Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction

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Object. Neurogenic stunned myocardium in aneurysmal subarachnoid hemorrhage (SAH) is associated with a wide spectrum of reversible left ventricular wall motion abnormalities and includes a subset of patients with a pattern of apical akinesia and concomitant sparing of basal segments called “tako-tsubo cardiomyopathy.”

Methods. After obtaining institutional review board approval, the authors retrospectively identified among all patients admitted to the Mayo Clinic’s Neurological Intensive Care Unit between January 1990 and January 2005 those with aneurysmal SAH who had met the echocardiographic criteria for tako-tsubo cardiomyopathy. Among 24 patients with SAH-induced reversible cardiac dysfunction, the authors identified eight with SAH-induced tako-tsubo cardiomyopathy. All eight patients were women with a mean age of 55.5 years (range 38.6–71.1). Seven patients presented with a poor-grade SAH, reflected by a Hunt and Hess grade of III or IV. Four patients underwent aneurysm clip application, and four underwent endovascular coil occlusion. The mean initial ejection fraction (EF) was 38% (range 25–55%), and the mean EF at recovery was 55% (range 40–68%). Cerebral vasospasm developed in six patients, but cerebral infarction developed in only three patients.

Conclusions. The authors describe the largest cohort with aneurysmal SAH–induced tako-tsubo cardiomyopathy. In the SAH population, tako-tsubo cardiomyopathy predominates in postmenopausal women and is often associated with pulmonary edema, prolonged intubation, and cerebral vasospasm. Additional studies are warranted to understand the complex mechanism involved in tako-tsubo cardiomyopathy and its intriguing relationship to neurogenic stunned myocardium.

KEY WORDS • subarachnoid hemorrhage • cardiac apical ballooning • tako-tsubo cardiomyopathy • neurogenic stunned myocardium

Abbreviations used in this paper: CK-MB = creatine kinase MB isoenzyme; CT = computed tomography; ECG = electrocardiography; EF = ejection fraction; LV = left ventricular; NICU = neurological intensive care unit; SAH = subarachnoid hemorrhage.
diography showed no change or worsening of the EF in four patients and an improvement in the EF in 24 patients; the improvement in the latter group was compatible with neurogenic stunned myocardium.

We selected patients who met the following criteria: 1) diagnosis of aneurysmal SAH based on CT or lumbar puncture and cerebral angiography; 2) echocardiogram during incident hospitalization revealing regional wall motion abnormalities preferentially affecting the apical and midventricular segments; 3) evidence of improvement in cardiac function and wall motion on subsequent studies; and 4) cardiac dysfunction unlikely to be attributable to coronary artery disease.

Results

Eight patients met the inclusion criteria consistent with an SAH-induced tako-tsubo cardiomyopathy (Table 1). All were women with a mean age of 55.5 years (range 38.6–71.1 years). Four patients had a history of hypertension; and six patients, a history of tobacco use. At the onset of SAH, six patients lost consciousness. A poor-grade SAH was reflected by Hunt and Hess grades of III or IV (seven patients) and World Federation of Neurosurgical Societies grades of IV or V (four patients).

Laboratory Findings

Values for the CK-MB levels were available in six patients and were elevated in four (CK-MB reference value ≤ 6.2 ng/ml; Table 2). Troponin T levels were available in seven patients and were elevated in six (troponin T reference value ≤ 0.03 ng/ml). Troponin T levels peaked on Day 1 of SAH, with a mean peak of 1.16 ng/ml (range 0.02–5.82 ng/ml).

Cardiac Testing

The acute-phase chest x-ray film in five patients demonstrated bilateral interstitial infiltrates consistent with pulmonary edema. Electrocardiography findings obtained within 24 hours of SAH onset showed abnormalities in all eight patients. The initial electrocardiogram demonstrated sinus rhythm at a rate of 66 to 118 bpm, and six patients had T wave abnormalities. Initial echocardiograms obtained 1 to 4 days after SAH revealed reduced EF and LV wall motion abnormalities in all patients (Fig. 3). The mean initial EF was 38% (range 25–55%). The results of a repeated echocardiography study performed 5 days to 13 years after SAH demonstrated an improved EF in all eight patients (Fig. 4). The mean follow-up EF was 55% (range 40–68%). Serial echocardiography data were available in three patients during their acute SAH hospitalization and showed steady improvement from 1 to 3 weeks after the onset of hemorrhage. Only one patient underwent cardiac angiography on Day 1 after SAH, and the results were unremarkable; details on this patient have been previously published.9

Fig. 1. Photograph illustrating a tako-tsubo, a Japanese octopus catcher pot, which is strung by rope from Japanese fishing boats. Anachoresis (living in crevices and holes) is typical behavior of octopuses. Photograph by Sarah H. Lee.

Fig. 2. Illustration of the heart depicting a normal (left) and abnormal (right) cardiac contraction. After aneurysmal SAH, the cardiac contraction becomes abnormal, with apical and midventricle akinesia consistent with tako-tsubo cardiomyopathy.

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Computed Tomography Findings

Seven patients had a Fisher Grade 3 SAH on CT; and one, a Fisher Grade 2 SAH. Six patients had findings compatible with hydrocephalus on an initial CT.

Hospital Course

Seven patients required intubation—five due to pulmonary edema (Table 3). The mean duration of intubation was 7 days (range 1–26 days). All patients underwent definitive treatment of aneurysms by Day 2 after SAH. Four patients underwent aneurysm clip application; and four, endovascular coil occlusion. Vasospasm documented on transcranial Doppler ultrasonography or angiography occurred in six patients, but only four patients became symptomatic. Six patients required intravenous pressors support for a mean duration of 4 days (range 1–11 days) to augment blood pressure. Signs of cerebral infarction, which were documented on a head CT, developed in three patients. Six patients required an external ventricular drain for hydrocephalus, but only three patients ultimately required a ventriculoperitoneal shunt. The mean duration of the hospital stay was 26 days (range 11–41 days).

Patient Outcome

One patient died during hospitalization for acute SAH on Day 26, after the withdrawal of care because of a poor neurological prognosis. A second patient died at 16 months post-SAH due to recurrent metastatic lung cancer. One patient was lost to follow-up evaluation. The neurological follow up in the remaining five patients ranged from 5 months to 2 years. Functional outcome for survivors, as measured using the modified Rankin Scale, ranged from a score of 0 to 2.

Discussion

Echocardiography is infrequently performed after SAH and in most NICU practices only when cardiac injury is suspected. In the majority of these patients the echocardiogram is nondiagnostic despite changes in the ECG signal or serum troponin level or a documented episode of cardiac arrhythmia. In the present series echocardiographic data in only one of four patients demonstrated an abnormality. We noted a tako-tsubo cardiomyopathy on one third of the echocardiograms revealing an abnormality as well as subsequent improvement in the EF. We present the largest cohort of patients with tako-tsubo cardiomyopathy caused by aneurysmal SAH thus far described. In agreement with previously published data, we found a predominance for SAH-induced tako-tsubo cardiomyopathy in postmenopausal women with a poor-grade SAH. Severe ventricular dysfunction after SAH is an independent predictor of stroke from vasospasm. It is unclear whether tako-tsubo cardiomyopathy also shares this increased risk of morbidity due to vasospasm or whether it is a covariate that simply reflects a more severe neurological injury.

Subarachnoid Hemorrhage–Induced Neurogenic Stunned Myocardium

Cardiac complications after SAH are well known, and ECG abnormalities (including QTc prolongation and T wave and ST segment abnormalities) occur in 25 to 75% of patients with SAH. Patients with elevated cardiac enzymes and changes on ECG studies are more likely to manifest echocardiographic and clinical evidence of LV dysfunction. Troponin is elevated in 20% of the pa-

<table>
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* COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GCS = Glasgow Coma Scale; H&H = Hunt and Hess; HTN = hypertension; LOC = loss of consciousness; T = intubated; WFNS = World Federation of Neurosurgical Societies.

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<td>Summary of initial data obtained in eight patients with tako-tsubo cardiomyopathy*</td>
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* IVCD = intraventricular conduction delay; FU = follow up; NA = not available; TWA = T wave abnormality; WMI = wall motion index.

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Patients with SAH and is a more sensitive and specific indicator of LV dysfunction than is CK-MB. A myriad of abnormal wall motion patterns after SAH, including hypokinesis consistently involving the apex and an apex-sparing pattern of LV dysfunction, have been reported. Many of these abnormalities are reversible, and SAH-induced cardiac dysfunction has often been referred to as “neurogenic stunned myocardium.” Subarachnoid hemorrhage–induced neurogenic stunned myocardium presenting as cardiac failure with headache can be mistakenly triaged to a critical care unit as acute myocardial infarction, delaying the diagnosis of SAH. A salient feature that favors SAH-induced cardiac dysfunction over acute myocardial infarction is the presence of severely reduced EF with large regions of akinesia accompanied by only modest elevations in troponin. The LV wall motion abnormalities after SAH predominate in female patients and are accompanied by more severe hemorrhage, as measured using the Hunt and Hess Scale.

The three main theories explaining cardiac dysfunction after SAH include multivessel coronary artery spasm causing ischemia, microvascular dysfunction, and catecholamine-mediated neurogenic myocardial stunning. Excess sympathetic nervous activation occurs after SAH, with an increase in plasma norepinephrine within 48 hours that persists during the 1st week after hemorrhage. Experimental study data on SAH in animals demonstrate not only immediate enhanced sympathetic activity with higher circulating catecholamine concentrations, but also enhanced cardiac sensitivity to norepinephrine infusion. Although the exact mechanism remains unknown, animal study results demonstrating normal cardiac microvascular perfusion and the absence of coronary artery stenosis or spasm represent substantial evidence that sympathetic overactivation via hypothalamic injury is the most likely cause of cardiac injury after SAH.

Tako-Tsubo Cardiomyopathy

Most series on tako-tsubo cardiomyopathy specifically excluded patients with SAH, and the proposed diagnostic criteria for apical ballooning syndrome require the exclusion of head trauma and intracranial bleeding. The salient diagnostic features of tako-tsubo cardiomyopathy include reversible wall motion abnormalities at the LV apex and/or midventricle, extending beyond a single coronary artery distribution; T wave and ST segment abnormalities on ECG; minor elevation in cardiac markers; and the absence of significant coronary artery disease. The syndrome tends to have a favorable prognosis, with authors of most series reporting an in-hospital mortality rate of less than 1%. Rare complications have been reported, including LV apical thrombus and fatal LV rupture.

Overlap Between Neurogenic Stunned Myocardium and Tako-Tsubo Cardiomyopathy

Ako and colleagues were the first to recognize that tako-tsubo cardiomyopathy has similarities to the cardiac dysfunction seen in SAH and proposed that the two entities share a similar mechanism. The hypothetical shared mechanism of these conditions is a state of massive catecholamine release. Cardiac findings similar to those already revealed in SAH have been demonstrated in tako-tsubo cardiomyopathy, including evidence of exaggerated sympathetic activation with elevated plasma catecholamine levels, absence of coronary artery spasm, and endomyocardial biopsy showing mononuclear infiltrates and contraction band changes. This theory of sympathetic overactivation is further substantiated by the rat model of stress-induced apical ballooning in which cardiac dysfunction is prevented by pretreatment with combined αβ-adrenoceptor blockade.
TABLE 3
Treatment course in eight patients with tako-tsubo cardiomyopathy

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<tr>
<th>Case No.</th>
<th>Intubated</th>
<th>Intravenous Pressors</th>
<th>Duration of Pressor Support (days)</th>
<th>Aneurysm Location</th>
<th>Size (mm)</th>
<th>Hydrocephalus</th>
<th>Vasospasm</th>
<th>Infarct Location†</th>
<th>FU</th>
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<td>EVD, VPS</td>
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* ACA = anterior cerebral artery; ACoA = anterior communicating artery; asymp = asymptomatic; EVD = extraventricular drain; do-bu = dobutamine; dopa = dopamine; ICA = internal carotid artery; mil = milrinone; mRS = modified Rankin Scale; norepi = norepinephrine; rt = right; PCoA = posterior communicating artery; phenyl = phenylephrine; pseudo = pseudoaneurysm; symp = symptomatic; vasop = vasopressin; VPS = ventriculoperitoneal shunt.
† According to CT studies.
‡ Did not have hydrocephalus.
§ At 16 months post-SAH.
|| The right PCA aneurysm underwent coil occlusion during the acute hospitalization; the asymptomatic left PCoA aneurysm underwent surgical clip application at a later date.
** At 26 days post-SAH.

“myocytolysis” or “myofibrillar degeneration”) has been classically associated with SAH, but in experimental SAH in animals, it has been demonstrated in a model of catastrophic cerebral insult in baboons that contraction band necrosis is a distinct form of myocyte injury characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an intersitial mononuclear inflammatory response. Novitzky and colleagues demonstrated in a model of catastrophic cerebral insult in baboons that contraction band necrosis is a completely blocked using cardiac sympathectomy or cardiac denervation but not vagotomy. The crucial mediator of neurogenic cardiac injury may be the endogenous neurotransmitter norepinephrine rather than circulating catecholamines, consistent with the hypothesis that contraction band necrosis still occurs after bilateral adrenalectomy. The results of these denervation studies in baboons suggest that protecting the heart from local release of norepinephrine rather than systemic release may be the key to preventing cardiac injury. Corresponding histological changes in contraction band necrosis have been associated with not only tako-tsubo cardiomyopathy and SAH, but also a variety of other conditions such as pheochromocytoma, near-drowning, fatal status asthmaticus, fatal status epilepticus, and violent assault. Cebelin and Hirsch reported contraction band necrosis on autopsies in 11 of 15 assault victims who had died with internal injuries insufficient to explain their deaths. The unifying pathophysiological mechanism shared by these conditions is a state of sympathetic discharge.

Practical Implications
Tako-tsubo cardiomyopathy is a rare complication of aneurysmal SAH, but the potential implications for neurosurgeons primarily responsible for the care of patients with SAH are substantial. For example, in stark contrast to the favorable prognosis of cardiac wall motion abnormalities in general, tako-tsubo cardiomyopathy due to SAH is associated with prolonged intubation and pressor requirements. Later management may be further complicated when the cardiomyopathy has not resolved and symptomatic cerebral vasospasm develops. Hemodynamic augmentation, consisting of increasing intravascular volume and blood pressure parameters, may be difficult to attain. Cardiac output must be supported with dobutamine or milrinone, especially if blood pressure stays unsatisfactorily low. The use of these inodilator agents in this context requires further study.

Conclusions
Subarachnoid hemorrhage–induced neurogenic stunned myocardium involves heterogeneous LV wall motion abnormalities in patients with tako-tsubo cardiomyopathy. Although tako-tsubo cardiomyopathy carries a favorable prognosis in the general population, this pattern of cardiac dysfunction in a population with SAH was associated with pulmonary edema, prolonged intubation, and cerebral vasospasm. Its occurrence in postmenopausal women is remarkable. Tako-tsubo cardiomyopathy and neurogenic cardiac stunning are both neurally mediated processes that share an overlapping phenotype. Additional studies are warranted to better elucidate the spectrum of cardiac abnormalities unified by catecholamine excess.
Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage

Acknowledgments

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