Cardiogenic shock due to Takotsubo cardiomyopathy associated with thyroid crisis: a case report

Xiaojuan Fan, MD¹, Ping Liu, MD, PhD¹, Ling Bai, MD, PhD¹

¹Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi’an Jiaotong University, Shaanxi, China

Correspondence: Ling Bai, Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi’an Jiaotong University, No.277, Yan Ta Xi Road, Xi’an, Shannxi 710061, PR China (E-mail: bailingb21@sina.com)

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Learning points

• Takotsubo cardiomyopathy and thyroid crisis can co-occur in the presence of thyrotoxicosis and result in refractory cardiogenic shock.

• Early combination of anti-thyroid crisis drugs and heart failure treatment is associated with good outcome in those patients.

• The combination of levosimendan and mechanical support may be the optimal strategy at early stage of Takotsubo cardiomyopathy when ventricular outflow tract obstruction is absent.

• Nifekalant can rapidly restore sinus rhythm when atrial fibrillation occurs in the presence of severe cardiac dysfunction and untreated hyperthyroidism.
<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>A 46-year-old female was transferred to our hospital due to chest pain, elevated cardiac marker, and abnormal electrocardiogram. Right after urgent coronary angiography excluded acute myocardial infarction, the patient developed cardiogenic shock. Echocardiography demonstrated a typical apical ballooning type of Takotsubo cardiomyopathy with left ventricular ejection fraction (LVEF) of 32%. A large dose of norepinephrine and dopamine, as well as intra-aortic balloon pump (IABP), were used to support the hemodynamic stability. Extracorporeal Membrane Oxygenation (ECMO) implantation was refused by the patient’s family member.</td>
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<td>Day 2</td>
<td>The patient persistently complained of chest tightness, accompanied by sweating and dysphoria. Thyroid function showed previously unknown hyperthyroidism.</td>
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<td>Day 3</td>
<td>Rapid atrial fibrillation (AF) occurred, and nifekalant successfully restored the sinus rhythm. Dexamethasone and Lithium Carbonate was initiated for thyroid crisis.</td>
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<td>Day 4</td>
<td>The patient still complained of chest tightness, palpation and sweating. Levosimendan was attempted without a loading dose.</td>
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<td>Day 5-6</td>
<td>The patient stopped sweating and complained of less discomfort. The vasopressor was reduced gradually and IABP was retrieved.</td>
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<td>Day 7</td>
<td>Echocardiography showed completely recovered LVEF of 64%.</td>
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<td><strong>Day 8-30</strong></td>
<td>The patient was transferred to the endocrine department and discharged with the diagnosis of thyrotoxicosis secondary to Graves' disease.</td>
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<td><strong>Follow-up at 3-month</strong></td>
<td>The thyroid function returned to normal. Echocardiography showed normal cardiac function.</td>
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¹Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi’an Jiaotong University, Shaanxi, China

Correspondence: Ling Bai, Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi’an Jiaotong University, No.277, Yan Ta Xi Road, Xi’an, Shannxi 710061, PR China (E-mail: bailingb21@sina.com)

Background The development of cardiogenic shock due to the coexistence of Takotsubo cardiomyopathy and thyroid crisis in patients has been scarcely reported.

Case summary A 46-year-old female presented with chest pain, palpitations, nausea, and vomiting for 8 hours. She was initially considered to have acute myocardial infarction due to elevated cardiac markers and abnormal electrocardiogram changes. Immediately after the coronary angiography revealed a normal coronary artery, the patient developed refractory cardiogenic shock. Echocardiography demonstrated a typical apical ballooning type of Takotsubo cardiomyopathy with a left ventricular ejection fraction (LVEF) of 32%. A combination of norepinephrine and dopamine and an intra-aortic balloon pump (IABP) was used to support haemodynamic stability but failed to improve the patient’s condition. Immediately after the laboratory tests revealed...
previously unknown hyperthyroidism on the second hospital day, a rapid atrial fbrillation suddenly occurred. Nifekalant successfully restored sinus rhythm in a short time. The patient persistently complained of chest tightness, palpitations and sweating for the first four days until levosimendan and antithyroid crisis treatment were used.

Discussion Takotsubo cardiomyopathy and thyroid crisis can co-occur and present as cardiogenic shock. In the presence of severe cardiac dysfunction and untreated hyperthyroidism, nifekalant is an ideal option for the new onset of atrial fibrillation. The combination of heart failure treatment and antithyroid crisis drugs can effectively restore cardiac function and is associated with good clinical outcomes.

Keywords Cardiogenic shock, Takotsubo cardiomyopathy, Thyroid crisis, Nifekalant, Levosimendan, case report

Introduction

Thyroid crisis is an extreme manifestation of thyrotoxicosis with a high mortality rate. Takotsubo cardiomyopathy is a form of reversible cardiomyopathy that has a similar mortality to myocardial infarction and is usually triggered by emotional or physical stressors, including thyrotoxicosis. Cardiogenic shock in the setting of the co-occurrence of thyroid crisis and Takotsubo cardiomyopathy would be a complicated and difficult situation to address. Here, we present a successfully treated case of cardiogenic shock due to Takotsubo cardiomyopathy associated with thyroid crisis in a patient with previously unknown hyperthyroidism.

Case summary
A 46-year-old female was transferred to our cardiac care unit (CCU) at midnight from her local hospital with complaints of chest pain, palpitations, nausea and vomiting that started 8 hours prior after having an argument with others. She had experienced natural menopause two years before and had no previous medical history.

On examination, she was fatigued, with a heart rate of 125 bpm and blood pressure (BP) of 90/60 mmHg. Her lungs were clear to auscultation. No abnormal heart sounds, bilateral cardiac enlargement, jugular venous distention, or lower extremity oedema were present. An initial electrocardiogram (ECG) showed poor R wave progression from lead V1 to V3 and diffuse ST-segment elevation in all leads except aVR and V1 (Figure 1). Quick bedside tests were notable for elevated high-sensitivity troponin-T (hs-TnT, 2.9 ng/mL, normal range 0~0.014) and N-terminal pro-BNP (NT-proBNP, 2639 pg/mL, normal range 0~125). A diagnosis of acute myocardial infarction was suspected. However, the urgent coronary angiography showed completely normal coronary distribution and blood flow (Video 1). Immediately after the patient returned to the CCU, her BP dropped to 80/50 mmHg, and her HR rose to 140 bpm. Echocardiography revealed severe left ventricular dysfunction (ejection fraction, LVEF=32%) and a distinctive left ventricular contraction pattern of mid-apical segment akinesia and basal segment hyperkinesia, consistent with the typical type of Takotsubo cardiomyopathy, without obstruction at the left ventricular outflow tract (Video 2). Tricuspid annular plane systolic excursion (TAPSE) was 16 mm, which indicated that right heart function was normal. Bedside chest X-ray showed no obvious lung or heart abnormality. According to
the Inter-TAK criteria, the diagnosis of Takotsubo cardiomyopathy was valid. Considering that dopamine has an adverse effect of tachycardia and that levosimendan may induce left ventricular outflow tract obstruction in this setting, norepinephrine was administered immediately. Several hours later, an extreme dose (0.8 µg/kg-min) of norepinephrine had failed to maintain BP, so an intra-aortic balloon pump (IABP) was implanted. However, the patient's condition continued to deteriorate, accompanied by agitation, decreased oxygen saturation and decreased BP. Moist rales could be heard in both lungs. Extracorporeal membrane oxygenation (ECMO) implantation was prepared but refused by the patient's family for economic reasons. With no other options, a large dose (12 µg/kg/min) of dopamine was added to maintain BP, along with noninvasive ventilation support and anxiolytics (propofol).

On the second day, the patient still complained of chest tightness accompanied by sweating and dysphoria. HR fluctuated between 130 and 140 bpm, and BP was maintained at approximately 100/60 mmHg under the combined action of norepinephrine, dopamine and IABP. NT-proBNP rose to 11482 pg/ml. Alanine transaminase (ALT) rose to 769 U/L from the normal baseline. Kidney function remained normal. Serial myocardial enzyme tests showed the peak value of creatine kinase isoenzyme (CKMB: 261 U/L, normal range 0-24) appearing eight hours after admission. Refractory cardiogenic shock caused by Takotsubo cardiomyopathy was considered. Unexpectedly, a routine test of thyroid function uncovered severe hyperthyroidism that night, with elevated total triiodothyronine (T3, 3.83 ng/ml, normal range 0.78–2.20) and...
free thyroxine (FT4, 89.2 pmol/L, normal range 9.05–25.5) and decreased thyrotropin (TSH, 0.09 uIU/ml, normal range 0.25–5). Thyroid microsomal antibody (37.4%, normal range <20) and thyroglobulin antibody (59.0%, normal range <30) were also elevated. By further consultation, we found that the patient actually had a sign of proptosis and symptoms of sweating, overeating, and weight loss of approximately 3 kg in the previous 2 months. Before we received advice from the endocrinologic specialist, the patient's condition underwent a new change.

At 3 A.M. on the third day, atrial fibrillation (AF) occurred with a rapid ventricular rate of approximately 170 bpm (Figure 2). Restoration of sinus rhythm was urgent. However, classical antiarrhythmic drugs could not be used because hyperthyroidism is a contraindication for amiodarone, and impaired LVEF is a contraindication for propafenone. A new class of antiarrhythmic drugs represented by nifekalant seemed to be the only choice. Two-thirds of the standard dose of nifekalant (0.2 mg/kg) was initiated, and sinus rhythm was restored transiently ten minutes after intravenous injection. An hour later, AF resolved under the continuous usage of nifekalant (0.3 mg/kg.h), but the patient was still in poor condition. NT-proBNP rose to 25621 pg/ml, and ALT rose to 1004 U/L. According to the Burch–Wartofsky criteria⁴, the patient received a score of 75 points (agitation=10; nausea, vomiting=10; atrial fibrillation=10; moderate pulmonary oedema=10; precipitating event=10; sinus tachycardia=25), making the diagnosis of thyroid crisis highly likely. Dexamethasone (2 mg, intravenously, every 4 fours) was initiated. Methimazole could not be used due to acute hepatic dysfunction. A potassium...
iodide oral solution was not used due to the lack of a purchase channel. Beta-blockers were not used at that time due to impaired cardiac function. Therefore, lithium carbonate (0.25 g, oral, twice daily) was used as an alternative agent to inhibit hormonal release. Other supportive measurements, such as intravenous fluids and oxygen, were also provided. On the 4th hospital day, the patient still complained of chest tightness, palpitations, and sweating, and demonstrated an altered mental status. NT-proBNP rose to 30682 pg/ml. Echocardiography showed that the LVEF was 31% with no improvement, and the TAPSE was 18 mm. With no other options and considering the issue of BP, we attempted levosimendan without a loading dose. Thankfully, there was no significant drop in BP in the following hours, so we combined a small dose of recombinant human brain natriuretic peptide to alleviate the patient’s chest tightness.

Finally, on the 5th day, the patient’s condition took a turn. She stopped sweating and had fewer complaints of discomfort. The vasopressor was reduced gradually, and the IABP was retrieved. Nifekalant was discontinued. The sinus rhythm fluctuated between 60 and 70 bpm (Figure 3). NT-proBNP dropped to 19820 pg/ml, and ALT decreased to 591 U/L.

On the 7th day, echocardiography showed completely recovered systolic function with LVEF of 64% (Video 3). NT-proBNP dropped to 12066 pg/ml (Figure 4). A small dose of beta-blocker (metoprolol, 47.5 mg once daily) was initiated. The patient was transferred to the endocrine department for special treatment on the 10th day. During her stay in the endocrine department, she was diagnosed with thyrotoxicosis secondary to...
Graves' disease. No other autoimmune diseases were involved. Dexamethasone was gradually reduced, and then oral methimazole was initiated with a starting dose of 10 mg twice a day. Lithium carbonate was discontinued because the patient developed an allergic rash. As her thyroid function improved, HR decreased to 50–60 bpm, and systolic BP was maintained between 90 and 100 mmHg. She received a reduced dose of metoprolol (23.75 mg once a day) and methimazole (5 mg three times a day) at discharge. No other drugs were used for cardiac reasons. After 3 months of titration with methimazole, her thyroid function returned to the normal range. Repeated echocardiography showed normal cardiac function. NT-proBNP was 247 pg/ml in the clinical follow-up.

Discussion

We presented a rare clinical case of cardiogenic shock following Takotsubo cardiomyopathy and thyroid crisis secondary to unknown thyrotoxicosis. In the progression of the disease, we encountered haemodynamic aggravation possibly caused by iodinated contrast-induced thyroid crisis, new onset of rapid AF with limited treatment options, and miraculous reversal of cardiac function under the combined usage of levosimendan and antithyroid crisis drugs.

Takotsubo cardiomyopathy associated with thyrotoxicosis is not rare because elevated thyroid hormone levels amplify catecholamine signalling and make Takotsubo cardiomyopathy more likely to occur. However, patients developing cardiogenic shock due to the co-occurrence of Takotsubo cardiomyopathy and thyroid crisis have been
scarcely reported. Thyrotoxicosis could present with altered mental status, fever, sweating, persistent tachycardia, heart failure and gastrointestinal symptoms such as nausea and vomiting. Thyroid crisis is an extreme manifestation of thyrotoxicosis which is usually evoked by precipitating factors such as stress and iodinated contrast media. Takotsubo cardiomyopathy is also associated with preceding emotional and physical triggers. In previous studies, researchers recognized Takotsubo cardiomyopathy as a presenting manifestation of thyroid crisis. However, in this case, it was difficult to identify whether thyroid crisis occurred simultaneously with Takotsubo cardiomyopathy triggered by the argument or was triggered by iodinated contrast media used in coronary angiography following Takotsubo cardiomyopathy. According to the haemodynamic change after the procedure, the latter was more likely. Iodinated contrast-induced thyroid crisis resulted in haemodynamic deterioration. Thyroid crisis is a clinical emergency with a mortality rate of up to 25%. Patients with cardiogenic shock following Takotsubo cardiomyopathy also have a poor in-hospital outcome. However, in the reported cases as well as in our case, the combination of antithyroid crisis medications and heart failure treatment was associated with good clinical outcomes, implying that early identification of the coexistence is important. Moreover, most Takotsubo cardiomyopathy patients need to undergo diagnostic coronary catheterization to exclude a culprit coronary artery lesion. Early recognition of thyrotoxicosis could remind the clinician to reduce the amount of contrast agent used and be aware of the occurrence of thyroid crisis.
In addition, two drugs were worth discussing in this case. The first one is nifekalant. Our patient experienced rapid AF in the setting of reduced LVEF and untreated hyperthyroidism. The restoration of sinus rhythm was critical for reducing myocardium oxygen consumption and stabilizing haemodynamics. Electrical cardioversion should be the first option upon haemodynamic collapse. However, fortunately, the patient was relatively stable under the use of vasopressors in the early phase after the occurrence of AF. At that time, choosing an anti-arrhythmic drug that would not affect cardiac and thyroid function was an issue. Nifekalant is a pure Class III antiarrhythmic drug that is highly selective for blocking the cardiac delayed rectifier potassium current. Compared with traditional medications, nifekalant has a more rapid time to onset with a shorter half-life and does not affect BP or cardiac function. Due to no experience in using this drug, we started with two-thirds of the standard dose. Surprisingly, the sinus rhythm demonstrated intermittent restoration in just ten minutes and showed persistent restoration in one hour. QT prolongation is a common feature in the setting of Takotsubo cardiomyopathy and is a major adverse effect of nifekalant. Patients with Takotsubo cardiomyopathy face a higher risk of QT prolongation and associated Torsades de pointes if receiving nifekalant therapy. However, it was not observed in our patient, which may have been due to persistent tachycardia and well-managed serum potassium levels (4.5~5.2 mmol/L). The second drug was levosimendan, which we used on the fourth hospital day when there was no other option. Levosimendan is recommended for treating Takotsubo cardiomyopathy if left ventricular outflow obstruction is absent. However,
deciding when to initiate is challenging, especially in patients with a condition complicated by cardiogenic shock. There is a lack of literature that would help clarify this issue\textsuperscript{9,10}. We used levosimendan on the fourth day, and the patient showed noticeable improvement the following day. Although levosimendan cannot take all the credit, it assumed an important role. However, in retrospect, it is worth considering the possibility of having used levosimendan and IABP as the first therapy instead of norepinephrine. Since catecholamines likely play a role in the pathophysiology of Takotsubo events, did norepinephrine and dopamine administration exacerbate the patient’s status in the early phase and delay her recovery? Although a previous report revealed that catecholamine administration was more prevalent in nonsurvivors than survivors\textsuperscript{6}, the adverse effects of catecholamines in patients with Takostubu cardiomyopathy are still uncertain. In our patient, the serial myocardial enzyme tests showed that the value of CKMB declined continuously after the peak value appeared eight hours after admission. This at least indicated that the usage of norepinephrine and dopamine did not result in further cardiac injury. Moreover, the patient’s full recovery in a week may also imply that catecholamine administration should be considered if other supports fail to maintain haemodynamic stability.

**Conclusions**

Cardiogenic shock could be a common presentation of coexisting Takotsubo cardiomyopathy and thyroid crisis. Early identification and combined treatment are associated with good outcomes.
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Data availability statement: All material is available from the corresponding authors upon reasonable request.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

Conflicts of interest: None.
References


Figure legends:

Figure 1. ECG on admission showing poor R wave progression from lead V1 to V3 and diffuse ST-segment elevation in all leads except aVR and V1.

Figure 2. ECG recorded at 3 A.M. on the third day showing atrial fibrillation (AF) with a ventricular rate of approximately 170 bpm.

Figure 3. ECG recorded on the fifth hospital day showing sinus rhythm with a heart rate of 62 bpm.

Figure 4. Temporal profile of NT-proBNP (normal range 0–125).
Figure 1
291x126 mm (8.2 x DPI)

Figure 2
283x125 mm (8.2 x DPI)
Figure 3
276x118 mm (8.2 x DPI)

Figure 4
127x76 mm (8.2 x DPI)