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REVIEW

Elevated troponin in patients with acute stroke – Is it a true heart attack?

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Abstract Although the prognostic value of a positive troponin in an acute stroke patient is still uncertain, it is a commonly encountered clinical situation given that Ischemic Heart Disease (IHD) and cerebrovascular disease (CVD) frequently co-exist in the same patient and share similar risk factors. Our objectives in this review are to (1) identify the biologic relationship between acute cerebrovascular stroke and elevated troponin levels, (2) determine the pathophysiologic differences between positive troponin in the setting of acute stroke versus acute myocardial infarction (AMI), and (3) examine whether positive troponin in the setting of acute stroke has prognostic significance. We also will provide an insight analysis of some of the available studies and will provide guidance for a management approach based on the available data according to the current guidelines.

Contents

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CVD, Cardiovascular Disease; CAST, Chinese Acute Stroke Trial; CT, computed tomography; CAD, Coronary Artery Disease; CK-MB, Creatine Kinase-MB; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; IST, International Stroke Trial; ICH, intracranial hemorrhage; IHD, Ischemic Heart Disease; LV, left ventricular; LDL, low-density lipoprotein; MI, myocardial infarction; NHS, neurogenic heart syndrome; SAH, subarachnoid hemorrhage; TRELAS, The Troponin Elevation in Acute Ischemic Stroke; TIA, Transient Ischemic Attacks; cTnI, Troponin I; cTnT, Troponin T

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1. Introduction

Concurrent stroke and myocardial infarction (MI) are not uncommon, clinical, observational and experimental trials have pointed to the coexistence between neurological and myocardial injury. Interestingly, with the development of highly sensitive cardiac biomarkers, more patients with stroke are being tested for troponin. A strong association seems to exist between both conditions causing both a diagnostic and management dilemma to clinicians.

Several unanswered questions have emerged. What are the mechanisms and the pathophysiology behind an elevated troponin in the setting of acute stroke? How does an elevated troponin affect prognosis and mortality? Should an elevated troponin alter the management approach?

In this review article we will discuss the pathophysiologic mechanism of cardiac muscle regulatory protein troponin T (cTnT) elevation in a stroke patient, its prognostic significance and its effect on patient management decisions.

2. Method

Twenty-six articles were identified in the period between 1997 and 2015 through searches on PubMed, Medline and the Cochrane Library using the following keywords: stroke, cardiac enzymes, cerebrovascular, troponin, myocardial infarction, and neurogenic heart syndrome were searched systematically to obtain relevant literature.

3. Discussion

Several studies have evaluated the incidence of elevated troponin in the acute stroke patient, the incidence varying between 5% and 10% depending on the troponin cut off limit.[1] Data from the RANTTAS trial placebo cohort suggest that angina, MI, and cardiac ischemia complicate 6% of acute strokes.[2]

Comparing troponin to Creatine Kinase-MB (CK-MB), troponin T has superior sensitivity and specificity for revealing minor myocardial injury.[3] In a study by Hakan et al., 32 patients with large cerebral hemispheric infarctions and with no history of coronary heart disease were evaluated for elevation of cardiac of troponin T, CK-MB, myoglobin and total CK. The investigators concluded that only troponin T is a more specific biochemical marker of myocardial injury in a stroke patient.[3]

Forty percent of the patients with subarachnoid hemorrhage (SAH) have an elevated cardiac biomarker while 10% have demonstrated left ventricular (LV) systolic dysfunction on echocardiography. When compared to men, women with SAH tend to have more LV systolic dysfunction.[4] In addition, stroke severity, not its location, was associated with higher troponin levels.[5]

TRELAS study compared coronary vessel status in acute ischemic stroke (AIS) patients with elevated cardiac troponin (cTn), to patients presenting with non-ST-elevation acute coronary syndrome (NSTE-ACS), Patients with elevated cTn levels (>50 ng/L) on presentation or during the following day underwent diagnostic coronary angiography within 72 h. Patients with impaired kidney function (creatinine >1.20 mg/dl) were excluded, the study concluded that despite similar baseline cTn levels, coronary culprit lesions are significantly less frequent in AIS patients compared to age- and gender-matched patients with NSTE-ACS.

In the small study by Darki et al., statistically significant results found an association of positive troponin level with positive echocardiogram; with the most common results being in the inferior or septal wall motion abnormalities.[7] A lower ejection fraction was strongly associated with cTI release.[8] In addition Raza et al., reported that the ejection fraction of less than 50% did not predict adverse outcomes, and the likely cause is very different from newly diagnosed cardiomyopathy but that it is possibly due to sympathetic nervous system surge that occurs during an acute stroke.[9]

4. Pathophysiology of Neurogenic Heart Syndrome (NHS)

The phenomenon has been explained as a neurally mediated process due to increase in catecholamine release as a result of hypoperfusion of the posterior hypothalamus causing autonomic nervous system imbalance and increased sympathetic output.[4,8]

Increased troponin I level is associated with elevation of circulating epinephrine in acute ischemic stroke[10]; therefore, activation of the sympathoadrenal system could be an important contributor to myocardial damage in these patients.[10]

Myofibrillar degeneration (coagulative myocytolysis and contraction band necrosis) is a common microscopic and pathologic picture seen in myocardial necrosis in stroke patients. Whereby cells die in a hyper-contracted state with prominent contraction bands, which happens within minutes and is associated with early calcification and mononuclear infiltration. This is in contrast to myocardial lesions due to coronary heart disease where the cells die in a relaxed state without prominent contraction bands known as coagulation necrosis - a process that can take hours or even days, with late calcification.[11]

Elevated catecholamine levels are often noted in stroke patients, which may account for the cardiac arrhythmias and ECG changes. The toxicity from catecholamine then causes cardiac necrosis.[11] Autonomic imbalance with exaggerated sympathetic activity is evident after a stroke. Hence the exaggerated release of catecholamines, and so acute lesions within the central autonomic system may result in acute derangement in the sympathetic and parasympathetic activity (see Diagram 1).[12]

5. Prognosis

In a 1997 observational study by James et al., of the 181 patients admitted for acute stroke, troponin T concentration was raised (>0.1 microgram/l) in Thirty patients who died in hospital (12/30 (40%) patients with a raised troponin T

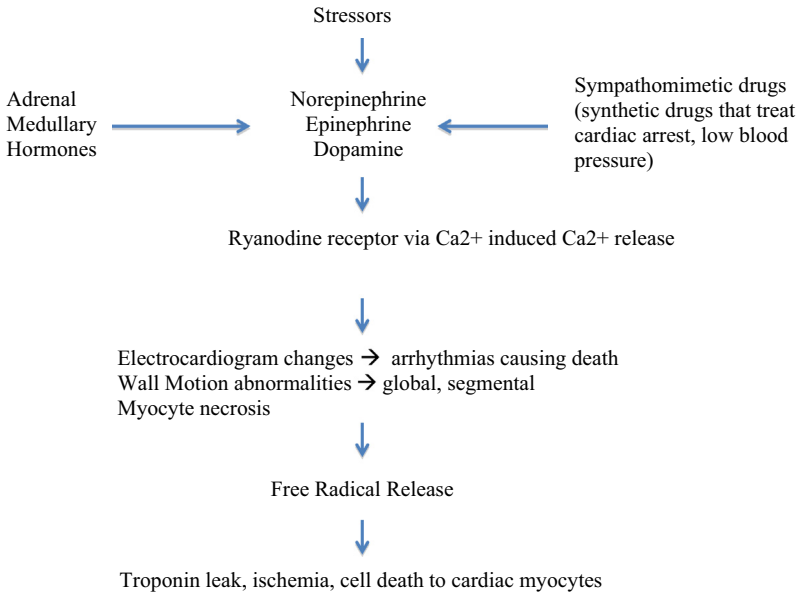

Diagram 1 Illustrates the pathophysiologic mechanism of increase catecholamine and the release of cardiac enzymes.

concentration versus 19/151 (13%) patients with a normal concentration (relative risk 3.2 (95% confidence 1.7 –5. 8; $P = 0.0025$)). The study concluded that elevated troponin on admission in acute stroke patient is a strong predictor of mortality and carries a worse prognosis.[13]

In a prospective study from 2000 to 2002, 279 patients were admitted to the stroke unit; Fure et al. reported that TnT was elevated ($>0.04\ \mu g\ L^{-1}$) in 26 patients (9.6%). The authors demonstrated that a rise in TnT was significantly associated with a poor short-term outcome.[14]

In another prospective study of 244 acute stroke patients, Jensen et al., detected elevated levels of TnT ($>0.03\ \mu g/L$) and creatine kinase-MB ($\geq 10\ \mu g/L$) in 25 patients(10%) and 21 patients (9%)of patients, respectively (1,15). Seven patients (3%) had elevations of TnT or creatine kinase-MB along with electrocardiographic changes suggesting acute myocardial infarctions. The study concluded that congestive heart failure and renal failure rather than myocardial infarction are the most likely causes of elevated troponin although one might speculate that the TnT release could be caused by scattered foci of necrosis as a result of heightened catecholamine levels during the stroke.[1,15] In patients with renal insufficiency such as CKD stage 3 –5, Elevations of cTnI not associated with ACS were common and there was an increase in mortality especially with higher concentrations (cTnI $> 0.03\ \mu g/L$).[16]

Patients with elevated troponin had a higher mortality within the following 2 years[13] Elevated levels of troponin are associated with poorer post-stroke performance and there was no threshold below which elevations of troponins were harmless.[1]

Etgen et al., found that the size of the cerebral lesion size and the presence of heart failure were the only prognostic factors for mortality, but the result could be confounded, because there is no information about whether the patients with heart failure had concomitant elevated levels of troponins.[17] cTn levels may be useful in acute stoke patients who may need earlier evaluation of CAD for further secondary prevention.[6]

In a retrospective study by Raza et al., an analysis of 566 patients admitted for acute stroke showed that 212 of them had troponin I measured and also had no clinical evidence of acute coronary syndrome (ACS), 17/212 (8%)had positive troponin. Patients were divided into positive troponin and normal troponin groups and were followed for 20.1 ± 10.3 months. Patients with positive troponin were found to have a higher risk for nonfatal myocardial infarction, major adverse cardiovascular events, and death from any cause as compared to the normal troponin group. The study concluded that elevated cardiac troponin in patients with acute stroke and no clinical evidence of ACS is strong predictor of long-term cardiac outcomes.[9]

In a prospective study by Etgen et al., 174 patients with MRI-confirmed ischemic stroke patients were followed with serial measurement of cardiac enzymes cTnT or cTnl at admission, day 1 and day 2. The highest elevation of troponin was seen on day 2 for cTnI in 8 of 103 (7.8%) and on day 3 for cTnT in 8 of 174 (4.6%). The study recommended that measurement of cTnT or cTnI should not currently be included in the routine diagnostic regimen of the acute stroke patient and it had no impact on patient outcome.[17]

In a separate prospective study by Abdi et al. of 114 stroke patients in the period between January of 2013 until August of 2013, troponin T was elevated (≥ 24 ng/l) in 20 (17.6%) of 114 patients, troponin T elevation in acute ischemic stroke patients was associated with higher age, creatinine, electrocardiogram (ECG) changes and severity of stroke, but location of stroke was not a determinant factor, investigators concluded that stroke severity, not its location, was associated with higher troponin levels.[5]

On the other hand Barber et al., in a prospective study of 222 stroke patients, measured both troponin I (cTnI) and catecholamines. Ischemic damage on brain computed tomography (CT) scan was graded using the Alberta Stroke Program Early CT Score (ASPECTS), researchers found that forty-five patients (20%) had troponin $I > 0.2\ \mu g/l$. These troponin-positive patients had higher epinephrine levels. The study concluded that raised troponin I is associated with elevation of circulating epinephrine. However, increased troponin is not associated with insular damage and does not independently predict poor outcome in acute ischemic stroke.[10]

Table 1 Different trials demonstrate the significance of elevated troponin in acute stroke.

Study	Study design	#	Frequency/incidence	Prognosis/significance	Study conclusion
Jensen et al. [1,20]	Prospective study August 2003 to October 2004	244	Elevated levels of TnT (> 0.03 μg/L) and creatine kinase-MB (≥10 μg/L) were observed in 25 patients (10%) and 21 patients (9%) of patients, respectively	7 patients (3%) had elevations of TnT or creatine kinase-MB and electrocardiographic changes suggesting acute myocardial infarctions	Heart and renal failure rather than myocardial infarction are the most likely causes of elevated troponin Patient with elevated troponin has a higher mortality within the following 2 years No threshold below which elevations of troponins are harmless
James et al. [4]	Observational study 1997	181	Troponin T concentration was raised (> 0.1 microgram/l) in 17% (30) of patients	Thirty-one patients died in hospital (12/30 (40%) patients with a raised troponin T concentration v 19/151 (13%) patients with a normal concentration	Serum troponin T concentration at hospital admission is a powerful predictor of mortality in patients admitted with an acute ischemic stroke
Raza et al.[9]	Retrospective study (2008–2010)	212	17 patients had positive troponins	Patients with positive troponin was found to have a higher risk for nonfatal myocardial infarction 41.2%, major adverse cardiovascular events 41.2%, and death from any cause 41.2% compared to 3.3%, 14.2% and 14.5% respectively in the normal troponin group	Elevated cardiac troponin in patients with acute stroke and no evidence of ACS is strong predictor of long-term cardiac outcomes
Barber et al.[11]	Prospective study	222	Forty-five patients (20%) had troponin I > 0.2 μg/l. These troponin-positive patients had higher epinephrine	Patient with elevated troponin I and epinephrine were more likely to have electrocardiograms coded as definite or possible acute myocardial infarction	Raised troponin I is associated with elevation of circulating epinephrine. Increased troponin is not associated with insular damage and does not independently predict poor outcome in acute ischemic stroke
Fure et al.[18]	Prospective study 2000–2002	279	TnT was elevated (> 0.04 μg L^{-1}) in 26 patients (9.6%)	The most frequent ECG changes were: prolonged QTc 36.0%, ST depression 24.5%, atrial fibrillation 19.9% and T wave inversion 17.8%. In logistic regression analyses, ST depression and Q waves were significantly associated with a rise in TnT	A rise in TnT was significantly associated with a poor short-term outcome (modified Rankin scale > 3)
Thorleif Etgen et al.[19]	Prospective study 2004	174	Elevated cTnT or cTnI concentration without evident myocardial lesion is found only in 4.6% to 7.8% of all acute ischemic strokes	The highest proportion of raised parameters was found at day 2 for cTnI in 8 of 103 (7.8%), at day 3 for cTnT in 8 of 174 (4.6%)	Measurement of cTnT or cTnI should not currently be included in the routine diagnostic, and it has no impact on the outcome[19] found that the size of the cerebral lesion size and the presence of heart failure were the only prognostic factors for mortality[1]
Thålin et al.[21]	Retrospective cohort study	247	There were 133 patients (54%) with TnI less than 0.03 μg/L (normal), 74 patients (30%) with TnI 0.03-0.11 μg/L (low elevation), and 40 patients (16%) with TnI greater than 0.11 μg/L (high elevation)	TnI elevations were associated with a higher age, prior ischemic stroke, chronic heart failure, renal insufficiency, stroke severity, and ST segment elevation or depression on admission. The rate of hyperlipidemia decreased with increasing TnI	Troponin elevation in patients with acute stroke, even when adjusted for several possible confounders, is associated with an almost 2-fold increased risk of 5-year mortality
Darki et al.[23]	Single center retrospective study	137	Twenty-four of 137 patients (17.5%) had a positive troponin level. Sixteen of 24 (67%) patients with a positive troponin level had a new wall motion abnormality on echocardiogram	On statistical analysis, significant association between troponin and brain natriuretic peptide elevation with positive segmental wall motion abnormality on echocardiogram	These study findings represent a new paradigm of interpreting elevated cardiac biomarkers and may help with risk stratification and diagnosis of patients presenting with AIS

Scheitz et al.[12]	Prospective study	1016	Peak cTnT levels were significantly associated with unfavorable outcome	Optimal cut-off for determining unfavorable outcome proved to be 16 mg/dL. Dynamic changes of cTnT were detected in 137 patients	Novel findings relevant for interpretation of highly sensitive cTnT assays in acute ischemic stroke. Myocardial injury is detectable in more than half patients, even moderately elevated cTnT is associated with unfavorable outcome (optimal cutoff and dynamic changes in cTnT indicate an increased risk of in-hospital death
Peddada et al.[27]	Retrospective study from 2008 to 2012	1145	199 (17%) had elevated troponin levels	Troponin positive patients had more cardiovascular risk factors, more intensive medical therapy, and greater use of cardiac procedures	Ischemic stroke patient with abnormal troponin levels are at a higher risk of in-hospital death, even after accounting for demographic and clinical characteristics, and any degree of troponin elevation identifies this higher level of risk. Troponins that continue to rise during the hospitalization identify stroke patients at markedly higher risk of mortality and both neurologic and non-neurologically mediated mortality rates are higher when troponin is elevated

A comparison of several trials demonstrating the significance of elevated troponin in acute stroke can be seen in Table 1.

5.1. Management

Management of acute coronary syndrome in the setting of acute stroke is challenging task, balancing the risks versus benefits of each of the treatment modalities. Although no Randomized Clinical Trials (RCT) were found in the literature to support the therapeutic consequences by sole increase of elevated troponins especially when the contemporary treatment approach is based on the presumed or confirmed stroke etiology, hence using only the clinician's judgment can be problematic and decisions should be made based on the expertise of both the cardiologist and neurologist.

Measurements of serial troponins are a key element in detecting acute coronary syndrome (ACS) in association with an acute neurogenic event like acute stroke. Andres B et al., concluded that high sensitive-TNI elevations without dynamic changes (defined as 30% increase or decrease of the critical value within 3 h of measurement) may occur in stroke patients without ACS due to different mechanisms that stress the heart; therefore, the authors recommended that trending troponin levels combined with further cardiology work up is essential for better management.[18]

Although no clear cut level for troponin elevation was defined to signify the extent of myocardial injury, the magnitude of troponin elevation in stroke patients without coronary artery occlusion is often less than that seen with acute MI due to coronary artery occlusion.[4,6,8] cTnI has superior sensitivity and specificity to CK-MB in revealing minor myocardial injury.[3]

Based on the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), the use of aspirin (300 mg and 160 mg respectively) within 48 h of acute stroke onset was associated with a significant reduction in stroke recurrence within 14 days as well as reduction of nonfatal stroke and death.[19,20]

Still undetermined is the use of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) in acute stroke patients. The results of two ongoing trials Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) and Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) are awaited to confirm whether or not dual antiplatelet will benefit patient with acute stroke.[21,22]

Scheiz et al., proposed an algorithm recently in Stroke for an approach to acutely versus chronically elevated troponin in acute ischemic stroke. In the patient with acute elevation further evaluation to assess if the MI is type 1 vs 2 is investigated. If here are no coronary causes of the elevation then it is possible to postulate that the patient might have NHS. In patient with chronically elevated troponins, evaluation of severity and treat appropriately.[12]

The immediate use of anticoagulation (unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants and thrombin inhibitors) in the setting of acute stroke has been associated with an increased risk of intracranial hemorrhage (ICH) with no short or long-term benefits,[23] the risk increasing with the increase in the cerebral infarction size. On the other hand, such ICH patients with ACS, including non-ST segment myocardial infarction and unstable angina

had decreased risk of AMI; however the use of heparins were similar to placebo in terms of the risk of mortality, revascularization, recurrent angina, and thrombocytopenia.[24]

In a large meta-analysis of data, statin therapy at stroke onset was associated with improved outcome.[25] Statin therapy is a cornerstone in ACS treatment and an intensive lipid-lowering statin regimen was found to provide greater protection against death or major cardiovascular events. Patients may benefit from early and continued lowering of low-density lipoprotein (LDL) cholesterol.[26]

6. Conclusions

Elevated troponin in the setting of acute stroke is not an uncommon problem and appears to have a different pathological mechanism compared with elevated troponin due to pure acute coronary occlusion. Stroke patients with elevated troponin have a worse prognosis and outcome when compared to those who do not. Managing such patients is often a challenge and requires a collaborate approach by both the cardiologist and the neurologist. Most experts would agree on the use of aspirin and statins, while anticoagulation in this setting could be associated with an increased risk of bleeding. The use of dual antiplatelet therapy has yet to be established. Further research is needed to determine the best therapeutic approach.

Conflicts of interest

Authors report no potential conflicts of interest.

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