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Elevation of Cardiac Troponins in Prolonged Status Epilepticus: A Retrospective Chart Analysis

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Abstract

Introduction—To determine the clinical significance of elevation of Troponin-I [cTn-I] during prolonged status epilepticus [pSE] SE is known to be accompanied by an increase in sympathetic outflow. Elevation of cTn-I has been linked to myocardial stress. We hypothesize that in patients with risk factors for coronary artery disease [CAD], pSE may lead to myocardial stress and an elevation of cTn-I.

Methods—This is a retrospective study of patients over the age of 18 years who were presented to Virginia Commonwealth University with SE between 2005 and 2010. Data was evaluated using the 30-minute definition for SE and 30 day mortality. Risk factors for CAD and cTn-I levels within the first 24 hours of diagnosis of pSE were analyzed.

Key findings—There were a total of 435 patients with a confirmed diagnosis of pSE, of which 266 had cTn-I concentrations reported. Statistical analysis showed a significant association between CAD risk factors and cTn-I elevation ($\chi^2 = 12.87$, p-value < 0.01), with Crude Odds Ratio of 4.7. In patients with a CAD risk factor, an elevation of cTn-I is associated with a significantly increased risk of mortality, with an Odds ratio of 8.0, ($\chi^2 = 40$, [95% CI 4.1–15.9] p-value < 0.01). Mortality was higher in those with an elevation of cTn-I [54.65%] as opposed to those who did not have an elevation [15.08%], irrespective of CAD risk factors. OR=6.7, ($\chi^2 = 45$, [95% CI=3.7–12.2] p-value < 0.01).

Conclusions—In patients with pSE values, elevated cTn-I values are seen four to five times more often in those with CAD risk factors, as opposed to those without the risks. An elevation of cTn-I in this subgroup of patients with CAD risk factors was associated with an eight to nine fold increase in their 30 day mortality as compared to patients with pSE, who did not have an elevation of cTn-I.

Keywords

Prolonged status epilepticus; Cardiac injury; Mortality

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Introduction

Status epilepticus (SE) as defined for most research studies is continuous or repetitive seizures without intervening recovery of consciousness for 30 minutes or more [1]. Current definitions of SE for clinical purposes is, seizures lasting 10 minutes or more or two or more seizures in that time frame without return to baseline. It is a neurological and medical emergency and is associated with mortality rate as high as 22% [2]. Prior studies have shown that mortality is higher in the neonates and elderly, those receiving mechanical ventilation, patients with hypoxic ischemic brain injury and cerebrovascular diseases [3]. In the case of non-convulsive SE, mortality was higher in patients who had SE secondary to underlying medical conditions, those with severe impairment of mental status and patients with acute complications [4]. Mortality associated with SE is attributed to acute hypertension and tachycardia leading to subsequent development of pulmonary edema, hypotension, cardiac arrhythmias and circulatory collapse [5–7]. Animal studies and case reports suggest a chronic alteration in autonomic regulation of cardiac function, characterized by increased sympathetic dominance of the vagal system as an underlying mechanism for cardiac arrhythmias and myocardial damage in form of contraction band necrosis, myocytolysis and Takotsubo cardiomyopathy in the setting of SE [8–10].

Troponins complex consists of three subunits—Troponin-C, Troponin-I and Troponin-T. These are located on the actin filament of striated muscles (Cardiac and Skeletal). Troponin-T and Troponin-I are only expressed in cardiac muscles and in the year 2000, the European Society of Cardiology and the American College of Cardiology committee jointly redefined myocardial infarction (MI) by an elevation of cardiac Troponin-T (cTn-T) or Troponin-I (cTn-I) in conjunction with clinical evidence of myocardial ischemia [11]. It is also known that elevation of cTn-T or cTn-I is seen in patients without acute coronary syndromes in conditions such as myocarditis, pulmonary embolism, acute and chronic heart failure, septic shock, use of cardio toxic drugs, and strenuous exercise [12–14]. There have been reports of spurious elevations of cTn-T along with myoglobin in patients with diabetes as well as chronic kidney disease. [15,16]. There is evidence to prove that elevation of cTn-I accurately predicts myocardial injury even in patients with renal failure [17].

Currently, published data regarding significance of elevated troponin in patients with prolonged status epilepticus [pSE] is limited. We hypothesized that pSE leading to sympathetic overflow, in patients with risk for coronary artery disease (CAD) causes myocardial stress. This in turn leads to an elevation of cTn-I and cTn-T due to myofibrillar injury. An increase in mortality among those patients with SE who have an elevation of cTn-I or T will corroborate this hypothesis. The purpose of this study is to find if a correlation exists between elevation of cTn-I and presence of CAD risk factors in patients with SE and to determine if this elevation of cTn-I would be associated with an increase in mortality.

Materials and Methods

This is a retrospective study on all patients over the age of 18 years who presented to Virginia Commonwealth University with status epilepticus between 2005 and 2010. Data from the Greater Richmond Metropolitan Area Status Epilepticus Project (GRMASE)

database were evaluated using the 30-minute definition for SE. This study was conducted with our institutional IRB approval [IRB number: HM10406] and patient information was de-identified. Both convulsive and non-convulsive seizures were included in the analysis. Age, risk factors for CAD (*as per current National Heart, Lung and Blood Institute guidelines*) and cTn-I levels during the period of SE or within the first 24 hours of diagnosis were collected. The number of risk factors was not quantified since this information may not always be accurately known at the time of presentation. Mortality data was collected at 30 days after cessation of SE.

The risk factors for CAD as described by the National heart, Lung and Blood Institute guidelines are dyslipidemia, high blood pressure, smoking, insulin resistance, diabetes, obesity, metabolic syndrome, lack of physical activity, unhealthy diet, family history of early heart disease and older age (men greater than 45 and women greater than 35).

There were a total of 435 patients with a confirmed diagnosis of SE at this institution in the above mentioned time period. cTn-I concentrations were measured at the time of admission or within 24 hours of onset of seizures in 266 of the 435 patients. A numerical cutoff value for enzyme elevation was not used for analysis of this study and data was gathered primarily as either within normal range or elevated. This had to be done since the normative values had changed along the time span of this study due to changes in the reagents and reporting values used by the laboratory and there is no way to correlate results from a Troponin-I assay to Troponin-T assay and often even between Troponin-I assays themselves. Therefore for each of the assay used, we collected data as either “*elevated*” or “*normal*” based on the upper limit of numerical cutoff value reported for the particular assay used at the time. Patients were excluded if they either had a concurrent myocardial infarction or their SE was secondary to anoxic brain injury due to cardiopulmonary arrest. This subset of thirty one patients were excluded since the elevation of cTn-I could be a direct result of the resuscitation, cardiac arrest and also because pSE in this population is traditionally associated with higher mortality rates. Of the data available for analysis with regards to etiology of pSE, 108 patients had pSE without any underlying co morbidities, 12 patients had pSE secondary to cerebrovascular accidents and 57 patients had pSE due to an acute symptomatic etiology such as underlying medical conditions, intracranial hemorrhage, intoxication, mass lesions and others. The data on remaining patients were either unavailable or unclear.

Chi-squared tests were performed to test the univariate association of cTn-I concentrations with CAD risk factor (yes or no). All statistical analyses were performed using SAS 9.3 (*SAS Institute Inc., Cary, NC, USA*).

Results and Discussion

Statistical analysis showed a significant association between CAD risk factors and cTn-I elevation ($\chi^2 = 12.87$, p-value <0.01). Fisher’s exact test was performed due to the small sample size of one cell and it verified the results (p<0.01). The Crude Odds Ratio for CAD risk factor is 4.7 (95% Confidence Interval [1.9, 11.5]), denoting the odds for a troponin

elevation in a patient with a CAD risk factor were 4.7 times higher than the odds for a troponin elevation in the absence of a CAD risk factor.

See Table 1: Association between elevation of cTn-I and presence or absence of CAD risk factors.

This test also showed no significant association between age and cTn-I concentration ($\chi^2 = 1.80$, $p\text{-value} = 0.1793$). The Crude Odds Ratio was 1.5 (95% C.I [0.8, 2.8]).

See Table 2: Association between age and elevation of cTn-I.

The results of the logistic regression model show that age alone is not a significant predictor of the probability of cTn-I elevation, but having a CAD risk factor is significantly associated with cTn-I elevation. That is, once adjusted for age, an individual with a CAD risk factor is 4.5 times as likely to have elevated cTn-I as is an individual in the same age group who does not have any CAD risk factors.

See Table 3: Logistic regression model of age grouping and cTn-I elevation.

Since age by itself was not found to be significant, the CAD risk factor was adjusted to include all age greater than 18 years, which was our target demographic. This relationship between CAD risk factor and cTn-I elevation was found to be statistically significant ($\chi^2 = 10.64$, $p\text{-value} < 0.01$). With the presence of one small cell size, the results of this test match that of Fisher's exact test. The odds ratio for this table is 6.1 (95% C.I. [1.8, 20.4]).

In patients with a CAD risk factor, an elevation of cTn-I is associated with a significantly increased risk of mortality with an odds ratio of 8.0, ($\chi^2 = 40$, [95% CI 4.1–15.9] $p\text{-value} < 0.01$). The same degree of association with increased mortality was not seen with relation to CAD risk factors alone. ($\chi^2 = 1.35$, [95% CI 0.6–2.6] $p\text{-value} = 0.3$). Mortality was higher in those with an elevation of cTn-I [54.65%], irrespective of whether they did or did not have CAD risk factors. OR=6.7, ($\chi^2 = 45$, [95% CI=3.7–12.2] $p\text{-value} < 0.01$). See Table 4: Association between mortality and cTn-I and CAD risk.

Overall 30 day mortality was 7.4% in those with pSE in this database, 38% in those with acute symptomatic etiology and 9.09% in those with concurrent cerebrovascular accidents. Statistically significant correlation between elevated cTn-I and mortality was strongest in patients with cryptogenic pSE: OR 17 (95%CI of 3.13–92, p value of 0.001). Those with acute symptomatic etiology for pSE and cerebrovascular accidents as cause of pSE did not show a similar correlation between elevated cTn-I and mortality on subgroup analysis. OR=4.15 (95% CI 1.09–15, p value of 0.03).

Conclusion

The most important findings from this study are that in patients with pSE an elevated cTn-I is seen four to five times more often than in those with CAD risk factors, as opposed to those without the risk factors. An elevation of cTn-I in this subgroup of patients with CAD risk factors was associated with an eight to nine fold increase in their 30 day mortality as compared to patients with pSE, who did not have an elevation of cTn-I. This trend was seen

irrespective of the age of the patient. Assuming optimal treatment, it is uncommon for patients to die during SE and generally SE related mortality peaks within 30 days after SE [18]. The major risks for death associated with pSE are, myoclonic SE in post anoxic patients, SE lasting more than 24 hours, acute symptomatic etiologies, and age [19]. Cardiac arrhythmias, Takotsubo cardiomyopathy are other etiologies implicated towards increasing mortality. SE following post anoxic brain injury and post cardiopulmonary resuscitation is traditionally associated with higher mortality, and this subgroup of patients were therefore excluded from this analysis.

The findings of this study suggest that in patients with risk factors of CAD, SE may act as an acute stressor. We hypothesize that with pSE, there is an increase in sympathetic outflow leading to an increase in oxygen demand of myocardium due to resultant tachycardia and other effects of sympathovagal dominance. Catecholamine released directly from nerve terminals into the myocardium are suspected to be the culprits leading to contraction band necrosis and cardiac damage [20]. In the presence of risk factors for CAD, a mismatch in demand and supply is assumed under these situations, which results in injury to myocardium leading to elevation of cTn-I.

Since data was gathered prospectively in this study, and analyzed later, the implications of elevated cTn-I in patients with SE, without symptoms or other signs of acute coronary syndrome was not known at the time. This is one of the limitations of this study. There were two patients who also demonstrated abnormalities on electrocardiogram. One of these patients did undergo coronary angiogram; however no significant abnormality was documented. Other limitations include lack of a concomitant electrocardiography test in these patients, lack of confirmatory coronary angiographic or pathology results to confirm our hypothesis. Other variables that have not been addressed in this study are refractoriness to treatment and duration of pSE, pre-existing co-morbidities that could also contribute to increased mortality. The lack of our ability to test these variables and their correlation to CAD risk and cTn-I elevation and subsequent mortality does limit the strength of our postulated causal association. In future, further studies can be undertaken to address these individually. We were unable to ascertain the correlation between the duration of status and mortality, due to the limitations of recollection bias that came with the retrospective nature of our study. While the troponin levels were all checked and only considered if drawn within 24 hours of onset of SE, the exact duration of episode of SE was not documented. We regret the lack of inclusion of this important piece of information. The lack of a numerical value for cTn-I level is also a limitation, but there is no way to correlate results between various Troponin-I assays.

This study is one of the largest published series to date and the statistical significance of association between increased mortality in patients with SE who have CAD risk factors and elevated cTn-I is overwhelming. Further prospective-interventional studies are warranted to determine if we can alter mortality risk by addressing the cardiac risk factors concurrently while treating SE. This will require close collaboration with cardiology and intensive care.

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Table 1

Association between elevation of cTn-I and presence or absence of CAD risk factors.

	cTn-I elevated	cTn-I normal	Total
CAD risk present	51*(p<0.01)	115	166
CAD risk absent	6	63	69
Total	57	178	235

Table 2

Association between age and elevation of cTn-I.

	cTn-I elevated	cTn-I normal	Total
Age over 60 years	34	88	122
Age less than 60 yr	23	90	113
Total	57	178	235

Table 3

Logistic regression model of age grouping and cTn-I elevation.

Parameter	Estimate	S.E.	Wald Chi-Sq	P-value	Adj. OR	95% Wald C.I.
Intercept	0.77	0.21	13.51	<0.01		
Age	0.12	0.32	0.14	0.71	1.1	(0.6, 2.1)
CAD Risk Factor	1.50	0.47	10.26	<0.01	4.5	(1.8, 11.3)

Table 4

Association between mortality and cTn-I and CAD risk.

	Alive	Dead	Total
Elevated cTn-I with CAD	37	44* (p<0.01)	81
Elevated cTn-I without CAD	2	3	5
Normal cTn-I with CAD	108	16	124
Normal cTn-I without CAD	44	11	55