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CASE SERIES

Role of Venoarterial Extracorporeal Membrane Oxygenation in Cardiogenic Shock Secondary to Takotsubo Syndrome: A Case Series

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Background: Takotsubo syndrome (TTS) is an acute, self-limiting disease characterized by left ventricular wall motion abnormalities and apical ballooning. The incidence of cardiac shock (CS) during the acute phase of TTS is a major cause of mortality. We reviewed three female patients with TTS due to different causes, all of whom rapidly progressed to CS as the main clinical manifestation.

Case Presentation: Case 1: A 28-year-old female developed chest pain after receiving the human papillomavirus vaccine, which quickly led to shock and cardiac arrest. Coronary angiography showed no obstructive lesions and left ventriculography indicate left ventricular hypokinesis in the anterior wall, apex, and inferior wall. Her blood pressure was difficult to maintain with medication, and venoarterial extracorporeal membrane oxygenation (VA-ECMO) was initiated. Five days later, her cardiac function improved, and VA-ECMO was discontinued. Case 2: A 54-year-old female experienced chest pain following severe anxiety due to family issues, which quickly progressed to CS. Coronary angiography revealed no obstructive lesions and left ventriculography showed significantly reduced wall motion and spherical expansion in the apex and anterior wall. Shock and pulmonary edema were refractory to medication, so VA-ECMO support was provided. Five days later, her cardiac function recovered, and VA-ECMO was weaned off. Case 3: A 40-year-old female presented with a headache and quickly developed dyspnea, followed by refractory shock. Coronary angiography showed no obstructive coronary lesions; echocardiography suggested general wall motion abnormalities, particularly in the apex and middle segments, consistent with apical ballooning syndrome. VA-ECMO was initiated in the emergency department, and an abdominal computerized tomography scan suggested a possible pheochromocytoma. Seven days later, her cardiac function improved, and VA-ECMO was decannulated.

Conclusion: Vaccination, anxiety, or pheochromocytoma can all potentially trigger TTS complicated by CS. VA-ECMO is a promising option for patients with TTS complicated by CS.

Keywords: takotsubo syndrome, venoarterial extracorporeal membrane oxygenation, vaccine, anxiety, pheochromocytoma, case series

Introduction

Takotsubo syndrome (TTS), also known as octopus pot cardiomyopathy, apical ballooning syndrome, or "broken heart syndrome", is an acute and reversible syndrome that most commonly presents with characteristic apical left ventricular ballooning.[1] Clinically, it presents as acute cardiac dysfunction without obstructive coronary artery lesions.[2] TTS is often associated with stressors such as emotional, surgical, pharmacological, traumatic, infectious, metabolic, and acute neurological events.[3] The pathogenesis of TTS may involve abnormal elevation of catecholamines,[4] as well as inflammation, endothelial dysfunction, thyroid dysfunction, and estrogen levels.[5–7] In addition, a very important pathogenesis of TTS increasingly being identified is the theory of corticosteroid dysregulation and altered mechanism.[8,9] Diagnosis typically follows InterTAK diagnostic criteria in Table 1.[10] For suspected TTS cases, coronary angiography is essential to rule out obstructive coronary artery disease, while left ventriculography assesses left ventricular systolic function, characteristic wall motion abnormalities, and different morphological types.[3] TTS variants

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Table 1 International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

1	Patients show transient[a] left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).[b]
2	An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory.
3	Neurologic disorders (eg subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.
4	New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5	Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6	Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7	Patients have no evidence of infectious myocarditis.[b]
8	Postmenopausal women are predominantly affected.

Notes: [a]Wall motion abnormalities may remain for a prolonged period of time or documentation of recovery may not be possible. For example, death before evidence of recovery is captured. [b]Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of takotsubo syndrome.

have been described four major types based on the distribution of regional wall motion abnormalities.[2] The most common TTS type is the apical ballooning type also known as the classic TTS form,[2] which occurs in our three cases.

Despite being considered a self-limiting condition,[1] growing evidence suggests that the incidence of cardiac shock (CS) and mortality in TTS patients is comparable to that of acute coronary syndrome (ACS) patients.[11–13] In 1750 patients with TTS of 26 centers in Europe and the United States, the rate of death was 4.1%.[12] The prevalence of CS in TTS patients ranges from 6% to 20%,[14,15] with an in-hospital mortality rate as high as 15% in CS patients.[15] Given the reversibility of TTS, venoarterial extracorporeal membrane oxygenation (VA-ECMO) has emerged as a useful bridge to myocardial recovery, supporting TTS patients with CS.[16]

We presented three classic cases of TTS in female patients with different underlying causes, all characterized by rapid progression to CS. All three cases underwent VA-ECMO for peripheral position. Specifically, They were catheterised by vascular surgeons through percutaneous femoral arterial/venous puncture or incision under anaesthesia. The distal perfusion catheter was placed prophylactically in patients catheterised through an incision. Finally, all three cases were successfully treated with VA-ECMO.

Case Presentation

Case 1

A 28-year-old female with a history of a cesarean section two years ago presented with a four-day history of chest pain, followed by a two-day decline in consciousness. The patient had received a human papillomavirus (HPV) vaccine at an external hospital four days prior, followed by fever and chest pain. Two days before admission, she became disoriented and presented to the hospital with a blood pressure of 60/30 mmHg. She was treated with continuous intravenous drip of compound sodium chloride injection and vasopressors. One day before admission, she experienced cardiac arrest and was resuscitated with cardiopulmonary resuscitation and endotracheal intubation after approximately five minutes. Due to her critical condition, she was transferred to the intensive care unit (ICU). On admission, she was receiving 1.5 μg/kg/min norepinephrine, 10 μg/kg/min of dobutamine, and 3 μg/kg/min of metaraminol infusions, with a heart rate of 104 beats/min and a blood pressure of 100/42 mmHg. She was intubated and sedated, exhibiting signs of hypoperfusion and hypothermia. Her heart rhythm was regular with diminished heart sounds, and rales were audible in the bilateral lower lungs. Initial laboratory tests in Table 2 showed elevated levels of high-sensitivity troponin (HS-TnT), creatine kinase (CK), creatine kinase-MB (CK-MB), lactate, pro-B-type natriuretic peptide (Pro-BNP), white blood cells (WBC), and C-reactive protein

Table 2 Laboratory Data of the Three Patients

Laboratory Results	Case 1	Case 2	Case 3
CK, U/L	576	640	1688
CK-MB, U/L	61	29	244
HS-TnT, ng/L	388	892	3220
Pro-BNP, pg/mL	>35000	>35000	3404
Lactate, mmol/L	>15	2.3	6.66
WBC, ×10^9/L	14.57	14.4	19.65
CRP, mg/L	37.99	60.79	10.3

Abbreviations: CK, Creatine kinase; CK-MB, Creatine kinase-MB; CRP, C-reactive protein; HS-TnT, High-sensitivity troponin T; Pro-BNP, Pro-B-type natriuretic peptide; WBC, White blood cell.

(CRP). The electrocardiogram (ECG) revealed sinus tachycardia, low voltage in all leads, and ST-segment changes indicative of myocardial injury (Figure 1A). Bedside echocardiography demonstrated reduced motion in the anterior wall and mid-segment of the interventricular septum, with a decreased left ventricular ejection fraction (LVEF) of 32%. Coronary angiography did not reveal obstructive coronary artery disease, with TIMI 3 flow in all vessels (Figure 1B and C). Left ventriculography showed left ventricular hypokinesis in the apex, anterior wall (Figure 1D and E). A diagnosis of TTS with CS was made. Despite high-dose vasopressor support, she continued to have persistent hypotension due to pump failure, so VA-ECMO was initiated. The patient was also treated with antibiotics, other extracorporeal organ support including mechanical ventilation and continuous veno-venous hemofiltration (CVVH). Since the patient's family members were unwilling to undergo the implantation of the pulmonary artery catheter, we used bedside echocardiography for real-time cardiac function assessment. Her LVEF improved rapidly, and she was successfully weaned from VA-ECMO on the fifth day. She was discharged on the fourteenth day. Six months after discharge, her echocardiographic follow-up showed normal cardiac function.

Case 2

A 54-year-old woman with a 20-year history of bronchiectasis was admitted with chest discomfort for 12 hours. Over the past two weeks, she had experienced increasing anxiety due to family matters. Twelve hours before admission, she developed oppressive chest pain radiating to her back, accompanied by dyspnea. An emergency ECG revealed sinus tachycardia, low voltage in limb leads, occasional ventricular premature beats (Figure 2A). Initial laboratory data, detailed in Table 2, showed significant elevations in HS-TnT, CK, Pro-BNP, and CRP, with mild increases in CK-MB and WBC count, and normal lactate levels. Emergent coronary angiography showed a myocardial bridge in the left anterior descending artery, but no obstructive coronary disease, with TIMI 3 flow (Figure 2B and C). Left ventriculography demonstrated reduced wall motion in the apex and anterior wall, with spherical expansion (Figure 2D and E). During the procedure, her blood pressure dropped, prompting norepinephrine administration. She was diagnosed with TTS complicated by CS. Upon admission to the ICU, she was on norepinephrine infusion at 0.7 μg/kg/min, with a blood pressure of 90/75 mmHg, a heart rate of 125 beats/min, a respiratory rate of 34 breaths/min, and an oxygen saturation of 75%. She was alert but appeared apathetic, with cyanosis of the lips, a regular rhythm, and bilateral pulmonary rales. Despite vasopressors, her shock and pulmonary edema continued, necessitating VA-ECMO support and mechanical ventilation via endotracheal intubation. Additional treatments included antimicrobial therapy and psychological counseling. VA-ECMO assistance improved her shock and hypoxia rapidly. Five days later, her cardiac function recovered, and VA-ECMO was removed. Vasopressors were discontinued on the sixth day, and the patient was discharged on the twelfth day. Six months after discharge, her echocardiographic follow-up showed normal cardiac function.

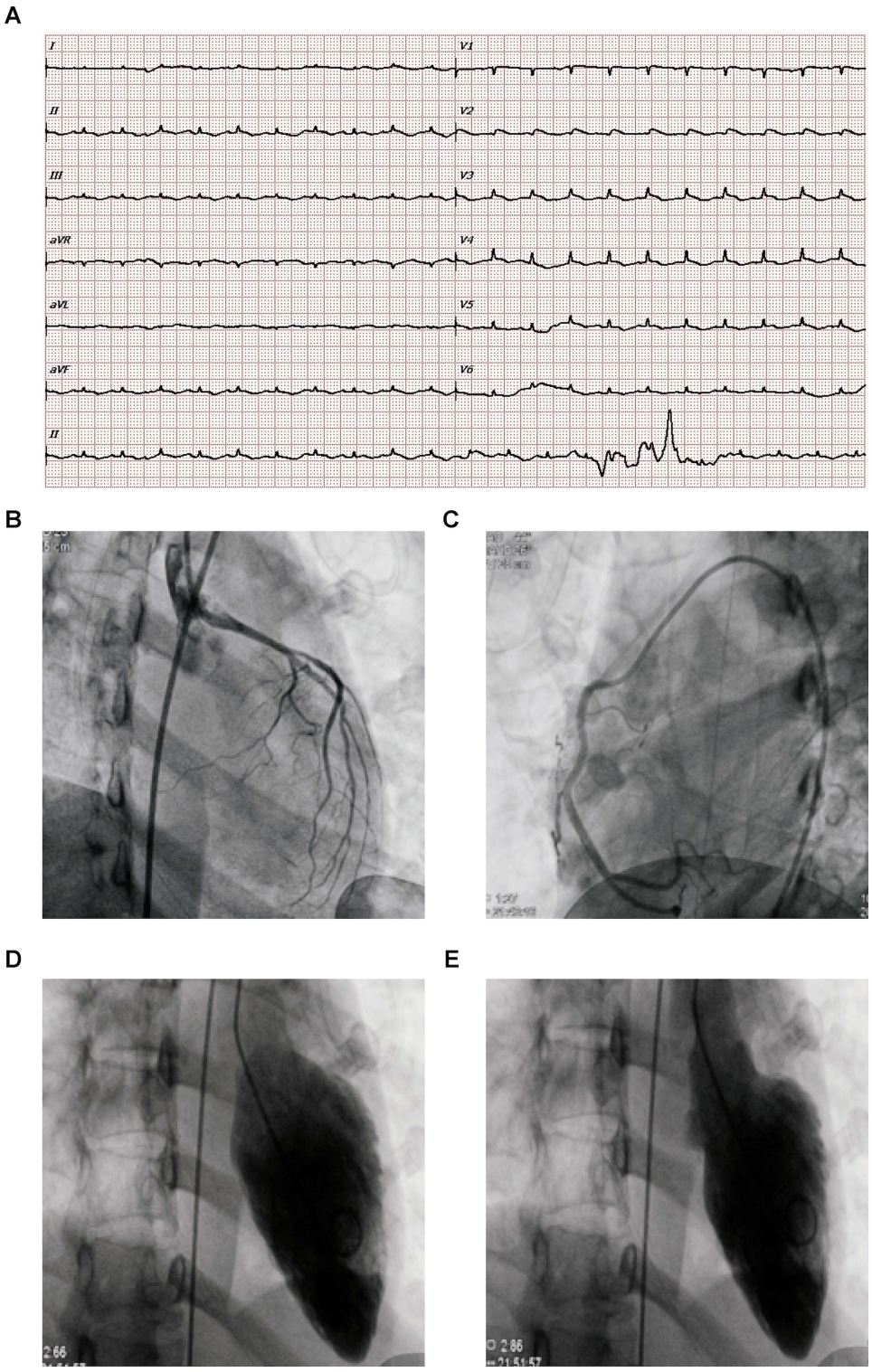

Figure 1 Electrocardiogram, coronary angiography, and left ventriculography of case 1. Electrocardiogram showing sinus tachycardia, low voltage in all leads, and ST-segment changes indicative of myocardial injury (**A**). Coronary angiography of the left coronary tree (**B**) and of the right coronary tree (**C**) with no angiographic evidence of obstructive disease. Left ventriculography showing left ventricular hypokinesis in the apex, anterior wall (**D** and **E**).

Case 3

A 40-year-old woman was transferred from an external hospital due to a sudden onset of headache for one day, along with dyspnea and palpitations for over 10 hours. She had no significant medical history. The day before admission, she

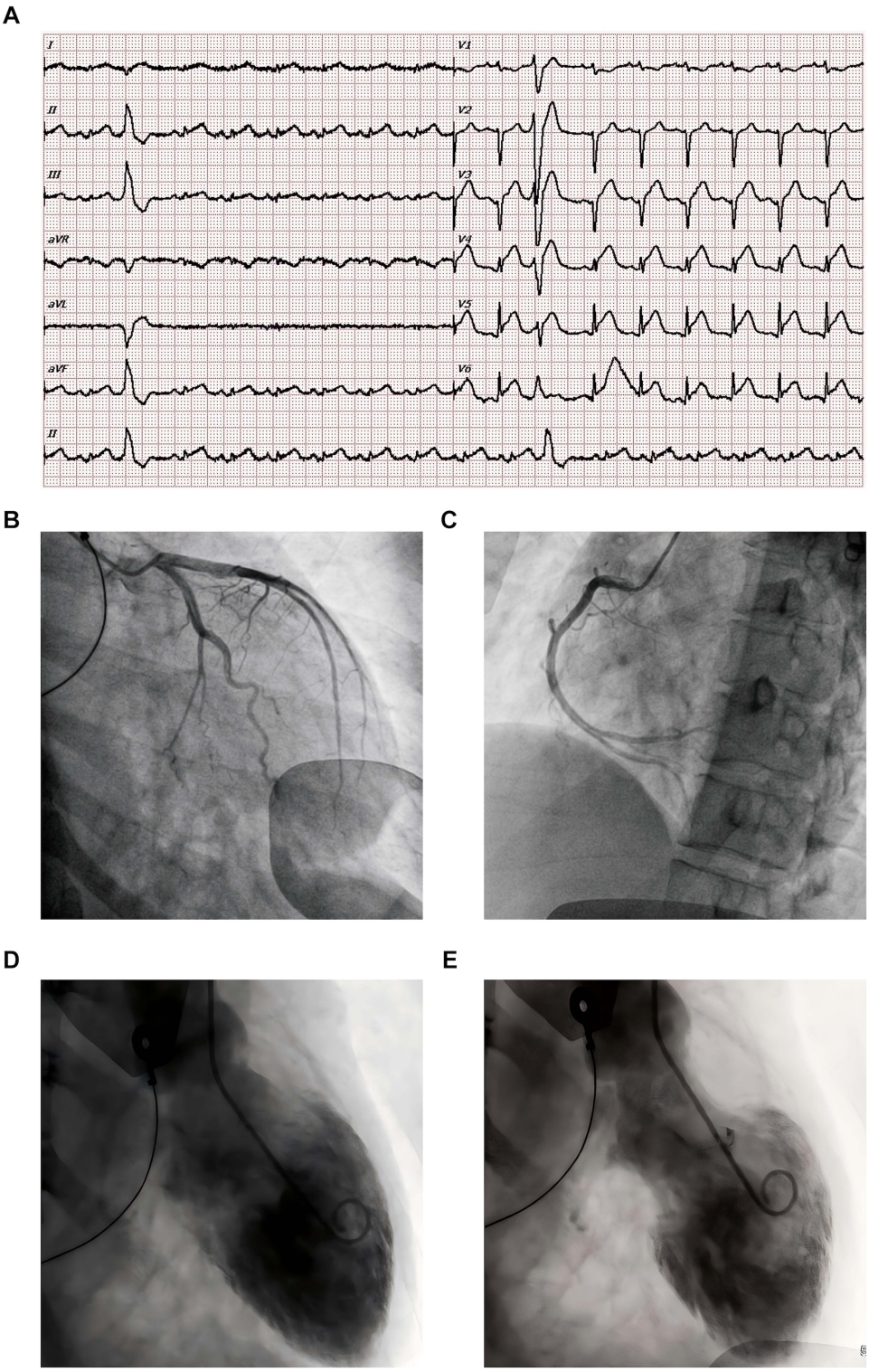

Figure 2 Electrocardiogram, coronary angiography, and left ventriculography of case 2. Electrocardiogram showing sinus tachycardia, low voltage in limb leads, occasional ventricular premature beats (**A**). Coronary angiography showing a myocardial bridge in the left anterior descending artery, but no obstructive coronary disease, with TIMI 3 flow (**B** and **C**). Left ventriculography showing reduced wall motion in the apex and anterior wall, with spherical expansion (**D** and **E**).

visited an outside hospital with a headache. Ten hours later, she developed dyspnea and palpitations, accompanied by productive cough with pink frothy sputum, unmeasurable blood pressure, tachycardia with a heart rate of 166 beats per minute, tachypnea with a respiratory rate of 40 breaths per minute, and an oxygen saturation of 86%. Troponin levels

were elevated at 1457 ng/mL. An echocardiogram indicated reduced LVEF of 21%. She was intubated, ventilated, and administered vasopressors. Emergency coronary angiography did not show any obstructive lesions (Figure 3B and C). Due to the failure of medications to maintain hemodynamic stability, she underwent continuous cardiopulmonary

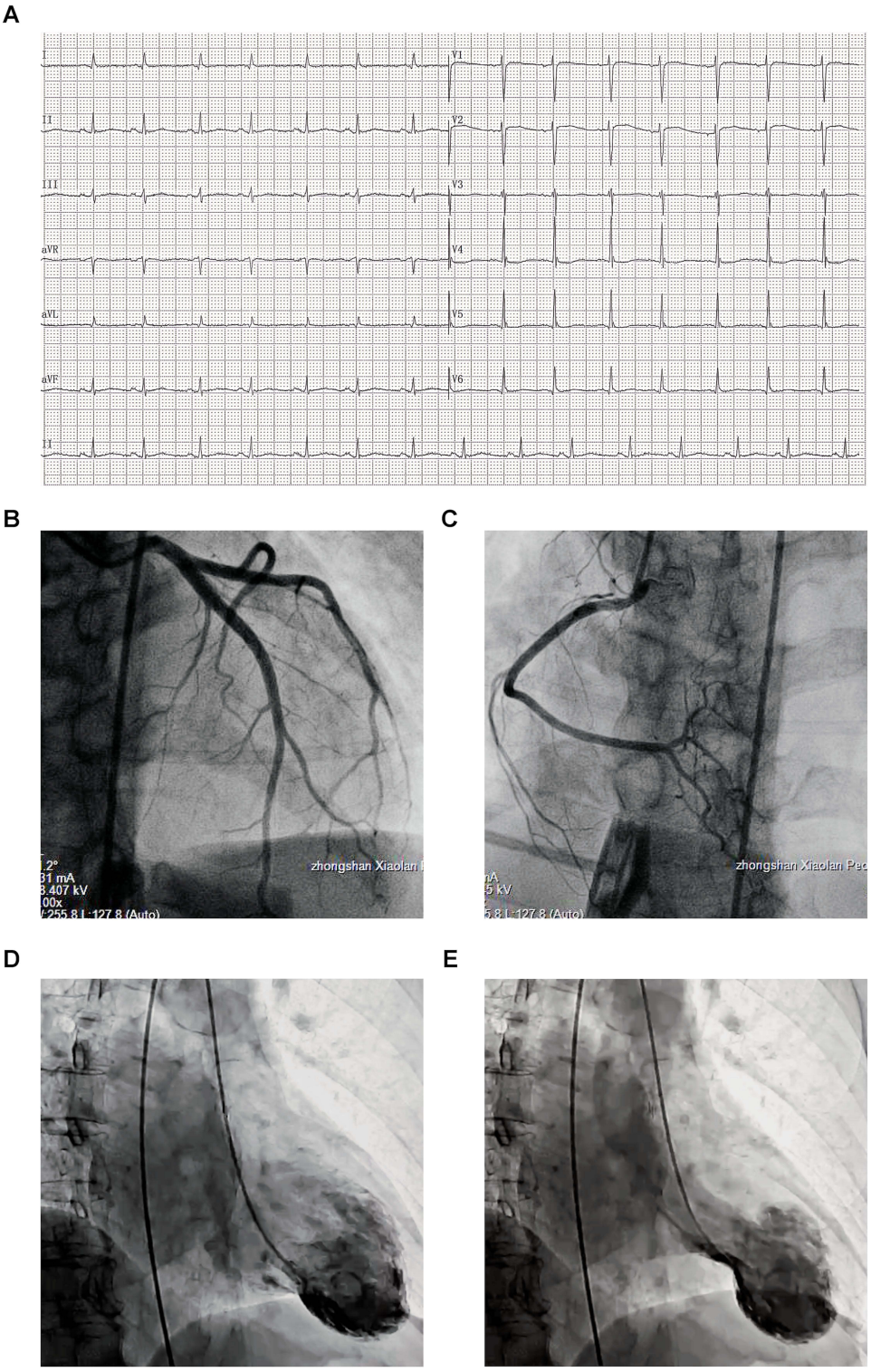

Figure 3 Electrocardiogram, coronary angiography, and left ventriculography of case 3. Electrocardiogram showing T-wave changes (**A**). Coronary angiography showing non-occlusive left anterior descending artery and non-occlusive right coronary artery (**B** and **C**). Left ventriculography showing apical akinesia with basal hyperkinesis (**D** and **E**).

resuscitation during transport to our hospital, where immediate VA-ECMO support was initiated upon arrival at our emergency department. She was then admitted to the ICU. Upon admission, she was receiving norepinephrine infusion at a rate of 2 μg/kg/min, with a mean arterial pressure of 102 mmHg, a heart rate of 100 beats per minute, and was in a sedated state. Lung sounds were decreased, with minimal wet rales in the lower lobes, and heart sounds were faint. Initial laboratory data, detailed in Table 2, indicated significant elevations in HS-TnT, CK, CK-MB, Pro-BNP, lactate, WBC count, and CRP. An ECG showed T-wave changes (Figure 3A). Left ventriculography showed apical akinesia with basal hyperkinesis (Figure 3D and E). An echocardiogram suggested increased thickness of the interventricular septum, global hypokinesis with more pronounced changes in the apex and middle segments, suggestive of apical ballooning syndrome, and poor left ventricular systolic function with LVEF of 10%. The diagnosis was TTS with CS. In addition to VA-ECMO and mechanical ventilation support, she received antimicrobial therapy, and CVVH to maintain hemodynamic stability. Hemodynamic stability was achieved on the second day of VA-ECMO support, with a reduced norepinephrine dose to 0.6 μg/kg/min and a blood pressure of 105/50 mmHg. An abdominal computerized tomography scan suggested a soft tissue mass in the right adrenal gland area, and subsequent blood and urine tests suggested a pheochromocytoma. After seven days of VA-ECMO support, her cardiac function recovered, and VA-ECMO was withdrawn. She was discharged fifteen days after hospitalization, and was prescribed with oral doxazosin and metoprolol. Six months after discharge, her echocardiographic follow-up showed normal cardiac function. Seven months after discharge, she underwent a laparoscopic resection of a right adrenal tumor at our hospital, with postoperative pathology confirming pheochromocytoma.

Discussion

TTS is defined by transient regional systolic dysfunction of the left ventricle without evidence of acute plaque rupture or significant obstructive coronary artery disease on angiography.[17] Coronary angiography in all three cases presented ruled out obstructive coronary lesions and flow obstruction, and both left ventriculography and echocardiography revealed the characteristic findings of apical ballooning and systolic dysfunction. The three patients each had distinct triggers for TTS: rare vaccine administration, typical emotional factors, and a physical condition, pheochromocytoma. Despite these differences, all three were female and presented with rapid progression to CS as the initial presentation. Prompt VA-ECMO support during CS led to hemodynamic improvement, and all three female patients with TTS and CS eventually recovered normal cardiac systolic function and were discharged successfully.

The first TTS patient had recently received an HPV vaccine. Vaccines are generally safe and effective in preventing infectious diseases.[18] Although rare, TTS associated with vaccination has been reported, primarily with coronavirus disease 2019 (COVID-19) and influenza vaccines.[19–21] The link between HPV vaccination and TTS may be due to the strong immune response triggered by mRNA vaccines,[22] along with the escalation of the inflammatory cascade and increased levels of inflammatory cytokines.[23,24] Systemic inflammation could lead to endothelial dysfunction, contributing to the development of TTS.[25] Endothelial dysfunction is encompassed by complex pathophysiology that is based on the immune-inflammatory axis from various Inflammatory cytokines.[26,27] A recent retrospective study utilizing multiple global databases to search for TTS case reports identified 19 patients with vaccine-related TTS, most of whom improved and were discharged after treatment.[28] During the COVID-19 pandemic, there were also reports of two adolescent boys who died suddenly following COVID-19 vaccination, with pathological findings in their cardiac tissue consistent with those of TTS patients.[29] Our case represents the first reported instance of a patient with HPV vaccine-related TTS presenting with rapid progression to CS.

The second TTS patient, a middle-aged woman, had significant anxiety due to personal family issues before the onset of her symptoms. It is indeed typical for TTS to occur in postmenopausal women who have experienced a preceding emotional or physical stressor.[3] Anxiety is associated with TTS;[30–32] individuals with anxiety may have increased sympathetic activity leading to excessive catecholamines,[2,33] or an abnormal hypothalamic-pituitary-adrenal axis response, which may weaken the ability to inhibit catecholamine secretion.[34] Excessive catecholamine stimulation can result in severe myocardial systolic dysfunction, leading to the characteristic apical akinesis.[35] Several anxiety-related TTS cases have been reported,[36,37] but TTS cases presenting with rapid progression to CS are less common.

Table 3 Previously Reported Takotsubo Syndrome Complicated by Cardiogenic Shock Cases Managed with Venoarterial Extracorporeal Membrane Oxygenation

NO.	Journal	Year	Trigger	Duration of Support	Outcome
1	Minerva Anestesiol	2022	Liver transplantation	5 days	Alive and discharge
2	Ann Cardiol Angeiol	2022	COVID-19	7 days	Alive and discharge
3	Open Med (Wars)	2022	Paraganglioma	7 days	Alive and discharge
4	ASAIO J	2022	Stress	7 days	Alive and discharge
5	J Med Case Rep	2021	Venlafaxine	36 hours	Alive and discharge
6	Eur Heart J Case Rep	2020	Pheochromocytoma	10 days	Alive and discharge
7	Acute Crit Care	2020	Mitral valve replacement	20 days	Alive and discharge
8	BMC Pediatr	2019	Acute brain haemorrhage	57 hours	Alive and discharge
9	JACC Case Rep	2019	Pheochromocytoma	3 days	Alive and discharge
10	Cardiovasc Revasc Med	2016	Ibuprofen combined with diphenhydramine	2 days	Alive and discharge

As our understanding of TTS deepens and more retrospective studies are conducted, it is clear that despite its nickname "broken heart syndrome", TTS is often triggered by physical factors more than emotional stress.[2] A systematic review using multiple databases to search for case reports before 2018 supports this finding.[38] Pheochromocytoma, a rare neuroendocrine tumor secreting catecholamines, can also cause TTS due to excessive catecholamine secretion.[39] While TTS complicated with CS due to catecholamine excess is not commonly the initial symptom of pheochromocytoma, CS can be a primary presentation in undiagnosed patients,[40] as seen in our third case.

While TTS has traditionally been viewed as a self-limiting condition, its high risk and potential for acute complications are increasingly recognized. Although sex is not associated with short-term outcomes and in-hospital mortality in CS-TTS,[41] female gender is one of the strongest risk factors for TTS.[12] A study from the International Takotsubo Registry comparing 1750 TTS patients with age- and gender-matched ACS patients found that the composite risk of using catecholamine drugs, requiring cardiopulmonary resuscitation, developing CS, and mortality was similar for TTS patients (19.1% vs 19.3%).[12] Another large-scale study of 88,849 TTS patients revealed a higher incidence of acute heart failure and CS compared to acute myocardial infarction (38.2% vs 32.6%).[42] During the acute phase of TTS, the incidence of CS is approximately 10% and is a leading cause of death.[43] Given that TTS with CS represents a temporary cardiac pump failure,[44,45] there is a growing body of research suggesting that mechanical circulatory support (MCS) should be considered as a bridging strategy for recovery in TTS patients with CS.[46] Timely use of MCS can overcome the risks and limitations of catecholamine vasopressors[47] and has demonstrated positive outcomes in TTS patients.[45,48] The intra-aortic balloon pump (IABP) is only able to increase the cardiac index to a limited extent,[49] The main advantages of the Impella in TTS-CS are that cardiac output can be increased simultaneously with venting of the overloaded left ventricular, thereby improving pulmonary congestion by reducing left ventricular preload and increasing cardiac output regardless of the heart rate.[50] Currently, there is no consensus on the preferred type of MCS. A recent case reports (Table 3), review and meta-analysis indicate an increasing use of VA-ECMO in TTS patients with CS,[46] which aligns with the findings in our three case reports. In addition, growing studies in recent years have reported that using VA-ECMO "the early the better" in CS treatments may be beneficial for improving multiple organ function and survival rates of the patients.[51]

Conclusion

Our case series highlights that TTS complicated with CS possibly associated with vaccination, anxiety, or pheochromocytoma. When cardiac symptoms such as chest pain and dyspnea arise following vaccination, anxiety, or the diagnosis of pheochromocytoma, caution and vigilance are warranted, as they may signal the onset of TTS, which

can rapidly progress to CS. VA-ECMO represents an effective form of mechanical support for TTS patients complicated by CS. Future validation through multicenter, large-sample size studies would reaffirm and enhance the findings.

Abbreviations

TTS, Takotsubo syndrome; CS, Cardiac shock; ICU, Intensive care unit; VA-ECMO, Venoarterial extracorporeal membrane oxygenation; ACS, Acute coronary syndrome; HPV, Human papillomavirus; HS-TnT, High-sensitivity troponin; CK, Creatine kinase; CK-MB, Creatine kinase-MB; Pro-BNP, Pro-B-type natriuretic peptide; WBC, White blood cell; CRP, C-reactive protein; ECG, Electrocardiogram; LVEF, left ventricular ejection fraction; CVVH, continuous veno-venous hemofiltration; COVID-19, Coronavirus disease 2019; MCS, Mechanical circulatory support.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Informed Consent

The design and methods of the case series are in accordance with the requirements of related regulations and procedures as well as the ethical principles. Prior to the commencement of the study, we carried out telephone follow - ups with three patients and extended invitations for them to visit the hospital to sign the informed consent form. The patients stated that they could not come to the hospital to sign, either because they were out of the local or due to personal circumstances. However, they verbally gave their consent for the implementation of the case series and its subsequent publication. We made audio recordings of these telephone follow - ups. Moreover, as the patient information in the article is anonymous, the case series had obtained approval from the Ethical Committee of Zhongshan People's Hospital (K2023-273).

Consent for Publication

Oral informed consent was obtained from the patients themselves and relevant individual's legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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