Stroke Risk Following Takotsubo Cardiomyopathy

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Abstract

Background and Purpose: Takotsubo cardiomyopathy, also known as stress cardiomyopathy, is an increasingly recognized cause of left ventricular dysfunction. Previously considered a benign disease, Takotsubo cardiomyopathy may be a risk factor of ischemic stroke based on recent small, single-center case series. The strength and temporal profile of this association remains uncertain. **Methods:** We performed a cohort-crossover study using administrative claims data on all emergency department visits and acute care hospitalizations from 2005 to 2015 in California, New York, and Florida. We identified patients with Takotsubo cardiomyopathy, excluding those with a prior or concomitant stroke diagnosis. We compared the risk of ischemic stroke in the first year after Takotsubo cardiomyopathy to the risk of ischemic stroke in the second year after Takotsubo cardiomyopathy. Takotsubo cardiomyopathy and ischemic stroke were ascertained using previously validated ICD-9-CM codes. Absolute risks and odds ratios (OR) were calculated using McNemar test for matched data. **Results:** Among 5283 patients with Takotsubo cardiomyopathy (mean age, 67 years; 92% female), we identified 49 ischemic strokes during the first year after Takotsubo cardiomyopathy versus 19 ischemic strokes during the second year after. The risk of stroke was significantly higher in the year after Takotsubo cardiomyopathy (absolute increase, 0.6%; 95% CI: 0.2-0.9; OR: 2.6; 95% CI: 1.5-4.6) as compared to the control period. **Conclusion:** We found a heightened risk of ischemic stroke in the year after a diagnosis of Takotsubo cardiomyopathy, although the absolute risk increase was small.

Keywords

stroke, cerebrovascular disorders, cardiomyopathy, cerebrovascular disorders, epidemiology, techniques

Takotsubo cardiomyopathy (TCM), also known as stress-related cardiomyopathy, is an increasingly recognized cause of symptoms of acute coronary syndrome.¹ While it has been considered a relatively benign and reversible condition, recent evidence suggests that TCM may be associated with substantial short- and long-term morbidities and mortalities.²⁻⁴ One serious complication of ventricular dysfunction is thromboembolic stroke. Data culled from case reports and small, single-center case series suggest that left ventricular thrombus complicates up to 5% of cases of TCM and may lead to ischemic stroke or transient ischemic attack in about 1% to 3% of cases.^{5,6} Data from the largest registry of patients with TCM suggest that the post-TCM stroke risk is 1% to 2% per patient-year, but the exact association between TCM and stroke is difficult to determine, especially as some of these patients presented with stroke, and thus the TCM may have been a neurogenic complication of the initial stroke.² In this study, we used a large administrative database to determine the magnitude and duration of stroke risk following TCM.

Methods

Study Design

We performed a crossover-cohort study using data from all emergency department visits and inpatient discharges from 2005 to 2011 in California, 2005 to 2015 in Florida, and 2006 to 2013 in New York, available through the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project.⁷ These states represent a demographically

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Table 1. Characteristics of Patients With Takotsubo Cardiomyopathy, Stratified by Ischemic Stroke Occurrence.

Characteristic ^a	Stroke (N = 68)	No stroke (N = 5215)	P value
Age, mean (SD), years	69.9 (14.4)	67.0 (13.0)	.07
Female	62 (91.2)	4806 (92.2)	.77
White	51 (75.0)	3980 (77.5)	<.01
Hypertension	49 (72.1)	3433 (35.8)	.28
Diabetes mellitus	27 (39.7)	1112 (21.3)	<.001
Atrial fibrillation	18 (26.5)	621 (11.9)	<.001
Coronary heart disease	41 (60.3)	2583 (49.5)	.08
Congestive heart failure	23 (33.8)	1248 (23.9)	.06
Chronic kidney disease	10 (14.7)	330 (6.3)	<.01
Chronic obstructive pulmonary disease	19 (27.9)	805 (15.4)	<.01
Tobacco use	13 (19.1)	865 (16.6)	.58

^aData are presented as number (%) unless otherwise specified.

heterogeneous population that accounts for nearly 20% of the US population. Each patient is assigned an individual linkage number that permits anonymous tracking through subsequent hospitalizations. Using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* system, up to 25 discharge diagnoses are coded at each encounter. This analysis of deidentified data was deemed exempt by the Weill Cornell Medicine institutional review board and the right to informed consent was waived.

Study Subjects

Our exposure of interest was a diagnosis of TCM in patients of 18 years or older, which we identified using the previously validated *ICD-9-CM* diagnosis code 429.83.^{8,9} We excluded all hospitalizations in which there was a concomitant diagnosis of TCM and stroke since we would be unable to determine whether a stroke preceded or was the result of TCM if it occurred within the hospitalization for TCM. Patients with a prior history of stroke were also excluded. To optimize longitudinal follow-up, we excluded nonresidents of California, Florida, and New York.

Measurements

Patients were followed for the outcome of ischemic stroke identified by *ICD-9-CM* codes 433.x1, 434.x1, or 436 in any diagnosis code position in the absence of a primary discharge code for rehabilitation (V57) or any codes for subarachnoid hemorrhage (430), intracerebral hemorrhage (431), or brain trauma (800-804 and 850-854). This combination of diagnosis codes has previously been validated, demonstrating a sensitivity of 86%, and a specificity of 95% for ischemic stroke.¹⁰

Statistical Analysis

The risk of ischemic stroke in the first year after TCM was compared with the risk of ischemic stroke in the second year after TCM in patients with our exposure of interest. This design mitigates the effects of unmeasured confounders by

having patients serve as their own comparison. We used McNemar test for matched data via the Stata `mcc` command (Stata/MP version 14, StataCorp).

Results

We identified 5283 patients with TCM without a concomitant diagnosis of stroke; 92% of the patients were female, and the mean age was 67.1 years old (SD: 13.0 years). Sixty-eight (1.3%) patients developed a stroke in 2 years following the index visit.

Forty-nine (0.9%) patients with TCM developed a stroke in the first year after the index visit. In comparison, 19 (0.4%) patients developed a stroke in the second year after TCM. The risk of stroke was significantly higher in the year after TCM (absolute increase, 0.6%; 95% CI: 0.2-0.9; OR: 2.6; 95% CI: 1.5-4.6) as compared to the second year after TCM.

There were no significant differences in age, sex, rates of hypertension, congestive heart failure, coronary heart disease, tobacco use, or alcohol use between patients who developed a stroke and those who did not. Patients who developed a stroke were more likely to have diabetes, chronic obstructive pulmonary disease, chronic kidney disease, and atrial fibrillation (see Table 1).

Discussion

Using data from a large population of patients, we found a significantly heightened relative risk of ischemic stroke in the first year of TCM as compared to the second year after TCM. The absolute risk of stroke following TCM was low.

Prior case series have suggested that there is a 1% to 3% risk of ischemic stroke following a diagnosis of TCM.^{5,6} These studies included strokes that occurred during the index TCM hospitalization, which might account for the slightly higher absolute risk than we found.¹¹ Patients with TCM often have other vascular risk factors, so based on case series, it has not been clear to what degree TCM itself contributed to stroke. In this context, our findings provide novel

information indicating that TCM is an independent risk factor of ischemic stroke.

The purported mechanism of ischemic stroke following TCM is cardioembolism due to left ventricular thrombus formation. Approximately, 5% to 8% of patients with TCM develop left ventricular thrombus, and of those with presumed cardioembolic events, about 40% have a left ventricular thrombus.^{5,12} Other mechanisms may also contribute to stroke risk. Patients with TCM are at risk of thrombogenic arrhythmias such as atrial fibrillation.¹³ Catecholamine-induced platelet activation and endothelial dysfunction may also contribute to stroke risk.^{14,15}

Our study has several important limitations. First, we relied on administrative data that may have led to misclassification of TCM or stroke events. To mitigate this, we used diagnostic code algorithms with excellent sensitivity and specificity, although it is likely that some of these patients did not undergo a complete workup including cardiac catheterization.⁹ Second, we lacked important clinical data such as the trigger of TCM, echocardiography results, and treatment modalities that may impact stroke risk. Third, due to the overall low number of stroke events, we were unable to parse out the duration of increased stroke risk to smaller time unit. Fourth, out of necessity, we did not include ischemic strokes that occurred during the index presentation which led to a more conservative estimation of the stroke risk. Finally, we designed our within-subjects study specifically to determine the magnitude and duration of stroke risk following TCM. Accordingly, we are unable to answer the question of why some patients develop stroke following a diagnosis of TCM while others do not. Our finding that patients who developed stroke had higher rates of diabetes, chronic obstructive pulmonary disease, chronic kidney disease, and atrial fibrillation is hypothesis generating and needs to be explored in further studies.

Compared to existing case series, our findings provide a stronger theoretical rationale for anticoagulation in patients with high-risk of TCM.^{5,16} Given the early heightened risk of stroke after TCM, further studies may be warranted to evaluate immediate and limited duration use of anticoagulation following TCM in order to prevent stroke. Further research is required to determine who is at highest risk of stroke following a TCM diagnosis.

Conclusion

We found a heightened risk of ischemic stroke in the year after a diagnosis of Takotsubo cardiomyopathy, although the absolute risk increase was small.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Kamel serves as the co-PI for the NIH-funded ARCADIA trial which receives in-kind study drug from the BMS-Pfizer Alliance and in-kind study assays from Roche Diagnostics, serves as a steering

committee member of Medtronic's Stroke AF trial (uncompensated), serves on an end point adjudication committee for a trial of empagliflozin for Boehringer-Ingelheim, and served on an advisory board for Roivant Sciences related to Factor XI inhibition.

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