ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3408–3412
Published online 3 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13397

CASE REPORT

A mid-ventricular variant of Takotsubo syndrome: was it triggered by insular cortex damage?

Ayano Osawa[1], Michiaki Nagai[1]*, Keigo Dote[1], Masaya Kato[1], Noboru Oda[1], Eiji Kunita[1], Eisuke Kagawa[1], Aya Yamane[1], Hiroshi Kobatake[1], Haruko Shiota[1], Naoki Ishibashi[1], Kazuki Takahashi[1] and Carola Y. Förster[2]

[1]*Department of Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan; and* [2]*Department of Anaesthesiology and Critical Care, Comprehensive Heart Failure Center (CHFC), University Hospital Würzburg, Würzburg, Germany*

Abstract

Takotsubo syndrome (TTS) is a transient cardiomyopathy that is often associated with cerebrovascular diseases. Earlier studies have supported the concept that the cardiovascular system is regulated by a central autonomic network (CAN) consisting of the insular cortex (IC), anterior cingulate gyrus and amygdala. We report the case of a 79-year-old female diagnosed with a mid-ventricular variant of TTS concomitant with right IC ischaemic stroke. After 12 h of hospitalization, she experienced a sudden collapse. Rapid cardiopulmonary resuscitation resulted in a return of spontaneous circulation. Subsequent left ventriculography revealed akinesis in the mid-portion of the left ventricle with vigorous contraction of the basal and apex segment. Two weeks after admission, cardiac ultrasound showed improved left ventricular contraction. Right IC ischaemia in this patient might have been associated with a dysregulation of the CAN and subsequent increased sympathetic nervous system activity that triggered TTS.

Keywords Takotsubo syndrome; Mid-ventricular variant; Central autonomic network; Insular cortex; Ischaemic stroke; Laterality

Received: 3 February 2021; Revised: 31 March 2021; Accepted: 19 April 2021
**Correspondence to: Michiaki Nagai, Department of Cardiology, Hiroshima City Asa Hospital, 2-1-1, Kabeminami, Aaskita-ku, Hiroshima 731-0293, Japan. Tel: +81-82-815-5211; Fax: +81-82-814-1791. Email: nagai10m@r6.dion.ne.jp*

Introduction

Takotsubo syndrome (TTS) is a transient cardiomyopathy that is often associated with acute emotional or physical stress.[1] Several reports have suggested that ischaemic stroke may be a trigger of TTS.[1] On the other hand, earlier studies have supported the concept that the cardiovascular system is regulated by a central autonomic network (CAN) consisting of the insular cortex (IC), anterior cingulate gyrus and amygdala.[2] As the IC cerebrovasculature often tends to be damaged in patients with stroke, autonomic instability is suggested to be induced by IC lesions, resulting in functional disturbance.[2]

Case report

A 79-year-old Japanese female, who presented with difficulty in articulation and slight paralysis in the left hand, was admitted to our hospital. After arrival, magnetic resonance imaging (MRI) scan was performed, and she was diagnosed with cerebral ischaemia involving the right IC (*Figure 1*). She was given an infusion of fluid (60 mL/h) and oral aspirin (100 mg/day), along with unfractionated heparin (10 000 IU/day) as a prophylactic agent to prevent deep vein thrombosis. After 12 h of hospitalization, she experienced a collapse with loss of consciousness. Shock and dyspnoea were observed with pulseless electrical activity. Soon after, cardiopulmonary resuscitation was started. After three i.v. injections of adrenaline (1 mg each), her spontaneous circulation returned. Electrocardiography monitoring revealed ST-segment elevation in the posterior chest leads with reciprocal change in the inferior chest leads (*Figure 2*), and transthoracic echocardiography (TTE) demonstrated akinesis in the anterolateral wall of the left ventricle (LV). We suspected that the patient had experienced an acute myocardial infarction. However, subsequent angiography did not disclose any stenosis within the coronary arteries (*Figure 3*). Left

Figure 1 Brain magnetic resonance imaging. Acute cerebral lesions including the right IC were observed in the diffusion-weighted *(A)* and fluid-attenuated inversion recovery *(B)* images.

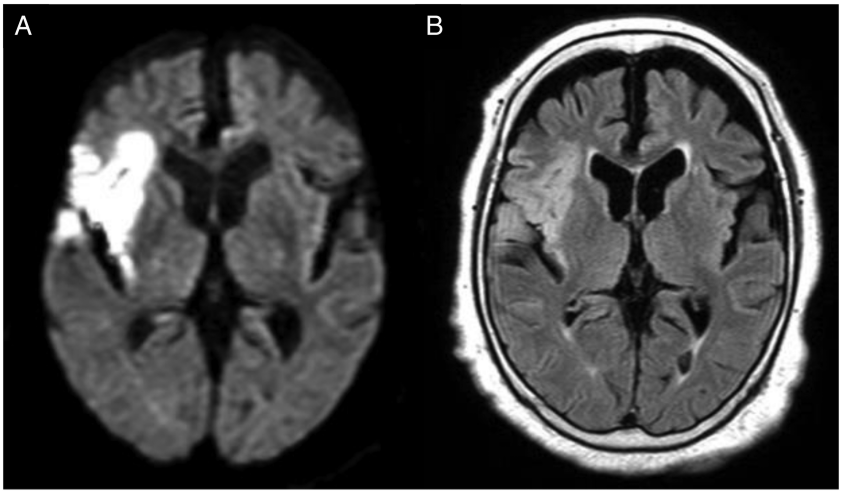
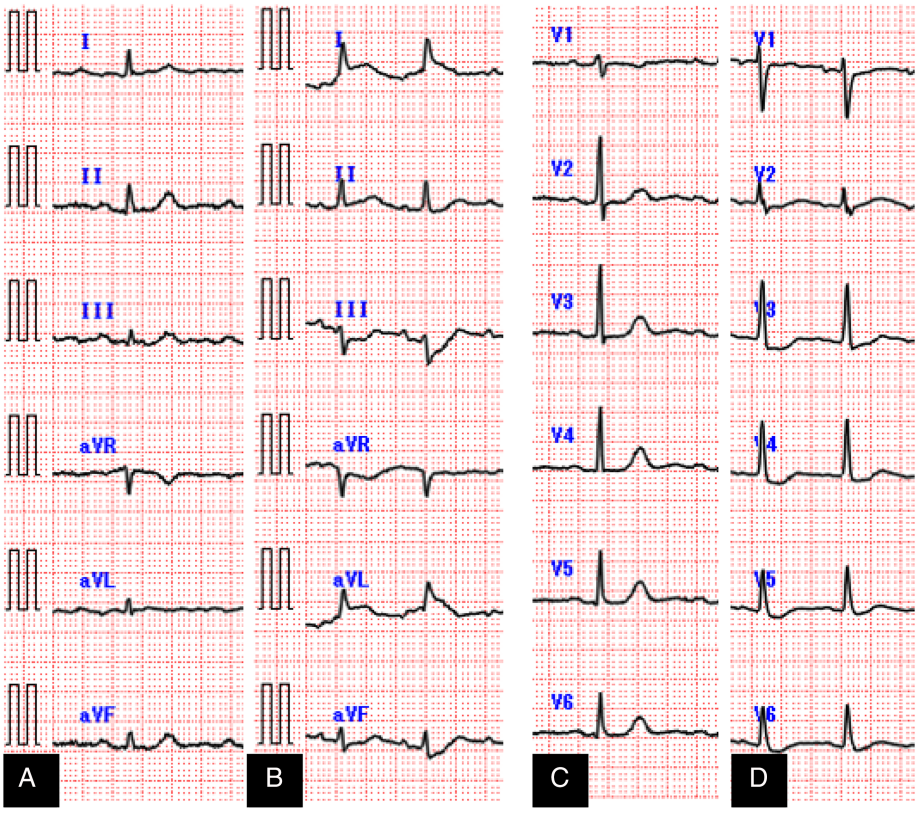


Figure 2 Time course of ECG changes. The time course of ECG changes in the extremity leads (A,B) and chest leads (C,D) between the patient's admission and the time of ROSC.



ventriculography revealed akinesis in the mid-portion of the LV with vigorous contraction of the basal and apex segment, diagnosed as a mid-ventricular variant of TTS (*Figure 4*). Although the high-sensitivity troponin was elevated (1830 ng/L), the plasma levels of epinephrine, norepinephrine and dopamine were 0.01 (normal: less than 0.12), 2.5

Figure 3 Coronary artery angiography. No stenosis was observed in the right coronary artery *(A)*, left anterior descending artery or circumflex artery *(B)*.

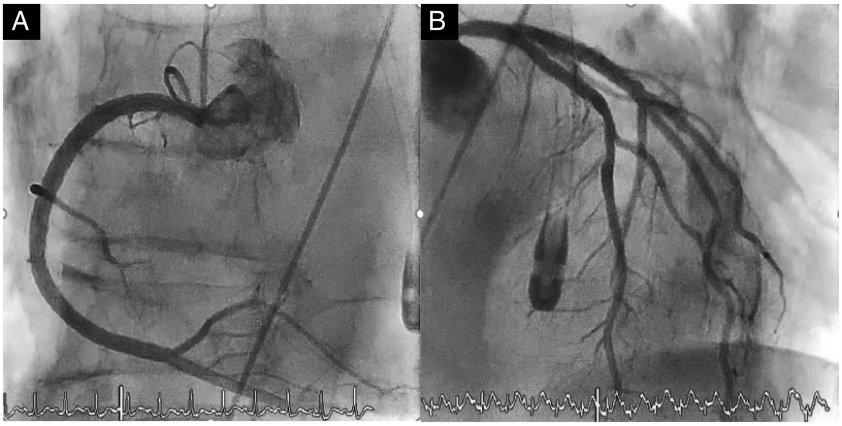
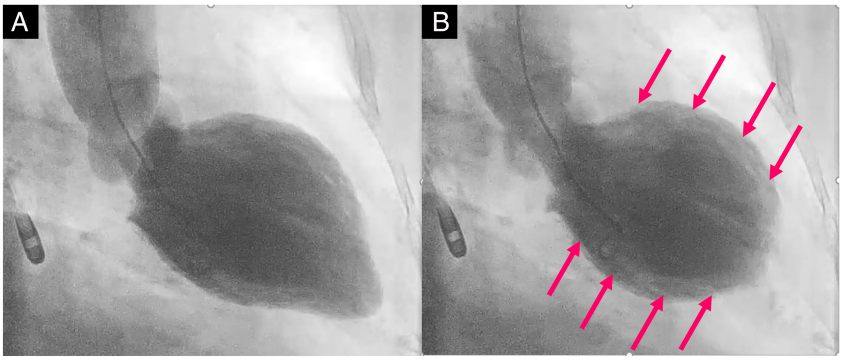


Figure 4 Left ventriculography. End-diastolic phase left ventriculogram *(A)* and end-systolic phase left ventriculogram *(B)*. The extensive area around the mid-portion shows akinesis (arrows), and the basal and apex portion display hypercontraction, especially in the end-systolic phase (B).



(normal: 0.06–0.5) and 0.02 ng/mL (normal: less than 0.03). Two weeks after admission, TTE showed improved contraction in the LV with an ejection fraction of more than 60%.

Discussion

In the present case of a postmenopausal female with cerebral ischaemia involving the right IC, a mid-ventricular variant of TTS was observed without obstructive coronary disease.

In a previous study of 569 consecutive patients with acute ischaemic stroke, seven patients were diagnosed as having TTS.[3] All seven patients were female, and six were aged ≥75 years. The culprit infarcts included or were close to the IC in six patients. Female gender and IC damage were revealed as predominant features in stroke patients who developed TTS.[3] Among the mechanisms potentially linking the IC-involved stroke to TTS, sympathetic nervous system (SNS) activation is among the most likely.[1] There is evidence that higher SNS activation plays an important role in the development of TTS.[1] On the other hand, in an animal study, LV dysfunction occurred in nine of 14 mice with left permanent middle cerebral artery (MCA) occlusion.[4] In these nine mice, the severity of the left IC lesions and the serum and heart norepinephrine levels were significantly higher than those in mice with normal cardiac function.[4] SNS activation might have played an important role for cardiac dysregulation because the plasma level of norepinephrine was higher than the normal level in this patient with IC infarction.

However, the lesion laterality of IC in our patient (right IC) was different from that applied in the animal model in the above-described study (left IC).[4] In individuals with drug-refractory epilepsy, right hemispheric inactivation induced increases in the high frequency of heart rate and blood pressure, and left hemispheric inactivation induces increases in the low frequency of heart rate and blood pressure.[5] Importantly, within the human IC, tachycardia or pressor effects are significantly increased after stimulation of the right IC, whereas bradycardia or depressor effects were significantly increased after stimulation of the left IC.[6] The right IC is associated with SNS activity, and the left

DOI: 10.1002/ehf2.13397

IC is supposed to be associated with parasympathetic nervous system activity.

Experimental stroke models have shown that occlusion of the right MCA results in neurochemical derangements in the ipsilateral IC and amygdala, which leads to enhancement of SNS outflow to the heart, resulting in an increase in synaptic norepinephrine levels.[7] Enhanced SNS outflow could also occur as a result of cerebral ischaemia, and experimental brain stimulation could induce cardiac changes similar to those observed in acute cerebrovascular disease.[8] In addition, a recent functional MRI study has shown that baseline sympatho-vagal balance depended on the integrity of lateralized salience network hubs consisting of the right amygdala for the SNS and the left IC for the parasympathetic nervous system.[9] Because the right IC was damaged while the right amygdala was preserved in this TTS patient, the insulo-amygdala functional connectivity might have been shifted towards increased right amygdala activity due to right IC damage, which could finally form the basis for SNS hyperactivity.

In the present case, a mid-ventricular variant of TTS was observed. In a previous study on 1750 patients with TTS, the most common type of TTS was the apical type (81.7%), followed by the mid-ventricular type (14.6%).[10] Although IC damage is suggested to be involved in the pivotal role of triggering TTS,[1] until now, there has been no report of a patient with mid-ventricular-type TTS due to IC damage. In the apical type of TTS, the impact of the high catecholamines up to the myocardium dictated by beta-adrenoceptor (βAR) gradients is suggested to contribute to a final common endpoint of acute apical dysfunction.[11] βAR gradients in LV might differ between the apical type and mid-ventricular type. On the other hand, the function of murine cardiacβ1AR is suppressed by overexpressed human β2AR.[12] A bell-shaped dose–response relationship was observed for myocardial contraction, and at the highest doses of epinephrine, a negative inotrope was found via the β2AR.[12] In the case of our present patient, the β2ARs might be most highly distributed in the mid-portion of LV.

Also in the present patient, a mid-ventricular variant of TTS was observed. The right IC ischaemic damage might serve as a pivotal pathophysiology for the increased SNS. In addition, the level of overexpressed β2ARs in the mid-ventricular portion was suggested to be higher in this postmenopausal female. In an experimental model,[13] the blood–brain barrier (BBB)-compromising impact of catecholamines combined with hypoxia was shown to be associated with the alterations in cellular and molecular expression, which were suitable to form the basis for periinsular BBB damage linking to the CAN dysregulation with increased SNS activity.[13]

Further studies will be needed to elucidate the pathophysiology underlying the relationship between postmenopausal status, CAN dysregulation and the TTS variant in relation to increased SNS activity more precisely.

Conflict of interest

The authors declare no conflict of interest.

References

1. Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, Nakano Y, Yamane A, Higashihara T, Miyauchi S, Tsuchiya A, Harada W, Kario K. The insular cortex and Takotsubo cardiomyopathy. *Curr Pharm Des* 2017; **23**: 879–888.
2. Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. *J Am Soc Hypertens* 2010; **4**: 174–182.
3. Yoshimura S, Toyoda K, Ohara T, Nagasawa H, Ohtani N, Kuwashiro T, Naritomi H, Minematsu K. Takotsubo cardiomyopathy in acute ischemic stroke. *Ann Neurol* 2008; **64**: 547–554.
4. Min J, Farooq MU, Greenberg E, Aloka F, Bhatt A, Kassab M, Morgan JP, Majid A. Cardiac dysfunction after left permanent cerebral focal ischemia. *Brain Heart Connect Stroke* 2009; **40**: 2560–2563.
5. Hilz MJ, Dutsch M, Perrine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. *Ann Neurol* 2001; **49**: 575–584.
6. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992; **42**: 1727–1732.
7. Cechetto DF, Hachinski V. Cardiovascular consequences of experimental stroke. In Cechetto D. F., Hachinski V., eds. *Bailliere's clinical neurology, neurocardiology*, Vol. **6**. London, UK: WB Saunders; 1997. p 297–308.
8. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation* 2008; **118**: 397–409.
9. Sturm VE, Brown JA, Hua AY, Lwi SJ, Zhou J, Kurth F, Eickhoff SB, Rosen HJ, Kramer JH, Miller BL, Levenson RW, Seeley WW. Network architecture underlying basal autonomic outflow: evidence from frontotemporal dementia. *J Neurosci* 2018; **38**: 8943–8955.
10. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015; **373**: 929–938.
11. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol* 2015; **12**: 387–397.
12. Heubach JF, Blaschke M, Harding SE, Ravens U, Kaumann AJ. Cardiostimulant

and cardiodepressant effects through overexpressed human beta2-adrenoceptors in murine heart: regional differences and functional role of beta1-adrenoceptors. *Naunyn Schmiedebergs Arch Pharmacol* 2003; **367**: 380–390.
13. Ittner C, Burek M, Störk S, Nagai M, Förster CY. Increased catecholamine levels and inflammatory mediators alter barrier properties of brain microvascular endothelial cells in vitro. *Front Cardiovasc Med* 2020; **7**: 73.