Cardiac Involvement in Patients With Acute Neurologic Disease

Confirmation With Cardiac Troponin I

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**Background:** Patients with acute neurologic illness often manifest findings suggestive of cardiac injury. Their proper interpretation is unclear. Accordingly, we conducted a blinded evaluation to assess the incidence of cardiac injury determined by elevations of cardiac troponin I (cTnI) in patients presenting within 24 hours of a neurologic event and to determine their short- and long-term prognostic effect.

**Methods:** Blood samples for measurement of cTnI levels were obtained on hospital admission and daily for 3 days and were run by immunoassay. Extensive clinical evaluations including electrocardiograms and echocardiograms were obtained from all patients; daily follow-up evaluations were performed. The clinical electrocardiographic, echocardiographic, and biochemical data were analyzed independently by blinded observers.

**Results:** Peak levels of cTnI were elevated ($0.4 \mu g/L$) in 17 patients (19%) (mean±SD, 2.5±2.7 µg/L). All patients with elevated cTnI levels had clinical, electrocardiographic, or echocardiographic evidence of cardiac injury except those (n=5) with minor elevations. One-year mortality was 29% (23/80). Early death (≤30 days) accounted for 44% of total mortality (n=10) and was significantly higher in patients with elevated cTnI levels (Wilcoxon $P=0.01$; odds ratio, 6.4). This difference was less marked by 1 year (Wilcoxon $P=0.07$).

**Conclusions:** There is a substantial prevalence of myocardial injury in patients with acute neurologic illness. Cardiac injury in this population, as in others, seems to adversely affect prognosis.

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**Patients** with acute neurologic illness often manifest electrocardiographic (ECG) abnormalities suggestive of cardiac injury. The classic ECG changes of deep T-wave inversion were initially described in 1938 and occur most often after subarachnoid hemorrhage, although they also have been described after thromboembolic strokes, intracranial space-occupying lesions, and meningitis. The etiology of these ECG changes and their prognostic significance is unclear. The lack of specificity of elevations of total creatine kinase (CK) and also, to some extent, CK-MB elevations have confounded attempts to better define the presence of myocardial injury in this group because these patients often have concomitant skeletal muscle injury related to the presence of seizures or direct skeletal muscle trauma.

Cardiac troponin I (cTnI) is a biochemical marker of myocardial injury that is more sensitive and significantly more specific than CK-MB.

In addition, elevated cTnI levels persist in the blood for several days, facilitating detection. This marker has been used to confirm the presence of myocardial injury in complex clinical situations, and elevations presage an adverse prognosis in a variety of patients with acute illness, including acute coronary syndromes.

The purpose of this study was to use the cTnI level to determine the incidence of cardiac injury in patients with acute neurologic illness and then to define its clinical correlates.

**RESULTS**

**DEMOGRAPHICS AND BASELINE CHARACTERISTICS**

In the final cohort of 89 patients, 51 (57%) were enrolled 12 to 24 hours after the acute neurologic event; the rest were included earlier (24 [27%] in the first 6 hours and 14 [16%] between 6 and 12 hours). The average age of patients was 59±20 years (Table 1) and was not different in pa-
PATIENTS AND METHODS

PATIENT SELECTION

The study was done in collaboration with the Neurosurgery Department at the State University of New York Health Science Center at Syracuse from June 1996 to August 1997. One hundred four consecutive consenting patients presenting within 24 hours of an acute neurologic event requiring admission to the university hospital and patients after acute intracranial surgical procedures (<24 hours) were enrolled in the study.

Immediately after hospital admission, after obtaining informed consent for participation in the study, all patients underwent 12-lead ECG and 2-dimensional echocardiography, and blood samples were obtained for measurement of cTnI.

Serial blood samples were drawn every morning with the routine blood work for the next 3 to 5 days. The ECG was repeated on day 5 in all patients. Patients who demonstrated an abnormality of wall motion on their initial echocardiograms underwent an additional study on the fifth day. Fifteen patients were excluded because of an inadequate number of cTnI samples (<3 samples). Thus, the final cohort consisted of 89 patients.

EVALUATION OF CLINICAL COURSE

All decisions regarding the clinical care of patients were made by the primary neurosurgery team. The clinical profiles of patients were recorded on a predesigned form at the time of initial inclusion, and their subsequent progress (on a daily basis) was tabulated by an investigator (S.D.) unaware of the cTnI data. Patients were followed up until hospital discharge or death. Data were collected concerning (1) chest pain, characterized as noncardiac, cardiac, or uncertain; (2) congestive heart failure, determined after clinical assessment; (3) arrhythmias other than sinus tachycardia; (4) hypotension (mean arterial pressure <65 mm Hg); (5) tachycardia (heart rate >120 beats/min); (6) use of mechanical ventilation; (7) use of intravenous vasopressors (dopamine hydrochloride, dobutamine, amrinone, isoproterenol hydrochloride, norepinephrine bitartrate, phenylephrine, or vasopressin); and (8) use of intravenous vasodilators (sodium nitroprusside or nitroglycerin). Events potentially related to cardiovascular problems that were poorly explained (eg, unexplained hypotension) were categorized as unexpected clinical events. Because of the high degree of variability in the treatments used and clinical courses of the patients, the previous variables were used to assess the possibility of myocardial injury. The effects of intercurrent therapy and intervening surgery made their use as dependent variables impossible.

All echocardiograms were performed with an ultrasound imaging system (HP Sonos 1500; Hewlett Packard Company, Andover, Mass) using a 3.5-mHz transducer. Two-dimensional echocardiographic images were obtained as recommended by the American Society of Echocardiography and were interpreted by readers unaware of other clinical and biochemical information. A 16-segment model, as recommended by the American Society of Echocardiography, was used to analyze and quantitate regional wall-motion abnormalities.

Patients with cTnI level elevations. There were larger numbers of men than women (63%±6% vs 37%±6%; P<.02) and whites than other ethnic groups. Common risk factors for coronary heart disease (hypertension, diabetes, smoking, etc) were seen in a significant proportion of patients and were equally distributed in all groups (Table 2).

The majority of patients enrolled in the study, in all subgroups, manifested head injury (38%; n=34), including subdural hematoma (42%), or stroke (45%) as the admitting neurologic diagnosis (Table 1). Patients with stroke predominantly had intracranial and subarachnoid hemorrhage (84%; n=34), which amounted to 38% of the total population. Seizures, either as an individual presenting symptom (2 patients) or accompanying other neurologic presentations (4 of 6 patients in the multiple diagnosis group), were uncommon in our study population (overall =7%).

ELEVATED cTnI LEVELS

Seventeen patients (19%) manifested elevated cTnI levels (≥0.4 µg/L) in the first 5 days after enrollment. Elevations occurred comparably in men and women (59% and 41%, respectively). Levels of cTnI were elevated more frequently in patients who presented with seizures as the admitting diagnosis or who developed them during the course of hospitalization. Elevations occurred in 2 patients admitted with an initial diagnosis of seizures and 2 of 4 patients who developed seizures later. Thus, 50% of patients with seizures had elevations of cTnI levels. There was no relation between risk factors and evidence
A prospective determination of the presence or absence of myocardial injury was made by the investigators. A diagnosis of cardiac injury was considered suggestive if there were clinical signs of cardiac dysfunction (as per the aforementioned list) in conjunction with new ECG evidence of myocardial damage (ST-T segment elevation >1 mm or depression >2 mm, significant [≥0.08 mV] Q waves, or T-wave inversion >1 mm in 2 or more contiguous leads) or new transient or permanent wall-motion abnormalities by echocardiography.

EVALUATION OF cTnI

Blood samples were centrifuged at 2000 g for 15 minutes, stored at −70°C, thawed once, and then assayed in batches. Values of cTnI are stable for months when handled in this manner. Assays were performed by individuals blinded to the clinical data.

The concentration of cTnI was measured with immunoassay on the Baxter Stratus analyzer (Dade Behring Inc, Dover, Del), which uses 2 cTnI-specific monoclonal antibodies that recognize different epitopes of cTnI and have no detectable cross-reactivity with skeletal muscle TnI. Values of cTnI are undetectable in healthy volunteers. The lower limit of detection was 0.4 µg/L. Studies performed with this assay on blood samples from hospitalized patients without known myocardial infarction have defined the upper reference limit to be 0.6 µg/L (99th percentile value by nonparametric analysis). Use of these criteria provides greater sensitivity than CK-MB for detection of myocardial infarction and improved specificity. Both values have been used in clinical studies.

ECG FINDINGS

The ECG changes observed in our study can be broadly interpreted as being suggestive of myocardial injury or not (see the “Patients and Methods” section). There were a few ECG tracings (n=4) that, because of paced rhythms, etc., were called indeterminate. Because of the referral nature of the population, previous ECGs were rarely available for comparison.

Electrocardiographic evidence of myocardial injury was more frequently observed in patients (n=10) with elevated cTnI values and in patients (n=13) with clinical evidence of cardiac injury (59% and 76%, respectively). Overall, 23 patients (35%) in the entire cohort had ECGs suggestive of cardiac injury. No statistically significant differences in the incidence of cTnI elevations were seen in patients with ECG evidence of myocardial injury compared with patients showing nonspecific changes or normal ECGs.
ECHOCARDIOGRAPHY RESULTS

Echocardiographic abnormalities in the form of global right or left ventricular dysfunction or regional wall-motion abnormalities were seen in 20 (23%) of 87 patients who underwent echocardiography on hospital admission. Ten patients had global ventricular dysfunction and 10 had regional wall-motion abnormalities. Two patients had a combination of global dysfunction with more pronounced regional changes. Echocardiographic abnormalities at hospital admission were seen in 9 (39%) of 23 patients who died (early and late mortality). No particular pattern of abnormality could be discerned.

Table 3. Profile of Electrocardiographic (ECG) Changes in Patients With Elevated Cardiac Troponin I (cTnI) Levels and Patients With Clinical Evidence of Cardiac Injury

<table>
<thead>
<tr>
<th>ECG Findings</th>
<th>Elevated cTnI (≥0.4 µg/L) (n = 17)</th>
<th>Clinical Evidence of Cardiac Injury (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant for myocardial injury</td>
<td>24 (35)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Nonspecific and/or normal</td>
<td>40 (59)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>4 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage) of patients.

Table 4. Demographic Profile, Coronary Artery Disease (CAD) Risks, Cardiac Comorbidities, and Presenting Neurologic Diagnosis in Patients Alive and Those Who Died Within a Year of Enrollment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (n = 57)</th>
<th>Died (n = 23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (63)</td>
<td>15 (65)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>21 (37)</td>
<td>8 (35)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>50 (88)</td>
<td>22 (96)</td>
<td>NS</td>
</tr>
<tr>
<td>African American</td>
<td>6 (11)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean ± SD, y</strong></td>
<td>54 ± 19</td>
<td>74 ± 8</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td><strong>CAD risks and other cardiac comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (39)</td>
<td>15 (63)</td>
<td>.049†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (12)</td>
<td>9 (38)</td>
<td>.009†</td>
</tr>
<tr>
<td>High cholesterol level</td>
<td>11 (19)</td>
<td>3 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>25 (44)</td>
<td>10 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Known CAD</td>
<td>8 (14)</td>
<td>8 (33)</td>
<td>.046†</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>5 (9)</td>
<td>4 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2 (4)</td>
<td>2 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>10 (18)</td>
<td>8 (33)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>24 (42)</td>
<td>11 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>Head injury</td>
<td>24 (42)</td>
<td>7 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Space-occupying lesion</td>
<td>1 (2)</td>
<td>2 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple diagnoses</td>
<td>5 (9)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage) of patients except where noted otherwise. NS indicates not significant.
† Statistically significant.

NEUROSURGICAL PROCEDURES

Thirty patients (34%) underwent a neurosurgical procedure (craniotomy) for indications such as evacuation of a subdural hematoma, clipping of an aneurysm, removal of a space-occupying lesion, or relief of increased intracranial pressure. Elevations in cTnI values were seen in 6 of these patients (20%), accounting for 35% (6/17) of the total cTnI level elevations. Five patients (20%) who underwent neurosurgical interventions died.

MORTALITY AND OUTCOME

Overall 1-year mortality for all patients whose status could be verified through death certificates or contact with the next of the kin was 23 (29%) of 80 patients (Table 4). Early death (≤30 days) occurred in 10 patients (13% of all patients) and accounted for 44% of all deaths. Patients who died (early and late) were significantly older than the rest of the study population (74 ± 8 vs 54 ± 19 years; corresponding odds ratio for age in predicting mortality at 30 days, 3.8). In addition, diabetes, hypertension, and the presence of coronary artery disease (CAD) at hospital admission were significant risk factors for a fatal outcome. Levels of cTnI were elevated in 7 (31%) of these 23 patients to a peak level of 4.67 ± 3.51 µg/L (excluding the one patient who developed acute myocardial infarction with peak cTnI levels of 50.7 µg/L) and were significantly higher than the peak levels observed in patients with elevations who survived (0.80 ± 0.42 µg/L; P < .002). All patients who had elevated cTnI levels and died demonstrated clinical or ECG evidence of myocardial injury.

Cumulative survival (Figure) in patients with and without cTnI elevations showed early divergence up to 1 month. The difference in mortality at 30 days was significantly higher in the group with elevated cTnI levels (Wilcoxon P = .01), but the survival curves were only marginally different at 1 year (Wilcoxon P = .07). The odds ratio for 30-day mortality was 6.4 by logistic regression for patients with elevated cTnI levels. The predictive effect was more pronounced in the presence of known cardiac disease.

RELATION OF CLINICAL EVIDENCE OF CARDIAC INJURY WITH ELEVATED cTnI LEVELS

Overall, elevated cTnI levels were closely related to clinical evidence of cardiac injury. Only 3 patients (7%) were suspected of having cardiac injury and did not manifest elevations of cTnI values. In contrast, 29% of patients,
all with minor elevations of cTnl (mean, 0.58±0.15 µg/L; range, 0.5-0.8 µg/L), did not manifest clinical, ECG, or echocardiographic criteria of cardiac injury. This finding is likely due to the fact that biochemical markers such as cTnl are more sensitive than other criteria for detection of cardiac injury.

As might be expected, risk factors for CAD as well as preexisting CAD were more common in patients with elevated cTnl values, suggesting that many of the elevations might be related to the presence of underlying coronary heart disease exacerbated by the stress of a neurologic event. Such findings are compatible with those of other studies14 in critically ill patients.

**RELATION BETWEEN ECG CHANGES AND cTnl ELEVATIONS**

Patients with elevated cTnl levels and those with clinical evidence of myocardial injury had a higher frequency of ECG manifestations compatible with injury and ischemia (Q waves and ST-T changes) (Table 3). However, there were a substantial number of patients with ECG changes that were not associated with elevations in cTnl values (13 [57%] of 23 patients) and a significant number of elevations of cTnl levels associated with normal ECG findings or only minor nonspecific changes.

These discrepancies likely reflect the fact that biochemical markers are more sensitive than ECG in detecting subtle degrees of cardiac injury and that ECG changes might not necessarily reflect acute events. Furthermore, it might be that the mechanism of cardiac injury and the ECG changes in this setting are not ischemic. To determine evidence of myocardial injury, ECG changes were used conjointly with the clinical profile of the patient and the echocardiographic data.

**RELATION OF ELEVATED cTnl LEVELS TO PROGNOSIS**

Overall 1-year mortality of 29% (23/80) observed in our study was somewhat less than has been observed in this population previously.6,21 Early mortality (≤30 days) accounted for 10 (44%) of 23 deaths. As expected, patients who died (early and at 1 year) were significantly older.

Although not designed as a study of prognosis, follow-up revealed that patients with cTnl elevations, irrespective of all other factors, had significantly higher mortality. This effect was manifest early, but the curves continued to diverge until 30 days (Figure).

This adverse outcome was maintained during the 1-year period. All 8 patients with adverse outcomes had elevations of cTnl values and demonstrated evidence of myocardial injury clinically. These observations suggest that the presence of concomitant cardiac injury might be an important predictor of outcome and are consistent with those of other studies15-17,22-24 in cardiac and critically ill noncardiac patients.

The mechanism perpetuating cardiac injury in this patient population remains undefined. Although many patients had risk factors, only one patient had overt evidence of ischemic cardiac injury (acute myocardial infarction). Hence, cardiac damage in this setting might have been precipitated by autonomic dysfunction (catecholamine surge, etc) in association with other hemodynamic and/or metabolic insults that accompany acute neurologic syndromes with or without coronary artery abnormalities.

The increased frequency of elevated cTnl levels in patients with seizures might be due to the multiple stresses that seizure activity evokes (diffuse cerebral stimulation, edema, respiratory and metabolic acidosis due to apnea, increased oxygen requirements, etc). Such stresses could induce minor degrees of myocardial injury even in the absence of preexisting CAD, although it would be more likely if CAD was present. Because of the high specificity of cTnl for the heart, we can exclude skeletal muscle injury as the etiology of the elevations.12 This observation in patients with seizures deserves further evaluation in a larger patient population and may be important in the long-term treatment of patients with seizures.

**COMPARISON WITH OTHER STUDIES**

The average age of the patients (59±20 years) in our study is comparable to that observed in other studies in similar populations.21 As in other studies, patients who died were significantly older (74±8 years).

Elevated cTnl values (≥0.4 µg/L) were seen in 17 patients (19%), which is similar to the results of Horowitz et al.21 However, their observations were made only in patients with subarachnoid hemorrhage. Our population consisted predominantly of patients with hemorrhagic strokes, head injuries, and intracranial space–occupying lesions.

A substantial proportion of the ECG changes observed in our study were associated with biochemical confirmation of cardiac injury. Thus, some of the changes likely reflect true cardiovascular injury and are not solely neurologic abnormalities. Electrocardiographic changes can also occur in response to selective stimulation of the hypothalamus, which elicits increases in the sympathetic drive in the presumed absence of prototypical car-

![Kaplan-Meier plot of survival in patients with and without elevated cardiac troponin I (cTnl) levels. The curves separate early (≤30 days), and the difference in outcome persists for the rest of the year. The outcome difference at 30 days was statistically significant (Wilcoxon P<.001).](https://archinte.jamanetwork.com/fullarticle/1212192)
In rats, a rapid increase in intracranial pressure evokes myocardial injury, perhaps secondary to transient microvascular spasm. Thus, regardless of the etiology, the central nervous system can induce cardiac injury. On the other hand, Kolin and Norris, in an autopsy study of 58 patients who died of an acute neurologic event, demonstrated transtumeral and subendocardial focal damage that was present in greater frequency than in a control autopsy population. Conversely, Koskelo et al., in a case series of 3 patients with subarachnoid hemorrhage who died, demonstrated, on necropsy, changes compatible with subendocardial infarction in the hearts of these patients, implying that the ECG changes are reflective of true myocardial injury. Kono et al. demonstrated angiographically apical left ventricular wall-motion abnormalities, which they called "neurogenic stunned myocardium," in patients with subarachnoid hemorrhage and associated ECG changes with normal coronary arteries. Results of more recent clinical trials correlating ECG changes and cardiac injury using biochemical markers have not been as concordant. It is likely that both cardiac injury and reflex mechanisms are responsible for the ECG changes observed.

LIMITATIONS

The population of our study reflects the patients admitted to the neurosurgery service at a tertiary care hospital, which might explain the predominance of certain diagnostic groups (intracranial space-occupying lesions and subdural hematomas). However, for the most part, the demographics, risk factors, etc, seen in this group are consistent with other similar trials. However, the diverse nature of our population prevents elucidation of disease-specific cardiac risk profiles.

CONCLUSIONS

The results of our study demonstrate, using a highly specific and sensitive biochemical marker of cardiac injury—cTnI—that the prevalence of myocardial injury in patients with acute neurologic illness is substantial and often is associated with ECG abnormalities. Evidence of cardiac injury based on cTnI is associated with clinical, ECG, or echocardiographic evidence in most cases. Furthermore, in keeping with other studies, cardiac injury has a significant effect on prognosis.

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