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CASE REPORT
Congenital heart disease

Reverse takotsubo cardiomyopathy caused by patent foramen ovale-related cryptogenic stroke: a case report

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Background Reverse takotsubo cardiomyopathy (rTTC) is recognized as an atypical type of TTC. It has been suggested that neurological events are typical trigger of rTTC, especially in young individuals.

Case summary In this case report, we describe a 16-year-girl who presented with neurological deficits due to embolic stroke and acute heart failure. Transthoracic echocardiography on admission revealed a severely reduced left ventricular (LV) function with akinesis of basal to mid LV, but normal contraction in apex. Coronary computed tomography angiography confirmed unobstructed coronary arteries. Two weeks later, her LV wall motion and ejection fraction were completely normalized. Transthoracic echocardiography and transoesophageal echocardiography demonstrated no evidence of intracardiac thrombus but showed a patent foramen ovale (PFO) with large shunt. After thorough work-up and brain–heart team discussion, we concluded that the patient developed rTTC due to cryptogenic stroke related with her PFO. She underwent percutaneous PFO closure for secondary prevention with good clinical course.

Discussion Reverse TTC is a rare condition. It should be considered in stroke patients with acute heart failure. Quick diagnosis and management with brain–heart team is crucial for better prognosis.

Keywords Reverse takotsubo cardiomyopathy • Patent foramen ovale • Cryptogenic stroke • Percutaneous PFO closure • Case report

Learning points

- Acute heart failure due to reverse takotsubo cardiomyopathy could be a critical cardiac manifestation in young patients presenting with a neurological event.
- Patent foramen ovale-related cryptogenic stroke is one of the major causes of the stroke in this population.
- Thorough work-up and discussion with brain–heart team is important for the appropriate management in these complicated cases.

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Introduction

An atypical type of takotsubo cardiomyopathy (TTC) is described as a condition that does not have a confirmed typical appearance of 'apical ballooning' observed in TTC.[1–3] It is generally referred to as 'reverse TTC (rTTC)' or 'inverted TTC'. The clinical setting and disease course are different from those of the typical TTC.[2,3] Previous reports demonstrated that physical stress, such as cerebrovascular disease, is the major trigger of rTTC compared with typical TTC, which is more likely to be triggered by emotional stress.[1–4] A patent foramen ovale (PFO) is an important cause for cryptogenic stroke, especially in younger patients. Recently, it has been demonstrated that percutaneous PFO closure is superior over antithrombotic therapy alone in patients with PFO-related cryptogenic stroke.[5] Here, we report a very rare case of rTTC caused by PFO-related cryptogenic stroke in a young girl, who underwent successful percutaneous PFO closure.

Timeline

Time	Event
Day 1	Admitted to intensive care unit in our hospital for stroke with acute heart failure. Transthoracic echocardiography revealed a severe akinesis of the basal and mid segments with apical sparing. Electrocardiogram showed sinus rhythm with non-significant ST depression in inferior leads and T-wave inversion in lead aVL. Reverse takotsubo cardiomyopathy (rTTC) was suspected.
Day 8	Transferred from intensive care unit to the neurology ward.
Day 14	Echocardiography showed that her left ventricular function was completely normalized.
Day 17	Transthoracic echocardiography and transoesophageal echocardiography revealed a shunt through the patent foramen ovale (PFO).
Day 25	A contrast-enhanced computed tomography did not reveal the presence of a tumour or a pulmonary arteriovenous fistula.
Day 34	Transferred to rehabilitation hospital. Final diagnosis of rTTC triggered by the cryptogenic stroke was made.
7 months	Percutaneous PFO closure performed.
13 months (6 months after PFO closure)	No recurrent adverse events.

Case presentation

A 16-year-old girl was transferred to the emergency room (ER) by ambulance due to dizziness, hemiplegia, and dyspnoea. She only had a remote history of asthma and denied any stressful events until the sudden onset of her symptoms. On admission, she had decreased level of consciousness with Glasgow Coma Scale of E2V2M5. She was afebrile and her vital signs showed an elevated blood pressure of 160/104 mmHg with pulse rate of 109 b.p.m. Physical examination revealed coarse crackles without heart murmur. Her oxygen saturation was 80% on room air, and a chest X-ray showed bilateral pulmonary oedema. She was intubated in ER due to respiratory failure. An urgent magnetic resonance image of the brain was organized which showed cerebral infarction in the right cerebellar hemisphere due to obstruction of the right vertebral artery (*Figure 1A* and *B*) without evidence of haemorrhage. An emergency cerebral angiogram confirmed a right vertebral artery occlusion with thrombus, there was no evidence of dissection (*Figure 1C*). She was admitted to the intensive care unit, where she was treated medically with unfractionated heparin, warfarin, and enalapril 2.5 mg daily. Electrocardiogram (ECG) showed sinus rhythm with non-significant ST depression in inferior leads and T-wave inversion in lead aVL (*Figure 2*). Troponin I was elevated at 1.531 ng/mL (normal <0.034 ng/mL). Bedside transthoracic echocardiography revealed severely reduced left ventricular (LV) function (LV ejection fraction 22%) and akinesis of the basal and mid LV with apical sparing (*Figure 3A*: systolic phase; *Figure 3B*: diastolic phase; see *Video 1*). The right ventricular function was preserved without dilatation. There was no LV thrombus nor pericardial effusion. Coronary computed tomography angiography showed no evidence of occlusion or dissection. Based on these findings, we tentatively diagnosed her cardiac condition as rTTC caused by the acute neurologic event. Follow-up echocardiography on Day 14 showed that her LV function had completely normalized (*Video 2*) with ECG normalized as well. Thorough work-up was conducted to identify the underlying cause of her embolic stroke. Cardiac monitoring and Holter ECG showed no significant atrial arrhythmia, such as atrial fibrillation. She did not take any oral contraceptives. Laboratory tests showed no evidence of hypercoagulable state; Protein S, Protein C, antithrombin III, antinuclear antibody, anti-cardiolipin antibody, and lupus anticoagulant were within normal range. No deep vein thrombosis was detected by venous ultrasonography in her lower extremities. A contrast-enhanced computed tomography did not reveal the presence of a tumour or a pulmonary arteriovenous fistula. Further work-up for connective tissue disorder and pheochromocytoma were all negative. Transthoracic echocardiography with bubble study showed a large right-to-left shunt (more than 30 bubbles) without Valsalva manoeuvre (*Figure 4*; see *Video 3*). Transoesophageal echocardiography (TOE) showed no evidence of intracardiac thrombus but revealed shunt flow through a PFO at rest (*Figure 5A*). The bubble study confirmed the right-to-left shunt through the PFO with Valsalva manoeuvre (*Figure 5B*).

Based on these test results and hospital course, the final diagnosis of rTTC triggered by the PFO-related cryptogenic stroke was made. On the hospital Day 34, she was transferred to the rehabilitation facility on long-term anticoagulation therapy with warfarin (target international normalized ratio 2.0–3.0). Two months after, transfer to a rehabilitation facility from our hospital, she was discharged to her home with mild neurological deficit of hand dexterity. During the outpatient follow-up, our brain–heart team, including neuro surgeons, interventional cardiologists, and cardiologists specializing in echocardiography, discussed consideration of

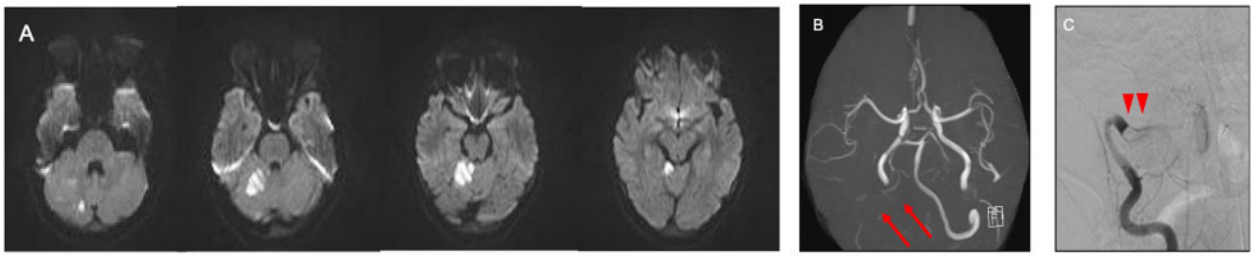

Figure 1 (*A*) Diffusion-weighted magnetic resonance image showing cerebral infarction in right cerebellar hemisphere. (*B*) Magnetic resonance angiography showing the absence of the right vertebral artery (red arrow). (*C*) Cerebral angiography showing a right vertebral artery occlusion with thrombus (red arrowhead).

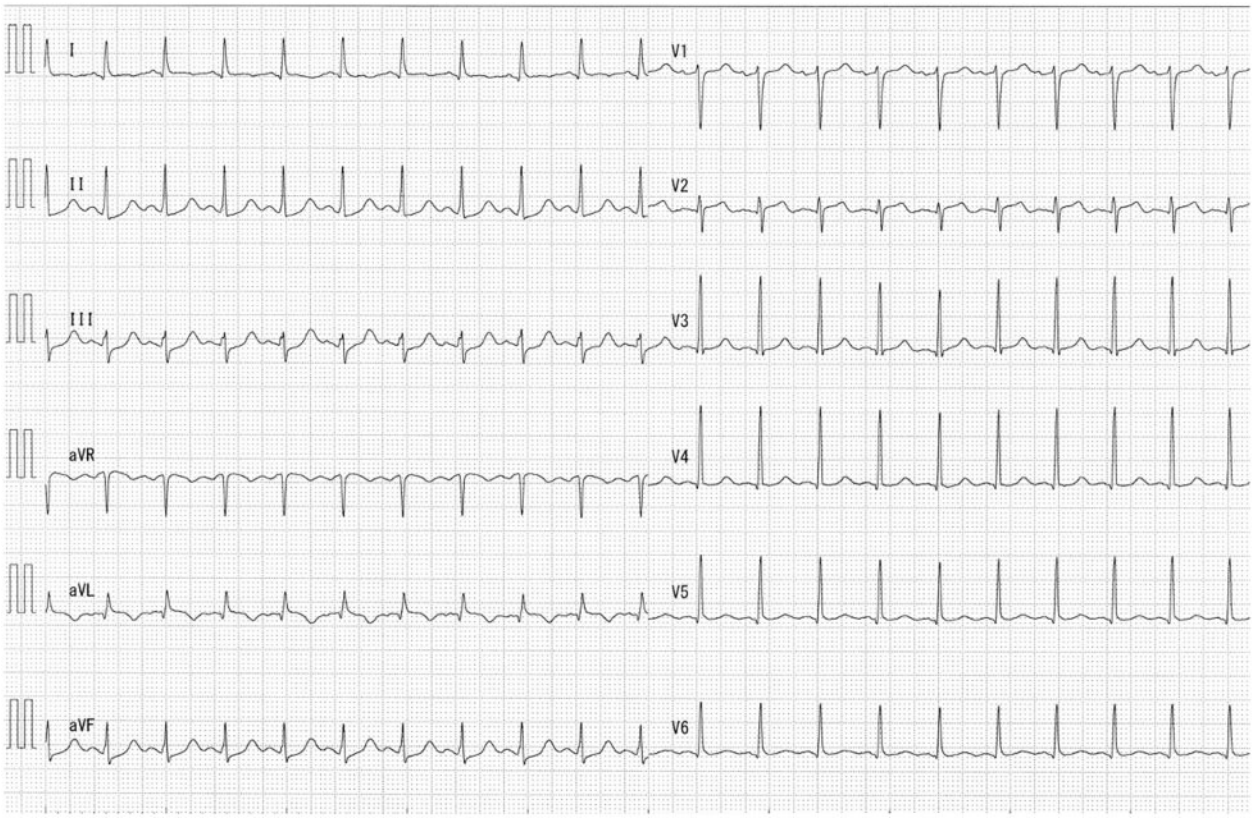

Figure 2 Electrocardiogram showing sinus rhythm with non-significant ST depression in inferior leads and T-wave inversion in lead aVL.

the percutaneous PFO closure and concluded that the benefits of the device treatment would outweigh the risks because of high chance of stroke recurrence in this case. Seven months after onset of the stroke, she underwent percutaneous PFO closure for secondary prevention of a cerebrovascular event. A 25 mm Amplatzer PFO Occluder (Abbott, Chicago, IL, USA) was deployed under TOE guidance. After deployment, TOE showed no residual shunt through the PFO. There were no procedural complications, and no recurrent adverse events at 6 months follow-up after procedure.

Discussion

This is a very rare case of PFO-related cryptogenic stroke resulting in rTTC in a teenage girl. Neurological disorders especially stroke and

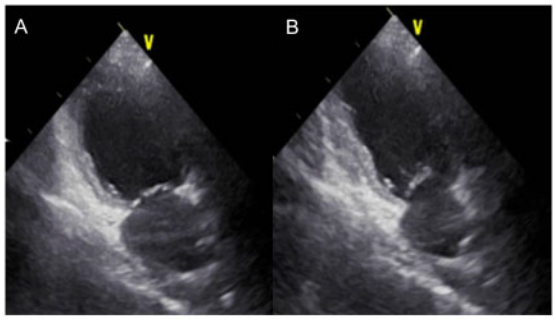

Figure 3 Transthoracic echocardiography in two-chamber view showing severe akinesis of the basal and mid segments with apical sparing. (*A*) Systolic phase. (*B*) Diastolic phase.

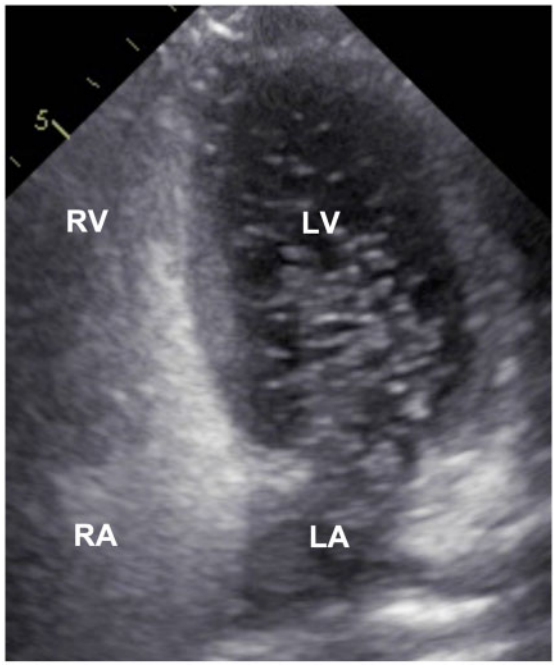

Figure 4 Transthoracic echocardiography in four-chamber view, using agitated saline contrast microbubbles without Valsalva manoeuvre, showing significant right-to-left shunting. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

subarachnoid haemorrhage have been linked with the trigger of TTC, and the role of the brain–heart axis in the pathogenesis of the TTC has been reported.[6] TTC is part of a broad spectrum of cardiac alterations that may occur during the first few days after occurrence of acute brain disease. Previous study demonstrated that TTC occurs secondary to stroke in ∼1% of patients.[7]

The rTTC, an atypical type of TTC, occurs in ∼2.2% of all TTC cases.[1] It is frequently associated with a cerebrovascular event and occurs in the younger population, compared with the classical type of TTC.[2–4] The higher frequency of adrenoreceptors in the basal left ventricular wall (compared to the apical segment) in this age bracket is thought to be one of the main reasons for the higher prevalence of rTTC in younger individuals.[4]

Patent foramen ovale-related stroke is rare condition, but it has been suggested that this condition may be a more important contributor to strokes in younger patients.[8–10] The data evaluating the role of PFO closure for recurrent stroke prevention in adolescent and young adults is limited. Previous studies indicate that existence of atrial septal aneurysm, large shunt, and/or shunt flow at rest through a PFO as a predictor of the recurrent stroke.[11–14] Therefore, we considered that PFO closure would be beneficial in long-term management of this teenage patient. Appropriate patient selection for PFO closure through a comprehensive stroke workup with brain–heart team is crucial in order to offer the procedure to the patients who will benefit the most and avoid unnecessary procedures especially in the younger patient (age < 18 years old).[15]

In conclusion, we experienced a case of rTTC in the context of a cryptogenic stroke secondary to a PFO, and percutaneous PFO closure was performed successfully. Further investigation is needed to confirm the incidence and mechanism of this rare condition.

Lead author biography

Hiroya Takafuji, MD, is a chief physician of cardiology at Tokyo Bay Urayasu Ichikawa Medical Center in Japan. He was training structural heart disease interventions from April 2016 to June 2019 at Tokushima Red Cross Hospital in Japan (under Dr Hosokawa S., Dr Ogura R., and Dr Izumi T.). His specialization is structural heart disease interventions, especially, congenital heart disease such as atrial septal defect and PFO.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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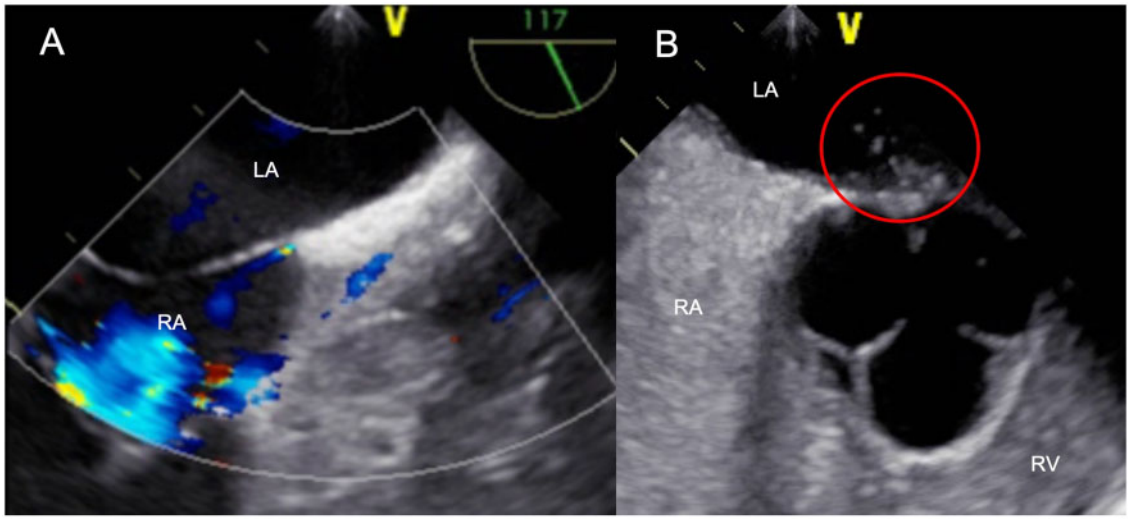
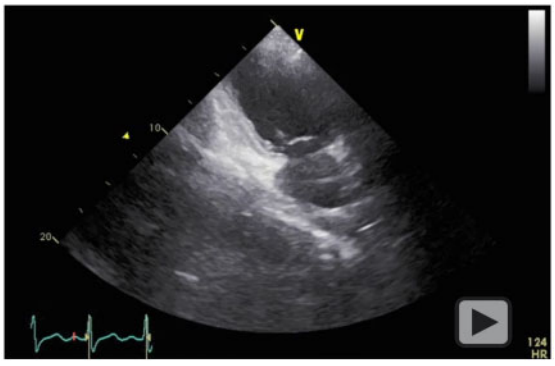
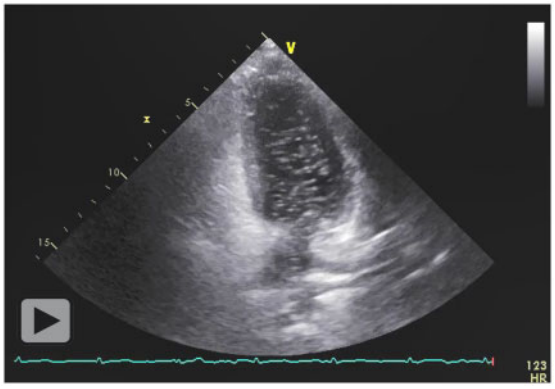


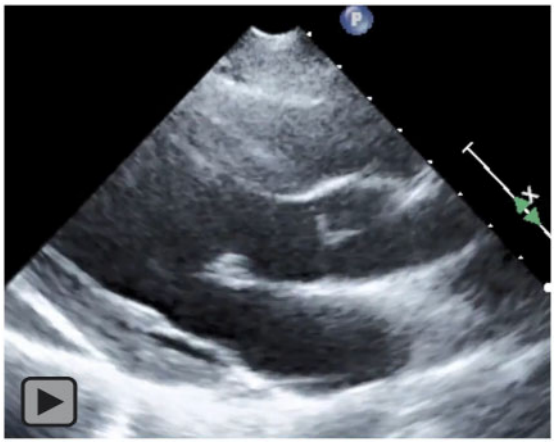
Figure 5 (*A*) Transoesophageal echocardiography with colour Doppler showing shunt flow through a patent foramen ovale. (*B*) Transoesophageal echocardiography with bubble study confirming the passage of microbubbles from the right atrium to the left atrium through a patent foramen ovale with Valsalva manoeuvre (red circle). LA, left atrium; RA, right atrium; RV, right ventricle.



Video 1 Transthoracic echocardiography revealed akinesis of the basal and mid left ventricle with apical sparing.



Video 3 Transthoracic echocardiography with bubble study showed a large right to left shunt.



Video 2 Follow-up echocardiography on Day 14 showed that left ventricle function had completely normalized.

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