

# Stroke

American Stroke  
Association<sup>SM</sup>

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American  
Heart Association



## **Predictors of Neurocardiogenic Injury After Subarachnoid Hemorrhage**

Poyee Tung, Alexander Kopelnik, Nader Banki, Ken Ong, Nerissa Ko, Michael T. Lawton, Daryl Gress, Barbara Drew, Elyse Foster, William Parmley and Jonathan Zaroff

*Stroke* 2004;35;548-551; originally published online Jan 22, 2004;

DOI: 10.1161/01.STR.0000114874.96688.54

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214  
Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online  
ISSN: 1524-4628

The online version of this article, along with updated information and services, is  
located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/35/2/548>

Subscriptions: Information about subscribing to Stroke is online at  
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters  
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:  
410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

# Predictors of Neurocardiogenic Injury After Subarachnoid Hemorrhage

Poyee Tung, MD; Alexander Kopelnik, MD; Nader Banki, MD; Ken Ong, MD; Nerissa Ko, MD; Michael T. Lawton, MD; Daryl Gress, MD; Barbara Drew, RN, PhD; Elyse Foster, MD; William Parmley, MD; Jonathan Zaroff, MD

**Background and Purpose**—Subarachnoid hemorrhage (SAH) frequently results in myocardial necrosis with release of cardiac enzymes. Historically, this necrosis has been attributed to coronary artery disease, coronary vasospasm, or oxygen supply-demand mismatch. Experimental evidence, however, indicates that excessive release of norepinephrine from the myocardial sympathetic nerves is the most likely cause. We hypothesized that myocardial necrosis after SAH is a neurally mediated process that is dependent on the severity of neurological injury.

**Methods**—Consecutive patients admitted with SAH were enrolled prospectively. Predictor variables reflecting demographic (age, sex, body surface area), hemodynamic (heart rate, systolic blood pressure), treatment (phenylephrine dose), and neurological (Hunt-Hess score) factors were recorded. Serial cardiac troponin I measurements and echocardiography were performed on days 1, 3, and 6 after enrollment. Troponin level was treated as a dichotomous outcome variable. We performed univariate and multivariate analyses on the relationships between the predictor variables and troponin level.

**Results**—The study included 223 patients with an average age of 54 years. Twenty percent of the subjects had troponin I levels  $>1.0 \mu\text{g/L}$  (range, 0.3 to  $50 \mu\text{g/L}$ ). By multivariate logistic regression, a Hunt-Hess score  $>2$ , female sex, larger body surface area and left ventricular mass, lower systolic blood pressure, and higher heart rate and phenylephrine dose were independent predictors of troponin elevation.

**Conclusions**—The degree of neurological injury as measured by the Hunt-Hess grade is a strong, independent predictor of myocardial necrosis after SAH. This finding supports the hypothesis that cardiac injury after SAH is a neurally mediated process. (*Stroke*. 2004;35:548-553.)

**Key Words:** heart failure, congestive ■ subarachnoid hemorrhage ■ troponin

Cardiac injury and dysfunction after subarachnoid hemorrhage (SAH) is a well-recognized phenomenon. ECG changes<sup>1,2</sup> and arrhythmias such as torsade de pointes<sup>3</sup> have been described in SAH patients. Left ventricular (LV) systolic dysfunction occurs in  $\approx 10\%$  of patients with SAH.<sup>4-6</sup> Serum elevations of cardiac enzymes<sup>7,8</sup> and pathological evidence of contraction band necrosis in heart autopsies provide evidence for the development of myocardial necrosis in SAH patients.<sup>9</sup> One prior study showed that 17% of SAH patients develop elevated serum levels of cardiac troponin I (cTI).<sup>10</sup>

The pathophysiology of cardiac injury after SAH remains controversial. Historically, coronary artery disease (CAD) and coronary vasospasm have been proposed as possible mechanisms.<sup>11,12</sup> However, some SAH patients have ECG and echocardiographic findings suggestive of myocardial infarction without angiographic evidence of CAD or vasospasm.<sup>13,14</sup> Another possible cause is myocardial ischemia secondary to excessive tachycardia and/or hypertension.

## See Editorial Comment, page 552

The most likely cause of cardiac dysfunction after SAH, however, is excessive catecholamine release within the myocardium.<sup>15</sup> The “catecholamine hypothesis” is supported by extensive research in animal models that demonstrated that experimental SAH or stimulation of cortical areas may result in excessive myocardial catecholamine release, ECG abnormalities, and contraction band necrosis.<sup>9,16-18</sup> The catecholamine hypothesis is also supported by the finding of patterns of LV wall motion abnormalities in SAH patients that are atypical of CAD but may correlate with the distribution of myocardial sympathetic nerve terminals.<sup>19</sup>

The hypothesis of the present study is that cardiac injury after SAH is a neurally mediated process that can be predicted by the severity of neurological injury, independent of hemodynamic and other clinical factors. In a prospective cohort study of SAH patients, we sought to determine the clinical predictors of myocardial necrosis as measured by serum levels of cTI.

Received August 25, 2003; final revision received October 1, 2003; accepted October 30, 2003.

From the Division of Cardiology (P.T., A.K., N.B., E.F., W.P., J.Z.), Division of Neuroradiology (K.O., N.K.), Department of Neurology (D.G.), Department of Neurological Surgery (M.T.L.), and Division of Physiological Nursing (B.D.), UCSF Medical Center, San Francisco, Calif.

Reprint requests to Jonathan Zaroff, MD, 505 Parnassus Ave, Moffitt Suite 1177, San Francisco, CA 94117-0124. E-mail Zaroff@medicine.ucsf.edu  
© 2004 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000114874.96688.54

**Materials and Methods**

From January 2000 to March 2002, the study enrolled consecutive patients admitted to the Neurological Intensive Care Unit. Inclusion criteria for the study were age >21 years and confirmed diagnosis of SAH by CT of the head or lumbar puncture. Patients were excluded if they had history of myocardial infarction, cardiomyopathy, or congestive heart failure.

The study protocol was approved by the UCSF Committee on Human Research, and informed consent was obtained from each patient or an appropriate designee. Study procedures were in accordance with institutional guidelines.

After enrollment, demographic and clinical data were collected from patient and family interviews and inspection of medical records. These data included age, sex, body surface area, history of CAD, and risk factors for CAD. The severity of neurological injury was graded using each subject’s admission Hunt-Hess score, defined as follows: 1=asymptomatic or mild headache and slight nuchal rigidity, 2=cranial nerve palsy, moderate to severe headache, or nuchal rigidity, 3=mild focal deficit, lethargy, or confusion, 4=stupor, moderate to severe hemiparesis, or early decerebrate rigidity, and 5=deep coma, decerebrate rigidity, or moribund appearance.

Each subject was assessed on 3 study days: the day of enrollment and 2 and 6 days after enrollment. On each study day, serum specimens were collected for measurement of cTI, and echocardiography was performed. The time in days from SAH symptom onset to measurement of cTI was recorded. Heart rate, systolic blood pressure (SBP), and dose of phenylephrine infused during echocardiography were recorded. Phenylephrine is frequently used at UCSF Medical Center to help prevent and treat cerebral vasospasm after SAH. In a subgroup of 50 study subjects, serum was collected as soon as possible after enrollment, and these banked specimens were later used for measurement of epinephrine and norepinephrine levels.

Two-dimensional transthoracic echocardiography was performed with an Acuson Sequoia 6.0 ultrasound system. The following echocardiographic images were obtained: parasternal long axis; parasternal short axis at the level of the mitral valve, papillary muscles, and apex; apical 2, 3, and 4-chamber views; subcostal long axis; and subcostal short axis at the level of the mitral valve, papillary muscles, and apex. For suboptimal studies, intravenous Optison contrast was administered to enhance visualization of the LV endocardium. LV ejection fraction (LVEF) and LV mass index (LVMI) were measured offline by a blinded observer using the biplane Simpson’s method of discs and the truncated ellipse method, respectively,<sup>20</sup> and commercially available software (ProSolv).

cTI was measured with a fluorescent enzyme immunoassay (Abbot Diagnostics). The lowest detectable level was 0.3 µg/L. The distribution of peak cTI levels was markedly skewed to the right (mean, 2.3 µg/L; median, 0.3 µg/L) with 66% of subjects having only normal levels (0.3 µg/L) and the remaining subjects having peak cTI levels ranging from 0.4 to 50 µg/L. For this reason, the level of cTI was treated as a dichotomous outcome variable with a value >1.0 µg/L considered abnormal for the primary analysis. A secondary analysis was performed with a cTI cutoff value of >0.3 µg/L. Serum levels of norepinephrine and epinephrine were measured with a competitive enzyme-linked immunosorbent assay (Alco Diagnostics).

Univariate and multivariate logistic regression was performed to quantify the relationships between the clinical and hemodynamic predictor variables and the level of cTI (STATA Software). Longitudinal data analysis was used to account for repeated measurements. A significant probability value was defined as *P*≤0.05.

**Results**

The study included 223 subjects. As shown in Table 1, the mean age of the 223 study subjects was 54 years, and 68% were women, a typical sex distribution for SAH. Hypertension and smoking were more common relative to other risk factors for CAD. The study group consisted of the full range

**TABLE 1. Clinical Characteristics**

Patients, n	223
Age (mean±SD), y	54±14
Female sex, n (%)	151 (68)
Body surface area (mean±SD), m <sup>2</sup>	1.8±0.2
Admission Hunt-Hess grade, n (%)	
I	80 (36)
II	33 (15)
III	60 (27)
IV	35 (16)
V	14 (6)
Risk factors for CAD, n (%)	
History of hypertension	92 (41)
History of diabetes	20 (9)
History of hyperlipidemia	26 (12)
History of smoking	96 (43)
Family history of CAD	29 (13)
History of amphetamine/cocaine use	26 (12)
History of CAD, n (%)	12 (5)

of SAH severity, with a mean±SD Hunt-Hess grade of 2.4±1.3.

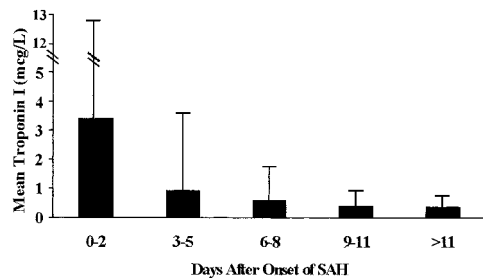
Hemodynamic and echocardiographic data are summarized in Table 2. The mean peak SBP over the 3 study days was 167 mm Hg, consistent with moderate systolic hypertension. The subjects’ LVEF ranged from 17% to 92%. The mean initial LVMI was 95 g/m<sup>2</sup> (92 g/m<sup>2</sup> for women, 99 g/m<sup>2</sup> for men), consistent with mild LV hypertrophy. Forty-nine percent of patients were receiving a phenylephrine infusion during at least 1 of the study echocardiograms with a mean peak dose of 107 µg/L. In the 50 subjects with banked serum available for catecholamine measurement, the mean level of norepinephrine was 694 pg/mL (SD, 698 pg/mL; median, 371 pg/mL; range, 50 to 3892 pg/mL) and the mean level of epinephrine was 85 pg/mL (SD, 63 pg/mL; median, 64 pg/mL; range, 9 to 291 pg/mL).

The peak cTI level was >1.0 µg/L in 43 of the 223 study subjects (20%). Repeated cTI measurements from all study days were used in the longitudinal analysis, and the mean cTI level was 1.2 µg/L (SD, 4.7 µg/L), with a median of 0.3 µg/L and a range of 0.3 to 50 µg/L. An inverse relationship was observed between the mean level of cTI among subjects and the time after onset of SAH symptoms (Figure 1).

The univariate relationships between the predictor variables and cTI release, as determined by logistic regression

**TABLE 2. Hemodynamic and Echocardiographic Data**

Variable	Mean±SD	Median
Peak SBP, mm Hg	167±26	166
Peak heart rate, bpm	90±20	86
Peak phenylephrine dose, µg · kg <sup>-1</sup> · min <sup>-1</sup>	107±164	0
Lowest LVEF, %	62±13	64
Initial LVMI, g/m <sup>2</sup>	94±23	94

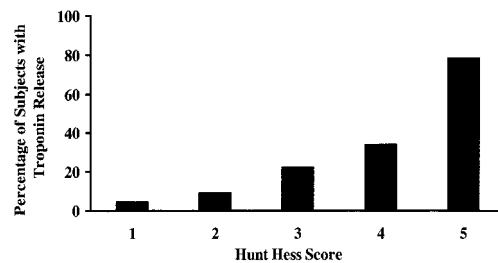


**Figure 1.** Mean level of cTI for study subjects grouped by number of days between onset of SAH symptoms and cTI measurement. Error bars indicate SD of cTI levels.

with longitudinal data analysis, are shown in Table 3. A Hunt-Hess grade of  $\geq 3$ , female sex, higher heart rates, lower SBPs, higher doses of phenylephrine, and shorter time from SAH symptom onset were all significant predictors of cTI release. A history of CAD and risk factors for CAD were not predictive of cTI release (data not shown). A lower LVEF was strongly associated with cTI release ( $P < 0.001$ ; odds ratio [OR], 1.07 per single-point decrease in LVEF; 95% confidence interval [CI], 1.04 to 1.09). There was no significant association between serum levels of either norepinephrine (OR, 1.00;  $P = 0.653$ ) or epinephrine (OR, 0.99;  $P = 0.505$ ) and cTI release.

After statistical adjustment by multivariate logistic regression with longitudinal data analysis, a Hunt-Hess grade of  $\geq 3$  was highly predictive of cTI release (Table 3). A strong relationship was observed between increasing Hunt-Hess grade and cTI release (Figure 2). Other independent predictors of cTI release included female sex, larger body surface area and LVMI, higher heart rate and phenylephrine dose, lower SBP, and a shorter time from SAH symptom onset. A multivariate model that defined a cTI level of  $>0.3 \mu\text{g/L}$  as abnormal produced similar results with 2 exceptions: age was a significant predictor (OR, 1.73 per 10-year increase;  $P = 0.012$ ), and LVMI was not (OR, 1.17;  $P = 0.384$ ).

As shown in Table 3, female sex was associated with an adjusted OR of 35.0 ( $P = 0.009$ ) for cTI release. As shown in Table 4, the observed sex effect was due primarily to lower risk of cTI release in older men because 0 of the 32 men  $>50$  years of age had cTI release as opposed to 6 of the 39 men



**Figure 2.** Percentage of subjects with cTI release for study subjects grouped by admission Hunt-Hess grade.

$\leq 50$  years old ( $\chi^2$ ,  $P = 0.031$ ). There was no significant difference in the probability of cTI release in women  $>50$  compared with those  $\leq 50$  years of age ( $\chi^2$ ,  $P = 0.25$ ).

As shown in Table 3, there was a 48% decrease in the risk of cTI release for every 20-mm Hg increase in SBP. The relationship between lower SBP and cTI release was minimally affected by the addition of LVEF to the multivariate model (adjusted OR, 0.60 per 20-mm Hg increase in SBP;  $P = 0.073$ ). There were no interactions in the multivariate model of statistical significance that affected the predictor variables.

## Discussion

The present study demonstrates that 20% of patients with SAH develop cTI  $>1.0 \mu\text{g/L}$ , a result that is consistent with prior reports.<sup>21,22</sup> The larger sample size of the present study (223 subjects) allowed unique exploration of the risk factors for the development of myocardial necrosis after SAH.

An incremental and independent relationship was observed between the Hunt-Hess grade, which is widely used in assessing the severity of neurological injury after SAH, and the probability of cTI release. This finding is consistent with a previous study by Parekh et al<sup>22</sup> that showed that patients with more severe grades of SAH had a higher incidence of cTI release. The results of these studies indicate that the severity of neurological injury is strongly related to myocardial necrosis and support the hypothesis that SAH-associated heart damage is a form of neurocardiogenic injury.

It is well-recognized that high sympathetic tone and elevated circulating levels of catecholamines may occur after

**TABLE 3. Determinants of Myocardial Necrosis**

Predictors	Univariate			Multivariate		
	OR	P	95% CI	OR	P	95% CI
Age (per 10-y increase)	1.16	0.262	0.90–1.49	1.54	0.112	0.90–2.62
Female (vs male) sex	2.98	0.019	1.20–7.43	34.96	0.009	2.47–495.01
Body surface area (per 0.2-m <sup>2</sup> increase)	1.03	0.847	0.78–1.36	2.20	0.025	1.11–4.39
Hunt-Hess $>2$ (vs 1–2)	8.47	$<0.001$	3.43–20.92	6.62	0.026	1.25–34.82
SBP (per 20-mm Hg increase)	0.78	0.019	0.64–0.96	0.52	0.007	0.32–0.83
Heart rate (per 10-bpm increase)	1.26	0.001	1.10–1.43	1.61	0.005	1.16–2.25
Phenylephrine dose (per 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increase)	1.17	$<0.001$	1.07–1.28	1.47	0.010	1.10–1.98
LVMI (per 20-g/m <sup>2</sup> increase)	1.23	0.083	0.97–1.55	1.74	0.032	1.05–2.89
SAH to cTI* (per 1-d increase)	0.86	0.001	0.78–0.94	0.70	0.008	0.54–0.91

\*Time from SAH symptom onset to measurement of cTI.

TABLE 4. Age, Sex, and cTI Release

	Subjects with cTI Release, n (%)					
	Age <30 y	Age 31–40 y	Age 41–50 y	Age 51–60 y	Age 61–70 y	Age >70 y
Women (n=149)	1 (33.3)	3 (23.1)	3 (11.5)	13 (25.5)	12 (35.3)	5 (22.7)
Men (n=71)	2 (25.0)	1 (12.5)	3 (13.0)	0	0	0

head injury and particularly after SAH.<sup>23,24</sup> Previous studies indicate that serum levels of catecholamines correlate with the severity of neurological injury and neurological outcome.<sup>18</sup> However, animal models indicate that the direct release of toxic levels of catecholamines into the myocardium by the cardiac sympathetic nerve terminals is a more likely cause of neurocardiogenic injury than is adrenal release of catecholamines into the systemic circulation.<sup>25</sup> Higher Hunt-Hess grades indicate greater neurological injury and thus may be associated with a greater degree of sympathetic outflow to the heart. Such an association would explain the finding in the present study that higher Hunt-Hess grades, as opposed to serum levels of catecholamines, predict myocardial necrosis.

In the present study, higher phenylephrine doses, lower SBP, and higher heart rate were independent predictors of cTI release. These data were minimally affected by the addition of LVEF to the multivariate model, suggesting that the results are only partially confounded by worsening systolic function of the LV, which was associated with cTI release and could conceivably result in a lower SBP and/or a need for greater pressor doses to maintain SBP. An elevated LVMI was a multivariate predictor of cTI release, possibly because of increased myocardial oxygen demand in patients with LV hypertrophy. Taken together, the hemodynamic and echocardiographic data suggest that cTI release may, in some cases, be due to the combination of LV hypertrophy and hemodynamic factors. The multifactorial nature of cTI release is also illustrated by the increase in ORs after statistical adjustment (negative confounding) that was observed for some of the predictor variables, most notably sex and body surface area.

The multivariate model indicates that the higher risk of cTI release observed in patients treated with higher doses of phenylephrine is not mediated by higher SBP. Coronary vasospasm represents a possible mechanism for phenylephrine-induced myocardial necrosis although epicardial coronary vasospasm has not been reported in humans. Furthermore, experimental evidence suggests that microvascular ischemia is not required for SAH-induced cardiac injury.<sup>26</sup> The results of the present study are in contrast with previous data demonstrating that high-dose phenylephrine use in SAH patients was associated with a low incidence of creatine phosphokinase-MB fraction elevation and no change in cardiac index despite increased afterload.<sup>27</sup> These differences may be due to the higher sensitivity of cTI than creatine phosphokinase-MB for detecting myocardial necrosis. In addition, the larger sample size of the present study increased the power to detect a smaller effect of phenylephrine dose on cTI release.

The reduced incidence of myocardial necrosis among older men in the present study was an unexpected finding. Although it has been reported that younger women have higher

short-term mortality after acute myocardial infarction and after coronary artery bypass grafting,<sup>28–31</sup> sex effects have not previously been observed in experimental or clinical models of neurocardiogenic injury. Estrogen status in the pathogenesis of CAD is a subject of much controversy, given that hormonal replacement may have both adverse proinflammatory properties<sup>32</sup> and beneficial sympathetic inhibitory effects.<sup>33</sup> However, in the present study, the incidence of cTI release did not vary significantly by age among women. Further research is required to explore sex differences after neurocardiogenic injury.

In conclusion, the present study demonstrates that the degree of neurological injury is a strong predictor of myocardial necrosis after SAH, even after adjustment for clinical and hemodynamic factors. These findings support a neurocardiogenic cause of cardiac injury and dysfunction after SAH.

### Acknowledgment

This study was supported by NIH/NHLBI 1 K23 HL04054-01 (principal investigator, Dr Zaroff)

### References

- Rudehill A, Olsson GL, Sundqvist K, Gordon E. ECG abnormalities in patients with subarachnoid haemorrhage and intracranial tumours. *J Neurol Neurosurg Psychiatry*. 1987;50:1375–1381.
- Zaroff J, Rordorf G, Newell J, Ogilvy C, Levinson J. Cardiac outcome in patients with subarachnoid hemorrhage and electrocardiographic abnormalities. *Neurosurgery*. 1999;44:34–39.
- Andreoli A, di Pasquale G, Pinelli G, Grazi P, Tognetti F, Testa C. Subarachnoid hemorrhage: frequency and severity of cardiac arrhythmias. *Stroke*. 1987;18:558–564.
- Kuroiwa T, Morita H, Tanabe H, Ohta T. Significance of ST segment elevation in electrocardiograms in patients with ruptured cerebral aneurysms. *Acta Neurochir (Wien)*. 1995;133:141–146.
- Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. *J Am Coll Cardiol*. 1994;24:636–640.
- Davies KR, Gelb AW, Manninen PH, Boughner DR, Bisnaire D. Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities. *Br J Anaesth*. 1991;67:58–63.
- Fabinyi G, Hunt D, McKinley L. Myocardial creatine kinase isoenzyme in serum after subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 1977;40:818–820.
- Norris JW, Hachinski VC, Myers MG, Callow J, Wong T, Moore RW. Serum cardiac enzymes in stroke. *Stroke*. 1979;10:548–553.
- Doshi R, Neil-Dwyer G. Hypothalamic and myocardial lesions after subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 1977;40:821–826.
- Horowitz MB, Willet D, Keffer J. The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 1998;140:87–93.
- Yuki K, Kodama Y, Onda J, Emoto K, Morimoto T, Uozumi T. Coronary vasospasm following subarachnoid hemorrhage as a cause of stunned myocardium: case report. *J Neurosurg*. 1991;75:308–311.

12. Toyama T, Tanaka H, Nuruki K, Shirao T. Prinzmetal's variant angina associated with subarachnoid hemorrhage: a case report. *Angiology*. 1979;30:211–218.
13. Samuels MA. Neurogenic heart disease: a unifying hypothesis. *Am J Cardiol*. 1987;60:15J–19J.
14. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. *J Am Coll Cardiol*. 1994;24:636–640.
15. Kantor HL, Krishnan SC. Cardiac problems in patients with neurologic disease. *Cardiol Clin*. 1995;13:179–208.
16. Oppenheimer S, Wilson J, Guiraudon C, Cechetto D. Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? *Brain Res*. 1991;550:115–121.
17. Hachinski VC, Smith KE, Silver MD, Gibson CJ, Ciriello J. Acute myocardial and plasma catecholamine changes in experimental stroke. *Stroke*. 1986;17:387–390.
18. Woolf PD, Hamill RW, Lee LA, Cox C, McDonald JV. The predictive value of catecholamines in assessing outcome in traumatic brain injury. *J Neurosurg*. 1987;66:875–882.
19. Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. *J Am Soc Echocardiogr*. 2000;13:774–779.
20. Schiller N, Shah P, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358–367.
21. Horowitz MB, Willet D, Keffer J. The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 1998;140:87–93.
22. Parekh N, Venkatesh B, Cross D, Leditschke A, Atherton J, Miles W, Winning A, Clague A, Rickard C. Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. *J Am Coll Cardiol*. 2000;36:1328–1335.
23. Lambert G, Naredi S, Eden E, Rydenhag B, Friberg P. Sympathetic nervous activation following subarachnoid hemorrhage: Influence of intravenous clonidine. *Acta Anaesthesiol Scand*. 2002;46:160–165.
24. Naredi S, Lambert G, Eden E, Zall S, Runnerstam M, Rydenhag B, Friberg P. Increased sympathetic nervous activity in patients with non-traumatic subarachnoid hemorrhage. *Stroke*. 2000;31:901–906.
25. Mertes P, Carreau J, Jaboin Y, Pinelli G, el Abassi K, Dopff C, Atkinson J, Villemot J, Burlet C, Boulange M. Estimation of myocardial interstitial norepinephrine release after brain death using cardiac microdialysis. *Transplantation*. 1994;57:371–377.
26. Zaroff JG, Rordorf GA, Titus JS, Newell JB, Nowak NJ, Torchiana DF, Aretz HT, Picard MH, Macdonald RL. Regional myocardial perfusion after experimental subarachnoid hemorrhage. *Stroke*. 2000;31:1136–1143.
27. Miller JA, Dacey RG Jr, Diringner MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. *Stroke*. 1995;26:2260–2266.
28. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction: National Registry of Myocardial Infarction 2 Participants. *N Engl J Med*. 1999;341:217–225.
29. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: Evidence for a higher mortality in younger women. *Circulation*. 2002;105:1176–1181.
30. MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, Finlayson A, Redpath A, Gilmour H, McMurray JJ. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol*. 2001;38:729–735.
31. Losordo DW, Kearney M, Kim EA, Jekanowski J, Isner JM. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. *Circulation*. 1994;89:1501–1510.
32. Ayanian JZ. Increased mortality among middle-aged women after myocardial infarction: searching for mechanisms and solutions. *Ann Intern Med*. 2001;134:239–241.
33. Vongpatanasin W, Tuncel M, Mansour Y, Arbique D, Victor RG. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation*. 2001;103:2903–2908.

## Editorial Comment

### Myocardial Damage in Patients With Subarachnoid Hemorrhage

Cardiac effects of intracranial hemorrhage were initially described in 1903 by Cushing, who noted alterations in blood pressure and cardiac rhythm in such patients.<sup>1</sup> However, since ECG was not available at that time, it was not until 1947 that Byer et al described ECG changes in a patient with subarachnoid hemorrhage (SAH).<sup>2</sup> Later, a series of experiments described the effect of hypothalamic stimulation on ECG morphology and rhythm indicating that myocardial damage need not be present for ECG changes to occur.<sup>3,4</sup> Indeed, some form of ECG changes are noted in almost all patients with SAH.<sup>5</sup> Up to 10% of the patients with SAH are noted to have a potentially lethal arrhythmia such as ventricular tachycardia and fibrillation, and it has been suggested that this may account for some of the mortality in patients not reaching medical care with SAH.

A series of autopsy studies in patients with SAH demonstrated petechial subendocardial hemorrhage, and histologically, myocardial cell cytoplasm with dense eosinophilic transverse bands.<sup>6,7</sup> This occurred not only in patients with SAH with ECG changes but also in those without such

changes. Similar lesions could be created in experimental animals by stimulation of the stellate ganglion and infusion of catecholamines, and clinically this was seen in patients with a pheochromocytoma.<sup>8–10</sup> Such evidence suggests that myocardial damage in patients with SAH is likely an effect of increased catecholamines on the myocardial cells rather than due to preexisting coronary artery disease. Increase in catecholamine level can be significant, and experimentally up to a 30-fold increase in plasma concentration is noted within 5 minutes after SAH induction in dogs.<sup>11</sup> However, it is not clear if it is increased plasma catecholamine, locally released catecholamine, or both that lead to the pattern of myocardial necrosis seen in SAH patients.

In our patients, myocardial necrosis is reflected by enzyme release such as CPK-MB and troponin I. Recent studies indicate that ≈40% of patients with SAH demonstrate increased serum markers for myocardial necrosis. Presumably, these are the patients in whom characteristic histological lesions are seen. However, since ECG changes in SAH are largely neurally mediated and myocardial lesions tend to be

small and patchy, elevated enzymes can occur in the absence of ECG changes. On the other hand, functional testing of the heart, such as by echocardiogram, is a more accurate method to assess the effect of SAH on ventricular function, and using this method approximately 10% of patients with SAH demonstrate left ventricular (LV) wall motion abnormalities; a subset of these patients will have irreversible myocardial damage, but most regain LV function in several weeks.

The article by Tung et al<sup>12</sup> confirms that a commonly and widely used neurological grade on admission predicts myocardial damage as measured by cardiac enzyme release. This study is notable in that it consists of a large number of consecutive patients from a single center, minimizing potential bias seen in multicenter studies. Unlike some of the previous reports, this report did not demonstrate catecholamine level to be related to the degree of cardiac enzyme release. However, the number of subjects considered for this analysis was small (50 of 233), and sample collection took place at a considerable time interval after the onset of a bleed, which will affect the catecholamine levels.

Tung et al also confirm the importance of gender in myocardial injury seen in patients with SAH. This was suggested by Mayer et al, who showed abnormal LV function to be more common in women with SAH, and by Sato et al, who demonstrated that women tended to have LV wall motion abnormalities more frequently compared with men.<sup>13,14</sup> The reasons for this are unclear. Lambert et al demonstrated higher catecholamine spillover from cerebrospinal fluid to plasma in women after SAH, indicating that the catecholamine release may be different for men and women.<sup>15</sup> There are also known to be differences between the autonomic nervous systems of men and women, possibly contributing to a difference in sympathetic nervous activation in women with SAH compared to men.<sup>16,17</sup>

Tung et al noted that increased heart rate and ventricular mass were independent predictors of myocardial enzyme release, suggesting that increased oxygen demand in patients with SAH is associated with myocardial damage. Additionally, phenylephrine dose was independently associated with myocardial enzyme release, suggesting that it either caused reduced oxygen delivery to the myocardial tissue or acted synergistically with existing catecholamines to increase the myocardial damage.

As indicated by Tung et al, the causal factors for myocardial damage in patients with SAH are many and include not only aspects of autonomic nervous function and the effect of catecholamines but also factors affecting myocardial oxygen demand and the effect of medications administered in the

course of treatment. It is with studies such as this one by Tung et al that we hope to gain knowledge to potentially reduce mortality from cardiac causes in patients with SAH.

**Shunichi Homma, MD, Guest Editor**  
**Cairistine Grahame-Clarke, MRCP, PhD, Guest Editor**  
*Division of Cardiology*  
*Columbia University College of Physicians & Surgeons*  
*New York, NY*

## References

1. Cushing H. The blood pressure reaction of acute cerebral compression illustrated by cases of intracranial hemorrhage. *Am J Med Sci.* 1903;125:1017–1044.
2. Byer E, Ashman R, Toth LA. Electrocardiograms with large, upright and long qt-intervals. *Am Heart J.* 1947;33:796–806.
3. Weinberg SJ, Fuster JM. Electrocardiographic changes produced by localized hypothalamic stimulations. *Ann Intern Med.* 1960;53:332–341.
4. Attar HJ, Gutierrez MT, Bellet S, Ravens JR. Effects of stimulation of hypothalamic and reticular activating systems on production of cardiac arrhythmia. *Circ Res.* 1963;12:14–21.
5. Davis TP, Alexander J, Lesch M. Electrocardiographic changes associated with acute cerebrovascular disease: a clinical review. *Prog Cardiovasc Dis.* 1993;36:245–260.
6. Koskelo P, Punsar S, Sipilae W. Subendocardial hemorrhage and ECG changes in intracranial bleeding. *Br Med J.* 1964;5396:1479–1480.
7. Greenhoot JH, Reichenbach DD. Cardiac injury and subarachnoid hemorrhage: a clinical, pathological and physiological correlation. *J Neurosurg.* 1969;30:521–531.
8. Kaye MP, McDonald RH, Randall WC. Systolic hypertension and subendocardial hemorrhages produced by electrical stimulation of the stellate ganglion. *Circ Res.* 1961;9:1164–1170.
9. Todd GL, Baroldi G, Pieper GM, Clayton FC, Eliot RS. Experimental catecholamine-induced myocardial necrosis, I: morphology, quantification and regional distribution of acute contraction band lesions. *J Mol Cell Cardiol.* 1985;17:317–338.
10. Baroldi G, Mittleman RW, Parolini M, Silver MD, Fineschi V. Myocardial contraction bands: definition, quantification and significance in forensic pathology. *Int J Legal Med.* 2001;115:142–151.
11. Masuda T, Sato K, Yamamoto S, Matsuyama N, Shimohama T, Matsunaga A, Obuchi S, Shiba Y, Shimizu S, Izumi T. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. *Stroke.* 2002;33:1671–1676.
12. Tung P, Kopelnik A, Banki N, Ong K, Ko N, Lawton MT, Gress D, Drew B, Foster E, Parmley W, Zaroff J. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke.* 2004;35:548–553.
13. Mayer SA, Lin J, Homma S, Solomon RA, Lennihan L, Sherman D, Fink ME, Beckford A, Klebanoff LM. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. *Stroke.* 1999;30:780–786.
14. Sato K, Masuda T, Izumi T. Subarachnoid hemorrhage and myocardial damage clinical and experimental studies. *Jpn Heart J.* 1999;40:683–701.
15. Lambert G, Naredi S, Eden E, Rydenhag B, Friberg P. Monoamine metabolism and sympathetic nervous activation following subarachnoid haemorrhage: influence of gender and hydrocephalus. *Brain Res Bull.* 2002;58:77–82.
16. Dart AM, Du XJ, Kingwell BA. Gender, sex hormones and autonomic nervous control of the cardiovascular system. *Cardiovasc Res.* 2002;53:678–687.
17. Sevre K, Lefrandt JD, Nordby G, Os I, Mulder M, Gans ROB, Rostrup M, Smit AJ. Autonomic function in hypertensive and normotensive subjects: the importance of gender. *Hypertension.* 2001;37:1351–1356.