ORIGINAL RESEARCH

Association Between Troponin Levels and Embolic Stroke of Undetermined Source

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***Background*—**Our aim was to determine whether patients with embolic strokes of undetermined source (ESUS) have higher rates of elevated troponin than patients with noncardioembolic strokes.

***Methods and Results*—**CAESAR (The Cornell Acute Stroke Academic Registry) prospectively enrolled all adults with acute stroke from 2011 to 2014. Two neurologists used standard definitions to retrospectively ascertain the etiology of stroke, with a third resolving disagreements. In this analysis we included patients with ESUS and, as controls, patients with small- and large-artery strokes; only patients with a troponin measured within 24 hours of stroke onset were included. A troponin elevation was defined as a value exceeding our laboratory's upper limit (0.04 ng/mL) without a clinically recognized acute ST-segment elevation myocardial infarction. Multiple logistic regression was used to evaluate the association between troponin elevation and ESUS after adjustment for demographics, stroke severity, insular infarction, and vascular risk factors. In a sensitivity analysis we excluded patients diagnosed with atrial fibrillation after discharge. Among 512 patients, 243 (47.5%) had ESUS, and 269 (52.5%) had small- or large-artery stroke. In multivariable analysis an elevated troponin was independently associated with ESUS (odds ratio 3.3; 95% confidence interval 1.2, 8.8). This result was unchanged after excluding patients diagnosed with atrial fibrillation after discharge (odds ratio 3.4; 95% confidence interval 1.3, 9.1), and the association remained significant when troponin was considered a continuous variable (odds ratio for log[troponin], 1.4; 95% confidence interval 1.1, 1.7).

***Conclusions*—**Elevations in cardiac troponin are more common in patients with ESUS than in those with noncardioembolic strokes. **(*J Am Heart Assoc*. 2017;6:e005905. DOI: 10.1161/JAHA.117.005905.)**

Key Words: cardiac biomarkers • cerebrovascular disease/stroke • embolism • infarction • troponin

Cardiovascular and cerebrovascular disease are 2 major causes of death and disability in the United States.[1,2] Because adverse cardiac events are associated with increased mortality after stroke, current American Heart Association/American Stroke Association guidelines recommend evaluating cardiac biomarkers (preferably cardiac troponin [cTn]) in all patients presenting with acute ischemic stroke.[3–5]

Although cTn is highly specific for myocardial injury, it does not reveal the underlying mechanism of injury.[6] The majority of patients with acute ischemic stroke have neither typical symptoms nor electrocardiographic evidence of acute coronary ischemia, but between 5% and 34% of these patients have cTn levels above the diagnostic threshold, suggesting ongoing myocardial injury, when conventional assays are used; when high-sensitivity assays are used, this rate can be as high as 60%.[7,8] Irrespective of the underlying mechanism, elevated cTn values are associated with worse clinical outcomes and a higher risk of mortality in patients with acute ischemic stroke.[8–11]

In order to gain further insight into the underlying pathophysiology of cTn in patients with ischemic stroke, we evaluated whether patients with elevations in cTn but without clinically recognized acute ST-segment elevation myocardial infarction (MI) were more likely to have embolic stroke of undetermined source (ESUS) than patients with small- or

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Clinical Perspective

What Is New?

- Elevated cardiac troponin levels are often found in patients with ischemic stroke, yet their underlying mechanism remains uncertain.
- In this study elevations in cardiac troponin were more common in patients with embolic stroke of undetermined source than in those with noncardioembolic strokes.

What Are the Clinical Implications?

- Further study is necessary to understand the clinical importance of cardiac troponin in cases of embolic stroke of undetermined source; elevations may signify acute myocardial injury as a cause or effect of embolic stroke of undetermined source.

large-artery strokes. We hypothesized that patients with ESUS would be more likely to have elevated cTn than patients with noncardioembolic strokes because many cases of ESUS are believed to originate from the heart.[12,13]

Methods

Design

We performed a retrospective cohort study using CAESAR (the Cornell Acute Stroke Academic Registry). All patients with stroke at New York-Presbyterian Hospital/Weill Cornell Medicine are prospectively enrolled into the American Heart Association's Get With The Guidelines-Stroke registry. This registry provides the foundation for CAESAR, which is then supplemented through retrospective collection of additional clinical, laboratory, and radiographic data. For this analysis we included all adults with acute ischemic stroke between 2011 and 2014. The etiology of stroke was retrospectively ascertained by 2 independent neurologists, with a third neurologist resolving any disagreements. We used the TOAST (from Trial of Org 10172 in Acute Stroke Treatment) criteria and consensus ESUS definition to adjudicate the etiology of all strokes.[12,14] For this study, all patients with cardioembolic stroke were excluded, given the known association between established cardioembolic risk factors and elevated cTn.[15,16] Patients with strokes from other determined etiologies were also excluded given the rarity of those individual stroke mechanisms. We also excluded patients who had an incomplete stroke workup, which comprised the following tests: at least 24 hours of telemetry, echocardiogram, brain MRI or CT of head, and head and neck vascular imaging. Thus, our final cohort consisted of all patients with ESUS and, as controls, those with small- or large-artery strokes who underwent a standard stroke workup. We then excluded all patients without a cTn value within 24 hours of stroke onset.

Measurements

Our predictor variable was a cTn elevation, defined in accordance with the third universal definition of MI as a cTn level value above the 99th percentile of our laboratory's upper limit of normal (0.04 ng/mL)[17,18] in the absence of a clinically recognized acute ST-segment elevation MI. The occurrence of a clinically recognized acute ST-segment elevation MI was based on documentation in the medical record by the primary neurology attending, cardiology attending, or the hospitalization diagnosis list. An attending cardiologist formally interpreted all ECGs. For the purposes of our study, only cTn values within 24 hours of acute ischemic stroke onset were considered in our primary analysis. Our outcome of interest was ESUS. To account for confounding factors that might explain differences in the association between elevations in cTn and stroke subtype, we identified the following risk factors using data from the Get With The Guidelines-Stroke registry: stroke onset to time of cTn testing, initial systolic blood pressure, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease (as defined by a history of MI or angina, or previous percutaneous coronary intervention), peripheral vascular disease, congestive heart failure, serum creatinine, chronic kidney disease, tobacco use, alcohol or drug abuse, and prior stroke.

In addition, we recorded information on both stroke severity and the presence of insular infarction, as these have been associated with elevations in cTn.[19–23] Stroke severity was measured using the National Institutes of Health Stroke Scale.

Statistical Analyses

The chi-squared test was used to compare the rate of ESUS versus small- or large-artery strokes in patients with cTn elevation. The Mann-Whitney U test was used for continuous variables because the data were not normally distributed. Multiple logistic regression was used to evaluate the association between cTn elevation in the absence of a clinically recognized ST-segment elevation MI and ESUS after adjustment for demographics, National Institutes of Health Stroke Scale score, insular infarction, and cardiovascular risk factors. Because the goal of the study was to isolate the association between cTn elevation and ESUS rather than to build a parsimonious prediction model, and because we had more than 10 outcomes per covariate, all covariates were included in the model regardless of statistical significance.

We performed 5 sensitivity analyses. In accordance with the third universal definition of MI, which states that cardiac

damage occurs with a rise and/or fall of cardiac biomarker values,[18] in the first sensitivity analysis, we considered our predictor variable to be a dynamic change in the initially elevated cTn to exclude patients with chronic elevations in cTn. A dynamic change in cTn was considered to occur when the cTn value had changed by at least 0.01 ng/mL >6 hours after the initial cTn was drawn.[17] In the second sensitivity analysis we excluded ESUS patients who were found to have atrial fibrillation during follow-up ambulatory heart-rhythm monitoring. Because baseline antithrombotic use may have potentially reduced myocardial injury and led to lower levels of cTn, in the third sensitivity analysis, we included baseline antithrombotic use as an additional covariate in our model. Some patients with ESUS and large- or small-artery strokes did not have an available cTn drawn within 24 hours of stroke onset, so in the fourth sensitivity analysis, we estimated missing cTn values using a multiple imputation analysis based on variables associated with an elevated cTn in a backward stepwise logistic regression with a P=0.2. In the fifth sensitivity analysis, rather than including all covariates in our multiple logistic model, in order to account for possible overfitting, we performed a backward stepwise logistic regression with a P=0.2. Finally, we also performed a multiple logistic regression using the logarithmically transformed cTn value as a continuous variable. The Weill Cornell Medicine Institutional Review Board approved this study and waived the requirement for patient consent. All statistical analyses were performed by A.E.M. and G.G. using Stata/MP (version 13, College Station, TX). The threshold of statistical significance was set at α=0.05.

Results

Between 2011 and 2014, we identified 642 patients with ESUS or small- or large-artery strokes, of whom 512 had an available cTn drawn within 24 hours of stroke onset. A similar number of patients with ESUS and with small- or large-artery strokes were excluded due to lack of cTn measurement within 24 hours of stroke onset (P=0.37). Of the 512 patients included in the analysis, 67 (13.1%) had an elevation in cTn in the absence of a clinically recognized acute ST-segment elevation MI, and 56 (10.9%) had a dynamic change in cTn levels. Patients with elevations in cTn were of similar age to patients without elevations in cTn (70.7 years versus 67.5 years) and more likely female. Patients with elevations in cTn had more severe strokes (median National Institutes of Health Stroke Scale 6 versus 3), had higher rates of insular infarction, were more likely to have coronary artery disease, chronic kidney disease, and a higher initial serum creatinine, and were less likely to be active smokers than patients without elevations in cTn (Table 1).

Table 1. Characteristics of Patients, Stratified by Presence of Elevated cTn

Characteristic*	Elevated cTn (N=67)	Normal cTn (N=445)	*P* Value
Age, mean (SD), y	70.7 (15.4)	67.5 (14.4)	0.05
Female	38 (56.7)	192 (43.2)	0.04
Race			0.46
White	59 (88.1)	386 (86.7)	
Black	2 (3.0)	33 (7.4)	
Hispanic	2 (3.0)	8 (1.8)	
Other	4 (6.0)	18 (4.0)	
Payment source			0.32
Medicare	37 (55.2)	193 (43.4)	
Medicaid	11 (16.4)	83 (18.7)	
Private	16 (26.9)	158 (35.5)	
Other	3 (4.5)	11 (2.5)	
Ischemic stroke subtype			0.003
Large-artery	18 (26.9)	132 (30.0)	
Small-artery	6 (9.0)	113 (25.4)	
ESUS	43 (64.2)	200 (44.9)	
Initial SBP, mean (SD)	154 (33)	156 (31)	0.78
Hypertension	48 (71.6)	319 (71.7)	0.99
Diabetes mellitus	21 (31.3)	129 (29.0)	0.69
Coronary heart disease	19 (28.4)	67 (15.1)	0.007
Congestive heart failure	1 (1.5)	7 (1.6)	0.96
Peripheral vascular disease	5 (7.5)	15 (3.4)	0.11
Dyslipidemia	29 (43.3)	227 (51.0)	0.24
Initial serum creatinine†, mean (SD)	1.55 (1.52)	1.0 (0.66)	0.003
Chronic kidney disease	6 (9.0)	3 (0.7)	<0.001
Valvular disease	1 (1.5)	1 (0.2)	0.12
Prior stroke	14 (20.9)	103 (23.2)	0.68
Tobacco use	2 (3.0)	52 (11.7)	0.03
Drug or alcohol use	0 (0)	7 (1.6)	0.30
Insular infarction	18 (26.9)	43 (9.7)	<0.001
NIHSS, median (IQR)	6 (2–16)	3 (1–6)	0.004
Stroke onset to cTn testing‡, mean (SD)	1.3 (0.3)	2.1 (0.2)	0.50
Baseline antithrombotic use	29 (43.3)	203 (45.6)	0.72

cTn indicates cardiac troponin; ESUS, embolic stroke of undetermined significance; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

*Data are presented as number (%) unless otherwise specified.

†Serum creatinine expressed as mg/dL.

‡Onset to cTn expressed in hours.

A total of 243 (47.5%) had ESUS, and 269 (52.5%) had a small- or large-artery stroke. Patients with ESUS were younger (mean age, 66.0 years versus 69.7 years) and more often female, had equally severe strokes (median NIHSS, 3) and similar rates of insular infarctions, had lower initial systolic blood pressure values, and were less likely to have hypertension, diabetes mellitus, dyslipidemia, or a history of prior stroke (Table 2).

In univariate analysis, 17.7% (95% confidence interval [CI], 12.9%, 22.5%) of patients with ESUS had an elevated cTn in the absence of a clinically recognized ST-segment elevation MI as compared to 8.9% (95% CI, 5.5%, 12.4%) of patients with noncardioembolic stroke (P=0.003). The median (interquartile range) value of cTn elevation was 0.17 ng/mL (0.08–0.59 ng/mL) in patients with ESUS as compared to 0.10 ng/mL (0.07–0.32 ng/mL) (P=0.003) in patients with small- or large-artery stroke.

After adjustment for demographics, stroke severity, insular involvement, and cardiovascular risk factors, elevated cTn in the absence of clinically recognized ST-segment elevation MI remained associated with ESUS (odds ratio [OR] 3.3; 95% CI 1.2, 8.8, P=0.017) (Table 3). This result was unchanged in all 5 sensitivity analyses: the analysis in which our predictor variable was a dynamic change in cTn levels (OR 3.0; 95% CI 1.0, 9.1, P=0.047), the analysis in which we excluded patients who had atrial fibrillation documented on postdischarge continuous heart-rhythm monitoring (OR 3.4; 95% CI 1.3, 9.1, P=0.01), the analysis in which we included baseline antithrombotic use as an additional covariate in our model (OR 3.3; 95% CI 1.2, 8.8, P=0.018), the analysis in which we performed a multiple imputation analysis to estimate cTn values for patients without an available cTn drawn within 24 hours of stroke onset (OR 2.2; 95% CI 1.2, 3.9, P=0.01), and the analysis in which we performed a backward stepwise logistic regression in order to account for residual overfitting (OR 3.9 95% CI 1.6, 9.6, P=0.003) (Table 3). When we assessed cTn as a continuous variable, the association between cTn and ESUS remained significant (OR for log[cTn] 1.4; 95% CI 1.1, 1.7).

Table 2. Characteristics of Patients, Stratified by Stroke Subtype

Characteristic*	ESUS (N=243)	Small- or Large-Artery Stroke (N=269)	*P* Value
Age, mean (SD), y	66.0 (16.0)	69.7 (12.9)	0.03
Female	126 (51.9)	104 (38.7)	0.003
Race			0.23
White	219 (90.1)	226 (84.0)	
Black	13 (5.4)	22 (8.2)	
Hispanic	3 (1.2)	7 (2.6)	
Other	8 (3.3)	14 (5.2)	
Payment source			0.36
Medicare	105 (43.2)	125 (46.5)	
Medicaid	42 (17.3)	52 (19.3)	
Private	92 (37.9)	84 (31.2)	
Other	4 (1.7)	8 (3.0)	
Initial SBP, mean (SD)	151 (29)	159 (32)	0.009
Hypertension	151 (62.1)	216 (80.3)	<0.001
Diabetes mellitus	50 (20.6)	100 (37.2)	<0.001
Coronary heart disease	33 (13.6)	53 (19.7)	0.06
Congestive heart failure	4 (1.7)	4 (1.5)	0.89
Peripheral vascular disease	8 (3.3)	12 (4.5)	0.50
Dyslipidemia	105 (43.2)	151 (56.1)	0.003
Initial serum creatinine,† mean (SD)	1.05 (0.90)	1.12 (0.80)	0.24
Chronic kidney disease	5 (2.1)	4 (1.5)	0.62
Valvular disease	1 (0.4)	1 (0.4)	0.94
Prior stroke	44 (18.1)	73 (27.1)	0.02
Tobacco use	20 (8.2)	34 (12.6)	0.11
Drug or alcohol use	3 (1.2)	4 (1.5)	0.81
Insular infarction	34 (14.0)	27 (10.0)	0.17
NIHSS, median (IQR)	3 (1–7)	3 (1–7)	0.77
Stroke onset to cTn testing‡, mean (SD)	1.8 (0.3)	2.2 (0.3)	0.12
Baseline antithrombotic use	95 (39.1)	137 (50.9)	0.007

cTn indicates cardiac troponin; ESUS, embolic stroke of undetermined significance; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.
*Data are presented as number (%) unless otherwise specified.
†Serum creatinine expressed as mg/dL.
‡Onset to cTn expressed in hours.

Discussion

Given the clinical and pathophysiological overlap of stroke and cardiovascular disease and the prognostic significance of cTn, the American Heart Association/American Stroke Association guidelines recommend evaluating cTn in every patient with an acute ischemic stroke.[3] Although cTn elevations are common in patients with acute ischemic stroke, the underlying mechanism remains unknown.[7–9,24,25] Our results suggest that patients with elevations in cTn but without clinically recognized acute ST-segment elevation MI are more likely to have ESUS as opposed to those who have had noncardioembolic strokes. This association remained significant even after stroke severity and insular involvement have been taken into consideration, when only patients with a dynamic change in cTn levels are considered, when patients

Table 3. Logistic Regression Models Evaluating the Relationship Between cTn and ESUS

	OR (95% CI)	*P* Value
Unadjusted	2.2 (1.3-3.7)	0.004
Primary analysis*	3.3 (1.2-8.8)	0.017
Sensitivity analysis 1†	3.0 (1.0-9.1)	0.047
Sensitivity analysis 2‡	3.4 (1.3-9.1)	0.01
Sensitivity analysis 3§	3.3 (1.2-8.8)	0.018
Sensitivity analysis 4‖	2.2 (1.2-3.9)	0.01
Sensitivity analysis 5¶	3.9 (1.6-9.6)	0.003

CI indicates confidence interval; cTn, cardiac troponin; ESUS, embolic stroke of undetermined source; OR, odds ratio.
*Adjusted for demographics, stroke severity, insular involvement, and cardiovascular risk factors.
†In which the predictor variable was a dynamic change in cTn levels.
‡In which patients with atrial fibrillation documented on postdischarge continuous heart-rhythm monitoring were excluded.
§In which baseline antithrombotic use was included as an additional covariate in our model.
‖In which a multiple imputation analysis was used to estimate cTn values for patients without an available cTn drawn within 24 hours of stroke onset.
¶In which backward stepwise logistic regression was used in order to account for residual overfitting in our primary model.

with atrial fibrillation discovered on follow-up prolonged rhythm monitoring have been excluded, and after accounting for baseline antithrombotic use.

Elevations in cTn may occur in patients with acute ischemic stroke who have concomitant acute plaque rupture causing myocardial ischemia. However, in the TRELAS (Troponin Elevation in Acute Ischemic Stroke) study, only 7/29 (24%) of patients with acute ischemic stroke with elevations in cTn were thought to have a culprit coronary lesion (the majority of which were asymptomatic), suggesting that there may be alternative mechanisms of cTn elevations in patients with acute ischemic stroke.[26] In the absence of a clinically apparent MI, tachyarrhythmia or nonischemic myocardial injury such as neurogenic stunned myocardium (Takotsubo cardiomyopathy) can also result in cTn elevations.[5,27,28] Neurogenic stunned myocardium may lead to severe cardiac dysfunction and cTn release through alterations in the neural outflow to the heart.[29] The insular cortex is believed to play a role in orchestrating central autonomic control, and there is some evidence that injury to the insular cortex may be associated with elevated circulating catecholamines leading to both stunned myocardium and elevated cTn levels.[19,21–23,30,31] Finally, chronic, stable conditions associated with elevated cTn such as congestive heart failure and chronic kidney disease may all lead to asymptomatic cTn elevations.[9] Even when these potential confounders were controlled for, an elevated cTn remained associated with ESUS.

It is unclear why patients with ESUS were more likely to have an elevated cTn than were patients with noncardioembolic strokes. Although patients with ESUS lack clear cardioembolic risk factors such as severe congestive heart failure, atrial fibrillation, or recent MI, a majority of emboli are still thought to arise from the heart.[12,13] Although nonischemic myocardial injury is a possible explanation for why patients with ESUS are more likely to develop cTn elevations than patients with small- or large-artery strokes, the association between elevations in cTn and ESUS remained unchanged after accounting for factors associated with the development of neurogenic stunned myocardium such as stroke severity and insular cortex involvement; we additionally excluded patients with an ejection fraction of less than 35% because this would be considered a cardioembolic risk factor.[14,19,21,22] Alternatively, patients with ESUS may have simultaneously embolized to both the brain and the coronary arteries, leading to a symptomatic cerebral infarct and an asymptomatic elevation in cTn. Last, ESUS may be due to an embolism from an unrecognized cardiac insult. Myocardial injury, as represented by an elevated cTn, may lead to abnormal ventricular contraction and, in turn, serve as a nidus for thrombus formation and subsequent cardioembolism.[32,33] Further research will be necessary to elucidate the pathogenesis linking myocardial injury and ESUS.

Irrespective of the mechanism of myocardial injury, elevated cTn carries prognostic information in patients with acute ischemic stroke. Multiple studies have shown that patients with acute ischemic stroke and elevated cardiac biomarkers face an increased risk of mortality and unfavorable functional outcome at discharge.[8–11] Because our study suggests that patients with ESUS have higher levels of cTn than those with small- or large-artery strokes, further data are necessary to assess whether stroke subtype affects outcomes in patients with ischemic stroke and elevated cTn.

Our study must be considered in light of its limitations. First, although we accounted for history of congestive heart failure and renal insufficiency, we could not account for patients with chronic baseline elevations in cTn; however, our results were unchanged when a dynamic change in cTn was set as our sole predictor variable. Second, not all patients with ESUS were evaluated with a transesophageal echocardiogram or bubble study, which may have revealed alternative mechanisms of stroke; however, we defined ESUS per consensus definitions, which consider a precordial transthoracic echocardiogram, electrocardiogram, and 24 hours of telemetry as sufficient to rule out causes of cardioembolism.[12] Third, CAESAR is a single-center registry, and therefore, the results of this study may not be generalizable to all patients with acute ischemic stroke. Fourth, we lacked cTn measurements in many patients with ESUS or small- or large-artery strokes, and therefore our results may reflect a bias of ordering cTn in patients with cardioembolic-appearing

strokes. However, a similar number of patients with ESUS and small- or large-artery strokes had missing cTn measurements within 24 hours of stroke onset, and our results were largely unchanged when we imputed missing cTn values based on variables associated with elevated cTn in a backward stepwise logistic regression analysis. Fifth, we may not have fully accounted for differences in premorbid antithrombotic use and adherence.

Although our findings must be interpreted in light of the wide confidence intervals in our adjusted analyses, which may be due to the number of cases in our single-center cohort, our results suggest that elevations in cTn without clinically apparent ST-segment elevation MI appear to be more common in patients with ESUS than in patients with small- or large-artery strokes.

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