Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage

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Object. Subarachnoid hemorrhage (SAH) has been associated with cardiac injury and left ventricular (LV) dysfunction. The incidence and natural history of neurocardiogenic injury after SAH remains poorly understood. The objective of this study was to describe the incidence, time course, recovery rate, and segmental patterns of LV dysfunction after SAH.

Methods. Echocardiography was performed three times over a 7-day period in 173 patients with SAH. The incidence of global (ejection fraction [EF] < 50%) and segmental (any regional wall-motion abnormality [RWMA]) LV dysfunction was measured. The time course of LV dysfunction was determined by comparing the prevalence of LVEF less than 50% and RWMA at 0 to 2, 3 to 5, and 6 to 8 days after SAH. The recovery rate was defined as the proportion of patients with partial or complete normalization of function. The distribution of RWMA among 16 LV segments was also determined. An LVEF less than 50% was found in 15% of patients, and 13% had an RWMA with a normal LVEF. There was a trend toward increased dysfunction at 0 to 2 days after SAH, compared with 3 to 8 days after SAH. Recovery of LV function was observed in 66% of patients. The most frequently abnormal LV segments were the basal and middle ventricular portions of the anteroseptal and anterior walls. The apex was rarely affected.

Conclusions. Left ventricular systolic dysfunction occurs frequently after SAH and usually improves over time. The observed segmental patterns of LV dysfunction often do not correlate with coronary artery distributions.

Key Words • subarachnoid hemorrhage • cardiac function • echocardiography • troponin

SUBARACHNOID hemorrhage occurs in approximately 27,000 Americans per year and causes 14,000 deaths. In 1954, Burch, et al., described “cerebral T wave” ECG abnormalities in patients with stroke and noted that the ECG findings were most marked in patients with SAH. Elevated troponin levels and myocardial contraction band necrosis have also been described after SAH and provide evidence that permanent cardiac damage may occur. Left ventricular systolic dysfunction can occur after SAH with an approximate incidence of 10%, based on a relatively small number of study patients. The observed patterns of RWMA of the left ventricle frequently do not match coronary artery distributions and may be due to excessive release of norepinephrine from the myocardial sympathetic nerves. It is unknown whether this form of neurally mediated heart disease results in permanent myocardial injury or reversible dysfunction.

The objectives of this study were to accurately quantify the incidence, time course, and recovery patterns of LV dysfunction after SAH by using serial echocardiographic measurements. In addition, a wall-motion analysis was performed to better define the regional patterns of LV dysfunction relative to the known distributions of human coronary arteries and myocardial sympathetic nerves.

Clinical Material and Methods

Between May 1999 and July 2002, we prospectively enrolled a consecutive series of patients admitted to the University of California, San Francisco Medical Center neuroscience intensive care unit with a diagnosis of aneurysmal SAH confirmed by computed tomography of the brain and/or lumbar puncture. We obtained written informed consent from patients or next of kin before enrollment. All patients underwent cerebral angiography. The large majority of the
culprit cerebral aneurysms revealed through angiography were treated by either percutaneous coil embolization or surgical clipping. The study exclusion criteria included a history of cardiomyopathy or prior myocardial infarction (by history of ECG findings of pathological Q waves), inadequate echocardiographic images, SAH due to trauma or mycotic aneurysm, and pregnancy.

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). Clinical and demographic data, including age, gender, history of coronary artery disease, and coronary risk factors, were collected.

Portable, transthoracic echocardiography (Acuson Sequoia; Acuson Corp., Mountain View, CA) was performed on the day of enrollment, 2 days after enrollment, and 5 days after enrollment. The number of days between SAH onset and each study was recorded. Data from patients who were discharged, who were transferred to another facility, or who died before completion of all three studies were excluded from the analysis.

Each echocardiogram included the following views of the left ventricle: parasternal long axis, parasternal short axis at three levels (base, middle ventricle, and apex), apical four chamber, apical two chamber, subcostal long axis, and subcostal short axis at three levels (base, middle ventricle, and apex). If the patient was observed to have global or regional LV dysfunction in an unblinded interpretation of a preliminary echocardiogram, a fourth echocardiogram was performed just before discharge from the hospital. Ultrasound system settings were chosen to maximize resolution of the LV endocardial borders, and all studies were performed using harmonic imaging. When necessary, contrast (Optison; Amersham Health, Princeton, NJ) was injected intravenously to allow better visualization of the LV endocardium. All images were acquired in digital format and transferred from the hard drive of the ultrasound system to a magnetooptical disk for offline analysis.

The final echocardiographic analysis was performed offline by observers who were blinded to the patients’ clinical information. Using commercially available digital image management and reporting software (ProSolv Cardiovascular; ProSolv, Indianapolis, IN), we digitally masked all patient-identifying information and randomly ordered the echocardiographic studies by code numbers before their review. Global systolic function was assessed by measuring LVEF using Simpson’s biplane method of discs. Because the LVEF results were not normally distributed (marked skew for the low values was present), an LVEF less than 50% was considered abnormal for analysis purposes.

Regional LV systolic function was quantified using a 16-segment model such that each segment was graded as normal (score = 1), hypokineti c (score = 2), or akinetic/dyskinetic (score = 3). The RWMS was calculated by averaging the score for each of the 16 segments. An RWMS higher than 1 was considered abnormal for analysis purposes. The analysis of the distribution of RWMAS was performed using each patient’s most abnormal (highest RWMS) echocardiogram. The prevalence and regional distribution of RWMAS (hypokinesis, akinesi s, or dyskinesis) for each of the 16 LV segments was calculated using these studies.

The time course of LV dysfunction was quantified by comparing the prevalence of LVEF less than 50% and RWMS higher than 1 at 0 to 2, 3 to 5, and 6 to 8 days after the onset of SAH symptoms. In this analysis, the presence or absence of a reduced LVEF and an elevated RWMS were the outcome variables and the time after SAH was the predictor variable, with an OR for each of the three time periods calculated using longitudinal (repeated-measures) data analysis.

To evaluate recovery of LV systolic dysfunction after SAH, we compared the highest RWMS with the final RWMS in the subset of patients who had both an RWMS higher than 1 during any study and more than one echocardiogram. In addition, we compared the second highest RWMS with the final RWMS for patients who had no improvement. For analysis, LV systolic dysfunction was considered completely recovered if the RWMAS were shown to resolve completely such that the RWMS was 1 at the time of the last echocardiogram for that patient. Partial recovery was defined as incomplete improvement in the RWMS at the time of the last echocardiogram. In addition, a Wilcoxon signed-rank test was performed to compare the mean initial RWMS with the mean final RWMS among the patients included in the recovery analysis.

To correlate LV systolic dysfunction with the presence or absence of myocardial necrosis, a serum sample was obtained for measurement of cTnl on the day of each study echocardiogram. The samples were analyzed using fluorescent enzyme immunoassay (Abbot Diagnostics, Abbott Park, IL). The lowest detectable level was 0.3 μg/L, and a level of 1.0 μg/L was considered elevated. The proportion of patients with an elevated serum level of cTnl was compared among the patients with and without RWMA using chi-square analysis. The mean cTnl level among the patients with and without RWMA was compared using Wilcoxon rank-sum analysis. Hospital mortality rates among the patients with and without RWMA were compared using chi-square analysis.

After the first 100 patients were enrolled in the study, we obtained institutional review board approval for the storage of plasma samples, which were collected on study Day 1 and frozen at −70°C. The purpose of this part of the study was to investigate the relationship between reduced LV systolic function and catecholamine levels. After study enrollment was complete, the plasma samples were thawed, and norepinephrine and epinephrine levels were measured using a competitive enzyme-linked immunosorbent assay (Alpco Diagnostics, Windham, NH).

### TABLE 1

<table>
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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>mean age (yrs)</td>
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<td>female sex (% of patients)</td>
<td>58</td>
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<tr>
<td>mean Hunt &amp; Hess grade</td>
<td>2.5 ± 1.3</td>
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<td>history (% of patients)</td>
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Left ventricular dysfunction after subarachnoid hemorrhage

The study included 173 patients and 489 echocardiograms. The mean patient age was 54 years, and 68% were women (Table 1). Hypertension and smoking were more common relative to other risk factors for coronary artery disease. Approximately 5% of the patients had a history of coronary artery disease. The mean Hunt and Hess score was 2.5 ± 1.3, and a broad spectrum of patients was enrolled, including 59 patients with Hunt and Hess Grade 1 and 14 patients with Grade V.

The distribution of LVEFs among all study echocardiograms is shown in Fig. 1. The mean LVEF for all study echocardiograms was 68 ± 13%, with a low value of 17%. The upper quartile of LVEF results ranged from 76 to 96%. Of the 173 patients enrolled in the study, 48 (28%) had evidence of regional LV dysfunction, with an RWMS higher than 1 on any study day. A subgroup of 25 of these 48 patients (15% of the total sample) had global LV dysfunction, with an LVEF less than 50% on any study day. The other 23 patients had RWMA with a normal LVEF.

Compared to patients without LV dysfunction, those with any RWMA were more likely to have an elevated serum cTnI (55% compared with 11%, p < 0.001) during the study. In addition, the average peak cTnI was significantly higher in the patients with RWMA (7.6 ± 13.7 μg/L compared with 0.9 ± 2.5 μg/L, p < 0.001). There was a trend toward an increased incidence of mortality in the hospital in patients with RWMA compared with those without RWMA (25% compared with 15%, p = 0.13). There was no association between RWMA and higher catecholamine levels (OR 1.15, 95% CI 0.91–1.45 per 50 pg/ml increase in epinephrine level; OR 0.95, 95% CI 0.69–1.30 per 200 pg/ml increase in norepinephrine level). All deaths were due to neurological deterioration, and none was caused by cardiac dysfunction.

To analyze the time course of cardiac dysfunction, the echocardiographic results were stratified by the time from SAH to imaging. As shown in Fig. 2, an RWMS higher than 1 was more prevalent within 0 to 2 days after SAH (23% of patients affected), compared to Days 3 through 5 (17% of patients affected), and Days 6 through 8 after SAH (18% of patients affected), although the observed difference did not reach statistical significance (OR 1.26, 95% CI 0.87–1.82 for Days 0–2, compared with Days 3–8). The prevalence of LVEF less than 50% was similar across the three time periods (7.5% at 0–2 days after SAH, 7.7% at 3–5 days after SAH, and 9.6% at 6–8 days after SAH, respectively).

For the recovery analysis, follow-up echocardiograms were obtained in 44 of 48 patients with an RWMS higher than 1. Four patients died before a follow-up echocardiogram could be obtained. Among the 44 patients, 11 (25%) had complete normalization of the RWMS and an additional 18 (41%) had at least partial improvement (Fig. 3). The mean follow-up RWMS was significantly lower than the mean initial RWMS (1.30 ± 0.36 compared with 1.46 ± 0.45, p = 0.013, Wilcoxon signed-rank test). Mortality rates were substantially higher among the nonimproving patients, compared with the improving patients (10%, compared with 40%, p = 0.02, chi-square test).

There was heterogeneity in the observed patterns of RWMA in the study patients. The prevalence of RWMA for each of the 16 LV segments among the patients with abnormal LV function is shown in Fig. 4. The most commonly abnormal LV segments were the basal portions of the anteroseptal and anterior walls and the middle ventricular portions of the anteroseptal, inferoseptal, anterior, and anterolateral walls. These segments were hypokinetic or akinetic in 54 to 63% of patients with any RWMA. The prevalence of RWMA at the LV apex and the basal portions of the inferior and posterolateral walls was relatively low.

Discussion

The five largest previous studies of LV dysfunction after SAH have reported an RWMA prevalence of 8 to 13%. The number of patients in these studies ranged from 35 to 99. In one of these studies, echocardiography was per-
data suggest that the initial neurological injury may be an important factor in the development of cardiac injury after SAH. Consistent with this finding, Parekh and colleagues have demonstrated that myocardial necrosis is more likely to occur in patients with more severe SAH grades. Improvement of the observed LV dysfunction suggests that this form of cardiac injury is not due to severe coronary artery disease. Also, treatment interventions such as infusion of colloids and pressor agents, which are frequently used during Days 3 through 8 after SAH, do not appear to be central factors in the development and time course of RWMAs.

Although case reports and small studies have indicated that SAH-induced cardiac injury may normalize over time, no large study has examined this aspect of the syndrome. The results of the current study show that the majority of patients with SAH experience complete or partial resolution of LV systolic dysfunction during acute hospitalization (Fig. 3). However, deterioration of LV function is frequently associated with progression to brain death.

Clinicians treating patients with SAH should be aware that cardiac injury and dysfunction occur frequently and that echocardiography should be performed when signs or symptoms of heart failure are present. Rarely, patients with SAH may develop cardiogenic shock. In these cases, a more aggressive diagnostic evaluation, including cardiac catheterization and pulmonary artery line placement, is recommended. If necessary, an intraaortic balloon pump may be placed to help maintain adequate cerebral perfusion pressure. However, because of the concern regarding the possibility of permanent or progressive LV dysfunction, surgical placement of an aneurysm clip should not be withheld or delayed in most cases. There does not appear to be an important difference in cardiac morbidity between patients receiving surgical aneurysm therapy and those receiving endovascular aneurysm therapy. Although standard treatments for cerebral vasospasm, such as triple-H therapy (hypertension, hypervolemia, and hemodilution), could potentially result in pulmonary edema in patients with LV dysfunction, such treatment should probably not be withheld. In fact, patients with SAH and reduced cardiac output may benefit from prophylactic hemodynamic augmentation to minimize the risk of delayed cerebral ischemia. In a small study of patients with SAH, LV dysfunction, vasospasm, and a suboptimal response to hyperdynamic and hypervolemic therapy, aggressive management with endovascular treatment and balloon angioplasty for severe cerebral vasospasm has been associated with improvement in cardiac function. In addition, many patients with SAH in whom brain death occurs should be considered potential heart donors for transplantation, despite the finding of LV systolic dysfunction on an initial echocardiogram, if cardiac function can be demonstrated to improve over time.

To date, only one retrospective study has provided an analysis of RWMAs in patients with SAH. In that study, several patients had a pattern of RWMA in which the basal portions of the anterior and anteroseptal walls were severely affected and there was relative sparing of the apical segments. It is interesting to note that other studies have described a pattern of severe apical dysfunction after SAH. In the current analysis, an echocardiography technician who was blinded to the patients’ clinical information performed a comprehensive analysis of RWMA using a standardized 16-segment model. As Fig. 4 shows, there
was marked heterogeneity in the segmental prevalence of RWMAs in the current study. The most frequently affected segments were the basal and middle ventricular portions of the anteroseptal and anterior walls and the middle ventricular portions of the inferoseptal and anterolateral walls. Although dysfunction of the LV apex was observed, the frequency of this abnormality was low, compared to the frequencies of abnormalities of the basal septum and anterior wall.

This apex-sparing pattern of LV dysfunction suggests that the injury is not the result of obstruction and/or vasospasm of the left anterior descending coronary artery. Although one might suspect that SAH-associated RWMAs that affect the apex of the left ventricle are caused by coronary disease or spasm, no published studies have implicated epicardial coronary obstruction as a causative factor. In fact, two previous studies have found no evidence of coronary artery disease or epicardial coronary spasm in patients with SAH who underwent cardiac catheterization during ongoing ECG ST segment elevation. Although many of the present study's patients with RWMAs had elevated serum levels of cTnI, 45% did not, indicating that myocardial necrosis is not a necessary causative factor for LV dysfunction after SAH.

Experimental data have indicated that excess release of catecholamines by the myocardial sympathetic nerve terminals is the most likely mechanism of cardiac injury and dysfunction after SAH. In an experimental model of sudden brain death, immediate and massive increases in myocardial norepinephrine levels were observed using microdialysis techniques, although serum catecholamine levels remained relatively unchanged. Unfortunately, in the current study, we were unable to measure serum catecholamine levels immediately after onset of SAH, which may account for a lack of association between reduced systolic function and catecholamine levels. Nevertheless, it is believed that high interstitial concentrations of norepinephrine result in myocyte calcium overload and cell death. In monkeys, a relative paucity of norepinephrine content in the apex of the left ventricle, compared to the basal septum, has been described. Clinical studies using meta-[123I]iodobenzylguanidine and myocardial scintigraphic imaging have demonstrated a relative paucity of sympathetic nerve terminals in the apex of the left ventricle of some humans. In the present study, the predominance of RWMAs at the basal septal segments with less frequent involvement of the apex is thus consistent with a catecholamine or neurally mediated injury.

Conclusions

Left ventricular systolic dysfunction occurs frequently after SAH and is most likely to be present in the first few
days after the onset of SAH symptoms. Over the course of a few weeks, the majority of patients with SAH and with LV dysfunction experience a partial or complete improvement in contractility of the left ventricle. The time course, recovery, and patterns of LV dysfunction occurring after SAH are frequently consistent with neurally mediated cardiac injury, as opposed to myocardial infarction.

References

N. Banki, et al.