

Cardiac troponin I elevation in subarachnoid hemorrhage: Should we worry?

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Cardiac Troponin Elevation, Cardiovascular Morbidity, and Outcome After Subarachnoid Hemorrhage

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Aim of the study

The objective of this study was to determine the prognostic significance and clinical impact of acute elevation of cardiac troponin I (cTNI) after subarachnoid hemorrhage (SAH); examining in-hospital complications and follow-up assessment as variables.

Patients and methods

Naidech and coworkers report on a prospective study of 253 SAH patients who underwent serial cTNI measurements for clinical or ECG signs of potential cardiac injury. These patients were selected from a cohort of 441 subjects enrolled in the Columbia University SAH Outcomes Project between November 1998 and October 2002. The diagnosis of SAH was established by CT scan or by xanthochromia of the cerebrospinal fluid if the CT was nondiagnostic. Patients with spontaneous aneurysmal and nonaneurysmal SAH were included in the study.

Those with SAH resulting from trauma, AV malformations, and other secondary causes were excluded, as were patients less than 18 years old and those admitted after 14 days since the hemorrhage.

All patients had an ECG on admission and had at least one cTNI measurements. When the first cTNI level was abnormal ($>0.3\mu\text{g/L}$ in their laboratory), daily serial measurements were obtained as clinically indicated, and a transthoracic echocardiogram was performed. When more than one cTNI measurement was obtained on any calendar day, the highest level was analyzed.

The calendar day of SAH onset was referred to as SAH day 0. Details about symptoms at the onset of hemorrhage, admission Glasgow Coma Scale, Hunt-Hess grade, Hijdra SAH CT score, and other clinical and laboratory findings were recorded. To evaluate acute physiological dysfunction, they calculated the SAH Physiological Derangement Score (oxygenation, serum bicarbonate, glucose level and blood pressure abnormalities; where 0=best, 8=worst).

Length of stay and significant complications that occurred were recorded at the completion of each patient's hospitalization. Delayed cerebral ischemia resulting from vasospasm was defined as delayed clinical deterioration, cerebral infarction, or both after other possible causes were excluded. Pulmonary edema was defined as the development of ≥ 2 characteristic clinical findings (pulmonary infiltrates on chest radiography, hypoxemia $\text{PO}_2/\text{FiO}_2 < 300$, and rales).

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Outcome was assessed with the modified Rankin Scale (MRS) at SAH day 14 (or discharge if earlier) and at 3 months by telephone or in-person interview of the patients and informants. Poor outcome was defined as severe functional disability or death (MRS, 4 to 6).

To determine whether the relationship between peak cTNI level and 3-month outcome was independent of initial hemorrhage severity, this relationship was examined after controlling for age, admission Hunt-Hess grade, and aneurysm size in millimeters, which are the 3 most consistently identified admission predictors of mortality and disability. Significance was judged at values of $p < 0.05$.

Results

Baseline characteristics of the study cohort included: age 55 ± 14 years, 72% females, 64% with hypertension and 4% of patients with history of heart disease. The majority of subjects were admitted with a mean Hunt-Hess grade of III (lethargy or confusion), a SAH mean sum score of 17 (0-30), and a mean SAH Physiological Derangement Score of 2 (0-8).

Of those who had cTNI measured, 174 patients (69%) had an abnormal admission ECG, 172 (68%) had detectable cTNI elevations, and 130 (51%) underwent echocardiography, which revealed abnormal LV wall motion in 55 patients (22%).

cTNI was first measured on the day of hemorrhage onset (SAH day 0) in 24% of patients ($n=61$), on day 1 in 36% ($n=92$), on day 2 in 11% ($n=28$), and on day 3 or later in 29% ($n=72$). In 80% of the patients ($n=200$), the first cTNI measurement was the highest; the median interval between hemorrhage onset and peak cTNI was 1.7 days; no patient had a peak cTNI level detected after hospital day 3. Thirty-two percent of tested patients ($n=81$) had no detectable cTNI; those with elevations were classified as >0 to $0.5 \mu\text{g/L}$ ($n=46$, 18%), >0.5 to $2.0 \mu\text{g/L}$ ($n=46$, 18%), >2.0 to $10.0 \mu\text{g/L}$ ($n=34$, 14%), and $>10.0 \mu\text{g/L}$ ($n=46$, 18%). Only 2 of the 172 patients with cTNI elevation had normal clinical examination, echocardiogram, and serial ECG's.

Admission clinical and radiographic variables predictive of increased peak cTNI levels included higher Hunt-Hess grade, intraventricular hemorrhage or global cerebral edema on admission CT, loss of consciousness at ictus, more severe physiological derangement, and an abnormal admission ECG. There was no association between peak cTNI and age, gender, extent of SAH, aneurysm location, or history of hypertension or cardiac disease.

Peak cTNI level was significantly associated with an increased risk of abnormal LV wall motion on echocardiography, pulmonary edema, hypotension treated with pressors, delayed cerebral ischemia (DCI) from vasospasm, and cerebral infarction from any cause. With peak cTNI levels $>0.5 \mu\text{g/L}$, the risk of DCI exceeded 50%; with levels $>2.0 \mu\text{g/L}$, the risk of pulmonary edema exceeded 30%; and with levels $>10.0 \mu\text{g/L}$, the risk of developing hypotension exceeded 40%.

Three month outcome data were available in 180 patients (71%); in another 50 patients (20%), the day 14 or discharge MRS score was available. Overall, 30% of patients were dead, 21% were severely disabled (MRS, 4 to 5), 40% were mildly to moderate disabled (MRS, 2 to 4), and 19% had no disability (MRS, 0 to 1) at 3 months. Quintile of cTNI elevation was significantly associated with an increased likelihood of death and death or severe disability at 3 months. After correction for admission Hunt-Hess grade, age, and aneurysm size, quintile of peak cTNI remained associated with death or severe disability at discharge (odds ratio, 1.4 per quintile; 95% CI, 1.1 to 1.9; $p=0.02$) but was no longer associated with these outcomes at 3 months (OR 1.2; 95% CI, 0.9 to 1.6; $p=0.20$). Among those who survived to hospital discharge, quintile of peak cTNI was also associated with increased hospital length of stay (mean 22.9 days; $p=0.01$).

In order to determine the extent to which these findings reflected a neurogenic mechanism of myocardial injury, Naidech and coworkers repeated all analyses after excluding patients with a known history of heart disease of any type ($n=10$). All significant associations identified in the primary analysis retained their significance.

Conclusions

These investigators concluded that cTNI measurements after SAH have prognostic significance, particularly with regard to the risk of cardiovascular complications and DCI. Peak cTNI levels were predictive of an increased risk of hypotension treated with vasopressors, pulmonary edema, LV systolic dysfunction on echocardiography, and DCI from vasospasm. Peak cTNI levels were also associated with an increased risk of death or severe disability at discharge after controlling for other important determinants of outcome.

Commentary

SAH is a neurological and a systemic disease with a high incidence of serious, and potentially life-threaten-

ing cardiopulmonary abnormalities [1]. Aneurysmal SAH occurs at an estimated rate of 2 to 22.5 per 100,000 populations. In North America this translates into approximately 30,000 affected persons per year. The fatality rate of patients with SAH is approximately 50%, and another 10-20% of patients remain dependent and require help with daily activities [2,3]. In addition to neurological signs and symptoms, ECG abnormalities unexplained by pre-existing coronary artery disease are frequently reported in these patients [4]. These abnormalities are often unrecognized or misinterpreted, potentially placing the patient at risk for inappropriate management [4,5].

The connection between the central nervous system and the heart was first described by Cushing at the turn of the previous century. Cardiac abnormalities were described thereafter, associated with various CNS diseases. There are various proposed mechanisms for which the CNS directly and indirectly affects cardiac function including a complex network of cortical and subcortical neural systems in the telencephalon, diencephalon, pons, and medulla provides autonomic nervous system control [6]. Some authors have postulated that cardiopulmonary dysfunction is induced by an excessive discharge of catecholamines following the marked activation of the sympathetic nervous system immediately after the onset of SAH [7]. Recently, clinical studies have shown wall

motion abnormalities of the LV that develop in the acute phase of SAH [8, 9]. In an animal model by Masuda and coworkers, elevated activity of the sympathetic nervous system observed in the acute phase of SAH induced myocardial damage and contributed to the development of cardiac dysfunction [10]. Several studies have examined cardiac enzyme release in non-cardiac settings. Few studies evaluating the importance of the elevation of troponin I in SAH have been performed; all of them show a direct relationship between the cardiac outcome and this elevation. But these studies have been limited to a cardiac stand point, excluding neurological, pulmonary and hemodynamic complications and outcome.

The clear relationship between the level of elevation of troponin I and the in-hospital complications and functional outcome shown in this study, made with a large sample of patients, confirms that all other smaller studies indicate a need for measurement of this enzyme in SAH.

Conclusions

Troponin I can be used as a marker not only for cardiac outcome in patients with SAH; but also as predictive for complications such as DCI, hypotension and pulmonary edema. More over it can be used as a prognostic factor in terms of functionality.

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