Cerebral Hemorrhage: Precipitating Event for a Tako-tsubo-like Cardiomyopathy?

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ABSTRACT

There have been some reports in medical literature of patients with profound, reversible left-ventricular (LV) dysfunction after sudden emotional stress. Originally, in Japan, the pattern was called tako-tsubo cardiomyopathy. ST-segment elevation is seen with this syndrome, and it may look like acute ST-elevation myocardial infarction. However, it has also been well established that a subarachnoid hemorrhage can manifest with cardiac abnormalities. The authors describe a case involving a cerebral hemorrhage and a potential tako-tsubo-like cardiomyopathy in the same patient. In conclusion, even though the patient's presentation appears to be a tako-tsubo syndrome, the radiographic evidence of a cerebral hemorrhage presents as a stronger etiology for the cardiac changes that occur in our patient.

Key words: tako-tsubo, cardiomyopathy, ST-segment elevation, subarachnoid hemorrhage

Reports of patients with profound, reversible left ventricular (LV) dysfunction after sudden emotional stress have sparsely appeared in the medical literature in the last 15–20 y.^{1–6} Early reports originated in Japan, where the pattern of left ventricular dysfunction has been referred to as tako-tsubo cardiomyopathy, named after the fishing pot with a narrow neck and wide base that is used as a trap for the octopus. The term “transient left ventricular apical ballooning” has also been used to describe similar cardiac contractile abnormalities in patients after emotional or physical stress.^{5,7} The majority of researchers consider tako-tsubo syndrome as a form of myocardial stunning that mimics acute ST-elevation myocardial infarction with impairment of left ventricular apical function but the mechanism remains a mystery.

It is also well known that a subarachnoid hemorrhage can manifest with cardiac abnormalities.^{8–10} Electrocardiograph (ECG) changes occur in 50%–100% of patients during the acute stage of subarachnoid hemorrhage (SAH). The most frequent anomalies reported have been elevation or depression of the ST-segment, very negative or positive deep T waves, lengthening of the QT interval and the presence of U waves.^{8–10}

The authors describe a case involving a cerebral hemorrhage and a potential tako-tsubo-like cardiomyopathy in the same patient.

Case Report

A 70-year-old woman presented to the emergency department via ambulance from a nursing home with a chief complaint of altered mental status. The patient arrived at the nursing home in the morning, but by the afternoon the staff found that her consciousness was disturbed, she was

unable to speak, and she had developed a cold sweat. The patient was unable to communicate her complaints. The nursing home called for an ambulance and she arrived at the emergency room (ER).

The patient's past medical history was positive for diabetes mellitus type II and a cerebral infarction 15 y ago and negative for any past seizure activity. Since the cerebral infarct, the patient has been bedridden and suffers from left hemiplegia though she has been able to communicate adequately until the present events. She is supported by her husband who takes care of her and their home.

Upon arrival at the ER, the patient's Glasgow Coma Scale score was 6. Her blood pressure was 170/100, pulse was 110 and regular, respiratory rate was 12, and her SpO₂ was 95%. Her body temperature was 36.6 °C.

Her physical examination was as follows: head, ears, eyes, nose, and throat (HEENT) showed no eye deviation; lungs were clear and displayed no evidence of crackles on auscultation; heart sounds were negative for any gallop or murmur; the patient's abdomen was soft and nondistended; and the patient's extremities displayed no evidence of cyanosis or edema (her usual state of left hemiplegia was evident).

The patient underwent an ECG while the ER doctor waited for the laboratory results. The ER doctor noticed strange ST changes. He ordered a 12-lead ECG before sending the patient off for a computed tomography (CT) scan. It revealed normal sinus rhythm with ST-segment elevation in leads V2 and V6 (Figures 1, 2).

The patient's bloodwork revealed a white blood cell count of 6.1 (54% neutrophils, 38% lymphocytes). Her hemoglobin was 11.5, mean corpuscular volume 90.6, and her platelets were 270,000. Her liver enzymes were as follows: aspartate

Figure 1: Echocardiography shows acute dilatation of the left ventricle with exhaustion and stunting of the mid-left ventricle, resembling the tako-tsubo octopus trap.

aminotranferase of 34, alanine aminotransferase of 18, alkaline phosphatase of 405. The patient's lactic dehydrogenase was 405 while her gamma-glutamyl-transpeptidase was 10. Her amylase was 128 and her thymidine phosphorylase was 7.9. Her blood glucose was 243 and glycosylated hemoglobin was 7.9. She was H-FABP positive and her C-reactive protein was 0.06. The patient's electrolytes were as follows: sodium 144, potassium 4.8, and chloride 113. Her albumin was 3.6. Her serum creatinine was 1.6 and her blood urea nitrogen was 37.3. The patient's Day 1 cardiac enzymes revealed a troponin of 0.32, creatine kinase MB fraction of 2.06, and a creatine kinase of 90.

After the results of the 12-lead ECG, an echocardiogram was performed which demonstrated akinesis of the anterolateral, apical septal, apical inferior, and apical anterior segments (Figures 3, 4). Left ventricular wall motion dysfunction was evident, especially at the apex. Left ventricular function was depressed evident by an ejection fraction of 51%. The right ventricle was normal in size and function.

The patient was diagnosed with an acute myocardial infarction and sent to a neighboring hospital that had a cardiovascular specialty service and the capability to perform coronary artery angiography (CAG). The CAG showed that the left anterior descending (LAD) artery #8 had 90% occlusion, but the blood flow was very good. The cardiologist ruled that the CAG could not explain the ECG changes, the echo findings, or the LV dysfunction.

The patient's initial complaint of mental status changes finally prompted a CT scan. The head CT showed thalamus and intraventricular hemorrhage (Figure 5). The patient returned to the initial hospital for a neurosurgical evaluation. The neurosurgeon decided that the patient had no indication for surgery. The decision was made to closely monitor the patient without medication and she remained both clinically and hemodynamically stable.

Over the next few days, the ST segment trended downward and the negative T wave remained (Figure 6). Her cardiac enzymes trended up and peaked on Days 2 and 3

Figure 2: Echocardiography shows acute dilatation of the left ventricle with exhaustion and stunting of the mid-left ventricle, resembling the tako-tsubo octopus trap.

(Troponin 42.2, creatine kinase myocardial isoenzyme [CK-MB] 73.3, CPK 984) before trending down significantly by day 10. After 2 wk from presentation, the LV wall motion was improved. After 4 wk, the repeat echo demonstrated complete resolution of the previous regional systolic dysfunction.

Discussion

Reports of Tako-tsubo syndrome have increased over the last few years and cases have been found outside of Japan including the western world.⁷ It has become clear to clinicians that this is a unique phenomenon and that increased awareness of its existence is necessary to minimize erroneous administration of fibrinolytic agents and the overlooking of more ominous disease states in patients. The following general characteristics have been associated with Tako-tsubo syndrome:¹¹

1. Reversible (more than 2–3 wk) balloon-like left ventricular wall motion abnormality at the apex with

hypercontraction of the basal segments, in most cases extending far beyond the perfusion territory of a single coronary artery.

2. ST-T abnormalities on electrocardiogram, often mimicking acute myocardial infarction and most often accompanied by QT-prolongation.
3. Chest pain and/or dyspnea in most patients.
4. Absence of significant coronary arterial narrowing by angiography.
5. Induced by physical and emotional stress in most cases.
6. Most patients are elderly females.
7. The prognosis for survivors is favorable.
8. In the absence of known causes of reversible left ventricular wall motion abnormalities, including subarachnoid hemorrhage, pheochromocytoma, acute myocarditis and tachycardia-induced cardiomyopathy.

Figure 3: The ECG reveals sinus tachycardia with ST-elevation at leads V2-V5, suggestive of acute anterior wall myocardial infarction.

Figure 4: The ECG reveals sinus tachycardia with ST-elevation at leads V2-V5, suggestive of acute anterior wall myocardial infarction.

The ECG changes associated with Tako-tsubo syndrome can evolve during the first 2 to 3 hospital d.¹² Frequently, the ECG continues to show abnormalities long after left ventricular function has normalized and repeated deepening of the T wave at 2–3 wk is not associated with clinical or left ventricular deterioration. The ECG obtained at the time of admission can be quite varied. In the largest Japanese series of patients with left ventricular apical ballooning, 90% of the patients had ST-segment elevation.⁵ This finding is in contrast to the less frequent observation of ST-segment elevation that has been reported by others.^{7,12,13}

With more single case reports in the literature for Tako-tsubo syndrome, researchers have begun performing more traditional studies on these patients.

Figure 5: The CT scan of the head shows hyperdense areas on the right pons and hypothalamus consistent with acute hemorrhage.

In the Ibanez study published in Heart 2005 involving 5 patients, inclusion criteria included suspected acute coronary syndrome (ACS) based on chest pain, ECG changes, and enzymatic release; transient LV apical ballooning; absence of stenosis >50% in all major arteries.¹⁴ All signs and symptoms pointed to ACS, however CAD had been systematically ruled out, based on two features: early angiography showed no significant luminal stenosis and a large akinetic area so extensive that previous researchers have suggested it does not correspond to the perfusion territory of a single coronary artery.⁷ Ibanez observed in his 2003 study that all tako-tsubo patients had an LAD with a large diaphragmatic course, suggesting that all LV akinetic areas could be supplied by the LAD alone.¹⁵ The absence of significant coronary artery stenosis does not exclude the existence of CAD, because limitations of coronary angiography. Nissen and colleagues reported that coronary plaques responsible for ACS frequently show positive remodeling and are not easily diagnosed by coronary angiography when a thrombus has been resolved (Nissen SE, pathobiology, not angiography).¹⁶ It must be noted that our patient had a 90% occlusion in LAD #8 though blood flow was very good.

In all 5 cases, the intravascular ultrasound showed a single, ruptured, atherosclerotic plaque in the middle portion of the LAD, without any other atherosclerotic disease in the rest of the vessel; 3 cases with fibrous capsule rupture and intraplaque cavity, 1 case with fibrous capsule rupture without ulceration, and 1 case with an intimal

Figure 6: The ECG shows resolution of ST-elevation.

dissection flap.¹⁴ Ibanez prospectively described for the first time intravascular ultrasound features of the LAD in tako-tsubo patients. In all cases a disrupted atherosclerotic plaque was found. The characteristics of the plaque suggest they are unstable. The findings could explain the pathophysiology of tako-tsubo syndrome as being the presence of a ruptured plaque in the middle portion of a well developed LAD, supplying a vast LV territory. The disruption of that plaque could lead to ACS with early perfusion, and thus minimal enzymatic release and LV stunning rather than necrosis. Ibanez theorized from his work that the underlying cause is an ACS with early reperfusion and wide LV stunned myocardium.¹⁴

Other possible causes of myocardial stunning is epicardial coronary artery spasm.^{6,13} Patients with increased sympathetic tone due to mental stress can have evidence of such spasm. Another possibility is microvascular spasm within the heart in response to a sudden release of stress hormones.^{6,13} Finally, direct injury to cardiac myocytes might help explain the phenomenon of cardiac stunning. Catecholamines could injure myocytes through the disruption of intracellular calcium metabolism as well as through increased production of free radicals.¹²

The high incidence of stress before the onset of symptoms has led to the most widely accepted theory of catecholamine involvement in the pathogenesis of tako-tsubo syndrome. Acute stress has been associated with raised proinflammatory cytokines and norepinephrine concentrations, both of which induce vasoconstriction and

elevated blood pressure, thus making a vulnerable plaque prone to rupture.¹⁷

Winnstein et al. performed a study of patients with stress-induced cardiomyopathy where the median age was 63 years and 95% were women. Clinical presentations included chest pain, pulmonary edema, and cardiogenic shock. Diffuse T-wave inversion and a prolonged QT interval occurred in most patients. Seventeen patients had mildly elevated serum troponin I levels, but only 1 of 19 had angiographic evidence of clinically significant coronary disease. Severe LV dysfunction was present on admission (median ejection fraction, 0.20; interquartile range, 0.15 to 0.30) and rapidly resolved in all patients (ejection fraction at 2–4 weeks, 0.60; interquartile range, 0.55 to 0.65; $p < 0.001$). Plasma catecholamine levels at presentation were markedly higher among patients with stress-induced cardiomyopathy than those with Killip class III myocardial infarction.¹²

The researchers concluded that emotional stress can precipitate severe, reversible LV dysfunction in patients without coronary disease. Exaggerated sympathetic stimulation is probably central to the cause of this syndrome.¹²

This exaggerated sympathetic stimulation is a proposed theory to explain the cardiac changes consistent with SAH. Two common mechanisms that might mediate ECG changes in patients with SAH are autonomic neural stimulation from the hypothalamus or elevated levels of circulating catecholamine. Hypothalamic stimulation may cause ECG changes without associated myocardial damage whereas elevated catecholamine levels have been correlated with QT interval prolongation and myocardial damage.¹⁸ Some

SAH patients do show evidence of structural cardiac damage. Plasma levels of CK-MB are mildly elevated in 20%–50% of patients.^{8,19} Also, echocardiography studies have demonstrated reversible abnormalities of left ventricular contraction after SAH.²⁰

Conclusion

The majority of cases of tako-tsubo have found emotional stress as the trigger with minimal morbidity and mortality associated with it. It must be noted, however, that the first death attributed to tako-tsubo syndrome was reported in 2004 and the authors suggest that it may be a newly recognized cause of sudden cardiac death.²¹

Given that the left ventricular dysfunction of Tako-tsubo syndrome has similarities to that seen in patients with acute brain injury,²² which was the case in our patient, awareness of this underrecognized phenomenon has clinical importance. Also drug therapy used in acute coronary events like aspirin, enoxaparin/heparin, or thrombolytic agents can have devastating effects on a patient already experiencing cerebral hemorrhage. The importance of this case lies in what it reminds clinicians: the patient must be thoroughly examined lest one misses a life-threatening coexisting problem and an adequate differential diagnosis must be established for each patient. It is the authors' conclusion that even though the patient's presentation appears to be a Tako-tsubo syndrome, the radiographic evidence of a cerebral hemorrhage presents as a stronger etiology for the cardiac changes that occur in our patient.

References

1. Pavin D, Le Breton H, Daubert C: Human stress cardiomyopathy mimicking acute myocardial syndrome. *Heart* 1997;78:509–511
2. Kawai S, Suzuki H, Yamaguchi H: Ampulla cardiomyopathy ('Takotsubo' cardiomyopathy) –reversible left ventricular dysfunction: with ST segment elevation. *Jpn Circ J* 2000;64:156–159
3. Villareal RP, Achari A, Wilansky S, Wilson JM: Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc* 2001;76:79–83
4. Brandspiegel HZ, Marinchak RA, Rials SJ, Kowey PR: A broken heart. *Circulation* 1998;98:1349–1349
5. Tsuchihashi K, Ueshima K, Uchida T: Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. *J Am Coll Cardiol* 2001;38:11–18
6. Kurisu S, Sato H, Kawagoe T: Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002;143:448–455
7. Desmet WJ, Adriaenssens BF, Dens JA: Apical ballooning of the left ventricle: first series in white patients. *Heart* 2003;89:1027–1031
8. Mayer SA, LiMandri G, Homma S: Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. *J Neurosurg* 1995;83:889–896
9. Brouwers PJAM, Wijndicks EFM, Hasan D: Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage. *Stroke* 1989;20:1162–1167
10. Salvati M, Cosentino F, Artico M: Electrocardiographic changes in subarachnoid hemorrhage secondary to cerebral aneurysm: report of 70 cases. *Ital J Neurol Sci* 1992;13:409–413
11. Desmet W: Dynamic LV obstruction in apical ballooning syndrome: The chicken or the egg. *Eur J Echocardiogr* 2006;1:1–4
12. Wittstein IS, Thiemann DR, Lima JAC: Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539–548
13. Sharkey SW, Lesser JR, Zenovich AG: Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111:472–479
14. Ibanez B, Navarro F, Cordoba M: Transient left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma? *Heart* 2005;91:102–104
15. Ibanez B, Navarro F, Farre J: "Tako-tsubo" transient left ventricular apical ballooning is associated with a left anterior descending coronary with a long course along the apical diaphragmatic surface of the left ventricle. *Rev Esp Cardiol* 2004;57:209–216
16. Nissen SE: Pathobiology, not angiography, should guide management in acute coronary syndrome/non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2003;41:S 103–112
17. Gidron Y, Gilutz H, Berger R: Molecular and cellular interface between behavior and acute coronary syndromes. *Cardiovasc Res* 2002;56:15–21
18. Randell T, Tanskanen P, Scheinin M: QT dispersion after subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 1999; 11:163–166
19. Lanzino G, Kongable GL, Kassell NF: Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 1994;3:156–162
20. Mayer SA, Lin J, Homma S: Myocardial injury and left ventricular performance after subarachnoid hemorrhage. *Stroke* 1999;30:780–786
21. Akashi JY, Tejima T, Sakurada H: Left ventricular rupture associated with Takotsubo cardiomyopathy. *Mayo Clin Proc* 2004;79:821–824
22. Ako J, Honda Y, Fitzgerald PJ: Tako-tsubo-like left ventricular dysfunction. *Circulation* 2003;108:e158–e158