Acute Hypoxia From Different Clinical Entities Can Potentially Break the Heart: Takotsubo Cardiomyopathy

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ABSTRACT

Takotsubo syndrome is characterized by transient regional left ventricular wall motion abnormalities and elevated troponin levels like those seen in classic myocardial infarction but without evidence of obstructive coronary artery disease. We present two uncommon cases of Takotsubo syndrome. In Case 1, a 64-year-old man presented with chronic obstructive pulmonary disease exacerbation who later developed chest pain and acute hypoxic respiratory failure. In Case 2, a 77-year-old woman with myasthenia gravis was admitted for acute hypoxic hypercapnic respiratory failure requiring mechanical ventilation following a myasthenic crisis. In both cases, serum high sensitivity troponin was elevated, electrocardiograph showed findings suggestive of infarction, and coronary angiogram did not show evidence of obstructive coronary artery disease. Echocardiogram in both patients revealed abnormal left ventricular wall motion, likely secondary to Takotsubo syndrome.

Takotsubo syndrome is uncommon in the setting of chronic obstructive pulmonary disease exacerbation or myasthenic crisis, and proposed mechanisms for the disease include catecholamine surge, vasospasm of coronary arteries, and microvascular dysfunction. Takotsubo syndrome is reversible; thus, it is important to remove any trigger leading to catecholamine surge. Identification of such triggers and early diagnosis could help optimize pharmacotherapy.

INTRODUCTION

Takotsubo syndrome (TTS) also is known as stress-induced cardiomyopathy and "broken-heart syndrome." It is characterized by transient left ventricular (LV) systolic dysfunction with apical ballooning that presents similar to myocardial infarction but does not show angiographic evidence of coronary artery disease or atherosclerotic plaque rupture.[1] The pathophysiological mechanism of the disease remains mostly unknown; however, triggers for TTS typically include intense emotional or physical stress, and it is proposed that catecholamine excess, coronary artery vasospasm, and microvascular dysfunction are the main contributors.[2] In fact, patients with TTS were found to have 10 to 20 times higher levels of circulating catecholamines when compared to normal, as well as higher catecholamine levels than a matched cohort of ST-elevated myocardial infarction patients.[3] Specific precipitating triggers that have been noted include exercise and dobutamine stress tests, electroconvulsive therapy, surgery, respiratory failure, seizures, central nervous system disorders, acute critical illness, or profound mental stress.[4] It has also been suggested that those with psychiatric or neurologic disorders may be predisposed to TTS.[5,6] Considering the catecholamine surge and activation of excessive adrenergic drive that can characterize many of these disorders, it logically follows that their presence could predispose to TTS. However, literature documenting TTS is sparse.

In this case series, we report two incidences of TTS in the milieu of two different hospital admitting pathologies that led to acute hypoxic respiratory failure – one in a patient admitted for a chronic obstructive pulmonary disease (COPD) exacerbation and the other for myasthenic crisis (MC).

CASE PRESENTATIONS

Case 1

A 64-year-old man with a past medical history of 31 pack-years of cigarette smoking and COPD presented with acute shortness

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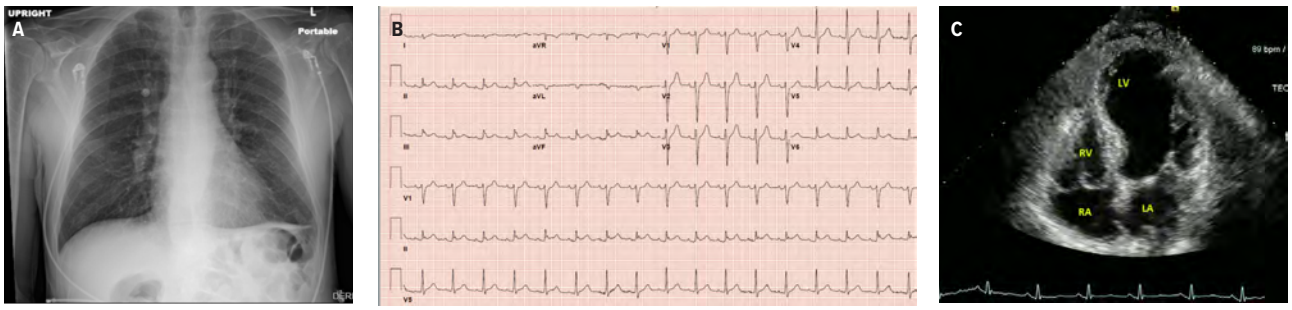
Figure 1. Case 1 Patient's (A) Chest X-Ray, (B) Electrocardiogram, and (C) Echocardiogram



of breath. He had chills and cough that started a few days prior. On lung auscultation, he had decreased air entry in the lung bases bilaterally. Laboratory investigation revealed elevated inflammatory markers (Table 1). Initial chest x-ray did not reveal evidence of acute cardiopulmonary pathology (Figure 1A).

In the emergency department, the patient was started on nebulized albuterol-ipratropium, azithromycin, and prednisone for his COPD exacerbation. Approximately 1 hour after starting nebulization, he began having chest pain and worsening shortness of breath. He became hypoxic, and arterial blood gas suggested acute hypoxic respiratory failure with PaO_2 being 79 mmHg on 2 liters of oxygen. Due to a continuous increase in supplemental oxygen demand and worsening respiratory distress, he was initiated on bilevel positive airway pressure (BiPAP). Labs drawn immediately after the onset of chest pain revealed elevated high-sensitivity troponin (TnI-HS) levels of 236 ng/L, followed by 2033 ng/L obtained 2 hours later (normal reference values = 0-57 ng/L). Electrocardiogram (ECG) revealed minimal ST elevation in leads II, III, and aVF (Figure 1B).

The patient was taken for immediate coronary angiogram, which did not show evidence of occlusive coronary artery disease (Appendix 1). He was intubated during the angiogram due to worsening hypoxia secondary to supination in the setting of COPD exacerbation; however, after the angiogram, he was extubated, reinitiated on BiPAP, and remained hemodynamically stable throughout hospitalization. Subsequent echocardiogram revealed abnormal LV wall motion indicative of TTS (Figure 1B and Appendix 2), with a left ventricle ejection fraction (LVEF) of 25%. LV global longitudinal strain was not measured. The patient's previous echocardiogram, which was obtained 14 months prior, showed normal LV function with LVEF of 62%. He was initiated on metoprolol and lisinopril, which were continued at discharge with the suggestion to start spironolactone as an outpatient. After approximately 1 month, a follow-up echocardiogram revealed no obvious regional wall motion abnormalities and an LVEF that had improved to 60%.

Case 2

A 77-year-old woman with a past medical history of myasthenia

Table 1. Lab Results for Patients 1 and 2

	Patient 1	Patient 2
Complete blood cell count		
White blood cell	12.4	16.8
Hemoglobin	13.9	11.9
Hematocrit	40.9	35
Platelets	252	228
Coagulation tests		
International normalized ratio	1.1	—
Partial thromboplastin time	25.7	—
Basic metabolic panel		
Sodium	134	140
Potassium	4.9	3.7
Chloride	102	109
Bicarbonate	23	22
Blood urea nitrogen	21	8
Creatinine	1.5	0.6
eGFR	47.1	>90
Glucose	137	180
Calcium	8.5	8.7
Total calcium	4.9	5.2
Magnesium	2.3	2.0
Phosphorus	4.4	5.7
Lipid Panel		
Cholesterol	214	58
High-density lipoprotein	51	21
Low-density lipoprotein	151	26
Triglycerides	58	56
Cardiac Markers		
TnI-HS (T_0)	236	6060
TnI-HS (T_0 + 2)	2033	—
B-type natriuretic peptide	25	25
Inflammatory Markers		
C-reactive protein	2.1	—
Procalcitonin	0.11	—
Lactate	1.4	1.9
Arterial blood gas		
pH	7.23	7.16
pCO_2	45	76
pO_2	129	115
Bicarbonate	19	27
Micro		
Urine analysis	Neg	—
Respiratory Viral Panel	Neg	—
COVID	—	Neg

Abbreviations: eGFR, estimated glomerular filtration rate; TnI-HS, high-sensitivity troponin.

Figure 2. Case 2 Patient's (A) Chest X-Ray, (B) Electrocardiogram, and (C) Echocardiogram

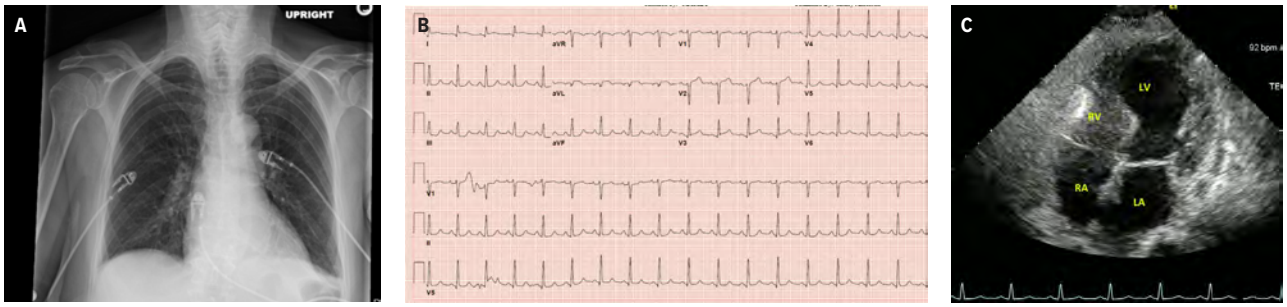


Table 2. Mayo Clinic Diagnostic Criteria for Takotsubo Syndrome

A	Transient left ventricular mid-segment hypokinesis, akinesis, or dyskinesis with or without apical involvement which are typically regional and extend beyond a single epicardial coronary distribution.
B	Absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture.
C	New electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin.
D	Absence of pheochromocytoma or myocarditis.

gravis (MG), hypertension, and dyslipidemia was admitted to the medical intensive care unit with sudden onset shortness of breath, hypoxia with fingertip pulse oximeter revealing oxygen saturation of 81%, dysphagia, and dysphonia requiring emergency endotracheal intubation and mechanical ventilation. Her chest x-ray was unremarkable for evidence of acute cardiopulmonary disease (Figure 2A), and her initial arterial blood gas was suggestive of hypercapnia with $PaCO_2$ of 76 mmHg, and TnI-HS was 6060 (Appendix 3). ECG demonstrated lateral injury pattern (Figure 2B). Coronary angiogram did not show significant obstructive coronary artery stenosis (Appendix 3). Echocardiogram revealed abnormal LV wall motion with LVEF of 23% (Figure 2B and Appendix 4). LV global longitudinal strain was not measured. She had no previous echocardiograms for comparison and had no history of exertional symptoms to suggest heart failure. Thus, the findings of elevated TnI-HS, combined with the lack of obstructive disease and decreased LVEF, were suggestive of TTS.

The patient was initiated on metoprolol and lisinopril. Since her presenting symptoms were thought to be the consequence of hypoxia from MC, she underwent plasmapheresis and received pyridostigmine, azathioprine, and prednisone. With this therapy, she was able to be successfully extubated, and her shortness of breath, dysphagia, and dysphonia resolved during hospitalization. Prior to discharge, her guideline-directed medical therapy of lisinopril and aspirin were discontinued due to clinical improvement and no further indication for the medications. Her follow-up echocardiogram after a week of hospital admission revealed an improvement in LVEF to 54%.

Of note, we excluded other possible clinical conditions with similar cardiac presentation, such as drug- or cocaine-related acute coronary syndrome, myocarditis, and pheochromocytoma. These etiologies were all unlikely, as neither patient had history of drug exposure; the preceding classic symptoms of fever, episodic headache, diaphoresis, and tachycardia were not present; and they had unremarkable urine drug screenings during their respective hospitalizations.

DISCUSSION

TTS is a transient cardiac syndrome seen in 1% to 2% of troponin-positive patients that mimics acute coronary syndrome at the time of presentation. It is characterized by regional LV systolic dysfunction extending beyond a coronary territory, without any or minimal evidence of obstructive coronary artery disease or plaque complication following invasive angiography.[1,7,8] Though the exact pathogenesis of this clinical condition remains unclear, some of the proposed pathophysiological mechanisms include catecholamine surge, coronary artery vasospasm, or microvascular dysfunction.[2,7,9] Predisposing factors reported in the international Takotsubo registry study include severe emotional and physical stress in 36% and 27.7% of patients, respectively, while in about 28.5% there were no evident triggers.[5]

Diagnosis of TTS requires fulfillment of the Mayo Clinic diagnostic criteria (Table 2).[1,9] It is important to rule out similar cardiac presentation, such as drug- or cocaine-related acute coronary syndrome, myocarditis, and pheochromocytoma, which could be indicated by a history of drug exposure or a positive urine drug screening, as well as symptoms of fever, episodic headache, diaphoresis, and tachycardia. The case study patients fulfilled all these criteria and, as a result, had definitive diagnoses of TTS.

As noted in the cases, the clinically observed pathophysiology of events triggering acute LV dysfunction included acute hypoxia resulting from ventilation-perfusion mismatch and hypoventilation from acute COPD exacerbation and MC, respectively. TTS, in the setting of acute hypoxic respiratory failure due to COPD exacerbation and MC, is uncommon, and cases have been more commonly described in patients with subarachnoid hemorrhage[7] or epilepsy.[8] These separate clinical entities cause

hypoxia via ventilation-perfusion mismatch and hypoventilation, respectively, which triggers compensatory processes of tachypnea, tachycardia, increased work of breathing, and catecholamine surge. Significant physical, psychological and neurohumoral stress leads to catecholamine-induced microvascular spasm, which may result in myocardial stunning or have a direct catecholamine-associated myocardial toxicity, leading to reversible LV ballooning seen in TTS.[3,7,10,11]

Acute hypoxia has diverse organ-system manifestations – aside from activation of several cardiovascular autonomic processes, it also exerts a stunning effect at the myocardium, which has been demonstrated in patients with ECG changes, elevated TnI-HS levels, and LV motion abnormalities seen on echocardiogram.[7,12,13] Post ischemic dysfunction – or myocardial stunning – is the mechanical dysfunction that persists after reperfusion, despite the absence of irreversible damage. It is a relatively mild, sublethal injury that must be kept quite distinct from myocardial infarction.

While the myocardial stunning effect resembles that described in acute coronary ischemia, there are no obstructive or complicated coronary lesions demonstrated on invasive angiogram in TTS patients, as in the case study patients. The complete reversal of LV dysfunction following management and resolution of each acute hypoxic episode—demonstrated by normalization of both patients' LVEFs within 1 month—supports these cardiomyopathic episodes as transient myocardial hypoxic responses.[7,9]

Additionally, COPD management with administration of albuterol can increase physiological stress on the myocardium through other mechanisms, including beta-2 vasodilatory effects on blood vessels with resultant reflex tachycardia and mild inotropic effects on the heart.[14] These effects can further increase myocardial oxygen demand.

The LV dysfunction and wall motion abnormalities seen in TTS are usually reversible with supportive management aimed at resolution of physical psychological stress, close hemodynamic monitoring, and prevention of acute complications like cardiogenic shock, acute heart failure, and thromboembolism – which, if present, require evidenced-based guideline-directed therapies.[7,9]

Clinical presentation, as in the case study patients, often resembles acute coronary events and, as a result, requires initial management with aspirin, heparin, and beta-blockers, as indicated. With definitive diagnosis of TTS, some of these therapies, like aspirin, should be deescalated, unless there are other indications. Though conservative management usually leads to positive outcomes and spontaneous recovery of LV function within a few weeks, prognosis may be worsened in patients with physical stressors or concomitant illness.[9]

Though TTS is typically reversible, it can result in severe LV systolic dysfunction, which can worsen outcomes in the setting of hospitalization for a preexisting condition, such as a COPD exacerbation or MC. As a result, a high index of suspicion is required to identify TTS and reduce predisposing triggers, as well as initiate prompt management to optimize patient outcomes.

CONCLUSIONS

Though TTS in the setting of acute hypoxic respiratory failure and MC is an uncommon occurrence – and only a handful of cases have been reported – it remains a potentially life-threatening complication of which the medical community must be aware. Since TTS is reversible, it is important to remove any underlying trigger. Thus, identification of COPD exacerbation and/or MC should prompt the clinician to screen for features of TTS, as the early diagnosis could help optimize pharmacotherapy.

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Appendices: Available at wmjonline.org.

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