Acute Neurocardiogenic Injury After Subarachnoid Hemorrhage

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Background—Left ventricular (LV) systolic dysfunction has been reported in humans with subarachnoid hemorrhage (SAH), and its underlying pathophysiology remains controversial. Possible mechanisms include myocardial ischemia versus excessive catecholamine release from sympathetic nerve terminals.

Methods and Results—For 38 months, echocardiography and myocardial scintigraphy with technetium sestamibi (MIBI) and meta-[^1^2I]iodobenzylguanidine (MIBG) were performed on 42 patients admitted with SAH to assess myocardial perfusion and sympathetic innervation, respectively. A blinded observer interpreted the scintigraphic images. Cardiac troponin I (cTI) was measured to quantify the degree of myocyte necrosis. Blinded observers calculated the LV ejection fraction and graded each LV segment as normal (score=1), hypokinetic (score=2), or akinetic (score=3). A wall-motion score was calculated by averaging the sum of the 16 segments. All subjects with interpretable scans (N=41) had normal MIBI uptake. Twelve subjects had either global (n=9) or regional (n=3) absence of MIBG uptake. In comparison with patients with normal MIBG uptake, those with evidence of functional denervation were more likely to have LV regional wall-motion abnormalities (92% versus 52%, P=0.030) and cTI levels >1 μg/L (58% versus 21%, P=0.029).

Conclusions—LV systolic dysfunction in humans with SAH is associated with normal myocardial perfusion and abnormal sympathetic innervation. These findings may be explained by excessive release of norepinephrine from myocardial sympathetic nerves, which could damage both myocytes and nerve terminals. (Circulation. 2005;112:3314-3319.)

Key Words: echocardiography ■ scintigraphy ■ nervous system, sympathetic ■ hemorrhage

Subarachnoid hemorrhage (SAH) occurs in ~27 000 Americans per year and causes 14 000 deaths. An association between brain hemorrhage and cardiac dysfunction was first reported in 1954 in an article describing “cerebral T wave” electrocardiographic abnormalities in humans with SAH. Elevated cardiac enzyme levels and myocardial contraction-band necrosis have been described after SAH and provide evidence that permanent cardiac damage may occur. Left ventricular (LV) systolic dysfunction has also been described and has an approximate incidence of 10%. Myocardial ischemia and/or infarction have been implicated as the cause of cardiac abnormalities after SAH; however, the observed patterns of regional wall-motion abnormalities (RWMA) of the LV frequently do not match coronary artery distributions. Other mechanisms of injury such as coronary vasospasm and supply-demand mismatch from hypertension and tachycardia have been proposed. An alternative hypothesis suggests that after SAH, myocardial sympathetic nerve terminals release an excessive amount of norepinephrine, which results in cardiac injury and dysfunction. Although there is little direct clinical data to suggest that catecholamine-induced neurocardiogenic injury occurs in humans, experimental results support this hypothesis. The aim of the present study was to determine whether or not LV dysfunction after SAH is associated with abnormalities of myocardial sympathetic innervation.

Methods

Study Design

This was a scintigraphic substudy of a prospective cohort of SAH patients admitted to the UCSF Neurosciences Intensive Care Unit between February 1999 and January 2003. The parent cohort study was designed to describe the prevalence and clinical predictors of cardiac injury and dysfunction after SAH. The inclusion criteria for the parent cohort study were age >21 years and a confirmed diagnosis of SAH by computed tomography of the brain or lumbar puncture. The exclusion criteria were SAH due to trauma or mycotic aneurysm, pregnancy, and a history of cardiomyopathy or prior myocardial infarction. Between February 1999 and January 2002, the inclusion criterion for the scintigraphic substudy was evidence of LV systolic dysfunction (WMAs) on the preliminary (unblinded) review of any study echocardiogram. To include more patients without LV dysfunction, however, the protocol was modified in January 2002 so that all patients enrolled into the parent cohort study who provided additional consent for scintigraphic imaging were included in the study.

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3314
substudy. The UCSF Committee on Human Research approved the study, and all patients or next of kin gave written, informed consent.

Patient Population and Clinical Data Collection
Clinical and demographic data including age, sex, body surface area, history of coronary artery disease, and coronary risk factors were collected. All patients underwent cerebral angiography. The majority of culprit cerebral aneurysms identified by angiography were treated by either endovascular coiling or neurosurgical clipping, depending on individual anatomy. Aneurysm location was noted, and the neurological status was assessed at the time of admission and graded according to the Hunt and Hess scale, which ranges from 1 (slight headache) to 5 (deep coma). Inpatient mortality data were also collected.

The presence or absence of cerebral vasospasm by imaging (transcranial Doppler or cerebral angiography) during hospitalization was noted. In addition, the use of induced hypertension with intravenous phenylephrine to prevent or treat vasospasm was recorded, as well as the peak dose received. Data regarding symptomatic or clinical vasospasm were not recorded.

Myocardial Scintigraphic Imaging and Analysis
Myocardial sympathetic innervation was assessed by planar imaging in the anterior, 45° left anterior oblique, and left lateral positions in the anterior, and 45° left anterior oblique views of the LV: Parasternal long axis, parasternal short axis at the papillary muscle level, apical 2 chamber, apical 3 chamber, subcostal long axis, and subcostal short axis at 3 levels (base, midventricle, and apex). Ultrasound system settings were chosen to maximize resolution of the LV endocardial borders. When necessary, Optison was injected intravenously to better visualize the LV endocardium. All images were acquired in digital format and transferred from the hard drive of the ultrasound system to a magneto-optical disc for offline analysis.

Offline observers who were blinded to clinical information analyzed the echocardiographic images. With commercially available software (ProSolv), all patient-identifying information was digitally masked, and the echocardiographic studies were randomly ordered by code numbers before review. Global systolic function was assessed by measuring LV ejection fraction (LVEF) according to Simpson’s biplane method of discs.16 For each patient, the lowest LVEF recorded for the 3 study days was used in the analysis, and an LVEF <50% was considered abnormal.

Regional LV systolic function was quantified with a 16-segment model16 so that each segment was graded as normal (score=1), hypokinetic (score=2), or akinetic/dyskinetic (score=3). The RWM score (RWMS) was calculated by averaging the score for each of the 16 segments. For each patient, the highest RWMS recorded for the 3 study days was used in the analysis, and the presence of any RWMA (and thus, an RWMS >1) was considered abnormal.

Measurement of Cardiac Troponin I and Catecholamine Levels
To correlate cardiac sympathetic functional denervation with myocardial necrosis, a serum sample was obtained for measurement of cardiac troponin I (cTI) on the day of enrollment and 2 and 5 days later. The samples were analyzed with a fluorescent enzyme immunoassay (Abbot Diagnostics). The lowest detectable level was 0.3 μg/L, and the maximum quantifiable level was 50 μg/L. For each patient, the highest value of cTI was used in the analysis, and a cTI level >1.0 μg/L was considered abnormal.

After the first 100 patients were enrolled into the parent cohort study, institutional review board approval for long-term storage of blood samples was obtained. For every patient who provided consent for storage of banked samples, a blood sample was collected as soon as possible after enrollment, and the plasma was stored at −70°C until completion of the study. At that time, the samples were thawed, and norepinephrine and epinephrine levels were measured with a competitive ELISA (Alpco Diagnostics).

Statistical Analysis
Clinical data were compared between the patients with and without sympathetic functional denervation and with an MIBG H-M ratio greater than and less than the median ratio by Wilcoxon’s rank-sum, χ², and Fisher’s exact tests. The mean LVEF, RWMS, and cTI level were compared between the 2 groups with Wilcoxon’s rank-sum tests. The proportions of patients with LVEF <50%, RWMS >1, and cTI >1.0 μg/L were compared between the 2 groups by χ² and Fisher’s exact tests. All statistical analyses were performed with commercially available software (Stata).

Results
Patient Population
The parent cohort study enrolled 237 subjects between February 15, 1999, and January 2, 2003. We obtained scintigraphic images for 42 study subjects. One study patient was excluded from the qualitative analysis because of technically limited scintigraphic images. The H-M ratio could not be obtained for 5 patients because of technically limited images. As shown in Table 1, the mean age of the 41 study subjects was 54 years, and 78% were women. Only 7% of subjects had a history of coronary artery disease. Hypertension and smoking were the most common coronary risk factors.

| Table 1. Clinical Characteristics of the 41 Subjects |
|---------------------------------|-------|
| Age, y (mean±SD) | 54±13 |
| Sex, % female | 78 |
| Body surface area, cm² | 1.8±0.2 |
| Hunt-Hess grade, mean±SD | 2.4±1.2 |
| History of coronary artery disease, % | 7 |
| History of hypertension, % | 39 |
| History of smoking, % | 39 |
| History of diabetes mellitus, % | 7 |
| History of dyslipidemia, % | 10 |
TABLE 2. Myocardial Injury and Dysfunction by Functional Denervation Status

<table>
<thead>
<tr>
<th></th>
<th>Normal Innervation (n=29)</th>
<th>Functional Denervation (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt;50%</td>
<td>40%</td>
<td>50%</td>
<td>0.51*</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>54±16</td>
<td>50±12</td>
<td>0.25†</td>
</tr>
<tr>
<td>RWMS &gt;1.0</td>
<td>52%</td>
<td>92%</td>
<td>0.030‡</td>
</tr>
<tr>
<td>Mean RWMS</td>
<td>1.3±0.5</td>
<td>1.6±0.5</td>
<td>0.024†</td>
</tr>
<tr>
<td>cTI &gt;1.0</td>
<td>21%</td>
<td>58%</td>
<td>0.029‡</td>
</tr>
<tr>
<td>Mean cTI</td>
<td>2.9±8.6</td>
<td>5.9±14.0</td>
<td>0.007‡</td>
</tr>
</tbody>
</table>

*Abbreviations are as defined in text.*
†Wilcoxon’s rank-sum test.
‡Fisher’s exact test.

Patients with abnormal MIBG uptake were more likely to have an RWMA (92% versus 52%, P=0.030) and had a higher mean RWMS (1.6 versus 1.3, P=0.024). Myocardial necrosis was also more common in denervated subjects (58% of subjects had cTI >1.0 μg/L) than in subjects with normal innervation (21%, P=0.029).

The median MIBG H-M ratio was 1.57. As shown in Table 3, 19 patients had an H-M ratio >1.57 and 18 had a ratio ≤1.57. There was no significant difference in the average time from SAH symptom onset to the echocardiographic/troponin data collection among patients with low (less than the median) versus high (greater than the median) H-M MIBG ratios (5.9±3.2 versus 6.1±3.7 days, t test P=0.80). Patients with an MIBG H-M ratio ≤1.57 were more likely to have an RWMA (83% versus 47%, P=0.038) and a cTI level >1.0 μg/L (50% versus 16%, P=0.038).

A total of 26 of the study subjects had evidence of an RWMA, and 15 did not. Patients with an RWMA were more likely to have abnormal MIBG uptake (42% versus 7%, χ² P=0.016). Patients with an RWMA also had a lower median H-M MIBG ratio (1.45 versus 1.84, Wilcoxon’s rank-sum P=0.024). There were no significant differences between the frequency of abnormal MIBG uptake and the median H-M ratio among patients with versus without an LVEF <50%.

Myocardial Scintigraphy and Clinical Factors

As shown in Table 4, there was a trend for a higher mean Hunt-Hess grade in the denervated group than in the normal-innervation group (3.0 versus 2.2, P=0.06). There was also a trend for higher doses of phenylephrine in the denervated group. There were no significant differences in systolic blood pressure according to H-M MIBG ratio at any of the study’s time points.

The mean time from SAH symptom onset to scintigraphy was 11.7 days and was not significantly different between the 2 groups. There were no other significant between-group differences in clinical characteristics.

Three of the study subjects died during hospitalization (7%), 2 of whom had low H-M MIBG ratios and 1 of whom had a higher ratio. Twenty-six (70%) of the patients had imaging evidence of vasospasm by angiography or transcranial Doppler, a proportion similar to that in published studies,17 and 21 (57%) received hypertensive therapy with...
Evidence from animal models suggests that an excessive elevated circulating levels of catecholamines is known to occur in humans with brain injury, particularly after SAH. Moreover, some SAH patients have electrocardiographic and echocardiographic findings suggestive of myocardial infarction without angiographic evidence of coronary artery disease or vasospasm. Activation of the sympathetic nervous system with elevated circulating levels of catecholamines is known to occur in humans with brain injury, particularly after SAH. Moreover, some SAH patients have electrocardiographic and echocardiographic findings suggestive of myocardial infarction without angiographic evidence of coronary artery disease or vasospasm.

**TABLE 4. Clinical Characteristics by Functional Denervation Status**

<table>
<thead>
<tr>
<th></th>
<th>Normal Innervation (n=29)</th>
<th>Functional Denervation (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>55±12</td>
<td>51±14</td>
<td>0.46*</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>76</td>
<td>83</td>
<td>0.47†</td>
</tr>
<tr>
<td>Body surface area, cm²</td>
<td>1.8±0.3</td>
<td>1.7±0.2</td>
<td>0.23*</td>
</tr>
<tr>
<td>Hunt-Hess grade, mean±SD</td>
<td>2.2±1.1</td>
<td>3.0±1.4</td>
<td>0.060*</td>
</tr>
<tr>
<td>History of coronary artery disease, %</td>
<td>7</td>
<td>8</td>
<td>1.00†</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>45</td>
<td>25</td>
<td>0.31†</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td>38</td>
<td>42</td>
<td>1.00†</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>10</td>
<td>0</td>
<td>0.54†</td>
</tr>
<tr>
<td>History of dyslipidemia, %</td>
<td>7</td>
<td>17</td>
<td>0.57†</td>
</tr>
<tr>
<td>Time from SAH to imaging, days</td>
<td>12.1±5.7</td>
<td>11.0±4.1</td>
<td>0.73*</td>
</tr>
<tr>
<td>Aneurysm position, % left/right</td>
<td>26/61</td>
<td>36/36</td>
<td>0.40†</td>
</tr>
<tr>
<td>Aneurysm position, % anterior/posterior</td>
<td>84/16</td>
<td>64/36</td>
<td>0.21†</td>
</tr>
<tr>
<td>Hydrocephalus by head computed tomography, %</td>
<td>41</td>
<td>42</td>
<td>1.00†</td>
</tr>
<tr>
<td>Peak dose of phenylephrine, μg/min</td>
<td>126±183</td>
<td>276±239</td>
<td>0.067*</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text. *Wilcoxon’s rank-sum test. <mc>†Fisher’s exact test.

intravenous phenylephrine to prevent or treat vasospasm. There was no significant difference in the frequency of vasospasm or phenylephrine treatment according to the H-M MIBG ratio status. Fifteen (42%) of the subjects received neurointerventional treatment for cerebral vasospasm with either angioplasty or intra-arterial infusion of verapamil. There was no significant difference in the frequency of neurointerventional procedures according to the H-M MIBG ratio status.

Plasma catecholine levels were measured in 25 of the patients with a mean time from SAH symptom onset to blood sample collection of 4.8±3.8 days. There were no statistically significant differences in plasma norepinephrine or epinephrine levels between patients with low versus high MIBG H-M ratios.

**Discussion**

LV systolic dysfunction after SAH has been well described, although the pathophysiology remains unclear. Historically, cardiac dysfunction after SAH has been attributed to coronary thrombosis, epicardial coronary vasospasm, or oxygen supply-demand mismatch in the setting of hypertension and tachycardia, although there is little clinical evidence to support these mechanisms. Moreover, some SAH patients have electrocardiographic and echocardiographic findings suggestive of myocardial infarction without angiographic evidence of coronary artery disease or vasospasm.

Activation of the sympathetic nervous system with elevated circulating levels of catecholamines is known to occur in humans with brain injury, particularly after SAH. Evidence from animal models suggests that an excessive release of catecholamines from sympathetic nerves is the most likely cause of myocardial injury after SAH. This hypothesis is supported by an experimental model of sudden brain death in anesthetized pigs, which demonstrated immediate and massive increases in myocardial interstitial norepinephrine levels by microdialysis techniques. Importantly, serum catecholamine levels remained relatively unchanged in this model. The lack of correlation between plasma catecholamine levels and the MIBG H-M ratio in the present study is therefore not surprising. Also, an analysis from the parent cohort study showed no correlation between plasma catecholamine levels and cTI release. It is believed that high interstitial concentrations of norepinephrine result in myocyte calcium overload and cell death.

MIBG scintigraphy is an established method of mapping cardiac sympathetic innervation. MIBG enters cells through the same neuronal uptake mechanism as norepinephrine. However, unlike norepinephrine, it is not metabolized. MIBG has been used to assess localized adrenergic neuron function within discrete portions of the cardiac conduction system and has been shown to be a reliable marker for the detection of cardiac adrenergic neuronal damage in a rat model of cardiomyopathy.

The present study was designed to simultaneously evaluate myocardial sympathetic innervation, myocardial perfusion, and LV systolic function. All subjects had normal uptake of MIBI, indicating normal myocardial perfusion in the resting state. Twelve of 41 (29%) study subjects were found to have evidence of sympathetic functional denervation by MIBG scintigraphy, and the pattern of denervation was global in the majority of the subjects. There were significantly more RWMAs in patients with sympathetic functional denervation than in those with normal innervation. The 3-fold increase in the risk of myocardial necrosis observed in patients with sympathetic functional denervation suggests a relation between functional denervation and cardiomyocyte death.

The trend for a higher phenylephrine dose in the denervated group compared with the normal group is likely associative and not causal. We hypothesize that the patients with denervation, who were more likely to have LV dysfunction, required higher doses of phenylephrine to achieve a
target systolic blood pressure during treatment for cerebral vasospasm. Phenylephrine is not known to cause myocardial sympathetic nerve injury. However, higher phenylephrine doses are associated with a greater probability of troponin release after SAH, possibly because of increased afterload or coronary vasoconstriction. For this reason, the greater frequency of troponin release in the subjects with functional denervation may be partially explained by the higher doses of phenylephrine.

The degree of functional denervation on MIBG scintigraphy can be quantified by the H-M ratio. Dae et al demonstrated a significantly greater H-M ratio in normal hearts compared with denervated (posttransplant) hearts in humans. In our study, those study subjects with an MIBG H-M ratio below the median were more likely to have an RWMA and elevated cTnI levels in comparison with patients with higher H-M ratios. Therefore, the findings provide unique evidence for an association between functional myocardial sympathetic denervation and cardiac injury and dysfunction after SAH.

The exact nature of the relation between sympathetic functional denervation and myocardial injury and dysfunction in humans with SAH remains unclear. It is possible that acute brain injury results in a massive release of norepinephrine from the myocardial sympathetic nerve terminals in some cases. These high levels of norepinephrine in the myocardial interstitium may subsequently lead to myocyte necrosis and contractile dysfunction, as well as damage to the sympathetic nerve terminals themselves. Alternatively, it is possible that SAH may cause neuronal degeneration at the origin of sympathetic outflow to the heart, at regions such as the insula or hypothalamus. If an initial rise in sympathetic outflow to the heart is followed by a period of functional denervation, one might expect a dominance of vagal or inhibitory effects on the heart during the later period after SAH. This view is supported by the related clinical model of brain-dead organ donors, who have excessive activity of the inhibitory G protein Giα and LV dysfunction.

Previous studies have established other clinical models of myocardial sympathetic denervation. For example, global functional denervation has been described in recipients of cardiac transplants, and these patients have been shown to reinnervate over time. Myocardial denervation with abnormal MIBG uptake has also been described in patients with acute coronary syndromes and without Q-wave myocardial infarction. The absence of myocardial perfusion defects in the present study, however, suggests that the observed functional denervation was not due to large areas of myocardial infarction. Although ischemia was a possible cause for the regional patterns of functional denervation observed in 3 subjects, the global pattern of functional denervation observed in the majority of subjects with MIBG defects has not been described in patients with coronary syndromes.

One limitation of the present study is that the subjects were generally too unstable to be transported for single-photon emission computed tomography (as opposed to planar) scintigraphic imaging, and thus, subtle regional variations in MIBG uptake between apical and basal segments may not have been detected. In addition, perfusion imaging with either exercise or pharmacological stress could not be performed because of clinical instability.

Based on available evidence, aggressive treatment of SAH should not be withheld because of cardiac dysfunction. Specifically, there is no important difference in cardiac morbidity between surgical and endovascular aneurysm therapy. Although standard treatments for cerebral vasospasm such as “triple-H” therapy (hypertension, hypervolemia, and hemodilution) potentially result in pulmonary edema in patients with LV dysfunction, such treatments should probably not be withheld. Also, SAH patients with severely reduced cardiac output may benefit from prophylactic hemodynamic augmentation to minimize the risk of developing delayed cerebral ischemia. Finally, in a small study of SAH patients with LV dysfunction, vasospasm, and a suboptimal response to hyperdynamic and hypervolemic therapy, aggressive management with endovascular treatment and balloon angioplasty for severe cerebral vasospasm was associated with improvement in cardiac function.

In summary, this study provides novel data regarding the relation between functional myocardial sympathetic denervation and cardiac injury and dysfunction in patients with SAH. An excessive release of catecholamines from myocardial sympathetic nerves may cause damage to both the cardiomyocytes and the nerves themselves. Cardiac dysfunction after SAH appears to be a form of neurocardiogenic injury.\footnote{Doshi R, Neil-Dwyer G, Stott A. Hypothalamic and myocardial lesions after subarachnoid hemorrhage. J Neurol Neurosurg Psychiatry. 1977;40:821–826.}

\section*{Acknowledgments}

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\section*{References}

norepinephrine release after brain death using cardiac microdialysis. 


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