects may be explained by a reduction in cerebral perfusion pressure or other mechanisms, further research is required to determine whether or not they are causal in nature.

**Key Words:** Subarachnoid hemorrhage; natriuretic peptides; troponin; echocardiography

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Cardiac injury and dysfunction are common after aneurysmal subarachnoid hemorrhage (SAH) and are most likely caused by excessive catecholamine release within the myocardium *(1–3)*. Whether the occurrence of cardiac dysfunction negatively impacts neurological outcomes, however, remains controversial.The primary aim of this study was to quantify the effects of specific cardiovascular predictor variables on in-patient mortality with statistical adjustment for relevant covariates. The cardiovascular variables included levels cardiac troponin I (cTi) and B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), heart rate, and systolic blood pressure (SBP). The secondary aims of this study were to explore the associations between cardiac injury, LVEF,

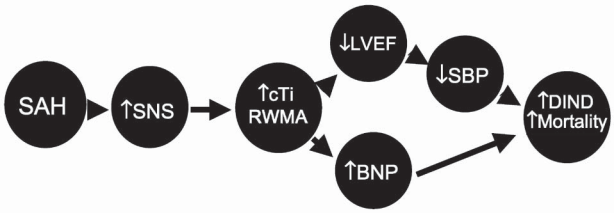


**Fig. 1.** Paradigm for the association between cardiac dysfunction and death after SAH. The figure proposes a mechanistic pathway to explain the effects of cardiovascular abnormalities on the risk of delayed ischemic neurological deficits (DIND) and mortality. SNS, sympathetic nervous system.

BNP, and SBP after SAH, as well as their relationship to cerebral vasospasm, exploring the paradigm shown in Figure 1.

## Materials and Methods

### Study Subjects

This is a secondary analysis from a prospective cohort study of patients with aneurysmal SAH. From February 1999 to November 2003, the study enrolled 300 patients admitted to the Neurological Intensive Care Unit. The inclusion criteria for the study were age over 21 years and SAH diagnosed by computed tomography (CT) or lumbar puncture. The exclusion criteria included a previous history of myocardial infarction, a known history of cardiomyopathy or LVEF less than 50%, and SAH caused by trauma or mycotic aneurysm.

In the majority of our SAH cases, cerebral aneurysms are identified by angiography and are treated by either percutaneous coiling or neurosurgical clipping. Patients who develop cerebral vasospasm typically receive induced hypertension using intravenous phenylephrine and in many cases are referred for neurointerventional treatment, defined as intraarterial infusion of calcium channel blockers and/or cerebral angioplasty.

The study protocol was approved by the University of California San Francisco (UCSF) Independent Review Board (IRB) and informed consent was obtained from each patient or an appropriate surrogate. The study procedures were in accordance with institutional guidelines.

### Clinical Data Collection

Patients were enrolled into the study as soon as possible after hospital admission. Demographic and clinical data were collected from patient and family interviews and inspection of the medical record. The study procedures included data collection, blood sampling, and portable echocardiography (ECG). These procedures were performed on the day of enrollment and repeated 2 and 5 days later.

### Biomarker Measurements

On each study day, serum specimens were collected for measurement of cTi (fluorescent enzyme immunoassay, Abbott Diagnostics, IL). The lowest detectable level was 0.3 ng/mL. After the first 100 patients were enrolled into the study, IRB approval for long-term storage of blood samples was obtained. For every patient who provided consent for storage of banked samples, blood was collected as soon as possible after enrollment and EDTA plasma was stored at –70ºC until completion of the study. Samples were then thawed and BNP levels were measured using the Centaur B-Type Natriuretic Peptide assay (Bayer Healthcare Corporation, Y). Detectable ranges were from 2–5000 pg/mL.

ECG Measurements

On each study day, transthoracic ECG was performed using an Acuson Sequoia® 6.0 ultrasound system (Mountain View, CA). The heart rate, SBP, and dose of phenylephrine infused during ECG were recorded.

A blinded observer measured LVEF and performed the analysis for regional wall motion abnormalities (RWMA) offline using standard methods *(4,5)* and commercially available software (ProSolv®, Indianapolis, IN).

### Clinical Outcomes Assessment

The clinical outcomes were in-patient mortality and cerebral vasospasm requiring neurointerventional treatment. By reviewing medical records, deaths caused by poor neurological status and withdrawal of care were further categorized by cause. The first category was death caused by SAH only, without evidence of delayed cerebral ischemia. The second category was deaths with evidence of delayed cerebral ischemia, defined as worsening neurological status after the initial bleed/rebleeding plus imaging evidence of vasospasm by transcranial Doppler or angiography, neurointerventional treatment for vasospasm, or head CT evidence of cerebral infarction.

### Statistical Analysis

For the primary analyses of in-patient mortality, a cTi level was considered abnormal if greater than 0.3 ng/mL, which indicates myocardial necrosis. Because the relationships between LVEF, heart rate, SBP, and BNP on mortality were nonlinear, specific cut-points were derived from univariate analyses. Multivariate logistic regression was performed to quantify the relationships between the predictor variables and mortality on the first and third study days, reporting odds ratios (OR) and 95% confidence intervals (CI). The covariates in these models were age, gender, Hunt & Hess score, fever (>38.5ºC), mechanical ventilation, phenylephrine dose, and time from SAH symptom onset. In order to verify that the results for the entire cohort were generalizable to patients presenting early after SAH symptom onset, the analyses were also repeated after restricting the group to those patients enrolled into the study within 2 days of symptom onset. Subjects without complete covariate data were excluded from the analysis.

In order to quantify the relationships between myocardial necrosis and RWMA with LVEF, univariate logistic regression was performed using a cTi level greater than 0.3 ng/mL and the presence of RWMA as predictors of a LVEF less than 50%. Data from all three study days were pooled and longitudinal data analysis was used to account for repeated measurements.

In order to quantify the relationship between LVEF and SBP, logistic regression was performed using data from all

three study days and longitudinal data analysis. The concomitant phenylephrine dose was included in the model as a covariate. A Wilcoxon rank sum test was performed to compare the phenylephrine dose on study day 3 among patients with a normal versus low (<50%) LVEF.

In order to quantify the relationship between BNP levels and cerebral vasospasm, a multivariate logistic regression analysis was performed using a BNP level greater than 600 pg/mL as the predictor variable and the need for neurointerventional treatment as the outcome variable. The covariates described previously were included in this model. All statistical analyses were performed using commercially available software (STATA®, College Station, TX) and a $p$ value less than 0.05 was considered statistically significant.

## Results

### Study Subjects and Timing of Study Procedures

The study included 300 patients, and their clinical characteristics are shown in Table 1. An aneurysm was identified in 257 (86%) subjects. The first and third study days occurred an average of 4.1 ± 3.9 and 9.1 ± 4.1 days after the onset of SAH symptoms, respectively. Prior to study day 3, 57 patients died or were discharged.

Prior to discharge from the hospital, 38 patients (13%) died. Of these deaths, 28 occurred after care was withdrawn because of poor neurological status. Of these cases, 15 were attributed solely to SAH and 13 had evidence of delayed cerebral ischemia. The remaining 10 deaths were caused primarily by nonneurological complications, including one patient with cardiogenic shock. Though the median Hunt & Hess grade was 4 in both the SAH-only and delayed ischemia groups, there were more patients with grade 5 in the bleeding group (7 versus 1) and more patients with grade 3 and 4 in the ischemia group (12 versus 6). Finally, 16 patients died prior to study day 3, including 10 patients in the bleeding group and 4 patients in the ischemia group.

**Table 1**
Baseline Characteristics

| | |
|---|---|
| Patients, n[a] | 300 |
| Age, mean ± SD[b] | 55 ± 13 |
| Female (%) | 69 |
| Admission Hunt & Hess grade (%) | |
| 1 | 37 |
| 2 | 14 |
| 3 | 29 |
| 4 | 15 |
| 5 | 5 |
| History of hypertension | 126 (42) |
| History of smoking | 127 (42) |
| Anterior aneurysm position, *n* (%) | 142 (55) |
| Posterior aneurysm position, *n* (%) | 115 (45) |
| Side of the aneurysm, *n* (%) | |
| Right | 128 (50) |
| Left | 97 (37) |
| Center | 27 (11) |
| Bilateral | 5 (2) |

[a]number; [b]standard deviation.

### Biomarker Measurements

The frequency of an elevated cTi greater than 0.3 ng/mL on study days 1 and 3 was 22 and 19%, respectively. A total of 150 patients provided stored plasma samples, which were obtained a mean of 5.1 ± 3.5 days after SAH symptom onset. The mean BNP level was 245 ± 454 pg/mL (median of 94 pg/mL).

### ECG and Hemodynamic Data

On study day 1, a LVEF less than 50% was present in 7% of patients and 18% had RWMA. On study day 3, 9% of patients had a LVEF less than 50%, 20% had a LVEF less than 60%, and 19% had RWMA. On study day 1, the mean heart rate was 80 ± 19 bpm and the mean SBP was 147 ± 27 mmHg. On study day 3, the mean heart rate was 81 ± 18 bpm and the mean SBP was 158 ± 24 mmHg.

### Myocardial Necrosis/RWMA and LVEF

There was a strong association between cTi release and a reduced LVEF. Across all 3 study days, a cTi greater than 0.3 ng/mL was associated with a 23% prevalence of a LVEF less than 50 versus 4% if the cTi level was 0.3 or less (logistic regression OR 7.7, 95% CI 4.4–13.6, $p < 0.001$). Among all ECG, 66% of studies with RWMA had a LVEF less than 60 versus 10% without RWMA (OR 30.1, 95% CI 15.9–60.0, $p < 0.001$).

### LVEF and Hypotension

Across all 3 study days, there was an association between LVEF and SBP. After adjustment for phenylephrine dose, a 10-point decrease in LVEF was associated with a 2.9 mmHg decrease in SBP (95% CI 1.3–4.6 mmHg, $p = 0.001$). The association was strongest on study day 3, when a LVEF less than 60% predicted a SBP less than 130 mmHg (OR 2.7 after adjustment of phenylephrine dose, 95% CI 1.1–6.5, $p = 0.024$).

A total of 101 subjects (34%) received intravenous phenylephrine on study day 3 to prevent or treat vasospasm. As shown in Figure 2, a LVEF less than 50% was associated with lower SBP despite higher phenylephrine doses. The mean phenylephrine dose was 231 ± 216 μg/(kg • minute) in patients with LVEF less than 50% on study day 3 versus 68 ± 125 in patients with LVEF of 50% or greater (Wilcoxon rank-sum $p < 0.001$).

### Cardiovascular Predictors of Death

On study day 1, a SBP greater than 180 mmHg was present in 12% of patients, and was associated with a statistically significant increase in the risk of death (OR 5.6, $p = 0.008$, Table 2). A BNP level greater than 600 pg/mL was present in 9% of patients, and was markedly predictive of death (OR 37.7, $p < 0.001$, Figure 3).

On study day 3, a cTi level greater than 0.3 ng/mL, a heart rate of 100 bpm or greater, and a SBP less than 130 mmHg were all associated with death (Table 3). There was a borderline association ($p = 0.050$) between a LVEF less than 60% and death.

A total of 119 of the subjects (40%) were enrolled into the study within 48 hours of SAH symptom onset. Restricting the mortality models to these subjects never resulted in a change in the direction of the effect and the ORs remained similar. Because of the small sample size relative to the number of

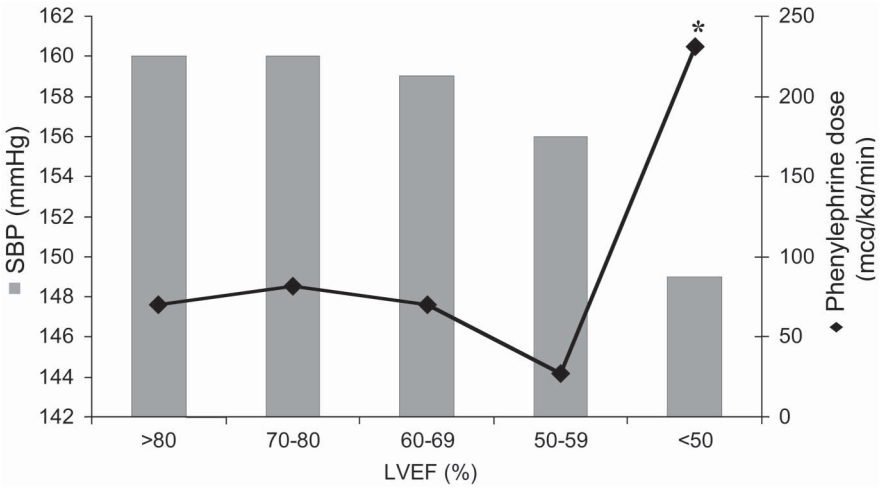


**Fig. 2.** Relationship between LVEF, SBP, and phenylephrine dose on study day 3. Wilcoxon rank-sum $p < 0.001$ versus LVEF 50% or greater.

**Table 2**
Early Cardiovascular Predictors of Death (Study Day 1, $N = 235$)

| *Predictors* | *OR*[a] | *p* | *95% CI* |
|---|---|---|---|
| cTi > 0.3 µg/L | 2.6 | 0.065 | 0.9–7.0 |
| LVEF < 50% | 2.4 | 0.18 | 0.7–10.0 |
| Heart rate ³ 100 bpm | 3.0 | 0.077 | 0.9–1.7 |
| SBP > 180 mmHg | 5.6 | 0.008 | 1.6–19.9 |
| BNP > 600 pg/mL[b] | 37.7 | <0.001 | 5.0–286.2 |

OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; bpm, beats per minute.

[a]Odds ratio corrected for age, gender, Hunt & Hess score, fever, mechanical ventilation, phenylephrine dose, and time from SAH symptom onset.

[b]$n = 150$

covariates, the CIs were larger and the *p* values were less likely to be statistically significant. One exception was the effect of a LVEF less than 50% on study day 1, which had a greater effect in the restricted analysis (OR 15.5, 95% CI 1.2–193.0, $p = 0.033$) in comparison to its nonsignificant effect in the entire cohort.

### *BNP and Interventional Vasospasm Treatment*

Of the entire patient population, 40% received neurointerventional treatment for vasospasm. For patients with a BNP greater than 600 pg/mL, the multivariate OR for interventional treatment was 5.0 versus patients with a BNP of 600 or less (95% CI 1.1–22.5, $p = 0.034$).

## Discussion

Cardiac injury and dysfunction occur frequently after SAH *(6–9)* and most likely represent a form of catecholamine toxicity *(10,11)*. Whether cardiac dysfunction negatively impacts neurological outcomes after SAH, however, remains controversial. The results of this study provide unique evidence that specific cardiovascular abnormalities are associated with in-patient mortality, after statistical adjustment for comorbid factors. In addition, this study may suggest potential causal mechanisms whereby cardiovascular dysfunction may worsen neurological outcomes, as shown in Figure 1.

The data from study day 1 was collected an average of 4.1 days after SAH, a time when the initial bleed and rebleeding would be expected to cause most of the neurological morbidity and mortality. The observed association between hypertension (SBP > 180 mmHg) and mortality on study day 1 may be caused by an increased risk of rebleeding.

The data from study day 3 was collected an average of 9.1 days after SAH symptom onset, a time frame during which cerebral ischemia would be expected to contribute to neurological morbidity and mortality. During this time period, the observed cardiac abnormalities were strongly associated with in-patient mortality. A relatively low blood pressure (SBP < 130 mmHg) was associated with an OR of 6.7 for death ($p = 0.007$) after adjustment for covariates, including phenylephrine dose. If the relationship between relative hypotension and death is causal, the likely mechanism is that hypotension results in reduced cerebral perfusion pressure (CPP), especially if cerebral vasospasm is present.

On study day 3, the relationship between a relatively low LVEF (<60%) and mortality was of borderline statistical significance. However, a low LVEF was associated with relative hypotension and a marked increase in the mean dose of phenylephrine used in the treatment of cerebral vasospasm (Figure 2). It is therefore possible that poor LV contractility may contribute to reduced CPP by lowering blood pressure and reducing the pressor effects of phenylephrine. Alternatively, it is possible that high doses of phenylephrine result in reduced LV contractility by increasing afterload.

There was a strong, independent association between tachycardia and mortality on study day 3. It is possible that increased activity of the sympathetic nervous system results in both tachycardia and a direct increase in cerebrovascular resistance *(12,13)*.

There is a strong association between cTi release and in-patient mortality. Higher Hunt & Hess grades are associated with both cTi release *(1)* and mortality *(14)*, but the relationship

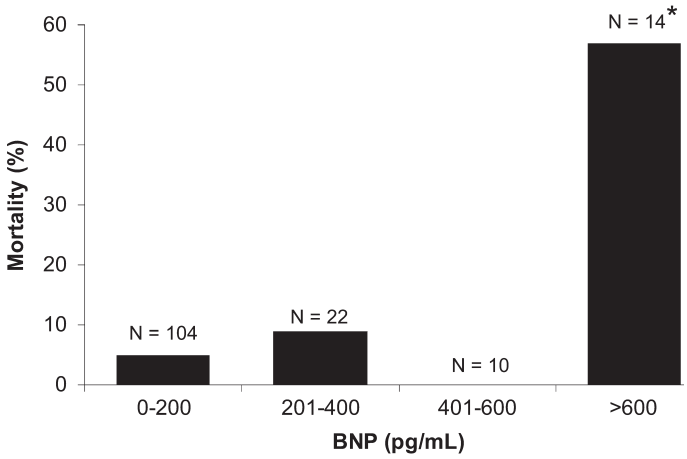


**Fig. 3.** BNP levels on study day 1 and mortality. Multivariate logistic regression OR = 37.7 (versus BNP < 600 pg/mL), 95% CI 5.0–286.2, $p < 0.001$.

**Table 3**
Late Cardiovascular Predictors of Death (Study Day 3, $N = 195$)

| *Predictors* | *OR*[a] | *p* | *95% CI* |
|---|---|---|---|
| cTi > 0.3 µg/L | 7.6 | 0.002 | 2.1–26.8 |
| LVEF < 60% | 3.2 | 0.050 | 1.0–10.4 |
| Heart rate ≥ 100 bpm | 4.9 | 0.009 | 1.5–16.0 |
| SBP < 130 mmHg | 6.7 | 0.007 | 1.7–26.8 |

OR, odds ratio; CI, confidence interval; cTi, cardiac troponin I levels; LVEF, left ventricular ejection fraction; bpm, beats per minute; SBP, systolic blood pressure.

[a]Odds ratio corrected for age, gender, Hunt & Hess score, fever, mechanical ventilation, phenylephrine dose, and time from SAH symptom onset.

between cTi and death was significant after adjustment for Hunt & Hess grade. The fact that a cTi level greater than 0.3 ng/mL was associated with a higher prevalence of a low LVEF suggests an indirect relationship between cTi release and reduced CPP.

LV systolic dysfunction also results in elevated circulating levels of BNP after SAH *(15)*. In the present study, plasma BNP levels were measured an average of 5.1 days after SAH symptom onset, during the early part of the vasospasm window. One novel finding of this study was a marked independent association between a high BNP level (>600 pg/mL) and inpatient mortality. Consistent with previous studies *(16,17)*, high BNP levels were also associated with neurointerventional treatment for cerebral vasospasm. BNP is a venodilator, arterial vasodilator, and also has a natriuretic effect; it has thus been proposed that high BNP levels may reduce CPP by lowering intravascular volume and blood pressure *(18,19)*.

In a prior study of patients with SAH, 23% of poor outcomes were attributed to delayed or postoperative ischemia (23%) *(20)*. The present study suggests that cardiac dysfunction may have a role in ischemia-related outcomes for two reasons. First, the robust association between BNP and death can be explained by established mechanisms, as previously described. Second, the other cardiac abnormalities (tachycardia, hypotension, reduced LVEF) are more predictive of death later during the hospitalization (study day 3), when ischemia is more likely to occur. In fact, 10 out of 15 patients who died of bleeding without ischemia died prior to study day 3.

The results of this study represent an important addition to the previous work in this field. Others have shown that ECG abnormalities are associated with poor neurological outcomes, though these studies had limited power to adjust for comorbid factors *(21–23)*. One study of 81 patients with SAH showed that the presence of a cardiac complication (ECG changes, myocardial necrosis, arrythmias, or pulmonary edema) was predictive of poor neurological outcome, but there was inadequate power to demonstrate a difference in mortality *(24)*. A reduced cardiac index has been associated with an increased risk of cerebral vasospasm, after adjusting for Fisher group *(25)*. In a study of 40 patients with SAH, increasing BNP levels were independently associated with a poor 2-week Glasgow Coma Score, after adjusting for Fisher group and Hunt & Hess grade *(26)*.

There are limitations to this study. Most importantly, its observational design prevents firm conclusions about the causal nature of the associations between cardiac abnormalities and mortality. The cut points used to dichotomize the cardiac predictor variables were derived from this dataset and should therefore be validated in a second cohort. The multivariate models included a relatively large number of covariates relative to the number of deaths, likely resulting in wide CIs around the OR estimates. Finally, Fisher grade could not be included in the models, as it is not routinely measured at UCSF.

Despite these limitations, the present study has important clinical implications. The data suggest that cardiac abnormalities during the clinical window of cerebral vasospasm are poor prognostic indicators. From a therapeutic standpoint, the data suggest that treatment for cerebral vasospasm with high-dose

phenylephrine is relatively ineffective in patients with a reduced LVEF. Treatment with milrinone or dobutamine may be more effective in this setting *(27)*. The data also suggest that treatments that could potentially prevent neurocardiogenic injury, such as β-blockers, should be studied in the current era of SAH therapy.

## Summary

The results of this study support a paradigm in which cardiac abnormalities contribute to morbidity and mortality after SAH. BNP and persistent cTi elevation, in addition to tachycardia and relative hypotension during the window of cerebral vasospasm, should be considered risk factors for death after SAH. Further research is required to determine whether or not the relationships between cardiac abnormalities and neurological outcome after SAH are causal in nature.

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