Incidence and predictors of stroke during the index event in an ethnically diverse Takotsubo cardiomyopathy population

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Summary

Takotsubo cardiomyopathy (TTS) is a peculiar clinical condition often affecting postmenopausal women after a stressful trigger. The underlying mechanisms have not been completely elucidated but several hypotheses have been advanced, with catecholamine cardiotoxicity, microvascular dysfunction and coronary artery spasm each suggested to play a role. The incidence of stroke after TTS appears to range from 0% to 7.7%, and interestingly TTS has been described as both a cause and a complication of stroke.
We sought to assess the incidence and predictors of stroke during the index event (peri-index event stroke) in a heterogeneous TTS population.
We conducted a retrospective descriptive study reviewing patients who were discharged with a diagnosis of TTS from the Einstein Medical Center, Philadelphia, PA and Danbury Hospital, Danbury, CT in the period between 2003 and 2014. A total of 206 patients met the modified Mayo Clinic criteria and were included in the study.
The patients' overall mean age was 67.8 years; 87% (n=179) were females and 25% (n=53) were African Americans. The following incidence rates were found: stroke 7%, in-hospital heart failure 26.7%, and in-hospital death 7%. On multivariate analysis independent predictors (expressed as odds ratios with 95% confidence intervals) of peri-index event stroke were: i) African American race (OR 3.2, 95% CI 1.2–10.2, p=0.048); ii) hypertension (OR 10.5, 95% CI 1.3–88, p=0.03).
ACE inhibitor use was a protective factor for developing peri-index event stroke (OR 0.15, 95% CI 0.04–0.5, p=0.001). There was a trend towards dual antiplatelet therapy (DAPT) being protective for stroke (OR 0.3, 95% CI 0.05–1.1, p=0.08).
The incidence of peri-index event stroke was 7%. African American race and hypertension were found to be independent predictors of peri-index event stroke. Prospective clinical trials are needed to confirm these findings and to better determine the impact of hypertension as a risk factor for stroke and to assess the role of DAPT in preventing it.

KEY WORDS: incidence, predictors, stroke, Takotsubo cardiomyopathy

Introduction

Takotsubo cardiomyopathy (TTS) is a peculiar clinical condition often affecting postmenopausal women after a stressful event. Its precise incidence is unknown, although it is believed to account for up to 2.5% of all patients with an initial primary diagnosis of an acute coronary syndrome (Gianni et al., 2006; de Gregorio et al., 2008; de Gregorio, 2010).
The underlying mechanisms have not been completely elucidated but several hypotheses have been advanced, such as a role for catecholamine cardiotoxicity, microvascular dysfunction and coronary artery spasm (Bybee and Prasad, 2008).
In the literature the incidence of stroke after TTS has ranged from 0% to 7.7%, and interestingly TTS has been described as both a cause and a complication of stroke (de Gregorio et al., 2008; de Gregorio, 2010; Bybee and Prasad, 2008; Ouchi et al., 2016; Young et al., 2014).

Psychosocial stress may raise the risk of thromboembolic events by causing an increase in circulating levels of the proinflammatory cytokine interleukin 6 (IL-6). Both IL-6 and IL-7 have been implicated in the pathogenesis of left ventricular dysfunction (Pyo et al., 2003; von Känel and Dimsdale, 2000; Yun-Choi et al., 2000; Tomoda et al., 1999; Núñez-Gil et al., 2012; Damås et al., 2003).

TTS can cause intracardiac thrombus formation particularly in the setting of a reduced left ventricular ejection fraction (LVEF), therefore increasing the risk of thromboembolic complications (Gianni et al., 2006; de Gregorio et al., 2008; Bybee and Prasad, 2008; Young et al., 2014).

Curiously, stroke itself can be a potential TTS trigger. In experimental stroke models, the occlusion of the right middle cerebral artery has resulted in neurochemical derangements in the ipsilateral insular cortex and amygdala, leading to an increase of the sympathetic outflow to the heart and potentially cardiotoxic circulating norepinephrine levels (Cechetto and Hachinski, 1997).

Yoshimura et al. (2008) examined seven stroke patients who developed TTS soon after a stroke typically involving the insular cortex or adjacent areas and known to be associated with cardiovascular complications such as hypertensive episodes and dysautonomic symptoms (Cereda et al., 2002; Ay et al., 2006).

In this particular clinical scenario, a stroke-induced abnormal catecholamine release was the most likely culprit of the onset of TTS.

Since the precise temporal relationship between stroke and TTS is frequently unclear and several TTS patients may have other independent risk factors for stroke, we sought to assess the incidence and predictors of peri-index event stroke in a heterogeneous TTS population.

Materials and methods

We conducted a retrospective, descriptive study reviewing patients who were discharged with a diagnosis of TTS from the Einstein Medical Center, Philadelphia, PA and Danbury Hospital, Danbury, CT in the period between 2003 and 2014. The inclusion criteria were the modified Mayo Clinic criteria for the diagnosis of TTS (Bybee and Prasad, 2008): i) akinesia or dyskinesia of left ventricular segments with regional wall motion abnormalities that extended beyond the distribution of a single epicardial vessel, ii) absence of obstructive coronary artery disease, iii) new electrocardiographic abnormalities, iv) absence of pheochromocytoma or myocarditis. A total of 206 TTS patients from different racial and ethnic backgrounds (Whites and African Americans) were included.

Baseline demographic characteristics, past medical history, medications upon admission, initial and peak troponin I levels obtained at least 6–8 hours apart, 12-lead electrocardiogram, LVEF assessed by 2-D echocardiogram, and cardiac catheterization data were collected after study approval by the institutional review board at both sites.

Emergency department and inpatient records were reviewed and all medications prescribed during the index hospitalization were documented. The TTS patients also underwent reassessment of LVEF, within six months of the index event, to document LVEF recovery.

Using a multiple logistic model, we sought to determine independent predictors of *peri-index event stroke*, defined as new focal neurological symptom occurring during the hospitalization or up to 30 days after discharge in patients discharged with a diagnosis of TTS. All patients who developed new focal neurological symptoms underwent a CT scan of the brain. One patient had evidence of hemorrhagic stroke during the hospital stay.

The following variables, with $p \leq 0.10$ in the univariate analysis, were included in the multivariate model: age, race, hypertension, chest pain upon presentation, in-hospital heart failure, aspirin use, dual antiplatelet therapy (DAPT) and angiotensin-converting enzyme (ACE) inhibitor use.

A significant percentage of cases occurred in patients already hospitalized for another medical, surgical, obstetric, anesthetic, or neurological condition. In these particular subjects, the sudden activation of the sympathetic nervous system and rise in catecholamines was triggered by a stressor considered to be physical rather than emotional.

Depression and anxiety were defined according to the World Health Organization recommendations. Depression is a mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Moreover, depression is often accompanied by symptoms of anxiety.

Anxiety disorders as such are a group of illnesses characterized by the presence of excessive worry, fear or tension that causes significant discomfort or a clinically significant decline in the individual's level of activity.

The values in this study are presented as numbers and percentages or mean values ± standard deviation (SD) for categorical and quantitative variables, respectively. The chi-square and the Student t-test were used to assess statistical differences in categorical and continuous variables, respectively. A two-tailed $p<0.05$ was considered statistically significant. All analyses were performed employing SPSS v 22.0 (IBM, Chicago, IL).

Results

A total of 206 patients met the modified Mayo Clinic criteria and were eligible for study entry. Table I shows the baseline characteristics of the study population. Overall, they had a mean age of 67.8 years; 87%

(n=179) were females and 25% (n=53) were African Americans. The following incidence rates were found: stroke 7%, in-hospital heart failure 26.7%, and in-hospital death 7%.

Table II shows the number of patients receiving aspirin, aspirin+clopidogrel, beta blocker, statin and ACE inhibitor therapy during the index event.

Table I - Baseline characteristics of the patients (n=206).

Characteristic	Value
Age (years), mean	67.8
Length of stay (days) ± SD	9±13
Gender (% females)	87% (n=179)
African American ethnicity (%)	26% (n=53)
Cardiovascular risk factors	
- Hypertension	66% (n=141)
- Hyperlipidemia	43% (n=92)
- Diabetes mellitus	19% (n=41)
- Current smoker	40% (n=83)
Clinical presentation	
- Chest pain	48% (n=100)
- Physical stressor	68% (n=142)
- Emotional stressor	31% (n=64)
Depression	20% (n=43)
Anxiety	22% (n=47)
Troponin I upon admission (ng/ml), mean±SD	1.42±3.5
Peak troponin I during hospitalization (ng/ml), mean±SD	4.27±9.7
Left ventricular ejection fraction	
- Initial ejection fraction (%), mean±SD	34.2±10.7
- Follow-up ejection fraction (%), mean±SD	40±25
Left ventricular thrombus	3% (n=6)
In-hospital heart failure	27% (n=55)
In-hospital death	7% (n=15)
Recurrence	3% (n=6)
Peri-index event stroke	7% (n=15)

Table II – Medications used in the study population.

Medications	Value
Aspirin alone	41% (n=85)
Clopidogrel alone	0.5% (n=1)
DAPT (aspirin + clopidogrel)	43% (n=88)
Beta blocker	75% (n=156)
Statin	70% (n=146)
ACE inhibitor	57% (n=119)

Abbreviations: DAPT=dual antiplatelet therapy; ACE=angiotensin-converting enzyme

Antiplatelet therapy (aspirin and aspirin+clopidogrel) and beta blockers were the most prescribed medications during the hospital stay (84% and 76%, respectively).

Table III shows the baseline characteristics of patients who developed peri-index event stroke versus those who did not. Overall, in an unadjusted model, patients diagnosed with stroke were older (74±9 versus 67±14; p=0.04), more likely to be African American (53.3% versus 23.6%; p=0.01), had a higher prevalence of hypertension (93.3% versus 66.5%; p=0.03), and were less likely to be on DAPT (13.4% versus 45%; p=0.02).

Table IV show the medications used in the two groups.

Table V shows the results of the multivariate analysis. Independent predictors of peri-index event stroke were: i) African American race: OR 3.2, 95% CI 1.2–10.2, p=0.048; ii) hypertension: OR 10.5, 95% CI 1.3–88, p=0.03.

ACE inhibitor use was protective for developing stroke during the index event: OR 0.15, 95% CI 0.04–0.5, p=0.001.

There was a trend towards DAPT being protective for stroke: OR 0.3, 95% CI 0.05–1.1, p=0.08.

Discussion

In this study African American race and hypertension were independent predictors of peri-index event stroke among TTS patients.

TTS is becoming increasingly recognized and diagnosed since its presentation is often similar to that of an acute coronary syndrome. The pathophysiology involved has not been completely elucidated, however it is believed that plasma catecholamines and exaggerated sympathetic activation may play an important role (de Gregorio et al., 2008; Kurowski et al., 2007; Nabi et al., 2010).

Psychosocial and physical stress cause increased circulating levels of several interleukins (ILs), in particular IL-6 and IL-7, both of which have previously been observed to rise in TTS patients (Damås et al., 2003). These proinflammatory ILs have been implicated in the pathogenesis of coronary artery disease and left ventricular dysfunction (Pyo et al., 2003; Damås et al., 2003).

Past research (Pirzer et al., 2012) has also shown high levels of catecholamines during the acute phase of TTS and even higher levels of epinephrine, both leading to increased platelet activation and aggregation and therefore predisposing TTS patients to a hypercoagulable state and worse cardiovascular outcomes. Pirzer et al. (2012) described that few days after hospitalization IL-7 levels were significantly higher in TTS patients than in patients who had an acute myocardial infarction.

Agents such as aspirin, which suppresses the production of prostaglandins and decreases plasma levels of inflammatory biomarkers such as IL-6 and TNF-α, and clopidogrel, which acts via the inhibition of platelet

aggregation, have protective cardiovascular effects in patients with coronary artery disease. Recent data (Dias et al., 2015) have shown that using aspirin or aspirin+clopidogrel throughout the hospital course after TTS, and targeting catecholamines and inflammatory biomarkers could be approaches associated with better cardiovascular outcomes during the index event.

The fear that cardiac thrombus formation may frequently occur during episodes of TTS and in the setting of a severely reduced LVEF has led previous authors to suggest anticoagulation therapy in all TTS patients until wall motion abnormalities improve (Mitsuma et al., 2010), but data on this particular topic are still limited. There seems to be agreement that anticoagulation therapy should be started in TTS patients who develop left ventricular thrombi (de Gregorio et al., 2008; de Gregorio, 2010; Ouchi et al., 2016), and it may be appropriate to start this therapy in patients at higher risk of thromboembolic disease.

We observed a significant racial discrepancy in stroke incidence among patients who suffered TTS. Past

Table III - Peri-index event stroke versus no peri-index event stroke.

Characteristic	Peri-index event stroke (n=15)	No peri-index event stroke (n=191)	p-value
Age (years), mean ± SD	74±9	67±14	0.04
Females, % (n)	80% (n=12)	93.3% (n=167)	0.4
African Americans, % (n)	53.3% (n=8)	23.6% (n=45)	0.01
Cardiovascular risk factors			
- Hypertension	93.3% (n=14)	66.5% (n=127)	0.03
- Hyperlipidemia	47% (n=7)	44.5% (n=85)	0.9
- Diabetes mellitus	33.3% (n=5)	18.8% (n=36)	0.2
- Current smoker	33.3% (n=5)	41% (n=78)	0.5
- New onset of atrial fibrillation	6.7% (n=1)	8.4% (n=16)	0.8
Clinical presentation			
- Chest pain upon presentation	26.7% (n=4)	50.3% (n=96)	0.07
- Physical stressor	80% (n=12)	68% (n=130)	0.3
- Depression	26.7% (n=4))	21% (n=39)	0.5
- Anxiety	6.7% (n=1)	24% (n=46)	0.1
- ASA	66.7% (n=10)	39.3% (n=75)	0.04
- DAPT	13.4% (n=2)	45% (n=86)	0.02
- Peak troponin I during hospitalization (ng/ml) mean±SD	6.1±10.3	4.1± 9.7	0.15
- Initial ejection fraction (%), mean±SD	34±11	34.2±10.7	0.6
- Left ventricular thrombus	6.7% (n=1)	2.6% (n=5)	0.3
- In-hospital heart failure	33.3% (n=5)	26% (n=50)	0.04
- In-hospital death	20% (n=3)	6.3% (n=12)	0.05

Abbreviations: ASA=aspirin; DAPT=dual antiplatelet therapy; ACE=angiotensin-converting enzyme; ns=not significant

Table IV - Medication in stroke group versus no peri-index event stroke group.

Medication	Total	Peri-index event stroke	No peri-index event stroke	p-value
Aspirin alone	(n=85)	11.8% (n=10)	88.2% (n=75)	0.04
Clopidogrel alone	(n=1)	1	0	ns
DAPT (aspirin + clopidogrel)	(n=88)	2.3% (n=2)	97.7% (n=86)	0.02
Beta blocker	(n=156)	7.1% (n=11)	92.9% (n=145)	ns
Statin	(n=146)	7.5% (n=11)	92.5% (n=135)	ns
ACE inhibitor	(n=119)	7.3% (n=4)	92.7% (n=115)	0.01

Abbreviations: DAPT=dual antiplatelet therapy; ACE=angiotensin-converting enzyme; ns=not significant

studies (Walker et al., 1992; Mills et al., 1995) indicate that hypertensive patients not only exhibit exaggerated cardiovascular responses, but also an enhanced catecholamine response to stressors. Although data on overall racial differences in plasma catecholamines at rest are still inconsistent, there is some evidence suggesting that African Americans may have higher levels of epinephrine than whites at the highest work rate (Walker et al., 1992).

Mills et al. (1995) also examined the effects of ethnicity and hypertension on β_2-adrenergic receptors and on plasma catecholamines and concluded that African American hypertensive men showed an increased β-receptor sensitivity and density compared with white hypertensive men. The literature contains evidence of an apical-basal gradient of β-adrenergic receptors (βARs) and sympathetic innervation in the mammalian left ventricle, the apex being characterized by highest βAR but lowest sympathetic nerve density (Lyon et al., 2008).

During episodes of stress and in order to ensure appropriate ventricular ejection there is an increased apical responsiveness to circulating catecholamines, especially epinephrine, however epinephrine itself at high levels can be a negative inotrope. It is possible that African Americans are more prone to worse cardiovascular outcomes, including stroke, given their increased β-receptor sensitivity and density and higher epinephrine levels in comparison to Whites.

In patients with preexistent hypertension, the structure and function of the microcirculation are both altered. Several vasomotor regulatory mechanisms become abnormal leading to enhanced vasoconstriction and eventually reduced vasodilator responses. The increased peripheral resistance leads to worsening hypertension through a "vicious cycle" in which the abnormal microvasculature maintains and further amplifies the blood pressure. Acute elevations of catecholamines may cause significant endothelial damage to a microvasculature already impaired by longstanding hypertension, predisposing to acute cerebrovascular events.

ACE inhibitor use prior to the index event and hospitalization appears to be protective for significant cerebrovascular outcomes during the index event. It is intuitive to believe that better blood pressure control prior to and during the index event and hospitalization leads to fewer cerebrovascular complications, particularly in patients who already have an abnormal microvasculature due to longstanding hypertension.

Table V - Multivariate analysis for peri-index event stroke.

Variable	Peri-index event stroke OR (95% CI)	p-value
African American race	3.2 (1.2–10.2)	0.048
Dual antiplatelet therapy	0.3 (0.05–1.1)	0.08
Hypertension	10.5 (1.2–88)	0.03
ACE inhibitor	0.15 (0.04–0.5)	0.001

However, we do believe that these results should be interpreted with caution given the observational and retrospective nature of this study (Serné et al., 2007). Moreover, ACE inhibitors should also be used with caution since some TTS patients have systemic arterial vasodilatation and low systemic vascular resistance reflecting a maladaptive regulation by the peripheral sympathetic nervous system, which may be further exacerbated by ACE inhibitors. Further prospective clinical trials are needed to confirm these findings (Akashi et al., 2015).

Our study presents some limitations: it is a retrospective descriptive study and our sample size was relatively small, therefore our results should be interpreted with caution and ideally confirmed by large scale prospective studies.

In conclusion, the incidence of peri-index event stroke in this study was 7%, with African American race and hypertension emerging as independent predictors of cerebrovascular events. Prospective clinical trials are needed to confirm these findings and to better determine the impact of hypertension as a risk factor for stroke and to assess the role of DAPT in preventing it.

References

Akashi YJ, Nef HM, Lyon AR (2015). Epidemiology and pathophysiology of Takotsubo syndrome. Nat Rev Cardiol 7:387-397.

Ay H, Koroshetz WJ, Benner T, et al (2006). Neuroanatomic correlates of stroke-related myocardial injury. Neurology 66:1325-1329.

Bybee KA, Prasad A (2008). Stress-related cardiomyopathy syndromes. Circulation 118:397-409.

Cechetto DF, Hachinski V (1997). Cardiovascular consequences of experimental stroke. In: Cechetto DF, Hachinski V (eds) Bailliere's Clinical Neurology, Neurocardiology. Vol 6. London, WB Saunders, pp 297-308.

Cereda C, Ghika J, Maeder P, et al (2002). Strokes restricted to the insular cortex. Neurology 59:1950-1955.

Damås JK, Waehre T, Yndestad A, et al (2003). Interleukin-7-mediated inflammation in unstable angina: possible role of chemokines and platelets. Circulation 107:2670-2676.

de Gregorio C (2010). Cardioembolic outcomes in stress-related cardiomyopathy complicated by ventricular thrombus: a systematic review of 26 clinical studies. Int J Cardiol 141:11-17.

de Gregorio C, Grimaldi P, Lentini C (2008). Left ventricular thrombus formation and cardioembolic complications in patients with Takotsubo-like syndrome: a systematic review. Int J Cardiol 131:18-24.

Dias A, Franco E, Koshkelashvili N, et al (2015). Antiplatelet therapy in Takotsubo cardiomyopathy: does it improve cardiovascular outcomes during index event? Heart Vessels doi: 10.1007/s00380-015-0729-2

Gianni M, Dentali F, Grandi AM, et al (2006). Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J 27:1523-1529.

Kurowski V, Kaiser A, von Hof K, et al (2007) Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. Chest 132:809-816.

Lyon AR, Rees PS, Prasad S, et al (2008). Stress (Takotsubo) cardiomyopathy: a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med 5:22-29.

Mills PJ, Dimsdale JE, Ziegler MG, et al (1995). Racial differences in epinephrine and beta 2-adrenergic receptors. Hypertension 25:88-91.

Mitsuma W, Kodama M, Ito M, et al (2010). Thromboembolism in Takotsubo cardiomyopathy. Int J Cardiol 139:98-100.

Nabi H, Hall M, Koskenvuo M, et al (2010). Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study. Biol Psychiatry 67:378-385.

Núñez-Gil IJ, Molina M, Bernardo E, et al (2012). Tako-tsubo syndrome and heart failure: long-term follow-up. Rev Esp Cardiol (Engl Ed) 65:996-1002.

Ouchi K, Nakamura F, Ikutomi M, et al (2016). Usefulness of contrast computed tomography to detect left ventricular apical thrombus associated with takotsubo cardiomyopathy. Heart Vessels 31:822-827.

Pirzer R, Elmas E, Haghi D, et al (2012). Platelet and monocyte activity markers and mediators of inflammation in Takotsubo cardiomyopathy. Heart Vessels 27:186-192.

Pyo MK, Yun-Choi HS, Hong YJ (2003). Apparent heterogeneous responsiveness of human platelet rich plasma to catecholamines. Platelets 14:171-178.

Serné EH, de Jongh RT, Eringa EC, et al (2007). Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome. Hypertension 50:204-211.

Tomoda F, Takata M, Kagitani S, et al (1999). Different platelet aggregability during mental stress in two stages of essential hypertension. Am J Hypertens 12:1063-1070.

von Känel R, Dimsdale JE (2000). Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. Eur J Haematol 65:357-369.

Walker AJ, Bassett DR Jr, Duey WJ, et al (1992). Cardio-vascular and plasma catecholamine responses to exercise in blacks and whites. Hypertension 20:542-548.

Yoshimura S, Toyoda K, Ohara T, et al (2008). Takotsubo cardiomyopathy in acute ischemic stroke. Ann Neurol 64:547-554.

Young ML, Stoehr J, Aguilar MI, et al (2014). Takotsubo cardiomyopathy and stroke. Int J Cardiol 176:574-576.

Yun-Choi HS, Park KM, Pyo MK (2000). Epinephrine induced platelet aggregation in rat platelet-rich plasma. Thromb Res 100:511-518.