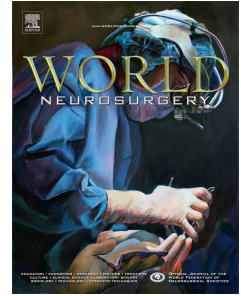


# Accepted Manuscript

Delayed normalization of electrocardiograms in patients with takotsubo cardiomyopathy due to aneurysmal subarachnoid hemorrhage

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**Title page****Title:**

Delayed normalization of electrocardiograms in patients with takotsubo cardiomyopathy due to aneurysmal subarachnoid hemorrhage

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**Keywords:**

electrocardiogram, subarachnoid hemorrhage, takotsubo cardiomyopathy

**Abbreviations**

BNP: brain natriuretic peptide

CFR: coronary flow reserve

CT: computed tomography

ECG: electrocardiography

EF: ejection fraction

H&K: Hunt & Kosnik

LVG: left ventriculography

MRI: magnetic resonance imaging

mRS: modified Rankin Scale

NPE: neurogenic pulmonary edema

SAH: subarachnoid hemorrhage

TCM: takotsubo cardiomyopathy

TdP: torsades de pointes

TTE: transthoracic echocardiography

WFNS: World Federation of Neurosurgical Societies

## **Abstract**

### **Background**

Takotsubo cardiomyopathy (TCM) is caused by excessive physical and mental stress, and sometimes causes potentially fatal arrhythmias such as torsades de pointes. This study characterized the features of TCM due to aneurysmal subarachnoid hemorrhage (SAH), particularly the delayed normalization of electrocardiograms compared to that of transthoracic echocardiograms.

### **Methods**

Ten patients with TCM were selected from the 450 SAH patients treated in our hospital between January 2007 and November 2015. We retrospectively examined these 10 patients with regard to various factors, including durations of abnormal electrocardiographic and echocardiographic findings.

### **Results**

All 10 patients were female. Mean age at diagnosis was 69.3 years (range, 40-90 years). Electrocardiographic findings were as follows: inverted or flattened T waves (100%); QTc prolongation  $>0.45$  s (90.0%); ST segment elevation (60.0%); and ST segment depression (20.0%). Echocardiograms showed typical findings of TCM in nine cases and inverted TCM in one case. In one case, ventral fibrillation was observed. Normalization of electrocardiograms was consistently delayed compared to that of echocardiograms, by more than 3 weeks in at least 5 cases (50%). If follow-up of electrocardiographic parameters is discontinued at the point of normalization of wall motion and the end of the vasospasm period, fatal arrhythmia may occur in the aftermath.

### **Conclusion**

This study showed a notable delay in recovery of abnormal electrocardiographic findings, compared to the recovery of echocardiographic findings. Sufficient attention to persistent abnormalities on electrocardiography is warranted, even after improvements in cardiac wall motion and the vasospasm period.

## **Introduction**

Takotsubo cardiomyopathy (TCM) was first reported by Sato et al. in 1990<sup>1</sup>, as a clinical condition brought on by excessive psychosomatic stress. Excessive catecholamine concentrations and microcirculation disorder, among others, have been suggested as etiologies, but the exact mechanism remains unknown<sup>2</sup>. The typical echocardiographic findings are hyperkinesis of the basal part of the mid-ventricular segment and hypokinesis or akinesis of the apical segment, which does not match the perfusion pattern of the coronary arteries. TCM is known to be associated with electrocardiographic abnormalities such as ST elevation, prolonged QTc, and inverted T waves, and sometimes causes potentially fatal arrhythmias such as torsades de pointes (TdP)<sup>2,3</sup>. The modified guidelines of the Mayo Clinic include cerebrovascular diseases in the diagnosis of TCM<sup>4</sup> and multiple reports have examined TCM related to subarachnoid hemorrhage (SAH)<sup>5-12</sup>. The present report proposes further finding, particularly regarding the different timings for normalization of electrocardiograms and echocardiograms in TCM related to SAH.

## **Material and methods**

Between January 2007 to November 2015, a total of 450 patients with aneurysmal (including dissecting aneurysms) SAH had been admitted to our hospital. Ten of these cases were confirmed as presenting with TCM in the clinical records. All patients underwent electrocardiography (ECG) and chest x-ray on admission. Patients who presented with clinical symptoms of heart failure such as dyspnea, palpitation, stridor, pink blood-tinged mucus, and coarse crackles on auscultation also underwent transthoracic echocardiography (TTE). Patients with no medical justification for treating aneurysm did not undergo TTE. We selected the ten patients who met the following criteria: 1) TTE findings with hyperkinesis of the basal part of the mid-ventricular segment and hypokinesis or akinesis of the apical part, which does not match the territory of the coronary arteries. So-called “inverted takotsubo cardiomyopathy” associated with hypokinesis or akinesis of the basal contraction and apical sparing was also included. 2) Improvement of abnormal findings of TTE on subsequent studies. After hospitalization, patients were monitored in the Stroke Care Unit for at least the 2-week cerebral vasospasm period. Until surgery, patients were sedated with propofol to prevent rebleeding. We maintained normovolemia after surgical treatment. For patients with symptomatic cerebral vasospasm, dobutamine was administered only if cardiac function had improved. We examined the following items: age, sex, location of aneurysm, World Federation of Neurosurgical Societies (WFNS) grading scale, Hunt & Kosnik (H&K) grading, Fisher classification, presence or absence of neurogenic pulmonary edema (NPE), type of surgical treatment, modified Rankin Scale (mRS) score, abnormal findings on ECG and their duration; and abnormal findings of TTE and their duration. TTE was not performed either every day or on specific days. The schedule of TTE varied according to the condition of patients and plans for other examination.

## **Results**

### ***Participants and characteristics***

TCM was detected in 10 of the 450 patients (2.2%). The clinical features of these patients are presented in Table 1. All 10 TCM patients were women and mean age at diagnosis was 69.3 years (range, 40-90 years). Nine of the ten developed TCM after menopause. Locations of aneurysms (including dissecting aneurysms) were as follows: internal carotid-posterior communicating artery aneurysm, 5 cases; anterior communicating artery aneurysm, 2 cases; basilar tip aneurysm, 1 case; dissecting aneurysm of the vertebral artery, 1 case; and distal posterior cerebral artery aneurysm, 1 case. Mean WFNS grading scale and H&K grading were 3.7 and 3.6, respectively. Fisher classification was as follows: group 2, 1 case; group 3, 5 cases; and group 4, 4 cases. Eight patients developed NPE. Five patients underwent neck clipping and 3 patients underwent coil embolization (including internal trapping). Two patients were treated conservatively. Mean mRS score was 2.6. In the course of treatment for heart failure, two patients received human atrial natriuretic peptide (Patients 4 and 8) and four patients received furosemide (Patients 2, 4, 6, and 10). Two patients needed treatment with a ventilator (Patients 2 and 8). One patient needed administration of propranolol for tachycardia due to atrial flutter (Patient 5). However, all patients were free from symptoms of heart failure and were not receiving treatment for heart failure at the time of confirmation of TTE normalization.

### ***Electrocardiographic findings***

ECG abnormalities were observed in all 10 patients. Frequent abnormal findings were inverted or flattened T waves (100%), QTc prolongation ( $>0.45$  s, 90.0%), ST segment elevation (60.0%), and ST segment depression (20.0%). Duration of abnormal ECG findings was relatively long. Five of the 10 patients needed over 4 weeks to achieve normalization of ECG findings. In 2 patients, re-exacerbation of inverted T waves was observed after improving once. Transient ventricular fibrillation was observed on day 1 in 1 patient, and tachycardia due to atrial flutter was observed in another patient. ECG findings are summarized in Table 1.

### ***Transthoracic echocardiographic findings***

Typical findings of TCM were found in 9 cases and inverted TCM was found in 1 patient. Abnormal TTE findings normalized in 4-16 days. One case showed left ventricular thrombus on day 5. That patient showed no arrhythmia, but did show a low ejection fraction (EF) of 32%. No anticoagulant therapy was performed and the thrombus disappeared spontaneously by day 16. TTE findings are summarized in Table 1.

### ***Time lag between abnormal period of ECG and TTE***

The time lag between normalization of ECG findings and that of TTE findings was over 3 weeks in at least 5 cases (50%). The temporal courses of ECG and TTE are summarized in

Table 2.

***Representative case***

A 64-year-old woman experienced sudden onset of headache and vomiting. The next day (day 1), she consulted our hospital. She was slightly somnolent, but no other neurological abnormalities were noted. Computed tomography (CT) revealed SAH in the prepontine cistern and bilateral Sylvian fissures (Figure 1), along with mild hydrocephalus. The WFNS grading scale was 2. Cerebral angiography showed no saccular aneurysm, but did reveal an irregularly shaped right vertebral artery, consistent with a diagnosis of SAH from dissecting aneurysm (Figure 2). ECG on admission (day 1) showed prolonged QTc, inverted T waves, and ST segment elevation in leads I, II, III, and V2-V6 (Figure 3). Chest x-ray showed no NPE. On day 2, brain natriuretic peptide (BNP) increased to 1023.2 pg/ml and positive results were seen for troponin I (3.64 ng/ml). Abnormalities on ECG and blood testing suggested TCM or ischemic heart disease. TTE, coronary angiography (CAG), and left ventriculography (LVG) were therefore performed by cardiologists on day 2. These examinations showed hypokinesis of the mid-apical wall. EF was 44.1% and coronaries appeared normal, consistent with a diagnosis of TCM. On day 3, parent artery occlusion via endovascular treatment was performed to prevent rebleeding (Figure 2) and was completed uneventfully. The patient showed a good course postoperatively and was discharged on day 23 without neurological deficit. TTE findings had fully recovered by day 11. ECG findings had not recovered by day 43 at the outpatient clinic, with slightly inverted T waves, but eventually recovered by 5 months after onset of SAH. The temporal course of ECG is shown in Figure 3. The time lag between normalization of ECG findings and that of TTE findings was over 1 month.

**Discussion**

TCM was first reported in 1990 by a Japanese cardiologist<sup>1</sup>, and was characterized by hyperkinesia of the basal segment with or without akinesis or hypokinesia of the apical and mid-ventricular segments of the left ventricle in the absence of notable coronary artery disease<sup>13-19</sup>. The mortality rate is reported to be up to 2%<sup>20</sup>, with a recurrence rate of 5-11.4%<sup>21,22</sup>. Ninety percent of TCM cases occur in women, particularly postmenopausal women. The prevalence of TCM following aneurysmal SAH is reportedly 4-15%<sup>6,23</sup>.

***Etiologies of TCM***

The mechanisms underlying TCM have yet to be precisely elucidated<sup>4</sup>, but some etiologies have been suggested, such as higher catecholamine levels, epicardial spasm, coronary microcirculatory impairment, and relevance of estrogen. Wittstein et al. made the first report on the role of catecholamines in TCM, showing that plasma catecholamine levels were higher in TCM patients than in Killip III myocardial infarction patients<sup>24</sup>. Other reports have examined the relationship between high levels of catecholamines and TCM<sup>25-28</sup>. Ischemic

changes from epicardial spasm unlikely as this does not account for the various wall-motion abnormalities<sup>19</sup>. Galiuto et al showed decreases in coronary flow reserve (CFR) and velocity<sup>29</sup>, which support coronary microcirculatory impairment theory. Multiple reports support this theory<sup>30,31</sup>. Previous reports have shown that TCM is likely to develop in postmenopausal women<sup>14,16,24</sup>. Estrogen is supposed to play various roles, such as preventing some cardiovascular impairment, sympathoadrenal activation, and vagal inhibition<sup>32,33</sup>.

### ***Temporal course and ECG findings***

Wall motion in TCM is said to recover within 1-2 weeks<sup>16,24</sup>. Kurisu et al. compared the temporal course of ECG findings between TCM and myocardial infarction<sup>34</sup>. They say typical ECG on admission showed ST segment elevation or inverted T waves, with the ST segment level usually improving within 3 days, while the inverted T wave deepened progressively to peak after approximately 3 days and improved in  $105 \pm 32$  days. However, patients with a history of cerebrovascular accident were excluded from this study. To the best of our knowledge, the present study is the first to focus on the time lag between normalization of ECG and TTE in patients with subarachnoid hemorrhage. Inverted T waves in TCM are supposed to result from dispersion of repolarization caused by abnormal prolongation of action potentials<sup>35</sup>. The relationship between QTc prolongation and delayed ventricular repolarization (increase in action potential duration) in ventricular myocytes has been reported<sup>36-41</sup>.

### ***TCM and Arrhythmia***

Relationships are known to exist between TCM and multiple types of arrhythmia, including auriculoventricular block, sinus bradycardia, paroxysmal atrial fibrillation, ventricular tachycardia, and ventricular fibrillation<sup>13,14,42-45</sup>. QTc prolongation is suggested to cause malignant arrhythmia, including TdP<sup>46,47</sup>. Migliore et al. reported that 8.2% of patients hospitalized with TCM develop fatal arrhythmia<sup>47</sup>. Predictive ECG findings include QTc prolongation and diffuse inverted T waves. Of note is the finding that 0.5% of TCM patients suffered sudden cardiac death weeks to months after the onset<sup>35</sup>, whereas another study found no sudden deaths after normalization of the QTc interval<sup>47</sup>.

### ***Necessity for attention to ECG in SAH patients with TCM***

Cerebral vasospasm usually occurs within 2 weeks after the onset of SAH. Because wall motion recovers within 1-2 weeks, patients would have little opportunity to undergo ECG after the acute period. Although abnormal electrocardiography itself is not considered to involve functional consequences, such findings may be associated with fatal arrhythmia in the chronic period as indicated above, and restrictions on the management of patients may be warranted, such as administration of inotropic agents, rehabilitation, and general anesthesia in cases of cranioplasty, shunt operation, and the like. Therefore, TCM patients should receive attention to ECG for longer periods than standard SAH patients.

***Limitations***

We did not perform TTE for all SAH patients, as this modality is not performed for severe cases with no indications for surgical treatment or patients without symptoms of heart failure. These facts may have led to the lower incidence of TCM than described in previous reports.

**Conclusions**

This study showed that a time lag exists between normalization of electrocardiographic and echocardiographic findings. Sufficient attention to ECG is needed, even after improvements in cardiac wall motion-

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**Figure Legends**

**Figure 1:** Computed tomography on admission

**Figure 2:** Vertebral angiography (VAG)

**Figure 3:** Temporal course of ECG

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## References

1. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure*. Tokyo: Kagakuhyouronsha; 1990:56-64.
2. Bybee KA, Kara T, Prasad A, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *AnnIntern Med*. 2004;141:858-865.
3. Kawai S, Kitabatake A, Tomoike H. Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. *Circ J*. 2007;71:990-992.
4. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (tako-tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155:408-417
5. Mayer SA, LiMandri G, Sherman D, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. *J Neurosurg* 1995;83:889-896.
6. Lee VH, Connolly HM, Fulgham JR, Manno EM, Brown RD Jr, Wijdicks EF. Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction. *J Neurosurg*. 2006;105:264-270.
7. Inamasu J, Nakatsukasa M, Mayanagi K, et al. Subarachnoid hemorrhage complicated with neurogenic pulmonary edema and takotsubo-like cardiomyopathy. *Neurol Med Chir (Tokyo)*. 2012;52:49-55.
8. Saito R, Takahashi T, Noshita N, et al. Takotsubo cardiomyopathy induced by dobutamine infusion during hypertensive therapy for symptomatic vasospasm after subarachnoid hemorrhage -case report-. *Neurol Med Chir (Tokyo)*. 2010;50:393-395.
9. Ono Y, Kawamura T, Ito J, Kanayama S, Miura T, Kikuchi F. Ampulla (takotsubo) cardiomyopathy associated with subarachnoid hemorrhage worsening in the late phase of vasospasm -case report-. *Neurol Med Chir (Tokyo)*. 2004;44:72-74.
10. Yokota H, Sugiura S, Ida Y, Itoh H. Neurogenic stress cardiomyopathy following aneurysmal subarachnoid hemorrhage in a very elderly patient. *Neurol Med Chir (Tokyo)*. 2011;51:842-846.
11. Hakeem A, Marks AD, Bhatti S, Chang SM. When the worst headache becomes the worst heartache! *Stroke*. 2007;38:3292-3295
12. Maekawa H, Hadeishi H: Takotsubo cardiomyopathy following subarachnoid haemorrhage. *Pract Neurol*. 2014;14:252-255
13. Kawai S, Suzuki H, Yamaguchi H, et al. Ampulla cardiomyopathy ('takotsubo' cardiomyopathy)-reversible left ventricular dysfunction: with ST segment elevation. *Jpn Circ J*. 2000;64:156-159.
14. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *J Am Coll Cardiol*. 2001;38:11-18.
15. Akashi YJ, Musha H, Nakazawa K, Miyake F. Plasma brain natriuretic peptide in

takotsubo cardiomyopathy. *QJM*. 2004;97:599-607

16. Kurisu S, Sato, H, Kawagoe T, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J*. 2002;43:448-455.
17. Abe Y, Kondo M, Matsuoka R, Araki M, Dohyama K, Tanio H. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol*. 2003;41:737-742.
18. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J*. 2006;27:1523-1529.
19. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation*. 2008;118:2754-2762.
20. Mariscalco G, Cattaneo P, Rossi A, et al. Tako-tsubo cardiomyopathy complicated by ventricular septal perforation and septal dissection. *Heart Vessels*. 2010;25:73-75.
21. Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol*. 2007;50:448-452.
22. Sharkey SW, Windenburg DC, Lesser JR, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol*. 2010;55:333-341.
23. Banki N, Kopelnik A, Tung P, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. *J Neurosurg*. 2006;105:15-20.
24. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352:539-548.
25. Kume T, Kawamoto T, Okura H, et al. Local release of catecholamines from the hearts of patients with tako-tsubo-like left ventricular dysfunction. *Circ J*. 2008;72:106-108.
26. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (takotsubo) cardiomyopathy: a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med*. 2008;5:22-29.
27. Paur H, Wright PT, Sikkil MB, et al. High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenoceptor/Gi-dependent manner: a new model of takotsubo cardiomyopathy. *Circulation*. 2012;126:697-706.
28. Heubach JF, Ravens U, Kaumann AJ. Epinephrine activates both Gs and Gi pathways, but norepinephrine activates only the Gs pathway through human beta2-adrenoceptors overexpressed in mouse heart. *Mol Pharmacol*. 2004;65:1313-1322.
29. Galiuto L, De Caterina AR, Porfidia A, et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning or tako-tsubo syndrome. *Eur Heart J*. 2010;31:1319-1327.
30. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. *Circ J*. 2005;69:934-939.
31. Elesber A, Lerman A, Bybee KA, et al. Myocardial perfusion in apical ballooning syndrome correlate of myocardial injury. *Am Heart J*. 2006;152:469.e9-e13.
32. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular

system. *N Engl J Med*. 1999;340:1801-1811.

33. Ueyama T, Ishikura F, Matsuda A, et al. Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart. *Circ J*. 2007;71:565-573.

34. Kurisu S, Inoue I, Kawagoe T, et al. Time course of electrocardiographic changes in patients with tako-tsubo syndrome: comparison with acute myocardial infarction with minimal enzymatic release. *Circ J*. 2004;68:77-81.

35. Syed FF, Asirvatham SJ, Francis J: Arrhythmia occurrence with takotsubo cardiomyopathy: a literature review. *Europace*. 2011;13:780-788.

36. Antzelevitch C. Ionic, molecular, and cellular bases of QT-interval prolongation and torsade de pointes. *Europace*. 2007;9 Suppl 4:iv4-iv15.

37. Bonnemeier H, Hartmann F, Wiegand UK, Bode F, Katus HA, Richardt G. Course and prognostic implications of QT interval and QT interval variability after primary coronary angioplasty in acute myocardial infarction. *J Am Coll Cardiol*. 2001;37:44-50.

38. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J*. 1990;63:342-344.

39. Day CP, McComb JM, Matthews J, Campbell RW. Reduction in QT dispersion by sotalol following myocardial infarction. *Eur Heart J*. 1991;12:423-427.

40. Day CP, McComb JM, Campbell RW. QT dispersion in sinus beats and ventricular extrasystoles in normal hearts. *Br Heart J*. 1992;67:39-41.

41. Obayashi T, Tokunaga T, Iizumi T, Shiigai T, Hiroe M, Marumo F. Transient QT interval prolongation with inverted T waves indicates myocardial salvage on dual radionuclide single-photon emission computed tomography in acute anterior myocardial infarction. *Jpn Circ J*. 2001;65:7-10.

42. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Koike H, Sasaka K. The clinical features of takotsubo cardiomyopathy. *QJM*. 2003;96:563-573.

43. Saito M, Hayashi Y, Sasaki O, Inoue M, Fujioka S, Kouno M. A case of foxhole-shaped left ventricular abnormality induced by complete atrioventricular block with delayed recovery of wall motion. *Nippon Ronen Igakkai Zasshi*. 2004;41:546-551.

44. Denney SD, Lakkireddy DR, Khan IA. Long QT syndrome and torsade de pointes in transient left ventricular apical ballooning syndrome. *Int J Cardiol*. 2005;100:499-501.

45. Sasaki O, Nishioka T, Akima T, et al. Association of takotsubo cardiomyopathy and long QT syndrome. *Circ J*. 2006;70:1220-1222.

46. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, et al. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsades de pointes. *Heart Rhythm*. 2011;8:555-561.

47. Migliore F, Zorzi A, Peruzza F, et al. Incidence and management of life-threatening arrhythmias in takotsubo syndrome. *Int J Cardiol*. 2013;166:261-263.

Table 1: Characteristics of the TCM patients

No.	Age	Sex	Aneurysm	WFNS grade	Fisher group	Treatment	mRS	NPE	ECG findings	TTE findings
1	90	F	Rt.IC-PC	2	3	conservative	3	+	inverted T QTc prolongation ST elevation	EF57%
2	65	F	Rt.IC-PC	4	4	clipping	2	-	inverted T QTc prolongation ST elevation	EF48%
3	63	F	Acom	5	4	coiling	2	+	inverted T QTc prolongation ST elevation	EF44%
4	67	F	BA top	2	3	clipping	2	+	ST elevation	EF32% thrombus
5	64	F	Rt.VA dissection	2	2	coiling (internal trapping)	0	-	inverted T QTc prolongation ST elevation AF	EF44%
6	75	F	Acom	5	4	clipping	5	+	inverted T QTc prolongation	EF35%
7	81	F	Lt.PCA dissection	4	3	coiling (internal trapping)	4	+	ST depression ST elevation flattened T wave	EF47%
8	71	F	Lt.IC-PC	5	4	conservative	6	+	inverted T inverted P QTc prolongation Vf (day 1)	EF 29%
9	77	F	Rt.IC-PC	4	3	clipping	2	+	inverted T QTc prolongation ST elevation ST depression	EF 45%
10	40	F	Rt.IC-PC	4	3	clipping	0	+	flattened T wave ST elevaton	EF 46%

\*IC-PC: internal carotidartery-posterior communicating artery

\*Acom: anterior communicating artery

\*VA: vertebral artery

\*BA: basilar artery

\*NPE: neurogenic pulmonary edema

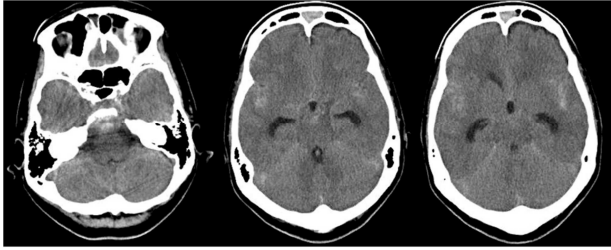
\*Vf: ventricular fibrillation

\*AF: atrial flutter

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Table 2: Normalization time of ECG and TTE

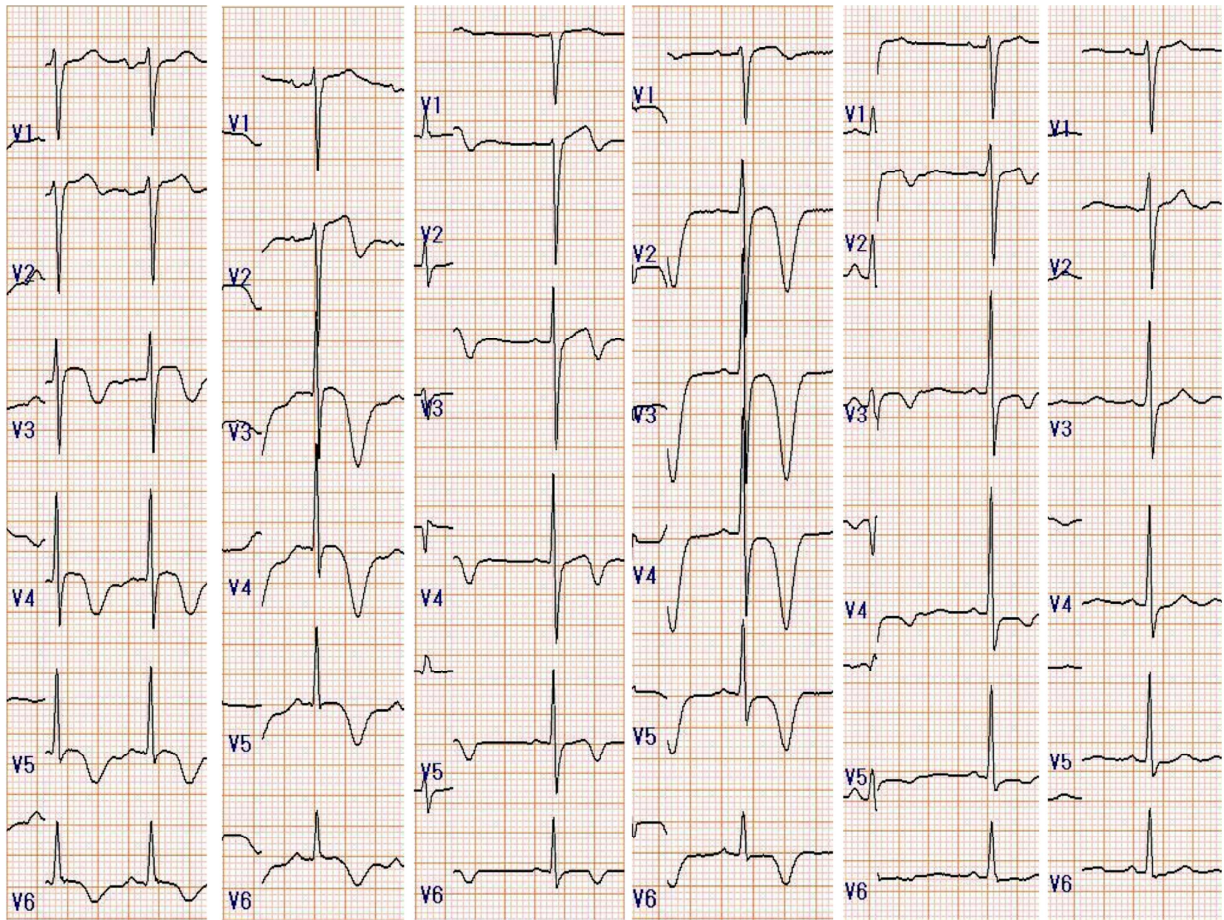
<b>No.</b>	<b>Normalization of TTE</b>	<b>Last abnormal ECG</b>	<b>Normalization of ECG</b>
1	day 5	day 7	Not available
2	day 9	day 47	Not available
3	day 4	day 28	6 months
4	day 16	day 47	7 months
5	day 11	day 43	5 months
6	day 10	day1	Not available
7	day11	day 15	Not available
8	Not available	day 8	Not available
9	day6	day 29	day 66
10	day6	day 1	day 3



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**Highlights**

- Some of the patients of subarachnoid hemorrhage suffer from takotsubo cardiomyopathy.
- Abnormal cardiac wall motion usually recovers within the acute period.
- Abnormalities on electrocardiograms can remain much longer than that of cardiac wall motion.
- Abnormalities in electrocardiography may cause some fatal arrhythmia such as Torsades de Pointes.
- Sufficient attention to electrocardiograms is necessary after the acute period.

**Conflict of Interests**

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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