Cardiac Biomarkers Predict Large Vessel Occlusion in Patients with Ischemic Stroke

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Background and Purpose: Cardiac biomarkers may help identify stroke mechanisms and may aid in improving stroke prevention strategies. There is limited data on the association between these biomarkers and acute ischemic stroke (AIS) caused by large vessel occlusion (LVO). We hypothesized that cardiac biomarkers (cardiac troponin and left atrial diameter [LAD]) would be associated with the presence of LVO. *Methods:* Data were abstracted from a single center prospective AIS database over 18 months and included all patients with AIS with CT angiography of the head and neck. The presence of LVO was defined as proximal LVO of the internal carotid artery terminus, middle cerebral artery (M1 or proximal M2), or basilar artery. Univariate analyses and predefined multivariable models were performed to determine the association between cardiac biomarkers (positive troponin [troponin ≥0.1 ng/mL] and LAD on transthoracic echocardiogram) and LVO adjusting for demographic factors (age and sex), risk factors (hypertension, diabetes, hyperlipidemia, history of stroke, congestive heart failure, coronary heart disease, and smoking), and atrial fibrillation (AF). *Results:* We identified 1234 patients admitted with AIS; 886 patients (71.8%) had vascular imaging to detect LVO. Of those with imaging available, 374 patients (42.2%) had LVO and 207 patients (23.4%) underwent thrombectomy. There was an association between positive troponin and LVO after adjusting for age, sex and other risk factors (adjusted OR 1.69 [1.08-2.63], $P = .022$) and this association persisted after including AF in the model (adjusted OR 1.60 [1.02-2.53], $P = 0.043$). There was an association between LAD and LVO after adjusting for age, sex, and risk factors (adjusted OR per mm 1.03 [1.01-1.05], $P = 0.013$) but this association was not present when AF was added to the model (adjusted OR 1.01 [0.99-1.04], $P = .346$). Sensitivity analyses using thrombectomy as an outcome yielded similar findings. *Conclusions:* Cardiac biomarkers, particularly serum troponin levels, are associated with acute LVO in patients with ischemic stroke. Prospective studies are ongoing to confirm this association and to test

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whether anticoagulation reduces the risk of recurrent embolism in this patient population.

Key Words: Troponin—left atrial enlargement-–stroke—large vessel occlusion—cardiac biomarkers

Introduction

The annual incidence of ischemic stroke in the United States is approximately 680,000, with nearly about 10% related to a large vessel occlusion (LVO),[1] a proportion of which may benefit from endovascular treatment. Several clinical scores based on symptoms and signs have been used to predict LVO.

Cardiac biomarkers may help identify stroke mechanisms and may aid in improving stroke prevention strategies. Recent studies have shown an association between cardiac biomarkers and ischemic stroke, particularly those related to embolism.[2]

While recent evidence suggests that atrial fibrillation (AF) is associated with LVO,[3] there is limited data on the association between other cardiac biomarkers and LVO in patients with acute ischemic stroke (AIS). We aim to determine the association between cardiac biomarkers (cardiac troponin and left atrial diameter [LAD]) and the presence of LVO in a cohort of patients with AIS.

Methods

Study Cohort

Institutional review board approval was obtained to analyze data from the Rhode Island Hospital prospective AIS database collected for quality improvement purposes and stored in RedCap (Nashville, TN). We included consecutive patients between January 1st, 2016 and June 30th, 2017 with a discharge diagnosis of AIS admitted within 24 hours from last known normal time who underwent emergent vascular imaging using computerized tomography angiography (CTA) of the brain and neck upon arrival to the emergency department to evaluate for the presence of acute LVO. In our institution, almost all patients with suspected AIS presenting within 24 hours of symptoms undergo emergent CTA head and neck in the emergency department to screen for LVO. During the study period, patients eligible for MT were those with proximal large artery occlusion (intracranial internal carotid artery, middle cerebral artery M1 or proximal M2 segments, or basilar artery) whose Alberta Stroke Program Early CT score was 6 or more presenting within 6 hours from onset of a disabling neurological deficit or between 6 and 24 hours based on advanced neuroimaging.

In general, patients with a suspected diagnosis of ischemic stroke are admitted to the hospital for a diagnostic evaluation that includes vascular imaging (CTA or MRA), brain imaging (CT or MRI), telemetry, laboratory testing including serum troponin levels on admission, and 2-dimensional transthoracic echocardiography.[4]

Primary Predictors

The primary predictors were:

- The anterior-posterior LAD measured in mm on 2-dimensional echocardiography using echocardiography guidelines.
- Serum troponin levels on admission and divided into 2 groups: positive (troponin $\geq$0.1 ng/m) and negative (troponin <0.1 ng/mL) based on our lab's guidelines for troponin assay positivity.

Study Variables

The following covariates were prospectively collected and abstracted from the database

- Demographic variables: age and sex
- Clinical risk factors: history of hypertension, history of hyperlipidemia, history of diabetes, history of AF or AF on admission, history of coronary heart disease, and history of congestive heart failure, active smoking
- In-hospital treatments: intravenous alteplase

Outcomes

The study outcomes were:

- The primary outcome was the presence of LVO defined as occlusion of a proximal intracranial artery: intracranial internal carotid artery, middle cerebral artery M1 segment and proximal M2 segment, and basilar artery.
- The secondary outcome was whether the patient underwent mechanical thrombectomy (MT) (MT versus non-MT).

Statistical Analysis

Patients were divided into 2 groups based on the presence of LVO (LVO versus non-LVO) and whether they underwent MT (MT versus non-MT). We performed univariate analyses to compare demographic and clinical

characteristics between the LVO and the non-LVO groups. We used ANOVA for categorical variables and *t* tests for continuous variables. We then performed prespecified multivariable analyses to determine the association between LAD and positive troponin with the primary and secondary outcomes.

The models used were:

- Model 1 adjusted for age and sex
- Model 2 adjusted for age, sex, history of hypertension, history of diabetes, history of hyperlipidemia, history of coronary artery disease, history of congestive heart failure, active smoking, and history of prior stroke
- Model 3 adjusted for age, sex, history of hypertension, history of diabetes, history of hyperlipidemia, history of coronary artery disease, history of congestive heart failure, active smoking, and history of prior stroke, and history of AF

Statistical analysis was performed using SPSS version 20.0 (Chicago, IL) and *P* less than .05 was considered statistically significant.

Results

Baseline Characteristics and Univariate Analyses

We identified 1234 patients admitted with AIS during the study period; 886 patients (71.8%) presented within 24 hours of onset and a CTA angiogram performed in the emergency department to assess for LVO. Of those with imaging available, 374 patients (42.2%) had LVO and 207 patients (23.4%) underwent MT (Figure 1). Serum troponin level on admission was performed on 809 patients (91.3%) and LAD on transthoracic echocardiogram was reported on 594 patients (67.0%).

On univariate analyses, patients with LVO were more likely to have a positive troponin level (17.0% versus 9.4%, $P = .002$). In addition, the LAD was larger in patients with LVO compared to those without LVO (38.6 ± 7.9 mm versus 36.9 ± 7.8 mm, $P = .011$). Table 1.

Multivariable Models Showing Association with LAD, Troponin Positivity, and LVO

There was an association between positive troponin and LVO after adjusting for age, sex, and other risk factors (adjusted OR 1.69 [1.08-2.63], $P = .022$) and this association persisted after including AF in the model (adjusted OR 1.60 [1.02-2.53], $P = .043$). Table 2.

On the other hand, there was an association between LAD and LVO after adjusting for age, sex, and risk factors (adjusted OR per mm 1.03 [1.01-1.05], $P = .013$), but this association was not present when AF was added to the model (adjusted OR 1.01 [.99-1.04], $P = .346$). Table 2.

Multivariable Models Showing Association with LAD, Troponin Positivity, and MT

There was an association between positive troponin and MT after adjusting for age and sex and other risk factors (adjusted OR 1.59 (.99-2.54), $P = .056$) and a trend after including AF in the model (adjusted OR 1.50 [.93-2.44], $P = .096$). Table 2.

There was an association between LAD and MT after adjusting for age, sex, and risk factors (adjusted OR per mm 1.04 [1.01-1.07)] $P = .004$) but this association was not present when AF was added to the model (adjusted OR 1.02 [.99-1.04], $P = .355$). Table 2.

Discussion

This study demonstrated that biomarkers of cardiac dysfunction, particularly serum troponin level, are associated with acute LVO in patients with AIS with the association between troponin positivity and LVO persisting after adjusting for AF as opposed to the association between LAD and LVO that disappears when AF was added to the model.

Mechanism of Associations

Recently atrial dysfunction or "cardiopathy" defined as the presence of serum, electrocardiographic, or echocardiographic biomarkers, has been introduced as a potential cardioembolic mechanism[2,5]

Left atrial enlargement predisposes to stasis and thrombus formation and embolic stroke risk. Studies have shown an association between LAD and ischemic stroke risk[6] and vascular brain injury, even after adjusting for AF. In fact, a recent analysis from the Northern Manhattan Stroke Study showed that moderate to severe left atrial dilatation was associated with embolic stroke subtypes and this association persisted even after adjusting for AF.[7] In our study, however, the association between left atrial enlargement and LVO disappeared when AF was added to the model. This could be explained by the fact the association between left atrial enlargement and LVO, was mediated by AF or our study being underpowered to determine an association. This may be the case as previous studies showed an association between AF and left atrial enlargement.[8,9] Conversely, it is possible that large and proximal clots in patients with left atrial enlargement are more likely to form in the setting of AF and that left atrial enlargement alone without AF is less likely to produce large thrombi that would cause LVO.

Serum troponin level is another biomarker of global cardiac dysfunction that has been shown to be associated with ischemic stroke risk particularly those related to embolism.[2] In fact, a recent study showed that a positive serum troponin level in the setting of ischemic stroke is independently associated with cardioembolic and cryptogenic stroke subtypes.[10] This study however, did not

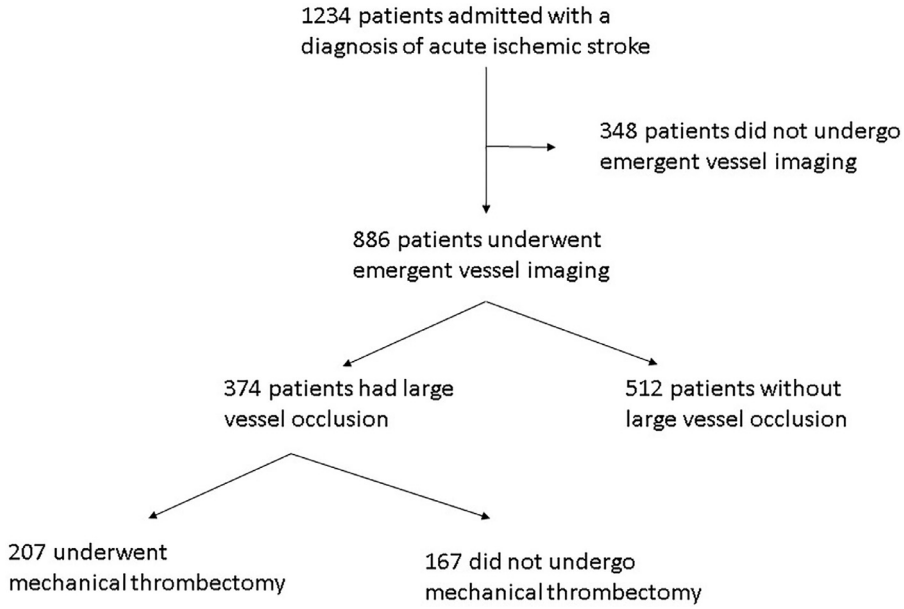

Figure 1. *Diagram showing the study flow chart and final study sample size.*

investigate the association between serum troponin level and the presence of LVO. This association is particularly important as it may lead to therapeutic implications in the acute stroke setting. Therefore, our study suggest that positive troponin level may reflect underlying cardiac disease and not only increases the propensity to cardioembolism but also to LVO. The association between positive troponin and LVO persisted after adjusting for AF which could be explained by the fact that troponin is marker of global cardiac dysfunction as opposed to AF which reflects atrial dysfunction (Tables 1 and 2).

Clinical Implications

Currently, patients with the presence of cardiac biomarkers but without proven AF are recommended for treatment with antiplatelet agents for secondary stroke prevention.[11] This study suggests that patients with certain cardiac biomarkers have a propensity to forming clots and presenting with proximal LVO and therefore it is possible that as in patients with AF, patients with these biomarkers but without AF may constitute a group of patients who may benefit from anticoagulation therapy for secondary stroke prevention. In fact, while the Warfarin-Aspirin Recurrent Stroke Study showed no benefit of Warfarin over Aspirin in the risk of stroke or death at 2 years,[12] a post hoc analysis showed that in patients with elevated amino terminal pro-B-type natriuretic peptide (NT-proBNP) (>750 ng/mL; which is a biomarker of atrial cardiopathy) warfarin was superior to aspirin in reducing the primary outcome.[13] Prospective studies are ongoing to explore cut-off values for these biomarkers in patients with ESUS, confirm this association, and to test whether anticoagulation reduces the risk of recurrent embolism in this patient population (NCT03192215).

Table 1. *Univariate analyses showing baseline characteristics of patients with or without large vessel occlusion*

	Large vessel occlusion (N = 374)	No large vessel occlusion (N = 488)	*P* value
Age in years (mean ± SD)	73.6 ± 14.9	70.3 ± 15.1	.001
Sex (% men)	179 (47.9%)	284 (58.2%)	.003
Hypertension (%)	284 (75.9%)	359 (73.6%)	.478
Diabetes (%)	77 (20.6%)	170 (34.8%)	<.001
Hyperlipidemia (%)	173 (46.3%)	239 (49.0%)	.450
Coronary heart disease (%)	88 (23.5%)	87 (17.8%)	.041
Congestive heart failure (%)	49 (13.1%)	32 (6.6%)	.001
Prior stroke (%)	66 (17.6%)	126 (25.8%)	.005
Active smoking (%)	68 (18.2%)	88 (18.0%)	1.000
Atrial fibrillation (%)	158 (42.2%)	92 (18.9%)	<.001
Positive troponin (%)	60/353 (17.0%)	43/456 (9.4%)	.002
Left atrial diameter in mm (mean ± SD)	38.6 ± 7.9	36.9 ± 7.8	.011

Table 2. *Multivariable analyses showing association between left atrial diameter and positive troponin with large vessel occlusion and mechanical thrombectomy*

	Left atrial diameter OR per mm, 95% CI, *P* value	Positive troponin OR 95% CI, *P* value
Large vessel occlusion		
Unadjusted	1.03 (1.01-1.05), *P* = .012	1.96 (1.29-2.99), *P*= .002
Model 1	1.03 (1.01-1.05), *P* = .008	1.86 (1.21-2.84), *P* = .004
Model 2	1.03 (1.01-1.05), *P* = .013	1.69 (1.08-2.63), *P* = .022
Model 3	1.01 (.99-1.04), *P* = .346	1.60 (1.02-2.53), *P* = .043
Mechanical thrombectomy		
Unadjusted	1.03 (1.01-1.06), *P* = .008	1.76 (1.13-2.74), *P* = .013
Model 1	1.04 (1.01-1.06), *P* = .005	1.73 (1.10-2.71), *P* = .017
Model 2	1.04 (1.01-1.07), *P* = .004	1.59 (.99-2.54), *P* = .056
Model 3	1.02 (.99-1.04), *P* = 0.355	1.50 (0.93-2.44), *P* = 0.096

Strengths and Limitations

This study has several limitations. First, it is a single center retrospective study which limits generalizability. Second, despite our institution's protocol to obtain intracranial CTA on all patients with suspected stroke presenting within 24 hour from onset, some patients presented outside the 24 hour window and did not get emergent vascular imaging which may have introduced bias. Third, the association between cardiac biomarkers and LVO does not imply causality and therefore these biomarkers, particularly troponin levels, may have been elevated due to a neurocardiogenic response from the stroke. Fourth, since this study was performed at a comprehensive stroke center, it was subject to referral bias. This explains the relatively high rates of LVOs detected in our study. Fifth, while nearly 95% of patients had a transthoracic echocardiography performed, about 67% of patients had LAD measurements obtained and this may introduce an element of selection bias. Our study has several strengths including its relatively large sample size with a large number of patients getting vascular imaging, troponin levels, and transthoracic echocardiography and providing real world contemporary data in the era of MT.

Conclusions

Cardiac biomarkers, particularly troponin level, are associated with acute LVO in patients with ischemic stroke. Prospective studies are ongoing to confirm this association and to test whether anticoagulation reduces the risk of recurrent embolism in this patient population.

Author Contributions

Andrew Chang: Data analysis, manuscript revision. Brittany Ricci: Data collection, manuscript revision. Brian MacGrory: Data collection, manuscript revision. Shawna Cutting: outcome adjudication and data collection. Tina Burton: Manuscript revision. Katarina Dakay: Manuscript revision. Mahesh Jayaraman: Manuscript revision and data collection. Christopher Song: Manuscript revision and preparation. Michael Reznik: Manuscript revision. Alexander Merkler: Manuscript revision, study concept and design. Michael P. Lerario: Manuscript revision. Hooman Kamel: Manuscript revision, study concept and design. Mitchell S.V. Elkind: Manuscript revision, study concept and design. Karen L. Furie: Manuscript revision, study concept and design. Shadi Yaghi: Data collection, study concept and design, outcome adjudication, manuscript preparation.

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