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Troponin Elevations After Electroconvulsive Therapy: The Need for Caution

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ABSTRACT

BACKGROUND: Electroconvulsive therapy is used to treat patients with severe or resistant depression. Troponin elevations are associated with an adverse prognosis, and it is well known that central nervous system insults can cause biochemical evidence of cardiac injury. No study previously has studied this with electroconvulsive therapy.

METHODS: Patients scheduled for electroconvulsive therapy were enrolled. Clinical information, an electrocardiogram, and a baseline sample for cardiac troponin I and T (cTnI and cTnT) were obtained. Electroconvulsive therapy was done with standard techniques. Subsequently, electrocardiograms and additional samples were obtained. cTnT was measured with the Roche assay and cTnI with the Dade Stratus equipment. Values above the 99th percentile were considered abnormal.

RESULTS: Seventy patients completed the study. Four patients had elevated levels of cTn before treatment. In 3 patients, the elevations persisted. Four additional patients developed elevated cTn levels during electroconvulsive therapy. Two of the patients with cTn elevations died. No other events occurred during follow-up.

CONCLUSIONS: Elevations of cTn occurred in 11.5% of patients treated with electroconvulsive therapy. Some of the elevations preceded therapy and some occurred during treatment. Given the adverse prognostic importance of cTn elevations in general, in addition to additional studies, an increased degree of medical scrutiny may be appropriate for this group of patients and for those receiving electroconvulsive therapy. © 2011 Elsevier Inc. All rights reserved.

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KEYWORDS: Electroconvulsive therapy; Troponin

Electroconvulsive therapy often is used therapeutically when conventional antidepressant medications or psychotherapy are poorly tolerated or ineffective.[1,2] Electroconvulsive therapy is considered a safe procedure, with a short-term mortality rate reported to be 0.002%.[3] However, major cardiac events can occur.[4-10] Electroconvulsive therapy-associated electrocardiographic and echocardiographic abnormalities after electroconvulsive therapy have been described, including transient left ventricular (LV) systolic dysfunction documented by echocardiography.[11-14] In patients with known cardiac disease at high risk, beta-receptor antagonists are recommended before the first session.[15] However, there are conflicting data about the effects of beta-receptor antagonists both in terms of their cardioprotective effects and their potential to obviate the potential benefits of electroconvulsive therapy.[16,17] A previous prospective study identified no increase in serum cardiac enzyme levels in 29 patients after electroconvulsive therapy; however, that study was conducted in 1985 when elevated creatine kinase levels were used to identify myocardial

injury.[18] Contemporary biochemical markers such as cardiac troponin (cTn) have now supplanted total creatine kinase and its MB isoenzyme for the evaluation of possible myocardial injury because of their improved sensitivity and specificity.[19] There is no known association between elevated cTn and electroconvulsive therapy, as this possible association has not been investigated. However, serum cTn elevations do occur with other neurological events such as intracranial bleeding and tumors, especially when associated with electrocardiogram (ECG) changes. Such affected patients often have adverse short- and long-term prognoses.[20-25] Furthermore, there is a close association between coronary heart disease and depression, and patients who manifest both conditions have an adverse prognosis.[26-32] For these reasons, we sought to investigate prospectively whether electroconvulsive therapy evokes myocardial injury as evidenced by the release of cTn.

> ### CLINICAL SIGNIFICANCE
>
> - Elevations of cardiac troponin are markers of cardiac injury.
> - We observed elevations in several patients who were depressed before electroconvulsive therapy (ECT).
> - Some of these elevations persisted during ECT and some patients developed new elevations during ECT.
> - These observations suggest the need for caution in the initial evaluation of these patients and during the course of ECT.

METHODS

This study was approved by the Mayo Clinic Institutional Review Board in accordance with federal regulations. Seventy-five adult patients (age ≥18 years) referred for electroconvulsive therapy for the treatment of severe depression participated in the study after informed consent had been obtained from either the patient or legally authorized surrogate decision-maker. Electroconvulsive therapy was administered 3 times per week until the patients' symptoms resolved or their clinical response plateaued.

Before enrollment in the study, all patients underwent a pre-electroconvulsive therapy medical evaluation by an internist who screened the patients for the presence of heart disease (which is standard procedure at our institution). Patients with a history suggestive of acute coronary disease syndrome within the last 6 months were excluded from the study. Beta-receptor antagonists were ordered by the consulting internists as deemed necessary. All patients provided written informed consent in accordance with the informed consent regulations in 21 CRF 50.[33] Thereafter, 4 cm³ blood samples were obtained from the patients at baseline, 4 hours after electroconvulsive therapy, and at 18 hours after electroconvulsive therapy. We recorded patients' age, sex, past medical history as it applied to coronary artery disease and coronary artery disease risk factors (hypertension, hypercholesterolemia, tobacco history, diabetes mellitus, and family history of early myocardial infarction), cardiac medications, body mass index, creatinine, and the result of prior cardiac imaging studies or functional evaluations. We collected blood samples and ECGs for patients' first 3 electro-

convulsive therapy sessions, resulting in 9 samples per patient for the measurement of serum cTn.

Standard procedures were followed for the administration of electroconvulsive therapy. The procedure included premedication with an anticholinergic agent (intravenous glycopyrrolate or atropine), an anesthetic induction agent (intravenous thiopental or methohexital), and a muscle relaxant (intravenous succinylcholine). One hundred percent oxygen was administered by facemask during the procedure. Electrodes were placed either unilaterally with right D'Elia positioning or bilaterally in the frontal temporal regions. Electroconvulsive therapy was administered with a Thymatron DG/X device (Somatics, Inc., Lake Bluff, Ill). One electromyographic channel was monitored peripherally and 1 electroencephalographic channel was monitored centrally to determine the duration of the seizure activity. The titration method of Sackeim and associates[34] was used to determine the seizure threshold. A stimulus with intensity greater than that of the seizure threshold was delivered as recommended. An adequate seizure was defined by the presence of motor activity for ≥25 seconds. A seizure lasting <25 seconds was followed 90 seconds later by delivery of a second stimulus with a higher intensity. The patient's blood pressure, heart rate and rhythm, and peripheral oxygenation were monitored before, during, and after the procedure.

Cardiac troponin T (cTnT) was measured on the Roche Elecsys® Troponin T immunoassay (Roche Diagnostics, Indianapolis, Ind). The limit of detection for this assay is ≤0.01 ng/mL, with coefficient of variability of 10% at a value of 0.035 ng/mL. Values above the 99th percentile value of <0.01 ng/mL were considered abnormal. Cardiac troponin I (cTnI) was measured using the Dade Status CS analyzer (Dade, Newark, Del).[19] The limit of detection of the assay is 0.01 ng/mL, with a coefficient of variability of 6.5% at the upper limit of normal range of 0.06 ng/mL.[31] Values equal to or above the 99th percentile value of 0.07 ng/mL were considered abnormal. If values were constant over the sampling interval, they were retested after treatment with heterophilic blocking tubes to eliminate any elevations related to cross-reacting antibodies.[35]

Patient information was abstracted from the medical record. Adverse events were unstable angina, myocardial infarction, congestive heart failure, malignant cardiac arrhythmia, stroke, or death.

Categorical clinical and electroconvulsive therapy variables were summarized as percentages, and continuous variables as the mean value ± SD or the median value (with

ranges) where appropriate. Comparisons between patient subgroups were made with the Fisher's exact test for categorical variables and the 2-sample t test for continuous variables. A P-value $<.05$ was considered significant. Differences in cardiac troponin values were evaluated to confirm that they were true positives. Discrepancies from cTnI and cTnT were resolved to confirm the values by rerunning all positive studies that were not positive by both measurements (ie, cTnI and cTnT). Samples were rerun with a new assay batch as a new sample. In addition, they also were run after incubation in heterophilic blocking tubes to confirm that there no heterophilic antibodies present affecting the accuracy of the tests.

RESULTS

Overall, 75 patients were enrolled in the study. Of these, 70 (93%) patients completed the study. The average number of electroconvulsive therapy sessions per course was 8 (range 4-11). Patient characteristics are summarized in the Table 1. The mean age $\pm$ SD was 55 ± 17 years, and about half (51%) were men. The most common coronary artery disease risk factor was hypertension (46%), followed by tobacco use (26%) and diabetes (14%). The average creatinine was 0.97 ± 0.2 mg/dL. None of the patients were treated with hemodialysis. Nineteen patients (27%) were taking a beta-receptor antagonist, 16 (23%) were taking an angiotensin-

receptor antagonist, and 29 (41%) were taking lipid-lowering drugs. Six patients (9%) had a history of prior coronary artery bypass grafting or percutaneous intervention. Thirty-two patients (43%) had a pre-electroconvulsive therapy assessment of ejection fraction, and 7 patients had stress tests.

Eight patients (11%) had an elevated serum cTn on at least one occasion during the study. In 5 of these patients, elevations of cTnT and cTnI occurred conjointly. The values from 2 of these patients are shown in the Figure 1. There were 3 instances in which values of cTnI were elevated and cTnT was not. To eliminate the question of cross-reactivity or heterophilic antibodies, samples were re-evaluated after treatment with heterophilic blocking tubes. All values remained the same.

Four patients had elevated cTn in the initial pre-electroconvulsive therapy blood specimen. Of these, 3 patients' cTn levels remained elevated throughout the study. One patient had elevated cTn levels after the first 2 electroconvulsive therapy sessions, with a clear trend down before returning to near normal values after the final electroconvulsive therapy session (6 days later). Notably, of these 4 patients, 2 died within 3 months of electroconvulsive therapy, but records were inadequate to establish the causes of death.

Four patients with elevations had normal cTn T/I values initially. Two patients had an elevated cTn level after the first electroconvulsive therapy session before returning to normal on the pre-electroconvulsive therapy troponin value before the second session without further elevations. The remaining 2 patients' troponin levels became elevated after the second electroconvulsive therapy session. One patient's cTn level remained elevated throughout the study. The other patient's cTn level returned to normal after 72 hours.

Two patients who developed elevations had pre-electroconvulsive therapy stress testing; one was positive and the other negative. One patient with an elevation had a history of coronary artery bypass grafting. There were no significant findings on the electrocardiograms. Thirty percent (18/61) of the patients without elevations in cTn were taking a beta-receptor antagonist, compared with only 11% (1/9) in the group with elevated cTn. None of the observed differences between the groups were statistically significant.

Two of the patients with elevated cTn subsequently died. No other clinical events were noted during follow-up of 18 months after reviewing the electronic medical record.

DISCUSSION

These data suggest that additional scrutiny both in the screening and follow-up of patients undergoing electroconvulsive therapy may be advisable. Our study was not configured as an outcome study but in many clinical situations, elevations of cTn are potent negative prognostic factors.[36,37] Thus, some consideration concerning the etiology and pathogenesis of the elevations we observed may be prudent.

Half of the patients who manifested elevations of cTn had them at time of admission. Despite this fact, none of

Table Characteristics of the Study Population

	Total Population n = 70	Normal TNT n = 62	Elevated TNT n = 8
Male, n (%)	36 (51)	31 (50)	5 (63)
Female, n (%)	34 (49)	31 (50)	3 (37)
Age, mean (SD)	55 ($\pm$ 17)	55 ($\pm$ 16)	56 ($\pm$ 17)
History atrial fibrillation, n (%)	3 (4)	2 (3)	1 (13)
Anticoagulation therapy, n (%)	5 (7)	4 (6)	1 (13)
Antiplatelet therapy, n (%)	25 (36)	24 (39)	1 (13)
Risk factors:			
Hypertension, n (%)	32 (46)	29 (47)	3 (37)
Diabetes mellitus, n (%)	10 (14)	9 (15)	1 (13)
Prior CVA/TIA, n (%)	3 (4)	3 (5)	0 (0)
Tobacco users	18 (26)	14 (23)	4 (50)
Prior CABG/PCI	6 (9)	5 (8)	1 (13)
Creatinine	0.97 ($\pm$ 0.2)	0.96 ($\pm$ 0.2)	1.00 ($\pm$ 0.3)
Beta-blocker	19 (27)	18 (29)	1 (13)
ACE-I/ARB	16 (23)	15 (24)	1 (13)
Cholesterol medication	29 (41)	27 (44)	2 (25)

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.
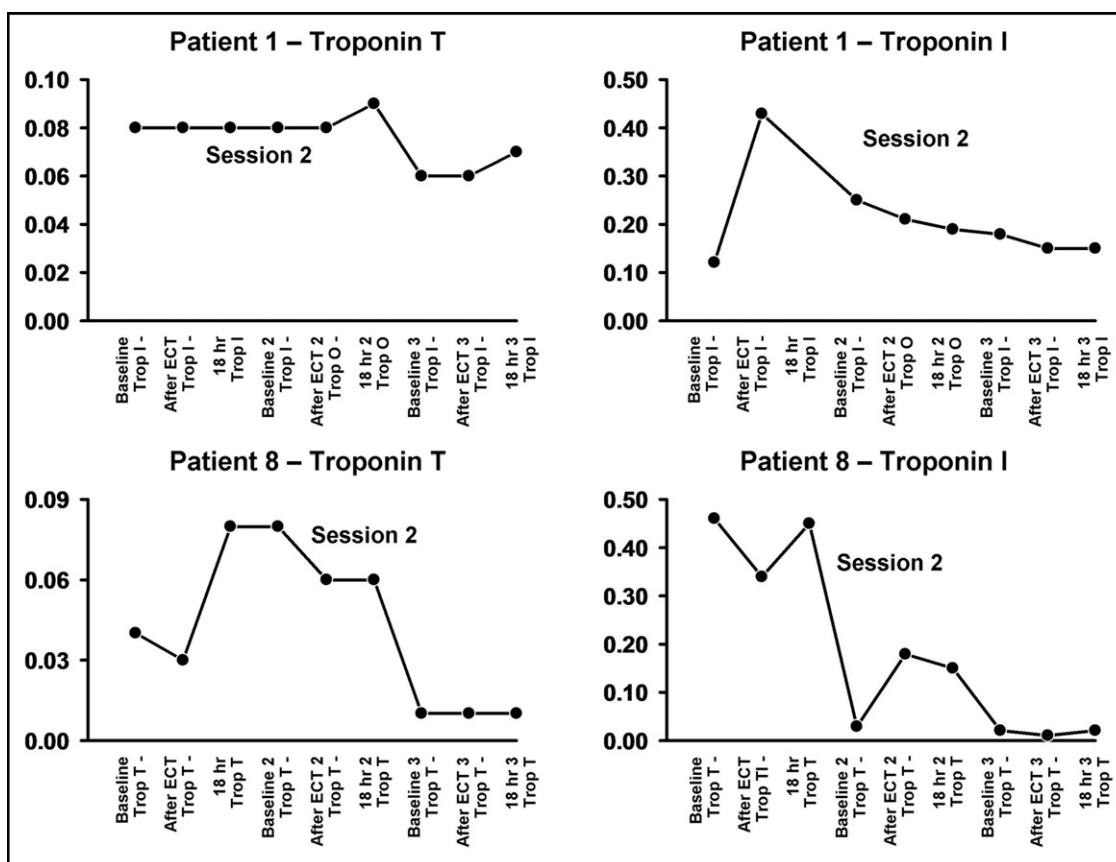
Figure CTnT and CTnI values from 2 of the patients who manifested elevations with electroconvulsive therapy.

these individuals were thought to have had a recent acute coronary syndrome. However, patients who are depressed often experience physical symptoms and thus can be hard to evaluate clinically.[38] We cannot exclude the possibility that some of these patients had unstable coronary artery disease that was missed. We also cannot exclude the possibility that they had chronic heart disease, be it heart failure or coronary artery disease, and manifested elevated cTn values for that reason. Regardless of the etiology of the elevations, the data suggest that the evaluation of this subgroup of patients may need to be done more robustly or perhaps even with cTn screening because only 1 patient with an elevation was treated with a beta-receptor antagonist. That patient had been treated with a beta-receptor antagonist chronically for hypertension. Importantly, this was the group most apt to have subsequent elevations during electroconvulsive therapy, and 2 of these patients died subsequently. Clinically, both the initial elevations and those post electroconvulsive therapy were apparently silent and therefore, no specific treatment was initiated. No ECG changes were detected, even with additional review of the ECGs after knowledge that cTn elevations had occurred. If it is the case that detection of coronary artery disease detection is inhibited by the presence of depression, that might provide an explanation for the poor prognosis observed in these patients. Of

equal importance, patients with elevated cTn are probably a group who should be treated with beta-receptor antagonists before electroconvulsive therapy. Obviously, additional data are needed in this important area.

The group that has normal baseline cTn that then develops elevations is even more problematic. Elevations at baseline imply cardiac disease. They can be due to many processes, but given the frequency of coronary artery disease and its association with depression, it is probably reasonable to be concerned about this diagnosis. It also is possible that, like other central nervous system (CNS) disease processes, depression of itself evokes cardiac injury and thus, elevations in cTn. With CNS insults, it is often felt that the elevations are related to catecholamine release or to the location of the neurological lesion. These mechanisms could contribute to the development of elevations post electroconvulsive therapy as well.[20] Either way, in most series of neurological disease, they too are associated with an adverse prognosis.[20,22,24,25] These patients may be even more difficult to identify before treatment.

Regardless of the mechanism, our data fit well with those who have reported LV systolic dysfunction occurring after electroconvulsive therapy.[13,39] Three small prospective studies have evaluated this issue of patients who underwent 2-dimensional echocardiography soon after electroconvul-

sive therapy.[11,13,40] In the first study,[13] transient LV regional wall motion abnormalities developed in 5 of 11 patients who were imaged immediately after electroconvulsive therapy. In the second study,[40] 13 patients were randomized to pretreatment with esmolol or placebo before their first and second electroconvulsive therapy sessions. Echocardiography was performed soon after electroconvulsive therapy. Only 1 patient developed new regional wall motion abnormalities. In the third study,[11] 5 of 11 young adults who were imaged 20 minutes after electroconvulsive therapy developed new regional wall motion abnormalities; these had resolved by the time of the next echocardiogram, which was 6 hours after electroconvulsive therapy. We unfortunately do not have echocardiographic data, but one might hypothesize that the regional wall motion abnormalities might be associated with the troponin elevations we observed. In one echocardiogram study, it appeared that echo abnormalities were present after the initial session but not subsequently. This could be a manifestation of the second phase of ischemic preconditioning.[41] We cannot confirm that finding. Of those who had normal baseline troponin values, 2 had elevations after the first session and 2 after the second session.

There were a few instances when cTnI and cTnT were discordant. To ensure that these were not falsely elevated because of heterophile contamination, these values were run a second time after the use of additional blocking antibodies. All of the patients were confirmed to have true positive elevations in cTnI. The discrepancy between the 2 measurements of cTn likely reflects the increased sensitivity of this cTnI assay compared with cTnT.

CONCLUSION

These data suggest that additional research is necessary to evaluate further the risk, if any, to patients with depression who are candidates for electroconvulsive therapy. Our data do not necessarily impugn electroconvulsive therapy. It is conceivable that patients with severe depression itself have such elevations absent electroconvulsive therapy because of either concomitant coronary artery disease or the CNS effects of depression itself. These data open rich new avenues for research and suggest that biomarkers such as cardiac troponin may be helpful in elucidating the frequency and importance of these findings.

ACKNOWLEDGMENT

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